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ORIGINAL RESEARCH

Combined TACE with Targeted and Immunotherapy versus TACE Alone Improves DFS in HCC with MVI: A Multicenter Propensity Score Matching Study

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Background: Hepatocellular carcinoma (HCC) with microvascular invasion (MVI) is associated with high recurrence and poor survival outcomes. Although adjuvant therapies such as transcatheter arterial chemoembolization (TACE), targeted therapy, and immunotherapy show potential in improving outcomes, the optimal postoperative treatment strategy remains undetermined. This study evaluates the efficacy of different adjuvant treatments on disease-free survival (DFS) and overall survival (OS) in HCC patients with MVI following curative resection.

Methods: A retrospective cohort of 409 HCC patients with MVI who underwent curative resection from three clinical centers between 2017 and 2024 was analyzed. Patients were stratified into three groups: TACE alone (n=132), TACE + targeted therapy (n=58), and TACE + targeted immunotherapy (n=68). Propensity score matching (PSM) was employed to balance confounding factors. Kaplan-Meier survival curves and Cox regression models were used to assess DFS and OS. A nomogram was constructed for individualized DFS prediction.

Results: After PSM, both the TACE + targeted therapy and TACE + targeted immunotherapy groups exhibited significantly prolonged DFS compared to TACE alone (median DFS: 16 vs 22 and 21 months, respectively; p=0.027). No significant differences were observed in OS across the groups. The nomogram for DFS demonstrated robust predictive performance, with a C-index of 0.709 and 0.645 in the training and validation cohorts, respectively, supporting its utility in clinical decision-making.

Conclusion: In HCC patients with MVI, adjuvant TACE combined with targeted therapy or targeted immunotherapy significantly enhances DFS, though no OS benefit was observed. The developed nomogram provides a reliable tool for risk stratification and personalized postoperative management in this high-risk patient population.

Keywords: hepatocellular carcinoma, microvascular invasion, postoperative adjuvant therapy, targeted therapy, immunotherapy, transcatheter arterial chemoembolization

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Introduction

Based on the latest data from the National Cancer Center of China, derived from cancer registries and follow-up monitoring, hepatocellular carcinoma (HCC) ranks fourth in incidence and second in mortality among all cancers in China.[1] Despite advances in medical treatments, the five-year survival rate for liver cancer remains at only 15%, with a recurrence rate within five years as high as 70%.[2] In addition, HCC patients with high-risk factors for recurrence—such as microvascular invasion (MVI), tumor diameter ≥5 cm, elevated AFP levels, and multiple tumors—face a significantly increased risk of recurrence.[3–6] For patients at high risk of recurrence, as recommended by the latest American Association for the Study of Liver Diseases guidelines,[7] adjuvant therapies such as hepatic arterial infusion chemotherapy (HAIC), transcatheter arterial chemoembolization (TACE), targeted therapy, and immunotherapy are employed to reduce this risk. While TACE and HAIC have been standard treatments for preventing HCC recurrence and have shown some efficacy, their results remain suboptimal. Although combined targeted and immunotherapy offers new hope, these treatments are effective only in a subset of patients.[8–10] Current studies indicate that the best objective response rate (ORR) for combined targeted and immunotherapy in HCC does not exceed 30%.[11] The success of the IMbrave150 trial marks a significant advancement in the treatment of advanced unresectable HCC, demonstrating superior overall survival (OS) and progression-free survival (PFS) with atezolizumab and bevacizumab compared to sorafenib.[12] In the IMbrave050 trial, among patients with resected or ablated high-risk HCC, those treated with atezolizumab plus bevacizumab exhibited significantly improved recurrence-free survival (RFS) compared to those under active surveillance.[13] Following IMbrave 050, an increasing array of combined targeted and immunotherapy regimens, such as Lenvatinib,[14] Apatinib,[15] Regorafenib,[16] Sintilimab,[17] Carrelizumab,[18] and Tislelizumab,[19] are being used for advanced unresectable HCC. The efficacy of these combinations varies, and treatment choices are constrained by factors such as the patient's economic status, overall health, side effects, and tumor heterogeneity.

MVI is recognized as a key factor influencing the prognosis of HCC and is closely associated with the tumor's aggressive nature.[20] Although emerging techniques, such as computed tomography (CT), magnetic resonance imaging (MRI), ultrasound and positron emission tomography (PET)/ CT, have shown potential in preoperatively predicting HCC-MVI status, their inherent limitations have hindered widespread clinical application. It has been identified in numerous studies as a critical determinant of early recurrence (within 24 months) following surgery.[4,21] As a result, patients with MVI often undergo additional postoperative adjuvant therapies, such as HAIC or TACE, sometimes in combination with targeted therapy or immunotherapy. Despite advancements, there is still a gap in research comparing the effectiveness of various postoperative treatment options for MVI-complicated resectable HCC. Clinicians often base adjuvant therapy decisions on experience and patient tolerance, lacking evidence from clinical trials to determine the best treatment for a patient. However, clinical trials are time-consuming and costly, making real-world studies on adjuvant therapy for HCC essential, as they can provide quicker recommendations with less resource expenditure. This study aims to evaluate the effects of three treatment strategies—TACE, TACE combined with targeted therapy, and TACE combined with both targeted and immunotherapy—on disease-free survival (DFS) and OS in HCC patients with MVI. Additionally, a nomogram for predicting DFS has been developed to offer clinicians further guidance when choosing among different therapeutic options.

Methods

Patients

This retrospective study included patients diagnosed with HCC who underwent radical hepatic resection between 2017 and 2024 at three medical centers in China: The Department of Liver Surgery, Peking Union Medical College Hospital, Beijing, China; the Department of Liver Surgery, China-Japan Friendship Hospital, Beijing, China; and the Department of Liver Surgery, Sun Yat-sen University Cancer Center, Guangzhou, China. Inclusion criteria were: 1) Complete (R0) resection (The total removal of all tumors detectable via preoperative imaging and intraoperative exploration, with negative surgical resection margins, no macrovascular or bile duct invasion, and no lymph node or distant metastasis. For patients with positive AFP, the level should return to normal within two months post-surgery. Additionally, tumor-free status must be confirmed by ultrasound, CT, or MRI conducted 1–2 months post-operatively).; 2) Age between 18 and 75

years; 3) Pathologically confirmed HCC with MVI; 4) Eastern Cooperative Oncology Group performance score (ECOG PS) of ≤ 1. Exclusion criteria included: 1) Patients with recurrent HCC (the reappearance of HCC after a R0 resection); 2) History of HCC rupture with bleeding; 3) Concurrent other malignant tumors (also excludes long-term remission malignancies); 4) Neoadjuvant therapy for HCC, including TACE, targeted, immunological, or radiation therapies. The study received approval from the Ethics Committee of Peking Union Medical College Hospital (ID: I-23PJ964), and all patients provided written informed consent.

Preoperative Assessment

All patients underwent comprehensive preoperative evaluations, including routine blood tests (complete blood count, liver and renal function tests, viral load, coagulation profile, tumor markers), electrocardiograms, pulmonary function tests, abdominal ultrasound, and enhanced abdominal CT or MRI. Patients anticipated to require extensive liver resection were further assessed for hepatic reserve function using the indocyanine green 15-minute retention test. Specific surgical techniques for liver resection, as detailed in prior literature,[22] were consistently applied, with intraoperative ultrasound used to define resection margins closely for patients with multiple lesions or tumors near vital vessels.

Postoperative Management

Postoperatively, treatment options were selected based on the patient's condition and personal preferences. Patients were categorized into three treatment groups: 1) TACE only; 2) TACE combined with targeted therapy; 3) TACE combined with targeted and immunotherapy. TACE procedures, initiated 4–6 weeks post-surgery, involved hepatic artery angiography via a femoral artery catheter inserted using the Seldinger technique. The regimen included 200 mg/m² carboplatin, 6 mg/m² mitomycin, a 4–5 mL iodized oil emulsion, and 40 mg/m² epirubicin hydrochloride. A comprehensive evaluation, including physical exams, blood tests, and a CT scan, was conducted approximately two weeks later to decide on subsequent TACE sessions based on tumor markers and CT findings. The selection of targeted and immunotherapy agents was influenced by factors such as the patient's economic status, potential side effects, and overall physical condition. Specific targeted therapies included Lenvatinib,[14] Apatinib,[15] Regorafenib,[16] Bevacizumab,[23] among others. The immunotherapy agents used were Sintilimab,[17] Carrelizumab,[18] Atezolizumab,[23] Tislelizumab,[19] among others. Pre-immunotherapy evaluations included routine blood tests, electrocardiograms, thyroid function tests, and chest CT scans, ensuring only qualified patients received further treatment.

Pathological Grading of MVI

M0: No MVI detected; M1 (low-risk group): ≤5 MVI lesions, all located within 1 cm of the primary tumor; M2 (high-risk group): >5 MVI lesions, or any MVI found more than 1 cm away from the primary tumor.[24] The pathological diagnosis followed the chinese guidelines for the standardized pathological evaluation of primary liver cancer.

Follow-Up

Patients were followed up every three months during the first two years post-surgery, then every six months thereafter. Each follow-up included evaluations of tumor markers, abdominal ultrasound, and enhanced abdominal CT or MRI, with chest CT, bone scans, and PET-CT conducted if distant metastasis was suspected. Follow-up ceased upon patient death or loss to follow-up, with the last follow-up date recorded as June 17, 2024. Treatment for recurrence was tailored based on tumor characteristics, liver and renal function, economic status, and overall health. The primary outcome was DFS, with OS as a secondary outcome.

Out of the initial cohort of 409 patients, 21 (5.1%) were lost to follow-up in the DFS analysis, and 51 (12.5%) in the OS analysis. For analytical purposes, these patients were not excluded from the study; instead, their last known follow-up times were utilized as censored data points in the survival analysis. This approach allowed us to effectively handle the censored data using the Kaplan-Meier method, ensuring comprehensive inclusion of all available data and maintaining the integrity of our statistical evaluations.

Data Analysis

Continuous variables are presented as medians with interquartile ranges (IQR) and categorical variables as frequencies and percentages. Statistical comparisons used chi-square or Fisher's exact test for categorical variables. Survival analysis employed the Kaplan-Meier method with comparisons via the Log rank test. Cox proportional hazards models identified independent prognostic factors for DFS and OS. PSM was applied to balance baseline characteristics across the three groups using the caliper matching technique. To prevent overfitting, we carefully selected a limited number of clinically significant and statistically justified variables for the PSM, ensuring each contributed meaningfully to model balance and robustness. The variables included were PT, tumor differentiation, resection margin, tumor size, AFP, tumor number, satellite number, liver cirrhosis, MVI, and tumor embolus. The selection of variables primarily relies on their significance in prior research or their statistical indispensability. For instance, Prothrombin Time (PT) serves as a crucial coagulation marker and is associated with liver functionality. Tumor differentiation reflects the biological characteristics of the tumor. Furthermore, factors such as resection margin,[25,26] AFP,[27] tumor size and count,[28] satellite lesion number, and liver cirrhosis play pivotal roles in determining the prognosis of HCC.[29] A caliper width of 0.25 and a matching ratio of 1:1 were employed to ensure closely matched pairs. The first step was to balance the TACE + targeted therapy group and TACE + targeted immunotherapy groups. The same PSM approach was applied between the TACE group and the combined two groups. To develop a prognostic model for HCC patients with MVI, we constructed a nomogram using a dataset that underwent PSM. The PSM-adjusted dataset served as the training set, and the entire cohort was used for validation. The primary goal was to create a robust tool to predict DFS for this high-risk patient population. All statistical analyses were two-tailed with a significance level set at $P < 0.05$, conducted using the R programming language (version 4.4.0, R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics

From 2017 to 2024, a total of 409 patients from three different centers were enrolled in this study. All patients underwent curative liver resection, and postoperative pathology confirmed the presence of MVI. Among these patients, 132 received TACE alone, 58 received TACE + targeted therapy, and 68 received TACE + targeted immunotherapy (Figure 1). The remaining 151 patients did not receive any of the aforementioned treatment protocols, with 88 of these patients not receiving any form of postoperative adjuvant therapy (Supplementary Table 1). Statistically significant differences were observed in baseline characteristics such as PT and resection margin among the three treatment groups. After two rounds of PSM, the number of patients in the TACE group, TACE + targeted therapy group, and TACE + targeted immunotherapy group were 69, 34, and 35, respectively. Following PSM, no statistically significant differences were found in baseline characteristics among the three groups. The baseline characteristics before and after matching are summarized in Table 1.

Univariate and Multivariate Analysis for DFS and OS

After PSM, we performed univariate and multivariate regression analyses for DFS and OS, with the results presented in Table 2. The associated factors for poor DFS were ALB <35 g/L (HR 2.540, p=0.047), poor Child-Pugh class (HR 9.858, p=0.027), AFP >400 ng/mL (HR 1.844, P=0.015), and high MVI grade (HR 1.966, P=0.010). Independent protective factors for DFS were the TACE + targeted therapy group (HR 0.433, P=0.017) and the TACE + targeted immunotherapy group (HR 0.446, P=0.018). For OS, high MVI grade was identified as an associate factor (HR 2.681, P=0.038). However, neither the TACE + targeted therapy group nor the TACE + targeted immunotherapy group were independent protective factors for OS.

Influence of Three Different Postoperative Treatments on DFS and OS Before and After PSM

Before PSM, among the 258 patients in the three treatment groups, 137 experienced recurrence and 38 died. The Kaplan-Meier survival curves for DFS and OS before PSM are shown in Figure 2. Compared to the TACE group,

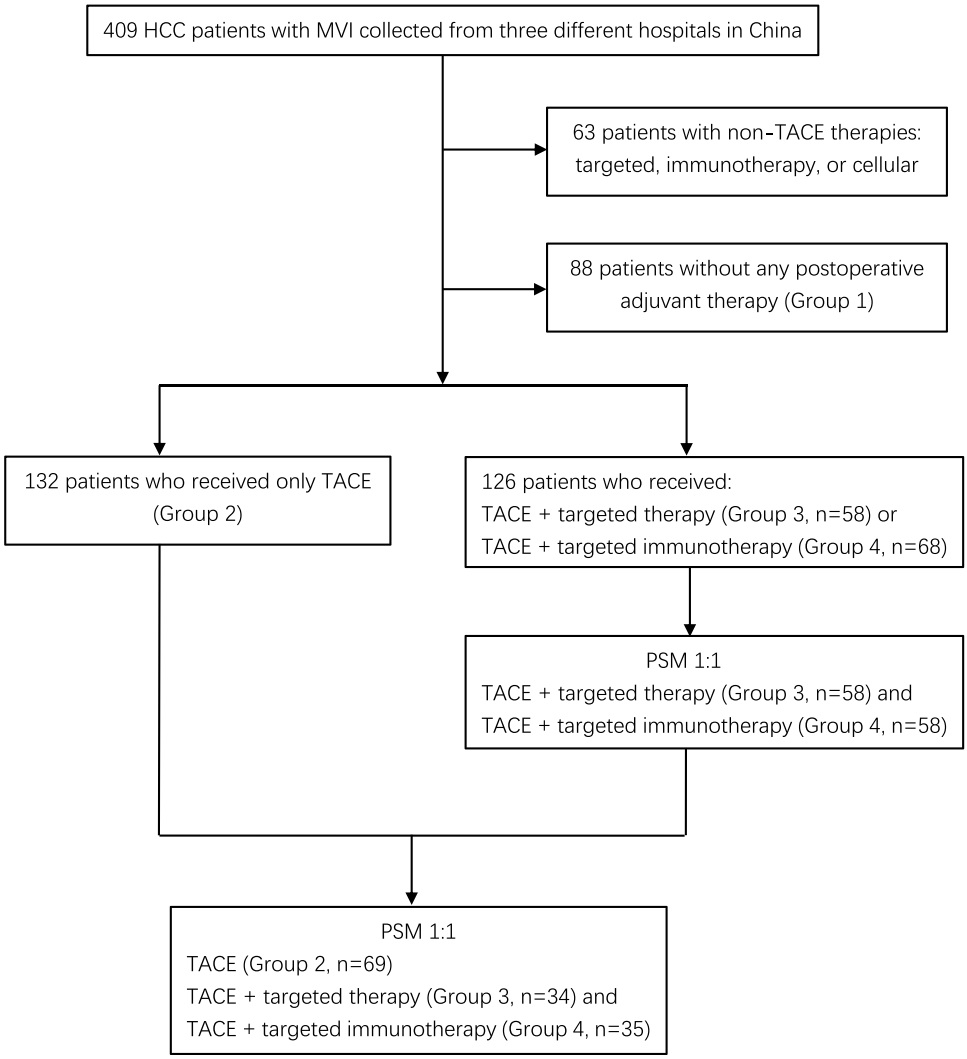

Figure 1 Flow chart.

both the TACE + targeted therapy group and the TACE + targeted immunotherapy group significantly improved DFS (median DFS 16, 22, and 21 months, respectively, P=0.028). However, there was no statistically significant difference in DFS between the TACE + targeted therapy group and the TACE + targeted immunotherapy group (P=0.777). In terms of OS, no significant differences were observed among the three groups (P=0.67). After PSM, among the 138 patients in the three treatment groups, 66 experienced recurrence and 18 died. The Kaplan-Meier survival curves for DFS and OS after PSM are shown in Figure 3. Following PSM, both the TACE + targeted therapy group and the TACE + targeted immunotherapy group continued to demonstrate significant improvements in DFS compared to the TACE group (P=0.0069). Specifically, the TACE + targeted therapy group showed improved DFS compared to the TACE group (P=0.027), as did the TACE + targeted immunotherapy group (P=0.027). However, there remained no statistically significant difference in DFS between the TACE + targeted therapy group and the TACE + targeted immunotherapy group (P=0.893). Regarding OS, no significant differences were found among the three groups after PSM (P=0.82). For the 88 patients who did not receive any postoperative adjuvant therapy (Group 1), details of their DFS and OS can be found in Supplementary Figure 1.

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Table 1 Baseline Variables of All HCC Patients Before and After PSM

Variable	Before PSM				After PSM			
	Group 2	Group 3	Group 4	P	Group 2	Group 3	Group 4	P
n	132	58	68		69	34	35	
Gender, n (%)				0.298				0.161
Male	114 (86.4)	45 (77.6)	58 (85.3)		62 (89.9)	26 (76.5)	31 (88.6)	
Female	18 (13.6)	13 (22.4)	10 (14.7)		7 (10.1)	8 (23.5)	4 (11.4)	
Age (%)				0.133				0.746
<65	88 (66.7)	47 (81)	52 (70.6)		51 (73.9)	26 (76.5)	24 (68.6)	
≥65	44 (33.3)	11 (19)	16 (29.4)		18 (26.1)	8 (23.5)	11 (31.4)	
HBsAg (%)				0.242				0.429
Negative	35 (26.5)	13 (22.4)	24 (35.3)		19 (27.5)	8 (23.5)	13 (37.1)	
Positive	97 (73.5)	45 (77.6)	44 (64.7)		50 (72.5)	26 (76.5)	22 (62.9)	
HBV-DNA				0.218				0.618
≤20	110 (83.3)	43 (74.1)	58 (85.3)		56 (81.2)	26 (76.5)	30 (85.7)	
>20	22 (16.7)	15 (25.9)	10 (14.7)		13 (18.8)	8 (23.5)	5 (14.3)	
HCV-Ab				0.381				0.175
Negative	119 (90.2)	54 (93.1)	65 (95.6)		60 (87)	32 (94.1)	34 (97.1)	
Positive	13 (9.8)	4 (6.9)	3 (4.4)		9 (13)	2 (5.9)	1 (2.9)	
Tbil (%)				0.130				0.087
≤17.1	90 (68.2)	33 (56.9)	50 (73.5)		48 (69.6)	18 (52.9)	27 (77.1)	
>17.1	43 (31.8)	25 (43.1)	18 (26.5)		21 (30.4)	16 (47.1)	8 (22.9)	
ALB (%)				0.413				0.131
<35	7 (5.3)	3 (5.2)	1 (1.5)		6 (8.7)	1 (2.9)	0 (0)	
≥35	125 (94.7)	55 (94.8)	67 (98.5)		63 (91.3)	33 (97.1)	35 (100)	
ALBI (%)				0.770				0.670
I	102 (77.3)	44 (75.9)	55 (80.9)		52 (75.4)	27 (79.4)	29 (82.9)	
II	30 (22.7)	14 (24.1)	13 (19.1)		17 (24.6)	7 (20.4)	6 (17.1)	
Child-Pugh. grade				0.546				0.604
A	130 (99.2)	57 (98.3)	68 (100)		68 (98.6)	34 (100)	35 (100)	
B	2 (0.8)	1 (1.7)	0 (0)		1 (1.4)	0 (0)	0 (0)	
PT (s)				0.047				0.594
≤14	130 (98.5)	53 (91.4)	66 (97.1)		67 (97.1)	33 (97.1)	35 (100)	
>14	2 (1.5)	5 (8.6)	2 (2.9)		2 (2.9)	1 (2.9)	0 (0)	
AFP (%)				0.373				0.980
≤400	89 (67.4)	39 (67.2)	52 (76.5)		46 (66.7)	23 (67.6)	24 (68.6)	
>400	43 (32.6)	19 (32.8)	16 (23.5)		23 (33.3)	11 (32.4)	11 (31.4)	
Tumor differentiation				0.834				0.549
Low	41 (31.1)	20 (34.5)	20 (29.4)		27 (39.1)	13 (38.2)	10 (28.6)	
High-median	91 (68.9)	38 (65.5)	48 (70.6)		42 (60.9)	21 (61.8)	25 (71.4)	
Margin, n (%)				0.020				0.541
<0.5 cm	91 (68.9)	41 (70.7)	59 (86.8)		55 (79.7)	30 (88.2)	28 (80)	
≥0.5 cm	41 (31.1)	18 (29.3)	9 (13.2)		14 (20.3)	4 (11.8)	7 (20)	
Tumor number				0.385				0.167
1	106 (80.3)	45 (77.6)	58 (85.3)		58 (84.1)	26 (76.5)	31 (88.6)	
2	22 (16.7)	11 (19.0)	6 (8.8)		10 (14.5)	7 (20.6)	2 (5.7)	
3	3 (2.3)	1 (1.7)	4 (5.9)		1 (1.4)	0 (0)	2 (5.7)	
4	1 (0.8)	1 (1.7)	0 (0)		0 (0)	1 (2.9)	0 (0)	
Tumor number grade				0.523				0.392
1 (≤1)	106 (80.3)	45 (77.6)	58 (85.3)		58 (84.1)	26 (76.5)	31 (88.6)	
2 (>1)	26 (19.7)	13 (22.4)	10 (14.7)		11 (15.9)	8 (23.5)	4 (11.4)	

(*Continued*)

Table 1 (Continued).

Variable	Before PSM				After PSM			
	Group 2	Group 3	Group 4	P	Group 2	Group 3	Group 4	P
Tumor size (cm)				0.101				0.978
≤5	73 (55.3)	31 (53.4)	27 (39.7)		37 (53.6)	18 (52.9)	18 (51.4)	
>5	59 (44.7)	27 (46.6)	41 (60.3)		32 (46.4)	16 (47.1)	17 (48.6)	
CNLC				0.772				0.897
Ia	50 (37.9)	24 (41.1)	20 (29.4)		24 (34.8)	11 (32.4)	12 (34.3)	
Ib	47 (35.6)	21 (36.2)	29 (42.6)		27 (39.1)	14 (41.2)	14 (40)	
IIa	17 (12.9)	5 (8.6)	7 (10.3)		8 (11.6)	3 (8.8)	3 (8.6)	
IIb	1 (0.8)	1 (1.7)	0 (0)		0 (0)	1 (2.9)	0 (0)	
IIIa	17 (12.9)	7 (12.1)	12 (17.6)		10 (14.5)	5 (14.7)	6 (17.1)	
BCLC				0.531				0.715
0	7 (5.3)	7 (12.1)	3 (4.4)		2 (2.9)	4 (11.8)	2 (5.7)	
A	89 (67.4)	37 (63.8)	46 (67.6)		49 (71)	21 (61.8)	24 (68.6)	
B	19 (14.4)	7 (12.1)	7 (10.3)		8 (11.6)	4 (11.8)	3 (8.6)	
C	17 (12.9)	7 (12.1)	12 (17.6)		10 (14.5)	5 (14.7)	6 (17.1)	
Satellite number				0.199				0.997
Absent	102 (77.3)	40 (69)	45 (66.2)		49 (71)	24 (70.6)	25 (71.4)	
Present	30 (22.7)	18 (31)	23 (33.8)		20 (29)	10 (29.4)	10 (28.6)	
Tumor embolus				0.654				0.896
Absent	115 (87.1)	50 (86.2)	56 (82.4)		59 (85.5)	28 (82.4)	29 (82.9)	
Present	17 (12.9)	8 (13.8)	12 (17.6)		10 (14.5)	6 (17.6)	6 (17.1)	
MVI				0.550				0.807
1	85 (64.4)	39 (67.2)	49 (72.1)		52 (75.4)	24 (70.6)	27 (77.1)	
2	47 (35.6)	19 (32.8)	19 (27.9)		17 (24.6)	10 (29.4)	8 (22.9)	
Cirrhosis (%)				0.423				0.640
Absent	36 (27.3)	11 (19)	15 (22.1)		20 (29)	7 (20.6)	10 (28.6)	
Present	96 (72.7)	47 (81)	53 (77.9)		49 (71)	27 (79.4)	25 (71.4)	

Nomogram

Patients with HCC and MVI typically have poor prognoses, but there is a lack of reliable markers to predict outcomes in this subgroup. To address this, we developed a nomogram model using the post-PSM dataset as the training set and validated it using the entire dataset. Our aim was to create an effective prognostic tool for this high-risk population.

Nomogram Variable Screening, Construction, and Validation

Based on the results of the prior univariate and multivariate analyses, along with clinically relevant and commonly used indicators, we selected AFP, MVI, postoperative treatments as the key variables for our model. Using these selected variables, we constructed a nomogram. Figure 4A illustrates an example of using the nomogram to predict the probability of DFS for an individual patient. The total score for each patient was calculated by summing the individual scores corresponding to each variable, as determined by the nomogram. The C-index for the nomogram was 0.709 [95% CI = 0.639–0.780] in the training cohort and 0.645 (95% CI = 0.589–0.702) in the validation cohort (Figure 4B). Calibration curves demonstrated a high level of agreement between the predicted and observed survival probabilities in the training cohort, although this consistency was somewhat reduced in the validation cohort. The AUC for predicting DFS within 1 year was greater than 0.7 in the training cohort, with an AUC of 0.669 in the validation cohort (Figure 4C). To assess the clinical applicability of the nomogram, we conducted Decision Curve Analysis (DCA) (Figure 4D). The DCA showed that the nomogram provided a consistently greater net benefit across a threshold probability range of 0.1 to 0.8 compared to both the "treat-all" and "treat-none" strategies. Notably, within the clinically relevant threshold range of 0.2 to 0.5, the nomogram showed the most significant improvement in net benefit, suggesting that the model has strong potential for guiding individualized treatment decisions. For example, at a

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Table 2 Univariate and Multivariate Analysis for DFS and OS in HCC Patients After PSM

Cohort	Variables	DFS						OS		
		Univariate	95% CI	P	Multivariate	95% CI	P	Univariate	95% CI	P
		HR			HR			HR		
After PSM (n=138)	**Type of treatment**									
	TACE	Reference			Reference			Reference		
	Group 3 vs TACE	0.433	0.218–0.861	0.017	0.492	0.245–0.987	0.046	0.984	0.306–3.163	0.978
	Group 4 vs TACE	0.446	0.229–0.869	0.018	0.479	0.243–0.944	0.033	0.667	0.179–2.486	0.547
	Gender (Male vs Female)	1.376	0.697–2.716	0.358				1.537	0.439–5.379	0.501
	Age (≥65 vs < 65 years)	0.879	0.505–1.531	0.649				1.291	0.477–3.493	0.615
	HBsAg (Positive vs Negative)	1.361	0.749–2.475	0.312				1.369	0.449–4.177	0.581
	HBV-DNA (>20 vs ≤20)	1.291	0.723–2.308	0.388				2.582	0.952–7.004	0.062
	HCV-Ab (Present vs Absent)	0.943	0.378–2.353	0.899				0.464	0.060–3.572	0.461
	TBIL (>17.1 vs ≤17.1)	1.084	0.650–1.807	0.758				0.346	0.098–1.213	0.097
	ALB (<35 vs ≥35)	2.540	1.014–6.361	0.047	1.557	0.552–4.388	0.403	2.932	0.660–13.036	0.158
	ALBI grade (II vs I)	0.908	0.509–1.619	0.744				0.868	0.284–2.653	0.805
	Child Pugh (B vs A)	9.858	1.299–74.798	0.027	2.587	0.27–24.833	0.41	0.000	0.000 - Inf	0.998
	PT (>14 vs ≤14)	0.000	0.000 - Inf	0.996				0.000	0.000 - Inf	0.997
	AFP (>400 vs ≤400)	1.844	1.124–3.026	0.015	1.617	0.966–2.705	0.067	1.470	0.567–3.813	0.428
	Tumor differentiation (High-median vs Low)	0.810	0.492–1.332	0.405				2.007	0.660–6.102	0.220
	Margin (≥0.5 vs <0.5)	1.298	0.702–2.400	0.406				0.265	0.035–2.001	0.198
	Tumor number grade (2 vs 1)	1.493	0.837–2.665	0.175				1.771	0.627–5.004	0.281
	Tumor size (>5 vs ≤5)	1.190	0.728–1.947	0.487				0.681	0.268–1.731	0.419
	CNLC (Ib vs Ia)	1.534	0.835–2.820	0.168				0.953	0.275–3.305	0.940
	CNLC (IIa vs Ia)	1.776	0.789–3.994	0.165				1.893	0.445–8.058	0.388
	CNLC (IIb vs Ia)	0.000	0.000 - Inf	0.996				0.000	0.000 - Inf	0.998
	CNLC (IIIa vs Ia)	2.062	0.981–4.334	0.056				2.371	0.680–8.270	0.176
	BCLC (A vs 0)	4.471	0.615–32.497	0.139				0.955	0.116–7.850	0.966
	BCLC (B vs 0)	5.466	0.691–43.229	0.107				1.799	0.186–17.437	0.612
	BCLC (C vs 0)	6.733	0.873–51.951	0.067				2.329	0.269–20.194	0.443
	Satellite (Present vs Absent)	1.343	0.791–2.281	0.275				1.784	0.691–4.607	0.232
	Tumor embolus (Present vs Absent)	1.659	0.900–3.060	0.105				2.070	0.730–5.870	0.171
	MVI (2 vs 1)	1.966	1.177–3.283	0.010	1.543	0.898–2.651	0.116	2.681	1.055–6.817	0.038
	Liver cirrhosis (Present vs Absent)	0.963	0.535–1.733	0.899				0.689	0.241–1.973	0.488

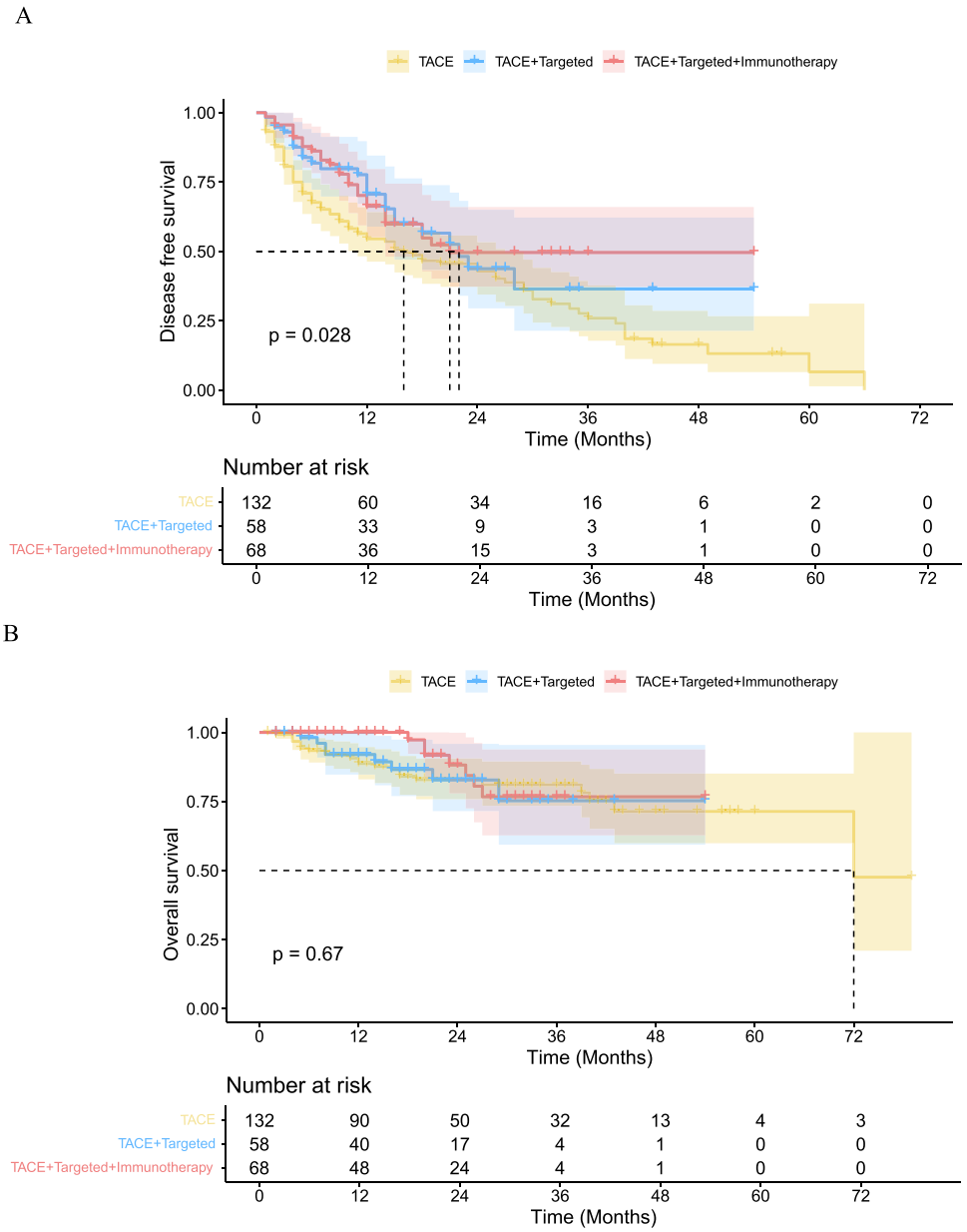

Figure 2 The Kaplan-Meier survival analysis of HCC patients DFS (**A**) and OS (**B**) before PSM between group 2, group 3 and group 4. Group 2, TACE; Group 3, TACE + Targeted; Group 4, TACE +Targeted + Immunotherapy.

threshold probability of 0.3, the nomogram demonstrated a net benefit higher than 60%, which was higher than both alternative strategies. In conclusion, the nomogram for DFS exhibited strong predictive accuracy and calibration performance.

Risk Stratification Based on the Cox Model

We developed a risk stratification system for HCC patients with MVI, leveraging a risk score derived from a multivariate Cox regression model. This model underpinned the development of our nomogram, providing a systematic approach to evaluate patient prognosis. The risk score for each HCC patient was computed using the formula:

$$\text{Risk Score} = \Sigma(\text{Expi} \times \text{bi})$$

where Expi denotes the expression of each prognostic factor, including group, AFP level, and MVI status, and bi represents the corresponding regression coefficient obtained from the Cox model.

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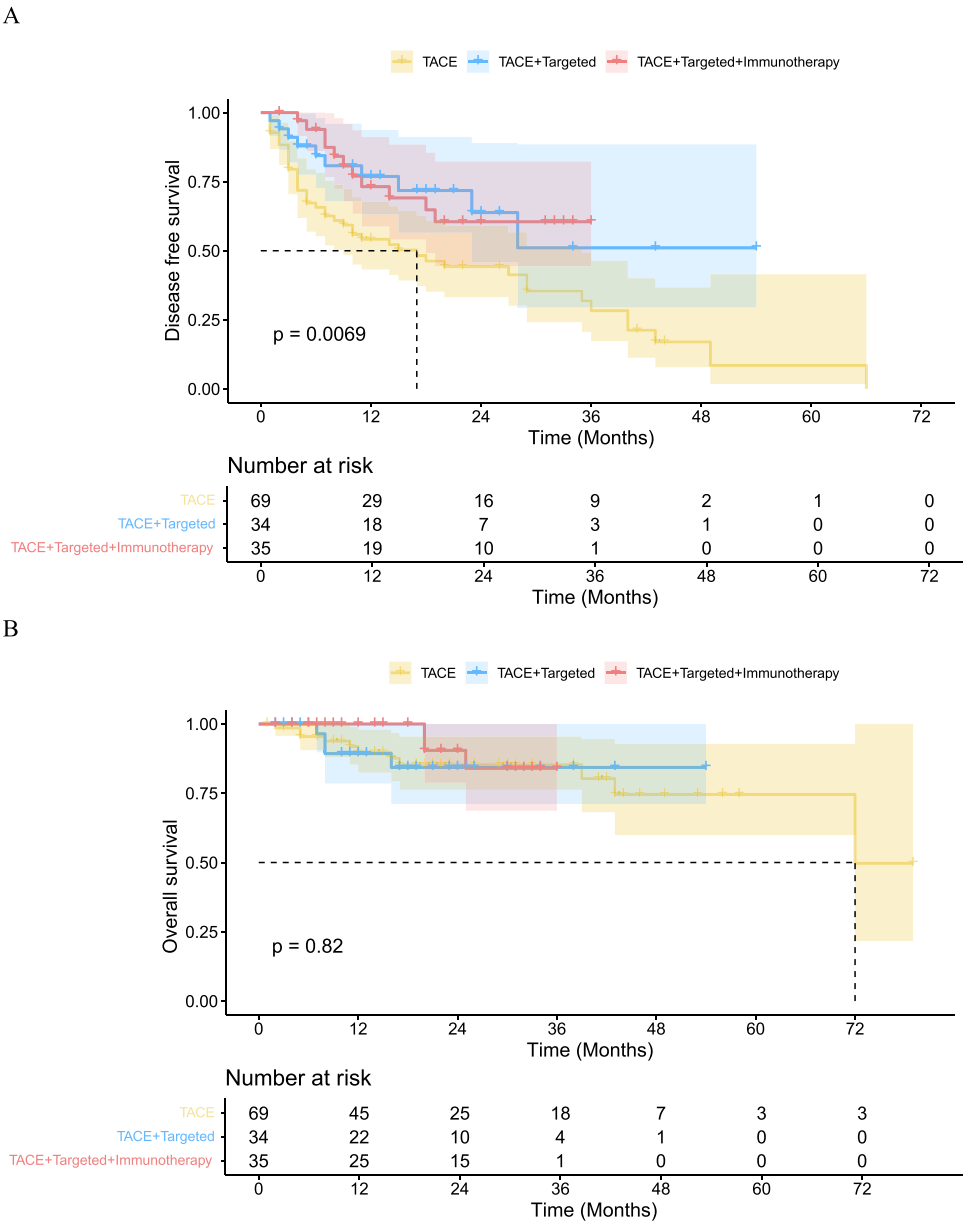

Figure 3 The Kaplan-Meier survival analysis of HCC patients DFS (**A**) and OS (**B**) after PSM between group 2, group 3 and group 4. Group 2, TACE; Group 3, TACE + Targeted; Group 4, TACE +Targeted + Immunotherapy.

To categorize patients into risk groups, we employed the median risk score from the training cohort as the cutoff point. Specifically, the cutoff value was established at 1, which effectively divided the cohort into low-risk (total points < 1) and high-risk (total points ≥ 1) groups. This method was selected to ensure a balanced distribution of patients across the risk categories, facilitating more precise comparisons in subsequent analyses. The Kaplan-Meier DFS curves demonstrated clear differentiation between the two groups, while the Kaplan-Meier OS curves showed limited discriminatory ability in both the training and validation cohorts (Figures 5 and 6).

Discussion

HCC has a poor long-term prognosis, characterized by a 70% recurrence rate within 5 years of surgical resection, often leading to incurable advanced-stage disease and a 5-year survival rate of less than 15%.[30] Despite advancements in surgical techniques and equipment that have allowed more HCC cases to be surgically resected, improving long-term

outcomes remains a significant challenge. Previous studies have demonstrated that adjuvant therapies, such as TACE, targeted therapy, and immunotherapy, can enhance both DFS and OS compared to no postoperative treatment.[12,31] However, a standardized postoperative treatment regimen is still lacking. Questions such as which patients would benefit from TACE alone, which require a combination of TACE with targeted and immunotherapy, and whether the combination of targeted therapy and immunotherapy can extend OS remain unanswered, requiring further clinical trials for clarification. This study aimed to assess the effects of three distinct postoperative treatment strategies on the prognosis of HCC patients with MVI in a real-world setting.

The findings of this study indicate that both TACE + targeted therapy and TACE + targeted immunotherapy significantly improve DFS compared to TACE alone. In multivariate analysis, both combination therapies were identified

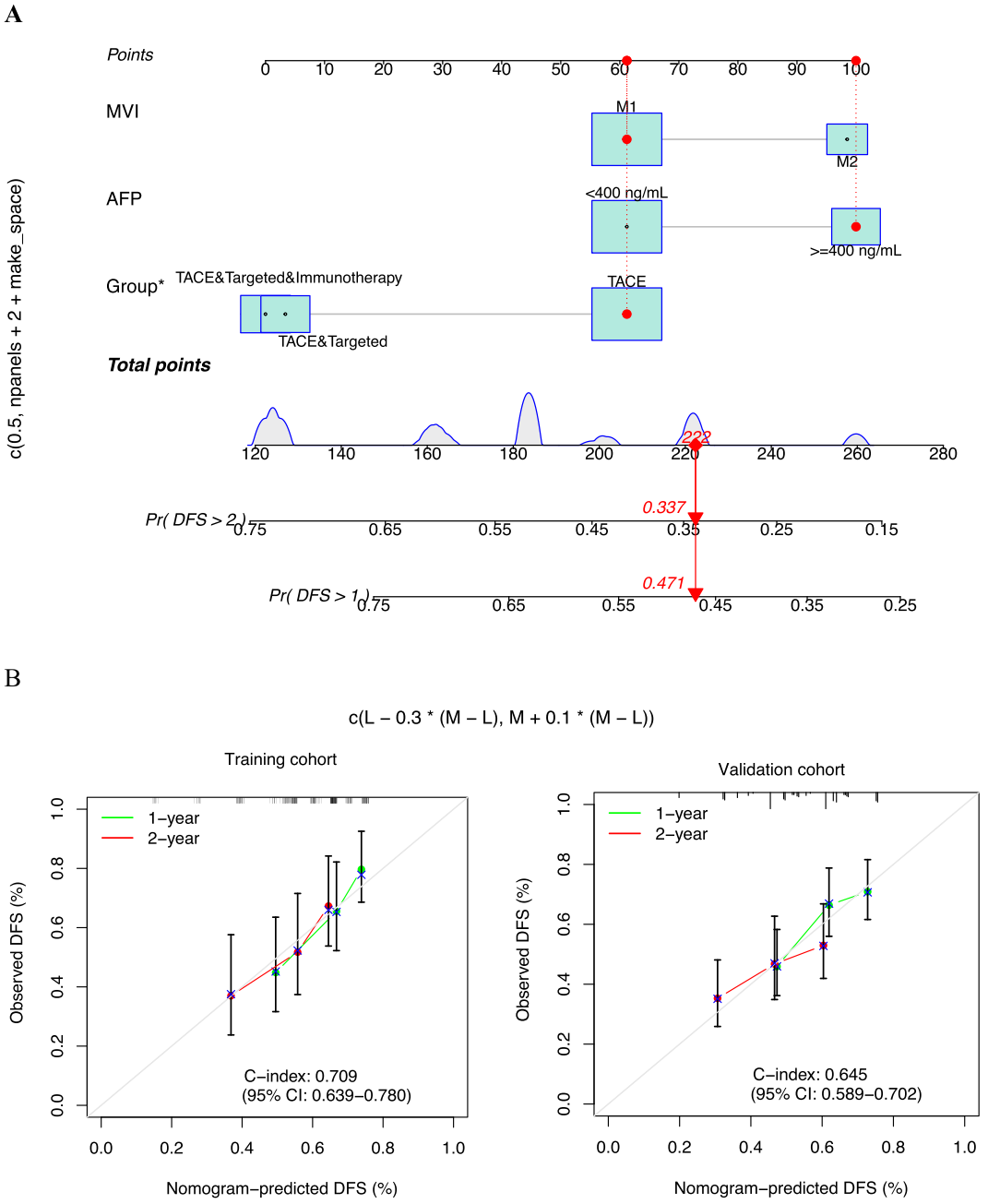

Figure 4 Contiune.

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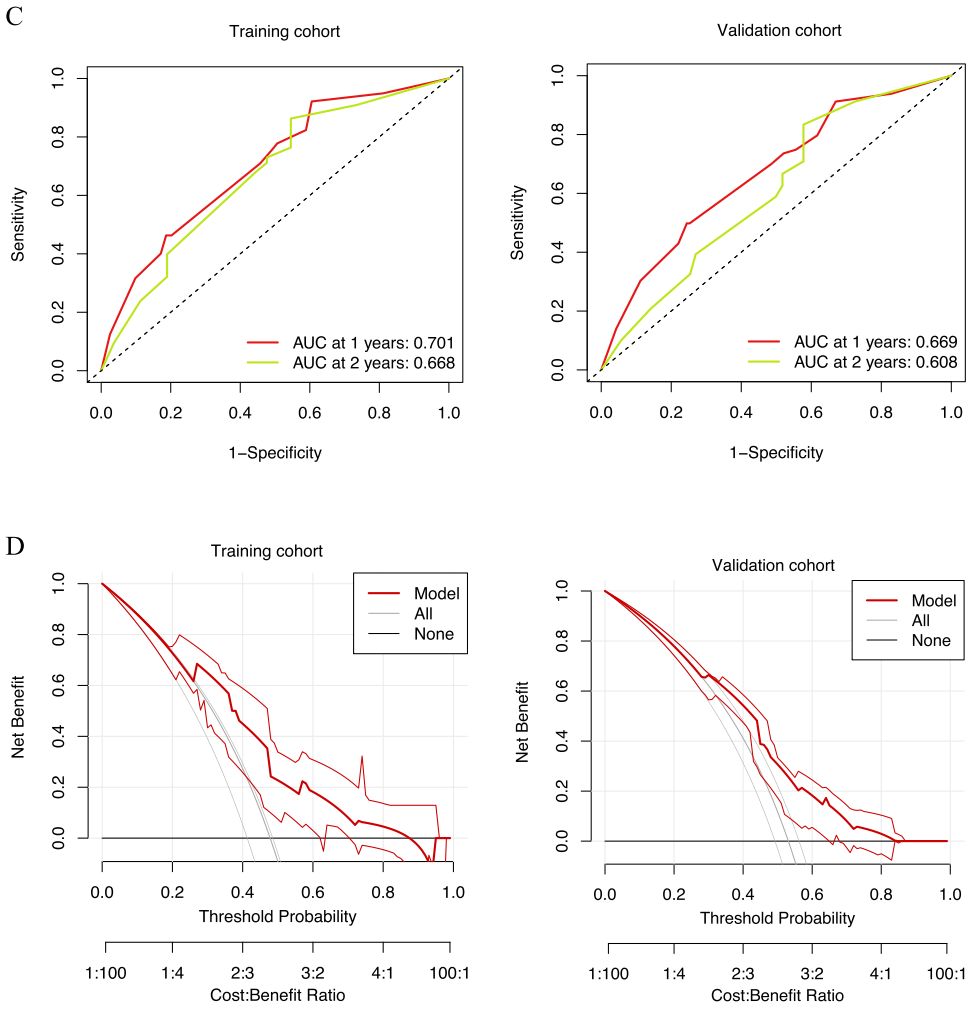

Figure 4 Comprehensive evaluation of the nomogram model. (**A**). A constructed nomogram for prognostic prediction. We constructed a nomogram to predict DFS for an HCC patient with MVI. This particular patient had MVI1, an AFP level of ≥400 ng/mL, underwent R0 resection, and received TACE but did not undergo targeted therapy or immunotherapy. The distributions of categorical variables are represented by the size of each box, while the significance of each variable is determined based on the standard deviation across the nomogram scale. To use the nomogram, the individual patient's specific points (marked by black dots) are plotted along the respective variable axes. Red lines and dots extend upward to identify the points contributed by each variable, which are then summed (222 points) on the Total Points axis. Finally, a line is drawn downward from the total points to the survival axes, yielding the 1-year (47.1%) and 2-year (33.7%) DFS probabilities. (**B**). Calibration curves of the nomogram. Calibration curves for 1-year and 2-year DFS in HCC patients with MVI were generated for both the training and validation cohorts. The red and green dots, computed through bootstrapping, represent the nomogram's performance. The closer the solid red and green lines align with the light gray line, the more precise the model's survival predictions are. (**C**). ROC curves of the nomogram. ROC curves for the nomogram were generated to assess the AUC for 1-year and 2-year DFS in HCC patients with MVI, in both the training and validation cohorts. The 95% confidence intervals were estimated using the bootstrapping cross-validation method. (**D**). Decision curve analysis of the nomogram in both the training and validation cohorts.

as independent protective factors for DFS. However, neither of the two combinations demonstrated a significant benefit in extending OS compared to TACE alone. Furthermore, direct comparison of TACE + targeted therapy with TACE + targeted immunotherapy revealed no significant differences between the two groups in terms of their effects on DFS and OS.

The results of our study reinforce the importance of postoperative adjuvant therapies in improving DFS among HCC patients with MVI. This is consistent with prior research suggesting that adjuvant therapies help to control tumor progression and reduce the likelihood of recurrence.[12,13,32] IMbrave150 evaluated the combination of atezolizumab and bevacizumab versus sorafenib in patients with unresectable HCC, showing improved OS and PFS.[12] In contrast, our study focuses on postoperative patients, broadening the understanding of adjuvant therapy's role post-resection. Similarly, IMbrave050 assessed adjuvant atezolizumab plus bevacizumab in high-risk resected or ablated patients, finding enhanced RFS, which supports our results.[13] While IMbrave050 concentrated on specific agents, our study includes a wider range of adjuvant treatments, providing comprehensive insights into postoperative management and

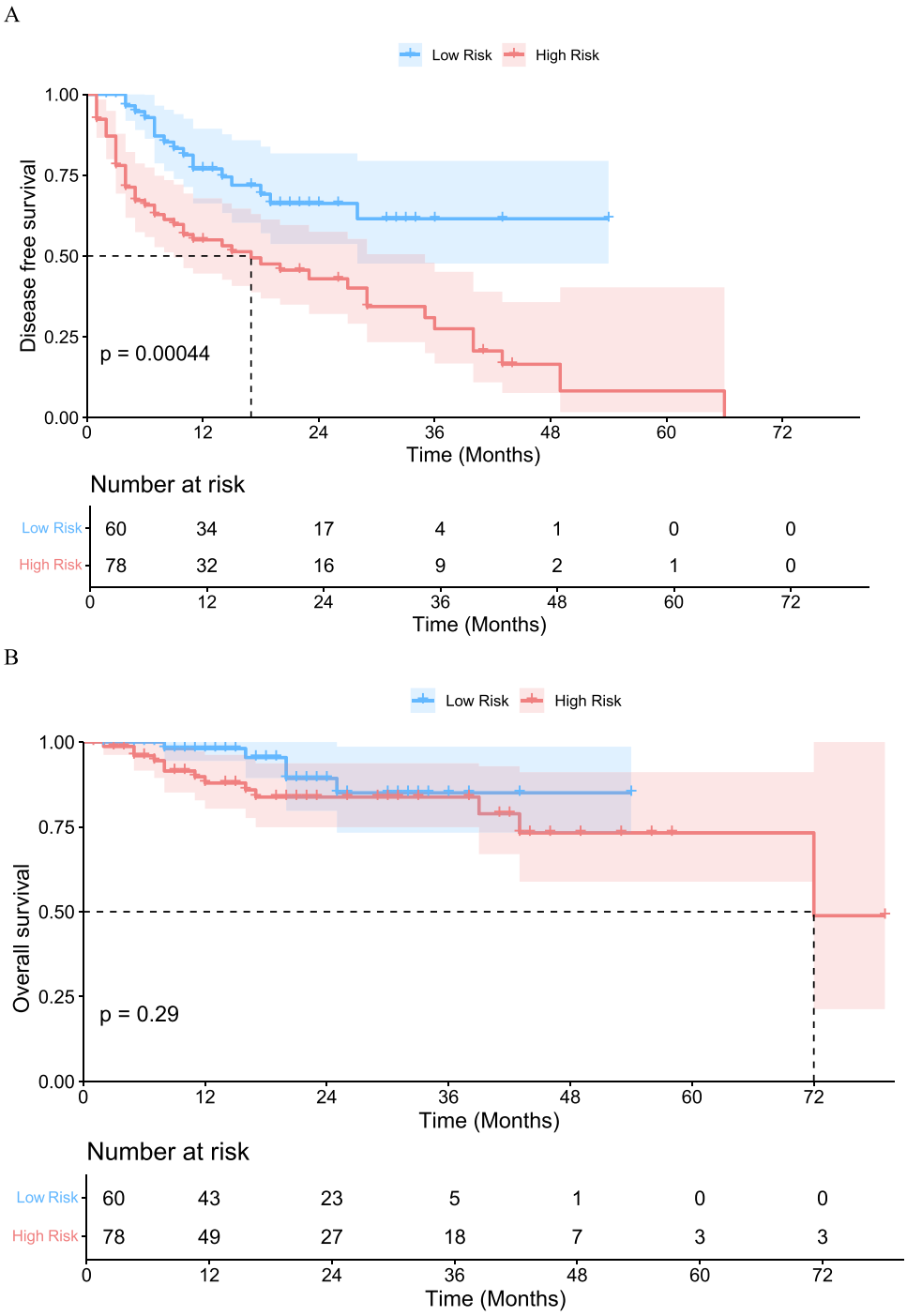

Figure 5 Kaplan-Meier survival curves for high-risk and low-risk groups stratified by the Cox model, tested on the training dataset. (**A**) Kaplan-Meier curve comparing DFS between the high-risk and low-risk groups in the post-PSM dataset. (**B**) Kaplan-Meier curve comparing OS between the high-risk and low-risk groups in the post-PSM dataset.

confirming the utility of diverse adjuvant therapies in the postoperative setting. However, there were no differences in DFS and OS between the TACE + targeted therapy and TACE + targeted immunotherapy groups, which is inconsistent with many previous studies. According to a meta-analysis and trial sequential analysis[33] TACE + targeted immunotherapy demonstrated superior outcomes in overall response rate (ORR), progression-free survival (PFS), and OS compared to TACE + targeted therapy for BCLC stages B and C HCC. Additionally, a target trial emulation study (CHANCE2201) found that both ORR and median OS and PFS were longer in the TACE + targeted immunotherapy group compared to

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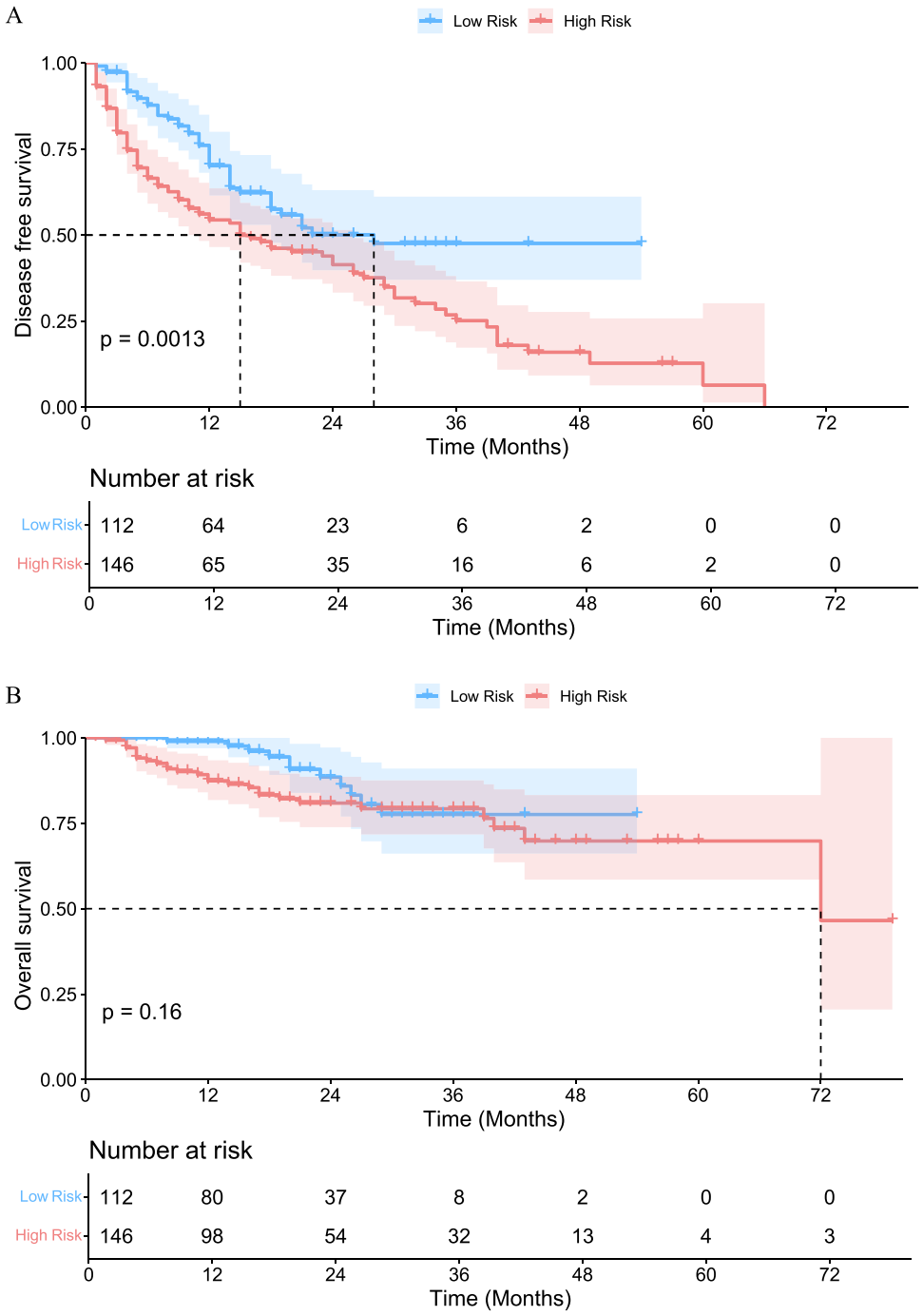

Figure 6 Kaplan-Meier survival curves for high-risk and low-risk groups stratified by the Cox model applied to the entire dataset after validation on the PSM dataset. (**A**) Kaplan-Meier curve comparing DFS between the high-risk and low-risk groups in the entire dataset. (**B**) Kaplan-Meier curve comparing OS between the high-risk and low-risk groups in the entire dataset.

targeted immunotherapy alone.[34] There are several potential explanations for these results. In this study, patients experiencing recurrence may undergo subsequent surgeries, TACE, or switch to different targeted and immunotherapy agents, all of which could influence OS. Additionally, this analysis only accounted for the duration of targeted or immunotherapy usage, without considering the variability in patients' responses to different drug types. Therefore, the potential benefits of adding immunotherapy to TACE + targeted therapy may not be fully demonstrated, given the complex treatment landscape and individual patient differences. This may also reflect the inherent challenges of treating

HCC, where factors such as liver function, comorbidities, and tumor biology may further limit the efficacy of combination therapies on OS.

The lack of significant differences in OS among the three groups further suggests that the benefit of adjuvant therapy may be more pronounced in controlling early recurrence rather than in prolonging OS. The absence of a standardized postoperative treatment regimen for HCC patients with MVI remains a challenge. Our study contributes to the growing body of evidence supporting the use of combination adjuvant therapies in selected patients, but it also highlights the need for further investigation into the optimal treatment strategies. For instance, identifying which patients might benefit from TACE alone versus those who require additional targeted or immunotherapy is crucial. Furthermore, exploring whether certain subsets of patients may derive a survival benefit from combining targeted and immunotherapy treatments will require additional randomized controlled trials and longer follow-up.

In addition to the impact of different postoperative treatment strategies on DFS and OS, our study also developed and validated a nomogram specifically for HCC patients with MVI. The nomogram integrates key clinical variables, including AFP, MVI grade, TACE, TACE + targeted therapy, and TACE + targeted immunotherapy, to predict DFS. The model demonstrated good predictive accuracy, with a C-index of 0.709 in the training cohort and 0.645 in the validation cohort. Calibration curves further supported the reliability of the model, particularly in the training cohort, although some reduction in calibration was noted in the validation cohort. Moreover, the decision curve analysis confirmed the clinical utility of the nomogram, showing that it consistently provided a greater net benefit compared to both the "treat-all" and "treat-none" strategies, particularly within a threshold probability range of 0.2 to 0.5. This suggests that the nomogram has strong potential to guide individualized treatment decisions, helping clinicians better stratify patients based on their recurrence risk and tailor postoperative management accordingly. We also developed a risk stratification system based on the total points derived from the nomogram. Patients were classified into low-risk and high-risk groups, with clear distinctions in DFS between the two groups. However, the nomogram's ability to discriminate between groups in terms of OS was more limited, reflecting the findings in our treatment analysis. Nonetheless, this stratification system could serve as a valuable tool in clinical practice for identifying patients at higher risk of recurrence who may benefit from more aggressive adjuvant therapies.

As a retrospective study, our analysis is subject to inherent biases despite the use of PSM to balance baseline characteristics. Although PSM can mitigate some confounding factors, it cannot eliminate all potential biases, particularly those related to unmeasured variables. Another limitation of our study is the diversity of targeted and immunotherapy drugs used across the patient cohort. We did not differentiate between the specific types of drugs administered in each group, which may have influenced the outcomes. Future studies should aim to analyze the efficacy of individual agents or combinations to better understand their respective contributions to patient prognosis. Lastly, the majority of patients in our cohort had hepatitis B virus (HBV)-related HCC, which is common in regions where HBV is endemic. Consequently, our findings may not be fully generalizable to populations with hepatitis C virus (HCV)-related or alcohol-related HCC. Further research involving more diverse patient populations is necessary to confirm the applicability of our results across different etiologies of HCC.

Conclusion

In conclusion, our study demonstrates that both TACE combined with targeted therapy and TACE combined with targeted immunotherapy significantly improve DFS in HCC patients with MVI compared to TACE alone, though no significant differences were observed in OS. The nomogram we developed showed good predictive accuracy for DFS, offering a valuable tool for risk stratification and guiding individualized treatment. Despite the study's retrospective nature and variation in drug use, our findings underscore the importance of combination therapies in reducing recurrence, with further research needed to optimize long-term outcomes.

Abbreviations

HCC, hepatocellular carcinoma; MVI, microvascular invasion; TACE, transcatheter arterial chemoembolization; DFS, disease-free survival; OS, overall survival; PSM, propensity score matching; ORR, objective response rate; PFS, progression-free survival; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission

tomography; HAIC, hepatic arterial infusion chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance score; PT, prothrombin time; AFP, alpha-fetoprotein; ALB, albumin; DCA, decision curve analysis; HBV, hepatitis B virus; HCV, hepatitis C virus.

Data Sharing Statement

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Informed consent was obtained from all individual participants included in the study. This study was approved by the Ethics Research Board of Peking Union Medical College Hospital, ID: I-23PJ964, and complies with the Declaration of Helsinki. Patients provided signed informed consent for the publication of their data.

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Consent for Publication

Informed consent was obtained from all individual participants included in the study. All authors gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no conflicts of interest to declare in this work.

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