

The Risk Factors for Bleeding of Fundal Varices in Patients with Liver Cirrhosis

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Background/Aims: The relationship between portal hemodynamics and fundal varices has not been well documented. The purpose of this study was to understand the pathophysiology of fundal varices and to investigate bleeding risk factors related to the presence of spontaneous portosystemic shunts, and to examine the hepatic venous pressure gradient (HVPG) between fundal varices and other varices.

Methods: In total, 85 patients with cirrhosis who underwent HVPG and gastroscopic examination between July 2009 and March 2011 were included in this study. The interrelationship between HVPG and the types of varices or the presence of spontaneous portosystemic shunts was studied. **Results:** There was no significant difference in the HVPG between fundal varices (n=12) and esophageal varices and gastroesophageal varices type 1 (GOV1) groups (n=73) (17.1±7.7 mm Hg vs 19.7±5.3 mm Hg). Additionally, there was no significant difference in the HVPG between varices with spontaneous portosystemic shunts (n=28) and varices without these shunts (n=57) (18.3±5.8 mm Hg vs 17.0±8.1 mm Hg). Spontaneous portosystemic shunts increased in fundal varices compared with esophageal varices and GOV1 (8/12 patients [66.7%] vs 20/73 patients [27.4%]; p=0.016). **Conclusions:** Fundal varices had a high prevalence of spontaneous portosystemic shunts compared with other varices. However, the portal pressure in fundal varices was not different from the pressure in esophageal varices and GOV1. (**Gut Liver 2013;7:704-711**)

Key Words: Cirrhosis; Hypertension, portal; Hepatic venous pressure gradient; Fundal varices; Portosystemic shunt, surgical

INTRODUCTION

Portal hypertension is defined as a pathological increase of portal pressure gradient resulting in the formation of portal-systemic collaterals that shunt part of the portal blood flow to the systemic circulation bypassing the liver. Clinically significant portal hypertension is diagnosed when clinical manifestations of the disease appear or when portal pressure gradient exceeds the threshold value of 10 mm Hg.¹ Gastric varices (GVs) are found in approximately 22% to 57% of cirrhotic patients with portal hypertension.^{2,3} Although the rates of bleeding in GVVs have been reported to be lower than those in esophageal varices (EVs), rupture from GVVs, particularly from fundal varices (FVs), tends to be more severe, requiring more transfusions and having a higher mortality rate.^{2,4} Gastroesophageal varices type 2 (GOV2) and isolated GVVs are referred to as gastric FVs, together.^{4,5} Gastric FVs are frequently supplied from the short gastric vein, drain blood from the fundus into the splenic vein, in contrast to gastroesophageal varices type 1 (GOV1) which are known to be supplied from the left (coronary) gastric vein.^{6,7} Therefore, the characteristics and clinical outcomes are different between these two. EVs are known to be frequently supplied from the left (coronary) gastric vein. So, EVs and GOV1 have similar hemodynamics.^{4,7} In a study by Sarin *et al.*,² the prevalence of large EVs in GOV1 was more commonly associated with large EVs than with GOV2 and the majority of GOV1 disappeared within 6 months after the obliteration of EVs, whereas GOV2 did not. However, few reports exist on hemodynamic features of FVs and risk factors for FVs bleeding in association with the presence of portosystemic shunt.

In this study, we investigated hepatic venous pressure gradient (HVPG) of gastric FVs with the presence of spontaneous

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portosystemic shunts as compared with EVs and GOV1 to clarify the hemodynamics of FVs.

MATERIALS AND METHODS

1. Patients

During the period from July 2009 to March 2011, 85 patients with liver cirrhosis who had EVs or GOVs or both were investigated with HVPG measurements at Soonchunhyang University Hospital, Seoul, South Korea. All patients had liver cirrhosis diagnosed on the basis of imaging findings, histologic findings, clinical symptoms, and biochemistry findings. Exclusion criteria included hemodynamic instability, severe comorbidity disease, uncontrolled bleeding tendency, and use of vasoactive drugs in the previous 2 weeks.

After the measurement of HVPG, they were tracked for follow-up observation retrospectively to determine whether they had variceal bleeding based on the history of hematemesis or melena and endoscopic findings. The mean follow-up period was 419 days (range, 36 to 652 days). In acute variceal bleeding, HVPG was evaluated within 2 weeks after the endoscopic treatment. The correlation between the results of HVPG measurements and endoscopically assessed degrees of varices was analyzed. The diagnosis of GOVs was confirmed using endoscopy by the agreement of two experienced endoscopists. This study was approved by the local institutional review board and conducted in accordance with the principles set forth in the Declaration of Helsinki. Written informed consent was obtained from all patients.

2. Variceal bleeding

Variceal bleeding was classified as bleeding during follow-up and past variceal bleeding. Variceal bleeding during follow-up was defined as presence of gastrointestinal bleeding signs (e.g., hematemesis, melena, unexplained anemia) and endoscopic findings after HVPG measurement. Past variceal bleeding was defined as history of endoscopic therapeutic procedures within 3 months from HVPG measure time.

3. HVPG measurement

HVPG measurements of patients were performed after overnight fasting using electrocardiogram and vital sign monitoring by an experienced radiologist. Under local anesthesia and under aseptic conditions, the venous introducer was placed in the right jugular vein. HVPG was estimated from the measurements of the wedged hepatic venous pressure (WHVP) and free hepatic venous pressure, respectively. WHVP was measured while occluding the hepatic vein when the tracing was stable. Adequate occlusion of the hepatic vein was checked using an injection of contrast dye that shows typical wedged pattern without the reflux of contrast. These measurements were duplicated before the catheter was withdrawn. The HVPG was measured at least three

times to demonstrate the reproducible values. In the cirrhotic liver, the pressure of the static column of blood created by balloon inflation could not be decompressed at the sinusoidal level due to sinusoidal narrowing and disruption of the normal inter sinusoidal architecture by fibrosis and nodule formation. For this reason, WHVP equilibrated with portal pressure.^{8,9}

4. Classification of GOVs

We used the classification system proposed originally by Sarin *et al.*² GOV are varices that extend from the esophagus into the stomach. GOV were further subclassified as GOV1 (EVs extending down to cardia or lesser curvature) and GOV2 (EVs extending to gastric fundus).² In order to make hemodynamic and clinical correlations, EVs and GOV1 were classified as group 1 because they have similar hemodynamic, and GOV2 were classified as group 2. The endoscopic findings of GOVs or EVs were classified into three types: F1, small or tortuous; F2, medium-sized or beady; and F3, enlarged, nodular or tumor-shaped according to the General Rules for Recording Endoscopic Findings set by the Japanese Research Society for Portal Hypertension and Hashizumeet classification.

5. Portosystemic shunts

A postcontrast computed tomography (CT) was performed to confirm the presence of a portosystemic shunts in all patients. The collaterals that connect gastric veins (short gastric veins, posterior gastric veins, left and right gastric veins) and the left renal vein observed in abdominal CT were defined as gastrorenal shunts. Splenorenal shunts were noted as the connections between the splenic vein and the left renal vein.

6. Statistical analysis

Data was expressed as mean±SD, range, or number (%) as appropriate. When comparing the baseline characteristics of patients in two different groups, chi-square test and Fisher exact test were used for categorical data, and Student t-test and Mann-Whitney U test were used for continuous variables. The result with $p < 0.05$ by 2-tailed test was considered significant. Data analysis was performed using SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Baseline characteristics

Patient characteristics are summarized in Table 1. Eighty-five patients (69 men, 16 women; mean age, 55.6 years) with liver cirrhosis were enrolled in this investigation. The majority of patients had alcohol-related (46.1%) or hepatitis B virus-related (38.8%) cirrhosis. Group 1 (EVs and GOV1) consisted of 73 (85.9%) patients and group 2 (GOV2) consisted of 12 (14.1%) patients. Taking β -blocker history was not differenced between two groups. There were 28 portosystemic shunts of which the

Table 1. Baseline Characteristics of the Patients

Characteristic	Group 1 (EVs+GOV1*)	Group 2 (GOV2*)	p-value
Gender, male/female	73 (57/16)	12 (12/0)	0.072
Age, yr	55.2±9.1 (31-71)	58.3±10.0 (48-79)	0.297
Cause			
HBV/HCV/Alcohol/Others [†]	29/1/33/10	4/0/7/1	0.830
Taking β -blocker	24 (32.9)	5 (41.7)	0.552
HVPG	17.1±7.7	19.7±5.3	0.268
Endoscopic finding			
Small (F1)/Medium (F2)/Large (F3)	27/30/16	5/4/3	0.879
Portosystemic shunt	20 (27.4)	8 (66.7)	0.016*
Child-Pugh score	6.85±1.7	8.67±2.2	<0.01*
MELD score	9.75±4.2	11.83±4.3	0.115
Laboratory findings			
Hemoglobin, g/dL	11.1±10.5	10.5±2.0	0.351
Platelet, $\times 10^3/\mu\text{L}$	108.6±53.0	135.3±73.8	0.132
INR	1.2±0.2	1.4±0.4	0.005*
Albumin, g/dL	3.2±0.6	2.9±0.4	0.048*
Bilirubin, mg/dL	2.1±2.8	3.5±3.9	0.127
Creatinine, mg/dL	0.8±0.3	0.7±0.2	0.092

Data are presented as number (%), mean±SD (range), or mean±SD.

HBV, hepatitis B virus; HCV, hepatitis C virus; HVPG, hepatic venous pressure gradient; MELD, model for end-stage liver disease; INR, international normalized ratio.

*Gastric varices (GOV1+GOV2)=33 (38.8% of total varices); [†]Others, cryptogenic (n=9)/autoimmune (n=1)/primary biliary cirrhosis (n=1).

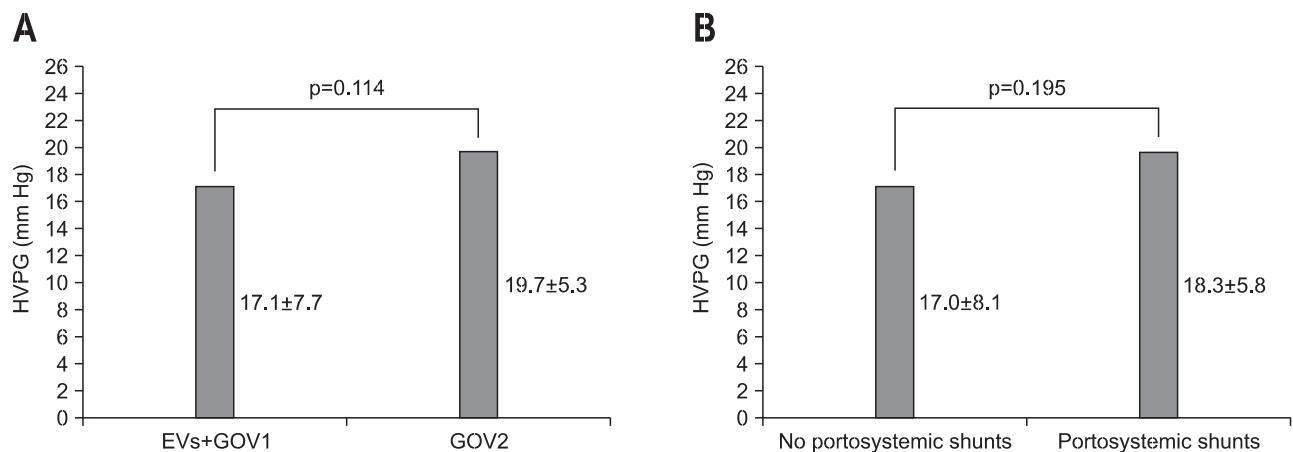


Fig. 1. (A) The hepatic venous pressure gradient (HVPG) was not different between groups 1 and 2. (B) The HVPG of varices was not different between those varices with portosystemic shunts and those varices without shunts.

majority were gastrosplenic and splenosplenic shunts.

2. Interrelationship between HVPG and types of varices and shunt

The mean HVPG of group 1 was 17.1±7.7 mm Hg and that of group 2 was 19.7±5.3 mm Hg ($p=0.114$) (Fig. 1A). The HVPG of varices with and without portosystemic shunts were 18.3±5.8 and 17.0±8.1 mm Hg, respectively ($p=0.195$) (Fig. 1B).

Portosystemic shunts were found in 20 patients (27.4%) in group 1 and eight patients (66.7%) in group 2 ($p=0.016$) (Table 2).

3. Relationship between HVPG and variceal bleeding history, endoscopic finding

The HVPG of varices with and without variceal bleeding history were 18.2±6.9 and 16.6±8.1 mm Hg, respectively ($p=0.428$). In subgroup analysis with group 1 and group 2, there was no

difference in the HVPG and variceal bleeding history.

The HVPG of varices with large size (F2 and F3) were significantly higher (18.7 ± 7.4 mm Hg vs 15.4 ± 7.2 mm Hg, $p=0.049$). However, red color sign was not significant.

4. Endoscopic finding between group with variceal bleeding and without

In the variceal bleeding groups, endoscopic findings of F2 and F3 were significantly higher (81.3% vs 50.9%, $p=0.006$) and red color sign was presented more frequently than the group without variceal bleeding (70.5% vs 42.2%, $p=0.045$). Endoscopic findings of F2 and F3 (odds ratio, 5.73; confidence interval, 1.602 to 20.484; $p=0.007$) showed association with variceal bleeding after multiple adjustments. F2/F3 and presence of red color sign were not differenced between group 1 and group 2 with variceal bleeding, respectively ($p=0.06$, $p=0.637$).

5. The comparison of bleeding risk factors between group 1 and group 2 with bleeding

There were 32 cases of variceal bleeding (37.6%) including past bleeding history associated with endoscopic treatment (Tables 3 and 4). There were 26 cases (35.6%) of variceal bleeding in group 1 and six cases (50.0%) in group 2 ($p=0.355$). During follow-up, six patients (19%) in group 1 and two patients (33.3%) in group 2 had variceal bleeding according to history data and endoscopic findings. HVPG, presence of shunt, taking of β -blocker, Child-Turcotte-Pugh score, model for end-stage liver disease (MELD) score were not differenced significantly between two bleeding groups.

There was no difference in the frequency of bleeding between the group with portosystemic shunt and the group without ($p=0.246$) (Fig. 2A). In group 2, patients without portosystemic shunt had a significantly higher frequency of bleeding compared to patients with portosystemic shunt ($p=0.014$) (Fig. 2B).

Table 2. Summary of Portosystemic Shunts

	Value
Total no. of portosystemic shunt	28 (32.9)
Group 1 (n=73)	20 (27.4)
Gastrorenal shunt	5 (25.0)
Splenorenal shunt	10 (50.0)
Gastrorenal shunt with splenorenal shunt	0
Others	5 (25.0)
Group 2 (n=12)	8 (66.7)
Gastrorenal shunt	4 (50.0)
Splenorenal shunt	1 (12.5)
Gastrorenal shunt with splenorenal shunt	3 (37.5)
Others	0
	$p=0.016$

Data are presented as number (%).

All the patients without portosystemic shunt in group 2 experienced bleeding from varices at least once. Variceal bleeding in group 2 with more portosystemic shunt number tended to be less frequent than in those without ($p=0.065$).

6. Correlation between HVPG and hepatic function

The correlation between HVPG and Child-Pugh score and MELD score were examined. There was a positive and significant correlation between HVPG and Child-Pugh score ($r=0.438$, $p=0.000$) (Fig. 3A). MELD score also showed a positive and significant correlation with the HVPG ($r=0.343$, $p=0.001$) (Fig. 3B).

DISCUSSION

It is generally believed that mean portal pressure in patients with GVVs is lower than that in patients with EVs,^{6,10-12} because spontaneous portosystemic splenorenal or gastrosplenic shunts are more common in GVVs than in EVs.^{6,13} Contrary to what was traditionally thought, HVPG in gastric FVs was not different from that of EVs in the current study despite high prevalence of spontaneous portosystemic shunts in comparison with EVs. The

Table 3. Summary of Variceal Bleeding

	Value
Total no. of patients with bleeding	32 (37.6)
Group 1	26 (81.2)
Past bleeding with endoscopic treatment	20 (77.0)
Bleeding during follow-up	4 (15.3)
Both past bleeding and bleeding during follow-up	2 (7.7)
Group 2	6 (18.8)
Past bleeding with endoscopic treatment	4 (66.7)
Bleeding during follow-up	2 (33.3)
	$p=0.355$

Data are presented as number (%).

Table 4. Summary of Site Variceal Bleeding

	Value
Total no. of patients with bleeding	32 (37.6)
Group 1	26 (81.2)
Esophageal varices bleeding	24 (92.3)
Gastric varices bleeding	0
Esophageal and gastric varices bleeding	2 (7.7)
Group 2	6 (18.8)
Esophageal varices bleeding	2 (33.3)
Gastric varices bleeding	2 (33.3)
Esophageal and gastric varices bleeding	2 (33.3)
	$p<0.01$

Data are presented as number (%).

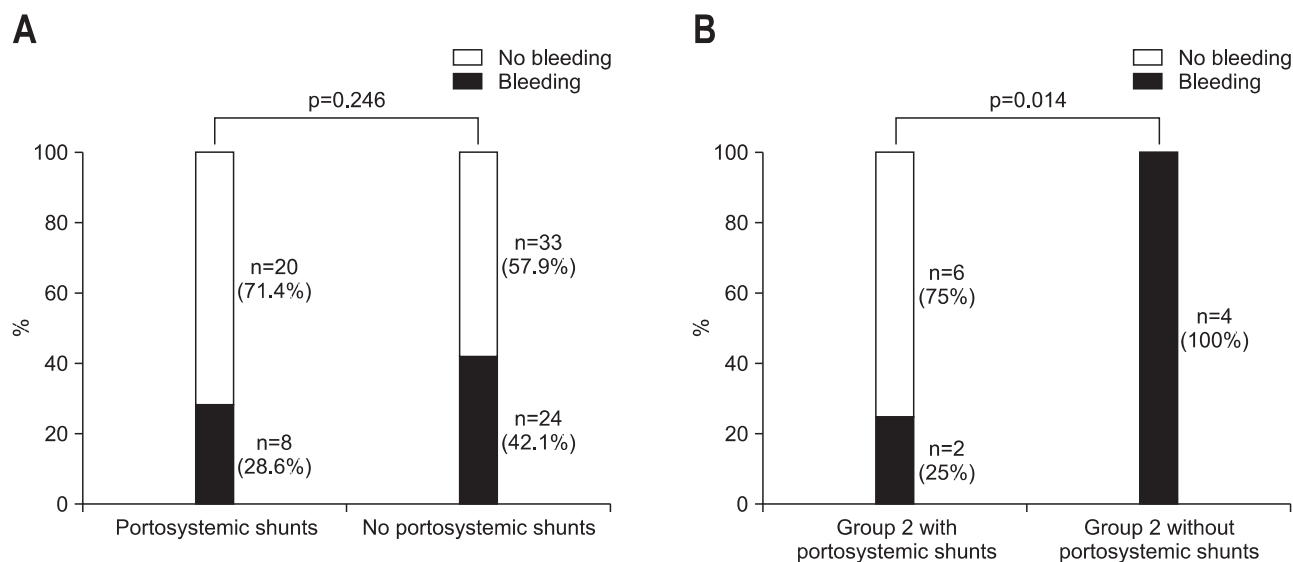


Fig. 2. (A) There was no difference in the frequency of bleeding between the group with portosystemic shunts and the group without the shunts. (B) Group 2, without portosystemic shunts, had a significantly higher frequency of bleeding.

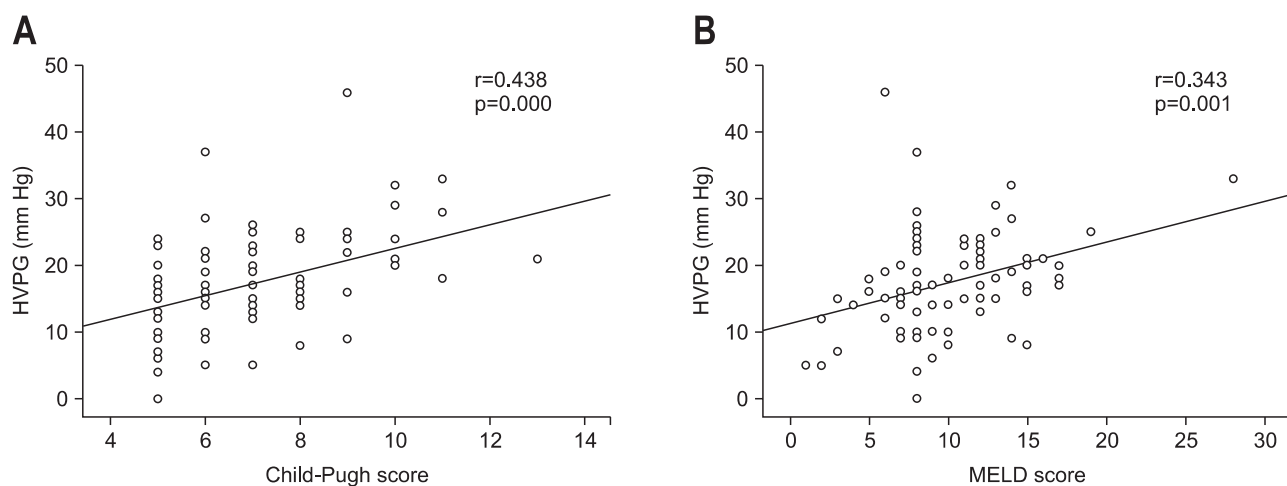


Fig. 3. The hepatic venous pressure gradient (HVPG) had significant positive correlation with both (A) the Child-Pugh score and (B) model for end-stage liver disease (MELD) score.

interrelationships between the types and degrees of spontaneous portal systemic shunts and portal vein pressure have not been clarified yet. It is generally believed that spontaneous portal systemic shunting occurs as portal vein pressure increases. Vascular resistance against portal blood flow increases in cirrhosis, inducing the congestion of blood in the splenic and mesenteric veins that lie upstream portal trunk. As blood stagnates in the stagnant route, hepatofugal collateral vessels are created as escape routes that involve veins of the esophagus, stomach, pelvis (hemorrhoids), retroperitoneum, liver, abdominal wall, and other areas. One might expect that as the collateral circulation develops, the portal vein pressure would fall. However, the inconsistent relationship between spontaneous portal systemic shunting and portal vein pressure remains one of the much challenging issues for the understanding of the hemodynamics in portal hy-

perension. In a study by Ohnishi *et al.*,¹⁴ there was a tendency of progressively high values of portal vein pressure being associated with increasing total collateral circulation up to certain levels. To understand the interrelationship between the increase of portal vein pressure and the type and degree of spontaneous portosystemic shunts, it is necessary to use a large number of patients for the follow-up observations of the development of spontaneous portosystemic shunts in connection with increased portal vein pressure.

Hemodynamic studies have shown that patients with varices always have a considerable increase of portal pressure gradient or its equivalent, the HVPG in cirrhosis.⁸ Measurement of the HVPG has been proposed for the following indications: 1) to monitor portal pressure in patients taking drugs; 2) as a prognostic marker; 3) as an end-point in trials using pharmacologic

agents for the treatment of portal hypertension; 4) to assess the risk of hepatic resection in cirrhotic patients; and 5) to investigate the cause of portal hypertension.

HVPG was correlated with the liver function and risk of variceal bleeding. The threshold portal pressure gradient or HVPG of about 12 mm Hg is needed for varices to bleed,¹⁵⁻¹⁷ as was prospectively validated in a placebo-controlled trial of prophylactic propranolol.^{18,19} However, for GVs, portal pressure gradient of ≥ 12 mm Hg is not required for bleeding to occur and a large proportion of bleedings still occur below this threshold, probably related to the high incidence of spontaneous gastrosplenic shunts among GVs patients. A number of studies have now shown that a significant proportion of GVs bleed at portal pressure gradient < 12 mm Hg.^{10,11} In our study, HVPG relationship between with and without variceal bleeding groups was not differentiated as similar previous study.

In the study of Villanueva *et al.*,²⁰ the intervals to HVPG remeasurement for therapeutic response evaluation were 3 months. However, there are currently no clear guidelines that define the optimal time and interval for HVPG measurement. We analyzed by the limitation to past bleeding as within 3 months from HVPG measurement time. We found no significant association of HVPG level with the history of bleeding.

The important predictors of bleeding from GVs include the presence of large varices, red color sign, and advanced Child-Pugh stage.^{4,21} In this study, variceal size (F2/F3) and presence of red color sign were higher in variceal bleeding group similar to previous study. However, difference according to GOV type was not revealed. Variceal rupture in gastric FVs with portosystemic shunt had a less frequent than in those without. This means gastric FVs without gastrosplenic shunt or splenorenal shunt could be a risk factor for gastric fundal variceal bleeding. Most FVs are fed by the short or posterior gastric vein and drain to the inferior vena cava through well developed gastrosplenic shunt. Patient's varices without gastrosplenic shunt had thinner veins and a lower blood-flow volume than with. However, the hemodynamics was more complicated than that in the without gastrosplenic shunt group.²² The portal hemodynamics of GVs without gastrosplenic shunt was not well known. Matsumoto *et al.*¹³ showed that it is likely to develop high risk EVs after the occlusion of gastric FVs with gastrosplenic shunt. Sakai *et al.*²³ reported that patients with gastrosplenic shunt showed a significantly lower recurrence rate of EVs after sclerotherapy compared with patients without it. And, in previous study, worsening of EVs was reported after balloon occluded retrograde transvenous obliteration (B-RTO) in long-term follow-up.²⁴ It was suggested that reflux into the left gastric vein of these patients in who blood flow from the gastric wall vessels and the left gastric vein drained into gastrosplenic shunt increased after B-RTO. Increased hepatofugal flow in the left gastric vein after B-RTO is also thought to have caused EVs.¹³ Surgical distal splenorenal shunt was effective in controlling gastric variceal haemorrhage.²⁵ This

suggests that portosystemic shunt has a role of limiting the increase of portal pressure to a certain level and is the main route for reducing the portal venous pressure.

Although a prospective study involving a large number of patients is needed, it is possible to reduce gastric fundal variceal bleeding by reducing the portal flow to GVs through newly made gastrosplenic shunt. Under the similar principle, the transjugular intrahepatic portosystemic stent shunt (TIPSS) has been evaluated for its effectiveness in the management of gastric fundal variceal bleeding.^{11,26} TIPSS is clearly very effective in controlling active bleeding and has been considered to be effective as a secondary prophylaxis, but still carries a fairly high rate of hepatic encephalopathy.²⁷ However, the severity of gastric fundal variceal bleeding and the associated mortality is significantly high. Therefore gastrosplenic shunt could be utilized as a new method to prevent gastric fundal variceal bleeding. Gastric fundal variceal bleeding with an increased number of portosystemic shunt tended to be less frequent. This suggests that increased shunting has a support role of limiting the increase of portal pressure to a certain level. However, our study is too small to prove result. More controlled and large scale studies are needed.

This study examined the severity of liver disease, as defined by MELD score or Child-Pugh score, in association with the HVPG. It is well known that patients with advanced cirrhosis have greater magnitudes of portal hypertension and Child's class is associated with portal venous pressure.²⁸⁻³⁰

One clear limitation of our study is its retrospective study design. The other limitation is the use of endoscopy to diagnose GVs. Standard endoscopy underestimates the true prevalence of pathologically dilated gastric veins in patients with portal hypertension. GVs lie in the submucosa, deeper than EVs, and GVs may not be clearly distinguishable from gastric rugae. Endoscopic ultrasonography have shown that a significant number of GVs were not evident in endoscopy.³¹ However, endoscopy still is recommended most frequently as a standard for the diagnosis of GOV because it is the best noninvasive tool.³²

In previous reports, HVPG was significantly lower in patients with GVs than those without.^{6,33} In our study, FVs had high prevalence of spontaneous portosystemic shunts compared with EVs and GOV1, but portal pressure in FVs was not different from that of EVs and GOV1. Because our study was designed by similar hemodynamic classification according to major blood supply (EVs/GOV1 vs FVs) and investigated small number of patients, this suggests that makes HVPG results unlike the previous study.

These findings indicate that the development of spontaneous portosystemic shunt may steal a part of portal venous flow and keep the portal venous pressure from increasing beyond a certain level. In this study, all the patients without portosystemic shunt in fundal variceal group experienced bleeding from varices at least once. Since gastric FVs without gastrosplenic

shunt had to bleed more frequently than those with it, producing gastrosystemic shunts in high risk group may be considered and its results should be confirmed in a prospective, randomized, controlled trial involving a large group of patients.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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