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ORIGINAL RESEARCH

Efficacy and Safety of Transarterial Chemoembolization and Repeated Partial Splenic Embolization for Hepatocellular Carcinoma with Hypersplenism and Thrombocytopenia

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Aim: Partial splenic embolization (PSE) combined with transarterial chemoembolization (TACE) has been reported in treatment of hepatocellular carcinoma (HCC) with cirrhotic hypersplenism and thrombocytopenia. However, efficacy and safety of repeated PSE when required are unclear. This study aims to investigate post-procedural changes in peripheral blood cell and hepatic function, progression-free survival (PFS), and safety of HCC patients with hypersplenism received TACE and repeated PSE compared to those received TACE alone.

Methods: This retrospective study included 102 HCC patients with hypersplenism who received TACE (n = 73) or TACE+PSE (n = 29) from January 2014 to December 2021. Changes in peripheral blood cell and hepatic function were investigated at 1 week, 2, 6, 12, 18, and 24 months. TACE procedure sessions and adverse events were recorded. PFS and prognostic factors were analyzed.

Results: Despite response to initial PSE being limited, repeated PSE increased platelet (PLT) again, which peaked at 18 months. It also continued to improve red blood cell (RBC) and hemoglobin, which showed significant differences in changes from baseline between two groups until 24 months, as well as Child-Pugh scores at 12 and 18 months. Mean TACE procedure sessions were significantly higher in TACE+PSE group than that in TACE alone group (4.55 vs 3.26, $P = 0.019$). TACE+PSE group had longer median PFS (19.4 vs 9.5 months, $P = 0.023$) than TACE alone group, where PSE was an independent protective factor (HR, 0.508; $P = 0.014$). Initial and repeated PSE showed no significant differences in safety.

Conclusion: Repeated PSE is effective in increasing PLT again and improving RBC, hemoglobin and liver function. It contributed to performing serial TACE procedures thereafter. TACE combined with repeated PSE has significantly longer PFS than TACE alone, where PSE was an independent protective factor. Moreover, the safety of repeated PSE was comparable to initial PSE.

Keywords: hepatocellular carcinoma, hypersplenism, transarterial chemoembolization, partial splenic embolization

Introduction

Hepatocellular carcinoma (HCC) accounts for most cases of primary liver cancer, which is the third-leading cause of cancer death worldwide.[1] As a critical risk factor for HCC, liver cirrhosis presents in up to 90% of HCC patients.[2] Hypersplenism is a well-known complication of cirrhosis and is characterized by hemocytopenia, particularly thrombocytopenia.[3] Thrombocytopenia may hinder the treatments for HCC due to the increased risk of bleeding.[4] Meanwhile, it has been shown that hypersplenism and thrombocytopenia are potentially associated with poor patient prognosis.[3]

Partial splenic embolization (PSE) has become increasingly popular in the management of hypersplenism and thrombocytopenia induced by cirrhosis over recent years.[5–7] It has demonstrated effectiveness in improving platelet (PLT) count as a minimally invasive alternative to splenectomy. Previous studies have shown that the increment of PLT after PSE greatly depends on the splenic infarction ratio.[8] However, the incidence of complications after PSE also increases as the infarction ratio increases. Infarction ratio higher than 70% is associated with major complications such as

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splenic abscess, according to a systematic review.[9] PSE with lower infarction ratio is safer but less effective and more likely to relapse. In this situation, repeated PSE is expected.[10,11]

Transarterial chemoembolization (TACE) is currently widely used for unresectable HCC.[2] To date, several researchers have reported the beneficial effects of TACE combined with concurrent PSE in HCC patients with hypersplenism and thrombocytopenia.[12–18] Nevertheless, some patients were lack of response to initial PSE, resulting in unsatisfactory PLT count during the follow-up period.[13] For these patients, repeated PSE was conceivably required. To the best of our knowledge, no study has focused on the efficacy and safety of repeated PSE in such patients. The clinical results of TACE combined with repeated PSE for HCC patients with hypersplenism and thrombocytopenia are absent in the literature. Therefore, we conducted this study to investigate the post-procedural changes in peripheral blood cell counts, post-procedural changes in hepatic function, progression-free survival (PFS), and adverse events in HCC patients with hypersplenism and thrombocytopenia who received TACE combined with repeated PSE compared to those who received TACE alone.

Methods

Patients

The Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology approved this retrospective study, and the requirement for informed consent was waived due to the retrospective nature. The study was performed according to the principles of the Declaration of Helsinki, and the confidentiality of patient data was ensured. We reviewed the medical records of 2403 consecutive HCC patients who underwent TACE in our institution from January 2014 to December 2021.

The flow of patients' selection is depicted in Figure 1. We included adult patients (1) with histopathologically or clinically confirmed HCC; (2) with cirrhosis and hypersplenism featuring thrombocytopenia (PLT $< 100 \times 10^9$/L); (3)

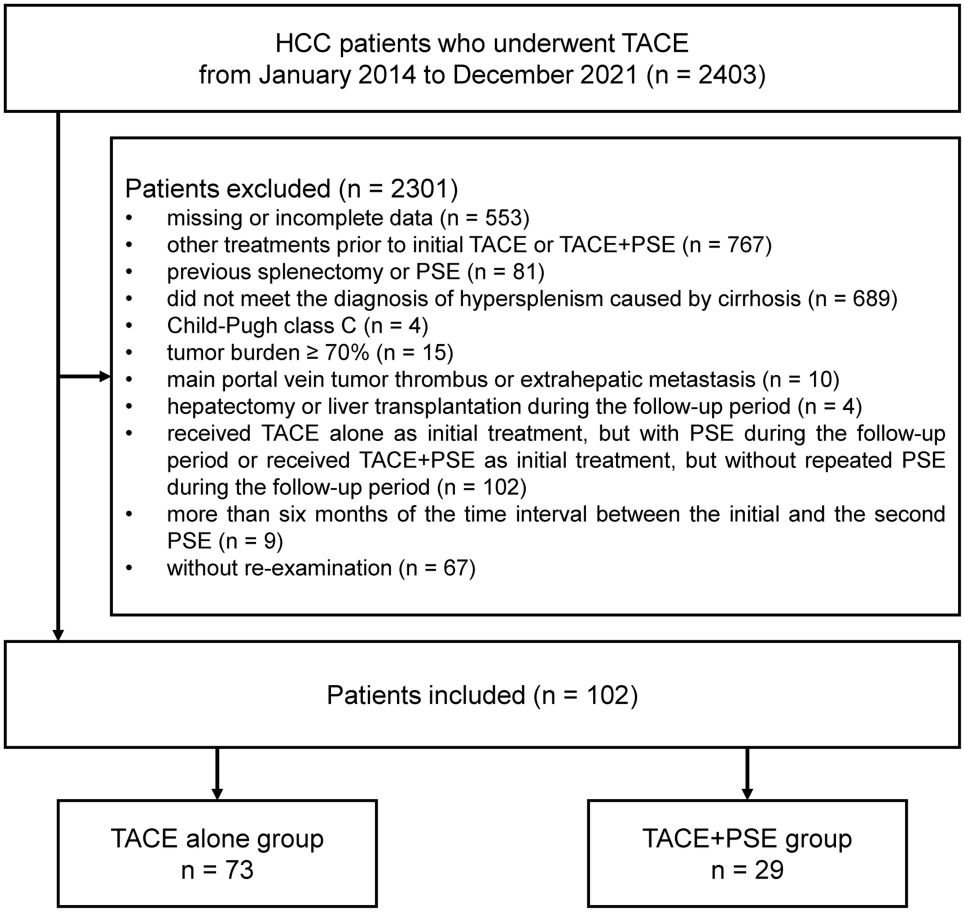

Figure 1 Patients selection.
Abbreviations: HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; PSE, partial splenic embolization.

with Child-Pugh class A or B; (4) with Barcelona Clinic Liver Cancer (BCLC) stage 0, A, B, or C; (5) with tumor volume accounting for less than 70% of liver volume; (6) without main portal vein tumor thrombus or extrahepatic metastasis; (7) received TACE alone as initial treatment, without PSE during the follow-up period or received TACE +PSE (TACE combined with concurrent PSE) as initial treatment, with repeated PSE during the follow-up period. The exclusion criteria were as follows: (1) missing or incomplete clinical information; (2) previous history of splenectomy or PSE; (3) received hepatectomy or liver transplantation during the follow-up period; (4) more than six months of the time interval between the initial and the second PSE; (5) without re-examination.

TACE and PSE Procedures

TACE and PSE procedures were performed by experienced interventional radiologists. For patients in the TACE alone group, the right femoral artery was accessed with modified Seldinger technique, and a 5-F visceral catheter was introduced into the common hepatic artery. Selective arteriography was performed to detect the tumor and its supplying arteries. Then, a 2.7-F microcatheter (Progreat, Terumo, Tokyo, Japan) was advanced into the tumor-feeding arteries, and subsequent conventional transarterial chemoembolization (C-TACE) or drug-eluting bead transarterial chemoembolization (DEB-TACE) was performed as described previously.[19]

Patients in the TACE+PSE group received concurrent PSE immediately after TACE procedures. The catheter was advanced into the end of the splenic artery trunk, without entering into splenic segmental arteries. Following splenic angiography, an appropriate amount of PVA particles with size of 350–560 μm was injected for embolization. The target embolization ratio depended on the degree of hypersplenism, while generally controlled to not exceed 50%, estimated by repeated angiography during PSE. Antibiotics were administrated after PSE procedures to prevent infections. Two months later, these patients underwent the second PSE due to the failure in achieving two-fold increases in PLT counts. Some patients received more PSE during the subsequent follow-up period. The repeated PSE procedures were in concurrent combination with repeated TACE procedures.

Follow-Up and Assessment of Outcomes

Patients were evaluated with imaging examinations at 2 to 3 months after initial treatment and then every three months. The follow-up period ended on December 31, 2022.

We investigated the peripheral blood cell counts, Child-Pugh score, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) at 1 week, 2 months, 6 months, 12 months, 18 months, and 24 months after initial treatment. We also investigated these tests before and at 1 week and 2–3 months after each repeated PSE procedure. We measured the total splenic volume at baseline, residual splenic volume at 2 months after initial treatment, and residual splenic volume at 2–3 months after the final PSE, respectively. The splenic infarction ratio was calculated with the following formulas: (1) the infarcted splenic volume = total splenic volume at baseline − residual splenic volume; (2) the splenic infarction ratio = (infarcted splenic volume/total splenic volume at baseline) × 100%. Tumor response was evaluated at 2 months after initial treatments with the modified RECIST (mRECIST) criteria[20] and was classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Objective response rate (ORR) was the sum of rates of CR+PR, and disease control rate (DCR) was the sum of rates of CR+PR+SD. PFS was defined as the period between the initial treatment date and the tumor progression or death date. Post-procedural adverse events were recorded and further classified according to Abhinav Talwar's literature.[9]

Statistical Analysis

Continuous data were presented as means ± standard deviations or medians (interquartile ranges). Categorical data were presented as numbers and percentages. Comparisons of baseline characteristics between the two groups were performed with Student's *t*-test for the continuous variables and chi-square test for the categorical variables. The post-procedural changes in peripheral blood cell counts and hepatic function from baseline at each time point between the two groups were compared using independent samples *t*-test. Statistical testing of post-procedural ALT and AST results was performed after log transformation due to extremely skewed distributions. The comparison between initial and repeated PSE of changes in peripheral blood cell counts and hepatic function was performed with Student's *t*-test. The number of

TACE procedure sessions between two groups was compared using the Wilcoxon rank sum test. The Kaplan–Meier method was used to estimate the cumulative PFS rate, with Log rank test to evaluate the difference. Prognostic factors associated with PFS were further determined using the univariate and multivariate Cox proportional hazards model. Multivariate analysis included potential factors ($P < 0.05$) according to the results of univariate analysis. The differences in the incidence of adverse events were assessed using Fisher's exact test. All analyses were performed using R version 4.2.2, and a $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

A total of 102 patients were enrolled in this study, of whom 73 were treated with TACE alone and 29 received combination treatment of TACE and PSE. The baseline characteristics of 102 patients are summarized in Table 1. There were statistically significant differences in PLT, white blood cell (WBC), total bilirubin, and Child-Pugh score between the TACE alone group and the TACE+PSE group. The PLT (42.93 vs 74.34 × 10^9/L, $P < 0.001$) and WBC (2.32 vs 3.81 × 10^9/L, $P < 0.001$) in the TACE+PSE group were significantly lower than those in the TACE alone group at baseline. Meanwhile, the total bilirubin (32.25 vs 23.80 μmol/L, $P = 0.038$) and Child-Pugh scores (6.86 vs 6.25, $P = 0.040$) in the TACE+PSE group were significantly higher than those in the TACE alone group at baseline.

Table 1 Comparison of the Baseline Characteristics of Patients Between the TACE Alone Group and the TACE+PSE Group

Variables	TACE Alone Group (n = 73)	TACE+PSE Group (n = 29)	*P*
Gender			1.000
Male	59 (80.8)	23 (79.3)	
Female	14 (19.2)	6 (20.7)	
Age, years			0.063
≤60	39 (53.4)	22 (75.9)	
>60	34 (46.6)	7 (24.1)	
Etiology			0.618
HBV	53 (72.6)	24 (82.8)	
HCV	9 (12.3)	3 (10.3)	
NBNC	11 (15.1)	2 (6.9)	
PLT, × 10^9/L	74.34 ± 16.51	42.93 ± 11.16	< 0.001
RBC, × 10^{12}/L	3.82 ± 0.62	3.62 ± 0.51	0.091
Hemoglobin, g/L	119.29 ± 21.04	113.41 ± 17.35	0.152
WBC, × 10^9/L	3.81 ± 1.59	2.32 ± 0.78	< 0.001
Total bilirubin, μmol/L	23.80 ± 13.05	32.25 ± 19.54	0.038
Albumin, g/L	34.82 ± 4.76	33.76 ± 4.53	0.295
Child-Pugh score	6.25 ± 1.19	6.86 ± 1.38	0.040
Child-Pugh class			0.068
A	44 (60.3)	11 (37.9)	
B	29 (39.7)	18 (62.1)	
ALT, U/L	39.96 ± 31.88	30.45 ± 16.40	0.052
AST, U/L	53.17 ± 32.65	43.28 ± 20.00	0.068
Tumor number			0.132
Solitary	34 (46.6)	19 (65.5)	
Multiple	39 (53.4)	10 (34.5)	
Tumor location			0.564
Left lobe	8 (11.0)	3 (10.3)	
Right lobe	45 (61.6)	21 (72.4)	
Both lobe	20 (27.4)	5 (17.2)	

(*Continued*)

Table 1 (Continued).

Variables	TACE Alone Group (n = 73)	TACE+PSE Group (n = 29)	*P*
Tumor size, cm			0.487
≤3	28 (38.4)	14 (48.3)	
>3	45 (61.6)	15 (51.7)	
BCLC stage			0.580
0	5 (6.8)	3 (10.3)	
A	21 (28.8)	8 (27.6)	
B	18 (24.7)	4 (13.8)	
C	29 (39.7)	14 (48.3)	
Initial TACE method			0.798
C-TACE	57 (78.1)	24 (82.8)	
DEB-TACE	16 (21.9)	5 (17.2)	

Notes: Data are presented as means ± standard deviations.
Abbreviations: TACE, transarterial chemoembolization; PSE, partial splenic embolization; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-B, non-C hepatitis; PLT, platelet; RBC, red blood cell; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; C-TACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead transarterial chemoembolization.

Twenty-nine patients in the TACE+PSE group underwent a total of 80 sessions of PSE, including 29 sessions of initial PSE and 51 sessions of repeated PSE. The mean number of PSE procedures per patient in the TACE+PSE group was 2.76 sessions. The median splenic infarction ratio of initial PSE was 28.6% (interquartile ranges, 20.0–42.3), and the median final splenic infarction ratio was 67.1% (interquartile ranges, 50.3–74.7). Ten patients (34.5%) in the TACE+PSE group and 29 patients (39.7%) in the TACE alone group underwent other antitumor therapies during the follow-up period, where there was no significant difference between two groups ($P = 0.791$).

Changes in Peripheral Blood Cell Counts

Changes in peripheral blood cell counts in two groups during the follow-up period are shown in Table 2 and Figure 2. The detailed data are shown in Supplementary Table 1. The PLT in the TACE+PSE group rapidly increased at 1 week after initial

Table 2 Comparison of the Changes in Peripheral Blood Cell Counts from Baseline Between the TACE Alone Group and the TACE+PSE Group

Variables	Time Point	TACE Alone Group	TACE+PSE Group	*P*
PLT, × 10^9/L	1 week	0.23 ± 23.38	12.21 ± 20.91	0.019
	2 months	−3.17 ± 15.28	6.33 ± 10.75	0.002
	6 months	0.49 ± 23.01	16.83 ± 18.48	0.004
	12 months	−0.88 ± 17.10	37.71 ± 25.07	< 0.001
	18 months	2.57 ± 25.06	53.36 ± 25.25	< 0.001
	24 months	1.00 ± 16.13	38.71 ± 20.39	0.002
RBC, × 10^{12}/L	6 months	−0.12 ± 0.70	0.14 ± 0.30	0.046
	12 months	−0.24 ± 0.58	0.21 ± 0.41	0.008
	18 months	−0.58 ± 0.73	0.13 ± 0.56	0.012
	24 months	−0.67 ± 0.49	0.19 ± 0.37	< 0.001
Hemoglobin, g/L	6 months	−4.49 ± 17.61	4.91 ± 10.64	0.013
	12 months	−4.84 ± 15.29	9.86 ± 16.58	0.011
	18 months	−17.07 ± 25.10	10.73 ± 19.27	0.005
	24 months	−18.50 ± 13.87	8.00 ± 8.89	< 0.001

(*Continued*)

Table 2 (Continued).

Variables	Time Point	TACE Alone Group	TACE+PSE Group	*P*
WBC, × 10^9/L	1 week	0.88 ± 1.74	2.23 ± 1.65	< 0.001
	2 months	−0.67 ± 1.43	0.17 ± 0.90	0.003
	24 months	−0.19 ± 1.06	1.23 ± 0.93	0.009

Note: Data are presented as means ± standard deviations.
Abbreviations: TACE, transarterial chemoembolization; PSE, partial splenic embolization; PLT, platelet; RBC, red blood cell; WBC, white blood cell.

treatment with an increment of 12.21 ± 20.91 × 10^9/L. Then, it decreased at 2 months, but increased again at 6 months and peaked at 18 months with an increment of 53.36 ± 25.25 × 10^9/L. The TACE+PSE group showed a significant increase in PLT from baseline compared to TACE alone group at all time points investigated. Both red blood cell (RBC) and hemoglobin in two groups declined at 1 week after initial treatment and improved at 2 months. From 6 months after treatment, the RBC and hemoglobin had continued to improve and maintained at better than baseline until 24 months in the TACE+PSE group. In contrast, in the TACE alone group, the RBC and hemoglobin had continued to decline, with significant differences in changes from baseline compared to the TACE+PSE group. The increment of WBC in the TACE+PSE group was significantly higher than those in the TACE alone group at 1 week (2.23 ± 1.65 vs 0.88 ± 1.74 × 10^9/L), 2 months (0.17 ± 0.90 vs −0.67 ± 1.43 × 10^9/L) and 24 months (1.23 ± 0.93 vs −0.19 ± 1.06× 10^9/L).

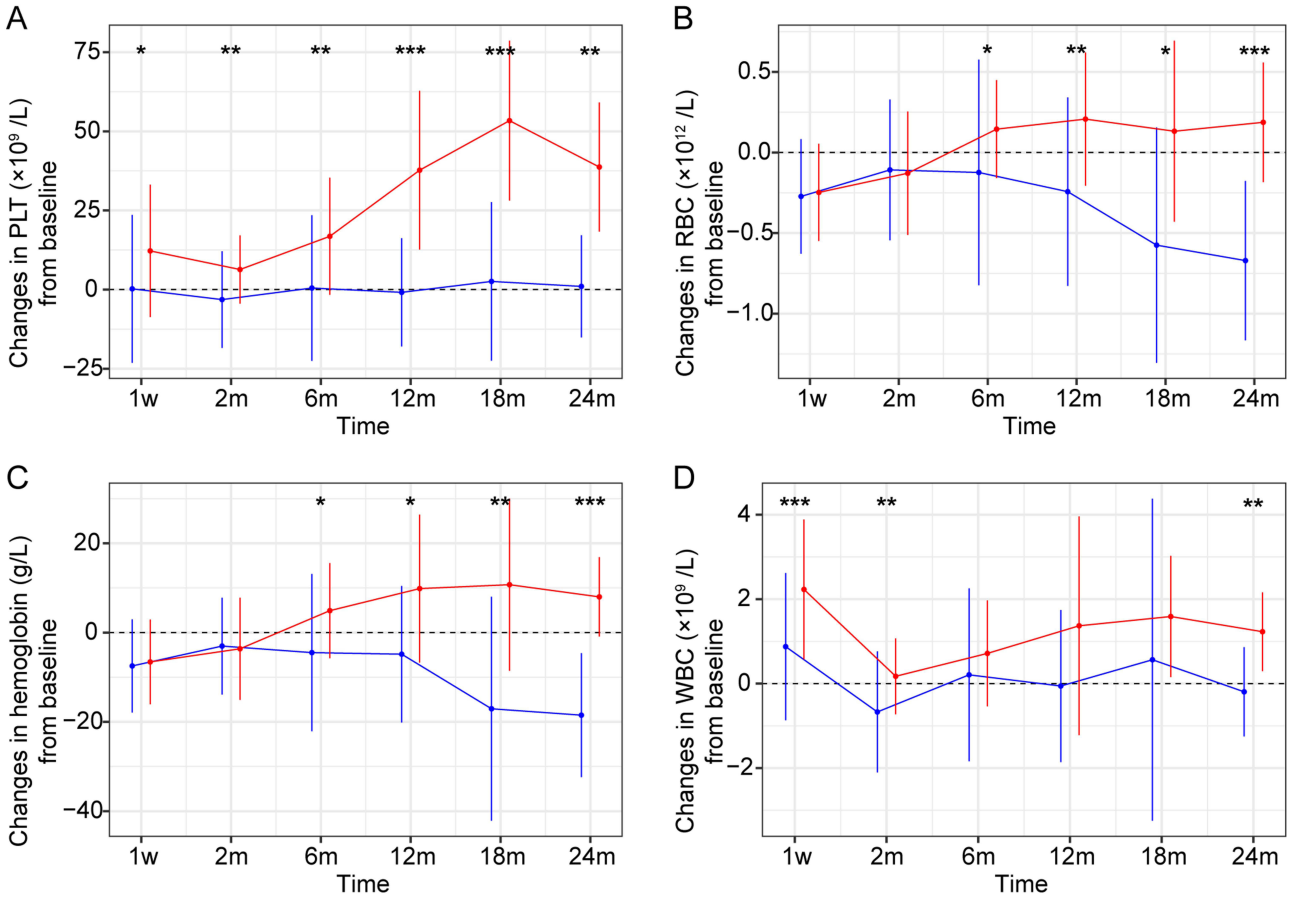

Figure 2 Changes in peripheral blood cell counts in two groups during the follow-up period. (**A**) Changes in PLT (platelet) from baseline; (**B**) Changes in RBC (red blood cell) from baseline; (**C**) Changes in hemoglobin from baseline; (**D**) Changes in WBC (white blood cell) from baseline. The blue points and lines indicate TACE alone group, and the red points and lines indicate TACE+PSE group. Data are presented as means ± standard deviations. *P < 0.05; **P < 0.01; ***P < 0.001.

The results of comparison between initial and repeated PSE of the effect on changes in peripheral blood cell counts are shown in Table 3. Repeated PSE was more effective in increasing PLT at 2–3 months after procedure than initial PSE (23.33 ± 30.42 vs 6.33 ± 10.75 × 10^9/L, $P = 0.001$). It was also more effective in maintaining RBC and hemoglobin, along with increasing WBC.

Changes in Hepatic Function

Changes in hepatic function in two groups during the follow-up period are shown in Table 4 and Figure 3. The detailed data are shown in Supplementary Table 2. Child-Pugh score worsened at 1 week after initial TACE+PSE, then gradually improved to better than baseline at 6 months, and maintained to 24 months. In the TACE alone group, Child-Pugh score similarly worsened at 1 week after initial TACE. Despite temporary improvement, it deteriorated again. Throughout the entire follow-up period, it did not return to the baseline. The changes in Child-Pugh score from baseline were significantly different at 12 months (−0.43 ± 1.50 in the TACE+PSE group vs 0.96 ± 1.87 in the TACE alone group, $P = 0.019$) and 18 months (−0.40 ± 1.43 in the TACE+PSE group vs 1.67 ± 1.61 in the TACE alone group, $P = 0.005$). The differences of changes in total bilirubin from baseline between two groups approached significantly at 24 months ($P = 0.067$), and the differences of changes in albumin between two groups approached significantly at 18 months ($P = 0.076$) and 24 months ($P = 0.066$). There were no statistically significant differences between the two groups in the changes of ALT and AST from baseline.

The results of comparison between initial and repeated PSE of the effect on changes in hepatic function are shown in Table 3. The deterioration in albumin (−1.24 ± 3.75 vs −3.35 ± 3.67 g/L, $P = 0.023$) and Child-Pugh score (0.10 ± 0.77 vs 0.79 ± 1.29, $P = 0.015$) was slighter at 1 week after repeated PSE than that after initial PSE. Furthermore, the hepatic function was improved to better than pre-procedure at 2–3 months after repeated PSE, whereas it remained worse than pre-procedure at 2–3 months after initial PSE. There were significant differences between initial and repeated PSE in changes in albumin (−2.10 ± 4.59 vs 1.23 ± 2.28, $P = 0.002$) and Child-Pugh score (0.31 ± 1.46 vs −0.37 ± 0.94, $P = 0.045$) at 2–3 months after procedures.

Tumor Response After Initial Treatments

In the TACE+PSE group, the tumor responses at 2 months after initial treatments consisted CR in 7 patients (24.1%), PR in 14 patients (48.3%), SD in 5 patients (17.2%) and PD in 3 patients (10.3%). In the TACE alone group, it consisted CR in 15 patients (20.5%), PR in 29 patients (39.7%), SD in 16 patients (21.9%) and PD in 13 patients (17.8%). There were

Table 3 Comparison Between Initial and Repeated PSE of the Changes in Peripheral Blood Cell Counts and Hepatic Function in 1 Week and 2–3 Months

Variables	Changes in 1 Week		Changes in 2–3 Months		P_1	P_2
	Initial PSE	Repeated PSE	Initial PSE	Repeated PSE		
PLT, × 10^9/L	12.21 ± 20.91	21.96 ± 36.01	6.33 ± 10.75	23.33 ± 30.42	0.145	0.001
RBC, × 10^{12}/L	−0.25 ± 0.30	−0.08 ± 0.29	−0.13 ± 0.38	0.15 ± 0.36	0.021	0.004
Hemoglobin, g/L	−6.57 ± 9.48	−2.37 ± 8.28	−3.63 ± 11.43	5.00 ± 11.65	0.058	0.003
WBC, × 10^9/L	2.23 ± 1.65	3.55 ± 3.63	0.17 ± 0.90	0.71 ± 1.29	0.036	0.046
Total bilirubin, μmol/L	6.33 ± 21.12	1.61 ± 11.32	−2.57 ± 12.58	1.03 ± 12.55	0.287	0.275
Albumin, g/L	−3.35 ± 3.67	−1.24 ± 3.75	−2.10 ± 4.59	1.23 ± 2.28	0.023	0.002
Child-Pugh score	0.79 ± 1.29	0.10 ± 0.77	0.31 ± 1.46	−0.37 ± 0.94	0.015	0.045
Log ALT, U/L	0.20 ± 0.69	−0.10 ± 0.77	−0.01 ± 0.55	−0.08 ± 0.44	0.100	0.601
Log AST, U/L	0.09 ± 0.49	−0.07 ± 0.58	0.07 ± 0.55	−0.07 ± 0.45	0.224	0.296

Notes: Data are presented as means ± standard deviations. *P1*: Comparison of the changes in peripheral blood cell counts and hepatic function in 1 week after initial and repeated PSE. *P2*: Comparison of the changes in peripheral blood cell counts and hepatic function in 2–3 months after initial and repeated PSE.

Abbreviations: PSE, partial splenic embolization; PLT, platelet; RBC, red blood cell; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 4 Comparison of the Changes in Hepatic Function from Baseline Between the TACE Alone Group and the TACE+PSE Group

Variables	Time Point	TACE Alone Group	TACE+PSE Group	*P*
Child-Pugh score	1 week	0.63 ± 0.80	0.79 ± 1.29	0.568
	2 months	0.38 ± 1.38	0.31 ± 1.46	0.831
	6 months	0.31 ± 1.55	−0.09 ± 1.27	0.294
	12 months	0.96 ± 1.87	−0.43 ± 1.50	0.019
	18 months	1.67 ± 1.61	−0.40 ± 1.43	0.005
	24 months	1.33 ± 1.67	−0.14 ± 1.57	0.075
Total bilirubin, μmol/L	24 months	9.83 ± 18.06	−4.10 ± 12.76	0.067
Albumin, g/L	18 months	−4.43 ± 3.05	0.13 ± 6.88	0.076
	24 months	−3.58 ± 4.55	1.37 ± 5.38	0.066

Notes: Data are presented as means ± standard deviations.
Abbreviations: TACE, transarterial chemoembolization; PSE, partial splenic embolization.

no significant differences in ORR (72.4% vs 60.3%, $P = 0.357$) and DCR (89.7% vs 82.2%, $P = 0.527$) between the TACE+PSE and the TACE alone group.

TACE Sessions, PFS and Prognostic Factors

The mean number of TACE procedures per patient was 4.55 sessions in the TACE+PSE group and 3.26 sessions in the TACE alone group, with a significant difference between the two groups ($P = 0.019$). As shown in Figure 4, in more detail, the mean number of TACE procedures per patient in the TACE+PSE group was significantly higher than those in the TACE alone group during 6–12 months (0.79 vs 0.56, $P = 0.031$), 12–18 months (0.72 vs 0.36, $P = 0.040$), and 18–24 months (0.55 vs 0.22, $P = 0.005$).

Patients in the TACE+PSE group had a median PFS of 19.4 months (95% CI, 9.6–31.3), compared with 9.5 months (95% CI, 7.3–11.6) for those in the TACE alone group ($P = 0.023$) (Figure 5). The 12-month, 24-month, 36-month PFS rate for the TACE+PSE group and the TACE alone group were 65.4% vs 35.1%, 45.9% vs 14.9%, and 17.2% vs 5.6%,

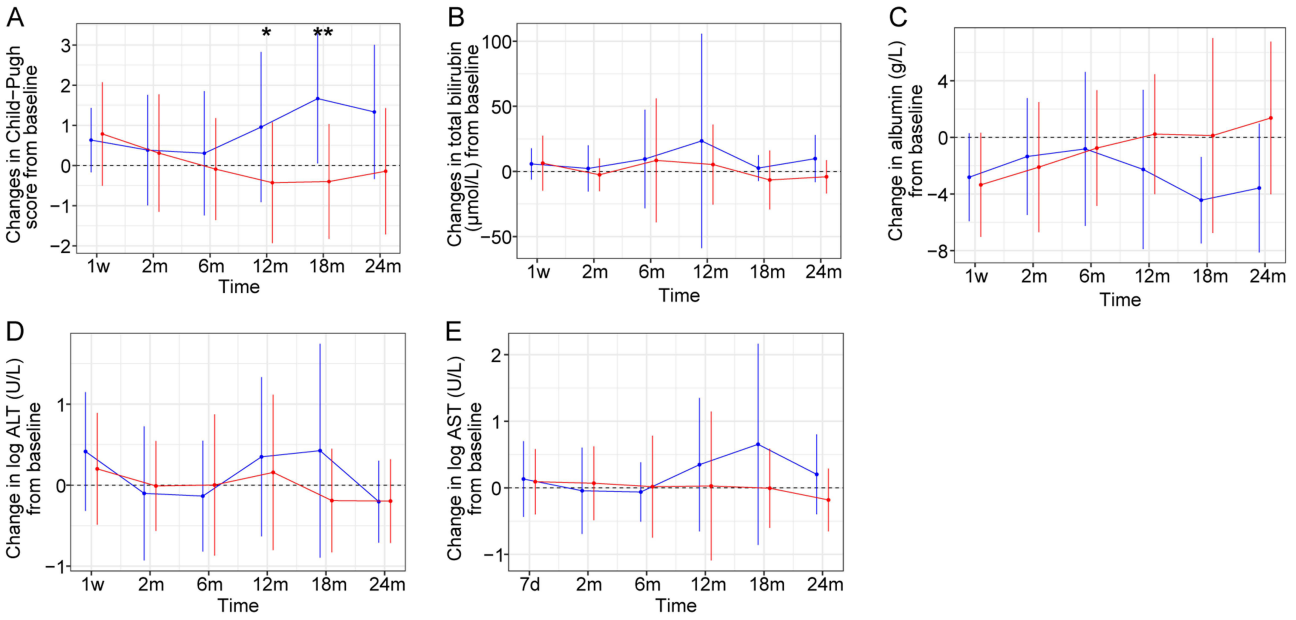

Figure 3 Changes in hepatic function in two groups during the follow-up period. (**A**) Changes in Child-Pugh score from baseline; (**B**) Changes in total bilirubin from baseline; (**C**) Changes in albumin from baseline; (**D**) Changes in log ALT (alanine aminotransferase) from baseline; (**E**) Changes in log AST (aspartate aminotransferase) from baseline. The blue points and lines indicate TACE alone group, and the red points and lines indicate TACE+PSE group. Data are presented as means ± standard deviations. *$P < 0.05$; **$P < 0.01$.

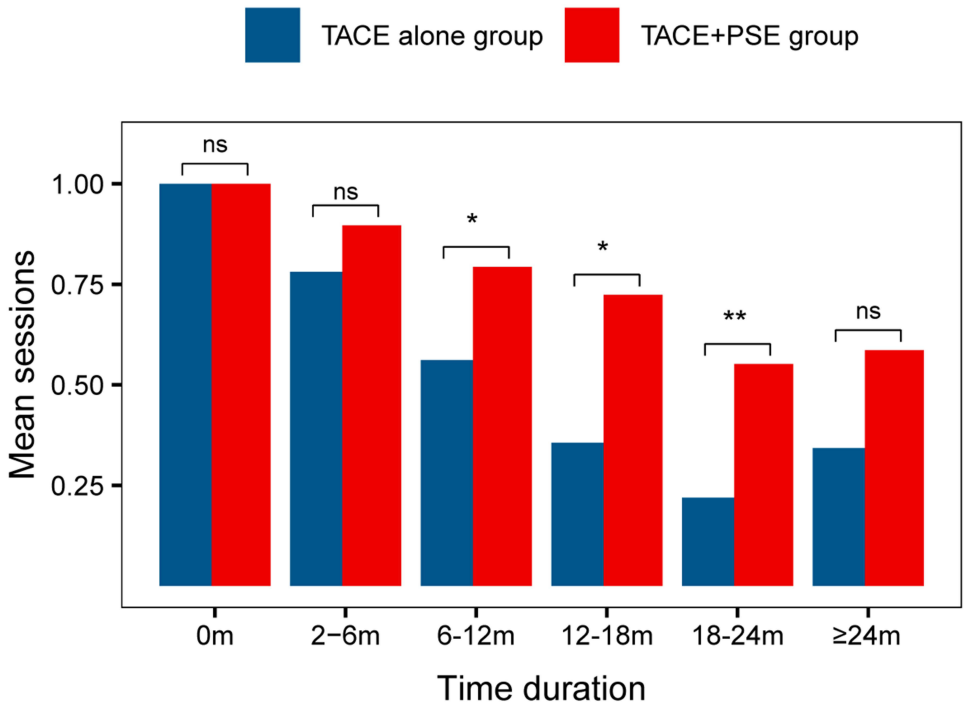

Figure 4 Mean number of TACE procedure sessions per patient during the follow-up period. *P < 0.05; **P < 0.01; ns: no significance.

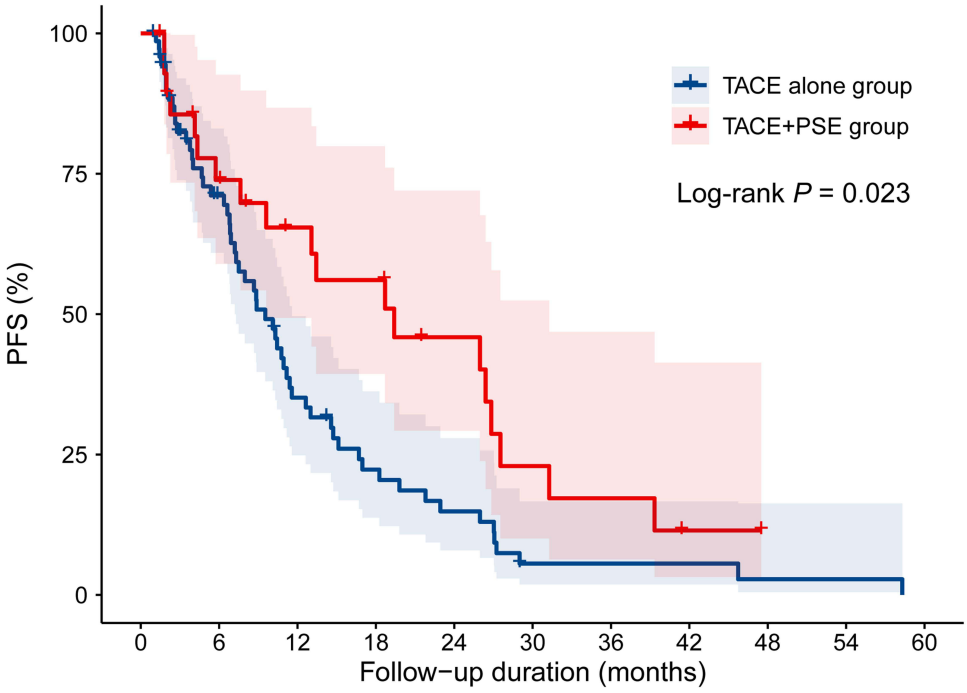

Figure 5 Kaplan–Meier curves of the progression-free survival times.

respectively. Tumor number, tumor location, tumor size, and TACE alone/TACE+PSE were selected as potential factors affecting PFS in the univariate analysis (Table 5). Multivariate analysis identified that PSE (HR, 0.508; 95% CI, 0.296–0.872; P = 0.014) was an independent protective factor for PFS, and tumor size >3 cm (HR, 2.006; 95% CI, 1.168–3.446; P = 0.012) was an independent risk factor for PFS.

Table 5 Univariate and Multivariate Analysis on Baseline Factors Associated with Progression-Free Survival

Variables	Category	Univariate		Multivariate[a]	
		P	HR	95% CI	*P*
Gender	Male	Reference			
	Female	0.262			
Age, years	≤60	Reference			
	>60	0.322			
Etiology	HBV	Reference			
	HCV	0.123			
	NBNC	0.696			
PLT		0.051			
RBC		0.694			
Hemoglobin		0.143			
WBC		0.204			
Total bilirubin		0.527			
Albumin		0.781			
Child-Pugh score		0.718			
Child-Pugh class	A	Reference			
	B	0.416			
ALT		0.179			
AST		0.224			
Tumor number	Solitary	Reference			
	Multiple	<0.001	1.370	0.758–2.475	0.297
Tumor location	Left lobe	Reference			
	Right lobe	0.393	1.288	0.590–2.813	0.526
	Both lobe	0.016	2.064	0.801–5.319	0.133
Tumor size, cm	≤3	Reference			
	>3	< 0.001	2.006	1.168–3.446	0.012
BCLC stage	0	Reference			
	A	0.155			
	B	0.077			
	C	0.107			
TACE method	C-TACE	Reference			
	DEB-TACE	0.269			
Group	TACE alone	Reference			
	TACE+PSE	0.025	0.508	0.296–0.872	0.014
Other treatments	Without	Reference			
	With	0.122			

Notes: [a]Multivariate analysis included potential factors that showed an association ($P < 0.05$) with progression-free survival according to univariate analysis.

Abbreviations: HR, hazard ratio; CI, confidence interval; TACE, transarterial chemoembolization; PSE, partial splenic embolization; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-B, non-C hepatitis; PLT, platelet; RBC, red blood cell; WBC, white blood cell; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCLC, Barcelona Clinic Liver Cancer; C-TACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead transarterial chemoembolization.

Adverse Events

We first investigated the complications after initial TACE alone and TACE+ PSE procedures (Table 6). Post-embolization syndrome was the most common complication after both procedures. The incidence of fever, pain, abdominal distention, nausea and vomiting was 41.4%, 72.4%, 51.7%, 37.9%, respectively, after initial TACE+PSE, compared with 34.2%, 56.2%, 24.7%, 23.3%, respectively, after initial TACE alone. There was statistically significant difference in the incidence of abdominal distention ($P = 0.011$). Portal vein thrombosis occurred in two patients after initial TACE

Table 6 Comparison of the Incidence of Complications After Initial TACE Alone Procedures, Initial TACE+PSE Procedures and Repeated TACE+PSE Procedures

Complications	Initial TACE Alone Procedures (n = 73)	Initial TACE+PSE Procedures (n = 29)	Repeated TACE+PSE Procedures (n = 51)	P_1	P_2
Fever	25 (34.2)	12 (41.4)	21 (41.2)	0.504	1.000
Pain	41 (56.2)	21 (72.4)	35 (68.6)	0.178	0.803
Abdominal distention	18 (24.7)	15 (51.7)	23 (45.1)	0.011	0.644
Nausea and vomiting	17 (23.3)	11 (37.9)	18 (35.3)	0.148	0.814
Portal vein thrombosis	0 (0.0)	2 (6.9)	1 (2.0)	0.079	0.296
Splenic vein thrombosis	0 (0.0)	0 (0.0)	1 (2.0)	1.000	1.000
Refractory ascites	1 (1.4)	0 (0.0)	0 (0.0)	1.000	1.000
Bacterial peritonitis	2 (2.7)	0 (0.0)	0 (0.0)	1.000	1.000
Large amount of pleural effusion	1 (1.4)	0 (0.0)	1 (2.0)	1.000	1.000
Gastrointestinal bleeding	1 (1.4)	1 (3.4)	2 (3.9)	0.490	1.000
Major complications	5 (6.8)	1 (3.4)	3 (5.9)	0.672	1.000
Death	1 (1.4)	0 (0.0)	1 (2.0)	1.000	1.000

Notes: Data are presented as numbers (%). P_1: Comparison of the incidence of complications after initial TACE alone procedures and initial TACE+PSE procedures. P_2: Comparison of the incidence of complications after initial TACE+PSE procedures and repeated TACE+PSE procedures.
Abbreviations: TACE, transarterial chemoembolization; PSE, partial splenic embolization.

+PSE and none after initial TACE alone. However, the thrombosis in two cases was asymptomatic, without the occurrence of ascites, and not considered as major complication. Five major complications were observed in 73 patients after initial TACE alone procedures, including one case of refractory ascites, two cases of bacterial peritonitis, one case of large amount of pleural effusion, and one case of gastrointestinal bleeding. By contrast, there was one case of major complication in 29 patients after initial TACE+PSE procedures, which was gastrointestinal bleeding. No statistically significant differences were found in the incidence of any major complications or overall. One patient died due to bacterial peritonitis after initial TACE alone.

With further analysis of the incidence of complications after initial and repeated TACE+PSE procedures, no statistically significant differences were detected (Table 6). After 51 repeated TACE+PSE procedures, there were, respectively, 41.2%, 68.6%, 45.1%, 35.3% of cases experienced fever, pain, abdominal distention, nausea and vomiting. Three major complications were observed, including one case of large amount of pleural effusion and two cases of gastrointestinal bleeding. Gastrointestinal bleeding in one patient led to death.

Discussion

In this study, we retrospectively evaluated the efficacy and safety of TACE combined with repeated PSE for HCC patients with hypersplenism and thrombocytopenia. We found that repeated PSE could increase the PLT again, maintain the RBC and hemoglobin and improve the hepatic function, without significant difference in the incidence of complications compared to initial PSE. In addition, our results suggested that TACE combined with repeated PSE prolonged the PFS.

PSE is an effective treatment for thrombocytopenia due to hypersplenism, with fewer complications than splenectomy.[7] Several studies have reported the success of TACE combined with concurrent PSE for the treatment of HCC patients with hypersplenism and thrombocytopenia.[12–18] The embolization ratio of PSE remains to be an important concern, since it is not only associated with the increase of PLT but also the risk of major complications. With evaluation of adverse events reported in thirty articles, Abhinav Talwar et al recommend not higher than 70% as relatively safe embolization ratio.[9] On the other hand, accurate estimation of the embolization ratio is difficult during the procedure at present. Despite the lack of consensus in the literature, we performed PSE with conservative embolization ratio for HCC patients who received simultaneous TACE. Some patients were lack of response to initial PSE, leading to the need for repeated PSE. However, we found no study about the efficacy and safety of TACE combined with repeated PSE.

The primary purpose of PSE was to elevate the PLT count when performed in combination with TACE for HCC patients. In our study, the increment of PLT at 1 week after initial TACE+PSE treatment was limited (12.21 ± 20.91 ×

10^9/L) and decreased to 6.33 ± 10.75 × 10^9/L at 2 months. The reasons may be the low pre-procedural PLT count and the cautious embolization ratio of initial PSE.[11] The median splenic infarction ratio of initial PSE was 28.6% in this study. Hence, we decided to conduct repeated PSE for these patients. We found that repeated PSE increased the PLT again and maintained it until 24 months, ensuring the feasibility of repeated TACE and other antitumor therapies. Notably, we also observed that there were no differences between two groups in the changes in RBC and hemoglobin from baseline at 1 week and 2 months after initial TACE+PSE, but significant differences after repeated PSE. Repeated PSE showed more effectiveness in increasing PLT, maintaining RBC and hemoglobin, as well as increasing WBC than initial PSE.

The effect of PSE in improving liver function was widely reported in early studies including non-HCC patients. According to Toru Ishikawa's investigation, this effect remained positive within a follow-up of six months when PSE was combined with TACE for HCC patients.[14] However, in a long-term follow-up study, the difference in Child-Pugh score between patients received TACE+PSE and TACE alone disappeared after six months.[15] In our results, the difference was not observed within six months after initial treatment, but became significant at 12 and 18 months, indicating that repeated PSE contributed to longer-term improvement of liver function. The comparison between initial and repeated PSE also showed the effect of repeated PSE to reverse deterioration of liver function after procedures.

Few studies focused on the effect of TACE combined with PSE in patient survival, and the results were controversial. One retrospective study from Korea, with a median follow-up period of 42.5 months, showed no better overall survival of TACE combined with PSE compared to TACE alone.[15] This study included a relatively small number of enrolled patients, and 36.7% of them were lost to follow-up. By contrast, another prospective study from China suggested that TACE combined with PSE could improve the median overall survival of HCC patients with hypersplenism.[18] In addition, the other retrospective study from China indicated that although no significant difference in overall survival, patients received TACE combined with PSE had longer PFS compared to those received TACE alone.[17] Our results demonstrated that TACE combined with repeated PSE could prolong the PFS significantly. The possible reasons were as follows. Firstly, the improvement of PLT and hepatic function resulting from repeated PSE contributed to perform serial TACE during the follow-up period. In this study, the mean number of TACE procedures was significantly higher in the TACE +PSE group during 6–12 months, 12–18 months and 18–24 months. Secondly, the immunity changes after PSE may enhance the antitumor effect. Yasushi Matsukiyo et al preliminarily found that the Th1 cells were significantly elevated at 4 weeks after PSE, whereas no significant changes of Treg cells.[21] The promotion of Th1 cells increases, and Th1/Treg balance has been demonstrated to be beneficial in countering tumor progression.[22,23] It should be noted that we did not observe significantly better ORR and DCR in the TACE+PSE group after initial treatments but longer PFS. This may be because the immunity activation after PSE took time and played a role in subsequent TACE and other treatments. Additionally, repeated PSE may contribute to the duration of the improvement of host immunity. Further studies are warranted to validate our results and investigate underlying mechanism.

With regard to safety, our results showed that concurrent PSE did not increase the incidence of complications except for abdominal distention as patients received initial TACE. This finding was consistent with previous evidence. As for major complications, only one patient (3.4%) experienced gastrointestinal bleeding after initial TACE+PSE. The median embolization ratio of initial PSE was 28.6% in our study, which could be attributed to this good outcome. In another published prospective study, the researchers set not higher than 50% of spleen volume as target embolization ratio and reported similar low major complication rate.[18] Furthermore, we also found no significant difference in the incidence of complications between repeated TACE+PSE and initial TACE+PSE.

There were two limitations in the current study. First, this was a single-center and retrospective study with small sample size. Second, the main cause of cirrhosis of included patients was hepatitis B virus. Despite such limitations, this research provides some reference for the management of patients with unsatisfactory PLT count after receiving initial TACE+PSE treatment. Our results showed that repeated PSE for these patients was effective in increasing PLT again, maintaining RBC and hemoglobin and improving liver function. It contributed to performing serial TACE procedures thereafter during the follow-up period. The PFS of these patients was significantly prolonged compared to those who received TACE alone, where PSE was an independent protective factor for PFS. Meanwhile, there was no difference in safety between repeated PSE and initial PSE.

Abbreviations

HCC, hepatocellular carcinoma; PSE, partial splenic embolization; PLT, platelet; TACE, transarterial chemoembolization; PFS, progression-free survival; BCLC, Barcelona Clinic Liver Cancer; TACE+PSE, transarterial chemoembolization combined with concurrent partial splenic embolization; C-TACE, conventional transarterial chemoembolization; DEB-TACE, drug-eluting bead transarterial chemoembolization; ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell; RBC, red blood cell; HBV, hepatitis B virus; HCV, hepatitis C virus; NBNC, non-B, non-C hepatitis; HR, hazard ratio; CI, confidence interval.

Data Sharing Statement

The data are available from the corresponding author upon reasonable request.

Ethical Statements

This study was approved by the ethics committee of Tongji Medical College, Huazhong University of Science and Technology, and the requirement for informed consent was waived due to its retrospective nature. The study was performed according to the principles of the Declaration of Helsinki and the confidentiality of patient data was ensured.

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Disclosure

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