

TACE Combined with Targeted Immunotherapy: A Strategy for Liver Transplantation Conversion and Survival Benefits in Patients with BCLC Stage B/C HCC

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Background: Patients with BCLC stage B or C hepatocellular carcinoma (HCC) often face long waiting times. The effectiveness of different tumor control strategies remains unclear. This study evaluates preoperative conversion therapies for liver transplantation (LT).

Methods: This study retrospectively analyzed 269 patients with HCC at BCLC stage B or C from a single center from January 2015 to August 2024. All these patients underwent liver transplantation. They were divided into three groups by treatment: transcatheter arterial chemoembolization (TACE) (n = 150), TACE + tyrosine kinase inhibitor (TKI) (n = 74), and TACE + TKI+immune checkpoint inhibitors (ICI) (n = 45). Preoperative assessments included blood tests, liver and kidney function, coagulation, tumor markers, and imaging to evaluate tumor response and monitor adverse events. Data collected included baseline characteristics, lab results, surgical details, preoperative treatment response, adverse events, 1-year survival, tumor-free survival, and donor information.

Results: Baseline characteristics were well-balanced across the three groups. The TACE + TKI + ICI group showed higher DCR, ORR, and CRR than both the TACE-alone and TACE + TKI groups (all $P < 0.05$; $\chi^2 = 11.592, 18.111, 17.558$). It also had longer RFS versus both control groups (vs. TACE alone: $P = 0.008$; vs. TACE + TKI: $P = 0.040$). One-year OS did not differ significantly among groups ($P = 0.707$). Safety analyses revealed no significant differences in preoperative lab values, adverse event rates, or intraoperative liver transplant parameters (all $P > 0.05$), confirming prior treatments did not compromise surgical feasibility or safety. Multivariate logistic regression identified treatment regimen as an independent predictor of DCR ($P=0.002$), ORR ($P<0.001$), and CRRP ($P<0.001$). Multivariate Cox regression confirmed it as an independent predictor of RFS ($P<0.01$). After a 1-month washout, rejection rates did not differ significantly among the three patient groups, and treatment method was not associated with rejection risk ($P=0.549$).

Conclusion: In the conversion therapy of HCC, the combination of TACE + TKI + ICI has demonstrated higher efficacy, longer recurrence-free survival, manageable safety, and does not interfere with subsequent LT.

Keywords: liver transplantation, conversion therapy, hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third leading cause of cancer-related death.¹ Its asymptomatic onset and complex epidemiology—driven by HBV, HCV, and alcoholic cirrhosis—mean high incidence and mortality are expected over the next two decades despite prevention efforts.² For patients with limited tumor burden who cannot undergo resection, liver transplantation (LT) is optimal, as it removes the tumor and treats underlying liver disease, offering a potential cure.³

LT is a key treatment for HCC.⁴ The Milan criteria define eligibility as a single tumor ≤ 5 cm or up to three tumors each ≤ 3 cm, without macrovascular invasion, lymph node involvement, or extrahepatic metastasis.⁵ These strict criteria limit access for patients with intermediate- to advanced-stage HCC, especially those at BCLC stage B or C.⁶ Extended criteria such as UCSF⁷ and the Hangzhou criteria⁸ have been proposed but have not significantly improved overall survival or substantially expanded access, leaving progress limited.⁹ Meanwhile, waiting-list mortality remains high: over 51,000 patients died awaiting LT in the past two decades¹⁰ and in China, only 6,170 of 14,399 transplant candidates received transplants in 2019.¹¹ Strict criteria and high waitlist mortality continue to hinder advances in HCC care. However, recent progress shows promise. Pre-transplant downstaging therapies can reduce tumor burden and enable transplantation for select patients beyond standard criteria, achieving survival rates comparable to those within criteria.¹² These protocols represent a significant advance in HCC management.

Current downstaging strategies include transcatheter arterial chemoembolization (TACE),¹³ tyrosine kinase inhibitors (TKIs),¹⁴ and immunotherapy.¹⁵ Conversion therapies like TACE, radiofrequency ablation, or radiotherapy are linked to 5-year survival rates of 50–60%.¹⁶ Lenvatinib, a multi-kinase inhibitor targeting VEGF receptors, improves overall and progression-free survival in unresectable HCC.¹⁷ Immune checkpoint inhibitors (ICIs), particularly anti-PD-1/PD-L1 agents, show promise in HCC treatment.¹⁸ As their role in systemic therapy grows, more transplant centers are exploring ICIs in LT recipients, though standardized protocols are lacking. "Conversion therapy" refers to the combined comprehensive treatment of TKI, ICI, and TACE to achieve the effect of alleviating tumor progression before surgery.

For HCC patients beyond Milan criteria, multimodal preoperative therapy aims to downstage tumors and enable successful transplantation. TACE not only targets tumors directly but also modulates the tumor microenvironment and reduces immunosuppression,¹⁹ potentially enhancing systemic therapies like ICIs and TKIs.²⁰ However, the combination of ICIs with locoregional treatments such as TACE as a neoadjuvant strategy—and its impact on post-transplant recurrence—remains unclear.²¹ To our knowledge, no study has yet evaluated how conversion therapy—combining TACE, TKIs, and ICIs—affects post-liver transplantation outcomes in patients with BCLC stage B or C HCC. ICIs are first-line systemic therapy for HCC and effectively control tumor progression. When combined with local therapies like TACE, they achieve >75% downstaging rates, enabling transplantation for patients initially outside transplant criteria. Although the liver is an immune-privileged site and rejection risk is relatively high, most cases respond well to intensified immunosuppression; graft loss or death from rejection remains rare (2–4%).^{22–24} No study has evaluated the impact of TACE + TKI + ICI conversion therapy on post-transplant outcomes in BCLC B/C HCC patients. At our center, the treatment-to-transplant washout period is 1–3 months. This is the first retrospective study to assess the safety and efficacy of pre-transplant TACE–ICI–TKI combination therapy in BCLC B/C HCC, and to examine its impact on transplantation outcomes and patient survival.

Methods

Ethics

The studies involving human participants were reviewed and approved by the Institutional Review Board of The First Affiliated Hospital of Sun Yat-sen University (Ethical Approval No. 2025-529). Our research complies with the Declaration of Helsinki. All organs were voluntarily donated, the donors signed written informed consent forms, and the organ donation process complies with the provisions of the Declaration of Istanbul. Written informed consent was obtained from all participants prior to their participation in the study. Additionally, written informed consent for the publication of any potentially identifiable images or data included in this article was obtained from the individuals involved.

Patients

A total of 312 patients with BCLC stage B or C HCC who underwent LT at the First Affiliated Hospital of Sun Yat-sen University from January 2015 to August 2024 were collected. Among them, 269 patients received TACE, TACE + TKI, or TACE + TKI + ICI before surgery. Patients who only received TACE treatment were assigned to the TACE group ($n = 150$), while those who received TACE combined with TKI and PD-1 inhibitor treatment were

assigned to the TACE + TKI + ICI group (n = 45). Patients who received TACE combined with TKI treatment were assigned to the TACE + TKI group (n = 74).

The preoperative diagnosis of HCC is established based on the following criteria: 1. If the diameter of the liver mass is ≥ 2 cm, and one of the two imaging examinations (CT and MRI) shows that the liver mass has the above-mentioned characteristics of liver cancer, HCC can be diagnosed. 2. If the diameter of the liver mass is between 1 and 2 cm, both CT and MRI imaging examinations need to show that the liver mass has the above - mentioned characteristics of liver cancer to diagnose HCC. 3. Serum AFP criteria: Serum AFP ≥ 400 $\mu\text{g/L}$ for 1 month or ≥ 200 $\mu\text{g/L}$ for 2 months, and other causes of AFP elevation can be excluded. For patients with serum AFP ≥ 400 $\mu\text{g/L}$ but no liver mass found by B – ultrasound, after excluding other causes of AFP elevation, multi-detector CT and/or dynamic contrast-enhanced MRI scans should be performed promptly. If the typical imaging features of HCC are presented, HCC can be diagnosed. 4. For patients with chronic HBV infection without cirrhosis or high - risk factors for HCC, the diagnosis of HCC should be confirmed by pathology, because the accuracy of non - invasive imaging diagnostic criteria is insufficient in these patient populations.

The Inclusion Criteria Were as Follows

(1) age ≥ 18 years; (2) diagnosis of HCC confirmed by histopathological or cytological examination, or based on clinical and imaging features in accordance with the American Association for the Study of Liver Diseases (AASLD) guidelines; (3) HCC classified as stage B or C according to the BCLC staging system; (4) prior treatment with TACE alone, TACE combined with TKIs, or TACE combined with TKIs and ICIs before LT; (5) presence of at least one measurable intrahepatic lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Exclusion Criteria Were

(1) patients who received treatments other than TACE, TKI, and ICI before surgery; (2) HCC patients not in BCLC stage B or C; (3) death due to early severe complications after LT; (4) autologous LT, multiple-organ transplantation, or multiple LT; (5) presence of multiple organ dysfunction; (6) poor patient compliance (missing patient records or loss to follow-up).

Preoperative Treatment Plan

Prior to initiating treatment, the patient's overall health status and liver function are assessed to exclude contraindications for the three available treatment options. Upon confirmation of diagnosis, treatment selection is guided by a multidisciplinary, expert-led clinical decision-making process that considers the patient's clinical condition, economic burden, and personal preferences. Before making a decision, the doctor will inform the patient and their family of the potential benefits, complications and costs of each treatment option. In this center, we adopt the sequential treatment method. Some studies have shown that sequential treatment has a better effect on the prognosis of HCC. Then, TACE, TACE + TKI, and TACE + TKI + ICI treatments will be adopted. The frequency of TACE treatment is once a month. TACE is performed by puncturing the femoral artery using the Seldinger technique. Digital subtraction angiography is used to determine the blood supply arteries of liver tumors and whether there are arteriovenous fistulas, and then catheterization is carried out to the tumor blood supply branches. Tumor vascular embolization was performed using drug-loaded microspheres or 40 mg of iodized oil containing epirubicin. In patients without signs of deterioration or organ function decline, TACE was repeated "on demand" after follow-up contrast-enhanced CT or MRI confirmed tumor survival. In this study, for patients with hepatitis B, entecavir is routinely used before surgery to control the progression of the disease. After transplantation, tacrolimus and mycophenolate mofetil are routinely used in combination for anti - rejection treatment. For patients with hepatitis B, entecavir is routinely used for antiviral treatment after surgery; for patients with hepatocellular carcinoma, tyrosine kinase inhibitors (TKI) are continued to be used for anti - tumor treatment after surgery.

Both groups of patients orally took Lenvatinib (Lenvima) (initial dose, 8mg/day [$<60\text{kg}$] or 12mg/day [$\geq 60\text{kg}$]) within 3 days before and after the first TACE treatment. In the TACE + TKI + ICI group, the PD-1 inhibitor (Tislelizumab, initial dose 200mg, 200mg every 3 weeks) was intravenously injected. According to adverse events, the

dose of Lenvatinib and PD-1 inhibitor could be halved or temporarily discontinued and then resumed after symptom relief. The treatment continued until the patient's LT.

All enrolled patients were followed up regularly before surgery, until the day before transplantation. The follow-up included complete blood cell count, liver, kidney, thyroid and heart function tests, tumor marker detection, coagulation function tests, abdominal CT, electrocardiogram and chest X-ray before each immunotherapy. We evaluated tumor changes through regular imaging studies, with computerized tomography (MRI/CT) performed every 4 weeks, and tumor response was assessed according to RECIST v1.1 criteria. This includes complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). CR refers to the tumor of the patient being downstaged, PR indicates a significant reduction in tumor size without reaching downstaging, SD means no significant change in the tumor but the progression is controlled, and PD indicates poor tumor control, with progressive growth and deterioration of the condition. At the same time, the disease control rate (DCR [CRR + PRR + SDR]) and objective response rate (ORR [CRR + PRR]) as well as the complete response rate (CRR) are evaluated.

Clinical Data and Postoperative Follow-Up

Baseline Data of the Recipient Patients

Collect the patients' basic information, including age, gender, recipient blood type, body mass index (BMI), etiology of liver cancer, history of previous chronic diseases (hypertension, coronary heart disease, diabetes), smoking and drinking history, as well as Child–Pugh score. Tumor - related data include the longest diameter of the tumor, the number of tumors, and tumor vascular invasion.

Donor Data

Analysis of donor age, gender, blood type, BMI, donor donation type, total bilirubin.

Preoperative Laboratory Tests for the Recipient

Preoperative laboratory tests collected include: AFP, preoperative white blood cells, hemoglobin, platelets, ALT, AST, total bilirubin, direct bilirubin, preoperative monocyte percentage, preoperative lymphocyte percentage, preoperative neutrophil percentage, albumin, prealbumin, alkaline phosphatase, GGT, cholinesterase, creatinine, prothrombin time, fibrinogen, INR.

Intraoperative Data of the Patient

Anhepatic phase time, cold ischemia time, total operation time, intraoperative plasma transfusion volume, intraoperative platelet transfusion volume, intraoperative red blood cell transfusion volume, total intraoperative fluid infusion volume, total intraoperative blood loss volume.

Preoperative Treatment Effect and Adverse Reactions

The treatment of the three groups was analyzed respectively, including the rate of ORR, DCR and CRR. The safety of the treatment was compared by contrasting adverse reactions, which included abdominal pain, fever, elevated ALT and AST, fatigue, nausea, vomiting, elevated bilirubin, rash, diarrhea, hypothyroidism, decreased white blood cell count, hand-foot syndrome, decreased appetite, and proteinuria. The grading of adverse events is based on the Clavien–Dindo system. The criterion for successful down - staging is that the tumor meets the criteria for liver transplantation after treatment. Treatment failure means the continued progression of the tumor. There should be no cases of dose reduction here. Discontinuation of the drug is due to successful down-staging.

Postoperative Follow-up

To clarify the long-term treatment effect of patients after surgery, the 1-year survival rate and tumor-free survival time of patients were collected. The calculation of recurrence-free survival (RFS) starts from the date of liver transplantation. The overall survival period refers to the survival time of patients starting from the time after liver transplantation. All

patients are monitored according to the standardized follow - up protocol of our center after liver transplantation. Enhanced CT or MRI scans of the chest and abdomen are performed every three months. When a suspicious lesion is detected by imaging examination, contrast-enhanced ultrasound or PET-CT will be used for further confirmation depending on the location and characteristics of the lesion. At the same time, we collected the probabilities of postoperative rejection occurrence in three groups of patients.

Data Analysis

Statistical analysis was conducted using IBM SPSS Statistics 22.0, and graphing was performed with GraphPad Prism 9.0 (GraphPad Software). Categorical data were analyzed using Pearson's chi-square test, and one-way ANOVA was used for comparisons across multiple groups. Data are presented as mean $\pm$ standard deviation. For non-normally distributed data, the Kruskal–Wallis *H*-test was applied, and results are shown as median (Mdn) and interquartile range (IQR). Binary logistic regression analysis was applied to ORR, CRR, and DCR. Multivariate analysis and Cox proportional - hazards regression were used for RFS and OS to control the interference of confounding factors. Survival curves were generated using the Kaplan–Meier method to assess 1-year overall survival (OS), and statistical significance was defined as $p < 0.05$.

Results

Baseline Data Characteristics of Patients

The baseline characteristics of the three patient groups were comparable, with no significant differences. Patients were similar in gender, age, blood type, Child-Pugh score, BMI, etiology, comorbidities, and smoking or drinking history. Most patients were male, and blood type O was most common. Hepatitis B virus was the primary cause of HCC, followed by hepatitis C and other causes. All patients had a Child-Pugh score of A or B. (Table 1) Donor characteristics—including age, gender, blood type, BMI, donor type, and total bilirubin—also showed no significant differences across groups. Most donors were male, with blood type O predominant and DBD the most common donor type. Pre-donation total bilirubin levels were not significantly different among the groups (TACE+TKI+ICI vs TACE+TKI vs TACE: 16.65 [11.13–30.08] vs 20.75 [11.90–33.70] vs 18.60 [12.55–25.40], $P = 0.241$) (Table 2).

Table 1 Receptor Basic Information

	TACE Group (n=150)	TACE+TKI Group (n=74)	TACE+TKI+ICI Group (n=45)	P value	χ^2
Gender	Male 140(93.3%) Female 10 (6.7%)	Male 70(94.6%) Female 4(5.4%)	Male 41(91.1%) Female 4(8.9%)	0.762	0.544
Blood Type	A 38(25.3%) B 44(29.3%) AB 10(6.7%) O 58(38.7%)	A 21(28.4%) B 22(29.7%) AB 4(5.4%) O 27(36.5%)	A 12(26.7%) B 12(26.7%) AB 5(11.1%) O 16(35.6%)	0.940	1.764
BMI	23.37(21.48–25.13)	23.35(21.39–24.58)	23.03(20.44–25.03)	0.634	–
Etiology	HBV 139(92.7%)	HBV 72(97.3%)	HBV 43(95.6%)	0.223	3.000
	HCV 5(3.3%)	HCV 1(1.4%)	HCV 2(4.4%)		
	Alcoholic liver disease 5 (3.3%)	Alcoholic liver disease 0	Alcoholic liver disease 0		
	Wilson's Disease 1(0.7%)	Wilson's Disease 0	Wilson's Disease 0		
	Autoimmune Hepatitis 0	Autoimmune Hepatitis 1 (1.4%)	Autoimmune Hepatitis 0		

(Continued)

Table 1 (Continued).

		TACE Group (n=150)	TACE+TKI Group (n=74)	TACE+TKI+ICI Group (n=45)	P value	χ^2
Age		51.00(43.00–59.00)	53.50(45.75–60.25)	54.00(46.50–60.00)	0.441	–
Chronic Diseases	Hypertension	Yes 15(10.0%) No 135(90.0%)	Yes 12(16.2%) No 62(83.8%)	Yes 7 (12.6%) No 38(84.4%)	0.341	2.150
	Diabetes	Yes 18(12.0%) No 132(88.0%)	Yes 7(9.5%) No 67(90.5%)	Yes 5(11.2%) No 40(88.8%)	0.851	0.323
	CHD	Yes 1(0.7%) No 149(99.3%)	Yes 0(0.0%) No 74(100%)	Yes 2(4.4%) No 43(95.6%)	0.06	5.631
Alcoholism		Yes 20(13.3%) No 130(86.7%)	Yes 14(18.9%) No 60(81.1%)	Yes 8(17.8%) No 37(82.2%)	0.505	1.366
Smoking History		Yes 41(27.3%) No 109(72.7%)	Yes 25(33.8%) No 49(66.2%)	Yes 12(26.7%) No 33(73.3%)	0.564	1.144
Child-Pugh Score		7.00(6.00–8.00)	7.00(6.00–8.00)	7.00(6.00–8.00)	0.310	–
Tumor longest diameter		47.00(30.75–79.25)	62.00(38.00–97.00)	45.50(28.50–78.25)	0.123	
Number of tumors		Solitary tumor 55 Multiple tumors 95	Solitary tumor 23 Multiple tumors 51	Solitary tumor 15 Multiple tumors 30	0.698	0.720
Infringe blood vessels		Yes 15(10.0%) No 135(90.0%)	Yes 12(16.2%) No 62(83.8%)	Yes 7 (12.6%) No 38(84.4%)	0.073	5.233

Table 2 Donor Clinical Data

	TACE Group (n=150)	TACE+TKI Group (n=74)	TACE+TKI+ICI Group (n=45)	P value	χ^2
Gender	Male 117(78.0%) Female 33 (22.0%)	Male 58(78.4%) Female 16(21.6%)	Male 33(73.3%) Female 12(26.7%)	0.781	0.495
Blood Type	A 38(25.3%) B 42(28.0%) AB 12(8.0%) O 58(38.7%)	A 22(29.7%) B 21(28.4%) AB 5(6.8%) O 26(35.1%)	A 12(26.7%) B 12(26.7%) AB 5(11.1%) O 16(35.6%)	0.974	1.255
BMI	22.32(20.76–24.22)	22.67(20.76–24.49)	22.49(19.72–24.22)	0.586	–
Donor Type	DBD 128(85.3%)	DBD 57(77.0%)	DBD 38(84.4%)	0.580	2.867
	DCD 18(12.0%)	DCD 13(17.6%)	DCD 6(13.3%)		
	DCDB 4(2.7%)	DCDB 4(5.4%)	DCDB 1(2.2%)		
Age	40.00(28.00–49.00)	41.00(29.50–49.00)	40.00(33.00–51.50)	0.718	–
Total Bilirubin	16.65(11.13–30.08)	20.75(11.90–33.70)	18.60(12.55–25.40)	0.241	–

The Effect of Preoperative Treatment for HCC and the Prognosis of Patients After Surgery

TACE+TKI+ICI is an efficient treatment approach for primary liver cancer. After analyzing the tumor control effects of other methods, the tumor control effect of the TKI+TACE+ICI group showed a significant advantage. Compared with the

Table 3 Preoperative Treatment Effect

	TACE Group (n=150)	TACE+TKI Group (n=74)	TACE+TKI+ICI Group (n=45)	P value	χ^2
DCR	Yes 93(62.0%) No 57 (38.0%)	Yes 51 (68.9%) No 23 (31.1%)	Yes 40(88.9%) No 5 (11.1%)	P=0.003	11.592
ORR	Yes 42(28.0%) No 108(72.0%)	Yes 31 (41.9%) No 43 (58.1%)	Yes 28(62.2%) No 17 (37.8%)	P<0.001	18.111
CRR	Yes 9(6.0%) No 141 (94.0%)	Yes 10(13.5%) No 64 (86.5%)	Yes 13(28.9%) No 32 (71.1%)	P<0.001	17.558
RFS	222.5(126.3–363.8)	257.0(134.0–401.0)	701.5(374.3–928.8)	P=0.011	–

other two groups, the TKI+TACE+ICI group had a DCR (TACE+TKI+ICI vs TACE+TKI vs TACE, 88.9% vs 68.9% vs 62.0%, $P=0.003$, $\chi^2=11.592$), a higher ORR (TACE+TKI+ICI vs TACE+TKI vs TACE, 62.2% vs 41.9% vs 28.0%, $P<0.001$, $\chi^2=18.111$), and a higher CRR (TACE+TKI+ICI vs TACE+TKI vs TACE, 28.9% vs 13.5% vs 6.0%, $P<0.001$, $\chi^2=17.558$) (Table 3). In this study, we followed up on the recurrence-free survival period (RFS) and 1-year overall survival (OS) of the patients. Compared with the other two groups, the TKI+TACE+ICI group had a longer RFS (TACE+TKI+ICI vs TACE+TKI vs TACE, 222.5 (126.3–363.8) vs 257.0 (134.0–401.0) vs 701.5 (374.3–928.8), $P=0.011$) (Table 3), but there was no significant statistical difference in 1-year OS (TACE+TKI+ICI vs TACE+TKI vs TACE, $P=0.707$) (Figure 1). Binary logistic analysis shows that after excluding the influence of confounding factors, ORR, CRR, and DCR are only associated with the choice of treatment methods (Tables 4–6). Cox proportional hazards regression analysis, a multi-factor survival analysis, shows that there is no significant difference in the postoperative survival among the three groups of patients. The postoperative RFS results indicate that the postoperative RFS time of patients in the TKI + TACE + ICI group is significantly prolonged (Tables 7 and 8).

Analysis of Treatment Safety

Safety of Preoperative Treatment

There were no significant differences among the three groups of patients in the preoperative laboratory test results of AFP, preoperative white blood cells, hemoglobin, platelets, ALT, AST, total bilirubin, direct bilirubin, preoperative monocyte percentage, preoperative lymphocyte percentage, preoperative neutrophil percentage, albumin, prealbumin, alkaline phosphatase, GGT, cholinesterase, creatinine, prothrombin time, fibrinogen, and INR (Table 9). All three groups of patients experienced different adverse events during the treatment process. Hypothyroidism was a unique adverse event during ICI treatment, while hand-foot syndrome, leukopenia, and proteinuria were adverse events during TKI

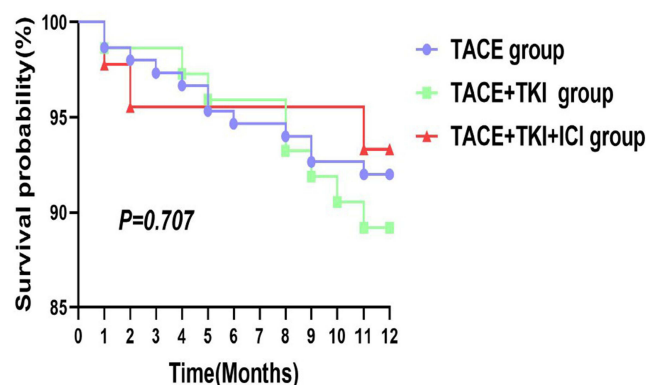


Figure 1 Kaplan-Meier curve illustrating the probability of an event-free outcome over a 12-month follow-up period. The numbers at selected time points indicate the percentage of patients remaining event-free. The log-rank test yielded a P-value of 0.707, indicating no statistically significant difference between the compared groups.

Table 4 Factors Associated with DCR in Multivariate Analysis

Parameter		Univariate Analysis		Multivariate Analysis	
		OR	P	OR	P
Etiology	HBV	1			
	HCV	1.072	0.923		
	Alcoholic liver disease	0.357	0.265		
Recipient age		1.023	0.063	1.019	0.145
Recipient BMI		0.796	0.562		
Recipient gender	Male	1			
	Female	0.522	0.734		
Preoperative AFP		1.000	0.203	1.000	0.461
Max tumor diameter		0.990	0.006	0.990	0.016
Number of tumor	≤2	1		1	
	>2	3.243	0.002	2.654	0.051
Microvascular invasion	No	1		1	
	Yes	0.393	<0.001	0.608	0.192
Bridging or downstaging therapy protocols	TACE+TKI+ICI	1		1	
	TACE+TKI	0.399	0.046	0.369	0.045
	TACE	0.315	0.006	0.252	0.003
Child-Pugh score		1.081	0.409	1.078	0.459

Table 5 Factors Associated with ORR in Multivariate Analysis

Parameter		Univariate Analysis		Multivariate Analysis	
		OR	P	OR	P
Etiology	HBV	1			
	HCV	1.072	0.919		
	Alcoholic liver disease	0.335	0.331		
Recipient age		1.008	0.525	1.005	0.673
Recipient BMI		0.993	0.860		
Recipient gender	Male	1			
	Female	0.988	0.980		
Preoperative AFP		1.000	0.421	1.000	0.410
Max tumor diameter		1.000	0.913	1.002	0.632
Number of tumor	≤2	1		1	
	>2	2.795	0.015	2.156	0.149

(Continued)

Table 5 (Continued).

Parameter		Univariate Analysis		Multivariate Analysis	
		OR	P	OR	P
Microvascular invasion	No	1		1	
	Yes	0.573	0.026	0.655	0.255
Bridging or downstaging therapy protocols	TACE+TKI+ICI	1		1	
	TACE+TKI	0.398	0.018	0.384	0.018
	TACE	0.310	0.001	0.295	0.001
Child-Pugh score		1.064	0.496	1.065	0.521

Table 6 Factors Associated with CRR in Multivariate Analysis

Parameter		Univariate Analysis		Multivariate Analysis	
		OR	P	OR	P
Etiology	HBV	1			
	HCV	0.847	0.812		
	Alcoholic liver disease	0.000	0.999		
Recipient age		1.019	0.300	1.019	0.352
Recipient BMI		0.985	0.797		
Recipient gender	Male	1			
	Female	1.277	0.709		
Preoperative AFP		1.000	0.594	1.000	0.879
Max tumor diameter		0.996	0.518	0.999	0.896
Number of tumor	≤2	1		1	
	>2	5.780	0.089	1.997	0.567
Microvascular invasion	No	1		1	
	Yes	0.263	0.015	0.249	0.042
Bridging or downstaging therapy protocols	TACE+TKI+ICI	1		1	
	TACE+TKI	0.574	0.032	0.572	0.037
	TACE	0.139	0.001	0.116	0.001
Child-Pugh score		0.930	0.586	0.933	0.648

treatment. There were no significant differences among the three groups of patients in terms of abdominal pain, fever, elevated ALT and AST, fatigue, nausea, vomiting, elevated bilirubin, rash, diarrhea, and decreased appetite. This indicates that there were no significant safety differences among the three groups in treatment. Timely management after the occurrence of symptoms would not cause serious adverse reactions to the patients (Table 10). There was no

Table 7 COX Regression Analysis for the RFS Analysis After Liver Transplantation

Parameter		Univariate Analysis		Multivariate Analysis	
		HR (95% CI)	P	HR (95% CI)	P
Etiology	HBV	I			
	HCV	0.766(0.283–2.068)	0.598		
	Alcoholic liver disease	1.748 (0.646–4.729)	0.271		
Smoking History	No	I		0.868(0.599–1.258)	0.454
	Yes	0.881(0.534–1.453)	0.621		
Recipient age		0.996(0.980–1.011)	0.580	0.997(0.981–1.013)	0.715
Recipient BMI		1.010(0.960–1.063)	0.693	1.004(0.953–1.058)	0.885
Recipient gender	Male	I			
	Female	0.520(0.244–1.111)	0.092	0.514(0.239–1.108)	0.089
Preoperative AFP		1.000(1.000–1.000)	0.413	1.000(1.000–1.000)	0.323
Max tumor diameter		0.998(0.994–1.003)	0.493	0.998(0.993–1.003)	0.441
Number of tumor	≤2	I		I	
	>2	0.910(0.579–1.430)	0.683	0.870(0.476–1.589)	0.650
Microvascular invasion	No	I		I	
	Yes	1.027(0.728–1.449)	0.877	0.961(0.600–1.541)	0.870
Bridging or downstaging therapy protocols	TACE+TKI+ICI	I		I	
	TACE+TKI	2.217(1.284–3.827)	0.004	2.219(1.278–3.851)	0.005
	TACE	1.917(1.154–3.184)	0.012	1.868(1.122–3.108)	0.016
Child-Pugh score		0.932(0.828–1.049)	0.245	0.949(0.844–1.067)	0.381
Donor gender	Male	I			
	Female	0.943(0.644–1.381)	0.764		
Donor age		0.996(0.985–1.007)	0.500		
Donor BMI		0.985(0.938–1.035)	0.560		
Donor type	DBD	I			
	DCD	1.148(0.729–1.807)	0.551		
	DBCD	1.481(0.652–3.362)	0.348		

statistically significant difference in the probability of postoperative rejection among the three groups of patients (Table 11).

Safety Analysis of Treatment for Transplantation Surgery

To investigate the impact of preoperative treatment on LT surgery, we analyzed the anhepatic phase time, cold ischemia time, total operation time, intraoperative plasma transfusion volume, intraoperative platelet transfusion volume, intraoperative red blood cell transfusion volume, intraoperative total fluid infusion volume, and intraoperative total blood loss

Table 8 COX Regression Analysis for the OS Analysis After Liver Transplantation

Parameter		Univariate Analysis		Multivariate Analysis	
		HR (95% CI)	P	HR (95% CI)	P
Etiology	HBV	I			
	HCV	1.593 (0.581–4.362)	0.365		
	Alcoholic liver disease	2.061 (0.649–6.547)	0.220		
Smoking History	No	I		0.929(0.548–1.577)	0.786
	Yes	0.881(0.534–1.453)	0.621		
Recipient age		0.984(0.963–1.005)	0.138	0.989(0.967–1.011)	0.321
Recipient BMI		1.037(0.968–1.112)	0.298	1.032(0.963–1.105)	0.371
Recipient gender	Male	I			
	Female	0.468(0.153–1.542)	0.221		
Extrahepatic diseases	No	I		I	
	Yes	1.427(0.859–2.520)	0.159	1.362(0.788–2.355)	0.268
Preoperative AFP		1.000(1.000–1.000)	0.194	1.000(1.000–1.000)	0.166
Max tumor diameter		0.999(0.992–1.005)	0.717	0.977(0.990–1.005)	0.504
Number of tumor	≤2	I		I	
	>2	1.360(0.654–2.827)	0.410	0.997(0.990–1.005)	0.838
Microvascular invasion	No	I		I	
	Yes	0.714(0.426–1.198)	0.202	0.669(0.333–1.344)	0.259
Bridging or downstaging therapy protocols	TACE+TKI+ICI	I		I	
	TACE+TKI	2.789(1.140–6.823)	0.25	2.746(1.116–6.757)	0.28
	TACE	2.780(1.189–6.496)	0.18	2.556(1.087–6.008)	0.31
Child-Pugh score		0.899(0.765–1.057)	0.197	0.937(0.797–1.101)	0.427
Donor gender	Male	I			
	Female	0.923(0.593–1.581)	0.771		
Donor age		1.002(0.987–1.018)	0.761		
Donor BMI		1.034(0.961–1.112)	0.371		
Donor type	DBD	I			
	DCD	1.368(0.761–2.522)	0.286		
	DBCD	1.737(0.631–4.778)	0.285		
Donor bilirubin level		0.995(0.984–1.007)	0.403		
Cold ischemia time		1.001(0.999–1.002)	0.517		
Total operative time		1.000(0.998–1.001)	0.676		
Live-free period		1.000(0.986–1.014)	0.998		

(Continued)

Table 8 (Continued).

Parameter	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P	HR (95% CI)	P
Preoperative ALT	1.002(1.000–1.004)	0.094	1.002(1.000–1.004)	0.067
Preoperative AST	1.001(0.997–1.005)	0.584		
Preoperative Albumin	1.015(0.973–1.059)	0.488		
Preoperative total bilirubin	0.999(0.995–1.003)	0.644		

Table 9 Preoperative Laboratory Test Results

	TACE Group (n=150)	TACE+TKI Group (n=74)	TACE+TKI+ICI Group (n=45)	P value
Preoperative AFP	29.46(5.328–734.3)	98.89(17.81–2265)	17.43(3.930–1679)	0.060
Preoperative WBC count	5.315(3.693–6.768)	5.290(4.145–6.818)	4.270(3.430–6.760)	0.480
Preoperative hemoglobin count	129.0(111.0–144.3)	129.0(108.8–143.5)	136.0(116.5–146.5)	0.444
Preoperative platelet count	123.0(76.75–187.5)	131.5(77.50–188.0)	128.0(70.50–216.0)	0.961
Preoperative neutrophil percentage	0.6170(0.5183–0.7277)	0.6400(0.5477–0.6858)	0.6047(0.4810–0.6881)	0.426
Preoperative lymphocyte percentage	0.2488(0.1657–0.3292)	0.2380(0.1807–0.2995)	0.2568(0.1915–0.3270)	0.731
Preoperative monocyte percentage	0.09000(0.07181–0.1124)	0.08794(0.06682–0.1146)	0.08400(0.06950–0.1143)	0.902
Preoperative ALT	40.00(26.75–64.25)	51.00(31.00–86.50)	42.00(31.50–58.00)	0.070
Preoperative AST	38.00(26.00–59.00)	46.00(28.75–76.00)	38.00(23.50–52.50)	0.063
Preoperative albumin	36.23±5.446	35.76±5.598	36.29±5.360	0.805
Preoperative prealbumin	135.5(90.00–207.3)	120.0(82.50–172.0)	136.0(100.5–201.5)	0.143
Preoperative alkaline phosphatase	109.0(82.50–147.3)	110.0(85.75–176.3)	120.0(82.00–179.5)	0.494
Preoperative GGT	95.00(48.50–177.3)	120.5(60.75–210.3)	126.0(56.50–270.0)	0.199
Preoperative cholinesterase	4663±2159	4156±1984	4876±2210	0.135
Preoperative total bilirubin	22.10(12.88–31.35)	22.75(16.58–36.63)	18.50(12.00–29.85)	0.194
Preoperative direct bilirubin	5.150(3.175–10.60)	5.900(4.150–11.28)	5.000(2.500–8.200)	0.235
Preoperative creatinine	75.50(62.00–87.25)	73.50(64.00–83.00)	72.00(61.50–83.00)	0.547
Preoperative prothrombin time	13.15(12.20–14.53)	13.20(12.18–15.00)	13.10(12.00–14.70)	0.996
Preoperative fibrinogen	2.710(1.918–3.460)	2.495(2.010–3.363)	2.540(1.535–3.370)	0.526
Preoperative INR	1.130(1.038–1.270)	1.120(1.030–1.273)	1.120(1.025–1.465)	0.877

Table 10 Adverse Event Assessment

Adverse events	Any Grade					Grade≥3				
	TACE (n=150)	TACE +TKI (n=74)	TACE+TKI +ICI (n=45)	P value	χ ²	TACE (n=150)	TACE +TKI (n=74)	TACE+TKI +ICI (n=45)	P value	χ ²
Abdominal Pain	34(22.67%)	16(21.62%)	9(20.00%)	0.928	0.150	0	0	0	–	–
Pyrexia	42(28.00%)	18(24.32%)	10(22.22%)	0.686	0.753	0	0	0	–	–
Increased ALT	31(20.67%)	13(17.57%)	8(17.78%)	0.823	0.389	2(1.33%)	1(1.35%)	1(2.22%)	0.81	0.737
Increased AST	30(20.00%)	13(17.57%)	8(17.78%)	0.887	0.240	2(1.33%)	1(1.35%)	1(2.22%)	0.81	0.737
Fatigue	33(22.00%)	18(24.32%)	12(26.67%)	0.792	0.467	6(4.00%)	3(4.05%)	2(4.45%)	0.991	0.018
Nausea	47(31.33%)	22(29.73%)	13(28.89%)	0.939	0.125	0	0	0	–	–
Vomiting	30(20.00%)	14(18.92%)	9(20.00%)	0.980	0.040	0	0	0	–	–
Elevated Bilirubin	14(9.33%)	7(9.46%)	4(8.89%)	0.994	0.011	3(2.00%)	1(1.35%)	0		
Diarrhea	17(11.33%)	9(12.16%)	6(13.33%)	0.933	0.139	2(1.33%)	1(1.35%)	1(2.22%)	0.81	0.737
Rash	15(10.00%)	8(10.81%)	5(11.11%)	0.969	0.064	0	0	0	–	–
Hypothyroidism	0	0	3(6.67%)	–	–	0	0	0	–	–
Decreased WBC Count	0	2(2.70%)	1(2.22%)	–	–	0	0	0	–	–
Hand-foot Syndrome	0	13(17.57%)	9(20.00%)	-	-	0	3(4.05%)	2(4.45%)		
Decreased Appetite	67(44.67%)	31(41.89%)	19(42.22%)	0.909	0.191	0	0	0	-	-
Proteinuria	0	2(2.70%)	1(2.22%)	-	-	0	0	0	-	-

Table 11 Factors Associated with Transplant Rejection in Multivariate Analysis

Parameters		Multivariate Analysis	
		P	OR (95% CI)
Donor age(years)		0.252	0.975
Donor gender	Male	0.110	5.503
	Female		
Cold ischemia time(min)		0.941	1.000
Graft type	DBD	0.621	
	DCD		
	DBCD		
Donor BMI		0.941	1.008

(Continued)

Table 11 (Continued).

Parameters		Multivariate Analysis	
		P	OR (95% CI)
Donor bilirubin		0.304	0.979
Donor kidney injury	Yes	0.366	0.578
	No		
Recipient age		0.599	1.016
Recipient BMI		0.167	1.122
Recipient gender	Male	0.897	0.862
	Female		
Child-Pugh score		0.765	0.940
Diabetes mellitus	Yes	0.390	0.521
	No		
Hypertension	Yes	0.187	4.402
	No		
Preoperative AFP		0.306	1.000
Max tumor diameter		0.694	1.003
Number of tumor	Solitary tumor	0.573	0.559
	Multiple tumors		
Microvascular invasion	Yes	0.462	0.577
	No		
Bridging or downstaging therapy protocols	TACE group	0.549	
	TACE+TKI group		
	TACE+TKI+ICI group		

volume. After preoperative treatment, there was no significant difference in the transplantation process among the three groups of patients. This indicates that different treatments have little effect on the surgical process (Table 12).

Discussion

In recent years, advances in understanding HCC molecular mechanisms and treatment strategies have enhanced the potential of combining TACE, TKIs, and ICIs as preoperative therapy for LT²². This study systematically evaluates their role in downstaging HCC and enabling successful transplant conversion.

TACE, a core local therapy, induces ischemic necrosis by embolizing tumor-feeding arteries and increases localized chemotherapy concentration, effectively controlling intrahepatic disease progression.²³ However, as monotherapy, its efficacy is limited. Complete arterial occlusion is difficult in larger tumors, and some patients fail to achieve downstaging.²⁴ TKIs, such as lenvatinib and sorafenib, inhibit tumor angiogenesis and delay disease progression by targeting multiple tyrosine kinases, but their use is limited by significant adverse effects and unclear optimal agent selection.²⁵ ICIs, including PD-1 and PD-L1 inhibitors, restore T-cell function and induce systemic anti-tumor

Table 12 Surgical Data

	TACE Group (n=150)	TACE+TKI Group (n=74)	TACE+TKI+ICI group (n=45)	P value
Anhepatic phase	56.50(43.75–66.25)	55.00(44.75–65.50)	52.00(45.50–59.00)	0.364
Cold ischemia time	422.5(336.8–523.8)	417.5(341.8–521.8)	394.0(317.0–488.0)	0.600
Total operation time	442.5(360.0–545.0)	475.0(420.0–540.0)	460.0(385.0–530.5)	0.289
Intraoperative red blood cell transfusion volume	3.575(0.000–6.000)	4.600(2.000–8.250)	2.600(1.150–6.250)	0.100
Intraoperative plasma transfusion volume	5.625(3.438–8.063)	6.375(4.000–9.125)	5.000(2.750–9.500)	0.210
Total volume of intravenous infusion	7575(5950–9585)	7930(6438–9913)	7140(5875–8665)	0.147
Intraoperative blood loss	1200(600.0–2200)	1500(800.0–2000)	1000(500.0–1990)	0.100

immunity²⁶ yet are contraindicated after transplantation due to the risk of graft rejection and show high inter-patient variability in efficacy. Notably, combining TACE, TKI, and ICI has a clear synergistic mechanism: TACE-induced tumor necrosis releases antigens and enhances tumor immunogenicity; TKIs inhibit angiogenesis and modulate the tumor microenvironment to reverse immunosuppression; ICIs further activate cellular immunity, enabling a systemic anti-tumor response. Thus, the triple therapy may promote substantial tumor shrinkage and increase pathological complete response rates, potentially improving eligibility for LT. However, its safety remains controversial.

A total of 269 liver transplant recipients were divided into three groups based on preoperative treatment. Baseline characteristics were comparable across groups, with no significant differences in gender, age, blood type, Child-Pugh score, BMI, etiology (mainly HBV), medical history, or smoking and drinking status. Donor characteristics were also similar, including gender, age, blood type, BMI, donor type (mostly DBD), and pre-donation bilirubin levels, supporting reliable intergroup comparisons.

The key finding is that triple therapy significantly outperformed TACE alone or TACE + TKI in DCR, ORR, and CRR. This supports the synergistic effect of local and systemic therapies: TACE induces tumor necrosis and antigen release, altering the immune microenvironment;²⁷ TKI inhibits angiogenesis and modulates immunity;²⁸ ICI relieves immune suppression and enhances anti-tumor responses.²⁹ Together, they enable multidimensional tumor control, improving downstaging success and conversion rates. Patients receiving triple therapy had significantly longer RFS after LT, suggesting not only local tumor reduction but also elimination of undetectable micrometastases. As post-transplant recurrence often originates from such micrometastases, preoperative immune activation may provide long-term protection beyond surgery, enabling a shift from “transplantable” to “long-term tumor-free after transplant.” Despite these benefits, there was no significant difference in 1-year OS among groups. This may be due to several factors: LT itself greatly improves outcomes for all bridged patients, potentially masking differences; the follow-up period may be too short to detect OS differences; and post-recurrence treatments may influence OS results.

The adverse event profile in this study was consistent with the known safety profiles of the drugs. Hypothyroidism in the ICI group³⁰ and hand-foot syndrome and proteinuria in the TKI group were target-specific, reflecting expected drug activity.³¹ Despite increased drug use with triple therapy, the incidence of common adverse events after TACE and systemic treatment—such as abdominal pain, fever, transient transaminase elevation, and nausea/vomiting—did not differ significantly across groups, indicating that intensified treatment did not worsen common toxicities.³² Safety data show that the TACE + TKI + ICI regimen improves tumor outcomes—including conversion rate, ORR, and RFS—while maintaining manageable safety. Most adverse reactions can be controlled through standard prevention, symptomatic management, and timely dose adjustments, without irreversible effects or impact on LT eligibility. Thus, in transplant centers with experienced multidisciplinary teams, this regimen offers favorable clinical feasibility and a positive risk-benefit profile. Based on prior and current efficacy and safety results, this study further supports TACE + TKI + ICI as a preferred pre-transplant strategy. It enhances tumor conversion and RFS without compromising transplant feasibility,

alleviating surgical concerns about treatment-related risks, and encourages broader use of effective downstaging or bridging therapies under multidisciplinary care to improve long-term outcomes. This study is a retrospective study, and there is a selection bias. Meanwhile, the follow-up time is relatively short. In the future, we will collect more data to make the results more widely applicable. As a first-line drug for the treatment of hepatocellular carcinoma (HCC), the application of immune checkpoint inhibitors (ICI) before liver transplantation is controversial. However, current research also shows that the reasonable and standardized application of ICI before surgery can minimize the occurrence of postoperative rejection. In this study, there was no statistically significant difference in the probability of postoperative rejection among the three groups of patients included.

Conclusion

This study found that combining TACE, TKI, and ICI yielded the best DCR, ORR, and CRR, demonstrating strong synergy between local therapy and systemic immunotherapy and targeted therapy. The regimen significantly prolonged RFS after LT, reduced tumor stage, and provided long-term benefits without delaying transplantation. Adverse events were controllable and did not increase common side effects, indicating good safety under standardized management. No significant difference in 1-year OS was observed across groups, likely due to high LT efficacy, short follow-up, and subsequent therapies; long-term survival benefits require further evaluation. As a single-center study with limited follow-up, future research will extend follow-up duration and include multi-center data to enhance validity and clinical relevance.

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Disclosure

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