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ORIGINAL RESEARCH

Survival Benefits of Transarterial Chemoembolization Plus Ablation Therapy in Patients With Intermediate or Advanced Hepatocellular Carcinoma: A Propensity Score Matching Study

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Purpose: To evaluate the survival outcomes of patients with intermediate to advanced hepatocellular carcinoma (HCC), patients who underwent transarterial chemoembolization (TACE) alone were compared with those who underwent a combination of TACE and ablation therapy.

Patients and Methods: This study retrospectively evaluated 536 HCC patients in our hospital from July 2016 to November 2022. All patients underwent TACE, with a subset also receiving ablation therapy. To ensure comparability, propensity score matching (PSM) was performed. We then compared overall survival (OS) and progression-free survival (PFS) between these two groups. Survival outcomes were analyzed utilizing Kaplan-Meier curves and compared via the Cox regression.

Results: 200 among these 536 HCC patients received TACE combined with ablation whereas the remaining 336 received TACE alone. With PFS analysis, the numbers were reduced to 176 in combination therapy group and 250 in TACE alone group. With and without PSM, the OS and PFS were consistently and significantly better in the former than the latter group. In patients with Barcelona Clinic Liver Cancer (BCLC) stage B or C, those who received combination therapy demonstrated significantly higher OS compared to those treated with TACE alone. For stage B patients, PFS was also significantly longer in the combination therapy group, before and after PSM [hazard ratio (HR), 0.563; 95% CI: 0.360–0.879; $P = 0.012$, HR, 0.613; 95% CI: 0.382–0.985; $P = 0.043$]. However, after PSM, no statistical difference in survival outcomes was observed between the two groups for stage C patients (HR, 0.673; 95% CI: 0.395–1.146; $P = 0.145$).

Conclusion: Our data suggested that for OS, the combination therapy has sustained benefits for both patients with stage B and C, But for PFS, the benefits of the combination therapy among the stage C patients, could not be persistently demonstrated by the current datasets.

Keywords: hepatocellular carcinoma, transarterial chemoembolization, ablation, overall survival, progression free survival

Introduction

Primary liver cancer is the sixth most common cancer in the world, with approximately 830,000 deaths every year, making it the third leading cause of cancer-related mortality.[1] Hepatocellular carcinoma (HCC) is the most common pathological type of primary liver cancer, accounting for nearly 90% of cases.[2] At present, anti- hepatitis B virus (HBV)

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and anti- hepatitis C virus (HCV) therapy can significantly reduce the risk of liver cancer, but still cannot completely avoid the occurrence and recurrence of HCC.[3]

Different stages of HCC have different treatment methods, but the recurrence and metastasis after treatment are still the most serious clinical problems.[4] Surgery is frequently regarded as an effective treatment for early-stage liver cancer.[5] However, HCC often presents with a silent onset, typically diagnosed at intermediate (BCLC stage B) to advanced (stage C) stages,[6] often against a backdrop of underlying liver conditions such as hepatitis and cirrhosis.[7] At the time of diagnose, only approximately 15% of patients are candidates for surgical resection or liver transplantation. Consequently, the majority of HCC patients often miss the opportunity for curative treatment by the time the disease is diagnosed.[8] Currently, locoregional therapies (LRTs) have gained widespread international acceptance as the primary treatment for patients with unresectable stage B and C HCC. These LRTs encompass transarterial chemoembolization (TACE) and ablative therapies, such as microwave ablation (MWA) and radiofrequency ablation (RFA), which have proven to be effective in managing such cases.[9,10] HCC is a highly heterogeneous disease, and the effect of any single treatment is often limited.[11] The combined treatment of two or more methods plays an important role in the treatment of stage C HCC and can make up for the deficiency of single treatment.[12] The combined treatment have been proven to be synergistically effective in managing the HCC cases.[13,14] TACE treatment can reduce tumor volume, and the "siphonic effect" of tumor on iodide makes it easier to locate lesions.[15,16] With the assistance of multi-modal imaging techniques, ablative therapy becomes more precise and comprehensive, resulting in a reduced incidence of complications.[17]

More specifically, several retrospective studies have reported that TACE combined with thermal ablation could not benefit the long-term survival of HCC patients with Barcelona Clinic Liver Cancer (BCLC) stage 0-B.[18,19] However, recent randomized controlled studies have consistently demonstrated that the integration of MWA or RFA following TACE significantly enhances treatment efficacy, without escalating the risk of major complications. Notably, this combination therapy was not constrained by the stage or tumor size.[20–22] Under these inconsistent findings among study, there is a need to check whether the outcome of treatment is affected by the tumor stage in our medical center which is in the endemic areas of HCC and TACE has been implements since 2015.

Our study was carried out to compare the survival advantages of TACE alone versus TACE combined with ablation therapy (MWA or RFA) in HCC patients with stage B/C, aiming to identify the most effective treatment strategy for these individuals.

Materials and Methods

Patients

This retrospective study was conducted at the Third People's Hospital of Kunming in China from July 2016 to November 2022. This hospital is a designated tertiary infectious disease hospital specializing in liver diseases, mainly admitting referred patients from this region. We obtained clinical data and follow-up data from the electronic medical system and the hospital's research information system related to liver diseases.

A total of 637 HCC patients received continuous TACE therapy, with some also undergoing ablative therapy. The inclusion criteria for this study were: (1) Age ≥18 years; (2) Diagnosis of primary HCC based on clinical, laboratory, and imaging examinations, adhering to the 2024 Chinese Guidelines for the diagnosis and treatment of primary liver cancer,[23] as well as the diagnostic criteria set by the European Association for the Study of the Liver (EASL)[24] and the American Association for the Study of Liver Diseases (AASLD)[25] after a review of each patient's chart by two experienced hepatologists; (3) Inoperable patients with stage B or C, with all tumor nodules having a maximum diameter of ≤70mm; (4) No previous anti-tumor therapies, including surgery, radiotherapy, or systemic therapy; (5) Patients who received TACE or TACE combined with ablation as initial treatment. The exclusion criteria were as follows: (1) HIV positive patients; (2) History of metastatic extrahepatic malignancy; (3) Other malignant tumors; (4) Incomplete clinical data; (5) Loss of follow-up.

Data Collection

Patient demographic and clinical data were collected. Patient demographics including age, gender, alcohol history. Clinical data including cause of liver disease, cirrhosis, laboratory tests, Child-Pugh category, MELD score,

complications, and number of TACE treatments. Laboratory tests including aspartate transaminase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), alpha-L-fucosidase (AFU), prothrombin time (PT), international normalized ratio (INR), carcinoembryonic antigen (CEA), alpha-fetoprotein (AFP). Complications including liver cancer rupture and hemorrhage, cirrhosis with esophageal and gastric varices, spontaneous peritonitis, hepatic encephalopathy, ascites, and portal hypertension. Additionally, Chest CT plain scan or magnetic resonance imaging (MRI) were collected one month after TACE or TACE plus ablation. Imaging data including the degree of ascites, portal hypertension, number of tumors, tumor size, the presence of tumor metastasis, and BCLC stage.

Treatment Procedures

Our hospital has standard treatment conditions for HCC. The Seldinger technique was commonly used for TACE treatment. Precisely guided by a microwire, a microcatheter was utilized to navigate into the pathological artery branch and deliver chemotherapeutic drugs based on ethiodized oil injection/LIPIODOL 10mL (containing 480mg/mL of iodine). Commonly used chemotherapy drugs included epirubicin, oxaliplatin, cisplatin and mitomycin. The dosage of chemotherapy drugs was selected according to the patient's tumor load, body surface area, physical condition, previous drug use and whether combined application. Finally, an appropriate amount of gelatine sponge granule embolization agent (diameter 350μm) was injected to reach the embolization end point. Post-treatment contrast imaging revealed successful deposition of lipiodide in the focal region of liver disease, indicating complete embolization of the tumor-supplying artery. This method effectively obstructed the arterial blood supply to liver cancer, enabling the sustained release of high-concentration chemotherapy drugs that targeted and induced ischemic necrosis and shrinkage of the tumor, all while minimizing the impact on healthy liver tissue. The decision regarding follow-up treatment was based on tumor response, liver function, renal function, physical status, and treatment tolerance.[26] The choice to repeat the TACE procedure was made after thorough evaluation by three experienced clinicians.

Sequential ablation was performed 1 to 4 weeks after the TACE procedure, primarily using MWA or RFA techniques. The tumor ablation criteria for HCC were determined according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST): a single tumor with a diameter of ≤50 mm, or 2–3 tumors with a maximum diameter of ≤30 mm. For single or multiple tumors with a diameter of 30–70 mm that were unsuitable for surgical resection, TACE followed by sequential ablation therapy was recommended.[23]

Percutaneous RFA was performed under imaging guidance. Before the procedure, CT or MRI scans were performed to confirm the tumor's location and characteristics, as well as to identify the target area. During the procedure, local anesthesia combined with intravenous sedation was employed; however, a small number of patients required general anesthesia. Additionally, the patients' vital signs and blood oxygen saturation were continuously monitored. Under CT guidance, the radiofrequency electrode needle was inserted to the ablation target. During RFA, treatment parameters were set based on the type of RFA device, the model of the radiofrequency electrode needle, the size of the tumor, and its relationship with surrounding tissues. When using ultrasound guidance, deeper tumors were ablated first, followed by more superficial tumors. To ensure the efficacy of tumor ablation therapy, the ablation should encompass the entire tumor as well as a 5 to 10 mm margin of paracancerous tissue surrounding it. For large tumors undergoing RFA (diameter > 50 mm), a multi-point overlapping conformal ablation technique was employed. When removing the RFA electrode, routine ablation of the tissue along the electrode path was performed to prevent bleeding and tumor dissemination. Imaging studies were conducted post-procedure to check for complications such as bleeding or pneumothorax. Similarly, all MWA procedures were performed percutaneously under ultrasound guidance. MWA generated heat in local tissues via microwave emitted by the ablation needle, causing tumor cell degeneration and coagulation necrosis. As a result, these two methods represent the most common used thermal ablation techniques.[27]

Follow-Up

Patients were followed up regularly every six months from the start of their first TACE treatment for a total of 18 months, with the follow-up period ending on May 27, 2024. The endpoints for the study were death or liver transplantation. Follow-up data included survival outcomes, laboratory tests (AST, ALT, ALP, AFU, PT, INR CEA, AFP), and imaging result (degree of ascites, portal hypertension, number of tumors, tumor size, tumor metastasis, and BCLC stage). The

primary endpoint was overall survival (OS), which was tracked during the 18-month follow-up period. OS was defined as the time from the initial TACE procedure to either the patient's death or the last 18-month follow-up. The secondary endpoint was progression-free survival (PFS), defined as the time from the start of TACE treatment to either radiological progression or death.

Statistical Analysis

Categorical variables are presented as frequency counts and percentages. The Shapiro–Wilk test was performed on continuous variables to explore the normality. For normally distributed continuous variables, the mean and standard deviation (SD) were reported, while for non-normally distributed variables, the median and interquartile range (IQR) was used. The Pearson χ^2 test was applied to categorical variables. For continuous variables with normal distribution, the *t*-test was carried out; for non-normally distributed variables, the Wilcoxon rank sum test (also known as the Mann–Whitney *U*-test) was utilized.

To ensure comparability between the TACE group and the TACE plus ablation group, we used the 1:1 nearest neighbor matching based on propensity scores.[28] A logistic regression model was used to estimate the propensity scores. Potentially confounding variables that could affect outcomes were included in the PSM. The following variables: patient demographics (age, gender, alcohol), cause of disease, cirrhosis, laboratory tests (AST, ALT, CEA, AFP), Child-Pugh category, MELD score, complications (including liver cancer rupture and hemorrhage, cirrhosis with esophageal and gastric varices, spontaneous peritonitis, hepatic encephalopathy, ascites, and portal hypertension), BCLC stage, number of TACE treatments.

Kaplan-Meier curves were constructed to evaluate PFS and OS, and the Cox regression was used to assess statistical differences between the two groups both before and after PSM matching. We ran Cox regression to calculate hazard ratio (HR) in order to get the effect size and its 95% CI. All analyses were performed using R software (version 4.2.3; https://www.rproject.org/). Statistical analyses employed two-tailed tests, with the threshold for statistical significance defined as 0.05.

Results

Study Population and Patient Characteristics

A total of 101 HCC patients were excluded, and 536 HCC patients were included in the study: 336 in the TACE alone group and 200 in the TACE plus ablation group. Clinical data were regularly followed up for 18 months to assess PFS in both groups. Among them, 426 cases had complete imaging data: 250 in the TACE alone group and 176 in the TACE plus ablation group. The flowchart of the inclusion process was shown in Figure 1, and the baseline characteristics of the 536 patients were presented in Table 1.

After PSM, the 536 patients were evenly divided into two groups: 200 in the TACE alone group and 200 in the TACE plus ablation group. Before and after PSM, viral hepatitis was the predominant cause of liver disease among HCC patients, with HBV being the most common. The matching process reduced significant difference in confounding factors between the two groups, including cause of liver disease, AST, ALP, Child-Pugh category, liver cancer rupture and bleeding, spontaneous peritonitis, hepatic encephalopathy, ascites, portal hypertension, and stage (Table 1).

Evaluation of PFS requires complete imaging data, 426 patients with complete imaging data were segregated into two groups: the TACE group (comprising 176 cases) and the TACE plus ablation group (also with 176 cases) after PSM. The baseline characteristics of patients with complete imaging data were detailed in Table 2. PSM effectively adjusted for confounding factors, ensuring comparability between the two groups in terms of cause of liver disease, AST, ALP, Child-Pugh category, liver cancer rupture and bleeding, spontaneous peritonitis, hepatic encephalopathy, ascites, portal hypertension, and stage.

To further assess the matching effect (OS and PFS), we visualized the absolute standardized mean difference (Figures S1 and S2), distribution of propensity score (Figures S3 and S4), Histogram and density curve (Figures S5 and S6) to demonstrated the efficiency of the matching process. PSM successfully achieved a balanced comparison between the TACE group and the TACE plus ablation group, ensuring the accuracy and reliability of the subsequent analysis.

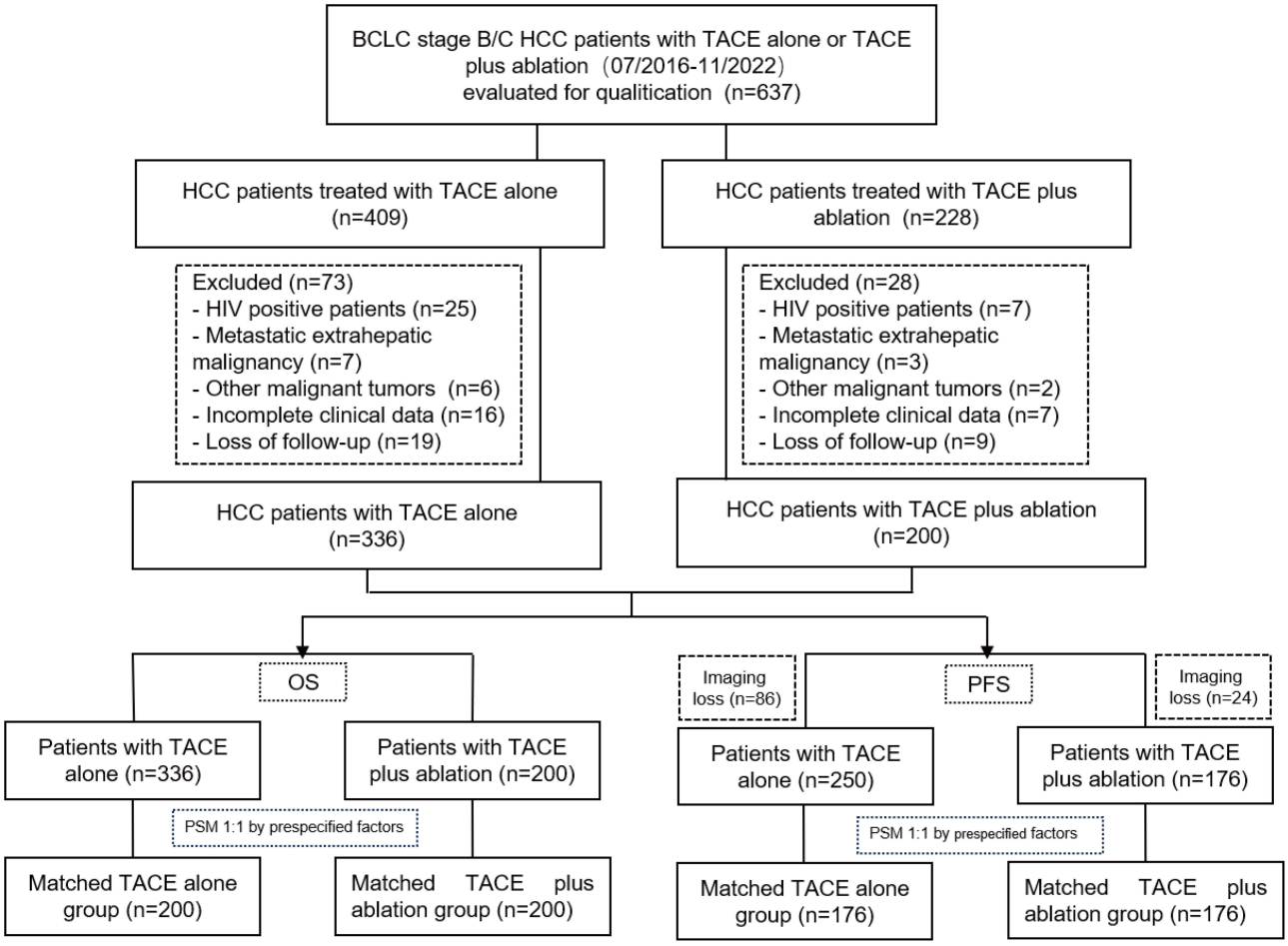

Figure 1 Flow chart of the screening procedure for HCC patients with BCLC stage B/C.
Abbreviations: BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; HIV, human immunodeficiency virus; PSM, propensity score matching.

OS Between TACE Alone Group and TACE Plus Ablation Group

The 18-month OS rates were 78.0% (95% CI: 72.5–84.0%) for the TACE plus ablation group and 56.5% (95% CI: 51.5–62.1%) for the TACE alone group. The HR for receiving combination therapy vs receiving TACE alone was 0.401 (95% CI: 0.286–0.562, $P < 0.0001$) (Figure 2A). Among the initial cohort of 536 patients, 190 (35.45%) died within the 18-month regular follow-up period. The median survival time was 5.0 months (95% CI: 4.70–6.14). Notably, the TACE alone group accounted for

Table 1 Baseline Characteristics of OS in the TACE Group Alone and in the TACE Plus Ablation Group

Parameter	Overall Series			Propensity Score-Matched Pairs		
	TACE Alone (n=336)	TACE Plus Ablation (n=200)	*P* value	TACE Alone (n=200)	TACE Plus Ablation (n=200)	*P* value
Age, mean (SD), y	53 (47.0, 59.0)	54 (48.0, 61.0)	0.339	53 (47.8, 60.3)	54 (48.0, 61.0)	0.594
Gender, n (%)			0.215			0.684
Male	292 (86.9)	166 (83.0)		169 (84.5)	166 (83.0)	
Female	44 (13.1)	34 (17.0)		31 (15.5)	34 (17.0)	
Alcohol, n (%)			0.537			0.546
Yes	152 (45.2)	85 (42.5)		91 (45.5)	85 (42.5)	
No	184 (54.8)	115 (57.5)		109 (54.5)	115 (57.5)	

(*Continued*)

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Table 1 (Continued).

Parameter	Overall Series			Propensity Score-Matched Pairs		
	TACE Alone (n=336)	**TACE Plus Ablation (n=200)**	***P* value**	**TACE Alone (n=200)**	**TACE Plus Ablation (n=200)**	***P* value**
Cause of disease, n (%)			0.084			0.828
HBV	217 (64.6)	143 (71.5)		139 (69.5)	143 (71.5)	
HCV	56 (16.7)	36 (18.0)		33 (16.5)	36 (18.0)	
Alcoholic hepatitis	7 (2.1)	5 (2.5)		5 (2.5)	5 (2.5)	
Multiple	41 (12.2)	11 (5.5)		15 (7.5)	11 (5.5)	
Others	15 (4.5)	5 (2.5)		8 (4.0)	5 (2.5)	
Cirrhosis, n (%)			0.066			0.203
Yes	298 (88.7)	187 (93.5)		180 (90.0)	187 (93.5)	
No	38 (11.3)	13 (6.5)		20 (10.0)	13 (6.5)	
AST (U/L, median [IQR])	51.5 (33.0, 92.0)	43 (32.0, 63.0)	0.002	42 (31.0, 65.2)	43 (32, 63)	0.682
ALT (U/L, median [IQR])	37 (25.0, 67.4)	35 (25.0, 55.2)	0.167	34 (24.8, 53.5)	35 (25.0, 55.2)	0.647
ALP (U/L, median [IQR])	147 (101.5, 211.5)	125 (98.0, 157.0)	< 0.001	131 (94.0, 183.0)	125 (98.0, 157.0)	0.192
AFU (U/L, median [IQR])	29 (24.0, 37.0)	29 (24.0, 34.0)	0.331	28 (23.0, 35.0)	29 (24.0, 34.0)	0.731
PT (s, median [IQR])	14.7 (14.1, 15.9)	14.6 (13.9, 15.7)	0.110	14.7 (14.1, 15.9)	14.6 (13.9, 15.7)	0.310
INR, median [IQR]	1.2 (1.1, 1.3)	1.2 (1.1, 1.3)	0.079	1.2 (1.1, 1.3)	1.2 (1.1, 1.3)	0.432
CEA (ng/mL, median [IQR])	2.8 (1.9, 4.3)	3 (2.0, 4.4)	0.785	2.7 (1.8, 3.9)	3 (2.0, 4.4)	0.248
AFP (ng/mL, median [IQR])	37.1 (5.2, 1316.4)	21.3 (7.3, 262.2)	0.097	18.3 (4.0, 215.0)	21.3 (7.3, 262.2)	0.149
Child-Pugh category, n (%)			< 0.001			0.426
A	141 (42.0)	110 (55.0)		102 (51.0)	110 (55.0)	
B	136 (40.5)	76 (38.0)		77 (38.5)	76 (38.0)	
C	59 (17.6)	14 (7.0)		21 (10.5)	14 (7.0)	
MELD score, median [IQR]	5.8 (3.2, 8.6)	6 (3.7, 8.1)	0.644	5.3 (3.3, 7.8)	6 (3.7, 8.1)	0.234
Liver cancer rupture and bleeding, n (%)			< 0.001			1.000
Yes	33 (9.8)	2 (1.0)		3 (1.5)	2 (1.0)	
No	303 (90.2)	198 (99.0)		197 (98.5)	198 (99.0)	
Cirrhosis with esophageal and gastric varices, n (%)			0.679			0.658
Yes	98 (29.2)	55 (27.5)		59 (29.5)	55 (27.5)	
No	238 (70.8)	145 (72.5)		141 (70.5)	145 (72.5)	
Spontaneous peritonitis, n (%)			< 0.001			0.485
Yes	86 (25.6)	16 (8.0)		20 (10.0)	16 (8.0)	
No	250 (74.4)	184 (92.0)		180 (90.0)	184 (92.0)	
Hepatic encephalopathy, n (%)			0.001			0.121
Stage 1–2	60 (17.9)	17 (8.5)		29 (14.5)	17 (8.5)	
Stage 3–4	10 (3.0)	1 (0.5)		1 (0.5)	1 (0.5)	
No	266 (79.2)	182 (91.0)		170 (85.0)	182 (91.0)	
Ascites, n (%)			0.002			0.298
Mild	84 (25.0)	39 (19.5)		42 (21.0)	39 (19.5)	
Moderate or severe	49 (14.6)	13 (6.5)		21 (10.5)	13 (6.5)	
No	203 (60.4)	148 (74.0)		137 (68.5)	148 (74.0)	
Portal hypertension, n (%)			0.047			0.214
Yes	106 (31.5)	80 (40.0)		68 (34.0)	80 (40.0)	
No	230 (68.5)	120 (60.0)		132 (66.0)	120 (60.0)	
BCLC stage, n (%)			0.016			0.826
B	204 (60.7)	142 (71.0)		140 (70.0)	142 (71.0)	
C	132 (39.3)	58 (29.0)		60 (30.0)	58 (29.0)	
No. of TACE cycles, median [IQR]	1 (1, 2)	2 (2, 4)	< 0.001	1 (1, 2)	2 (2, 4)	< 0.001

Abbreviations: TACE, transarterial chemoembolization; HBV, hepatitis B virus; HCV, hepatitis C virus; BCLC, Barcelona Clinic Liver Cancer; MELD, model for end-stage liver disease; AST, aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AFU, alpha-L-fucosidase; PT, prothrombin time; INR, international normalized ratio; CEA, carcinoembryonic antigen; AFP, alpha- fetoprotein.

Table 2 Baseline Characteristics of PFS in the TACE Group Alone and in the TACE Plus Ablation Group

Parameter	Progression Free Survival			Propensity Score-Matched Pairs		
	TACE Alone (n=250)	TACE Plus Ablation (n=176)	*P* value	TACE Alone (n=176)	TACE Plus Ablation (n=176)	*P* value
Age, mean (SD), y	54.3 (9.8)	54.9 (9.3)	0.537	54.5 (10.1)	54.9 (9.3)	0.738
Gender, n (%)			0.075			0.389
Male	220 (88.0)	144 (81.8)		150 (85.2)	144 (81.8)	
Female	30 (12.0)	32 (18.2)		26 (14.8)	32 (18.2)	
Alcohol, n (%)			0.813			1.000
Yes	108 (43.2)	74 (42.0)		74 (42.0)	74 (42.0)	
No	142 (56.8)	102 (58.0)		102 (58.0)	102 (58.0)	
Cause of disease, n (%)			0.105			0.818
HBV	165 (66.0)	126 (71.6)		125 (71.0)	126 (71.6)	
HCV	40 (16.0)	32 (18.2)		28 (15.9)	32 (18.2)	
Alcoholic hepatitis	5 (2.0)	5 (2.8)		4 (2.3)	5 (2.8)	
Multiple	29 (11.6)	8 (4.5)		11 (6.2)	8 (4.5)	
Others	11 (4.4)	5 (2.8)		8 (4.5)	5 (2.8)	
Cirrhosis, n (%)			0.171			0.127
Yes	225 (90.0)	165 (93.8)		157 (89.2)	165 (93.8)	
No	25 (10.0)	11 (6.2)		19 (10.8)	11 (6.2)	
AST (U/L, median [IQR])	51 (33.0, 86.0)	43 (32.8, 63.0)	0.013	44.5 (31.0, 66.2)	43 (32.8, 63.0)	0.999
ALT (U/L, median [IQR])	36.5 (25.0, 62.0)	35 (25.0, 55.2)	0.450	35 (25.0, 55.5)	35 (25.0, 55.2)	0.805
ALP (U/L, median [IQR])	149 (102.0, 206.0)	126 (98.0, 159.0)	0.001	132 (94.0, 191.5)	126 (98.0, 159.0)	0.160
AFU (U/L, median [IQR])	29 (23.0, 36.0)	29 (24.0, 34.5)	0.618	28 (23.0, 34.0)	29 (24.0, 34.5)	0.474
PT (s, median [IQR])	14.7 (14.1, 15.9)	14.5 (13.9, 15.7)	0.101	14.6 (14.1, 15.9)	14.5 (13.9, 15.7)	0.232
INR, median [IQR]	1.2 (1.1, 1.3)	1.2 (1.1, 1.3)	0.070	1.2 (1.1, 1.3)	1.2 (1.1, 1.3)	0.214
CEA (ng/mL, median [IQR])	2.9 (2.0, 4.4)	3 (2.0, 4.4)	0.860	2.7 (2.0, 3.8)	3 (2.0, 4.4)	0.249
AFP (ng/mL, median [IQR])	43.5 (5.1, 1268.1)	22.3 (7.6, 270.9)	0.233	20.8 (3.9, 305.4)	22.3 (7.6, 270.9)	0.319
Child-Pugh category, n (%)			0.003			0.157
A	102 (40.8)	98 (55.7)		83 (47.2)	98 (55.7)	
B	106 (42.4)	64 (36.4)		70 (39.8)	64 (36.4)	
C	42 (16.8)	14 (8.0)		23 (13.1)	14 (8.0)	
MELD score, median [IQR]	5.8 (3.4, 7.9)	5.8 (3.5, 8.2)	0.735	6.1 (3.8, 7.9)	5.8 (3.5, 8.2)	0.939
Liver cancer rupture and bleeding, n (%)			0.012			1.000
Yes	15 (6.0)	2 (1.1)		2 (1.1)	2 (1.1)	
No	235 (94.0)	174 (98.9)		174 (98.9)	174 (98.9)	
Cirrhosis with esophageal and gastric varices, n (%)			0.723			0.906
Yes	75 (30.0)	50 (28.4)		49 (27.8)	50 (28.4)	
No	175 (70.0)	126 (71.6)		127 (72.2)	126 (71.6)	
Spontaneous peritonitis, n (%)			< 0.001			0.126
Yes	58 (23.2)	15 (8.5)		24 (13.6)	15 (8.5)	
No	192 (76.8)	161 (91.5)		152 (86.4)	161 (91.5)	
Hepatic encephalopathy, n (%)			0.004			0.097
Stage 1–2	44 (17.6)	14 (8.0)		26 (14.8)	14 (8.0)	
Stage 3–4	6 (2.4)	1 (0.6)		1 (0.6)	1 (0.6)	
No	200 (80.0)	161 (91.5)		149 (84.7)	161 (91.5)	
Ascites, n (%)			0.019			0.286
Mild	60 (24.0)	36 (20.5)		39 (22.2)	36 (20.5)	
Moderate or severe	38 (15.2)	13 (7.4)		21 (11.9)	13 (7.4)	
No	152 (60.8)	127 (72.2)		116 (65.9)	127 (72.2)	
Portal hypertension, n (%)			0.009			0.019
Yes	72 (28.8)	72 (40.9)		51 (29.0)	72 (40.9)	
No	178 (71.2)	104 (59.1)		125 (71.0)	104 (59.1)	

(*Continued*)

Table 2 (Continued).

Parameter	Progression Free Survival			Propensity Score-Matched Pairs		
	TACE Alone (n=250)	TACE Plus Ablation (n=176)	*P* value	TACE Alone (n=176)	TACE Plus Ablation (n=176)	*P* value
BCLC stage, n (%)			0.009			0.299
B	148 (59.2)	126 (71.6)		117 (66.5)	126 (71.6)	
C	102 (40.8)	50 (28.4)		59 (33.5)	50 (28.4)	
No. of TACE cycles, median [IQR]	1 (1, 2)	2 (2,4)	< 0.001	1 (1, 2)	2 (2,4)	< 0.001

Abbreviations: TACE, transarterial chemoembolization; HBV, hepatitis B virus; HCV, hepatitis C virus; BCLC, Barcelona Clinic Liver Cancer; MELD, model for end-stage liver disease; AST, aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AFU, alpha-L-fucosidase; PT, prothrombin time; INR, international normalized ratio; CEA, carcinoembryonic antigen; AFP, alpha- fetoprotein.

146 deaths, with a median survival time of 4.4 months (95% CI: 3.91–4.90). In contrast, the TACE plus ablation group accounted for 44 deaths, with a significantly extended median survival time of 8.1 months (95% CI: 7.62–11.50) (Figure 2B).

Following PSM, the 18-month OS rate was 78.0% (95% CI: 72.5–84.0%) for the patients who received TACE plus ablation, compared to 64.5% (95% CI: 58.2–71.5%) for patients who received TACE alone. The risk of death for the combination therapy is 53.30% of that for TACE alone (95% CI: 0.366–0.776; $P = 0.001$) (Figure 2C). Among the 400

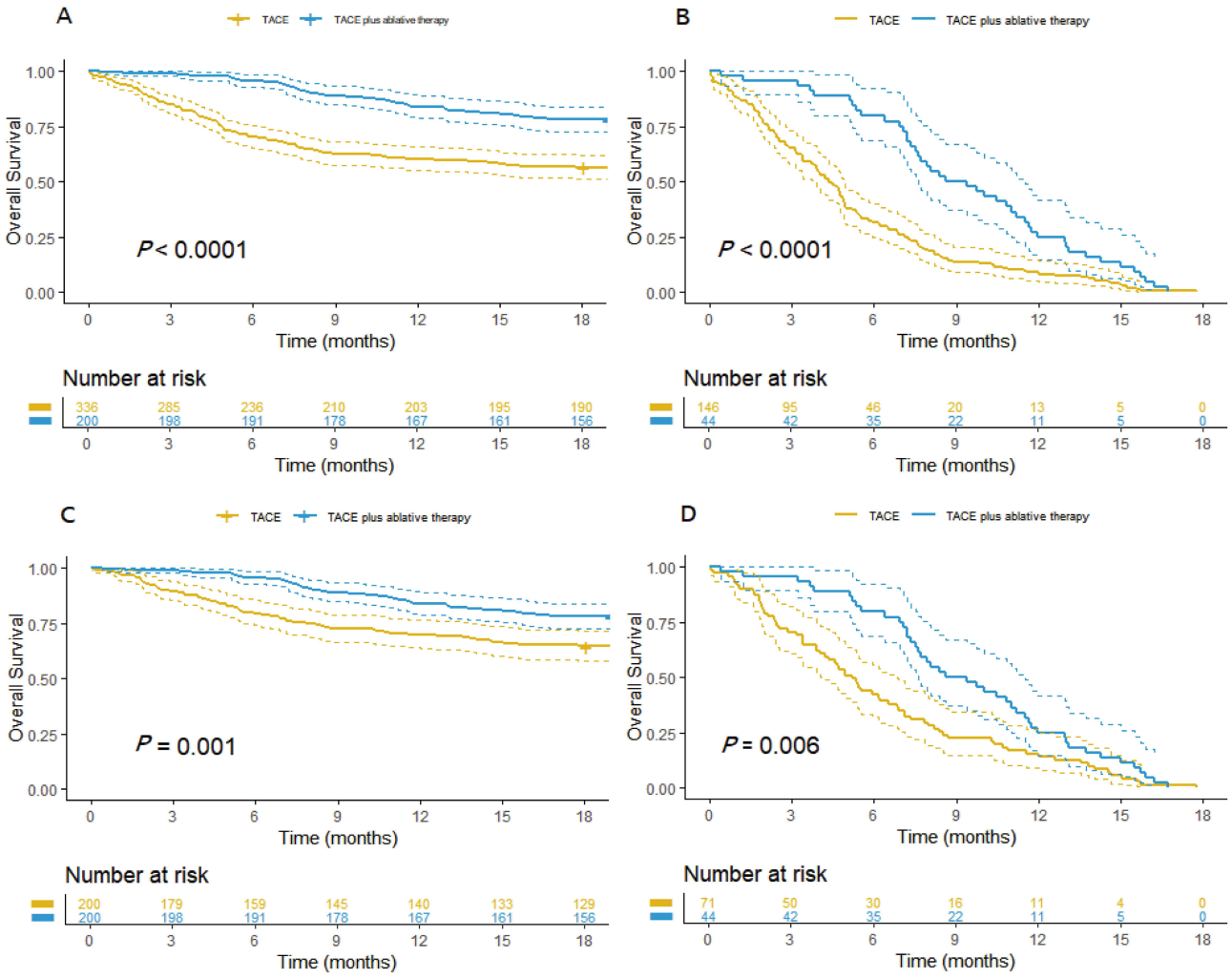

Figure 2 Kaplan-Meier curves of overall survival (OS) between TACE alone group and TACE plus ablation group. (**A**) Cumulative OS curves and, (**B**) OS curve of cumulative total deaths before propensity score matching (PSM). (**C**) cumulative OS curves and, (**D**) OS curve of cumulative total deaths after PSM.

patients, 115 (28.75%) died within the 18-month follow-up period, with a median survival time of 7.1 months (95% CI: 5.52–7.98). In the TACE alone group, there were 71 deaths, with a median survival time of 5.2 months (95% CI: 4.24–6.83). In contrast, the TACE plus ablation group had 44 deaths and maintained a significantly longer median survival time of 8.1 months (95% CI: 7.62–11.50) (Figure 2D).

OS Of HCC Patients With Different Stages

Among the 536 HCC patients at different stages, 204 stage B patients and 132 stage C patients underwent TACE alone, while 142 stage B patients and 58 stage C patients received TACE plus ablation therapy. At the 18-month follow-up, the OS rate for stage B HCC patients treated with TACE alone was 65.2% (95% CI: 59.0–72.1%), whereas those treated TACE plus ablation therapy had a significantly higher OS rate of 81.7% (95% CI: 75.6–88.3%) (Figure 3A). Similarly, for stage C patients, the OS rate with TACE alone therapy was 43.2% (95% CI: 35.5–52.5%), which notably improved to 69.0% (95% CI: 58.0–82.0%) when combined with ablation therapy ($P = 0.00044$) (Figure 3B).

Following PSM, both the TACE alone and TACE plus ablation groups included 200 patients each, with specific distributions among stages B and C. At the 18-month follow-up, the OS rate of stage B patients treated with TACE alone was 70.0% (95% CI: 62.8–78.0%), whereas those treated with TACE plus ablation had a significantly higher OS rate of 81.7%

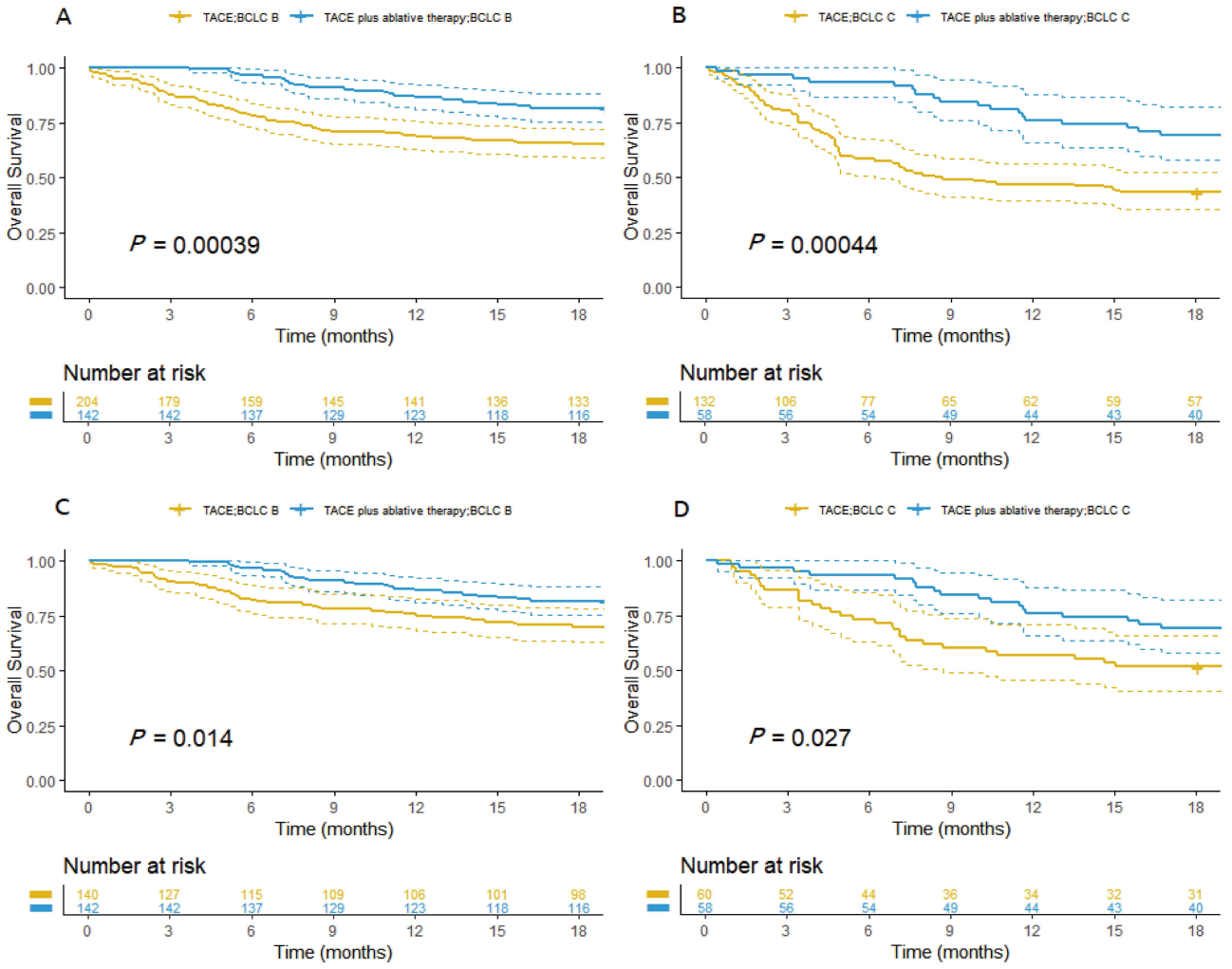

Figure 3 Kaplan–Meier curves of overall survival (OS) in Barcelona Clinic Liver Cancer (BCLC) stage B/C between TACE alone group and TACE plus ablation group. (**A**) Cumulative OS in stage B patients and, (**B**) Cumulative OS in stage C patients before propensity score matching (PSM). (**C**) Cumulative OS in stage B patients and, (**D**) Cumulative OS in stage C patients after PSM.

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(95% CI: 75.6–88.3%) (Figure 3C). For stage C patients, the OS rate with TACE alone was 51.7% (95% CI: 40.5–66.0%), which notably improved to 69.0% (95% CI: 0.580–0.820) when combined with ablation therapy ($P = 0.027$) (Figure 3D).

PFS Between TACE Alone Group and TACE Plus Ablation Group

Among these 426 patients with complete imaging data, 250 underwent TACE alone, while 176 received a combination of TACE plus ablation. At 18 months, the PFS rate was 54.4% (95% CI: 48.6–60.9%) for those treated with TACE alone, significantly lower than the 69.9% (95% CI: 63.4–77.0%) observed in patients treated with TACE plus ablation. The HR for combination therapy vs TACE alone was 0.540 (95% CI: 0.390–0.748; $P = 0.00021$) (Figure 4A). At the 18-month follow-up, 167 patients (39.20%) demonstrated PFS, with a median PFS duration of 5.5 months (95% CI: 4.93–6.93). In the TACE alone group, 114 patients (45.60%) had a median PFS duration of 4.7 months (95% CI: 3.81–5.42). In contrast, 53 patients (30.11%) in the TACE plus ablation group experienced a significantly longer median PFS duration of 7.9 months (95% CI: 7.20–10.45), showing a statistically significant difference ($P = 0.00041$) (Figure 4B).

After PSM, the cohort of 426 patients was balanced into two groups of 176 each to ensure comparability. The PFS rate at 18 months was 58.5% (95% CI: 51.7–66.3%) in patients treated with TACE alone, compared to 69.9% (95% CI: 63.4–77.0%) for those treated with TACE plus ablation. The HR for combination therapy vs TACE alone was 0.622 (95% CI: 0.437–0.886; $P = 0.009$) (Figure 4C). Among the 352 patients, 126 (35.80%) showed PFS at the 18-month follow-up, with a median PFS duration of 6.5 months (95% CI: 5.45–7.75). In the TACE alone group, 73 patients

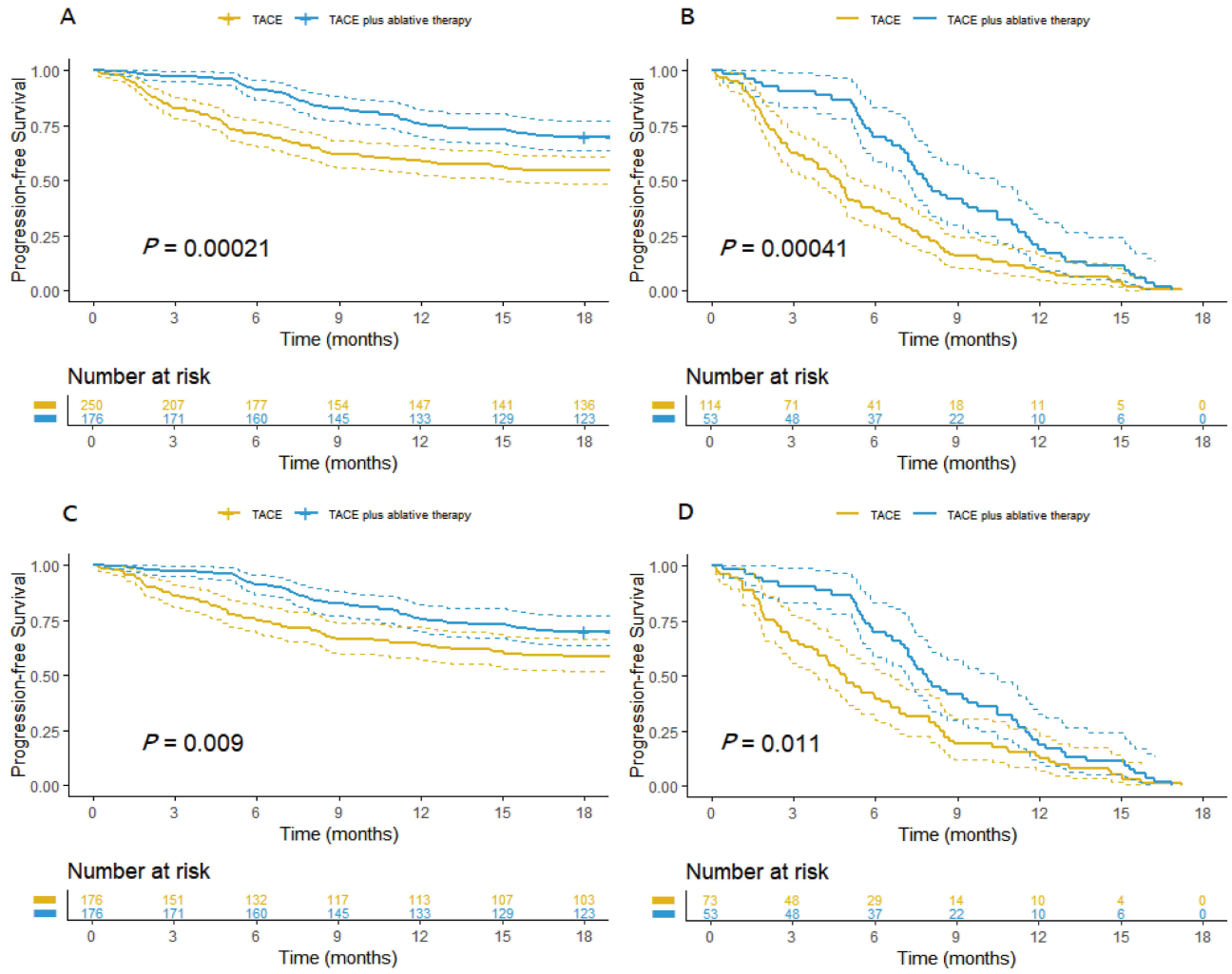

Figure 4 Kaplan–Meier curves of progression-free survival (PFS) between TACE group and TACE plus ablation group. (**A**) Cumulative PFS curves and, (**B**) PFS curve of cumulative total PFS patients before propensity score matching (PSM). (**C**) Cumulative PFS curves and, (**D**) PFS curve of cumulative total PFS patients after PSM.

(41.48%) had a median PFS duration of 4.9 months (95% CI: 3.90–6.51). In contrast, the TACE plus ablation group maintained its advantage, with 53 patients (30.11%) achieving a median PFS duration of 7.9 months (95% CI: 7.20–10.45), showing a statistically significant difference (P = 0.011) (Figure 4D).

PFS Of HCC Patients With Different Stages

Among the 426 HCC patients with complete imaging data, a subset analysis based on BCLC staging revealed distinct outcomes. At the 18-month follow-up, the PFS rate for stage B patients treated with TACE alone was 63.5% (95% CI: 56.2–71.8%), compared to a significantly higher PFS of 76.2% (95% CI: 69.1–84.0%) for those who received TACE plus ablation (P = 0.012) (Figure 5A). Similarly, for stage C patients, the PFS rate for TACE alone was 41.2% (95% CI: 32.7–51.9%), improving to 54.0% (95% CI: 41.8–69.7%) when combined with ablation therapy. The HR for TACE plus ablation therapy vs TACE alone was 0.606 (95% CI: 0.374–0.980; P = 0.041) (Figure 5B).

After PSM, both the TACE alone group and the TACE plus ablation therapy group included 176 patients each. The PFS rate for stage B patients treated with TACE alone was 65.8% (95% CI: 57.8–75.0%), whereas the PFS rate for those who underwent TACE plus ablation therapy was 76.2% (95% CI: 69.1–84.0%) (Figure 5C). For stage C patients, the PFS rate with TACE alone therapy was 44.1% (95% CI: 33.1–58.7%), compared to 54.0% (95% CI: 41.8–69.7%) for those receiving TACE plus ablation therapy. The HR for TACE plus ablation therapy vs TACE alone was 0.673 (95% CI: 0.395–1.146; P = 0.145) (Figure 5D).

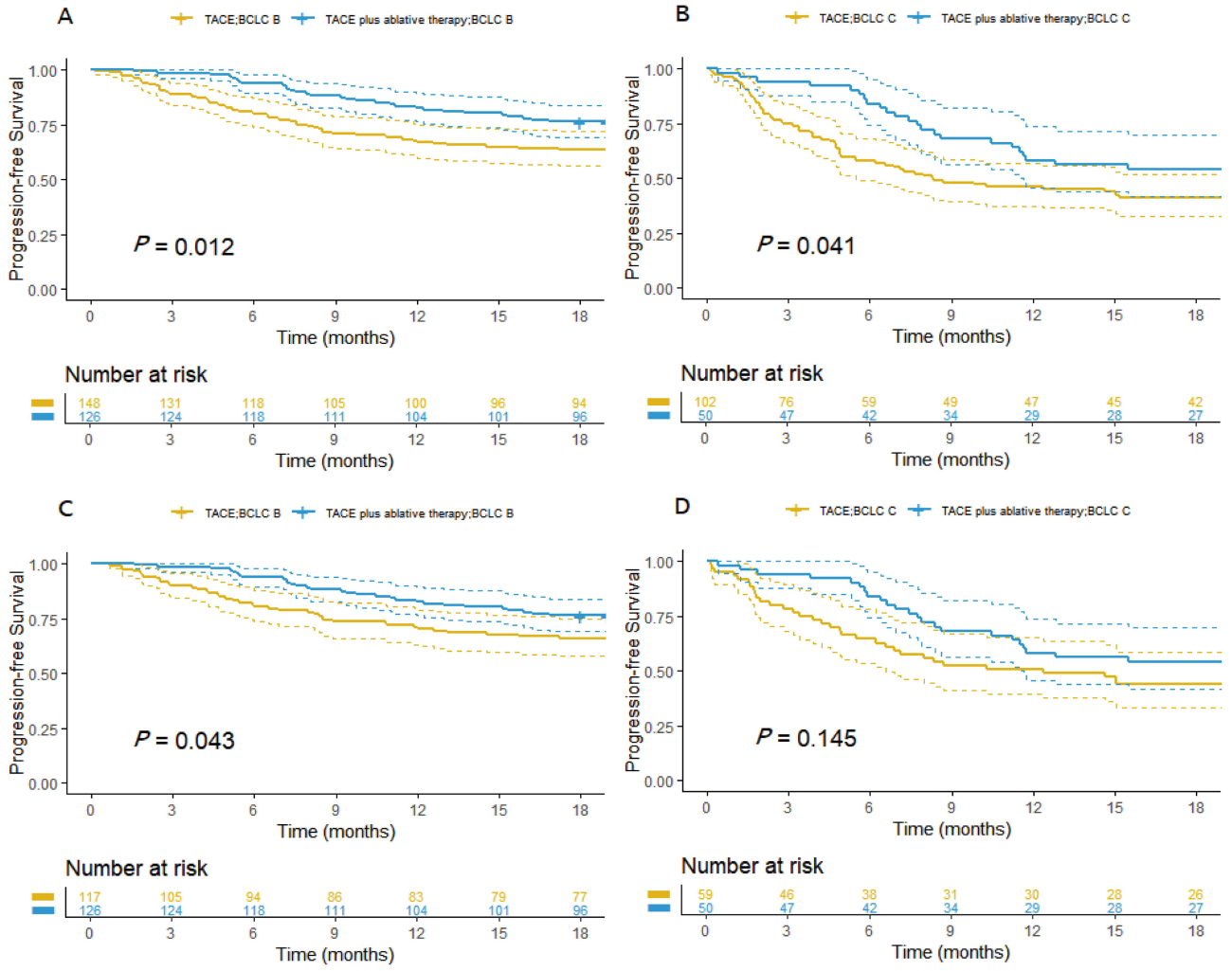

Figure 5 Kaplan–Meier curves of progression-free survival (PFS) in Barcelona Clinic Liver Cancer (BCLC) stage B/C between TACE alone group and TACE plus ablation group. (**A**) Cumulative PFS in stage B patients and, (**B**) Cumulative PFS in stage C patients before propensity score matching (PSM). (**C**) Cumulative PFS in stage B patients and, (**D**) Cumulative PFS in stage C patients after PSM.

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Discussion

This study revealed that adding ablative therapy after initial TACE treatment significantly prolonged both PFS and OS, regardless of whether patients were in stage B or C. However, for stage C patients, while the disease may continue to progress for a period, combination therapy can still effectively extend OS. Notably, few existing studies have utilized sequential ablation therapy, specifically involving MWA or RFA in the treatment of stage B or C HCC patients. In addition, our study included a large cohort of HCC patients and employed a PSM approach to enhance the accuracy and credibility of the results. These findings provide a valuable basis for clinical decision-making, highlight the benefits of combined ablation therapy in specific patient populations, outline its limitations in stage C cases.

In our study, HBV was the etiologic cause of HCC, and our results confirmed previous reports that viral hepatitis, particularly HBV-related viral hepatitis, is most prevalent in Asia and Africa.[29] Therefore, in our study, combination therapy may be more appropriate in Asia and Africa countries where HBV is the primary cause, and may not be appropriate in North America and Europe where alcohol-related liver disease (ALD), HCV and non-alcoholic fatty liver disease (NAFLD) are the most common causes.[30] Chen et al reported no difference in OS and recurrence-free survival (RFS) in HCV-associated and HBV-associated HCC patients treated with TACE combined with RFA.[31] Future research should explore more precise, etiology-specific treatment strategies to enhance therapeutic outcomes and survival rates for HCC patients with various underlying causes.

In this study, TACE combined with sequential RFA was employed for some patients with stage C HCC. Traditionally, the combination of TACE and RFA has primarily been used as a treatment option for early- to mid-stage HCC, particularly in patients who are not suitable candidates for surgical resection or liver transplantation.[22,32] The effectiveness and indications of RFA in the treatment of stage C HCC remain a topic of ongoing in both research and clinical practice. TACE and RFA are standard treatments for stage C HCC approved by the Food and Drug Administration (FDA).[33] Multiple studies have shown that TACE combined with RFA was recommended for unresectable single or multiple tumors with a maximum diameter of 30–70 mm, demonstrating superior efficacy compared to ablation alone.[23,34] The advantages of TACE followed by RFA include accurately determining the number and location of tumors through TACE imaging, facilitating precise RFA under CT guidance. Moreover, for tumor tissues that are inadequately ablated, subsequent TACE therapy can effectively identify and address these overlooked areas. Numerous studies have confirmed that the combination of TACE and RFA can significantly enhance the tumor remission rate and OS of patients with stage C HCC, facilitate downstaging of stage C HCC, and improve patients' quality of life.[35–37] These findings strengthen the evidence supporting the use of TACE combined with RFA in the treatment of patients with stage C HCC, further bolstering confidence in its efficacy and safety.

The study utilized MWA or RFA as the combined therapy methods, may bring additional survival benefits. In previous study, combination therapy has been found to significantly improve OS and PFS in stage B patients compared to TACE alone, without significantly increasing complication risks.[21,38] Recent researches have extensively explored the clinical efficacy of TACE combined with RFA for treating HCC patients in stage A/B.[22,32] TACE combined with MWA offered advantages in enhancing local tumor progression (LTP), prolonging OS, delaying disease progression, and reducing complications compared to TACE alone, regardless of tumor size.[20,39] Thus it can be seen that both MWA and RFA are well-established and widely used as ablation techniques.[40]

Before PSM, there was a statistical difference in PFS between the combination treatment group and the TACE alone group for stage C patients. However, after PSM, no statistical difference in PFS was observed between the two groups. This suggests that the initial differences were primarily due to variations in patient characteristics. PSM helped to balance the baseline characteristics, allowing for a more accurate assessment of the combined treatment effect. Combination therapy did not prolong the PFS in stage C patients, which may be attributed to the differences in tumor burden, liver function, and extrahepatic metastasis in stage C patients, thus affecting the prognosis of the disease.[41] Previous studies have suggested that TACE combined with RFA[42] and TACE combined with molecular-targeted agents including sorafenib or Lenvatinib might be more effective.[43] Peng et al have shown that Sorafenib combined with TACE-RFA has good tolerance and safety, and it can improve the OS and time to progression (TTP) in stage C HCC patients after initial liver resection, compared to Sorafenib alone.[44] In summary, future research should further explore the efficacy and

safety of different combination treatment regimens in patients with stage C HCC, as well as how to improve treatment outcomes through optimized patient selection and personalized treatment strategies.

Our study has several limitations. Firstly, as a retrospective study, it was subject to potential confounding factors, which we attempted to address using PSM but could not fully eliminate. Secondly, all procedures were performed at a single institution, which is an infectious disease hospital with a patient population primarily sourced from viral hepatitis cases. Thirdly, Due to incomplete imaging data, 110 fewer patients were included in the secondary outcome PFS assessment than in the primary outcome OS assessment. This exclusion may introduce bias because these patients may have specific clinical characteristics or treatment responses that may affect the generality and representativeness of our results.

Conclusion

In summary, for BCLC stage B patients, TACE plus ablation therapy demonstrated significant advantages in both PFS and OS. For stage C patients, while adjunct ablative therapy showed a benefit in prolonging OS, it did not achieve a statistically significant difference in controlling disease progression and extending PFS. These findings underscore the importance of tailoring treatment strategies to the patient's specific disease stage.

Data Sharing Statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding authors.

Ethical Statement

This study was approved by the Ethics Committee of Kunming Third People's Hospital (KSLL20230320031) and was conducted in accordance with the Declaration of Helsinki guidelines. As a retrospective study, it was exempt from informed consent requirements. The names and identification numbers of all patients included in this study were anonymized to ensure confidentiality and protect the identities of the participants.

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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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