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ORIGINAL RESEARCH

Post-TARE Survival Outcomes in Hepatocellular Carcinoma: Influence of Pre-TARE Immunotherapy and Targeted Therapy in a Real-World Cohort

Xiao-Yong Liu[1,*], Yu-Xing Yu[1,*], Jia-Huang Hong[2,*], Wen-Chang Yu[1], Su-Fang Qiu[3], Zhu-Ting Fang[1], Yu-Bin Hu[1]

[1]Department of Tumor and Vascular Interventional Radiology, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, 350000, People's Republic of China; [2]Department of Thoracic Oncology Surgery, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, 350000, People's Republic of China; [3]Department of Radiation Oncology, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, 350000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yu-Bin Hu, Department of Tumor and Vascular Interventional Radiology, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, 350000, People's Republic of China, Email huyb@fjzlhospital.com

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Background: Transarterial radioembolization (TARE) combined with systemic therapy has shown activity in unresectable hepatocellular carcinoma (HCC). However, the prognostic impact of different treatment exposures before TARE in real-world practice remains unclear.

Methods: This single-center retrospective study included 71 patients with HCC who underwent TARE between November 2022 and August 2025. TARE was defined as the unified clinical landmark for outcome assessment. Patients were stratified according to treatment exposure before TARE: those who received ≥2 cycles of immune checkpoint inhibitors combined with targeted therapy prior to TARE (Group 1) and those who underwent TARE as the initial major treatment (Group 2). Progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) were evaluated. Cox regression analyses were performed to identify prognostic factors, including baseline neutrophil-to-lymphocyte ratio (NLR).

Results: Group 2 achieved a significantly higher ORR than Group 1 (87.5% vs 56.4%, P = 0.004). Median PFS was significantly longer in Group 2 than in Group 1 (17.45 vs 4.86 months; hazard ratio = 0.327, 95% confidence interval: 0.125–0.856, P = 0.023). No significant difference in OS was observed during the current follow-up period. Patients with baseline NLR ≤3.28 experienced significantly prolonged PFS compared with those with NLR >3.28.

Conclusion: In this real-world cohort, treatment exposure prior to TARE was associated with post-TARE PFS and tumor response, but not with OS. These findings suggest that baseline treatment history and systemic inflammatory status influence post-TARE prognosis, rather than indicating the superiority of a specific treatment sequence. Prospective studies with longer follow-up are warranted.

Plain Language Summary: Hepatocellular carcinoma (HCC) is a common type of liver cancer, and many patients are not suitable for surgery at diagnosis. Transarterial radioembolization (TARE) is a locoregional treatment that delivers radiation directly to liver tumors and is increasingly used together with systemic therapies such as immunotherapy and targeted drugs. However, it is still unclear whether treatments given before TARE influence patient outcomes in real-world practice. In this retrospective study, we analyzed 71 patients with HCC who received TARE at a single center. Patients were divided into two groups: those who had received systemic therapy before TARE and those who underwent TARE as their initial major treatment. We evaluated tumor response and survival outcomes starting from the time of TARE. We found that patients who received TARE as the initial treatment had better tumor response and longer progression-free survival than those who had received systemic therapy before TARE. However, overall survival was similar between the two groups during the current follow-up period. In addition, patients with a lower neutrophil-to-lymphocyte

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ratio, a blood-based marker reflecting immune status, tended to have better outcomes after TARE. These findings suggest that previous treatment exposure and baseline immune status may influence outcomes after TARE, rather than indicating that one treatment sequence is definitively superior. Further prospective studies with longer follow-up are needed to confirm these results and guide treatment planning for patients with HCC.

Keywords: hepatocellular carcinoma, HCC, transarterial radioembolization, TARE, immune checkpoint inhibitors, ICIs, treatment exposure, neutrophil-to-lymphocyte ratio, NLR

Introduction

Hepatocellular carcinoma (HCC) is one of the most prevalent malignant tumors worldwide and the leading cause of liver-related cancer mortality.[1,2] According to global cancer statistics, the incidence and mortality rates of HCC are steadily increasing.[3] Primary treatment options include surgical resection, local therapies such as radiofrequency ablation and transarterial chemoembolization (TACE), and systemic therapies, including chemotherapy, targeted therapy, and immunotherapy.[4,5] However, most patients are diagnosed at intermediate or advanced stages, resulting in low cure rates, limited eligibility for surgical resection, and a high likelihood of recurrence during treatment.[3,6]

In recent years, systemic therapies have played an increasingly critical role in managing unresectable HCC, significantly extending median survival.[7,8] However, outcomes remain limited by individual variability and adverse events, including hypertension, hand-foot syndrome, gastrointestinal bleeding, and proteinuria, which compromise long-term disease control.[7–9] Furthermore, vascular endothelial growth factor-targeted therapies pose a high risk of bleeding in cirrhotic patients with esophageal varices, limiting their broader applicability.[10] Although immune checkpoint inhibitors (ICIs) have shown some efficacy in HCC, objective response rates (ORRs) remain suboptimal, ranging from 30.8% with pembrolizumab[11] to 30.6% with nivolumab.[12]

Transarterial radioembolization (TARE) has recently garnered attention for the management of unresectable HCC. TARE delivers Yttrium-90 (Y-90) microspheres to tumor-feeding arteries, enabling highly targeted radiotherapy. Studies have demonstrated that TARE achieves efficacy comparable to TACE in terms of tumor control and survival outcomes,[13–16] and in some cases, superior results relative to sorafenib monotherapy.[4,17] Additionally, TARE has the potential to delay disease progression, improve quality of life, and serve as a bridge to liver transplantation or surgical resection.[6,18]

Treatment sequence may influence patient survival, tumor burden, and treatment tolerance. Liver function plays a critical role in predicting the outcomes of Y-90 radioembolization. Although the traditional Child-Pugh (CP) classification remains commonly employed in clinical practice, newer methods such as the albumin-bilirubin (ALBI) score offer enhanced accuracy.[19] Additionally, inflammatory biomarkers, including the neutrophil-to-lymphocyte ratio (NLR), are gaining recognition for their ability to predict tumor biology and therapeutic response.[4,20]

Emerging evidence suggests that combining TARE with targeted therapy and ICIs offers therapeutic potential;[21] however, the optimal sequencing of TARE with systemic therapies remains unclear. In real-world clinical practice, many patients receive systemic therapy before TARE, whereas others undergo TARE as their first major treatment. Systemic therapy is typically evaluated every 2–3 cycles, and TARE follow-up commonly occurs at 1–3 months, providing natural clinical time points for defining treatment exposure windows.[4] Because these patients enter TARE with different baseline exposures and disease courses, TARE serves as a natural landmark for prognosis assessment, allowing evaluation of post-TARE survival without comparing treatment sequences as therapeutic strategies. Therefore, this study was designed as a post-TARE prognostic study, focusing on factors associated with outcomes after patients reached the common therapeutic landmark of receiving TARE. We examined baseline liver function, inflammatory biomarkers, and prior treatment exposure and analyzed their associations with post-TARE overall survival (OS) and progression-free survival (PFS). This study provides real-world evidence to support prognostic assessment and treatment planning in patients undergoing TARE.

Materials and Methods

Patient Selection

This was a single-center retrospective cohort study designed to evaluate post-TARE prognosis in patients with HCC. This study adhered to the principles of the Declaration of Helsinki. The Ethics Committees of Fujian Cancer Hospital and Fujian Medical University Cancer Hospital granted approval for the research (approval code K2025-207-01). Because patients may receive systemic or other interventional therapies at various stages prior to TARE, TARE was defined as the unified clinical landmark (time zero) for outcome assessment. This design reflects real-world treatment pathways and avoids treating different pre-TARE exposures as a controlled therapeutic strategy comparison.

Patient Cohort

A total of 71 patients with HCC who underwent TARE at Fujian Cancer Hospital between November 2022 and August 2025, with a final follow-up date of December 20, 2025, were included. The inclusion criteria were as follows: (1) diagnosis of HCC confirmed by imaging or pathology in accordance with the Barcelona Clinic Liver Cancer (BCLC) staging criteria; (2) absence of significant hepatopulmonary shunting; (3) preserved liver function, classified as CP class A to B9; and (4) completion of pretreatment single-photon emission computed tomography (SPECT) imaging with technetium-99m macroaggregated albumin (^{99}mTc-MAA), followed by at least 3 months of follow-up post-TARE.

Patients were categorized according to whether they had received systemic therapy before TARE:

Group 1 (initial ICIs with targeted therapy) consisted of patients who initially received ≥2 cycles of ICIs combined with targeted therapy. The average interval between ICI treatments was 21 days. After completing at least two cycles, patients underwent TARE, with or without subsequent TACE as a local intervention.

Group 2 (initial TARE) consisted of patients who initially received TARE or received only one dose of ICIs or targeted therapy either simultaneously with or within 1 week of TARE, with or without prior TACE as a local intervention. After TARE, patients received combination therapy with targeted agents and ICIs either within 1 month or within 1–3 months.

The grouping reflects treatment history before TARE rather than a prospective assignment of therapeutic strategy.

The definitions for pre-TARE and post-TARE systemic therapy windows were based on real-world clinical practice patterns at our institution. Patients who received ≥2 cycles of systemic therapy before TARE were classified as having received "pre-TARE systemic therapy", reflecting the minimum duration required to evaluate initial treatment response in routine oncology practice. Similarly, post-TARE systemic therapy within 1–3 months corresponds to the typical clinical window for response assessment and recovery after TARE. These operational definitions were applied to ensure consistency in group classification and reduce heterogeneity inherent in retrospective datasets. Treatment plans were established through multidisciplinary discussions involving specialists in interventional radiology, hepatobiliary surgery, nuclear medicine, and medical oncology. Among the 71 patients, Group 1 included 39 patients and Group 2 included 32 patients. All patients underwent comprehensive evaluations prior to treatment, including liver function tests, imaging (CT and MRI), and biomarker analysis. All relevant raw data and detailed therapy strategies are available in the Supplementary Material (Tables S1–S7). Raw data containing personal identifiers are not publicly accessible in accordance with patient privacy protection requirements and institutional regulations.

Clinical Data Collection

Collected data included demographic information (age and sex), hepatitis virus infection status, Eastern Cooperative Oncology Group (ECOG) performance status, CP classification, ALBI grade, and BCLC staging. Tumor characteristics assessed using contrast-enhanced CT or MRI included maximum tumor diameter, number of lesions, lesion distribution, and presence of portal vein tumor thrombus.

Lesion distribution was classified as solitary, confluent (coalescent nodules forming a single mass), or multifocal-scattered (diffuse intrahepatic distribution) phenotypes. Confluent lesions were defined as multiple lesions coalescing within a 2-cm radius with ill-defined margins on contrast-enhanced imaging. Scattered lesions were defined as multiple lesions with ≥1 cm spacing between adjacent lesions.

Laboratory data included platelet count, serum neutrophil count, lymphocyte count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, and total bilirubin. NLR was dichotomized using the median baseline value (3.28) of the entire cohort. Because no universally accepted cutoff for NLR exists in HCC and previous studies have reported heterogeneous thresholds,[22–25] we adopted a data-driven approach commonly used in exploratory prognostic studies. Sensitivity analyses using alternative NLR cutoffs reported in prior literature were not performed because of the limited sample size; therefore, the present analysis should be considered exploratory. Using the cohort-specific median minimizes model overfitting and ensures balanced group sizes, which is statistically appropriate for retrospective real-world cohorts with limited sample sizes. NLR was calculated, and patients were divided into two groups based on baseline NLR: ≤3.28 and >3.28.

TARE in HCC

All patients underwent pretreatment angiography and ^{99m}Tc-MAA infusion to assess hepatopulmonary shunting and intrahepatic microsphere distribution using planar scintigraphy. Radiation activity was determined using a modified partition model based on untreated liver volume, clinical objectives, and relevant scientific evidence.[26] The catheter position and infusion approach were determined by experienced interventional radiologists based on tumor vascularity and arterial anatomy, with segmental or lobar administration applied as appropriate. Y-90 radioembolization was performed using resin microspheres (SIR-Spheres®, Sirtex Medical Pty Ltd., Sydney, Australia). Prior to treatment, ^{99m}Tc-MAA scintigraphy was used to calculate the lung shunt fraction (LSF) and tumor-to-nontumoral liver uptake ratio (TNR). LSF was calculated as follows:

LSF (%) = (lung radioactivity count / [liver + lung radioactivity count]) × 100.

Only patients with an LSF <20% were considered eligible for TARE, in accordance with established safety recommendations. The TNR was calculated as the ratio of radiotracer uptake in tumor tissue to that in normal liver parenchyma.

Radiation activity and dosimetry were calculated using a modified partition model, taking into account tumor volume, non-tumoral liver volume, LSF, and predefined clinical dose constraints. The absorbed tumor dose was calculated as:

D (Gy) = [A (GBq) × CF] / TM (kg).

D: Tumor absorbed dose (unit: Gy, gray); A: Radioactive activity (unit: GBq, gigabecquerel); CF: Conversion factor obtained using the modified partition mo TM: Tumor target volume tissue mass (unit: kg, kilogram).

All dosimetric calculations were performed using dedicated Y-90 dosimetry software (MIRD-Y90 platform), ensuring standardized and reproducible dose planning. Y-90 resin microspheres were administered to liver segments, lobes, or the entire liver, depending on tumor distribution and treatment intent. The prescribed activity was individualized based on target liver volume and planned absorbed dose, in accordance with institutional protocols and current clinical guidelines. All TARE procedures were performed following established international recommendations and guidelines. Dose constraints for non-tumoral liver parenchyma were applied in accordance with institutional protocols and published safety recommendations.

Post-Treatment Assessment

Post-TARE imaging follow-up was conducted using plain or contrast-enhanced CT or MRI. The first follow-up occurred 1 month after TARE, followed by imaging every 2–3 months until disease progression, final radiological evaluation, or death, whichever occurred first. Disease progression was defined as the earliest radiological evidence requiring a change in treatment.

Tumor response was evaluated based on RECIST 1.1 and modified RECIST (mRECIST) criteria and classified as complete response, partial response, stable disease, or progressive disease. ORR and disease control rate (DCR) were calculated at the time of best disease control.

Using TARE as time zero prevents immortal-time bias that would occur if outcomes were measured from pre-TARE systemic therapy initiation for some patients. OS was measured from the date of the first TARE until death from any cause. PFS was calculated from the date of the first TARE to disease progression or death from any cause, whichever

occurred first. Clinical and laboratory follow-up was performed for 3 months post-treatment. Adverse events and severe toxicities were graded according to the Common Terminology Criteria for Adverse Events version 5.0.

Statistical Analysis

Statistical analyses were conducted using R software version 4.4.4. Baseline data were summarized using descriptive statistics. Categorical variables were expressed as frequencies and percentages, whereas continuous variables were expressed as mean ± standard deviation or medians with interquartile ranges.

Group comparisons were conducted using independent-sample t-tests or Wilcoxon rank-sum tests for continuous variables and chi-square tests, Yates' correction, or Fisher's exact tests for categorical variables. Survival outcomes were estimated using Kaplan–Meier curves.

Cox regression analysis was used to examine associations among predictive factors, biomarkers, and treatment strategies. Predictors with $P < 0.1$ in univariate analyses were included in multivariate regression models to determine independent associations with tumor response. Prior TACE was included as a predefined covariate in multivariate analyses because of its known prognostic relevance in HCC and substantial baseline imbalance between groups. Statistical significance was set at $P < 0.05$.

Results

Clinical Baseline Characteristics and Treatment Modalities

Table 1 summarizes the ICIs and targeted therapy regimens for all patients before and after TARE administration. Table 2 and Tables S1–S3 presents the baseline clinical characteristics and treatment strategies of the two patient groups.

This study enrolled a total of 71 patients with HCC who underwent TARE, stratified into two groups based on treatment sequence: Group 1 (pri-ICIs plus targeted therapy group, n=39) and Group 2 (pri-TARE group, n=32). Significant intergroup differences were observed in baseline clinical characteristics and treatment regimens between the two groups; detailed results are presented in Table 2 (Baseline Clinical Characteristics) and Table 1 (Detailed ICI and Targeted Therapy Regimens). Most variables (eg, sex, BCLC staging, liver function, hepatitis B virus infection status, ECOG performance status, and NLR) showed no significant differences, indicating good balance across most baseline characteristics.

Fundamental differences existed in pretreatment exposure to ICIs plus targeted therapy between the two groups; the core distinction lay in treatment duration and initiation timing, which were directly linked to the design principles of each group's treatment strategy (Table 1). Group 1 (pri-ICIs plus targeted therapy group) followed the strategy of "long-term combination therapy prior to TARE"; all patients received ≥2 cycles (21 days per cycle) of ICIs plus targeted therapy. Patients in Group 1 had a median duration of ICIs plus targeted therapy of 3 months (range: 1 month–2 years) and a median total number of ICI cycles of 6 (range: 2–36). The main regimens were "anti-angiogenic agent plus PD-1/PD-L1 inhibitor", such as bevacizumab combined with atezolizumab and lenvatinib combined with tislelizumab. Some patients underwent regimen adjustments based on treatment response (eg, lenvatinib switched to regorafenib, sintilimab switched to carrelizumab), but all maintained a long-term treatment paradigm. Additionally, seven patients (17.9%) in Group 1 had a history of prior surgical resection, indicating intrahepatic recurrence or metastasis.

In contrast, Group 2 (pri-TARE group) followed the strategy of "early TARE initiation". Most patients (n=25, 78.1%) had no pretreatment ICIs or targeted therapy; only eight patients (25%) had received ICIs or targeted therapy (one patient received single-agent ICI for one cycle; four patients received single-agent targeted therapy), all initiated concurrently within 1 week of TARE (ie, interval ≤7 days between ICI/targeted therapy and TARE). This exposure did not constitute long-term treatment (eg, Patient 7: one cycle of carrelizumab followed by TARE within 1 week; Patient 44: lenvatinib administered within 1 week of TARE), representing concurrent combination of TARE with ICI/targeted therapy rather than sequential TARE after long-term ICI/targeted therapy.

Highly significant differences in prior TACE history were observed between the two groups ($P < 0.001$; Table 2), and these differences were directly linked to each group's treatment strategy. In Group 1, 82.1% (n=31) of patients had undergone prior TACE, with two patients receiving ≥9 TACE sessions (Patient 16: 9 sessions; Patient 18: 12 sessions)

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Table 1 Detailed Regimens of ICIs and Targeted Therapies

Patient ID	Group	Prior Types of Targeted Therapy	Duration of Targeted Therapy (Until Received TARE)	Prior Type of ICIs	Prior Total Cycles of ICIs (21 Days per Cycle)	Prior TACE	Prior TACE times	Postoperative TARE of Combined ICIs and Targeted Therapy Strategy
1	Group2							Bevacizumab+Atezolizumab
2	Group1	Lenvatinib	1 month	Sintilimab	4	TACE	2	Regorafenib+Toripalimab, later changed to Anlotinib+Toripalimab, then to Bevacizumab+Carrelizumab
3	Group1	Bevacizumab	8 month	Atezolizumab	9	TACE	2	Regorafenib + Pembrolizumab
4	Group2							Lenvatinib+Tislelizumab
5	Group2							Regorafenib+Pembrolizumab
6	Group1	Bevacizumab+Lenvatinib	3 months	Atezolizumab	6			Atezolizumab+Bevacizumab
7	Group2			Carrelizumab	1(until received TARE within one week)			Lenvatinib+Tislelizumab
8	Group1	Bevacizumab	1.5 years	Atezolizumab	21	TACE	2	Atezolizumab+Bevacizumab
9	Group1	Donafenib, later changed to Lenvatinib	7 months	Sintilimab, later changed to Envafolimab	8	TACE	2	Apatinib+Envafolimab
10	Group1	Lenvatinib	1 month	Sintilimab	2	TACE	2	Donafenib+Tislelizumab
11	Group1	Lenvatinib	7 months	Tislelizumab	7			Regorafenib+Tislelizumab, later changed to Pembrolizumab
12	Group2							Apatinib+Carrelizumab
13	Group1	Bevacizumab	1 month	Atezolizumab	2	TACE	2	Atezolizumab + Bevacizumab, later changed to Regorafenib + Cardronilumab
14	Group2							Bevacizumab+Atezolizumab
15	Group2							Bevacizumab+Sintilimab, later changed to Sintilimab+Regorafenib, then to Apatinib+Carrelizumab
16	Group1	Bevacizumab + Lenvatinib, later changed to Regorafenib	2 years	Atezolizumab, later changed to Tislelizumab	21	TACE	9	Apatinib+Tislelizumab
17	Group1	Lenvatinib	3 months	Tislelizumab	4	TACE	1	Lenvatinib+Tislelizumab, later changed to Apatinib+Carrelizumab

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18	Group1	Donafenib, later changed to Bevacizumab, then to Lenvatinib, then to Atezolizumab, then to Regorafenib, and recently to Anlotinib	2 years	Atezolizumab, later changed to Pembrolizumab	22	TACE	12	Anlotinib + Pembrolizumab, then Anlotinib changed to Gefitinib+ Cadonilimab, then to Lenvatinib + Cadonilimab
19	Group2							Lenvatinib+Tislelizumab
20	Group1	Lenvatinib	1 month	Sintilimab	2	TACE	1	Apatinib+Carrelizumab
21	Group2					TACE	1	Bevacizumab+Atezolizumab
22	Group1	Bevacizumab + Lenvatinib, later changed to Regorafenib	4 months	Tislelizumab, later changed to Carrelizumab	12	TACE	1	Regorafenib+Carrelizumab
23	Group1	Lenvatinib, later changed to Bevacizumab, then to Donafenib, then to Regorafenib, and recently to Anlotinib	2 years	Sintilimab, later changed to Toripalimab, then to Pembrolizumab	36	TACE	7	Apatinib + Carrelizumab, later changed to Apatinib + Adebrelimab
24	Group1	Apatinib	1 month	Carrelizumab	2	TACE	1	Apatinib+Carrelizumab
25	Group2							Atezolizumab+Bevacizumab
26	Group2					TACE	1	Lenvatinib+Atezolizumab
27	Group1	Donafenib, later changed to Apatinib	3 months	Sintilimab, later changed to Carrelizumab	3	TACE	3	Apatinib+Carrelizumab
28	Group1	Apatinib	2 months	Carrelizumab	2	TACE	2	Apatinib + Tislelizumab, later changed to Regorafenib + Pembrolizumab
29	Group1	Apatinib	2 months	Carrelizumab	3			Apatinib+Carrelizumab
30	Group1	syPM8002	3 months	syPM8002	3			Regorafenib+ Tislelizumab, later changed to Donafenib + Tislelizumab
31	Group1	Apatinib	2 weeks	Carrelizumab	2	TACE	1	Apatinib+Carrelizumab
32	Group1	Apatinib	1 weeks	Carrelizumab	2			Apatinib+Carrelizumab
33	Group1	Bevacizumab	2 months	Atezolizumab	2	TACE	1	Atezolizumab + Bevacizumab
34	Group1	Bevacizumab	2 weeks	Atezolizumab	2			Atezolizumab + Bevacizumab
35	Group1	Bevacizumab	4 months	Atezolizumab	4	TACE	4	Atezolizumab + Bevacizumab
36	Group2							Atezolizumab+Bevacizumab
37	Group2	Lenvatinib	1 week			TACE	1	Lenvatinib+Pembrolizumab
38	Group2							Regorafenib+Tislelizumab
39	Group1	Apatinib	3 months	Carrelizumab	2	TACE	2	Apatinib+Carrelizumab

(*Continued*)

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Table 1 (Continued).

Patient ID	Group	Prior Types of Targeted Therapy	Duration of Targeted Therapy (Until Received TARE)	Prior Type of ICIs	Prior Total Cycles of ICIs (21 Days per Cycle)	Prior TACE	Prior TACE times	Postoperative TARE of Combined ICIs and Targeted Therapy Strategy
40	Group1	Lenvatinib	1 year	Pembrolizumab, later changed to Ipilimumab, then to Cadonilimab	17	TACE	4	Lenvatinib+Cadonilimab
41	Group1	Lenvatinib, later changed to Bevacizumab	5 months	Toripalimab, later changed to Sintilimab	6	TACE	2	Bevacizumab+Sintilimab, later changed to Tislelizumab+Regorafenib
42	Group1	Donafenib	3 months	Sintilimab	5	TACE	5	Donafenib+Sintilimab
43	Group1	Bevacizumab	5 months	Atezolizumab	5	TACE	3	Atezolizumab + Bevacizumab
44	Group2	Lenvatinib	1 week					Lenvatinib+Pembrolizumab
45	Group2							Tislelizumab
46	Group1	Bevacizumab	2 months	Sintilimab	2	TACE	1	Sintilimab+Bevacizumab
47	Group2							Donafenib+Tislelizumab
48	Group1	Bevacizumab	1 week	Atezolizumab	2	TACE	1	Atezolizumab+Bevacizumab
49	Group1	Lenvatinib	1 week	Atezolizumab	2			Atezolizumab+Bevacizumab
50	Group2							Atezolizumab+Bevacizumab
51	Group2							Atezolizumab+Bevacizumab
52	Group1	Lenvatinib	2 years	Sintilimab	4	TACE	2	Regorafenib+Tislelizumab
53	Group2							Donafenib, later changed to Apatinib + Carrelizumab
54	Group2			Atezolizumab	1(until received TARE within one week)			Atezolizumab
55	Group1	Bevacizumab	4 months	Atezolizumab	6	TACE	1	Apatinib+Atezolizumab
56	Group2	Apatinib	1 week					Apatinib+Carrelizumab
57	Group1	Apatinib	4 months	Carrelizumab	5			Apatinib+Carrelizumab
58	Group1	Lenvatinib	2 years	Tislelizumab	3	TACE	3	Apatinib+Tislelizumab, later changed to Carrelizumab
59	Group2							Donafenib+Tislelizumab
60	Group1	Lenvatinib, and changed for Bevacizumab, later changed to Regorafenib	1 years	Tislelizumab, later changed to Atezolizumab, then to Pembrolizumab	18	TACE	4	Regorafenib+Pembrolizumab
61	Group2							Apatinib+Carrelizumab

62	Group2					TACE	1	Donafenib+Tislelizumab, later changed to Lpilimumab
63	Group2	Lenvatinib	1 week					Donafenib+Tislelizumab
64	Group1	Apatinib	1 months	Carrelizumab	2	TACE	2	Apatinib+Carrelizumab
65	Group2							Atezolizumab+Bevacizumab
66	Group1	Lenvatinib	2 months	Tislelizumab	2	TACE	1	Lenvatinib+Tislelizumab
67	Group2							Atezolizumab+Bevacizumab
68	Group2	Donafenib	1 week	Sintilimab	1(until received TARE within one week)			Donafenib+Sintilimab
69	Group2	Donafenib	1 week	Tislelizumab	1(until received TARE within one week)	TACE	2	Apatinib+Tislelizumab
70	Group2	Bevacizumab	1 week	Atezolizumab	1(until received TARE within one week)			Atezolizumab+Bevacizumab
71	Group2							Lenvatinib+Pembrolizumab

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Table 2 Baseline Patient Features and Clinical Characteristics

Characteristics	Group 1	Group 2	pvalue	Statistic	Method
n	39	32			
Gender, n (%)			1.0000	2.05575E-31	Yates' correction
Male	34 (87.2%)	28 (87.5%)			
Female	5 (12.8%)	4 (12.5%)			
Age, mean ± sd	52.128 ± 10.063	57.938 ± 13.852	0.0448	−2.0441	*T* test
Weight (Kg), median (IQR)	60 (54, 66.5)	62.75 (59.5, 70.85)	0.1285		Wilcoxon
Hepatitis Virus Infection Status, n (%)			0.0641	3.4282	Chisq test
None	7 (17.9%)	12 (37.5%)			
HBV Carrier	32 (82.1%)	20 (62.5%)			
BCLC Stage, n (%)			0.1809	3.4200	Yates' correction
Stage A	2 (5.1%)	6 (18.8%)			
Stage B	7 (17.9%)	6 (18.8%)			
Stage C	30 (76.9%)	20 (62.5%)			
ECOG Performance Status, n (%)			0.7100		Fisher test
0	19 (48.7%)	16 (50%)			
1	20 (51.3%)	15 (46.9%)			
2	0 (0%)	1 (3.1%)			
CP Classification, n (%)			0.0913	6.4597	Yates' correction
A	25 (64.1%)	24 (75%)			
B7	11 (28.2%)	4 (12.5%)			
B8	1 (2.6%)	4 (12.5%)			
B9	2 (5.1%)	0 (0%)			
ALBI Index, mean ± sd	−2.1857 ± 0.43202	−2.3682 ± 0.50886	0.1067	1.6347	*T* test
ALBI Grade, n (%)			0.1702		Fisher test
Grade 1	7 (17.9%)	11 (34.4%)			
Grade 2	31 (79.5%)	21 (65.6%)			
Grade 3	1 (2.6%)	0 (0%)			
NLR, median (IQR)	3.277 (2.5235, 5.4155)	2.9838 (2.165, 4.5782)	0.667		Wilcoxon
LSF (%), median (IQR)	7.92 (4.87, 12.57)	5.96 (4.53, 11.535)	0.3097		Wilcoxon
TNR, median (IQR)	3.32 (3.12, 4.83)	3.59 (2.98, 4.255)	0.7256		Wilcoxon
TAD (Gy), median (IQR)	150 (130, 215)	150 (130, 200)	0.6757		Wilcoxon
TARE Treatment Pattern, n (%)			0.5696	1.1257	Yates' correction
Right Lobe	25 (64.1%)	22 (68.8%)			
Whole Liver	11 (28.2%)	6 (18.8%)			
Left Lobe	3 (7.7%)	4 (12.5%)			
International Classification of PVTT, n (%)			0.0336	8.6961	Yates' correction
None	18 (46.2%)	17 (53.1%)			
VP2	2 (5.1%)	1 (3.1%)			
VP3	4 (10.3%)	10 (31.2%)			
VP4	15 (38.5%)	4 (12.5%)			
Number of Lesions, n (%)			0.1289	13.8184	Yates' correction
One	1 (2.6%)	7 (21.9%)			
Two	1 (2.6%)	1 (3.1%)			
Three	1 (2.6%)	1 (3.1%)			
Four	3 (7.7%)	5 (15.6%)			
Five	3 (7.7%)	4 (12.5%)			
Six	11 (28.2%)	4 (12.5%)			
Eight	1 (2.6%)	0 (0%)			
Nine	3 (7.7%)	3 (9.4%)			
sixteen	2 (5.1%)	3 (9.4%)			
>twenty	13 (33.3%)	4 (12.5%)			
Lesion Distribution Pattern, n (%)			0.0280	7.1486	Yates' correction
Single Lesion	1 (2.6%)	7 (21.9%)			
Confluent Lesions	13 (33.3%)	11 (34.4%)			
Scattered Lesions	25 (64.1%)	14 (43.8%)			

(*Continued*)

Table 2 (Continued).

Characteristics	Group 1	Group 2	pvalue	Statistic	Method
Maximum Lesion Diameter, n (%)			0.2896	4.9773	Yates' correction
<2cm	3 (7.7%)	1 (3.1%)			
2-5cm	5 (12.8%)	1 (3.1%)			
5-10cm	11 (28.2%)	10 (31.2%)			
10-15cm	12 (30.8%)	16 (50%)			
>15cm	8 (20.5%)	4 (12.5%)			
Average Maximum Tumor Size (cm), mean ± sd	10.269 ± 5.6058	11.347 ± 3.8162	0.3581	−0.9252	*T* test
Distribution of Lesions in Liver, n (%)			0.4756	1.4862	Yates' correction
Right Lobe	17 (43.6%)	18 (56.2%)			
Bilobar	19 (48.7%)	11 (34.4%)			
Left Lobe	3 (7.7%)	3 (9.4%)			
Prior other treatment					
Prior TACE, n (%)	31 (79.5%)	5 (15.6%)	< 0.001	28.6807	Chisq test
Prior Radiotherapy, n (%)			1.0000		Fisher test
Radiotherapy for Inferior Vena Cava Tumor Thrombus	1 (2.6%)	0 (0%)			
Liver Lesion Radiotherapy	1 (2.6%)	0 (0%)			
Radiotherapy for Portal Vein Tumor Thrombus	1 (2.6%)	0 (0%)			
Radiotherapy for Inferior Vena Cava and Right Hepatic Vein Tumor Thrombus	1 (2.6%)	0 (0%)			
Radiotherapy for Portal Vein Tumor Thrombus	1 (2.6%)	0 (0%)			
Prior Surgery, n (%)			0.0248	7.3976	Yates' correction
Liver Lesion Resection	7 (17.9%)	0 (0%)			
Bone Metastasis Resection	1 (2.6%)	0 (0%)			
Postoperative other treatment					
Postoperative Liver Lesion Conversion Surgery, n (%)	2 (5.1%)	4 (12.5%)	0.4950	0.4657	Yates' correction
Bone Postoperative Metastasis Resection, n (%)	1 (2.6%)	0 (0%)	1.0000		Fisher test
Postoperative TACE, n (%)	20 (51.3%)	16 (50%)	0.9144	0.0116	Chisq test
Postoperative Ablation, n (%)	3 (7.7%)	4 (12.5%)	0.7825	0.0762	Yates' correction
Postoperative Iodine-125 Seed Implantation, n (%)	5 (12.8%)	0 (0%)	0.1021	2.6722	Yates' correction
Postoperative Radiotherapy, n (%)			0.4675	2.5435	Yates' correction
Bone Metastasis Radiotherapy	1 (2.6%)	1 (3.1%)			
Lymph Node Metastasis Radiotherapy	0 (0%)	1 (3.1%)			
Left Orbital Metastasis Radiotherapy	0 (0%)	1 (3.1%)			
Postoperative Systemic Chemotherapy, n (%)			1.0000		Fisher test
FOLFOX	1 (2.6%)	0 (0%)			
PEI for Hepatic Lesions, n (%)	0 (0%)	1 (3.1%)	0.4507		Fisher test
Secondary TARE plan, n (%)			0.4051	5.0895	Yates' correction
Plan 1	0 (0%)	2 (6.2%)			
Plan 2	2 (5.1%)	1 (3.1%)			
Plan 3	1 (2.6%)	0 (0%)			
Plan 4	1 (2.6%)	0 (0%)			
Plan 5	1 (2.6%)	0 (0%)			

Notes: ALBI Index = (log10 of Bilirubin × 0.66) + (Albumin × −0.085); ALBI Grade 1: ≤ −2.60, ALBI Grade 2: −2.60 to −1.39, ALBI Grade 3: > −1.39. Confluent Lesions, Multiple lesions merge at a single location, forming a large mass within the liver. These lesions often lack distinct boundaries, resulting in an aggregated tumor with unclear borders. Scattered Lesions, Multiple lesions are distributed diffusely throughout the liver. Each lesion typically maintains relatively clear boundaries, making them distinguishable from one another; PEI, Percutaneous Ethanol Injection; Plan 1: Progression after the first TARE followed by repeated TARE; Plan 2: Staged Treatment Plan: First stage: TARE for lesions in the right lobe of the liver; Second stage: TARE for lesions in the left lobe of the liver. Plan 3: After the first TARE for the right lobe of the liver, repeated TARE was performed due to metastasis in the left lobe of the liver; Plan 4: Staged Treatment Plan: First stage: SIRT for lesions in Segment V of the liver; Second stage: SIRT for lesions in Segments IV and VIII of the liver; Plan 5: Staged Treatment Plan: First stage: TARE for lesions in Segments VIII and VII of the liver; Second stage: TARE for lesions in Segments V, VI, and VII of the liver.

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; CP, Child-Pugh; ALBI, Albumin-Bilirubin; PVTT, portal vein tumor thrombus; TAD, tumor-absorbed dose; LSF, lung shunt fraction; TNR, tumor-to-nontumoral liver ratios; ICIs, immune checkpoint inhibitors; TARE, Transarterial radioembolization; TACE, transarterial chemoembolization.

and a median of two sessions. Prior TACE was defined as any TACE performed before the index TARE session, regardless of the number of sessions. To avoid misclassification, only TACE performed ≥4 weeks before TARE was considered "prior TACE", reflecting the minimum recovery interval in routine practice. This pattern was closely associated with Group 1's "long-term combination therapy" strategy: since Group 1 patients required pretreatment long-

term ICIs plus targeted therapy, TACE was often administered concurrently for local tumor control to slow progression and extend the treatment window, forming a "TACE + ICI/targeted therapy" long-term combination regimen. This resulted in significantly higher TACE exposure rates. In Group 2 (pri-TARE group), only 15.6% (n=5) of patients had prior TACE, all consisting of a single session. Further investigation revealed that these five patients underwent pretreatment ^{99}mTc-MAA scintigraphy (to assess LSF), and TACE was administered temporarily to prevent tumor progression during imaging, rather than as part of a long-term combination regimen; the remaining 27 patients (84.4%) in Group 2 underwent TARE directly, fully aligning with the "early TARE" strategy.

Post-TARE treatment for both groups primarily consisted of combined local intervention and systemic therapy, with no significant intergroup differences in the distribution of core regimens. Postoperative TACE was the most common local intervention, with similar administration rates between Group 1 (n=20, 51.3%) and Group 2 (n=16, 50%). Postoperative ablation (Group 1: 7.7% vs Group 2: 12.5%, P = 0.7825) and radiotherapy (Group 1: 2.6% vs Group 2: 9.3%) had low incidence rates. Postoperative Iodine-125 seed implantation was only observed in Group 1 (n=5, 12.5%) and absent in Group 2; all these treatments served primarily as salvage therapy.

A total of six patients (8.5%) in the entire cohort achieved downstaging to surgical resection, with two patients in Group 1 (n=2, 5.1%) and four patients in Group 2 (n=4, 12.5%). Although Group 2 had a higher downstaging rate, the difference between groups was not statistically significant (P = 0.4950).

Survival and Tumor Response

Tables 3 and S4 presents treatment responses according to the mRECIST and RECIST criteria. The ORR based on mRECIST was significantly higher in Group 2 than in Group 1 (87.5% vs 56.4%, P = 0.0043, chi-square = 8.1568). For best target liver

Table 3 Response to TARE Treatment

Characteristics	Group 1	Group 2	pvalue	Statistic	Method
n	39	32			
mRECIST criteria					
Best Treatment Response, n (%)			0.0415	8.2270	Yates' correction
CR	2 (5.1%)	2 (6.2%)			
PR	20 (51.3%)	26 (81.2%)			
SD	8 (20.5%)	2 (6.2%)			
PD	9 (23.1%)	2 (6.2%)			
ORR of Best Treatment Response, n (%)	22 (56.4%)	28 (87.5%)	**0.0043**	8.1568	Chisq test
DCR of Best Treatment Response, n (%)	30 (76.9%)	30 (93.8%)	0.1052	2.6248	Yates' correction
Best Target Tumor Lesion Response, n (%)			0.0473	7.9370	Yates' correction
CR	4 (10.3%)	2 (6.2%)			
PR	21 (53.8%)	27 (84.4%)			
SD	10 (25.6%)	2 (6.2%)			
PD	4 (10.3%)	1 (3.1%)			
ORR of Best Target Tumor Lesion Response, n (%)	25 (64.1%)	29 (90.6%)	**0.0092**	6.7898	Chisq test
DCR of Best Target Tumor Lesion Response, n (%)	35 (89.7%)	31 (96.9%)	0.4824	0.4934	Yates' correction
RECIST criteria					
Best Treatment Response, n (%)			0.1840	4.8385	Yates' correction
CR	0 (0%)	1 (3.1%)			
PR	11 (28.2%)	11 (34.4%)			
SD	19 (48.7%)	18 (56.2%)			
PD	9 (23.1%)	2 (6.2%)			
ORR of Best Treatment Response, n (%)	11 (28.2%)	12 (37.5%)	0.4050	0.6934	Chisq test
DCR of Best Treatment Response, n (%)	30 (76.9%)	30 (93.8%)	0.1052	2.6248	Yates' correction

(*Continued*)

Table 3 (Continued).

Characteristics	Group 1	Group 2	pvalue	Statistic	Method
Best Target Tumor Lesion Response, n (%)			0.5923	1.9052	Yates' correction
CR	2 (5.1%)	1 (3.1%)			
PR	11 (28.2%)	12 (37.5%)			
SD	22 (56.4%)	18 (56.2%)			
PD	4 (10.3%)	1 (3.1%)			
ORR of Best Target Tumor Lesion Response, n (%)	13 (33.3%)	13 (40.6%)	0.5257	0.4027	Chisq test
DCR of Best Target Tumor Lesion Response, n (%)	35 (89.7%)	31 (96.9%)	0.4824	0.4934	Yates' correction

Notes: This table presents the best treatment response and the best target tumor lesion response to Y-90 treatment, as categorized by the RECIST and mRECIST criteria. The data emphasize the efficacy of Y-90 treatment, particularly under the mRECIST criteria, in achieving disease control and tumor shrinkage in patients with hepatocellular carcinoma.
Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

tumor response, Group 2 also showed a significantly higher ORR than Group 1 (90.6% vs 64.1%, P = 0.0092, chi-square = 6.7898). Kaplan–Meier survival analysis of Table S5 demonstrated a significantly longer PFS in Group 2 compared with Group 1 (Figure 1A). The median PFS was 4.86 months (95% confidence interval [CI]: 3.45–8.80) in Group 1 and 17.45 months (95% CI: 9.86–NR) in Group 2. Patients in Group 1 had a significantly higher risk of progression than those in Group 2 (hazard ratio [HR] = 3.29, 95% CI: 1.52–7.09, P = 0.002). No significant difference was observed in PFS for hepatic target lesions between the two groups (Figure 1B). The median PFS for hepatic target lesions was 16.69 months (95% CI: 9.23–NR) in Group 1 and 19.19 months (95% CI: 17.45–NR) in Group 2 (HR = 1.52, 95% CI: 0.66–3.49, P = 0.320). Similarly, no statistically significant difference in OS was observed between the two groups (Figure 1C). The median OS was 25.92 months (95% CI: 16.69–NR) in Group 1, whereas the median OS in Group 2 was not reached (95% CI: 19.19–NR), with a corresponding HR of 1.34 (95% CI: 0.48–3.79, P = 0.578). Stratification by baseline NLR revealed that patients with NLR ≤3.28 had significantly better PFS than those with NLR >3.28 (Figure 1D). The median PFS was 9.86 months (95% CI: 7.36–NR) versus 4.24 months (95% CI: 3.02–NR), respectively, with a higher NLR associated with an increased risk of disease progression (HR = 2.42, 95% CI: 1.24–4.71, P = 0.010). For hepatic target lesions, patients with NLR ≤3.28 also demonstrated significantly longer PFS than those with NLR >3.28 (Figure 1E). The median PFS was 19.19 months (95% CI: 17.45–NR) versus 7.56 months (95% CI: 4.57–NR), corresponding to a higher risk of progression in patients with elevated NLR (HR = 4.29, 95% CI: 1.70–10.81, P = 0.002). Regarding OS, no statistically significant difference was observed between patients with NLR ≤3.28 and those with NLR >3.28 (Figure 1F). The median OS was 25.92 months (95% CI: 19.19–NR) versus 10.58 months (95% CI: 10.58–NR), respectively (HR = 2.37, 95% CI: 0.76–7.36, P = 0.135). NR indicates that the median survival was not reached at the time of analysis.

Safety Analysis

Tables 4 and S6 summarizes perioperative and postoperative 1- and 3-month complications. Perioperatively, elevated ALT and AST levels (Grade 1) occurred in 12.8% (n=5) of Group 1 patients and 12.5% (n=4) of Group 2 patients. At 1 month postoperatively, leukopenia (Grade 2) occurred in 5.1% (n=2) of Group 1 patients and 3.1% (n=1) of Group 2 patients. Radiation-induced pneumonitis (Grade 4) occurred in 2.6% (n=1) of Group 1 and 3.1% (n=1) of Group 2; both patients died from progression to radiation-induced pneumonitis (Grade 5) within 3 months postoperatively. Both cases occurred in the context of advanced disease and multiple prior treatments, with no protocol deviations in LSF assessment or dosimetry identified. At 3 months postoperatively, thrombocytopenia (Grade 2) occurred in 5.1% (n=2) of Group 1 patients and 9.4% (n=3) of Group 2 patients.

Univariate and Multivariate Cox Analysis of Predictors for Treatment Response

Tables 5 and S7 summarizes the results of the univariate and multivariate Cox regression analyses for factors associated with PFS after TARE. In the univariate analysis, patients who received pri-TARE therapy demonstrated significantly

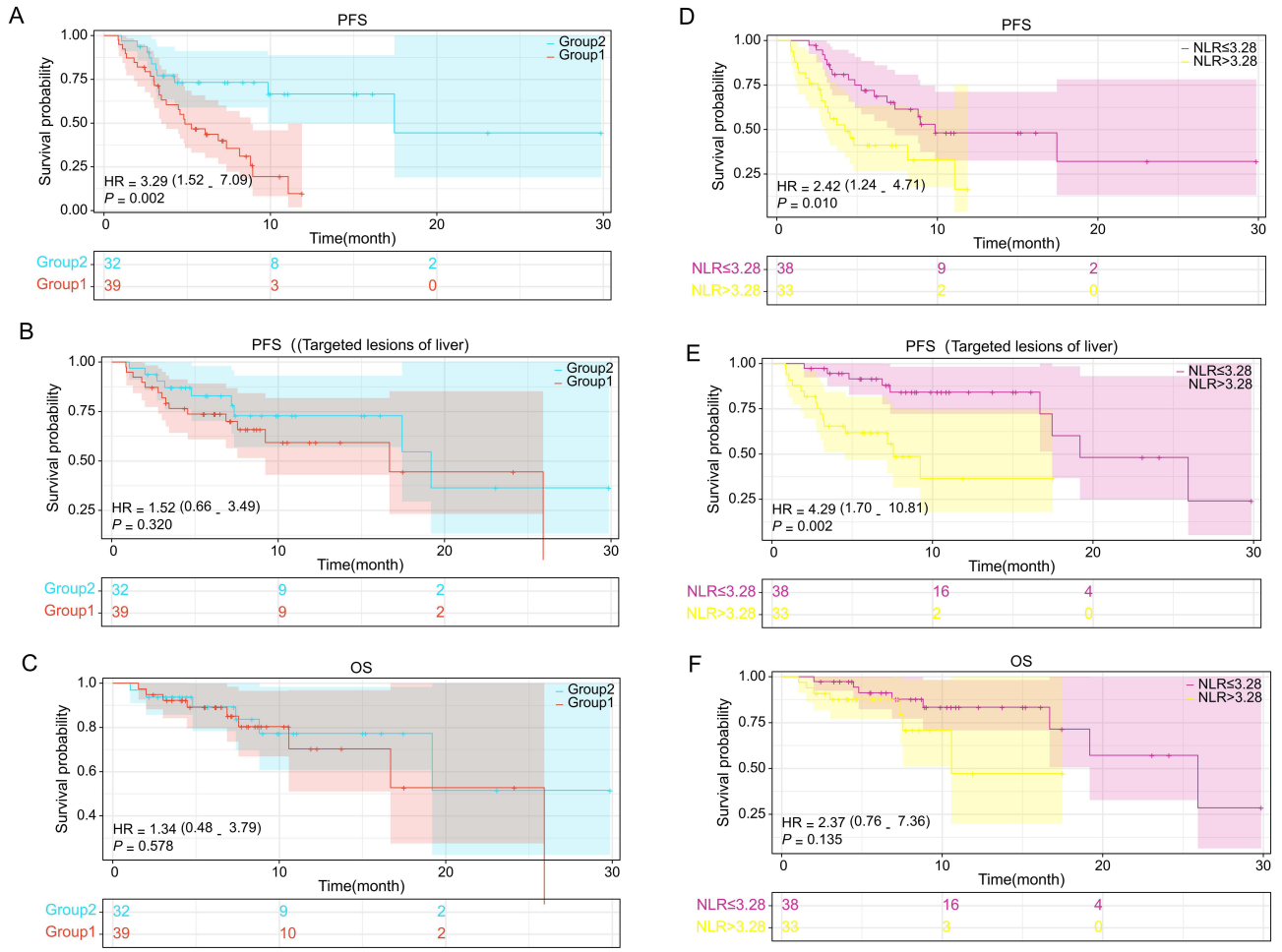

Figure 1 Survival analysis of patients. (**A**) PFS of Group 1: Median (IQR) =4.86 months (CI: 3.4497–8.8049); PFS of Group 2: Median (IQR) = 17.45 months (CI: 9.8563- NR); The hazard ratio (HR) =3.29 (95% CI: 1.52–7.09), P=0.002. (**B**) PFS for Hepatic Target Lesions of Group 1: Median (IQR) = 16.69 months (CI: 9.232- NR); PFS for Hepatic Target Lesions of Group 2: Median (IQR) = 19.19 months (CI: 17.446- NR); The hazard ratio (HR) =1.52 (95% CI: 0.66–3.49), P=0.320. (**C**) OS of Group 1: Median (IQR) = 25.92 months (CI: 16.69- NR); Median OS of Group 2 was not reached (CI: 19.187- NR); The hazard ratio (HR) =1.34 (95% CI: 0.48–3.79), P=0.578. (**D**) PFS of NLR ≤3.28: Median (IQR) =9.86 months (CI: 7.3593- NR); PFS of NLR>3.28: Median (IQR) = 4.24 months (CI: 3.0226- NR); The hazard ratio (HR) =2.42 (95% CI: 1.24–4.71), P=0.010. (**E**) PFS for Hepatic Target Lesions of NLR ≤3.28: Median (IQR) = 19.19 months (CI: 17.446- NR); PFS for Hepatic Target Lesions of NLR>3.28: Median (IQR) = 7.56 months (CI: 4.5667- NR); The hazard ratio (HR) =4.29 (95% CI: 1.70–10.81), P=0.002. (**F**) OS of NLR ≤3.28: Median (IQR) = 25.92 months (CI: 19.187- NR); OS of NLR>3.28: Median (IQR) = 10.58 months (CI: 10.579– NR); The hazard ratio (HR) =2.37 (95% CI: 0.76–7.36), P=0.135. NR indicates that the median survival was not reached due to insufficient events at the time of analysis.

improved PFS compared with those who received pri-ICIs combined with targeted therapy (HR: 0.304, 95% CI: 0.141–0.656, P = 0.002). This association remained statistically significant after multivariate adjustment (HR: 0.327, 95% CI: 0.125–0.856, P = 0.023), indicating a lower risk of disease progression following TARE. The NLR, reflecting the balance between circulating neutrophils and lymphocytes at baseline, also showed prognostic relevance. Patients with NLR >3.28 had a significantly higher risk of disease progression in the univariate analysis (HR: 2.415, 95% CI: 1.238–4.711, P = 0.010). Although this association did not reach conventional statistical significance after multivariate adjustment (HR: 1.920, 95% CI: 0.970–3.800, P = 0.061), the observed trend suggests a potential adverse prognostic impact of elevated NLR. Regarding liver function, CP class B was associated with inferior PFS compared with CP class A in the univariate analysis (HR: 2.183, 95% CI: 1.112–4.283, P = 0.023). However, this association was attenuated and no longer statistically significant after multivariate adjustment (HR: 1.608, 95% CI: 0.795–3.253, P = 0.186). Importantly, prior TACE is a well-recognized prognostic factor in HCC and showed substantial baseline imbalance between groups in this cohort; therefore, it was included as a predefined covariate in the multivariate analysis. In the univariate analysis, a history of prior TACE was associated with a borderline increased risk of PFS events (HR: 1.945, 95% CI: 0.982–3.851, P = 0.056). After adjustment for treatment exposure and other clinical covariates, prior TACE was

Table 4 Complications Analysis

Characteristics	Group 1	Group 2	pvalue	Statistic	Method
n	39	32			
Perioperative Complications, n (%)			0.0923	12.2601	Yates' correction
Abdominal pain (Grade 1)	0 (0%)	3 (9.4%)			
Elevated ALT and AST levels (Grade 1)	5 (12.8%)	4 (12.5%)			
RILD (Grade 4)	0 (0%)	1 (3.1%)			
Thrombocytopenia (Grade 2)	1 (2.6%)	0 (0%)			
Fever (Grade 1)	0 (0%)	2 (6.2%)			
Anemia (Grade 2)	4 (10.3%)	0 (0%)			
Elevated bilirubin levels (Grade 1)	1 (2.6%)	0 (0%)			
Postoperative 1-Month Complications, n (%)			0.3470	6.7255	Yates' correction
Leukopenia (Grade 2)	2 (5.1%)	1 (3.1%)			
Gastrointestinal bleeding (Grade 5)	1 (2.6%)	0 (0%)			
Radiation-induced pneumonitis (Grade 4)	1 (2.6%)	1 (3.1%)			
Liver failure (Grade 5)	0 (0%)	1 (3.1%)			
Thrombocytopenia (Grade 2)	3 (7.7%)	0 (0%)			
Elevated bilirubin levels (Grade 1)	2 (5.1%)	0 (0%)			
Postoperative 3-Month Complications, n (%)			0.5675	3.8754	Yates' correction
Thrombocytopenia (Grade 2)	2 (5.1%)	3 (9.4%)			
Elevated ALT and AST levels (Grade 1)	0 (0%)	1 (3.1%)			
Leukopenia (Grade 1)	0 (0%)	1 (3.1%)			
Radiation-induced pneumonitis (Grade 5)	1 (2.6%)	1 (3.1%)			
Anemia (Grade 2)	1 (2.6%)	0 (0%)			

Note: This table summarizes the safety profile of patients treated with Y-90 radioembolization.
Abbreviations: RILD, radioembolisation-induced liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 5 Cox Univariate and Multivariate Analysis

Characteristics	HR (95% CI) Univariate Analysis	P value	HR (95% CI) Multivariate Analysis	P value
Therapy				
Pri-ICIs add targeted therapy	Reference		Reference	
Pri-TARE	0.304 (0.141–0.656)	**0.002**	0.327 (0.125–0.856)	**0.023**
NLR group				
NLR≤3.28	Reference		Reference	
NLR>3.28	2.415 (1.238–4.711)	**0.010**	1.920 (0.970–3.800)	0.061
BCLC Stage				
Stage A	Reference			
Stage B	2.328 (0.607–8.919)	0.218		
Stage C	2.265 (0.681–7.538)	0.183		
Hepatitis Virus Infection Status				
None	Reference			
HBV Carrier	1.040 (0.501–2.158)	0.916		
CP Classification				
A	Reference		Reference	
B	2.183 (1.112–4.283)	**0.023**	1.608 (0.795–3.253)	0.186
ALBI Grade				
Grade 1	Reference			
Grade 2	1.182 (0.552–2.534)	0.667		
Grade 3	15.326 (1.653–142.119)	0.016		

(*Continued*)

Table 5 (Continued).

Characteristics	HR (95% CI) Univariate Analysis	P value	HR (95% CI) Multivariate Analysis	P value
Lesion Distribution Pattern				
Single Lesion	Reference			
Confluent Lesions	1.526 (0.428–5.442)	0.515		
Scattered Lesions	2.434 (0.724–8.181)	0.151		
International Classification of PVTT				
None	Reference			
VP2	1.410 (0.327–6.086)	0.645		
VP3	0.656 (0.245–1.754)	0.401		
VP4	0.931 (0.435–1.992)	0.854		
Prior TACE				
None	Reference		Reference	
TACE	1.945 (0.982–3.851)	0.056	0.871 (0.364–2.081)	0.756
Postoperative TACE				
TACE	Reference			
None	0.627 (0.318–1.236)	0.178		

Notes: Table 5 presents the results of univariate and multivariate Cox regression analyses on factors affecting PFS, with HR and 95% CI provided. Both analyses indicate that patients who received pri-TARE therapy had significantly better PFS compared to those who received pri-ICIs combined with targeted therapy.
Abbreviations: HCC Stage, Barcelona Clinic Liver Cancer; NLR, neutrophil-to-lymphocyte ratio; CP, Child-Pugh; ALBI, Albumin-Bilirubin; PVTT, portal vein tumor thrombus; ICIs, immune checkpoint inhibitors; TARE, Transarterial radioembolization; TACE, transarterial chemoembolization.

no longer significantly associated with PFS (HR: 0.871, 95% CI: 0.364–2.081, P = 0.756), suggesting that its apparent effect may be influenced by treatment selection and baseline disease characteristics rather than representing an independent prognostic determinant.

Other variables, including BCLC stage, hepatitis virus infection status, ALBI grade, lesion distribution pattern, and portal vein tumor thrombus classification, were not independently associated with PFS in the multivariate analysis.

Discussion

This study investigated post-TARE prognostic factors in patients with HCC and demonstrated significant differences in PFS between patients who received systemic therapy prior to TARE and those who underwent TARE as the initial treatment. As a real-world retrospective cohort, the two groups reflected distinct clinical pathways rather than predefined therapeutic strategies; therefore, the observed differences should be interpreted as post-TARE prognostic associations rather than causal comparisons of treatment sequences.

To mitigate immortal time bias, TARE was defined as the uniform starting point for survival analyses. Nevertheless, baseline heterogeneity inherent to retrospective designs could not be fully eliminated. Accordingly, the time windows used to define pre- and post-TARE systemic therapy were intended as pragmatic operational criteria to ensure consistent classification within a heterogeneous cohort, rather than recommendations for optimal treatment sequencing. The ≥2-cycle cutoff for pre-TARE systemic therapy aligns with routine clinical practice, in which at least two treatment cycles are required for initial radiologic response assessment, whereas the 1–3-month post-TARE window reflects standard follow-up intervals and the typical timeframe for resuming systemic therapy.

Our results showed that patients in the TARE-first group achieved significantly longer PFS compared with those who had received systemic therapy prior to TARE. This finding likely reflects the strong local tumor control capability of TARE, which delivers high-dose localized radiation to tumor-feeding arteries and effectively suppresses intrahepatic tumor progression. Importantly, this PFS advantage did not translate into a statistically significant OS benefit. Several factors may explain this discrepancy. First, OS analysis was limited by an insufficient number of death events and relatively short follow-up duration. Second, subsequent systemic therapies after progression may have attenuated OS differences between groups. Third, OS in HCC is heavily influenced by liver function deterioration and intrahepatic disease control rather than progression alone, further diluting the observable impact of initial treatment sequencing.

Consistent with our findings, previous studies have demonstrated robust local control achieved with TARE. De la Torre-Aláez et al reported an ORR of 41.5% and a median time to progression (TTP) of 8.8 months in patients undergoing downstaging prior to surgical resection.[27] Lee et al observed an ORR of 83.3% and a median TTP of 15.2 months in patients treated with TARE combined with durvalumab,[28] further highlighting the potent locoregional efficacy of TARE. By contrast, lenvatinib, a first-line multikinase inhibitor for advanced HCC, has demonstrated a modest ORR of approximately 24.1% when used as monotherapy,[29,30] highlighting the limitations of systemic therapy alone in achieving rapid intrahepatic tumor control. In addition, retrospective studies have shown that Y-90 radioembolization combined with atezolizumab and bevacizumab achieved ORRs of up to 58% and meaningful survival outcomes in advanced HCC.[10,31] Collectively, these data support the role of TARE as an effective modality for rapid tumor burden reduction and durable intrahepatic disease control.

Growing evidence also suggests a synergistic interaction between TARE and immunotherapy. Zhan et al reported favorable survival outcomes in patients receiving ICIs following TARE, with acceptable safety profiles.[32] Similarly, the combination of TARE with pembrolizumab has been associated with prolonged PFS and OS, as well as high DCRs.[11] Mechanistically, TARE induces immunogenic cell death, promotes tumor antigen release, and enhances T-cell activation, thereby facilitating systemic antitumor immune responses and potential abscopal effects.[21] Notably, Rivoltini et al observed that TARE-induced immunomodulatory effects peak approximately 1 month after treatment and decline thereafter, highlighting the importance of timely integration of immunotherapy.[33] Mathematical modeling further supports superior outcomes when Y-90 radioembolization is administered prior to ICIs rather than sequentially afterward.[21]

Beyond treatment sequencing, this study identified the NLR as a relevant prognostic biomarker in TARE-treated patients with HCC. Lower NLR was significantly associated with prolonged PFS, extending prior observations that primarily focused on OS outcomes.[25] NLR is thought to reflect the balance between protumor inflammatory activity and antitumor immune surveillance. Patients with lower NLR likely possess higher peripheral lymphocyte proportions, which may undergo stronger radiation-induced immune activation and enhance responses to subsequent immunotherapy. This interpretation is consistent with reports demonstrating improved outcomes in patients with HCC with low NLR receiving ICIs,[23] suggesting that NLR represents a cross-modal prognostic marker relevant across locoregional and systemic therapies. Although NLR did not retain independent significance in multivariable analysis, its consistent association with favorable outcomes supports its continued evaluation in larger prospective cohorts.

Liver function also played a critical role in post-TARE outcomes. Patients with CP class B experienced a higher risk of PFS events compared with those with CP class A, although baseline sample size imbalance limited the robustness of this comparison. Prior studies have consistently shown that liver function status strongly influences survival in TARE-treated HCC, with median OS substantially longer in CP class A patients than in CP class B patients.[34–36] Given that the majority of HCC-related deaths result from intrahepatic progression or liver failure rather than distant metastasis,[37] careful patient selection based on liver reserve remains essential.

The ALBI score, another validated indicator of liver function, has also been linked to TARE efficacy. Previous studies identified favorable ALBI scores as predictors of improved treatment response.[38] Although ALBI grade was not independently associated with PFS in our cohort, it remains a valuable tool for stratifying patients and optimizing treatment selection in future studies.

Some limitations of this study should be acknowledged. First, its retrospective design and non-randomized treatment exposure introduce potential selection bias. Second, follow-up duration was insufficient for mature OS analysis, limiting definitive survival comparisons. Third, heterogeneity in systemic therapy regimens precluded detailed evaluation of specific drug combinations. Finally, the prognostic value of NLR requires validation in larger, prospective cohorts. Future multicenter studies with standardized treatment protocols and longer follow-up are warranted to clarify optimal integration strategies for TARE, immunotherapy, and targeted therapy in HCC.

Conclusion

In conclusion, this study identified significant differences in post-TARE clinical outcomes between patients who received systemic therapy prior to TARE and those who underwent TARE as the initial treatment. The TARE-first group showed

better PFS and ORR, suggesting that baseline treatment exposure may influence post-TARE prognosis. These differences should be interpreted in the context of baseline treatment exposure and disease trajectory, rather than as evidence supporting a specific therapeutic sequence. These findings highlight the importance of treatment sequence as a clinical factor rather than confirming the superiority of any specific therapeutic strategy. Prospective trials are needed to validate these associations and further explore optimal treatment sequencing in HCC management.

Abbreviations

HCC, Hepatocellular carcinoma; TARE, Transarterial radioembolization; TACE, Transarterial chemoembolization; ICIs, Immune checkpoint inhibitors; ORR, Objective response rate; DCR, Disease control rate; OS, Overall survival; PFS, Progression-free survival; TTP, Time to progression; Y-90, Yttrium-90; ALBI, Albumin-bilirubin; NLR, Neutrophil-to-lymphocyte ratio; BCLC, Barcelona Clinic Liver Cancer; CP, Child-Pugh; ECOG, Eastern Cooperative Oncology Group; SPECT, Single photon emission computed tomography; ^{99}mTc-MAA, Technetium-99m macroaggregated albumin; LSF, Lung shunt fraction; TNR, Tumor-to-nontumoral liver uptake ratio; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase; RECIST, Response Evaluation Criteria in Solid Tumors; mRECIST, Modified Response Evaluation Criteria in Solid Tumors; CT, Computed tomography; MRI, Magnetic resonance imaging; HR, Hazard ratio; CI, Confidence interval; NR, Not reached; Gy, Gray; GBq, Gigabecquerel; MIRD, Medical Internal Radiation Dose.

Data Sharing Statement

The datasets generated during this retrospective study are available from the corresponding author upon reasonable request. All relevant raw data of patients in this study are available in the Supplementary Material. Raw data containing personal identifiers are not publicly accessible, in accordance with patient privacy protection requirements and institutional regulations. Aggregated data supporting the findings are included in this published article or its supplementary information files.

Ethics Approval

This study was designed as a non-interventional retrospective cohort study, employing de-identified clinical data extracted from the electronic medical record database of Fujian Cancer Hospital. All personal identifiers, including but not limited to patients' names, identification numbers, and contact details, were systematically eliminated to ensure the protection of patient privacy. Notably, the research process involved no direct interaction with patients and did not interfere with routine clinical diagnostic or therapeutic procedures. The Ethics Committees of both Fujian Cancer Hospital and Fujian Medical University Cancer Hospital granted approval for the research (approval code K2025-207-01). In accordance with regulatory guidelines for non-interventional retrospective research and ethical review standards applicable to medical institution, the committees determined that the study—relying on pre-collected, de-identified data—does not compromise patient rights or privacy. Consequently, the requirement for re-obtaining specific informed consent from participants was formally exempted.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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