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【 ORIGINAL ARTICLE 】

# Short-term Effects of Hepatic Arterial Buffer Responses Induced by Partial Splenic Embolization on the Hepatic Function of Patients with Cirrhosis According to the Child-Pugh Classification

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**Abstract:**

**Objective** This study primarily aimed to investigate the short-term effects of partial splenic embolization (PSE) on the Child-Pugh score and identify predictive factors for changes in the score caused by PSE. The secondary aim was to analyze changes in various parameters at one month postoperatively using these identified factors.

**Methods** Between September 2007 and December 2019, 118 patients with cirrhosis and hypersplenism underwent PSE at our hospital. Testing was conducted preoperatively and at one month after PSE.

**Results** Overall, the Child-Pugh score was not significantly changed postoperatively. The Child-Pugh score before PSE was identified as the strongest independent predictor of ameliorated and deteriorated Child-Pugh scores after PSE. Higher pretreatment Child-Pugh scores were correlated with higher posttreatment amelioration rates of the score. A significant decrease in the portal vein diameter and a significant increase in the common hepatic artery diameter were evident at the same level postoperatively in 64 patients with Child-Pugh class A (group A) and in 54 patients with Child-Pugh class B or C (group B/C) preoperatively. According to Murray's Law, PSE resulted in decreased portal venous flow and increased hepatic arterial flow, suggesting a hepatic arterial buffer response (HABR) induced by the procedure. Despite equivalent splenic infarction rates and similar posttreatment changes in hepatic hemodynamics, PSE significantly increased the Child-Pugh score of group A; however, the procedure significantly decreased the score of group B/C.

**Conclusion** Considering original portal venous-hepatic arterial hemodynamics, PSE is expected to produce HABR-mediated hepatic functional improvements in cirrhosis patients with Child-Pugh class B/C.

**Key words:** partial splenic embolization, hepatic function, Child-Pugh score, hepatic arterial buffer response

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## Introduction

Liver cirrhosis is often accompanied by splenomegaly and hypersplenism, which can be both a result of portal hypertension and a cause of worsening portal hypertension. The splenic venous return volume regulates the portal system pressure, especially in patients with advanced cirrhosis and severe hypersplenism (1, 2).

Partial splenic embolization (PSE), which was originally developed to manage primary and secondary hypersplenism by Spigos et al. (3), causes ischemic necrosis of the corresponding splenic tissue and reduction of the portal pressure by decreasing the splenic venous return. Therefore, the procedure can treat not only hematological abnormalities, including thrombocytopenia and leukopenia (4-6), but also impaired portal hemodynamics (7, 8). Previous studies have demonstrated the exact effect of PSE on portal pressure reduction (9, 10), and clinical trials have shown that endoscopic and endovascular therapies combined with PSE sig-

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nificantly decrease the bleeding and recurrence rates of esophagogastric varices (11-14). Furthermore, PSE for patients with cirrhosis and hypersplenism has been reported to achieve improved liver functional parameters, including increased albumin levels, elevated prothrombin time (PT) activities, increased cholinesterase levels, and reduced alanine aminotransferase (ALT) levels (15-17). However, we have encountered some cases in which scheduled therapies following PSE have been postponed due to increased postoperative Child-Pugh (C-P) scores, which are associated with a deteriorated hepatic functional reserve after PSE, despite undergoing technically successful procedures and no additional invasive treatments during the follow-up period.

To our knowledge, there have been no reports regarding predictors of changes in the liver function, especially in the C-P score, following PSE performed in patients with liver cirrhosis and hypersplenism. The present study thus consisted of two components: an investigation of the short-term effects of PSE on the C-P score and identification of predictive factors for changes in the score caused by procedure in patients with portal hypertension, and an analysis of the changes in various parameters at one month after PSE compared to that at the baseline, using predictors of changes in the postoperative C-P scores that were identified by the first component.

## Materials and Methods

### Study design and ethical considerations

This single-center, retrospective study reviewed laboratory data and imaging findings from the medical records. Informed consent pertaining to the use of available clinical data was preoperatively obtained in writing from each patient. The research was performed in accordance with the guidelines of the Declaration of Helsinki and was approved by the appropriate institutional review board.

### Patients

Patients with both cirrhosis and hypersplenism were enrolled in this study. The inclusion criteria for this clinical trial were thrombocytopenia with a platelet count of $<5\times10^4$/μL and/or refractory portal hypertension-related diseases, such as esophagogastric varices, due to high portal pressure. Exclusion criteria included the obstruction of the portal trunk, the presence of refractory ascites, and a C-P score ≥ 11. A diagnosis of cirrhosis was established by a combination of biochemical, clinical, and ultrasonographic findings. Between September 2009 and December 2019, 127 patients with cirrhosis and hypersplenism underwent PSE at our hospital; however, 9 patients who had received anticoagulants, including warfarin, were excluded from the analysis, as their PT activities were unsuitable for C-P score calculations. Finally, the preoperative and 1-month postoperative data of 118 patients were analyzed.

### Clinical and laboratory assessments

Hepatic function markers, including the total bilirubin, albumin, aspartate aminotransferase, ALT, gamma-glutamyl transpeptidase, cholinesterase, ammonia, and PT percentage activity, were evaluated both before and one month after PSE. In addition, a complete blood count, including the white blood cell (WBC) count, hemoglobin concentration, and platelet count; electrolyte levels, namely sodium and potassium; and the renal function, including the blood urea nitrogen and creatinine levels, were assessed. The aspartate aminotransferase-to-platelet ratio index and fibrosis-4 index were calculated preoperatively and at one month after PSE using previously reported equations (18, 19).

### PSE

The PSE procedures were performed by two expert accredited physicians. The therapeutic strategy was determined according to the platelet counts, spleen volume, and clinical course of the patient. In general, a platelet count of $<5\times10^4$/μL is thought to represent a high risk of bleeding; therefore, at our institute, PSE is recommended for patients with splenomegaly when a platelet count of $<5\times10^4$/μL persists in 3 consecutive blood samples and/or when portal hypertension-related diseases, such as esophagogastric varices, are refractory despite various therapies.

PSE was performed using the previously described Takatsuka method (20). In brief, a percutaneous catheter was inserted in the right femoral artery with the patient under local anesthesia (1% lidocaine), and its tip was advanced into the hilum of the splenic artery (SpA). Gelatin sponges were implanted proximal to the microcoils that remained straight to embolize the branches of the SpA, and its upper branch remained untreated to achieve a final embolization rate of 70-80%. Contrast-enhanced computed tomography (CE-CT) confirmed the infarct area at one week after PSE; the splenic infarction rate was then calculated. No other treatments were performed for approximately one month after PSE in order to allow the patients to recover physically.

### The measurement of portal-splenic hemodynamic parameters

Before and immediately after PSE, the wedged hepatic venous pressure (WHVP) was measured and the hepatic venous pressure gradient (HVPG) was calculated, as described previously (14, 21, 22). In brief, the right hepatic venous branch was catheterized, and the free hepatic venous pressure and WHVP were measured using diluted contrast medium before and after vein occlusion; this was achieved by inflating a balloon catheter (Terumo Clinical Supply, Gifu, Japan). The HVPG was defined as the pressure difference between the portal and hepatic veins and was calculated by subtracting the free hepatic venous pressure from the WHVP. The portal flow volume was calculated using the portal flow velocity and diameter of the main portal vein (PV) measured by Doppler ultrasonography before and one

**Table 1. Baseline Clinical Characteristics of All Patients.**

| | |
|---|---|
| **Age (years)** | 65.8±8.1 |
| **Sex (male/female)** | 63/55 |
| **C-P score** | 6.6±1.5 |
| **C-P class (A/B/C)** | 64/48/6 |
| **Cause of cirrhosis (HBV/HCV/HBV+HCV/Alc/NASH/other)** | 7/70/1/19/7/14 |
| **Platelet count ($\times10^4$/μL)** | 5.8±2.2 |
| **Spleen volume ($cm^3$)** | 519.9±318.9 |
| **Hepatocellular carcinoma (presence/absence)** | 46/72 |
| **Esophagogastric varices (presence/absence)** | 79/39 |

Data are presented as the mean and standard deviation.

Alc: alcohol, C-P: Child-Pugh, HBV: hepatitis B virus, HCV: hepatitis C virus, NASH: nonalcoholic steatohepatitis

month after PSE (14, 23). However, unlike the portal flow volume, measurements of the flow through the splenic vein (SpV), common hepatic artery (CHA), and SpA by Doppler ultrasonography are unfeasible in some cases. Therefore, in this study, the vessel diameter was used as a surrogate for the blood flow volume of portal venous-hepatic arterial systems, according to Murray's Law (24). The preoperative and one-month postoperative diameters of the PV and SpV were measured on coronal-section of CE-CT images, and those of CHA and SpA were measured on axial-section of CE-CT images. The liver and spleen volumes were measured using axial CE-CT images at 5-mm intervals preoperatively and 1 month postoperatively.

### Statistical analyses

Statistical analyses were performed using the JMP software program (version 13; SAS Institute, Cary, USA), and the data are expressed as the mean and standard deviations. The differences (δ values) in each parameter, index, and score were calculated using the following formula: δ = postoperative value - preoperative value. The paired *t*-test was used for pairwise comparisons between the pretreatment and posttreatment data, and the unpaired *t*-test was used to compare two independent samples. Categorical variables were analyzed using Fisher's exact test. To identify factors predicting the amelioration and deterioration of C-P scores at one month after PSE, univariate associations among the groups were assessed using the chi-square test. Multivariate logistic regression analyses of the factors identified as significant ($p<0.05$) by the univariate analyses were performed, and odds ratios (ORs), 95% confidence intervals (CIs), and p values were calculated. Predictors of changes in C-P scores caused by PSE were also assessed using receiver-operating characteristic (ROC) curve analyses. The area under the ROC (AUROC) curve was used to evaluate the ability of a factor to predict decreases and increases in C-P scores after PSE, and the optimum cut-off value for each predictor was determined. $p<0.05$ was considered statistically significant.

## Results

### Patient demographics

Table 1 presents the baseline clinical characteristics of all patients. Of the 118 patients included in this study, 63 were men, and 55 were women. The mean patient age was 65.8 years old. Sixty-four patients were classified as C-P class A, 48 as C-P class B, and 6 as C-P class C. The causes of cirrhosis included hepatitis B (n=7), hepatitis C (n=70), hepatitis B and C (n=1), alcohol consumption (n=19), and nonalcoholic steatohepatitis (n=7). Overall, 46 patients (39.0%) and 79 patients (66.9%) had hepatocellular carcinoma and esophagogastric varices, respectively, at the time of PSE. The PSE procedures were applied as pretreatments of various therapies for hepatocellular carcinoma in 35 patients, endoscopic or endovascular therapy for esophagogastric varices in 37 patients, induction of interferon therapy for hepatitis C virus infection in 35 patients, and anticancer chemotherapies in 11 patients. For the five patients who underwent repeated PSE, only data from the first procedure were included in this study.

### Hematological and hemodynamic changes caused by PSE

PSE resulted in a splenic infarction rate of 75.2%±13.2% and significantly increased platelet (5.8±2.2 to 12.1±4.3$\times10^4$/μL; $p<0.01$) and WBC counts (3,075.3±1,149.7 to 4,378.4±1,495.7/μL; $p<0.01$) at 1 month postoperatively. The procedure significantly reduced the WHVP (266.9±68.2 to 239.1±66.0 $mmH_2O$; $p<0.01$) and HVPG (162.0±56.8 to 126.1±52.5 $mmH_2O$; $p<0.01$). Although the portal flow volume was significantly decreased (1,271.9±623.8 to 1,065.4±473.0 mL/min; $p<0.01$), the liver volume was relatively unchanged (1,110.4±296.0 to 1,094.9±311.7 $cm^3$; $p=0.18$).

### Changes in C-P scores caused by PSE

The 1-month postoperative C-P score (6.5±1.2; $p=0.07$) was not significantly different from the preoperative C-P score (6.6±1.5). Postoperatively, the C-P score of 42 patients (35.6%) was ameliorated, that of 48 patients (40.7%) remained unchanged, and that of 28 patients (23.7%) was deteriorated (Fig. 1). Compared with the pretreatment values, the C-P score component values at 1 month after PSE had changed as follows: total bilirubin level, 1.5±0.7 to 1.2±0.5 mg/dL ($p<0.01$); albumin level, 3.5±0.5 to 3.3±0.5 g/dL ($p<0.01$); and PT activity, 70.9%±14.1% to 75.1%±15.2% ($p<0.01$), respectively.

### Changes in C-P scores caused by PSE based on preoperative clinical, biochemical, and hemodynamic parameters

Patients were divided into two groups: the ameliorated group (n=42), which included patients with decreased C-P scores postoperatively, and the non-ameliorated group (n=

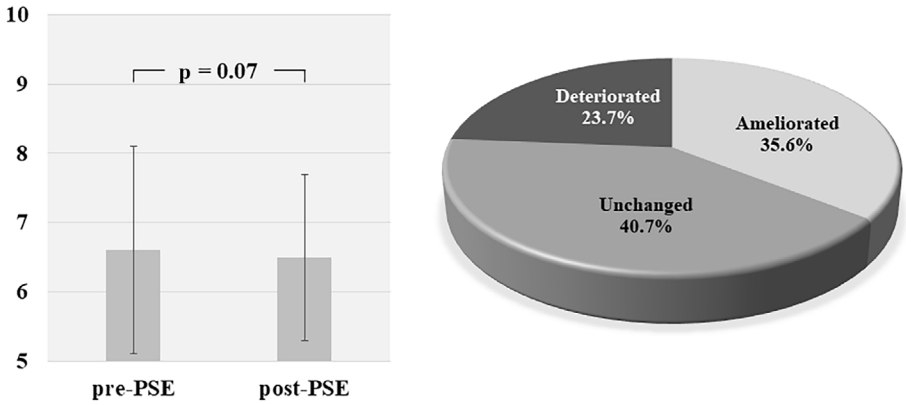


**Figure 1.** **Changes in C-P scores caused by PSE. The 1-month postoperative C-P score (6.5±1.2; p=0.07) is not significantly different from that of the preoperative C-P score (6.6±1.5). The C-P score for 42 patients (35.6%) is ameliorated, that for 48 patients (40.7%) remains unchanged, and that for 28 patients (23.7%) is deteriorated postoperatively. Data are presented as the mean and standard deviation. C-P: Child-Pugh, PSE: partial splenic embolization**

**Table 2.** **Results of Univariate and Multivariate Analyses to Predict Amelioration and Deterioration of C-P Scores Caused by PSE.**

| | Univariate analysis | | | Multivariate analysis | | |
|---|---|---|---|---|---|---|
| | **Ameliorated (n=42)** | **Non-ameliorated (n=76)** | **p** | **OR** | **95% CI** | **p** |
| **C-P score** | 7.8±1.3 | 5.9±1.1 | <0.0001 | 7.06 | 3.11 - 19.23 | <0.0001 |
| **PT (%)** | 62.3±10.8 | 75.6±13.5 | <0.0001 | 0.98 | 0.93 - 1.03 | 0.4488 |
| **Albumin (g/dL)** | 3.3±0.5 | 3.6±0.5 | 0.0009 | 6.05 | 1.35 - 32.92 | 0.0178 |
| **T-Bil (mg/dL)** | 1.8±0.9 | 1.3±0.6 | 0.0011 | 0.34 | 0.12 - 0.84 | 0.0188 |
| **LV/SPV ratio** | 2.2±1.1 | 3.2±2.0 | 0.0016 | 0.98 | 0.64 - 1.42 | 0.9334 |
| **Platelet ($\times10^4$/μL)** | 5.0±2.0 | 6.3±2.2 | 0.0021 | 0.96 | 0.71 - 1.29 | 0.7943 |
| **ALT (IU/mL)** | 33.6±16.0 | 45.9±38.6 | 0.0322 | 1.00 | 0.98 - 1.02 | 0.7370 |
| | **Deteriorated (n=28)** | **Non-deteriorated (n=90)** | **p** | **OR** | **95% CI** | **p** |
| **C-P score** | 5.8±1.0 | 6.9±1.5 | 0.0001 | 1.82 | 1.15 - 3.10 | 0.0103 |
| **PT (%)** | 77.3±16.0 | 68.9±12.9 | 0.0070 | 0.98 | 0.94 - 1.02 | 0.3257 |
| **WBC (/μL)** | 2,717.5±866.5 | 3,186.6±1,207.0 | 0.0453 | 1.00 | 1.00 - 1.00 | 0.0227 |

Data are presented as the mean and standard deviation.

ALT: alanine aminotransferase, C-P: Child-Pugh, CI: confidence interval, LV/SPV: liver volume to spleen volume, OR: odds ratio, PT: prothrombin time, T-Bil: total bilirubin, WBC: white blood cell

76), which included patients with unchanged and increased C-P scores postoperatively. Ameliorated C-P scores after PSE were significantly associated with higher C-P scores (p <0.0001), lower PT activity (p<0.0001), lower serum albumin levels (p=0.0009), higher total bilirubin levels (p= 0.0011), lower ratios of the liver volume to spleen volume (p=0.0016), lower platelet counts (p=0.0021), and lower ALT levels (p=0.0322) before treatment (Table 2). A multivariate logistic regression analysis identified the preoperative C-P score as the strongest independent predictor of C-P score amelioration following PSE (OR, 7.06; 95% CI, 3.11-19.23; p<0.0001) (Table 2). The ROC curve analysis showed that the AUROC curve for predicting decreases in C-P scores after PSE was 0.85965 and that the optimum preoperative C-P score cut-off value to achieve decreases in the C-P scores postoperatively was 7 (sensitivity, 83.3%; specificity, 75.0%). In addition, patients were divided into another two groups: the deteriorated group (n=28), which included patients with increased C-P scores postoperatively, and the non-deteriorated group (n=90), which included patients with unchanged and decreased C-P scores postoperatively. Univariate and multivariate analyses revealed that the C-P score before PSE was the factor most strongly and independently predictive of C-P score deterioration after PSE (OR, 1.82; 95% CI, 1.15-3.10; p=0.0103) (Table 2).

### *Changes in C-P scores caused by PSE according to the preoperative C-P classification and score*

Because the pretreatment hepatic functional reserve, measured as the preoperative C-P score, contributes to changes in the C-P score following PSE, patients were divided into two groups according to the pretreatment C-P

**Table 3. Preoperative Characteristics of Patients Classified as C-P Class A and Class B/C.**

| | Group A (C-P A, n=64) | Group B/C (C-P B/C, n=54) | p |
|---|---|---|---|
| **Age (years)** | 65.8±8.3 | 65.9±8.0 | 0.9237 |
| **Sex (male/female)** | 30/34 | 33/21 | 0.1246 |
| **Cause of cirrhosis (HBV/HCV/HBV+HCV/Alc/NASH/other)** | 2/44/0/10/3/5 | 5/25/1/10/4/9 | 0.0858 |
| **Platelet count ($\times 10^4/\mu L$)** | 6.5±2.3 | 5.0±1.8 | 0.0003 |
| **Spleen volume ($cm^3$)** | 428.5±227.6 | 628.2±375.4 | 0.0006 |
| **WHVP ($mmH_2O$)** | 247.8±62.4 | 296.4±64.5 | 0.0050 |
| **HVPG ($mmH_2O$)** | 156.3±58.1 | 173.2±50.0 | 0.2544 |
| **Hepatocellular carcinoma (presence/absence)** | 22/42 | 24/30 | 0.2971 |
| **Esophagogastric varices (presence/absence)** | 36/28 | 43/11 | 0.0069 |

Data are presented as the mean and standard deviation.

Alc: alcohol, C-P A: Child-Pugh class A, C-P B/C: Child-Pugh class B or C, HBV: hepatitis B virus, HCV: hepatitis C virus, HVPG: hepatic venous pressure gradient, NASH: nonalcoholic steatohepatitis, WHVP: wedged hepatic venous pressure

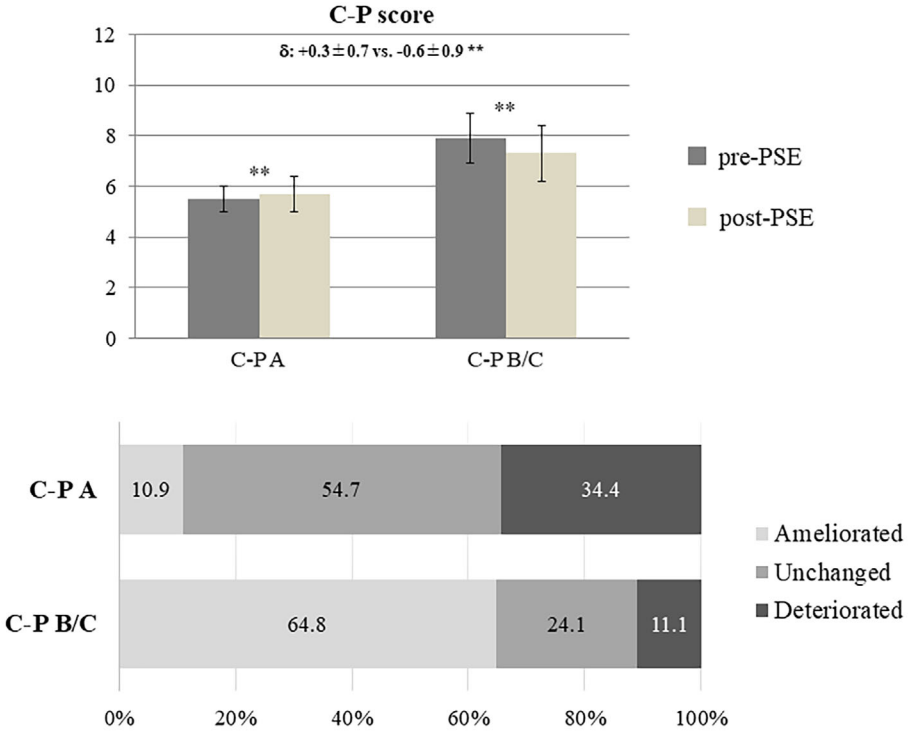


**Figure 2. Changes in C-P scores caused by PSE based on the preoperative C-P classification. Although PSE significantly increases the C-P score (5.5±0.5 to 5.7±0.7; p<0.01) of patients with C-P class A, the procedure significantly decreases the score (7.9±1.0 to 7.3±1.1; p<0.01) of those with C-P class B/C, indicating a completely opposite response to similar treatment approaches. The δ value of the C-P score of patients with C-P class A is +0.3±0.7 and that of patients with C-P class B/C is -0.6±0.9, showing a significant difference in changes in the C-P scores between the two groups (p<0.01). One month after PSE, the C-P scores of 10.9% of patients with C-P class A and 64.8% of patients with C-P class B/C are ameliorated, those of 54.7% of patients with C-P class A and 24.1% of patients with C-P class B/C are unchanged, and those of 34.4% of patients with C-P class A and 11.1% of patients with C-P class B/C are deteriorated. Data are presented as the mean and standard deviation. The δ value is calculated using the following formula: δ=postoperative value-preoperative value. **p<0.01 for comparisons between groups. C-P: Child-Pugh, C-P A: Child-Pugh class A, C-P B/C: Child-Pugh class B or C, PSE: partial splenic embolization**

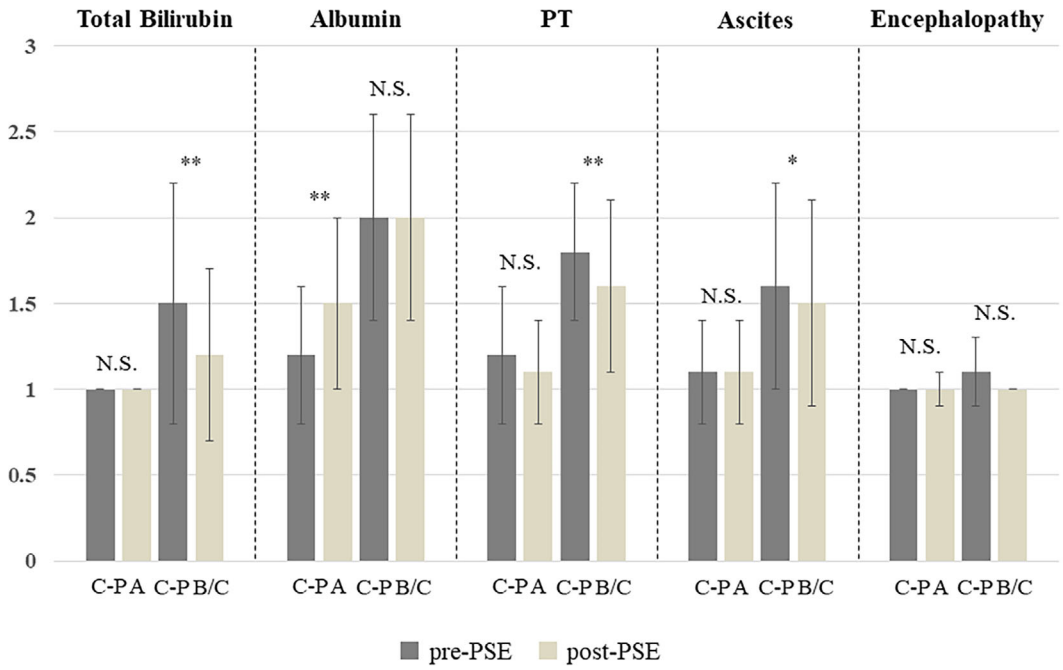


**Figure 3. Changes in scores of the C-P scoring system components caused by PSE based on the preoperative C-P classification. In patients with C-P class A, PSE significantly increases the postoperative albumin score (1.2±0.4 to 1.5±0.5; p<0.01); other scores are unchanged. Conversely, in patients with C-P class B/C, the procedure significantly decreases total bilirubin (1.5±0.7 to 1.2±0.5; p<0.01), PT (1.8±0.4 to 1.6±0.5; p<0.01), and ascites scores (1.6±0.6 to 1.5±0.6; p<0.05). Data are presented as the mean and standard deviation. *p<0.05 for comparisons between groups. **p<0.01 for comparisons between groups. C-P: Child-Pugh, C-P A: Child-Pugh class A, C-P B/C: Child-Pugh class B or C, N.S.: not significant, PT: prothrombin time, PSE: partial splenic embolization**

classification: patients with C-P class A (group A; n=64) and patients with C-P class B or C (group B/C; n=54). Table 3 shows the preoperative characteristics of groups A and B/C. Significant differences in the platelet counts (p=0.0003), spleen volumes (p=0.0006), WHVP (p=0.0050), and concomitant esophagogastric varices (p=0.0069) were found between the two groups. In contrast, there was no significant difference in the splenic infarction rates of group A and group B/C (76.3%±11.8% vs. 74.1%±14.6%; p=0.37). Although PSE significantly increased the C-P scores of patients with C-P class A (5.5±0.5 to 5.7±0.7; p<0.01), the procedure significantly decreased the C-P scores of those with C-P class B/C (7.9±1.0 to 7.3±1.1; p<0.01). In addition, the δ value of the C-P scores of group A was +0.3±0.7, and that of group B/C was −0.6±0.9, showing a significant difference in changes in C-P scores between the two groups (p<0.01) (Fig. 2). One month after PSE, the C-P scores of 10.9% of patients in group A and 64.8% of patients in group B/C were ameliorated, those of 54.7% of patients in group A and 24.1% of patients in group B/C were unchanged, and those of 34.4% of patients in group A and 11.1% of patients in group B/C were deteriorated (Fig. 2).

Next, changes in scores (1, 2, or 3) of the C-P scoring system components due to PSE were analyzed in both groups. Postoperatively, in patients with C-P class A, PSE significantly increased the albumin score (1.2±0.4 to 1.5±0.5; p<0.01); other scores were unchanged. Conversely, in patients with C-P class B/C, the procedure significantly decreased the total bilirubin (1.5±0.7 to 1.2±0.5; p<0.01), PT (1.8±0.4 to 1.6±0.5; p<0.01), and ascites scores (1.6±0.6 to 1.5±0.6; p<0.05) (Fig. 3). As shown in Fig. 4, there was a clear trend in the shift of C-P scores from before PSE to one month after PSE based on the preoperative C-P scores. Most patients with relatively low pretreatment C-P scores had unchanged or deteriorated scores after treatment. For example, of the 30 patients with a C-P score of 6 before PSE, 56.7% had an unchanged C-P score of 6, and 20.0% had a worsened C-P score of 7 after PSE. In contrast, as the preoperative C-P scores increased, the amelioration and deterioration rates of the postoperative C-P scores gradually increased and decreased, respectively. For example, of the 7 patients with a C-P score of 9 before PSE, 14.3% had an unchanged C-P score of 9, and 71.4% and 14.3% had improved C-P scores of 8 and 7, respectively, after PSE.

### *Comparisons of changes in biochemical, hematological, and hemodynamic parameters caused by PSE according to the preoperative C-P classification*

As shown in Fig. 5, although the trends in changes in biochemical parameters, such as the total bilirubin level, albumin level, cholinesterase level, and PT activity, after PSE were similar between patients with C-P class A and those

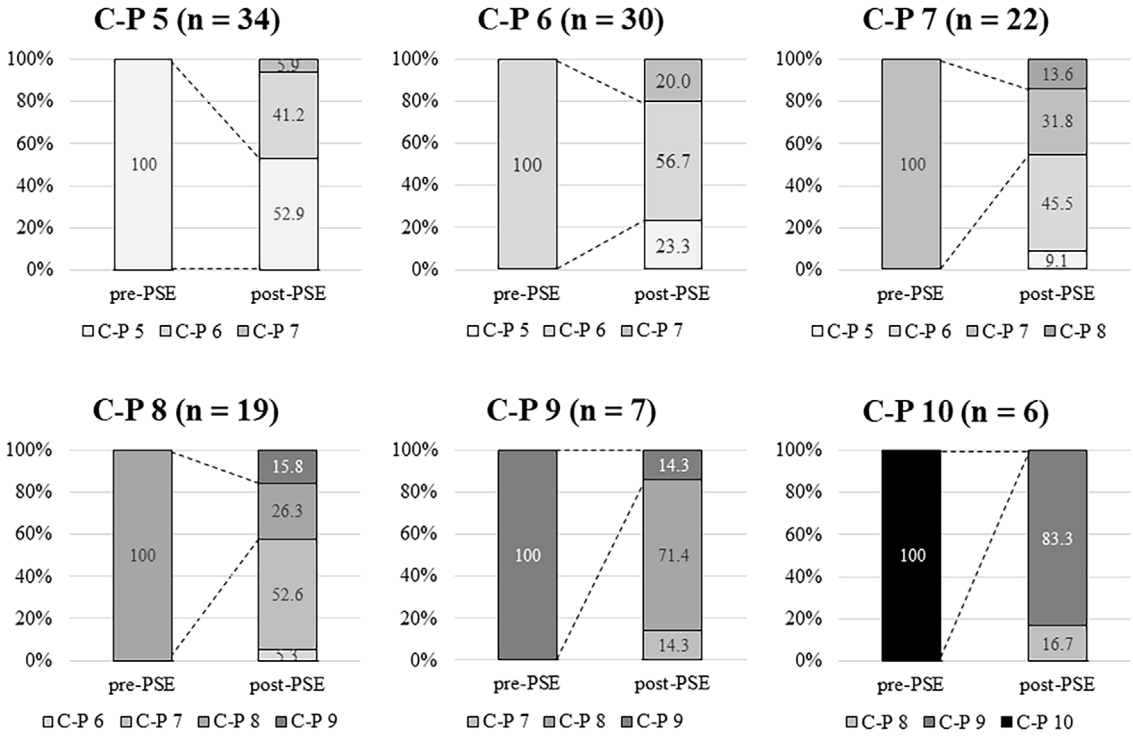


**Figure 4.** **Shift in C-P scores following PSE according to the preoperative C-P scores. There is a clear trend in the shift of the C-P scores from before PSE to one month after PSE based on the preoperative C-P scores. Most patients with lower pretreatment C-P scores show unchanged or deteriorated scores after treatment. In contrast, as the preoperative C-P scores increase, the amelioration and deterioration rates of the postoperative C-P scores gradually increase and decrease, respectively. Dotted lines represent the unchanged posttreatment C-P score compared to the pretreatment C-P score. C-P: Child-Pugh, PSE: partial splenic embolization**

with C-P class B/C, the δ values of biochemical parameters were significantly different between the two groups, with the exception of PT activity. In contrast, both the platelet and WBC counts were significantly increased by PSE in group A as well as group B/C, with no significant differences in the rates of increase (Fig. 6).

In addition, although PSE significantly decreased the SpA, SpV, and PV diameters; increased the CHA diameters; and decreased the WHVP and HVPG in both groups, no significant differences in the δ values of these hemodynamic parameters were found between the two groups (Fig. 7). Fig. 8 shows representative CE-CT images before and after PSE, showing that the procedure resulted in decreased diameters of the SpA (from 7.5 to 5.7 mm), SpV (from 8.9 to 6.0 mm), and PV (from 15.9 to 14.4 mm) and an increased diameter of the CHA (from 6.0 to 6.8 mm) in a C-P class B patient with a splenic infarction rate of 76.8%.

## Discussion

The present findings suggest that the pretreatment C-P score might be the strongest independent predictor of both ameliorated and deteriorated C-P scores at one month after PSE. We also found interesting and important results (Fig. 4) demonstrating that the higher the preoperative C-P scores, the higher the amelioration rates of postoperative C-P scores. Several reports have demonstrated PSE-associated clinical benefits, including not only an increase in blood cell counts (4-6) and a decrease in portal venous pressure (7, 8) but also an improvement in the hepatic function (4, 11, 15-17). Although some studies have shown that PSE can result in an ameliorated liver functional reserve, our data showed that chronological changes in C-P scores after the procedure were roughly equally divided into 3 categories: amelioration (35.6%), no change (40.7%), and deterioration (23.7%), without a significant overall C-P score reduction.

As reported by previous clinical studies, the increases in platelets and platelet-derived proliferative factors for hepatocytes, such as serotonin, insulin-like growth factor-1, and hepatocyte growth factor (HGF), after treatment may be related to PSE-induced functional improvements in the liver (25-27). Furthermore, decreased spleen-derived inhibitory factors for liver regeneration, such as transforming growth factor-β, caused by PSE may have a role in postoperative improvements in the hepatic function (28). Preliminary data from the present study showed that liver regeneration-related factors, including serotonin (31.3±22.5 to 62.1±40.2 ng/mL; $p<0.01$) and HGF (0.4±0.2 to 0.5±0.3 ng/mL; $p<0.05$), were significantly increased overall by PSE, with equivalent increases in these factors in both group A and group B/C. Furthermore, increased hepatocyte prolif-

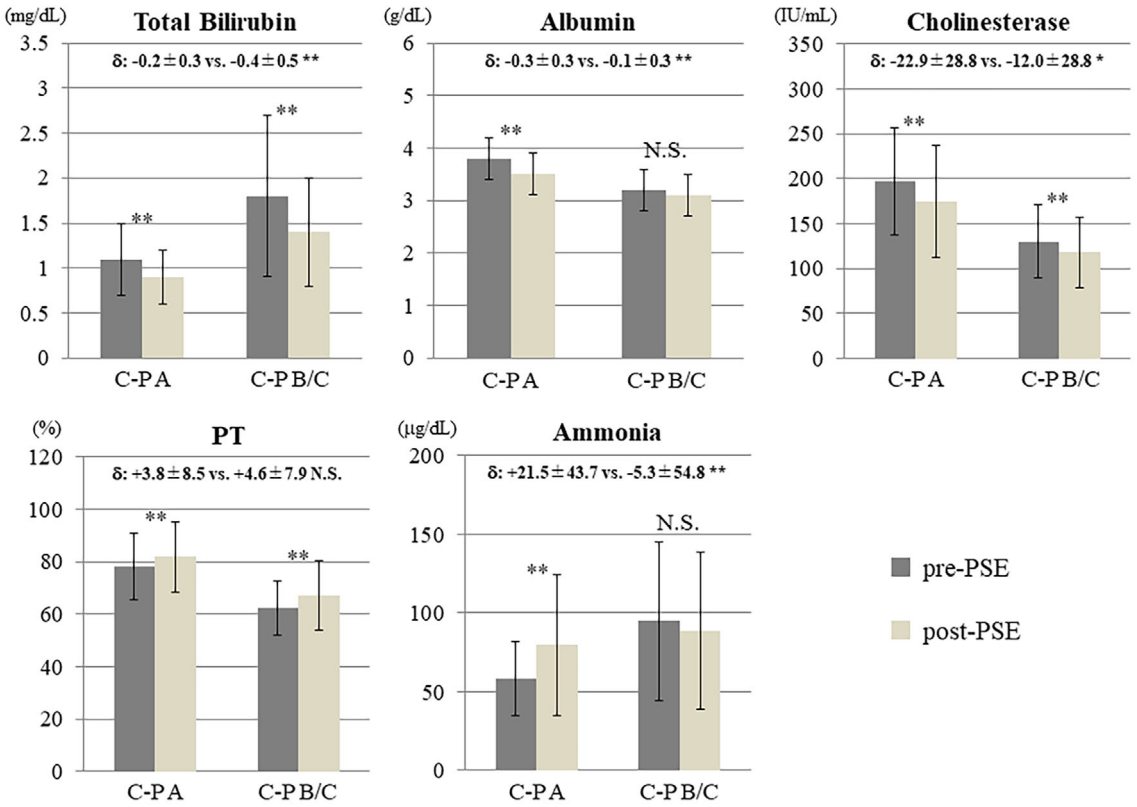


**Figure 5. Changes in biochemical parameters caused by PSE according to the preoperative C-P classification. Although the trend in changes in biochemical parameters, such as the total bilirubin level, albumin level, cholinesterase level, and PT activity, after PSE is similar for patients with C-P class A and those with C-P class B/C, the changes in the δ values of the parameters are significantly different between the two groups, with the exception of PT activity. Data are presented as the mean and standard deviation. The δ value is calculated using the following formula: δ=postoperative value-preoperative value. **p<0.01 for comparisons between groups. C-P: Child-Pugh, C-P A: Child-Pugh class A, C-P B/C: Child-Pugh class B or C, N.S.: not significant, PT: prothrombin time, PSE: partial splenic embolization**

erative activity represented by positive proliferating cell nuclear antigens has been reported in the liver after PSE (16), suggesting that the procedure induces a regenerative response in the liver. The mechanism by which PSE improves the liver function may also involve changes in the hepatic hemodynamics. Alterations in portal hemodynamics, such as a decreased total portal blood flow and relatively increased gastrointestinal-derived blood supply in contrast to decreased spleen-derived blood supply after the procedure, may contribute to the amelioration of the hepatic function induced by PSE through decreased liver congestion and an increased supply of cytokines and nutritious substances derived from the digestive tract (7, 29).

In our study, PSE did not significantly reduce the overall C-P score at one month postoperatively. However, significant differences were evident among patients with C-P class A and those with C-P class B/C, in relation to the short-term effects of PSE on the C-P score and individual hepatic functional parameters. These differences were seen despite the fact that both groups underwent technically similar PSE procedures with equivalent splenic infarction rates. This study focused on postoperative hemodynamic changes of the portal venous-hepatic arterial systems. After PSE, the diameters of the SpA, SpV, and PV were decreased, while those of the CHA were increased. Therefore, according to Murray's Law (24), which states that in an optimal configuration, the fluid flow rate inside the vessel is proportional to the cube of the vessel radius based on a constant fluid viscosity, PSE resulted in an increased hepatic arterial flow to compensate for the decreased portal venous flow. These distinctive hemodynamic changes suggest that the procedure induces a hepatic arterial buffer response (HABR), which is considered an important compensatory mechanism for maintaining the total blood flow of the liver by hepatic arterial vasodilatation on reduction of portal venous perfusion (30-32). However, no significant differences in changes in hepatic hemodynamics caused by PSE were found between group A and group B/C.

Despite a similar PSE-mediated HABR, significant differences were evident between the two groups in relation to the short-term effects of PSE on the hepatic functional reserve. Therefore, we investigated the original hepatic hemodynam-

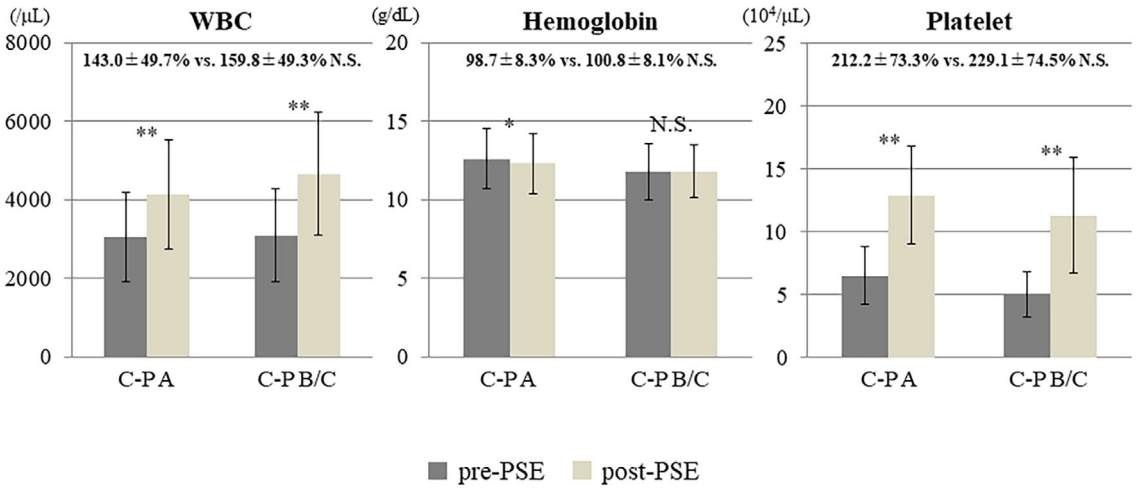


**Figure 6.** **Changes in hematological parameters caused by PSE according to the preoperative C-P classification. Both the platelet and WBC counts are significantly increased at one month after PSE in patients with C-P class A and those with C-P class B/C. Both parameters show statistically equivalent rates of increase between the two groups. Data are presented as the mean and standard deviation. *p<0.05 for comparisons between groups. **p<0.01 for comparisons between groups. C-P: Child-Pugh, C-P A: Child-Pugh class A, C-P B/C: Child-Pugh class B or C, Hb: hemoglobin, N.S.: not significant, PSE: partial splenic embolization, WBC: white blood cell**

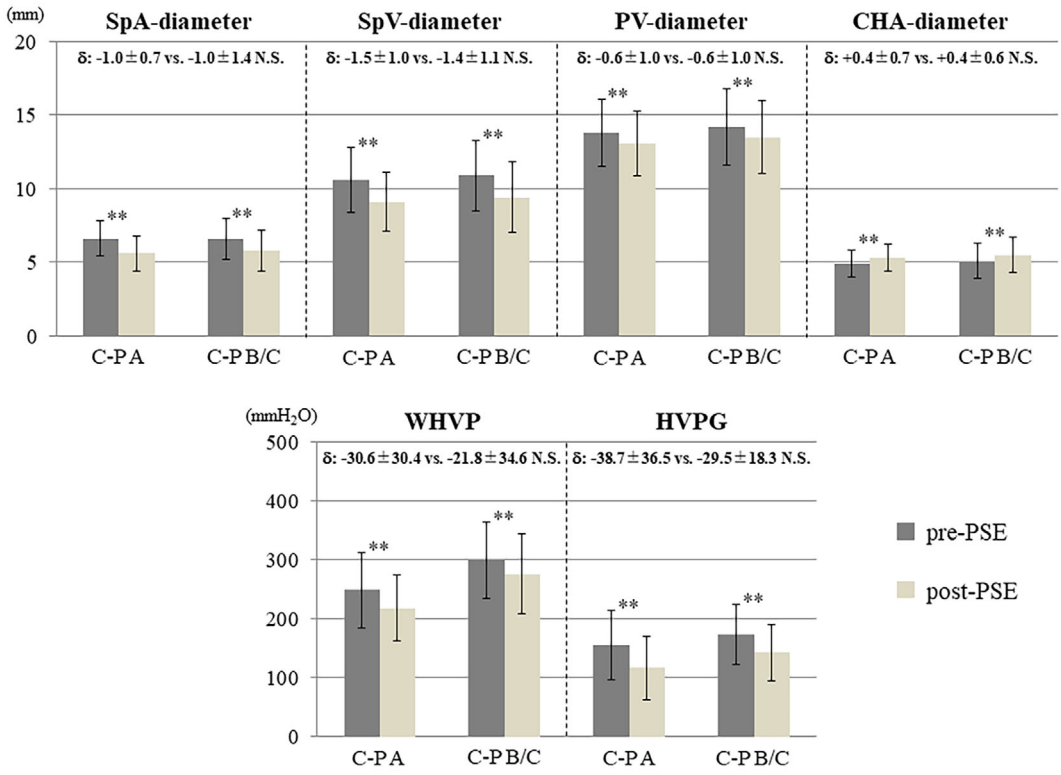


**Figure 7.** **Changes in hemodynamic parameters caused by PSE according to the preoperative C-P classification. Although PSE significantly decreases the SpA, SpV, and PV diameters, increases the CHA diameters, and decreases the WHVP and HVPG of patients with C-P class A and those with C-P class B/C, no significant differences in the δ values of these hemodynamic parameters are found between the two groups. Data are presented as the mean and standard deviation. The δ value is calculated using the following formula: δ=postoperative value-preoperative value. **p<0.01 for comparisons between groups. CHA: common hepatic artery, C-P: Child-Pugh, C-P A: Child-Pugh class A, C-P B/C: Child-Pugh class B or C, HVPG: hepatic venous pressure gradient, N.S.: not significant, PSE: partial splenic embolization, PV: portal vein, SpA: splenic artery, SpV: splenic vein, WHVP: wedged hepatic venous pressure**

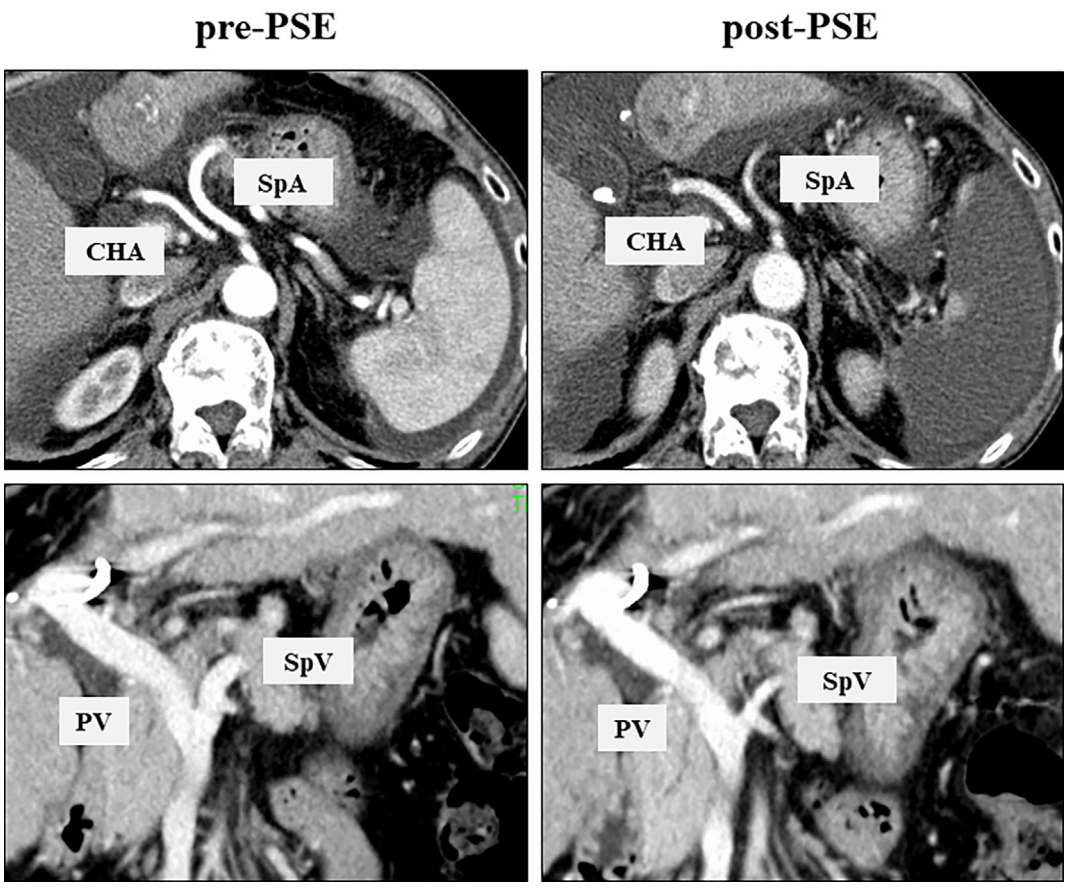


**Figure 8.** **Representative CE-CT images before and after PSE. PSE results in decreased SpA (from 7.5 to 5.7 mm), SpV (from 8.9 to 6.0 mm), and PV diameters (from 15.9 to 14.4 mm) and an increased CHA diameter (from 6.0 to 6.8 mm) in a C-P class B patient with a splenic infarction rate of 76.8%. CHA: common hepatic artery, PSE: partial splenic artery, PV: portal vein, SpA: splenic artery, SpV: splenic vein**

ics based on the pretreatment C-P classification. In general, the balance of the blood flow between the PV and hepatic artery shifts from portal venous-dominant to hepatic arterial-dominant as liver disease progresses. Therefore, the proportion of overall hepatic blood flow represented by the hepatic arterial flow increases as the C-P classification progresses from A to B/C (30, 33-35). We speculate that different hepatic functional responses to similar treatment approaches may be derived from the original pretreatment hemodynamics of portal venous-hepatic arterial systems based on C-P classification, but not from posttreatment hemodynamic changes caused by PSE-induced HABR. Therefore, PSE can produce better hepatic functional improvements mediated by HABR, especially in patients with decompensated cirrhosis classified as C-P class B/C.

Several studies have reported that severe complications after PSE occur more frequently in patients with higher C-P scores, particularly in those classified as having C-P class C disease (36-38). In our study, there was no significant difference in the incidence of complications between group A and group B/C (15.6% vs. 18.5%; p=0.68). This may be due to the fact that the splenic infarction volumes were within the recommended range in both groups (404.1±205.3 $cm^3$ for group A and 513.7±214.4 $cm^3$ for group B/C) according to previous reports demonstrating that a splenic infarction volume between 388 and 540 mL may be ideal for safe and effective PSE in patients with cirrhosis (37, 39). These findings suggest that, for decompensated patients with cirrhosis who are classified as C-P class B/C, PSE procedures can be actively performed to not only ameliorate hematological abnormalities and impaired portal hemodynamics but also improve the hepatic function. Furthermore, in such cases, the splenic infarction volume must be carefully considered in order to improve the efficacy and avoid severe complications. In addition, when PSE procedures need to be performed for patients with high C-P scores and large spleens, partitioned and repeated PSE should be considered as a safer and more reliable option.

To our knowledge, this is the first study to report significant differences in C-P score changes-particularly changes in hepatic functional parameters, rather than cirrhosis-related symptoms-caused by PSE, based on the preoperative C-P classification and score. However, the study results should be interpreted in the context of its limitations. First, this was a single-center, retrospective study. Second, a limited number of patients was analyzed. In this study, patients with C-P

class B and C-P class C were combined into one group; however, only six C-P class C patients were enrolled. Third, the follow-up period was only one month because we were hoping to obtain pure clinical data about the effects of PSE on the hepatic function without the influence of other medications or procedures. Fourth, although xenon CT can provide quantitative information regarding the hepatic arterial and portal venous tissue blood flow, we did not utilize this modality to measure the blood flow to the liver. Instead, the blood flow volume was inferred based on Murray's Law and vessel diameter measurements. Therefore, much larger and longer prospective studies with additional data are necessary to verify the results of this study.

In conclusion, PSE results in increased hepatic arterial flow to compensate for decreased portal venous flow, suggesting that HABR is induced by the procedure. Considering the original hepatic hemodynamics of portal venous-hepatic arterial systems based on the pretreatment C-P classification, at least in the short term, PSE is expected to produce HABR-mediated improvements in the hepatic function in patients with decompensated liver cirrhosis who have been classified as C-P class B/C.

**The authors state that they have no Conflict of Interest (COI).**

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