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Utility of Contrast-Enhanced Ultrasonography for the Evaluation of Partial Splenic Embolization

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Abstract **Background:** Abdominal ultrasonography (US) is often used to evaluate hepatic fibrosis and splenomegaly. Partial splenic embolization (PSE) is performed to improve thrombocytopenia associated with portal hypertension in liver cirrhosis. In general, the spleen infarction rate (SIR) after PSE is assessed using contrast-enhanced computed tomography (CT-SIR). We evaluated the SIR using contrast-enhanced US (US-SIR) owing to its non-invasive nature. **Methods:** Eighteen patients with portal hypertension who underwent PSE were included in this study. One week after PSE, the CT-SIR and US-SIR were calculated, respectively. **Results:** The mean platelet count was 4.6, 11.4, and 10.2 ($\times 10^4$ /μl) at one week before PSE, at one month, and at six months after PSE, respectively. One week after PSE, the CT-SIR and US-SIR were 74.9% and 77.4%, respectively, and the SIR showed significant correlation between CT-SIR and US-SIR ($p < 0.001$, R = 0.901). The increased platelet count at six months after PSE showed a correlation with CT-SIR ($p = 0.004$, R = 0.650) and US-SIR ($p = 0.009$, R = 0.599). **Conclusions:** We verified the usefulness of contrast-enhanced US assessment in SIR for patients with PSE.

Key words: partial splenic embolization, spleen infarction rate, contrast-enhanced ultrasonography

Introduction

Liver cirrhosis (LC) is commonly the end result of chronic liver disease caused by hepatitis C virus (HCV), hepatitis B virus (HBV), alcohol, and other factors.[1] Advanced liver fibrosis provokes portal hypertension (PH) symptoms such as splenomegaly, esophagogastric varices, and hepatic encephalopathy.[2] Abdominal ultrasonography (US), which is non-invasive and can be performed as needed, is widely used in the assessment of chronic liver disease including liver cirrhosis.[1]

Partial splenic embolization (PSE) is performed to treat hypersplenism due to PH.[3-8] The spleen infarction rate (SIR) after PSE is reportedly correlated with the increase in platelet count.[6-10] In these studies, the SIR was assessed using contrast-enhanced computed tomography (CECT). However, some invasive events, such as radiation exposure, were associated with this procedure, leading to subsequent nephrotoxicity. Thus, in this study, we attempted to evaluate a non-invasive

approach using contrast-enhanced US (CEUS) for determining the SIR.

Methods

This study was conducted in compliance with the ethical principles of the Declaration of Helsinki. The study protocol (H27-180) was approved by the Institutional Review Board of Yamaguchi University Hospital.

Patients

Between July 2013 and October 2016, 18 patients who were treated with PSE were included in this study. All patients showed cirrhotic pattern on US, in addition to thrombocytopenia.

Spleen infarction rate (SIR)

PSE was carried out according to the report of Yoshida et al.[4] The HI VISION Ascendus® (Hitachi Ltd., Tokyo, Japan, EUP-C715 & EUP-L52 probe) was used for US analysis. We evaluated splenic size by spleen index (SI) based on the report of Matsutani et al. (Fig. 1A).[11] In addition, real-time tissue elastography (RTE) of the liver was assessed by right intercostal scanning five times, from which we calculated the mean RTE. Furthermore, we evaluated the SIR using CEUS and CECT one week after PSE. Sonazoid® (NC100100, Daiichi Sankyo Company Limited, Tokyo, Japan) was used as the contrast agent in US. We set up a probe at a position that could show the spleen in the longitudinal plane 10 minutes after a bolus injection of Sonazoid (0.5 ml) followed by a normal saline (10 ml) flush and presented section images of the spleen in an arbitrary slice number (five to seven slices). We summed the splenic total cross sections and splenic non-infarcted area, and calculated SIR by US (US-SIR) (Fig. 1B). Splenic volume and SIR using CT (CT-SIR) were also calculated. Splenic volume was computed by multiplying the total splenic cross-sectional area of the 5-mm slice by 5 mm. In all cases, we obtained platelet count, albumin, total bilirubin, prothrombin time-international ratio (PT-INR) at four time points (before PSE, one week after PSE, one month after PSE, and six months after PSE) (Fig. 1C). We investigated parameters associated with changes in liver function, and platelet count.

Statistical analysis

All analyses were performed using JMP v.13.0 (SAS Institute Inc., Cary, NC, USA) software. Categorical variables were presented as frequencies, and inter-group comparisons were analyzed by the chi-squared test or Fisher's exact test. Continuous variables were expressed as the mean ± standard deviation

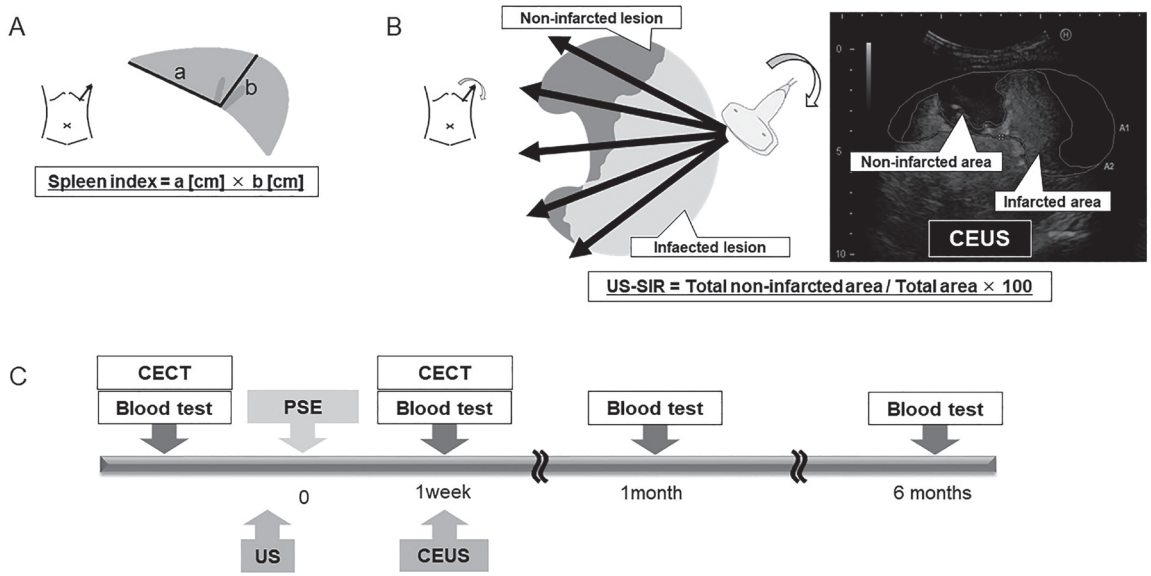

Fig. 1 A. Spleen index (SI) is calculated from a [cm] × b [cm]. B. The spleen infarction rate (SIR) using contrast-enhanced ultrasonography (CEUS). C. Schedule of the study.

or median (interquartile range). The results were evaluated with a paired or unpaired t-test, and Wilcoxon rank-sum test or Wilcoxon signed-rank test. Parameters correlated with the amount of platelet increase were analyzed by Spearman's rank moment correlation coefficient. Statistical significance was defined as a $p < 0.05$.

Results

Patient Characteristics

Patient characteristics and blood test at each time point were shown in Table 1. Patients were composed of 11 men and seven women [median age, 67.0 (63.3-72.8) years]. Eleven, two, and five patients had HCV, alcohol, and non-HBV non-HCV (NBNC) as cirrhotic etiology, respectively. All patients showed reduced platelet count, and all US related parameters [SI was 34.9 (27.3-39.5)] and mean RTE was 77.0 (66.6-85.8)] revealed the presence of liver cirrhosis.

PSE

Among 18 patients undergoing PSE, 10 patients (56%) were class Child-Pugh A before the procedure and 8 patients (44%) were class Child-Pugh B. Ascites was observed in 11 patients (61%) one week after PSE, but all adverse effects were non-serious. The median splenic volume by CT and SI were 577.4 (435.0-756.7) ml and 34.9 (27.3-39.5) ml, respectively. There was a significant positive correlation between splenic volume by CT and SI assessment by US ($p < 0.001$, $R = 0.935$) (Fig. 2A). We performed PSE with a goal of 70% apparent infarction on angiography, and SIR was evaluated one week after PSE. CT-SIR was 74.9% (69.7-4.2%) and US-SIR was 77.4% (73.6-84.2%), and they showed a significant correlation ($p < 0.001$, $R = 0.901$) (Fig. 2B). Albumin was significantly decreased after PSE at one month, but improved to the same level before PSE at six months. The platelet count was 4.6 (3.2-6.0), 12.8 (9.0-15.2), 11.4 (8.6-14.9), and 10.2 (7.2-12.6) ($\times 10^4$ /μl) at baseline, one week, one month, and six months after PSE, respectively (Fig. 3). This meant that the increased platelet count was 7.4 (5.0-10.3), 5.9 (4.0-8.6), and 4.9 (3.0-7.9) at one week, one month, and six months, respectively.

Factors of platelet elevation

The increased platelet count one month after PSE correlated with CT-SIR ($p = 0.046$, R = 0.476), but did not correlate with US-SIR ($p = 0.159$, R = 0.346) one week after PSE (Fig. 4A, B). At six months after PSE, the increased platelet count showed a correlation with not only CT-SIR ($p = 0.004$, R = 0.650), but also US-SIR ($p = 0.009$, R = 0.599) (Fig. 4C, D).

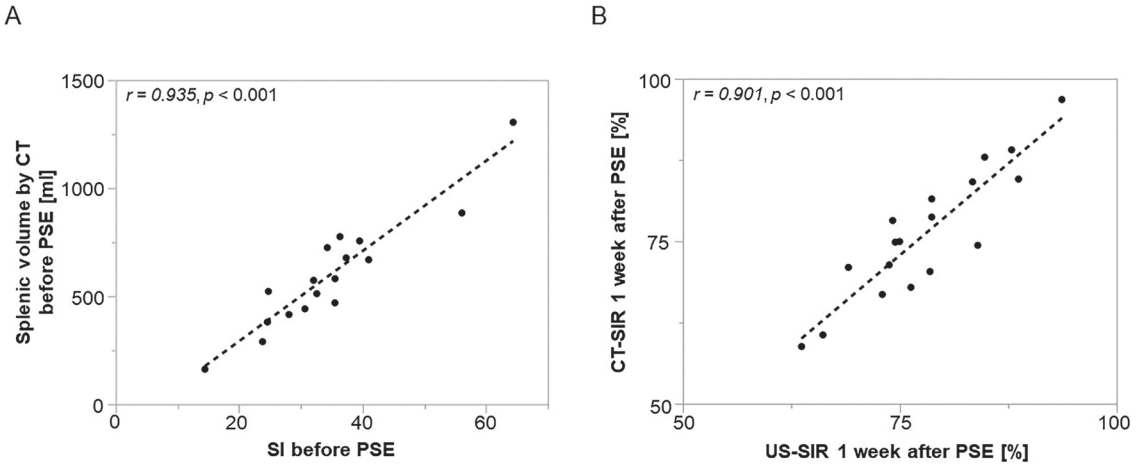

Fig. 2 A. There was a significant positive correlation between splenic volume as per computed tomographic analysis and spleen index (SI), both of which were measured before partial splenic embolization (PSE). B. One week after PSE, the spleen infarction rate (SIR), as measured via computed tomography (CT-SIR) and ultrasonography (US-SIR) showed a positive correlation.

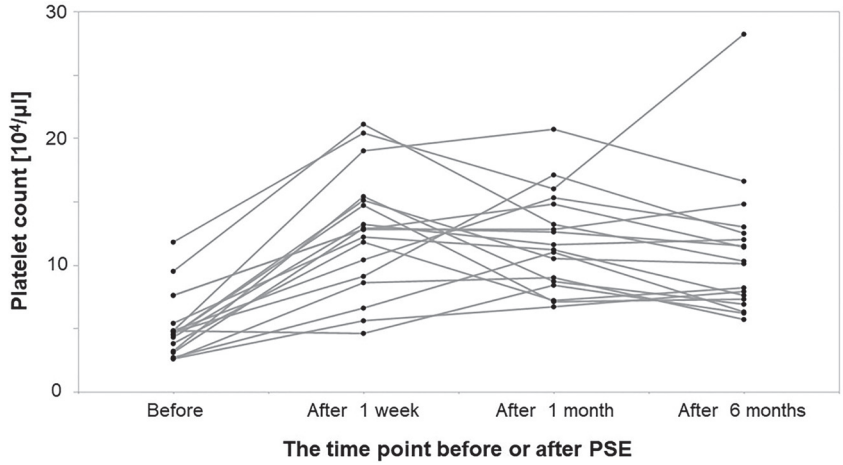

Fig. 3 Seventeen of 18 patients showed an increase in platelet count one week after partial splenic embolization (PSE). In one month and six months, the platelet count was increased in all cases compared with before PSE.

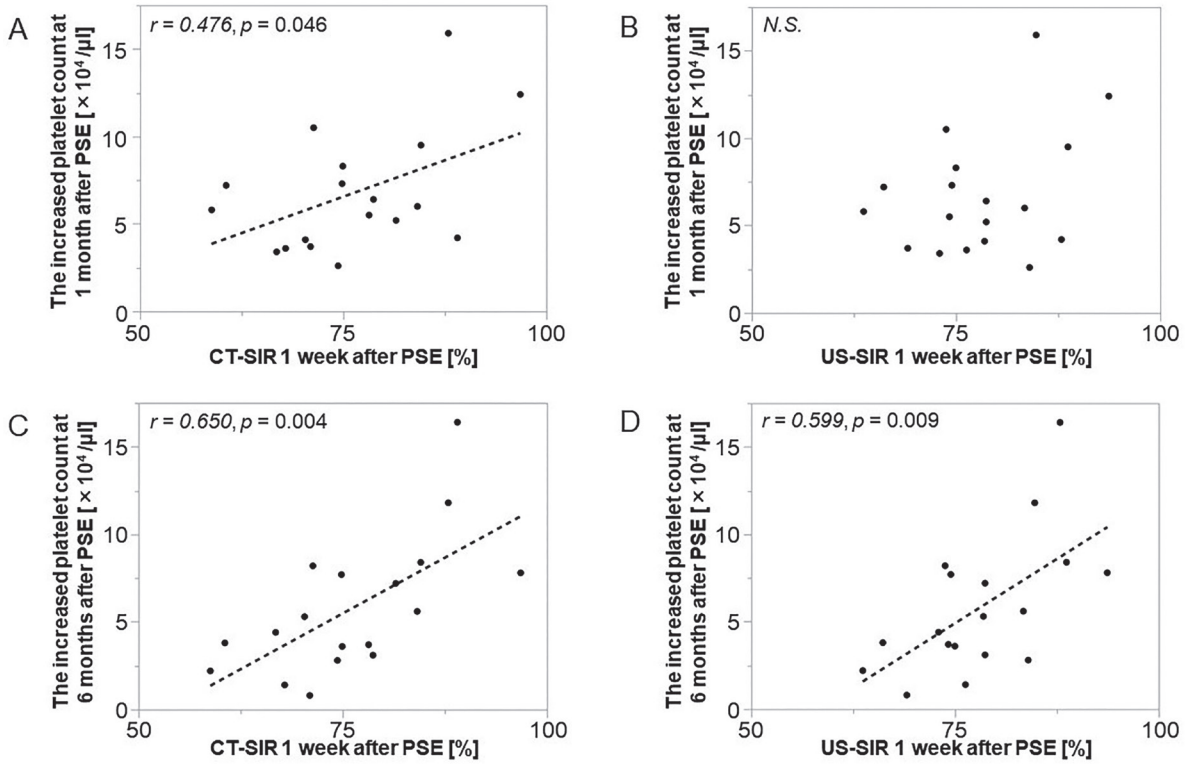

Fig. 4 A, B. The increased platelet count one month after partial splenic embolization (PSE) showed correlations with the spleen infraction rate (SIR) as measured via computed tomography (CT-SIR); however, it did not show correlations with the SIR as measured via ultrasonography (US-SIR). C, D. The increased platelet count six months after PSE showed positive correlation with CT-SIR and US-SIR, respectively.

Discussion

PSE was first reported by Spigos et al. in 1979.[12] It was established as a treatment for thrombocytopenia due to splenomegaly with LC, and is equivalent to surgical splenectomy.[4] Multiple studies have shown that the platelet count peaked one to two weeks after PSE and was two to three times greater at one month than that before PSE.[6-10] In our study, platelet count increased three times after one week and stabilized about twice from one month onward (Table 1, Fig. 3). Additionally, the splenic volume calculated from CT had a good correlation with SI by US in the present study (Fig. 2A). The SIR is reportedly correlated with the increase in platelet count and the incidence of adverse effects, and an approximate 50 to 70% infarction is considered as a standard.[6-10] Adverse effects related to PSE include fever, pain, nausea, vomiting, portal vein thrombus, pleural effusion, and splenic abscess.4,5 Nevertheless, the SIR and infarction volume were assessed using CECT in these previous studies.[6-10] Furthermore, radiation exposure and subsequent renal dysfunction are of clinical importance. Conversely, CEUS does not expose the patient to radiation and subsequent nephrotoxicity. We showed that significant linear correlation between CT-SIR and US-SIR ($p < 0.001$, $R = 0.901$) (Fig. 2B). Moreover, splenic infarction volume is related to increasing platelet count.[13] In our study, CT-SIR had a positive correlation with an increased platelet count (Fig. 4A, C). Alternatively, US-SIR was also related to an increased platelet count, however, it was a weak correlation at one month after PSE (Fig. 4B), and was significant at six months (Fig. 4D). Following two points are considered as this reason. First, there is measurement error of US-SIR than CT-SIR. Second, the platelet count presents high value due to inflammation at one month, however, it becomes stable at six month. US-SIR showed correlation with increased platelet count, because an error fades away in six months. We can perform CEUS at the bed side in real-time. Furthermore, US provides a diagnostic quality equivalent to CT and MRI, and is much more cost-effective.[14,15]

Hidaka et al. reported that spleen embolization volume could be assessed by three-dimensional US using Sonazoid.[16] We tried to calculate the SIR by a simpler and easier method using CEUS. We revealed that CEUS is available for the assessment of SIR without inferiority to CECT. Moreover, the SIR

Table 1 Patient data before and after PSE

Etiology (HCV/Alcohol/NBNC)		**11/2/5**
Sex (Male/Female)		**11/7**
Age [years]		**67.0** (63.3 - 72.8)
Platelet count [10^4/μl]	**Before**	**4.6** (3.2 - 6.0)
	After 1W	**12.8** (9.0 - 15.2)
	After 1M	**11.4** (8.6 - 14.9)
	After 6M	**10.2** (7.2 - 12.6)
Albumin [g/dl]	**Before**	**3.5** (3.0 - 3.7)
	After 1W	**2.9** (2.7 - 3.2)
	After 1M	**3.3** (2.9 - 3.5)
	After 6M	**3.6** (3.2 - 4.1)
Total bilirubin [mg/dl]	**Before**	**1.3** (1.1 - 1.7)
	After 1W	**1.4** (1.0 - 1.9)
	After 1M	**1.2** (0.9 - 1.6)
	After 6M	**1.2** (0.8 - 1.7)
PT-INR	**Before**	**1.19** (1.12 - 1.29)
	After 1W	**1.19** (1.15 - 1.29)
	After 1M	**1.16** (1.11 - 1.34)
	After 6M	**1.10** (1.02 - 1.23)

HCV, hepatitis C virus; NBNC, non-HBV non-HCV; PT-INR, prothrombin time-international ratio; W, week; M, month(s).

was correlated with platelet count and its increase six months after PSE. It is reported that splenic size is the most important factor among those related to thrombocytopenia and has a negative relationship with platelet count among those evaluable by US.[2,6]

There are some limitations to this study. First, US is affected by the shape of spleen in the measurement of operator's manipulation as compared with CT. Second, it was conducted at a single institution with a small cohort. However, as PSE is performed with limited number of cases, we believe our study is meaningful even if the small population. In conclusion, a favorable assessment of SIR was able to be carried out in this study using US. Particularly, US assessment is beneficial in infarcted rate, and we can use CEUS in place of CECT for evaluation of PSE.

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Conflict of Interest

The authors declare no conflict of interest.

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