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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Splenic non-infarction volume determines a clinically significant hepatic venous pressure gradient response to partial splenic embolization in patients with cirrhosis and hypersplenism

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Abstract

Background This study aimed to investigate changes in the hepatic venous pressure gradient (HVPG) by partial splenic embolization (PSE) and to identify the determinants of a clinically meaningful postoperative HVPG reduction.

Methods Sixty-eight patients with cirrhosis and hypersplenism who underwent PSE at our department between September 2007 and June 2020 were included. The HVPG was evaluated pre- and immediately post-PSE. The patients were divided into three groups according to their preprocedural HVPG: low-HVPG (< 10 mmHg, $n = 22$), intermediate-HVPG (10 mmHg ≤ HVPG < 16 mmHg, $n = 33$), and high-HVPG (≥ 16 mmHg, $n = 13$).

Results Overall, PSE significantly reduced HVPG from 12.2 ± 4.0 to 9.4 ± 3.6 mmHg ($p < 0.01$) with a relative decrease of 22.2 ± 20.4%. In addition, HVPG reductions were 19.4 ± 28.7%, 24.0 ± 15.9%, and 22.5 ± 13.3% in the low-, intermediate-, and high-HVPG groups, respectively, indicating no significant difference in HVPG reduction between the groups. An HVPG decrease of ≥ 20% from the baseline, defined in this study as a clinically significant HVPG response to PSE, was achieved in 55.9% of all patients. Multivariate logistic regression and receiver operating characteristic curve analyses identified splenic non-infarction volume as an independent determinant of a 20% decrease in HVPG ($p < 0.05$), with a cut-off of 139.2 cm^3 (sensitivity, 76.3%; specificity, 60.0%; $p < 0.05$).

Conclusions The splenic non-infarction volume, namely the residual functional spleen volume, independently determines a clinically significant HVPG response to PSE in patients with cirrhosis and hypersplenism.

Keywords Hepatic venous pressure gradient · Partial splenic embolization · Splenic non-infarction volume · Liver cirrhosis · Hypersplenism

Introduction

The hepatic venous pressure gradient (HVPG) is a surrogate of portal pressure and has been demonstrated to be closely related to the pathophysiological features of portal hypertension (PH). In addition, HVPG measurements play a significant role not only in the diagnosis of PH and the estimation of the severity of PH, but also in the evaluation of a patient's response to treatments for PH, including nonselective beta-blocker (NSBB) administration [1–5]. For instance, an HVPG ≥ 10 mmHg has been defined as a clinically significant PH [6, 7], and an HVPG decrease ≥ 10% from baseline has been suggested as a clinically relevant HVPG response and is recommended by the Baveno VI consensus for etiologic therapies [3]. Furthermore, decreasing the HVPG to below 12 mmHg or to 20% less than baseline has been reported to significantly reduce the risk of variceal hemorrhage, ascites, and encephalopathy [2, 8–10].

Liver cirrhosis is often accompanied by splenomegaly and hypersplenism, which may be a result of PH as well as a cause of worsening PH. Interventional radiology and surgical therapies have been widely attempted to manage these diseases. Partial splenic embolization (PSE), which was originally developed for primary and secondary

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hypersplenism by Spigos et al. [11], causes ischemic necrosis of the corresponding splenic tissue and portal pressure reduction by decreasing the splenic venous return. Therefore, the procedure can be used to treat impaired portal-splenic hemodynamics [12, 13] in addition to hematological abnormalities, particularly thrombocytopenia [14–16]. Previous studies have demonstrated the clinical benefits of PSE for the regulation of portal-splenic venous pressure [17–19].

The target splenic infarction rate typically ranges from 50 to 80% for PSE procedures. However, Noguchi et al. reported that an increase in platelet count positively correlates with the splenic infarction rate [15], whereas Han et al. showed that there were no therapeutic differences among patients with splenic infarction rates of 50, 70, and 80% [20]. In addition, a previous study by Hayashi et al. proposed the novel concept that splenic infarction volume, not the splenic infarction rate, may be a determining factor for increased platelet count after PSE [21].

Thus, while several studies have demonstrated predictors of an increase in platelet count after PSE [15, 20–22], to our knowledge, there are no reports regarding the prediction of portal pressure reduction, especially the decrease in the HVPG, following the procedure in patients with hypersplenism due to PH. Hence, this study primarily aimed to investigate the hemodynamic response to PSE, not only overall, but also by preprocedural severity of PH. The secondary aim was to identify determinants of a clinically meaningful reduction in HVPG postoperatively, based on studies evaluating the HVPG response to NSBBs [5], in patients with cirrhosis and hypersplenism.

Methods

Study design and ethical considerations

This single-center, retrospective study reviewed laboratory data and imaging findings from patient medical records. Informed consent pertaining to the use of available clinical data was obtained in writing from each patient preoperatively. The research was performed in accordance with the Declaration of Helsinki and was approved by the appropriate institutional review board (approval number: H2020-037).

Patients

Patients with cirrhosis, splenomegaly, and hypersplenism were enrolled in this study. The inclusion criteria for this clinical trial were thrombocytopenia with a platelet count of $< 5 \times 10^4/\mu L$ and/or refractory PH-related diseases, such as esophagogastric varices, due to high portal pressure. Exclusion criteria included obstruction of the portal trunk and the presence of refractory ascites. Cirrhosis was diagnosed on the basis of a combination of biochemical, clinical, and ultrasonographic findings. Between September 2007 and June 2020, 78 patients underwent PSE with preprocedural and postprocedural measurements of HVPG. However, 10 patients were excluded from this study due to the presence of venous-venous communication, which led to an underestimation of the HVPG. The final analysis included 68 patients. For six patients who underwent repeated PSE, only data from the first procedure were included in this study.

Biochemical and diagnostic imaging assessments

Hepatic function parameters, including total bilirubin, albumin, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, cholinesterase, prothrombin time percentage activity, and international normalized ratio were evaluated before and 1 month after PSE. Liver-related metabolic parameters, such as ammonia, indocyanine green retention rate at 15 min, branched-chain amino acids-to-tyrosine molar ratio (BTR), hemoglobin A1c, homeostasis model assessment of insulin resistance (HOMA-IR), and hepatic fibrosis markers and indices, such as hyaluronic acid, 7S domain of type IV collagen, aspartate aminotransferase-to-platelet ratio index, and fibrosis-4 index, were also assessed. Additionally, a complete blood count was evaluated before and 1 month after PSE. Child–Pugh (CP) and Model for End-Stage Liver Disease (MELD) scores were calculated. Platelet count increase, CP score change, and MELD score change were calculated using the following formulas: platelet count increase (%) = (1-month post-PSE value−pre-PSE value) × 100/pre-PSE value, and changes in CP and MELD scores = 1-month post-PSE value−pre-PSE value.

In addition, the liver and spleen volumes were measured using axial contrast-enhanced computed tomography (CE-CT) images at 5 mm intervals before and 1 month after PSE. Liver stiffness was also measured by transient elastography using the FibroScan system (Echosens SA, Paris, France) before and 1 month after PSE, as previously reported [23].

Partial splenic embolization

The PSE procedures were performed by two accredited expert physicians. The therapeutic strategy was determined according to the platelet count, splenic volume, and clinical course of the patient. In general, platelet counts $< 5 \times 10^4/\mu L$ are thought to represent a high risk of bleeding. Therefore, at our institution, PSE is recommended for patients with splenomegaly when a platelet

count of $< 5 \times 10^4/\mu L$ persists in three consecutive blood samples and/or when PH-related diseases, such as esophagogastric varices, are refractory despite various therapies.

PSE was performed using the previously described Takatsuka method [24]. Briefly, a percutaneous catheter was inserted in the right femoral artery under local anesthesia (1% lidocaine), and its tip was advanced into the hilum of the splenic artery. Gelatin sponges were implanted proximal to the microcoils that remained straight to embolize the branches of the splenic artery, and its upper branch remained untreated to achieve a final embolization rate of approximately 60–80%. Our therapeutic strategy for PSE is based on a previous report by Hayashi et al. which demonstrated that a splenic infarction volume of 388–540 cm^3 may be ideal for safe and effective PSE in patients with cirrhosis [21, 25]. CE-CT confirmed the infarct and non-infarct areas at 1 week after PSE. The splenic infarction rate, non-infarction rate, infarction volume, and non-infarction volume were calculated. No other treatments were performed for approximately 1 month after PSE to enable the patients to recover physically.

Measurements of hepatic venous pressure gradient

Before and immediately after PSE, wedged hepatic venous pressure (WHVP) was measured and the HVPG was calculated, as described previously [26]. Briefly, 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 Co., Ltd., Gifu, Japan). The HVPG was defined as the pressure difference between the portal and hepatic veins, and it was calculated by subtracting the free hepatic venous pressure from the WHVP. Finally, the HVPG value was converted from mmH_2O to mmHg.

Definition and categorization of PH

According to previous reports, PH is defined as an HVPG > 5 mmHg, and is clinically significant at ≥ 10 mmHg [2]. Additionally, subclinical, severe, and pronounced PH are defined as an HVPG between 5 and 10 mmHg, ≥ 12 mmHg, and ≥ 16 mmHg, respectively [1–4]. HVPG ≤ 5 mmHg is not considered PH [2]. Based on these definitions, patients in this study were divided into three categories by preoperative and postoperative HVPG: low-HVPG (HVPG < 10 mmHg), intermediate-HVPG (10 mmHg $\leq$ HVPG < 16 mmHg), and high-HVPG (HVPG ≥ 16 mmHg). In addition, an HVPG decrease from pre-PSE to immediately post-PSE was calculated using the following formula: HVPG decrease (%) = (pre-PSE value−post-PSE value) $\times$ 100/pre-PSE value.

Statistical analyses

The data are expressed as mean and standard deviation. Statistical analyses were performed using JMP software (version 13; SAS Institute Inc., Cary, NC, USA). The paired t-test was used for pairwise comparisons between the pretreatment and posttreatment data. To compare two independent samples, a parametric test, such as an unpaired t-test or Welch's t-test, or a nonparametric test, such as a Wilcoxon signed-rank test or Mann-Whitney U-test, was used according to normality of each variable and, if necessary, homogeneity of variance. Categorical variables were analyzed using the Fisher's exact test. To compare three independent samples, one-way analysis of variance or Kruskal-Wallis test was performed according to the normality of each variable and, if necessary, homogeneity of variance. The Bonferroni test or Steel-Dwass test was used for multiple comparisons. Patients who had received anticoagulants, including warfarin, for the treatment of portal and/or splenic venous thrombus were excluded from the paired t-test as their PT activities and INR were unsuitable for CP and MELD score calculations. To identify factors predicting an HVPG decrease $\geq 10\%$ and 20% compared to baseline by PSE, univariate associations among the groups were assessed using the above tests. Multivariate logistic regression analyses with the stepwise selection of the factors that were 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 HVPG decrease induced 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 the HVPG decrease following PSE, and the optimum cut-off value for each predictor was determined. A simple linear regression analysis was performed to study the correlation between procedural factors of PSE (splenic infarction rate, non-infarction rate, infarction volume, and non-infarction volume) and postprocedural HVPG decrease; the correlation coefficients and p values were also evaluated. Statistical significance was set at $p < 0.05$.

Results

Preprocedural characteristics of all patients

Table 1 presents the baseline clinical characteristics of all patients. Of the 68 patients included in this study, 34 were men and 34 were women. The mean patient age was 64.8 years. Forty patients were classified as CP class A, 27 as CP class B, and one as CP class C. The causes of

Table 1 Preprocedural, procedural, and postprocedural factors of all patients (n = 68)

a. Preprocedural factors	
HVPG (mmHg)	12.2 ± 4.0
Spleen volume (cm^3)	491.3 ± 314.0
Spleen volume/body surface area (cm^3/m^2)	309.6 ± 189.3
Platelet count ($\times 10^4/\mu L$)	6.2 ± 2.3
Liver stiffness (kPa)	28.4 ± 17.3
CP score	6.4 ± 1.4
MELD score	9.7 ± 2.3
b. Procedural factors	
Splenic infarction rate (%)	75.0 ± 11.1
Splenic non-infarction rate (%)	25.0 ± 11.1
Splenic infarction volume (cm^3)	432.0 ± 240.1
Splenic non-infarction volume (cm^3)	158.4 ± 145.3
c. Postprocedural factors	
HVPG decrease (%)	22.2 ± 20.4
Achievement rate of HVPG decrease ≥ 10% (%)	79.4
Achievement rate of HVPG decrease ≥ 20% (%)	55.9
Platelet count increase (%)	126.9 ± 77.6
CP score change	0.0 ± 0.8
MELD score change	− 0.9 ± 1.4
Incidence of complications (%)	16.2

CP Child–Pugh, *HVPG* hepatic venous pressure gradient, *MELD* Model for End-Stage Liver Disease

The data are presented as mean and standard deviation or as a percentage

cirrhosis included hepatitis B (n = 5), hepatitis C (n = 41), hepatitis B and C (n = 1), alcohol consumption (n = 11), and nonalcoholic steatohepatitis (n = 3). Overall, 22 patients (32.4%) and 43 patients (63.2%) had hepatocellular carcinoma (HCC) and esophagogastric varices, respectively, at the time of PSE. The PSE procedures were applied as pretreatments of various therapies for HCC in 12 patients, endoscopic or endovascular therapies for esophagogastric varices in 23 patients, induction of interferon therapies for hepatitis C virus infections in 23 patients, and for other therapies in 10 patients. The mean HVPG at baseline was 12.2 ± 4.0 mmHg.

Changes in HVPG and various parameters after PSE

As shown in Table 1, PSE resulted in a mean splenic infarction rate of 75.0 ± 11.1% and a mean splenic infarction volume of 432.0 ± 240.1 cm^3, evaluated at 1 week after PSE. The procedures significantly reduced HVPG from 12.2 ± 4.0 to 9.4 ± 3.6 mmHg ($p < 0.01$, Fig. 1a), and the mean relative reduction in HVPG by PSE was 22.2 ± 20.4% (Table 1). Following PSE, the HVPG decreased in 89.7% of patients (61/68), remained unchanged in 5.9% (4/68), and increased in 4.4% (3/68). The percentages of patients with low-HVPG before and after PSE were 32.4% and 57.4%; with intermediate-HVPG, these were 48.5% and 39.7%, and with high-HVPG, these were 19.1% and 2.9%, respectively (Fig. 1b). In the subgroup of patients with subclinical PH at baseline, PH resolved in 31.8% (7/22) after PSE, and among patients with clinically significant preprocedural PH, 41.3% (19/46) had subclinical PH after PSE. In addition, 79.4% of patients had a decrease in HVPG ≥ 10% and 55.9% of patients had a decrease in HVPG ≥ 20% (Table 1). In the subgroup of patients with severe PH at baseline, 55.9% (19/34) had an HVPG decrease ≥ 20%, 50.0% (17/34) had an HVPG decrease to below 12 mmHg, and either condition was achieved in 64.7% (22/34) after PSE. PSE resulted in an increased mean platelet count (6.2 ± 2.4 to 13.0 ± 4.1 $\times 10^4/\mu L$, $p < 0.01$), an unchanged mean CP score (6.3 ± 1.3 to 6.3 ± 1.2, $p = 0.8743$), and a decreased mean MELD score (9.6 ± 2.3 to 8.8 ± 1.9, $p < 0.01$). Following the procedure, complications requiring additional treatments occurred in 11 of 68 patients (ascites and/or pleural effusion in four, portal and/or splenic venous thrombus in six, and hyperammonemia in one).

Preprocedural, procedural, and postprocedural factors of patients with low-, intermediate-, and high-HVPG

The patients were divided into a low-HVPG group (n = 22), intermediate-HVPG group (n = 33), and high-HVPG group (n = 13) according to their preprocedural HVPG. HVPG was significantly reduced from 7.7 ± 1.6 to 6.4 ± 3.0 mmHg in the low-HVPG group ($p < 0.05$), from 12.8 ± 1.6 to 9.7 ± 2.2 mmHg in the intermediate-HVPG group ($p < 0.01$), and from 18.1 ± 2.0 to 13.9 ± 2.4 mmHg in the high-HVPG group ($p < 0.01$) (Fig. 2a). The mean relative reductions in the HVPG were 19.4 ± 28.7%, 24.0 ± 15.9%, and 22.5 ± 13.3% in the low-, intermediate-, and high-HVPG groups, respectively, and they were not significantly different in the three groups (Table 2). As shown in Fig. 2b, more than 90% of the 22 patients in the low-HVPG group before PSE remained in the same category after the procedure. Of 33 patients in the intermediate-HVPG group pre-PSE, 54.5% moved to the low-HVPG category post-PSE, while 45.5% remained in the intermediate-HVPG category post-PSE. In addition, more than 80% of the 13 patients in the high-HVPG group pre-PSE moved to the intermediate- or low-HVPG categories post-PSE. Although preprocedural HVPG was significantly different among the three groups, significant

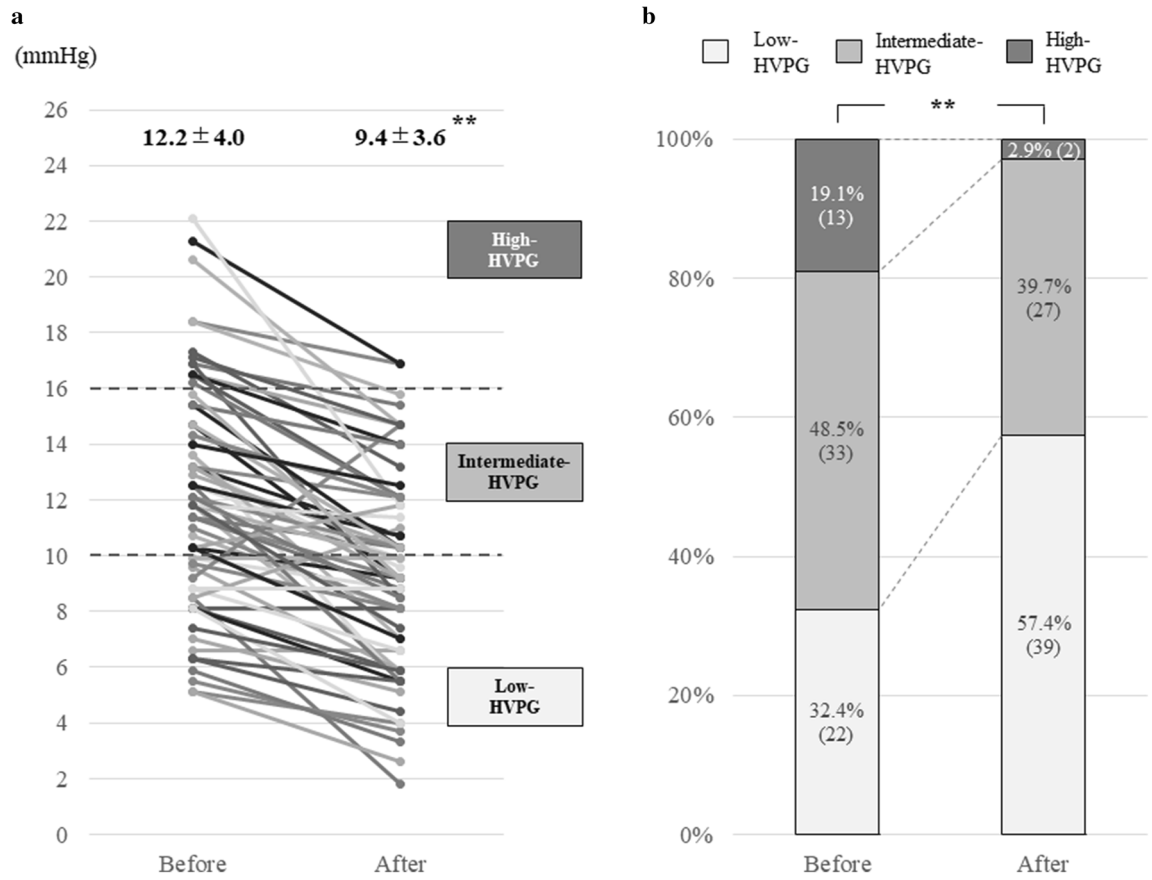

Fig. 1 Overall PSE-induced HVPG changes. **a** Individual changes in HVPG. PSE significantly reduced the mean HVPG from 12.2 ± 4.0 to 9.4 ± 3.6 mmHg ($p < 0.01$). Following PSE, HVPG decreased in 89.7% of patients (61/68), remained unchanged in 5.9% (4/68), and increased in 4.4% (3/68). **b** Changes in HVPG category. Before the PSE procedure, 32.4% of patients were categorized with low-HVPG. This increased to 57.4% after the PSE procedure. The intermediate-HVPG category included 48.5% of patients before the PSE procedure and 39.7% of patients after the procedure, and the high-HVPG category reduced from 19.1% of patients to 2.9% after the PSE procedure. These pre- and post-PSE changes were significant ($p < 0.01$). HVPG, hepatic venous pressure gradient; PSE, partial splenic embolization. Low-HVPG: HVPG < 10 mmHg, intermediate-HVPG: 10 mmHg ≤ HVPG < 16 mmHg, and high-HVPG: HVPG ≥ 16 mmHg. Data are presented as the mean and standard deviation. The numbers in parentheses represent the number of patients. $^{**}p < 0.01$ for comparisons between groups

differences in other preprocedural factors, including spleen volume, normalized spleen volume divided by body surface area, liver stiffness, and MELD score, were found only between the high- and low-HVPG groups (Table 2). The postprocedural changes in HVPG, platelet counts, CP scores, and MELD scores were not significantly different between the groups. In addition, there was no significant difference in the incidence of complications among them. While splenic infarction and non-infarction rates were similar in the three groups, the splenic infarction volume was significantly different due to a significant difference in preprocedural spleen volume between the high- and low-HVPG groups (Table 2).

Predictors of a clinically significant HVPG decrease induced by PSE

Although univariate analyses revealed that an HVPG decrease of ≥ 10% from baseline after PSE was statistically associated with some preprocedural factors, including lower MELD scores, lower total bilirubin levels, higher BTR, higher creatinine levels, and lower hyaluronic acid levels before the procedure, no significant differences in procedural factors were found between patients with an HVPG decrease ≥ 10% ($n = 54$) and those with an HVPG decrease < 10% ($n = 14$). In addition, a multivariate analysis identified no statistically independent predictors of an HVPG decrease ≥ 10% after PSE.

When comparing patients with ($n = 38$) or without ($n = 30$) an HVPG decrease ≥ 20%, the proportion of patients with lower pretreatment spleen volume

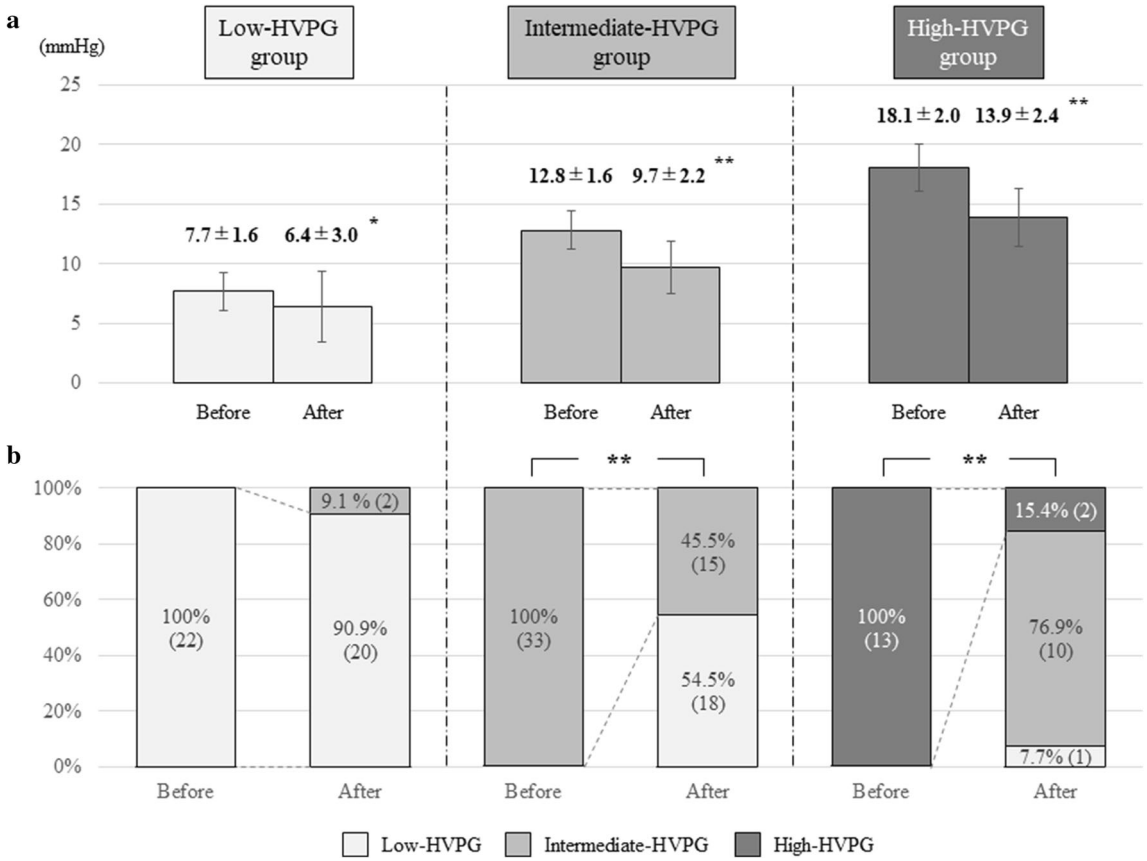

Fig. 2 PSE-induced HVPG changes in three groups divided by preprocedural HVPG. **a** Mean HVPG changes in each group. PSE significantly reduced the mean HVPG from 7.7 ± 1.6 to 6.4 ± 3.0 mmHg in the low-HVPG group ($p < 0.05$), from 12.8 ± 1.6 to 9.7 ± 2.2 mmHg in the intermediate-HVPG group ($p < 0.01$), and from 18.1 ± 2.0 to 13.9 ± 2.4 mmHg in the high-HVPG group ($p < 0.01$). **b** Changes in HVPG category in each group. More than 90% of the 22 patients in the low-HVPG group before PSE remained in this category after the procedure. Of the 33 patients who were in the intermediate-HVPG group pre-PSE, 45.5% were still in the same category post-PSE, and 54.5% were in the low-HVPG category post-PSE. In addition, more than 80% of the 13 patients who were in the high-HVPG group pre-PSE were in the intermediate- or low-HVPG categories post-PSE. Significant changes in HVPG categories induced by the procedure were found in the intermediate- and high-HVPG groups ($p < 0.01$). HVPG, hepatic venous pressure gradient; PSE, partial splenic embolization. Low-HVPG: HVPG < 10 mmHg, intermediate-HVPG: 10 mmHg ≤ HVPG < 16 mmHg, and high-HVPG: HVPG ≥ 16 mmHg. Data are presented as the mean and standard deviation. The numbers in parentheses represent the number of patients. *$p < 0.05$ for comparisons between groups. **$p < 0.01$ for comparisons between groups

($p = 0.0474$), higher pretreatment liver volume-to-spleen volume ratio ($p = 0.0380$), lower pretreatment MELD scores ($p = 0.0458$), lower pretreatment total bilirubin levels ($p = 0.0176$), higher pretreatment BTR ($p = 0.0428$), lower pretreatment HOMA-IR (p = 0.0440), and lower splenic non-infarction volume ($p = 0.0109$) was greater in patients with an HVPG decrease ≥ 20% (Table 3). A multivariate logistic regression analysis with the stepwise selection method revealed that the splenic non-infarction volume was the only significant and independent determinant of an HVPG decrease ≥ 20% (OR, 0.9949; 95% CI, 0.9901–0.9997; $p = 0.0376$) (Table 3). The AUROC curve for predicting an HVPG decrease ≥ 20% was 0.68114, and the optimum splenic non-infarction volume cut-off value to achieve an HVPG decrease ≥ 20% was 139.2 cm^3 (sensitivity, 76.3%; specificity, 60.0%; $p = 0.0182$). Additionally, the correlation between procedural factors of PSE (splenic infarction rate, non-infarction rate, infarction volume, and non-infarction volume) and a postprocedural HVPG decrease from the baseline was evaluated (Fig. 3). As shown in Fig. 3d, there was a significant correlation only between splenic non-infarction volume and the HVPG decrease ($r = -0.2408$, $p < 0.05$).

Preprocedural, procedural, and postprocedural factors of patients by splenic non-infarction volume identified by multivariate analyses for predictors of an HVPG decrease ≥ 20%

Compared to patients with a splenic non-infarction volume ≥ 139.2 cm^3 ($n = 28$) who obtained a lesser decrease

Table 2 Preprocedural, procedural, and postprocedural factors of patients with low-, intermediate-, and high-HVPG

	Low-HVPG group (n = 22)	Intermediate-HVPG group (n = 33)	High-HVPG group (n = 13)
a. Preprocedural factors			
HVPG (mmHg)	7.7 ± 1.6	12.8 ± 1.6§§	18.1 ± 2.0¶¶, **
Spleen volume (cm^3)	369.8 ± 157.3	523.5 ± 368.9	615.1 ± 312.6*
Spleen volume/body surface area (cm^3/m^2)	236.2 ± 101.5	321.3 ± 210.9	404.0 ± 208.5**
Platelet count ($\times 10^4/\mu L$)	6.7 ± 2.4	6.2 ± 2.3	5.5 ± 2.6
Liver stiffness (kPa)	20.8 ± 13.4	29.0 ± 18.5	39.1 ± 14.8**
CP score	5.9 ± 1.1	6.4 ± 1.2	7.0 ± 1.8
MELD score	8.9 ± 2.0	9.8 ± 2.3	10.9 ± 2.6*
b. Procedural factors			
Splenic infarction rate (%)	74.7 ± 11.6	75.1 ± 10.8	75.3 ± 12.0
Splenic non-infarction rate (%)	25.3 ± 11.6	24.9 ± 10.8	24.7 ± 12.0
Splenic infarction volume (cm^3)	340.3 ± 151.0	450.1 ± 286.9	541.2 ± 182.1**
Splenic non-infarction volume (cm^3)	114.6 ± 72.8	168.0 ± 164.7	208.2 ± 172.6
c. Postprocedural factors			
HVPG decrease (%)	19.4 ± 28.7	24.0 ± 15.9	22.5 ± 13.3
Achievement rate of HVPG decrease ≥ 10% (%)	72.7	81.8	84.6
Achievement rate of HVPG decrease ≥ 20% (%)	59.1	54.5	53.8
Platelet count increase (%)	109.3 ± 54.3	128.7 ± 91.4	152.0 ± 70.1
CP score change	− 0.2 ± 0.7	+ 0.1 ± 0.8	− 0.1 ± 0.9
MELD score change	− 0.7 ± 1.2	− 0.8 ± 1.4	− 1.3 ± 1.5
Incidence of complications (%)	13.6	15.2	23.1

HVPG hepatic venous pressure gradient, *MELD* Model for End-Stage Liver Disease

Low-HVPG HVPG < 10 mmHg, intermediate-HVPG: 10 mmHg ≤ HVPG < 16 mmHg, and high-HVPG: HVPG ≥ 16 mmHg

The data are presented as mean and standard deviation

§§$p < 0.01$ for the comparison between intermediate-HVPG group and low-HVPG group

¶¶$p < 0.01$ for the comparison between high-HVPG group and intermediate-HVPG group

*$p < 0.05$ for the comparison between high-HVPG group and low-HVPG group

**$p < 0.01$ for the comparison between high-HVPG group and low-HVPG group

in HVPG (13.9 ± 21.9%), patients with splenic non-infarction volume < 139.2 cm^3 ($n = 40$) who had a greater decrease in HVPG (28.0 ± 17.3%) also had better pre-PSE portal hypertensive and prognostic parameters, including lower HVPG ($p = 0.0397$), lower spleen volume ($p < 0.0001$), lower normalized spleen volume divided by body surface area ($p < 0.0001$), higher platelet counts ($p = 0.0064$), and lower MELD scores ($p = 0.0312$). Despite significant differences in HVPG decreases ($p = 0.0078$) between patients with a splenic non-infarction volume ≥ 139.2 cm^3 and those with a splenic non-infarction volume < 139.2 cm^3, no significant differences in postprocedural changes in hematological or liver functional parameters (such as platelet counts, CP scores, and MELD scores) were found (Table 4).

Case presentation

A 71-year-old female with nonalcoholic steatohepatitis-related cirrhosis classified as CP class A underwent a combination of PSE and endoscopic injection sclerotherapy (EIS) for refractory esophageal varices with red color signs resistant to two previous EIS procedures that were performed within 1 year (Fig. 4). Her pre-PSE spleen volume and post-PSE splenic non-infarction volume were 366.1 and 124.1 cm^3, respectively (Fig. 4a). The HVPG decreased from 15.8 to 9.2 mmHg with a relative reduction of 41.7% immediately post-PSE, and the procedure increased the platelet count from 8.3 to 15.2 $\times 10^4/\mu L$ with a relative elevation of 83.1% at 1 month post-PSE. One month after the PSE procedure, a third EIS was performed without any complications. No recurrence of

Table 3 Univariate and multivariate analyses for predictors of an HVPG decrease ≥ 20% after PSE

	HVPG decrease		*p* value	
	< 20% (*n* = 30)	≥ 20% (*n* = 38)	Univariate	Multivariate (final model)
HVPG (mmHg)	12.4 ± 3.4	12.0 ± 4.5	0.6679	N.A.
Liver volume (cm^3)	1101.5 ± 293.0	1103.1 ± 302.1	0.9830	N.A.
Spleen volume (cm^3)	574.1 ± 340.9	425.9 ± 278.4	0.0474	–
Spleen volume/body surface area (cm^3/m^2)	350.6 ± 199.7	277.2 ± 176.6	0.0871	N.A.
Liver volume/spleen volume (cm^3/cm^3)	2.7 ± 1.9	3.5 ± 2.0	0.0380	–
Liver stiffness (kPa)	28.6 ± 11.9	28.3 ± 20.0	0.2686	N.A.
CP score	6.6 ± 1.4	6.2 ± 1.3	0.2567	N.A.
MELD score	10.4 ± 2.7	9.2 ± 1.8	0.0458	–
T-Bil (mg/dL)	1.6 ± 0.8	1.2 ± 0.4	0.0176	–
Albumin (g/dL)	3.6 ± 0.5	3.6 ± 0.6	0.6606	N.A.
ALT (IU/L)	44.8 ± 39.4	43.1 ± 34.6	0.7688	N.A.
GGT (IU/L)	53.1 ± 39.7	43.7 ± 30.8	0.3052	N.A.
ChE (IU/L)	173.9 ± 57.1	183.1 ± 84.4	0.5975	N.A.
PT (%)	70.1 ± 13.5	75.3 ± 12.8	0.1140	N.A.
Ammonia (μg/dL)	76.7 ± 45.5	64.8 ± 36.6	0.3409	N.A.
ICG-R15 (%)	27.6 ± 13.9	27.4 ± 15.4	0.8121	N.A.
BTR	3.9 ± 1.4	5.0 ± 2.9	0.0428	0.1441
BUN (mg/dL)	15.1 ± 4.2	16.4 ± 4.5	0.2130	N.A.
Cre (mg/dL)	0.7 ± 0.2	0.8 ± 0.2	0.2009	N.A.
Na (mmol/L)	139.8 ± 2.2	138.5 ± 5.3	0.4835	N.A.
K (mmol/L)	3.9 ± 0.2	4.1 ± 0.4	0.3949	N.A.
HbA1c (%)	5.4 ± 1.6	5.4 ± 0.8	0.1865	N.A.
HOMA-IR	4.7 ± 3.3	3.2 ± 1.9	0.0440	0.1521
HA (ng/mL)	365.2 ± 337.5	407.6 ± 581.0	0.6246	N.A.
IV-Col-7S (ng/mL)	9.9 ± 3.6	8.6 ± 2.7	0.1040	N.A.
FIB-4 index	8.9 ± 4.9	10.2 ± 7.0	0.6082	N.A.
APRI	2.6 ± 1.6	2.6 ± 1.8	0.9360	N.A.
WBC count (/μL)	3031.0 ± 1122.3	2883.4 ± 1026.8	0.7387	N.A.
RBC count ($\times 10^4$/μL)	405.3 ± 67.5	389.0 ± 62.0	0.3040	N.A.
Platelet count ($\times 10^4$/μL)	6.2 ± 2.3	6.2 ± 2.5	0.8990	N.A.
Splenic infarction rate (%)	72.5 ± 11.6	76.9 ± 10.4	0.0713	N.A.
Splenic non-infarction rate (%)	27.5 ± 11.6	23.1 ± 10.4	0.0723	N.A.
Splenic infarction volume (cm^3)	494.0 ± 264.5	383.0 ± 209.7	0.0723	N.A.
Splenic non-infarction volume (cm^3)	204.0 ± 157.9	122.4 ± 125.1	0.0109	0.0376

ALT alanine aminotransferase, *APRI* aspartate aminotransferase-to-platelet ratio index, *BTR* branched-chain amino acids-to-tyrosine molar ratio; *BUN* blood urea nitrogen, *ChE* cholinesterase, *CP* Child–Pugh; *Cre* creatinine, *FIB-4* fibrosis-4, *GGT* gamma-glutamyl transpeptidase, *HA* hyaluronic acid, *HbA1c* hemoglobin A1c, *HOMA-IR* homeostasis model assessment of insulin resistance, *HVPG* hepatic venous pressure gradient, *ICG-R15* indocyanine green retention rate at 15 min, *IV-Col-7S* 7S domain of type IV collagen, *K* potassium, *MELD* Model for End-Stage Liver Disease, *Na* sodium, *N.A.* not applicable, *PSE* partial splenic embolization, *PT* prothrombin time, *RBC* red blood cell, *T-Bil* total bilirubin; *WBC* white blood cell

The data are presented as mean and standard deviation

esophageal varices had been observed at the 1 year follow-up, since the patient underwent combination therapy (Fig. 4b).

Discussion

The present study demonstrated that PSE significantly reduced the mean HVPG from 12.2 ± 4.0 to 9.4 ± 3.6 mmHg ($p < 0.01$), with a mean relative decrease

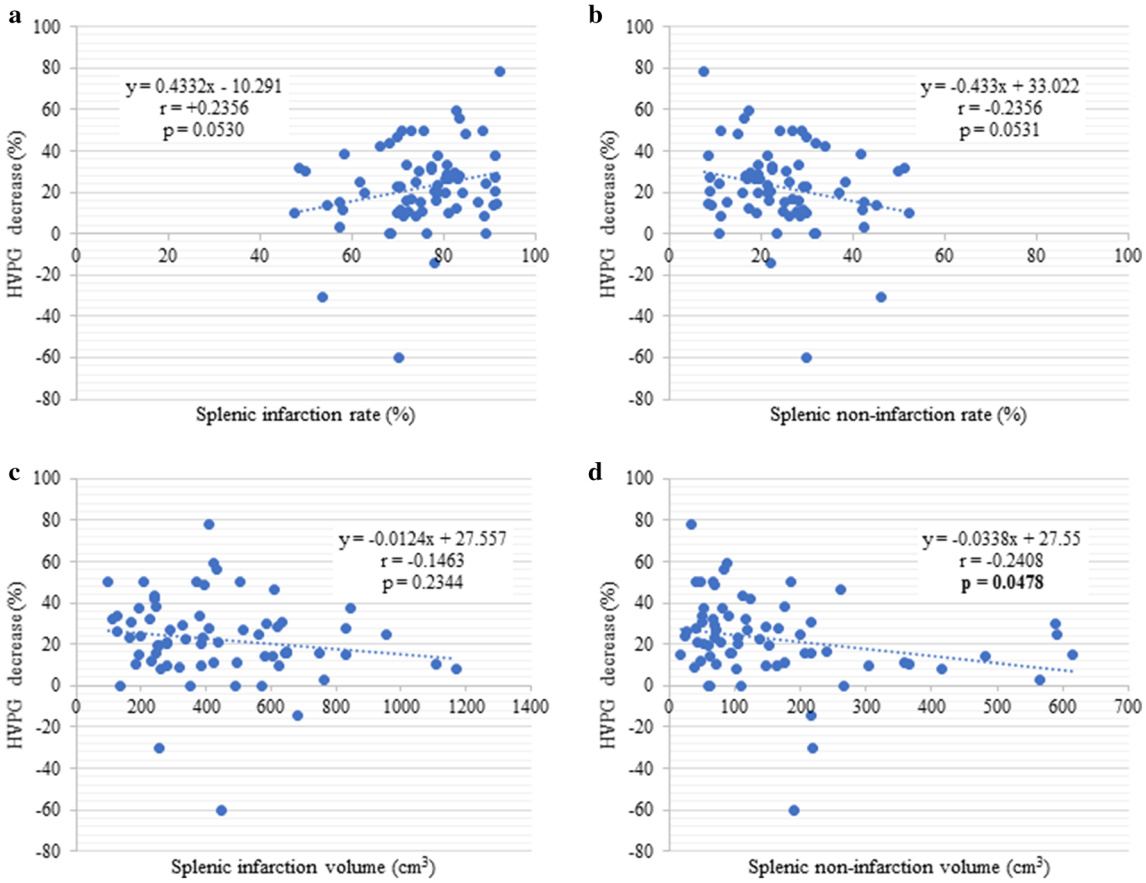

Fig. 3 Correlation between procedural factors of PSE and postprocedural HVPG decrease from the baseline. **a** Splenic infarction rate and HVPG decrease. **b** Splenic non-infarction rate and HVPG decrease. **c** Splenic infarction volume and HVPG decrease. **d** Splenic non-infarction volume and HVPG decrease. There was a significant correlation only between splenic non-infarction volume and HVPG decrease ($r = -0.2408$, $p < 0.05$). *HVPG* hepatic venous pressure gradient. *r* means correlation coefficient

of 22.2 ± 20.4%. An HVPG decrease of ≥ 10% was achieved in 79.4% of patients, and an HVPG decrease of ≥ 20% was observed in 55.9%. In addition, based on results from our analyses, no procedural factors are independent determinants of an HVPG decrease ≥ 10%, whereas splenic non-infarction volume can independently determine an HVPG decrease ≥ 20%, regardless of preprocedural clinical factors. Therefore, the conventional therapeutic strategy that emphasizes splenic infarction volume, as proposed by Hayashi et al. [21, 25], effectively results in a small reduction in HVPG in addition to an increase in platelet counts and prevention of severe complications. On the other hand, these results indicate that the novel therapeutic strategy based on splenic non-infarction volume can also effectively cause a large reduction in HVPG.

In general, WHVP corresponds to portal pressure, but can be affected by intra-abdominal pressure and central venous pressure. HVPG that is corrected by free hepatic venous pressure has recently been considered as an internal standard of portal pressure, and measurements of HVPG are the most reliable tool used by clinicians to predict the clinical outcome and dictate the decision-making in treating several complications in PH patients at this time [2, 8–10]. A large, longitudinal study including patients with compensated cirrhosis without varices demonstrated that patients with an HVPG < 10 mmHg carry a negligible risk of developing varices and a very low risk of decompensation, whereas 28% of patients with an HVPG ≥ 10 mmHg develop varices, and an HVPG ≥ 10 mmHg has been associated with a six-fold increase in HCC risk [6, 7, 27]. In addition, several studies have reported an increased mortality risk in patients with HVPG beyond the threshold of 16 mmHg [28, 29]. Investigating patients above this threshold, Ripoll et al. showed that each 1 mmHg increase in HVPG is associated with a 3% increase in mortality risk in those with decompensated cirrhosis, independent of MELD score [30]. Furthermore, previous reports have shown that reducing the HVPG to < 12 mmHg or reducing the basal levels by 20% in patients with cirrhosis can significantly contribute to a decreased risk of PH-related complications (such as

Table 4 Preprocedural, procedural, and postprocedural factors of patients by splenic non-infarction volume identified by multivariate analyses for predictors of an HVPG decrease ≥ 20%

	Splenic non-infarction volume		
	< 139.2 cm^3 (n = 40)	≥ 139.2 cm^3 (n = 28)	*p* value
a. Preprocedural factors			
HVPG (mmHg)	11.3 ± 4.2	13.4 ± 3.5	0.0397
Spleen volume (cm^3)	308.9 ± 123.6	751.7 ± 320.9	< 0.0001
Spleen volume/body surface area (cm^3/m^2)	201.7 ± 83.8	463.4 ± 192.5	< 0.0001
Platelet count (× $10^4/\mu L$)	6.9 ± 2.3	5.3 ± 2.3	0.0064
Liver stiffness (kPa)	28.6 ± 18.2	27.8 ± 15.3	0.8798
CP score	6.2 ± 1.3	6.6 ± 1.4	0.1898
MELD score	9.3 ± 2.1	10.5 ± 2.5	0.0312
b. Procedural factors			
Splenic infarction rate (%)	80.0 ± 9.1	67.9 ± 9.9	< 0.0001
Splenic non-infarction rate (%)	20.0 ± 9.1	32.1 ± 9.9	< 0.0001
Splenic infarction volume (cm^3)	314.4 ± 158.4	600.0 ± 238.7	< 0.0001
Splenic non-infarction volume (cm^3)	69.9 ± 28.2	284.8 ± 151.9	< 0.0001
c. Postprocedural factors			
HVPG decrease (%)	28.0 ± 17.3	13.9 ± 21.9	0.0078
Platelet count increase (%)	112.6 ± 72.7	147.3 ± 81.2	0.0582
CP score change	+ 0.1 ± 0.7	+ 0.1 ± 0.9	0.3493
MELD score change	− 0.7 ± 1.1	− 1.1 ± 1.7	0.1655

CP Child–Pugh, *HVPG* hepatic venous pressure gradient, *MELD* Model for End-Stage Liver Disease

The data are presented as mean and standard deviation

variceal hemorrhage, ascites, and encephalopathy), bacterial translocation, spontaneous bacterial peritonitis, hepatorenal syndrome, and HCC, and an increased survival rate independent of bleeding events, reflecting a favorable impact on the natural history of the disease [9, 10, 31]. Indeed, decreasing the HVPG to < 12 mmHg or an HVPG reduction ≥ 20% is reportedly achieved in approximately 50% of patients administered NSBBs such as propranolol [32]. This response rate is lower than that of patients with severe PH who responded to PSE in this study (64.7%). NSBBs have been reported to reduce portal pressure by approximately 15% through the reduction in portal venous inflow by decreasing cardiac output via β1-adrenergic blockade and by causing splanchnic vasoconstriction due to unopposed adrenergic tone via β2-adrenergic blockade [33]. In the present study, PSE resulted in a relative HVPG reduction of 22.2% by decreasing the splenic venous return, which accounts for more than 60% of the total portal venous blood flow in cirrhosis [34, 35], through decreasing the splenic arterial inflow. Thus, the portal pressure reduction induced by PSE may be superior to that induced by NSBB administration. As this procedure also increased blood cell count and improved hepatic function in this study, we believe that PSE is a more ideal therapy compared to pharmacotherapy for patients with cirrhosis and hypersplenism due to PH.

A previous study reported by Hayashi et al. proposed that an infarcted splenic volume of less than 388 mL could induce an insufficient increase in the platelet count (at 1 year) after PSE [21]. In addition, a massive infarcted volume of greater than 540 mL in a single PSE could be a significant risk factor for severe complications, such as splenic abscess, refractory ascites, or pleural effusion post-PSE [25]. Based on the above concept, PSE has been thought to be meaningless for patients with smaller spleens, especially considering the effect of infarct volume on platelet counts. However, from the perspective of portal pressure reduction, especially an HVPG decrease ≥ 20%, our study indicates that PSE is a rather meaningful treatment in patients with smaller spleens. Therefore, the indications for PSE should be expanded to include portal pressure control even in patients with mild splenomegaly without severe thrombocytopenia, as a significant decrease in HVPG can be obtained without an excessive increase in platelet count, as presented in Fig. 4.

The present study demonstrated that splenic non-infarction volume is an independent determinant of HVPG decrease ≥ 20% after PSE. A cut-off value of residual functional spleen volume of < 139.2 cm^3 was found in this

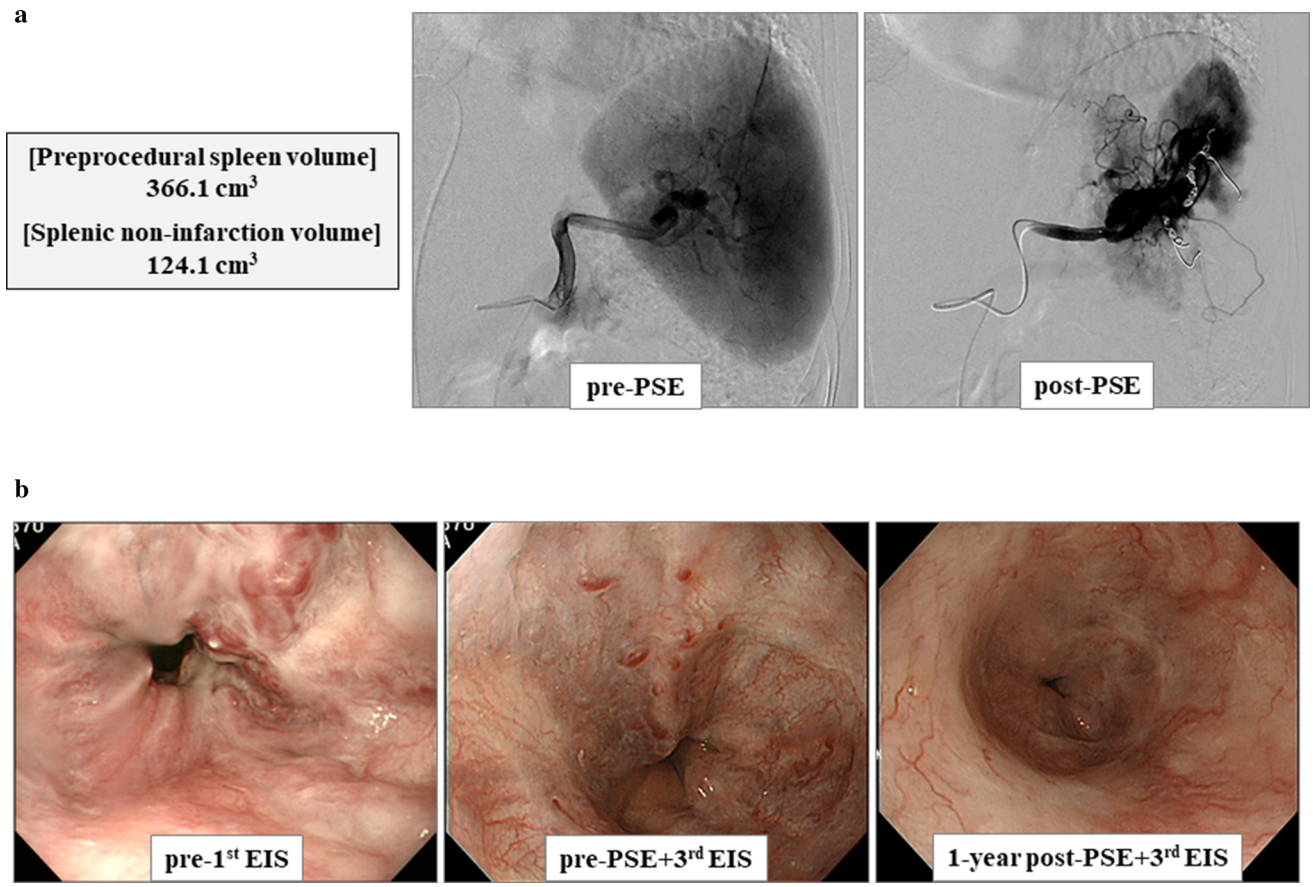

Fig. 4 Case presentation of combination therapy with PSE and EIS for refractory esophageal varices. **a** PSE. PSE was performed prior to the third EIS for esophageal varices in this patient. The pre-PSE spleen volume and post-PSE splenic non-infarction volume were 366.1 and 124.1 cm^3, respectively. **b** Chronological changes in endoscopic findings before and after the combination therapy. Despite two technically successful EIS procedures that were performed within 1 year of each other, refractory esophageal varices with red color signs remained. One month after PSE, the third EIS was performed without any complications, and no recurrence of esophageal varices had been observed during 1 year of follow-up since combination therapy. *EIS* endoscopic injection sclerotherapy, *PSE* partial splenic embolization

study. Previous studies have shown that age and body habitus play a role in the average spleen volume in Japanese patients. Kaneko et al. reported a mean normal spleen volume of 112 ± 40 cm^3 in 150 healthy Japanese volunteers [36] and 123 ± 45 cm^3 in 238 Japanese patients without chronic liver disease [37]. Harris et al. found the mean spleen volume to be 127.4 ± 62.9 cm^3 for the Japanese population (n = 230) [38]. Therefore, the therapeutic target of PSE is the normalization of splenic functional volume. In addition, a partitioned and repeated PSE can safely and reliably achieve a splenic non-infarction volume < 139.2 cm^3, even in patients with massive splenomegaly (for example, pre-PSE spleen volume > 1000 cm^3), resulting in an HVPG decrease ≥ 20%. Moreover, theoretically, surgical splenectomy, which removes the entire spleen, can achieve an HVPG decrease ≥ 20%.

Zhao et al. reported an immediate decrease in HVPG of 22.9% and an HVPG decrease of 17.7% 6 months post-PSE. There were no significant changes at 6 months after PSE when compared to the immediate post-PSE measurements, showing that PSE immediately reduced the portal pressure and it remained stable for 6 months after surgery [39]. The mean HVPG decrease, 22.2%, immediately post-PSE compared to pre-PSE in our study is equivalent to that in their previous study [39], and, based on their results, the effects of PSE in HVPG reduction observed in the present study are expected to be continued for a long time.

Finally, we propose that an HVPG decrease ≥ 20% should be considered a clinically significant HVPG response to PSE. To the best of our knowledge, this is the first report of splenic non-infarction volume as an independent procedural determinant of a clinically significant HVPG response to PSE. However, the study results should be interpreted in the context of the study's limitations. First, this was a single-center, retrospective study. Second, a limited number of patients were analyzed, and third, the HVPG was measured immediately after the procedure in

this study. Repeated HVPG measurements are a challenge, as they require specific expertise and hospitalization, making the procedure relatively burdensome and invasive. However, Yamamoto et al. recently reported a minimally invasive measurement of HVPG via the peripheral antecubital vein that was safe, feasible, and accurate [40]. As this HVPG measurement technique does not necessitate a long rest after the procedure, nor careful observation of the puncture site under admission, it could be performed repeatedly in an outpatient setting as a useful alternative to the conventional HVPG measurement methods. Therefore, prospective studies with larger sample sizes and longer follow-up periods using a novel HVPG measurement technique are necessary to verify the results of this study.

In conclusion, PSE resulted in a significant relative decrease in HVPG, independent of preprocedural HVPG. A splenic non-infarction volume $< 139.2\ cm^3$ is an independent determinant of a clinically significant HVPG response to PSE. Based on our results, a novel therapeutic strategy through a significant reduction in portal pressure induced by PSE needs to be developed for cirrhosis patients with PH-related diseases.

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