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Clinical efficacy of TACE using coil or gelatin sponge combined with targeted therapy in the treatment of giant hepatocellular carcinoma with arterioportal fistulas

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Abstract

Background The present study aimed to evaluate the effectiveness of spring coils or gelatin sponges for the embolization of giant hepatocellular carcinoma (HCC) with a hepatic arterioportal shunt (APS) in targeted therapy.

Methods A total of 81 patients with a large HCC complicated with APS were divided into two groups on the basis of the use of block-APS embolic agents: the coil group and the gelatin sponge group. Both groups received lipiodol transarterial chemoembolization (TACE) after APS was correspondingly blocked with a coil or gelatin sponge. Sorafenib or lenvatinib was administered 3–5 days before TACE.

Results Both groups showed improvement in the incidence of fistula one month after the first TACE session and the last TACE session compared with before treatment. In addition, the improvement in the incidence of fistulas in the coil group was greater than that in the gelatin sponge group [$p=0.003$], whereas the compensation of extrahepatic blood vessels was more severe in the coil group. There was no significant difference in median overall survival (OS) (11.13 months, 95% CI 7.67–14.59 months vs. 15.13 months, 95% CI 10.18–20.09 months, $p=0.303$) or progression-free survival (PFS) (5.37 months, 95% CI 5.04–5.70 months vs. 5.7 months, 95% CI 0.66–10.74 months, $p=0.376$) between the two groups. However, both groups showed early progression of intrahepatic lesions.

Conclusions Spring coil or gelatin sponge embolization combined with APS was used for giant HCC patients, which significantly improved the incidence of fistulas.

Keywords Arterioportal shunt, Transarterial chemoembolization, Hepatocellular carcinoma, Coil, Gelatin sponge

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Table 1 Cheng's classification of HCC with portal vein tumor thrombus

Type	Definition
I	tumor thrombus that involves segmental or sectoral branches of the portal vein or above
II	tumor thrombus that involves the right/left portal vein
III	tumor thrombus that involves the main portal vein
IV	tumor thrombus that involves the superior mesenteric vein

Background

Hepatocellular carcinoma (HCC) has a high incidence rate, and most patients have a delayed diagnosis. A total of 8.2% of HCC patients have giant tumors, 44–62.2% are complicated with portal vein tumor thrombus, about 47–63% are complicated with arteriovenous fistula [1–3], and 11.7% receive arteriovenous shunts during treatment [4]. Giant HCC tumors cannot be excised by surgery and may have a high postoperative recurrence rate [5]. The treatment of HCC combined with cancer thrombi and arteriovenous fistulas is complex and includes the loss of terminal embolic agents, the exacerbation of liver injury, etc., and the prognosis is worse than that of HCC alone. TACE is the primary treatment method for giant liver cancer combined with arteriovenous fistula; however, previous studies have shown low occlusion efficiency and a high reperfusion rate with this approach [3]. Targeting has been widely used in recent years, and the combination of targeting and TACE has significant survival benefits [6]. Nonetheless, this combination therapy for giant HCC with hepatic artery portal vein fistula has yet to be evaluated. Thus, the present study aimed to assess whether a targeted combination with TACE was effective and safe for giant liver cancer patients with arteriovenous fistulas.

Materials and methods

A total of 81/428 patients with liver cancer with TACE treated at the Interventional Department of Shandong Cancer Hospital from July 1, 2015, to December 31, 2022, were eligible for this study. The inclusion criteria were as follows: clinical or pathological diagnosis of liver cancer; main tumor diameter > 10 cm; concomitant hepatic artery portal vein fistula; TACE as the first local treatment; combination targeted therapy; and merging type 2 with portal vein cancer thrombus. The classification method is summarized in Table 1 [7]. The exclusion criteria were as follows: previous treatment received; Child-Pugh classification C grade; cancer thrombus in the main portal vein without effective compensation; Eastern Cooperative Oncology Group (ECOG) performance status score ≥ 2 points; incomplete data; and lack of standardized follow-up. Figure 1 displays the flowchart of the study cohort.

Diagnosis and grading of APS

APS was diagnosed based on either of two parameters: (i) premature enhancement or potent opacification of the main portal trunk and/or the first-order branches relative to the superior splenic or mesenteric vein or (ii) premature enhancement or potent opacification of

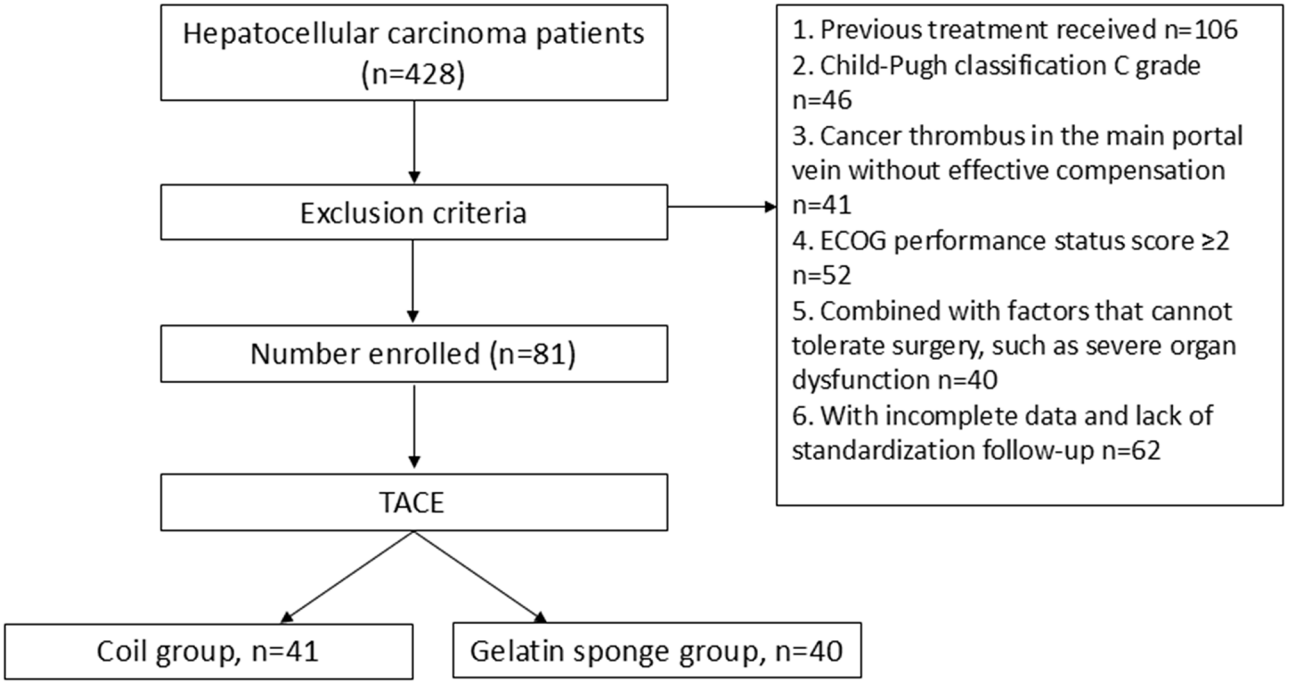

Fig. 1 Flowchart of the study cohort

second-order and small branches of portal veins relative to the main portal trunk.

The A-P shunts were classified into four grades. Specifically, atypical A-P shunts were Grade 0, whereas typical A-P shunts were Grade 1–3 according to the severity of APS (Table 2) [8].

Treatments

Treatment with TACE

First, hepatic common arteriography was conducted to visualize hepatic arterial vascularization and the intratumoral blood supply, especially to identify the APS position and the severity of APS. Second, a 2.7 French (Fr) microcatheter was inserted into the dominant artery of the APS fistula via the 5 Fr catheter. Then, the APS was occluded through embolic material injection.

Gelatin sponge particles (1 mm×1 mm×1 mm) were added to the contrast media in the gelatin sponge group. This mixture was injected via a 2-mL tuberculin syringe assisted by a fluoroscope until APS stasis or slow flow was reached. APS occlusion was confirmed by arteriography. In the spring coil group, the appropriate spring coil was selected on the basis of the vessel diameter and fistula size; it was pushed to the target position under the guidewire under fluoroscopic monitoring. Then, APS occlusion was verified by arteriography.

Following APS embolization, the tumor was subjected to routine intervention. An epirubicin/lipiodol emulsion < 20 mL and a small volume of gelatin sponge particles were injected via the catheter inserted in the tumor-feeding artery.

When TACE was repeated after one month, the APS condition was reevaluated by digital subtraction angiography (DSA) imaging, and the corresponding embolization treatment was selected on the basis of the fistula condition. Then, TACE treatments were performed on the basis of the activity of the intrahepatic lesions, and the fistula condition on DSA imaging was recorded during the final TACE.

Targeted therapy

Sorafenib (400 mg twice/day) or lenvatinib (≥ 60 kg, 12 mg; <60 kg, 8 mg/day) was administered in combination with or without 200 mg anti-programmed death 1 (PD-1) antibiotics 3–5 days before TACE treatment. If the tumor progressed after first-line treatment, the target drug was replaced with regorafenib (80–160 mg regorafenib once/day within 1–3 weeks every 4-week cycle) combined with or without PD-1 inhibitors.

Follow-up

Enhanced upper abdominal computed tomography (CT), chest CT, hepatic function, and alpha-fetoprotein levels were analyzed 4–6 weeks after the initial TACE treatment. In addition, brain CT examinations were also performed at three months, whereas whole-body bone scans were conducted at six months until death to evaluate metastasis. All the tumor lesions and portal vein tumor thrombi (PVTT) were assessed one month post-treatment via the modified Response Evaluation Criteria in Solid Tumors (mRECIST).

Study endpoints

The time point at which anti-tumor treatment began represented the start time, whereas patient death was deemed the endpoint for recording overall survival (OS). Progression-free survival (PFS) was defined as the duration from the start time to the date of intrahepatic progression, tumor thrombus progression, and extrahepatic progression; the shortest duration was deemed total PFS. All patients were followed up for ≥ 10 months following the initial TACE treatment. Our primary and secondary endpoints were OS and PFS, respectively.

Statistical analysis

To analyze baseline characteristics, categorical variables are presented as frequencies and percentages (n [%]), and continuous variables are presented as the means and standard deviations. The chi-square test was used to compare categorical variables. Survival was estimated by the Kaplan-Meier method, and any differences in survival were evaluated using a stratified log-rank test. Logistic regression analysis was used to screen for risk factors that may affect improvement in fistulas. A p-value lower than 0.05 was considered statistically significant. All the statistical analyses were performed with SPSS v23.0 for Windows (IBM, Chicago, USA).

Table 2 Grading of the A-P shunt

Grade	Definition
0	A-P shunt not seen on hepatic arterial angiography
1	Opacification of the second-order and smaller branches of portal veins at late-hepatic arterial phase, with transient wedge- or patchy-shaped enhancement in the periphery of HCC foci
2	Opacification of main portal trunk and/or first-order branches, accompanied by middle or late enhancement of HCC foci at late-hepatic arterial phase
3	Opacification of main portal trunk and/or first-order branches, accompanied by enhancement of hepatic artery and the branches at early-hepatic arterial phase, with premature or no enhancement of HCC foci

This study was approved by the Ethics Committee of Shandong Cancer Hospital and Institute, Shandong First Medical University, and Shandong Academy of Medical Sciences. All the participating patients signed informed consent before TACE treatment.

Results

Baseline characteristics

The present study included 41 patients in the coil group, who received 6.024 ± 3.630 TACEs, and 40 patients in the gelatin sponge groups, who received 5.925 ± 2.615 TACEs. Subsequently, 35 (85.4%) and 33 (82.5%) deaths were reported in the coil and gelatin sponge groups, respectively. The cohort primarily consisted of males [the coil group, 39 (95.1%); the gelatin sponge group, 36 (90.0%)] and middle-aged individuals < 60 years old [the coil group, 30 (73.2%); the gelatin sponge group, 30 (75.0%)]; this phenomenon may be associated with Chinese patients who also present hepatitis B cirrhosis. Viral hepatitis B was the main factor leading to chronic liver disease [coil group, 36 (87.8%); gelatin sponge group, 37 (92.5%)], with the majority of patients having cirrhosis diagnosed by imaging [coil group, 32 (78.0%); gelatin sponge group, 23 (57.5%)] and having Child-Pugh classification A [coil group, 37 (90.2%); gelatin sponge group, 36 (90.0%)]. Additionally, the majority of the cases had an AFP concentration > 400 ng/mL [the coil group, 28 (68.3%); the gelatin sponge group, 25 (62.5%)]. The giant lumps were often located in the right lobe [the coil group, 32 (78.0%); the gelatin sponge group, 28 (70.0%)]. Most cases had hepatic vein invasion [the coil group, 25 (61.0%); the gelatin sponge group, 31 (77.5%)], without extrahepatic metastasis [the coil group, 29 (70.7%); the gelatin sponge group, 28 (70.0%)]. However, a few patients had hepatic venous fistulas [the coil group, 12 (29.3%); the gelatin sponge group, 14 (35.0%)]. The classification of portal vein thrombosis was mainly type 2, followed by types 3 and 4. In most cases, combination immunotherapy was used [coil group, 29 (70.7%); gelatin sponge group, 31 (80%)]. Table 3 displays the baseline features of the patients.

Table 3 Baseline features of the patients

	Coil	Gelatin sponge	*P*
Count	41(50.6%)	40(49.4%)	
Gender			
Male	39(95.1%)	36(90%)	0.432
Female	2(4.9%)	4(10%)	
Age (years)			
>60	11(26.8%)	10(25.0%)	0.851
< 60	30(73.2%)	30(75.0%)	
AFP (ng/mL)			
>400 ng/mL	28(68.3%)	25(62.5%)	0.584
< 400 ng/mL	13(31.7%)	15(37.5%)	
Hepatitis	36(87.8%)	37(92.5%)	0.479
Child-Pugh classification A	37(90.2%)	36(90.0%)	1.000
B	4(9.8%)	4(10.0%)	
Liver cirrhosis	32(78.0%)	23(57.5%)	0.048
Extrahepatic metastasis	12(29.3%)	12(30.0%)	0.943
Pseudocapsule	23(56.1%)	13(32.5%)	0.033
Location			
Right lobe	32(78.0%)	28(70.0%)	0.409
Left lobe	9(22.0%)	12(30.0%)	
Grading of PVTT			
2	21(51.2%)	20(50.0%)	0.994
3	17(41.5%)	17(42.5%)	
4	3(7.3%)	3(7.5%)	
Invasion of hepatic vein	25(61.0%)	31(77.5%)	0.107
Arteriovenous fistula	12(29.3%)	14(35.0%)	0.581
	29(70.7%)	26(65.0%)	
immunotherapy	29(70.7%)	31(80%)	0.366
TACE	6.024 ±3.630	5.925 ±2.615	0.653
Survival status			
Dead	35(85.4%)	33(82.5%)	0.725
survival	6(14.6%)	7(17.5%)	

Note: BCLC: Barcelona Clinic Liver Cancer; AVS: arteriovenous shunting; PVTT: portal vein tumor thrombus; AFP: alpha-fetoprotein; $p < 0.05$ indicates statistical significance

Survival analysis and associated prognostic factors

Among the patients included in this study, 35 (85.4%) deaths were reported in the coil group, and 33 (82.5%) were reported in the gelatin sponge group. The median OS and PFS were 12.07 months (95% CI 7.90–16.23 months) and 5.43 months (95% CI 3.51–7.36 months), respectively, but these values differed significantly between the two treatment methods. Compared with the coil group, the gelatin sponge group had increased median OS (11.13 months, 95% CI 7.67–14.59 months vs. 15.13 months, 95% CI 10.18–20.09 months, $p = 0.303$) and PFS (5.37 months, 95% CI 5.04–5.70 months vs. 5.7 months, 95% CI 0.66–10.74 months, $p = 0.376$). Both groups exhibited early progression of intrahepatic lesions; however, no significant differences were detected in the intrahepatic, thrombus, or extrahepatic progression time or OS between the two groups. The detailed data are presented in Fig. 2; Table 4.

APS condition

Compared with those before treatment, the two groups treated with TACE combined with targeted therapy presented improvements in the incidence of fistulas one month after the first and last TACE procedures. In addition, the fistulae improved significantly after multiple TACEs compared with one month after the first TACE, indicating that multiple embolizations and long-term anti-vascular treatment can further alleviate fistulas. Compared with the gelatin sponge group, the coil group exhibited markedly greater improvement in the

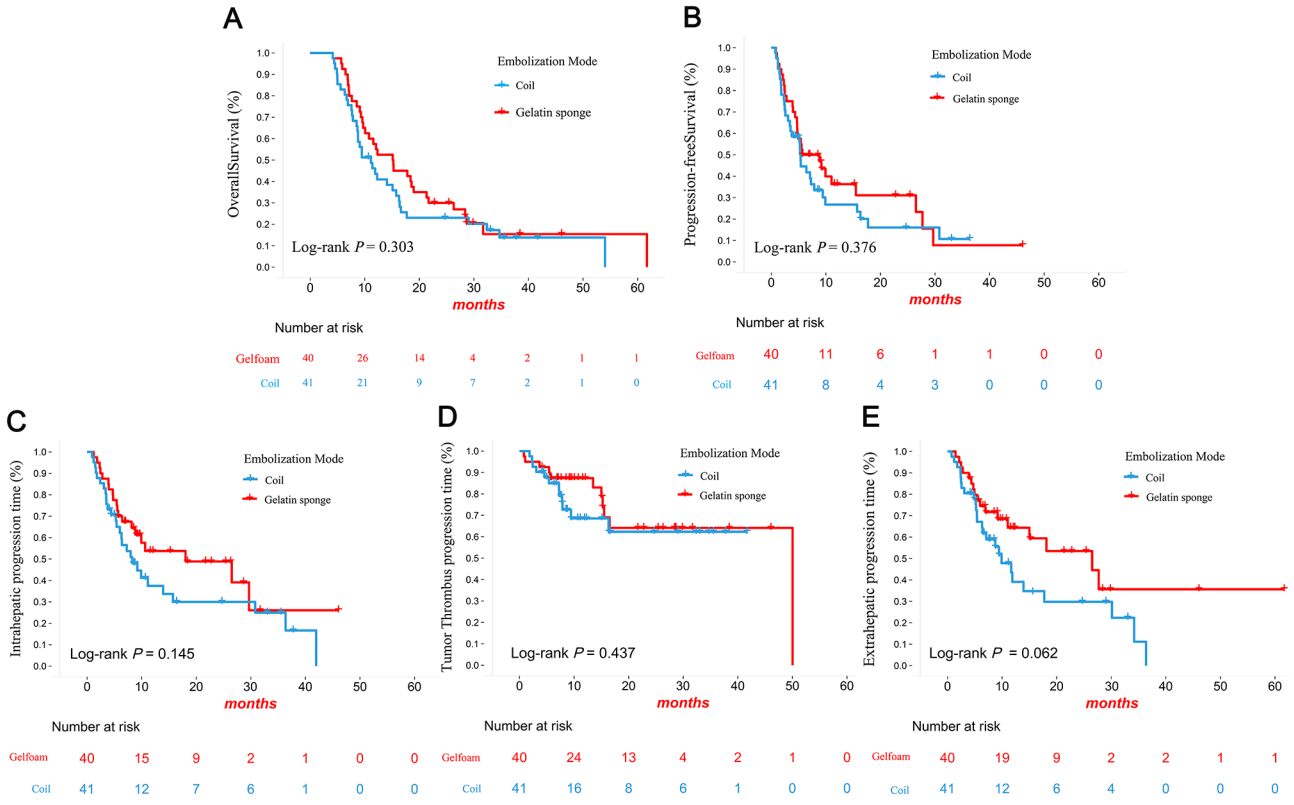

Fig. 2 Kaplan-Meier estimates of OS and PFS. (**A**) OS; (**B**) PFS; (**C**) intrahepatic progression; (**D**) tumor thrombus progression; (**E**) extrahepatic progression

Table 4 Prognosis of the two groups (median ± 95% CI)

	Coil (months)	Gelatin sponge (months)	Total	*P*
OS	11.13(7.67–14.59)	15.13(10.18–20.09)	12.07(7.90–16.23)	0.303
PFS	5.37(5.04–5.70)	5.7(0.66–10.74)	5.43(3.51–7.36)	0.376
Intrahepatic progression	8.27(4.45–12.08)	18.03(2.10–33.97)	9.93(4.73–15.14)	0.145
Thrombus progression	28.83(22.77–34.88)	36.04(28.44–43.63)	34.72(29.25–40.19)	0.437
Extrahepatic progression	9.9(5.80–14.00)	26.5(9.00–44.00)	13.93(6.81–21.05)	0.062
Advanced exhibition area				
0	8(19.5%)	12(30.0%)	20(24.7%)	0.701
1	16(39.0%)	15(37.5%)	31(38.3%)	
2	11(26.8%)	9(22.5%)	20(24.7%)	
3	6(14.6%)	4(10.0%)	10(12.3%)	

Note: CI: confidence interval; OS: overall survival; PFS: progression-free survival, $p < 0.05$ indicates statistical significance. In the Advanced exhibition area, 0 indicates no progression, 1 indicates intrahepatic progression, 2 indicates extrahepatic progression, and 3 indicates synchronous intrahepatic and extrahepatic progression

incidence of fistulas [36 (87.8%) vs. 23 (57.5%), $p = 0.003$]. Some patients who underwent coil embolization exhibited blood vessel truncation with the disappearance of the fistula, while new tumor blood vessels were difficult to detect. The compensation of extrahepatic blood vessels was more severe in the coil group than in the gelatin sponge group ($p < 0.001$), which made subsequent treatment challenging; however, the slow growth of these lesions might be related to the poor blood supply.

The coil group had better iodine oil deposition in the PVTT than the gelatin sponge group and significant deposits of iodized oil after multiple spring coil closures of APS, indicating that improved arteriovenous fistula reduced iodine oil loss and aggravated iodine oil deposition. After multiple TACEs, the extrahepatic blood supply of the coil group was greater than that of the gelatin sponge group; however, no cases of portal vein fistula were identified in the extrahepatic blood supply vessels. On the other hand, coil embolization treatment can be recommended for patients with severe local conditions, but short survival is expected. The detailed data are presented in Table 5.

Table 5 Effect of TACE on the incidence of Arterioportal shunts and cancer thrombus

	coil	gelatin sponge	total	*p*	p1	p2	p3
Lipiodol 1							
1	25(87.3%)	31(87.3%)					
2	13(87.3%)	7(87.3%)					
3	3(87.3%)	2(87.3%)					
mean ± SD	1.463 ±0.636	1.275 ±0.554		0.120			
Lipiodol 2							
1	17(87.3%)	28					
2	17(87.3%)	10					
3	7	2					
mean ± SD	1.756 ±0.734	1.350 ±0.580		0.007	0.009	0.005	0.417
Fistula0				0.063			
1	11	20					
2	22	17					
3	8	3					
mean ± SD	1.927 ±0.685	1.575 ±0.636		0.020			
Fistula1							
0	5	20					
1	24	20					
2	6	4					
3	0	2					
mean ± SD	0.878 ±0.640	0.850 ±0.802		0.607	0.000	0.000	0.000
Improvement of fistula 1	32(78.0%)	27(67.5%)		0.326			
Fistula2							
0	26	13					
1	13	25					
2	2	1					
3	0	1					
mean ± SD	0.415 ±0.591	0.750 ±0.630		0.010	0.000	0.000	0.000
Improvement of fistula 2	36(87.8%)	23(57.5%)		0.003			
collateral vessel							
0	2	2					
1	14	31					
2	25	7					
mean ± SD	1.561 ±0.594	1.125 ±0.463		0.000			

Note: Lipiodol 1: Lipiodol accumulation one month after the first TACE; Lipiodol 2: Lipiodol accumulation at the last follow-up. The lipiodol accumulation areas were divided into three groups: excellent (> 80%) was given 3 points, acceptable (50–80%) was given 2 points, or insufficient (< 50%) was given 1 point. Fistula 0: Fistula situation before the first TACE; Fistula 1: Fistula situation before the second TACE; Fistula 2: Fistula situation before the last TACE; Fistula 1: Fistula improvement before the second TACE compared with the first TACE; Fistula 2: Fistula improvement before the last TACE compared with the first TACE; Collateral vessel: Abnormal extrahepatic blood vessels supplying blood to the tumor: A lack of extrahepatic blood vessels was scored as 0 points, 1 extrahepatic blood vessel was scored as 1 point, and 2 or more extrahepatic blood vessels were scored as 2 points. *p*: Comparison between the coil and gelatin sponge groups; *p*1: comparison before and after treatment in both groups; *p*2: comparison before and after treatment in the coil group; *p*3: comparison before and after treatment in the gelatin sponge group; SD: standard deviation

Evaluation of liver function

Compared with that before treatment, hepatic function was not markedly altered after a single TACE, while fistulae improved, liver function did not improve significantly. This phenomenon was slightly different from that reported previously for improving liver function after fistula occlusion [5], which might be attributed to the combination of targeted therapy and immunotherapy in addition to TACE, which increased liver damage in this study. The final follow-up revealed a marked deterioration in liver function compared with that before treatment, which might be related to tumor progression, multiple TACEs, and worsening of liver injury caused by targeted drugs during the last hospitalization. Interestingly, compared with the coil group, the gelatin sponge group presented severely but not significantly deteriorated liver function, as shown in Table 6.

Fistula improvement

Univariate and multivariate analyses affecting OS.

Significant improvement in the fistula was defined as improvement by two grades, based on which the patients were classified into two groups: significant or insignificant improvement groups. Next, we performed

Table 6 Impact of TACE on liver function

	coil	gelatin sponge	total	*p*	p1	p2	p3
Child-Pugh 0	5.561 ±0.950	5.375 ±0.668	5.469 ±0.823	0.405			
Child-Pugh 1	5.561 ±0.867	5.575 ±0.844	5.568 ±0.851	0.918	0.404	0.980	0.194
Child-Pugh 2	6.659 ±1.460	7.025 ±1.732	6.840 ±1.600	0.401	0.000	0.000	0.000

Note: *p*: Comparison between the coil and gelatin sponge groups; *p*1: Comparison between before and after treatment in both groups; *p*2: Comparison between before and after treatment in the coil group; *p*3: Comparison between before and after treatment in the gelatin sponge group; Child-Pugh 0: Liver function before anti-tumor therapy; Child-Pugh 1: Liver function one month after the first TACE; Child-Pugh 2: Liver function at the last follow-up

Table 7 Risk factor analysis for improvement in fistula incidence

Variable	Improvement of fistula 1				Improvement of fistula 2			
	r1	OR1	OR1 95%CI	p1 value	r2	OR2	OR2 95%CI	p2 value
Embolization method	-1.582	0.205	0.040–1.056	0.058	-1.635	0.195	0.052–0.727	0.015
Gender Male/Female	-20.473	0.001	-	0.999	-1.656	0.191	0.012–2.943	0.235
Age(years) > 60/<60	0.523	1.687	2.80–10.166	0.568	-0.113	0.893	0.199–4.008	0.883
Extrahepatic metastasis	0.938	2.555	0.387–16.881	0.330	-0.003	0.997	0.247–4.032	0.997
Grading of PVTT								
2	Reference	-	-	0.161	Reference	-	-	0.199
3	-1.400	0.247	0.046–1.311	0.100	-0.849	0.428	0.112–1.640	0.216
4	-2.318	0.098	0.006–1.508	0.096	-1.985	0.137	0.013–1.488	0.102
Invasion of hepatic vein	1.190	3.286	0.602–17.937	0.170	1.395	4.035	0.933–17.452	0.062
Location Right/Left lobe	-0.729	0.483	0.074–3.135	0.445	-0.332	0.718	0.155–3.317	0.671
Pseudocapsule	-0.244	0.783	0.175–3.503	0.749	-1.236	0.290	0.081–1.043	0.058
Liver cirrhosis	0.087	1.091	0.206–5.786	0.918	0.684	1.983	0.486–8.089	0.340
Arteriovenous fistula	-0.373	0.688	0.148–3.211	0.635	-2.086	0.124	0.029–0.539	0.005
Hepatitis	0.095	1.100	0.059–20.471	0.949	-0.015	0.985	0.088–11.018	0.990
AFP(ng/mL) > 400/<400	0.458	1.580	0.336–7.426	0.562	-0.375	0.687	0.201–2.349	0.550
Immunotherapy	-0.132	0.876	0.151–5.084	0.883	0.412	1.510	0.343–6.643	0.586

Note: Improvement of fistula 1: Improvement in fistula before the second TACE compared to the first TACE; Improvement of fistula 2: Significant improvement in fistula before the last TACE compared to the first TACE; OR: odds ratio; r: correlation coefficients

correlation analysis to evaluate the factors associated with arteriovenous fistula improvement. The results revealed that the significant improvement in the incidence of fistula after the final TACE procedure was related to the embolization method and hepatic venous fistula, as shown in Table 7.

Other treatment-related toxicity

Liver injury after TACE was primarily evaluated on the basis of elevated transaminase and bilirubin levels. There was no significant difference in liver injury between the coil and gelatin sponge groups. The Common Terminology Criteria for Adverse Events (CTCAE) v5.0 grade 2 elevations in liver injury markers observed were alanine transaminase (ALT) elevation (coil 48.7% vs. gelatin sponge 45%), aspartate transaminase (AST) elevation (coil 48.7% vs. gelatin sponge 40%), and total bilirubin elevation (coil 22% vs. gelatin sponge 20%). Nausea, abdominal pain, fever, and other symptoms of post-embolism syndrome are common after TACE. The frequency of post-embolism symptoms for CTCAE grade 2 patients was nausea (31.7% for coil vs. 22.5% for gelatin sponge), abdominal pain (12.2% for coil vs. 10% for gelatin sponge), and fever (14.6% for coil vs. 20% for gelatin sponge). However, there were no significant differences between the 2 groups (Table 8). These findings suggest that there were no significant differences in liver injury or post-embolism syndrome between the 2 types of embolic agents. Correlation analysis revealed that there was no correlation between these abnormalities and PFS ($p > 0.05$).

Table 8 Other treatment-related toxicities

	coil	gelatin sponge	*p*	correlation
ALT elevation	20(48.7%)	18(45%)	0.735	0.353
AST elevation	20(48.7%)	16(40%)	0.429	0.502
TB elevation	9(22%)	8(20%)	0.637	0.841
Nausea	13(31.7%)	9(22.5%)	0.355	0.338
Abdominal pain	5(12.2%)	4(10%)	0.725	0.192
Fever	6(14.6%)	8(20%)	0.736	0.475

Note: Correlation: correlation analysis between these abnormalities and PFS; ALT: alanine transaminase; AST: aspartate transaminase; TB: total bilirubin. A P value < 0.05 was considered to indicate a statistically significant difference

Discussion

Liver cancer combined with cancer thrombus often presents as arteriovenous fistula, which is mutually causal and complementary to cancer thrombus. The mechanism of hepatic arteriovenous fistula is affected via an increase

in tumor vascular endothelial growth factor. This factor promotes the opening, proliferation, and expansion of the capillary network between the portal vein and peripheral hepatic artery to the tumor, directs erosion or destruction of the portal vein, or leads to the formation of a portal venous fistula. Tumor cells are directly injected into the small branches of the low-pressure portal vein through the blood flow of the high-pressure hepatic artery and are implanted in the portal vein. The resulting PVTT formation causes portal vein obstruction, further opening the anastomotic branch between the portal vein and hepatic artery in normal liver tissue and exacerbating the fistula.

DSA is the gold standard for diagnosing APS in patients with liver cancer. The main clinical manifestations of APS are bloating and abdominal pain. The long-term presence of APS can exacerbate liver cirrhosis, worsen liver function, and further increase portal vein pressure, thereby increasing the risk of esophageal and gastric variceal bleeding. The treatment of APS is crucial for the comprehensive treatment of liver cancer. Previous studies have shown that local treatment methods, such as TACE, hepatic arterial infusion chemotherapy (HAIC), radiotherapy, and systemic therapy (for instance, targeted immunity), improve APS [9, 10]. However, TACE is still the leading treatment for APS and focuses on embolization of the tumor thrombus via blood vessels, thereby improving the incidence of A-P fistula [11].

TACE treatment for APS has been widely employed for many years. Moreover, standardized therapy for APS embolization is still lacking. Many embolic materials, including gelatin sponges, coils, glue, absolute ethanol, and polyvinyl alcohol (PVA) particles, have been utilized. Zhao reported that drug-loaded microspheres block the fistula and improve the condition of the patient [12]. However, Shimose reported that the use of drug-loaded microspheres for embolization increases the incidence of APS [13]. Huang [10] compared the use of alcohol and gelatin sponges in the treatment of APS. The initial APS blockage rates in the alcohol and gelatin sponge groups were 70.3% (45/64) and 63.6% (21/33), the reperfusion rates after one month were 17.8% (8/45) and 85.7% (18/21), and the complete blockage rates after multiple embolizations were 82.8% (53/64) and 18.2% (6/33), respectively. Compared with the gelatin sponge group, the alcohol group had a significantly decreased reperfusion rate; however, the former is often accompanied by significant abdominal pain and may cause sclerosing cholangitis. Shi reported improvement in 12 APS patients treated with cyanoacrylate glue embolization after the first embolization. Among these patients, 80% improved with long-term APS [14]. Duan reported that Nbutyl 2cyanoacrylate (NBCA) glue in APS treatment resulted in an immediate improvement of 83.3% (30/36) and improvement rates at firsttime followup of 66.6% (20/30) [15]. Kim reported that the use of PVA embolization for APS resulted in an 80% improvement in APS after one TACE treatment and a subsequent follow-up visit [16]. However, in the present study, the improvement rate one month after the first TACE was 78.0% vs. 67.5% ($p = 0.326$), and the improvement rate in the last DSA was 87.8% vs. 57.5% ($p = 0.003$). Compared with that of permanent embolic agents, the improvement rate increased after the addition of the targeted drugs in the spring coil group. This phenomenon was similar to that in the gelatin sponge group, with higher improvement rates and lower reperfusion rates, indicating that adding targeted drugs might enhance improvement in the incidence of fistulas.

Compared with gelatin sponge particles, spring coil embolization showed a better trend one month after embolization than did the former during the last angiography. This phenomenon may be attributed to the fact that the spring coil is a permanent embolic agent with a low reperfusion rate, which blocks the fistula for a prolonged period and cuts off the blood supply vessel. On the other hand, tyrosine kinase inhibitor (TKI) drugs continue to inhibit angiogenesis, further improving APS. Compared with those in the gelatin sponge group, the fistula in the spring coil group improved markedly, whereas the erosion and loss of iodized oil were reduced, resulting in better deposition of iodized oil in the spring coil group. However, after TACE, the spring coil group had a heavier extrahepatic alternative blood supply than did the gelatin sponge group, which mainly consisted of the inferior phrenic artery, adrenal artery, and omental artery, increasing the difficulty of reTACE. However, these alternative blood supplies are rarely combined with significant APS.

Furthermore, HAIC treatment has been recommended for giant liver cancer patients complicated by portal vein thrombosis and arteriovenous fistula. Lin reported the use of HAIC combined with lenvatinib + PD-1 inhibitor for the treatment of liver cancer patients complicated by PVTT and APS. The median OS of the HAIC + lenvatinib + PD-1 group was 25.00 months, whereas that of the TACE + lenvatinib + PD-1 group was 19.30 months ($p = 0.035$); conversely, the median PFS of the two groups was 21.74 and 8.74 months, respectively ($p = 0.0066$) [17]. Survival analysis revealed that HAIC may have an advantage over TACE. However, the study did not analyze improvements in the incidence of fistulas, necessitating further comparisons in large-sample multicenter controlled studies. Compared with our findings, our study revealed a shorter OS and PFS, which might be associated with severe conditions in our enrolled patients: a tumor diameter > 10 cm and the presence of type 2 or greater PVTT.

The shortcomings of this study are as follows: a small number of enrolled patients, evaluation of only the fistula after the first and last TACE procedures, and lack of analysis of fistula changes and liver function changes throughout the treatment period.

Conclusion

Targeted combined TACE treatment for giant hepatocellular carcinoma with PVTT and APS significantly improved the incidence of fistulas. Moreover, the APS improved with multiple TACEs due to disease progression. Although the improvement in the incidence of fistulas in the coil group was greater than that in the gelatin sponge group, the OS and PFS did not differ significantly between the two groups.

Abbreviations

HCC	Hepatocellular carcinoma
APS	Arterioportal shunt
TACE	Transarterial chemoembolization
DSA	Digital subtraction angiography
BCLC	Barcelona clinic liver cancer
AVS	Arteriovenous shunting
PVTT	Portal vein tumor thrombus
AFP	Alpha-fetoprotein

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Central Hospital Affiliated to Shandong First Medical University. Written informed consent was waived for this study given its retrospective design.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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