




ORIGINAL ARTICLE

Spontaneous portosystemic shunt diameter predicts liver function after balloon-occluded retrograde transvenous obliteration

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Key words

balloon-occluded retrograde transvenous obliteration, hepatic venous pressure gradient, liver function, spontaneous portosystemic shunt diameter.

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Abstract

Background and Aim: Recently, balloon-occluded retrograde transvenous obliteration (BRTO), performed for spontaneous portosystemic shunts (SPSS), has been receiving attention as a measure to improve liver function in cirrhotic patients with portal hypertension. However, it is unclear whether SPSS diameter is associated with changes in hepatic venous pressure gradient (HVPG) and liver function after BRTO.

Methods: In 34 cirrhotic patients receiving BRTO for hepatic encephalopathy/gastric varices, the association of SPSS diameter with liver function at baseline and 6 months after BRTO and the accompanying changes in HVPG were investigated.

Results: Patients had Child–Pugh (CP) scores of A/B/C (7/19/8), SPSS diameters of ≤ 10 mm/11–20 mm/ > 20 mm (8/21/5), and an average observation period of 3.2 (0.3–8.5) years. SPSS diameter was significantly associated with male sex, alcohol use, and values of albumin, prothrombin time (PT%), and NH_3 at baseline. Moreover, the SPSS diameter was significantly correlated with the changes in HVPG observed upon BRTO ($r = 0.55$, $P = 0.005$), and a large shunt diameter was significantly associated with a greater increase in HVPG. At 6 months, significant improvements in albumin, PT%, bilirubin, and NH_3 were observed overall, but the improvement was marked in those with larger shunt diameters if they had CP A/B.

Conclusion: SPSS diameter was strongly associated with liver function at baseline and after BRTO and also with changes in HVPG, indicating that SPSS diameter is an important predictor of BRTO outcome.

Introduction

Portal hypertension is a major problem of liver cirrhosis, causing various complications, such as ascites, esophago-gastric varices, and hepatic encephalopathy.^{1,2} Quality of life (QOL) and overall survival (OS) are greatly affected by these complications. As a compensatory mechanism for portal hypertension, collateral circulations known as spontaneous portosystemic shunts (SPSS) often form naturally to lower portal pressure.^{3–8} SPSS are an incomplete and inadequate compensatory mechanism for portal hypertension and often may exacerbate liver dysfunction further by reducing hepatic portal blood flow. In addition, large-scale studies have shown that SPSS are present in 40–70% of cirrhotic patients and may reduce the QOL and survival of these patients.^{7,8} On the other hand, it is not clear how SPSS are associated with liver functional reserve.

Balloon-occluded retrograde transvenous obliteration (BRTO) is a procedure developed in Japan⁹ for the treatment of

refractory hepatic encephalopathy^{10–12} and intractable fundic gastric varices^{13–19} by the obstruction of spontaneous splenorenal (SR) or gastro-renal shunts (the major types of shunt in SPSS) through an intravenous catheter. With the accumulation of clinical cases, the BRTO procedure has gained a certain position as a treatment of refractory hepatic encephalopathy and intractable fundic gastric varices, and its effectiveness is described in the evidence-based clinical practice guideline for liver cirrhosis jointly published by the Japanese Society of Gastroenterology (JSGE) and the Japanese Society of Hepatology (JSH).^{20,21} In 2018, the BRTO procedure was covered by insurance in Japan. Moreover, it has been suggested that BRTO might even improve liver function.^{22–24} On the other hand, it is not completely clear which patients will benefit from BRTO. Conventionally, it has been considered that patients with greatly decompensated cirrhosis may not obtain a favorable outcome with BRTO, although such concrete conditions of decompensation are not evident.⁶

It was shown that patients with a 20% or greater increase in HVPG (hepatic venous pressure gradient) during the BRTO experienced an improvement in post-BRTO liver function.²³ However, this result has not been confirmed in other studies and, moreover, HVPG is only obtained with an invasive catheter procedure, and the prediction of baseline HVPG as well as its change following BRTO is difficult before the catheter procedure.

Apart from BRTO, some recent studies have reported the impact of the SPSS diameter on the future pathological state of the liver. Tsuji *et al.* reported that the existence of a large-sized SPSS in hepatitis C cirrhosis patients treated with direct-acting antivirals (DAAs) may predict hepatic complications related to portal hypertension, after successful elimination of the virus,²⁵ while Allard *et al.* reported that the presence of a large-sized SPSS may predict post-transplant portal thrombosis in patients undergoing liver transplantation.³ Based on these studies, we

hypothesized that the SPSS diameter might have some role in predicting the portal hypertension-related liver function at baseline and after BRTO, although such a role has not been fully clarified to date.

In this study, we investigated the impact of the SPSS diameter on liver function at baseline and 6 months after the BRTO procedure.

Methods

Patients. This is a single institutional and retrospective observational study. A total of 34 consecutive patients with liver cirrhosis who had SPSS and received BRTO for gastro-fundic varices or for hepatic encephalopathy at the University of Yamanashi Hospital from 2006 to 2018, and were available for follow-up for at least 6 months after BRTO, were included. The diagnosis of cirrhosis was made based on the findings of laboratory tests and abdominal ultrasonography, computer tomography (CT), or magnetic resonance imaging (MRI). In all patients, the sizes of their SPSS shunts had been evaluated within 6 months before BRTO.

BRTO was performed as described by Kanagawa *et al.*⁹ In order to prevent the development of adverse events related to BRTO, the procedure was not performed (i) if the hepatic vein wedge pressure exceeded 30 mmHg after the trial balloon occlusion of the SPSS shunt, or (ii) if the hepatic vein wedge pressure increased more than 1.5 times after the trial balloon occlusion of the SPSS.

The largest SPSS diameter found by imaging in each patient was used for the analysis. The reasons for BRTO were intractable gastric varices ($n = 18$) and refractory hepatic encephalopathy with shunt ($n = 16$), and the mean observation period was 1182 days (3.24 years).

The study protocol conformed to the ethical guidelines of the 2013 Declaration of Helsinki and was approved by the

Table 1 Backgrounds of the patients

Factors	$n = 34$
Median age, years (range)	66.5 (44–85)
Sex (male/female)	18/16
Etiology (HBV/HCV/alcohol plus HCV/alcohol/PBC/NASH/unknown)	3/16/3/4/2/2/4
Indication of BRTO (GV/HE)	18/16
Child–Pugh (A/B/C)	7/19/8
History of HCC, n (%)	15 (44.1%)
Median observation period, days (range)	1182 (224–5141)
Liver-related death, n (%)	17 (50%)

BRTO, balloon-occluded retrograde transvenous obliteration; GV, gastric varices; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HE, hepatic encephalopathy; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cholangitis.

Table 2 Characteristics of the patients classified by Child–Pugh scores

Characteristics	All $n = 34$	Child–Pugh score			P -value
		A $n = 7$	B $n = 19$	C $n = 8$	
Median age, years (range)	66.5 (44–85)	69 (61–76)	71 (47–85)	58.5 (44–78)	0.125
Sex (male/female)	18/16	1/6	9/8	7/1	0.018 *
Indication of BRTO (GV/HE)	18/16	7/0	10/9	1/7	0.003 **
History of HCC, n (%)	15 (44.1%)	1 (11%)	11 (64%)	3 (38%)	0.003 **
Alb (g/dL), median (range)	3.3 (1.8–4.3)	3.7 (3.4–4.3)	3.3 (2.5–4.2)	2.3 (1.8–3.1)	0.004**
T-Bil (mg/dL), median (range)	1.2 (0.3–5.6)	1.3 (0.6–2.4)	1.0 (0.3–2.3)	2.1 (0.5–5.6)	0.050
AST (U/L), median (range)	47 (14–138)	32 (14–91)	45 (14–138)	58 (36–82)	0.438
ALT (U/L), median (range)	27 (11–106)	26 (17–73)	29 (11–106)	25 (13–65)	0.807
Plt ($\times 10^{-4}/\mu\text{L}$), median (range)	8.2 (3.1–26.2)	9.6 (4.3–14.6)	8.3 (3.1–26.2)	7.2 (5.4–16.9)	0.830
PT (%), median (range)	66 (27–91)	78 (50–91)	66 (53–91)	57 (27–68)	0.033*
NH_3 ($\mu\text{L}/\text{dL}$), median (range)	104 (42–249)	66 (42–104)	104 (42–238)	123 (94–249)	0.015*
Diameter of shunt (mm), median (range)	15 (6–35)	11 (6–18)	13 (7–32)	22 (18–35)	< 0.001**

* $P < 0.05$,

** $P < 0.01$.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BRTO, balloon-occluded retrograde transvenous obliteration; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; GV, gastric varices; PT, prothrombin time.

Human Ethics Review Committee of the University of Yamanashi. Informed consent was obtained from each patient.

Armitage test. All tests were two-sided, and $P < 0.05$ was defined as statistically significant.

Statistical analysis. Continuous variables were reported as median (range), and categorical variables were reported as number (%). Continuous variables were compared using the Mann–Whitney U test or the Wilcoxon signed-rank test, and categorical data were compared using the Chi-square test or Fisher’s exact test. Trends in the analysis were analyzed using the Cochran–

Results

Backgrounds of the patients. Table 1 shows the backgrounds of the patients. The median age of the patients was 66.5 years, 53% were male, and the etiology of liver disease was both viral and non-viral, with 76% of patients (26/34) having

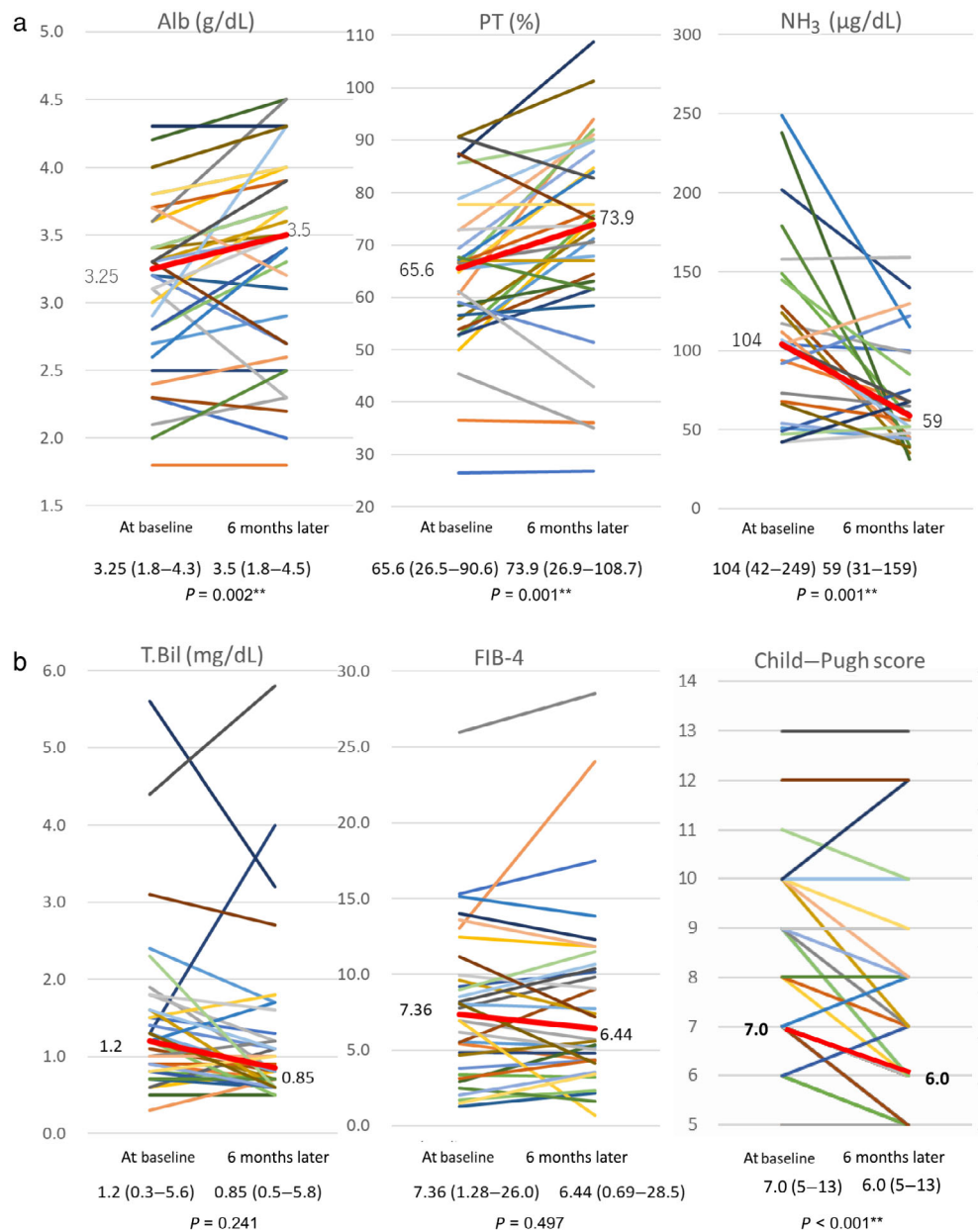


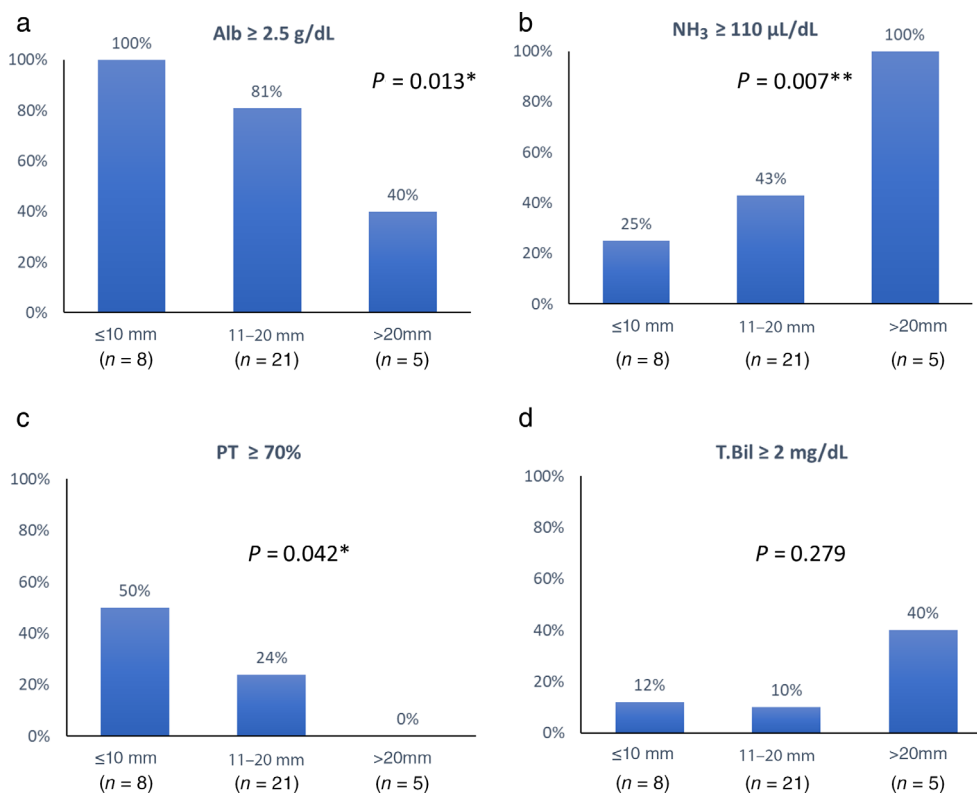
Figure 1 Changes in clinical parameters 6 months after balloon-occluded retrograde transvenous obliteration (BRTO) in 34 patients. (a) Changes in serum albumin (Alb), prothrombin time (PT, %), and NH₃. (b) Changes in total bilirubin, FIB-4 index, and Child–Pugh (CP) score. Significant improvements in albumin ($P = 0.001$), PT ($P = 0.001$), blood ammonia ($P = 0.001$), and CP score ($P < 0.001$) were observed 6 months after BRTO. Total bilirubin showed a tendency to decrease ($P = 0.241$), while no improvement was evident in FIB-4 ($P = 0.497$). $*P < 0.05$, $**P < 0.01$.

Table 3 Characteristics of the patients, classified by spontaneous portosystemic shunt diameter

Characteristics	Shunt diameter			P-value
	≤10 mm n = 8	11–20 mm n = 21	>20 mm n = 5	
Age: ≥65 years, n (%)	4 (50%)	13 (62%)	1 (20%)	0.466
Sex: Male, n (%)	3 (38%)	10 (48%)	5 (100%)	0.049*
Alcohol: Yes, n (%)	0 (0%)	3 (14%)	4 (80%)	0.008**
Alb: ≥2.5 g/dL, n (%)	8 (100%)	17 (81%)	2 (40%)	0.013*
T.Bil: ≥2 mg/dL, n (%)	1 (12%)	2 (10%)	2 (40%)	0.279
PT: ≥70%, n (%)	4 (50%)	5 (24%)	0 (0%)	0.042*
Encephalopathy: Yes, n (%)	2 (25%)	9 (43%)	5 (100%)	0.015*
NH ₃ : ≥110 µg/dL, n (%)	0 (0%)	7 (44%)	4 (80%)	0.007**
Ascites: Yes	3 (38%)	9 (43%)	3 (60%)	0.464
Indication (HE/GV)	2/6	9/21	5/0	0.002**
Child–Pugh A, n (%)	3 (38%)	4 (19%)	0 (0%)	0.099
HCC History, n (%)	3 (38%)	11 (52%)	1 (20%)	0.745
FIB-4: >5, n (%)	6 (75%)	15 (71%)	3 (60%)	0.271

P* < 0.05,*P* < 0.01.

FIB-4, fibrosis index based on four factors; GV, gastric varices; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HVPG, hepatic venous pressure gradient.

**Figure 2** Associations between spontaneous portosystemic shunt (SPSS) diameter and baseline clinical parameters of albumin (Alb), prothrombin time (PT, %), total bilirubin, and NH₃ prior to balloon-occluded retrograde transvenous obliteration. A larger shunt diameter was observed in males (*P* = 0.049), albumin <2.5 g/dL (*P* = 0.013), PT% <70% (*P* = 0.042), and NH₃ ≥110 µg/dL (*P* = 0.007). **P* < 0.05, ***P* < 0.01.

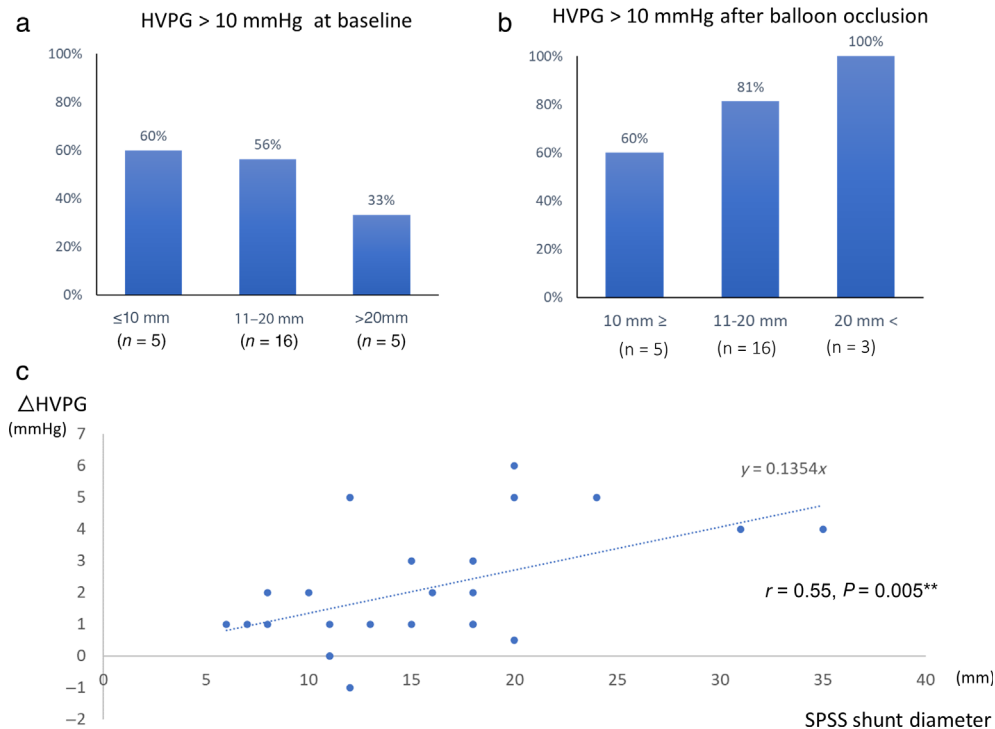


Figure 3 Association between spontaneous portosystemic shunt (SPSS) diameter and the changes in clinical parameters of hepatic venous pressure gradient (HVPG), albumin, total bilirubin, prothrombin time (PT, %), and NH_3 6 months after balloon-occluded retrograde transvenous obliteration. (a) It is seen that HVPG had a tendency to decrease with a large SPSS shunt diameter. (b) It is seen that HVPG had a tendency to increase after balloon occlusion with a large SPSS diameter. (c) It is seen that the SPSS diameter was significantly correlated with ΔHVPG . * $P < 0.05$, ** $P < 0.01$.

decompensated cirrhosis (Child–Pugh [CP] B or C). The reasons for BRTO were fundic gastric varices ($n = 18$) and refractory hepatic encephalopathy ($n = 16$), and the median observation period was 1182 days. One-half of these patients died of liver-related problems during the observation period. Table 2 shows the values of clinical factors stratified by CP scores. As shown here, there were more males ($P = 0.018$), lower albumin levels ($P = 0.004$), lower prothrombin time (PT%) ($P = 0.033$), and higher NH_3 ($P = 0.015$) with the increase of the CP score. The maximum SPSS diameter increased with the increase in the CP score ($P < 0.001$).

Changes in liver function after BRTO. The effect of SPSS diameter on changes in liver function 6 months after the BRTO procedure was investigated. Significant improvements in albumin ($P = 0.002$), PT ($P = 0.001$), ammonia ($P = 0.001$), and CP score ($P < 0.001$) were observed 6 months after BRTO. Total bilirubin (T.Bil) showed a tendency to decrease ($P = 0.241$), while no improvement was evident in FIB-4 ($P = 0.497$) (Fig. 1).

Relationship between the SPSS diameter and baseline liver function before BRTO. Next, we focused on the SPSS diameter and examined the relationship between the shunt diameter and baseline clinical factors (Table 3, Fig. 2).

A larger shunt diameter was observed in males ($P = 0.049$), albumin < 2.5 g/dL ($P = 0.013$), PT% $< 70\%$ ($P = 0.042$), and $\text{NH}_3 \geq 110$ $\mu\text{g/dL}$ ($P = 0.007$), while such an association was not observed in FIB-4 > 5 ($P = 0.271$). A large shunt diameter was also associated with alcohol intake ($P = 0.008$). The impact of alcohol on the SPSS diameter is also demonstrated in Figure S1, Supporting information, which shows the association between the liver disease etiology and the SPSS diameter.

Relationship between SPSS diameter and changes in HVPG. We then investigated the influence of SPSS diameter on baseline and the post-balloon occluded HVPG values, as well as the change in HVPG values from baseline to after balloon occlusion (ΔHVPG). In Figure 3a, it is seen that HVPG had a tendency to decrease with a large SPSS diameter, as reported previously.²⁶ In Figure 3b, it is also seen that HVPG had a tendency to increase after balloon occlusion with a large SPSS diameter. In particular, the SPSS diameter was significantly correlated with ΔHVPG (Pearson correlation coefficient, $r = 0.55$, $P = 0.005$, Fig. 3c).

Relationship between SPSS diameter and changes in liver function after BRTO. Successively, we examined the influence of SPSS diameter on changes in post-BRTO liver function. When we examined the relationship between the factors

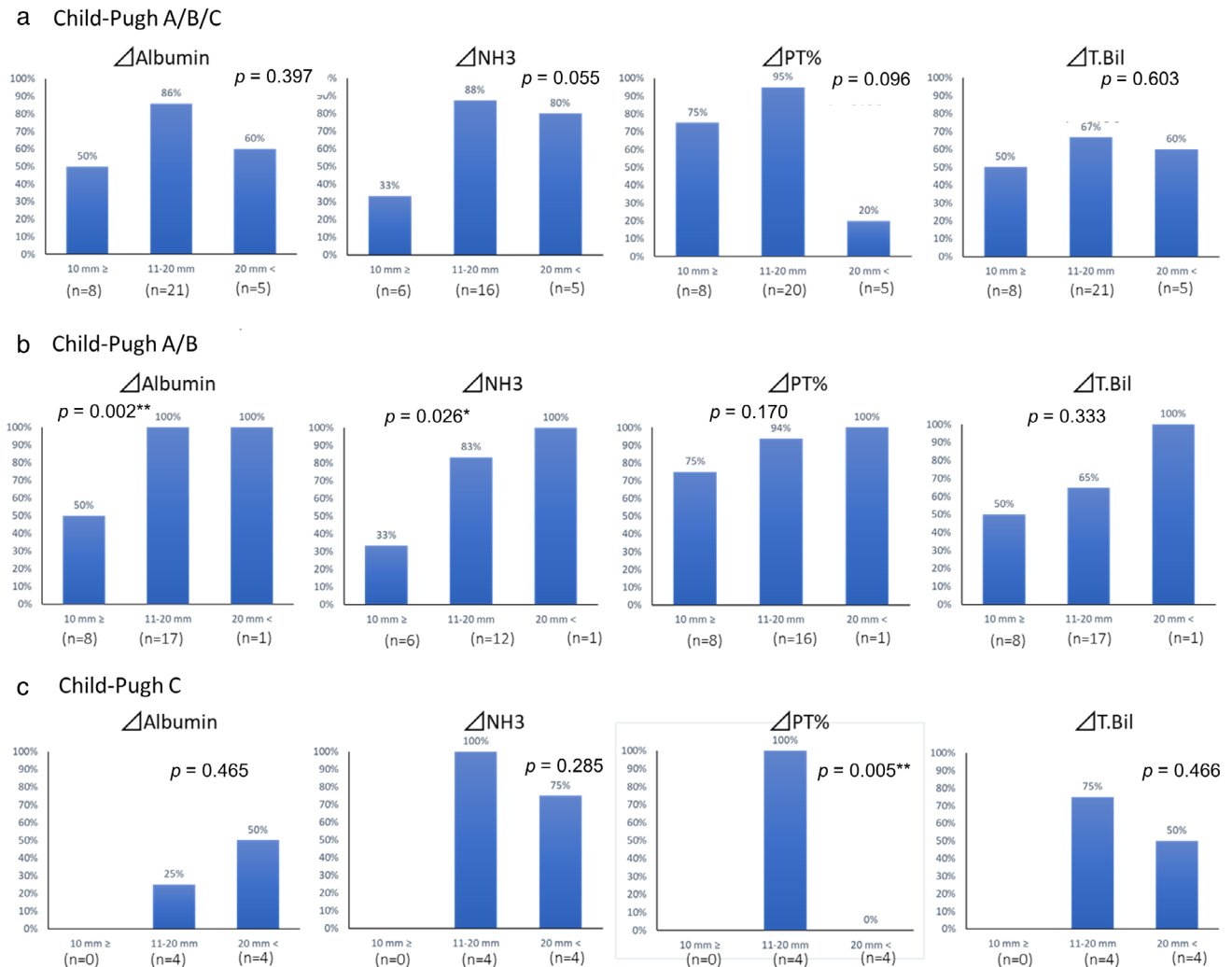


Figure 4 Association between spontaneous portosystemic shunt (SPSS) diameter and clinical parameters of albumin, prothrombin time (PT, %), total bilirubin, and NH₃ prior to and 6 months after balloon-occluded retrograde transvenous obliteration (a) in all patients, (b) in patients with Child-Pugh (CP) A/B, and (c) in patients with CP C. * $P < 0.05$, ** $P < 0.01$.

related to liver function and SPSS diameter in all CP score patients (Fig. 4a), we found that the improvement rate of albumin, PT, and NH₃ after BRTO tended to be low when the shunt diameter was 10 mm or less, and the improvement rate was most significant in those with a diameter between 10 and 20 mm, which was especially significant for NH₃. Because the CP score is a significant cofounding factor of the SPSS diameter, we next evaluated the changes in liver function classified by CP scores. Post-BRTO changes in liver function in CP A/B patients are shown in Figure 4b. Albumin, PT, NH₃, and T.Bil had a tendency to improve with a large shunt diameter, and the changes in albumin and NH₃ were significant. On the other hand, such a clear relationship was not observed in CP C patients, as shown in Figure 4c.

Changes in esophago-gastric varices and ascites after BRTO. Although BRTO might be a promising procedure

for the improvement of hepatic functional reserve, there are still some concerns about its adverse events. To clarify the impact of BRTO on esophago-gastric varices and ascites, we investigated the changes in esophago-gastric varices and ascites 6 months after BRTO. As shown in Figure S2a,b, while gastric varices improved significantly after BRTO, esophageal varices were significantly exacerbated, although only two patients with esophageal varices reached the F3 level. In ascites, no significant change was observed after BRTO (Figure S2c). In the investigation of factors associated with post-BRTO esophageal varices, we found that post-BRTO esophageal varices showed an association with FIB-4, although such an association was not found before BRTO (Figure S3).

Imaging examples of the SPSS. Example CT images of two patients with SPSS of 6 and 20 mm in diameter are shown in Figure S4. We present these patients as typical cases in which

differences in the SPSS diameter are associated with the clinical course. In case A with an SPSS diameter of 6 mm, liver function was maintained as CP A (score 5) at baseline. In this patient, Δ HVPG was limited to 1 mmHg at the time of BRTO, and there was no change in the CP score 6 months after the procedure. On the other hand, in case B with an SPSS diameter of 20 mm, liver function was CP B (score 9) at baseline. In this patient, Δ HVPG was as high as 5 mmHg at the time of BRTO, and liver function improved to CP A (score 6) 6 months after the procedure.

Discussion

In this study, we found that liver function in liver cirrhosis was negatively associated with the SPSS diameter and that an increase in shunt diameter was accompanied by an exacerbation of liver dysfunction. We also found that Δ HVPG was significantly associated with the SPSS diameter. Moreover, we showed that BRTO-induced liver functional improvement was dependent on the SPSS diameter, especially when liver function is preserved within CP A or B.

First, we could clearly demonstrate that the baseline liver function was associated with the diameter of the SPSS, and that albumin, T.Bil, PT%, NH_3 , and hepatic encephalopathy were exacerbated with a large diameter of the SPSS. Although it has been shown earlier that a large SPSS was associated with exacerbated liver dysfunction, there have been only a few studies reporting the quantitative relationship between the SPSS diameter and liver function.^{27,28} From this result alone, it is not clear whether a large shunt diameter is a result or cause of exacerbated liver dysfunction; however, because SPSS are formed as a compensation for portal hypertension but may exacerbate liver function through reducing hepatic flow portal blood flow, a large diameter could be both a result and a cause of exacerbated liver function. Considering that the SPSS diameter is quantitatively associated with liver dysfunction, it could act as a simple biomarker to evaluate the status of hepatic disease and associated portal hypertension. It is also suggested that the compensatory mechanism of the SPSS for portal hypertension might be limited in patients with small SPSS diameters. In addition to the factors influencing liver function, we found that alcohol intake and male sex were also associated with a large shunt diameter, as reported in previous studies (Table 3).²⁷ In our studies, middle-aged cirrhotic men with alcohol intake are the most frequent in the group of large shunts (data not shown).

Second, we showed that BRTO-induced liver functional improvement was dependent on the SPSS diameter, although the improvement was also affected by the baseline CP status. As mentioned in the Background section, SPSS occlusion by BRTO has been shown in recent years to improve liver function, and improved liver function has been reported in patients treated with BRTO for gastric varices and hepatic encephalopathy. However, no consensus has been established as an index enabling the prediction of the improvement of liver function before BRTO. Because large SPSS may be the result of a compensatory mechanism of portal hypertension, we hypothesized that the occlusion of large SPSS might improve liver function, and this study showed this to be true. Specifically, this study showed that the improvement of albumin and NH_3 , as well as the improved tendency of PT% and T.Bil, might be expected more frequently

after BRTO in patients with SPSS diameters of more than 10 mm when the baseline CP scores were within CP A or B (Fig. 4). However, the relationship between the shunt diameter and improvement of liver function becomes obscure in those with CP C, suggesting that the improvement of liver function may be limited in the severely decompensated liver.

Third, we also demonstrated the correlation between the shunt diameter and HVPG at baseline and post BRTO, and Δ HVPG. Although the correlation between the SPSS diameter and HVPG at baseline had been reported previously, our study is the first to report the correlation between the SPSS diameter and HVPG post BRTO and Δ HVPG. We observed that HVPG at baseline decreased as the shunt diameter increased, while HVPG increased post BRTO. Notably, Δ HVPG increased significantly in a linear fashion with the increase of the SPSS diameter, demonstrating the direct quantitative impact of the SPSS diameter on changes in HVPG after BRTO (Fig. 3). Considering that patients with large SPSS diameters might gain higher portal flow following elevation of HVPG after BRTO, it is natural that the larger the SPSS diameter, the greater the improvements in liver function. However, such a clear correlation was evident only when the baseline CP scores were within A or B, and not in C, indicating that the improvement of liver function might not parallel HVPG increase in some CP C patients, although some improvement was observed in most CP C cases. In a previous study, it was reported that an increase in HVPG of more than 20% following trial SPSS obstruction by balloon catheter at the time of BRTO could predict post-BRTO liver function improvement.²³ In this study, we also observed that an increase of HVPG of more than 20% at the BRTO procedure was associated with an improvement of the CP score (data not shown).

It is somewhat strange that the relationship between FIB-4, an index of fibrosis, and the SPSS diameter was not clear in this study. However, all of these patients had cirrhosis and had high FIB-4 values regardless of the SPSS diameter, and therefore fibrosis is considered a necessary condition for SPSS formation. On the other hand, the present results suggest that the SPSS diameter is determined not only by liver fibrosis but also by other factors such as the sex (male) and alcohol consumption as found by their relation with the SPSS diameter.

With regard to adverse events, BRTO has been reported to cause exacerbation of esophageal varices or ascites because the portal pressure reduced by SPSS might re-increase after the shunt closure.^{29,30} In this study, we found exacerbation of esophageal varices as reported previously (Figure S2a,b). On the other hand, probably because severely refractory patients with ascites were excluded from the analysis, we did not see apparent refractory ascites following the BRTO procedure (Figure S2c). Interestingly, we found a significant association between esophageal varices and FIB-4 after BRTO, while such an association was vague prior to BRTO, as shown in Figure S3. We suspect that the presence of the SPSS obscured the association between the esophageal varices and liver stiffness by lowering portal pressure, but the shunt closure procedure returned the association to its original relationship. Considering the result, we may predict the post-BRTO exacerbation of esophageal varices through FIB-4 to some extent. In contrast, no evident association was found between the SPSS diameter and esophageal varices (data not shown).

This study has some limitations. It is retrospective, and the number of patients included is not large. In addition, this is a single institutional study and the patients might not represent all the characteristics of patients with SPSS shunts, because the patients included were those with intractable gastric varices and refractory hepatic encephalopathy. Since these criteria for refractoriness may vary from institution to institution, there may be a bias in the selection of patients, even when targeting those with gastric varices and refractory hepatic encephalopathy. In this study, the largest SPSS in each patient was selected for measurement, and multiple shunts or shunts other than SPSS were not considered. The impact of the SPSS diameter on overall survival was not evaluated. Moreover, we could not analyze the relationship between the SPSS diameter and discontinuation of BRTO due to pressure over-increase at the time of procedure in this study because of the lack of appropriate databases.

In conclusion, our study showed that the SPSS diameter is strongly correlated with baseline liver function in cirrhotic patients: the larger the SPSS diameter, the lower the liver function. On the other hand, the shunt diameter was also related to the effect of shunt occlusion by BRTO, and the SPSS diameter could predict the increase of HVPG after BRTO, resulting in an improvement of liver function especially in patients with compensated liver function. Taken together, this study suggests that the SPSS diameter may be a clinically simple yet important indicator to evaluate the involvement of portal hypertension in the basic liver; moreover, it may also be a clinically important surrogate to predict liver function after BRTO.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Figure S1. Relationship between the etiology of liver disease and the SPSS diameter. “Others” includes patients with primary biliary cholangitis (PBC), nonalcoholic steatohepatitis (NASH), and unknown ($n = 4$). Data are expressed with box and whisker plots, where the center line represents the median, the box limits represent the interquartile range, and the whiskers represent the minimum to maximum data range. As shown here, alcohol is significantly associated with a larger SPSS diameter. $*P < 0.05$, $**P < 0.01$.

Figure S2. Impact of BRTO on esophago-gastric varices and ascites. (a) Gastric varices significantly improved at 6 months after

BRTO. On the other hand, (b) esophageal varices appear significantly worsened at 6 months after BRTO. (c) No evident influence by BRTO is observed on ascites. In the evaluation of esophago-gastric varices, endoscopic information was available at both baseline and 6 months after BRTO in 29 patients. In the evaluation of ascites, the information at both baseline and 6 months after BRTO was available in 33 patients. The analysis was performed by the Wilcoxon signed-rank test. In the analysis of esophago-gastric varices, information of 29 patients available for upper endoscopic findings both at baseline and at 6 months after BRTO was used in the analysis. In the analysis of ascites, information of 33 patients available for data at baseline and at 6 months after BRTO was used in the analysis. $*P < 0.05$, $**P < 0.01$.

Figure S3. The association between FIB-4 index and esophageal varices is shown (a) at baseline and (b) at 6 months after BRTO. Those with a higher FIB-4 index had significantly worse esophageal varices at 6 months post BRTO than those with a lower FIB-4 index, but such a relationship was not evident at pre-treatment time points. Information from 29 patients available for upper endoscopic findings both at baseline and at 6 months after BRTO was used in the analysis. $*P < 0.05$, $**P < 0.01$.

Figure S4. CT images of two cases with different SPSS diameter sizes, and their clinical courses. A case with SPSS diameter of 6 mm (a) and that of 20 mm (b) are shown. (a) In this case with an SPSS diameter of 6 mm, liver function was maintained as Child–Pugh (CP) A (score 5) at baseline. Δ HVPG was limited to 1 mmHg at the time of BRTO, and there was no change in CP score 6 months after the procedure. (b) In this case with an SPSS diameter of 20 mm, liver function was CP B (score 9) at baseline. Δ HVPG was as high as 5 mmHg at the time of BRTO, and liver function improved to CP A (score 6) 6 months after the procedure.