Original Article

Comparative efficacy of transarterial chemoembolization with and without PD-1 inhibitor in the treatment of unresectable liver cancer and construction and validation of prognostic models

Ming-Xing Wang[1#], Tong Lai[2#], Ai-Xin Liu[3#], Gong-Yi Wu[3], Qing-Ming Sun[1], Bao-Rui Zhang[2], Wan-Hui Dong[1]

[1]Department of Medical Oncology, Lu'an Hospital of Traditional Chinese Medicine Affiliated to Anhui University of Chinese Medicine, Lu'an, China; [2]Department of Acupuncture and Massage, Lu'an Hospital of Traditional Chinese Medicine Affiliated to Anhui University of Chinese Medicine, Lu'an, China; [3]Department of Orthopedics department, Lu'an Hospital of Traditional Chinese Medicine Affiliated to Anhui University of Chinese Medicine, Lu'an, China

Contributions: (I) Conception and design: MX Wang, WH Dong; (II) Administrative support: WH Dong, QM Sun; (III) Provision of study materials or patients: MX Wang, WH Dong; (IV) Collection and assembly of data: AX Liu, BR Zhang; (V) Data analysis and interpretation: T Lai, GY Wu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Wan-Hui Dong, MD. Department of Medical Oncology, Lu'an Hospital of Traditional Chinese Medicine to Anhui University of Chinese Medicine, No. 76 Renmin Road, Zhongshi Street, Jin'an District, Lu'an 237006, China. Email: dongwanhui@laszyy.cn; Bao-Rui Zhang, MD. Department of Acupuncture and Massage, Lu'an Hospital of Traditional Chinese Medicine to Anhui University of Chinese Medicine, No. 76 Renmin Road, Zhongshi Street, Jin'an District, Lu'an 237006, China. Email: zbr6452@163.com.

Background: In recent years, therapeutic strategies for liver cancer have been continuously evolving, with transarterial chemoembolization (TACE) being widely applied. Although TACE has demonstrated good short-term efficacy, long-term prognosis remains a challenge. This study aimed to investigate the clinical efficacy and safety of TACE combined with tyrosine kinase inhibitors (TKIs) and programmed cell death protein 1 (PD-1) inhibitors versus TACE combined with TKIs alone. Additionally, we explored prognostic factors, constructed a prognostic model, and validated it.

Methods: A retrospective analysis was conducted on 174 patients with unresectable hepatocellular carcinoma at Lu'an Hospital of Traditional Chinese Medicine Affiliated to Anhui University of Traditional Chinese Medicine from December 21, 2018, to January 15, 2023. Of these, 122 patients were treated with TACE + TKIs + PD-1, and 52 patients with TACE + TKIs. The objective was to compare overall survival (OS) and progression-free survival (PFS) between the two groups, analyze adverse events to assess the safety of the treatment regimen, explore risk factors affecting the prognosis of patients' OS and PFS, construct a prognostic model, and validate it through meta-analysis.

Results: The median OS in the TACE + TKIs + PD-1 group was significantly better than that in the TACE + TKIs group {20.8 months [95% confidence interval (CI): 13.6–28.0] *vs.* 14.7 months (95% CI: 11.6–17.8), P<0.001}. The median PFS in the TACE + TKIs + PD-1 group was also significantly better than that in the TACE + TKIs group [8.6 months (95% CI: 6.6–10.6) *vs.* 5.2 months (95% CI: 4.8–5.6), P<0.001]. The disease control rate (DCR) and objective response rate (ORR) were 82.8% and 37.7% in the TACE + TKIs + PD-1 group, and 57.7% and 28.9% in the TACE + TKIs group, respectively. The incidence of rash was significantly higher in the TACE + TKIs + PD-1 group than in the TACE + TKIs group. Multifactorial analysis identified treatment options (TACE + TKIs + PD-1 *vs.* TACE + TKIs) [hazard ratio (HR) =0.311, 95% CI: 0.192–0.503, P<0.001], Barcelona Clinic Liver Cancer (BCLC) stage (B/C) (HR =0.367, 95% CI: 0.235–0.574, P<0.001), and Eastern Cooperative Oncology Group performance status (ECOG PS) (1/0) (HR =1.974, 95% CI: 1.059–3.678, P=0.03) as independent prognostic factors for OS. Treatment options (HR =0.352, 95% CI: 0.221–0.559, P<0.001) and extrahepatic metastasis (yes/no) (HR =2.034, 95% CI: 1.201–3.444, P=0.008) were identified as independent prognostic factors for PFS. The results were confirmed through meta-validation. The area under the curve (AUC) for the 1-, 2-, and 3-year OS nomograms were

0.706, 0.775, and 0.741, respectively, indicating good predictive performance of the model.

Conclusions: The TACE + TKIs + PD-1 treatment regimen significantly outperformed TACE + TKIs in terms of OS, PFS, and DCR but increased the incidence of rash. An ECOG PS of 1 and BCLC-C stage were identified as risk factors for OS, while extrahepatic metastasis was an independent risk factor for PFS. The high accuracy of the survival prediction model constructed in this study provides a basis for clinical prognosis.

Keywords: Hepatic artery chemoembolization; tyrosine kinase inhibitor (TKI); programmed cell death protein 1 inhibitor (PD-1 inhibitor); immunotherapy; combination therapy

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Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors. Data from the year 2020 indicate that HCC ranks as the sixth leading malignancy in prevalence and is associated with the third highest rate of fatality (1). According to pathological classification, HCC, intrahepatic cholangiocellular carcinoma, and combined hepatocellular-cholangiocarcinoma are all subtypes of primary liver cancer, with HCC accounting for 75% to 95% of these cases (2). Due to its insidious onset and rapid progression, HCC is often diagnosed at an advanced stage, typically in the middle to late stages. This late diagnosis often means that patients have missed the opportunity for liver transplantation and radical resection or ablation, and only about one-third of patients are eligible for radical treatment (3). For patients with advanced tumors, besides conventional systemic treatments such as radiotherapy and chemotherapy, local therapies like transarterial chemoembolization (TACE) are among the standard therapeutic approaches for primary HCC (4-6).

HCC primarily receives its blood supply from the hepatic artery. The mechanism of TACE involves embolizing the hepatic artery and locally injecting chemotherapeutic drugs to induce ischemic necrosis in the tumor, thereby preventing recurrence and metastasis of HCC (7). The liver's dual blood supply means that TACE does not cause necrosis of the liver parenchyma adjacent to the tumor after embolization of the tumor vessels. Compared to systemic therapies, TACE can avoid many adverse effects, making it more suitable for patients with intermediate and advanced stages of HCC. A study has indicated that large or giant HCC can be down-staged after TACE, potentially providing opportunities for second-stage surgery (8). However, due to the heterogeneity of HCC, only about 30% of patients respond well to TACE, and repeated treatments can accelerate the deterioration of liver function, limiting subsequent therapeutic options. Moreover, TACE's efficacy is suboptimal for HCC tumors with a diameter of 10 cm or larger. Giant HCC often has abundant collateral circulation and multiple venous fistulas, complicating complete embolization (9-11). Additionally,

Highlight box

Key findings

- Our study identified a novel therapeutic approach for unresectable liver cancer, integrating transarterial chemoembolization (TACE) with tyrosine kinase inhibitors (TKIs) and programmed cell death protein 1 (PD-1) inhibitors, which significantly enhanced overall survival (OS) and progression-free survival (PFS).
- Additionally, the response rates were substantially boosted, with a disease control rate of 82.8% and an objective response rate of 37.7% in the TACE + TKIs + PD-1 group, surpassing the rates of TACE combined with TKIs alone.
- Furthermore, our study quantified prognostic factors. The prognostic model demonstrated high accuracy with an area under the curve of 0.706–0.775 for OS nomograms, confirming its robust predictive power and potential to transform clinical decision-making in liver cancer treatment.

What is known and what is new?

- Liver cancer is among the leading causes of cancer-related mortality worldwide, with unresectable hepatocellular carcinoma presenting a significant treatment challenge. Traditional approaches like TACE have shown efficacy but are limited in addressing advanced disease. Our study introduces a novel combination therapy by adding PD-1 inhibitors to the TACE + TKIs regimen, marking a significant advancement. This approach has demonstrated a substantial increase in median OS, PFS, and response rates.

What is the implication, and what should change now?

- The integration of PD-1 inhibitors with TACE and TKIs presents a more personalized and potent therapeutic strategy, potentially becoming the new standard of care. This calls for a re-evaluation of current treatment protocols and highlights the need to consider this triple therapy in clinical decision-making.

TACE can alter the tumor microenvironment, increasing the expression of various growth factors, which may lead to vascular regeneration and tumor metastasis (12). Therefore, identifying more effective treatment options is crucial.

Targeted therapy, which blocks tumor growth and metastasis by targeting specific molecules, represents a novel approach that has demonstrated significant clinical efficacy in oncology. Sorafenib marked the inaugural instance of a targeted therapy gaining regulatory approval for the management of HCC in its intermediate to advanced stages, and it has remained the only targeted drug approved for these stages of HCC over the past decade (13). The landscape of targeted therapy has evolved with the approval of lenvatinib as a first-line treatment for HCC, joined by regorafenib and cabozantinib as second-line options (14). A recent study reported an impressive objective response rate (ORR) of 54.1% with the combination of lenvatinib and TACE, along with a median overall survival (OS) of 17.8 months and a median progression-free survival (PFS) of 10.6 months. These findings suggest that the combination of lenvatinib with TACE could be a potent translational therapy (15), underscoring the potential of combining TACE with tyrosine kinase inhibitors (TKIs) as a therapeutic strategy.

Studies have revealed that tumor cells can proliferate by evading immune surveillance or by inducing immunosuppression, which involves inhibiting the activation of immunoreactive cells (16). Immunotherapy has the potential to enhance the OS rate in HCC by stimulating the immune system to recognize and target tumor cells more effectively (17). The field of immunotherapy, particularly immune checkpoint inhibitors (ICIs) such as programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitors, has seen significant advancements in recent years. Notably, PD-1 inhibitors have emerged as a crucial component in the treatment armamentarium for many cancers, including HCC, and have been shown to markedly improve outcomes for patients with intermediate- and advanced-stage disease (18-21). Post-TACE local hypoxia can upregulate PD-L1 expression and suppress T cell function, contributing to the establishment of an immunosuppressive microenvironment (22,23). These findings have piqued the scientific community's interest in exploring the synergistic potential of TACE and ICIs. In a retrospective study by Zhang *et al.* (24), the combination of TACE with the ICI camrelizumab achieved an ORR of 35.3%, with median PFS and OS of 6.1 and 13.3 months, respectively. This combination therapy has demonstrated effective tumor control and enhanced patient survival.

In recent years, the evolution of systemic therapeutic agents, including TKIs and ICIs, has marked a new era in the treatment of HCC. The synergistic effects observed with combination therapies have garnered significant attention, as they have the potential to enhance treatment outcomes (25-28). The efficacy of combined interventional and systemic therapies has been increasingly recognized, underscoring a paradigm shift in HCC management. An emerging body of research supports the superiority of TACE combination therapy over monotherapy in terms of treatment efficacy. However, the benefits of integrating TACE with targeted therapies and ICIs, particularly PD-1 inhibitors, remain to be fully elucidated. To address this knowledge gap, the retrospective cohort study presented in this paper aims to assess the clinical efficacy and associated risk factors of the TACE + TKIs + PD-1 inhibitor regimen compared to TACE + TKIs alone. Additionally, the study endeavors to construct and validate a prognostic model to better predict patient outcomes. We present this article in accordance with the TRIPOD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-1521/rc).

Methods

Study design and patients

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Lu'an Hospital of Traditional Chinese Medicine Affiliated to Anhui University of Traditional Chinese Medicine (No. LASZYY-LL-2024016) and individual consent for this retrospective analysis was waived. It included a total of 174 patients with unresectable HCC treated from December 21, 2018, to January 15, 2023. Of these, 122 patients were treated with TACE + TKIs + PD-1, and 52 patients were treated with TACE + TKIs. Triple therapy was defined as the use of TKIs within 1 month following TACE and the use of ICIs within 3 months following TACE.

Inclusion criteria

(I) All patients were confirmed to have HCC by previous surgical specimens, pathology of liver puncture specimens, and immunohistochemical examination.
(II) Barcelona Clinic Liver Cancer (BCLC) stage B or C (29).

(III) Child-Pugh score of A or B (30).
(IV) Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0–1 (31).
(V) Age between 18 and 75 years.
(VI) At least one evaluable target lesion according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) (32).

Exclusion criteria

(I) Combination with other treatments, such as radiofrequency ablation or radiation therapy.
(II) Presence of other primary malignant tumors.
(III) Contraindications to interventional procedures, such as cardiovascular or cerebrovascular diseases.
(IV) Presence of serious infections.
(V) Child-Pugh grade greater than B.
(VI) Incomplete data.

Treatment

After all patients were admitted to the hospital, they underwent preoperative examinations. Patients were informed of the available treatment options, and treatment plans were developed according to their wishes following the signing of informed consent forms. TACE was performed with an aim to achieve super-selective embolization. The femoral artery was punctured using the Seldinger method, and hepatic arteriography was conducted to clarify the location, number, and size of the tumors. A microcatheter was then super-selectively intubated to the target blood vessel. Once in place, 50 mg of lobaplatin was slowly injected into the target vessel. Subsequently, an appropriate amount of iodized oil emulsion was administered to embolize the tumor's blood supply artery based on the tumor size. The iodized oil emulsion was prepared by selecting 5–15 mL of poppy ethyl iodine oil for the lesion size and adding 40 mg of epirubicin to fully emulsify the mixture. Postoperative treatments, including hepatoprotection, hydration, and symptom management, were performed. TACE was repeated every 5–6 weeks based on the patient's condition and the operator's assessment.

ICIs, such as camrelizumab or sintilimab, were administered at a dose of 200 mg intravenously once every 3 weeks. TKIs were selected based on the patient's condition and administered orally, including lenvatinib at 8 mg/day (for weight <60 kg) or 12 mg/day (for weight ≥60 kg), sorafenib at 800 mg/day, and donafenib at 400 mg/day. Initially, the dosage should be sufficient to ensure efficacy. If patients experienced intolerable adverse reactions with poor symptomatic relief, the drug dosage could be reduced or the administration interval adjusted. In cases of serious adverse reactions, TKIs and ICIs treatments should be discontinued, and appropriate symptomatic treatment initiated. Patients in remission could resume drug use, whereas those deemed ineffective or who had discontinued the drug for over 6 weeks should permanently cease treatment.

For patients with liver function dropping to Child-Pugh class C, TKIs treatment should be discontinued 3 days before TACE and resumed only after postoperative liver function recovery. All patients with hepatitis B received oral antiviral therapy with entecavir or tenofovir. Follow-up treatment involved continued combined maintenance therapy of TKIs + ICIs for patients deemed temporarily unfit for interventional surgery based on laboratory and imaging examinations. Regular reviews were conducted to determine the necessity of further interventional surgery based on the patient's actual condition.

Follow-up and endpoints

The follow-up period commenced from the date of the first intervention, with all laboratory tests conducted prior to each intervention. At least one imaging examination was required within one month prior to the baseline, followed by subsequent enhanced computed tomography (CT) or magnetic resonance imaging (MRI) scans collected every 6–8 weeks. The final follow-up was conducted on May 22, 2024. The primary endpoint was OS, with secondary endpoints including tumor response, the number of treatments administered, and PFS. PFS was defined as the time from the start of follow-up to tumor progression or death from any cause, with the date of the last imaging evidence recorded as censored data if the patient was still alive and had no evidence of imaging progression. OS was defined as the time from the start of follow-up to death from any cause or the last follow-up contact. Tumor response was categorized based on the best remission response observed during the follow-up period, assessed according to the mRECIST, and included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Patient data on age, gender, alpha-fetoprotein (AFP) levels, ECOG PS, tumor size, Child-Pugh classification, hepatic vein invasion, BCLC stage, extrahepatic metastasis, number of tumors, cirrhosis status, number of TACE sessions, hepatitis B infection, albumin, and gamma-glutamyl transferase levels were collected as predictive factors

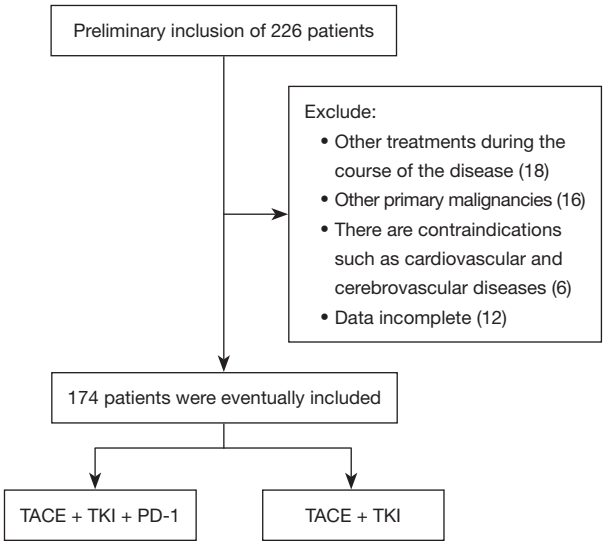

Figure 1 Flowchart for screening patients. TACE, transarterial chemoembolization; TKIs, tyrosine kinase inhibitors; PD-1, programmed cell death protein 1.

for patient survival prognosis. Given that most patients experienced adverse events (AEs) such as pain, fever, malaise, and elevated transaminases following TACE, and all these events resolved with symptomatic treatment, the assessment of AEs was performed 1 month post-intervention to exclude postoperative complications. Safety was evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE). Patients with significant missing data were promptly excluded from the study.

Statistical methods

Statistical analyses were conducted using SPSS software, version 25.0. Variables exhibiting a Gaussian distribution were depicted as the mean accompanied by the standard deviation, with differences assessed through the application of the *t*-test for independent samples. In contrast, categorical data were presented as counts alongside their respective percentages, and their comparison was facilitated by employing the Chi-squared statistical test or the Fisher's exact test, contingent upon the suitability of the data for these tests. The survival curves for PFS and OS were delineated using the Kaplan-Meier approach, with the disparities in survival profiles across groups being appraised through the log-rank statistical test. The effects of various clinical and pathological characteristics on patient survival (OS and PFS) were assessed using Cox proportional hazards regression modeling. Initially, univariate Cox regression analyses were performed to identify potential prognostic factors and their associations with OS and PFS. Factors with P values below the threshold of 0.05 were selected for inclusion in the multivariate Cox proportional hazards models, thereby enabling the identification of variables that are independently associated with prognosis. Hazard ratios (HR) greater than 1 indicated a worse prognostic factor correlation, while HR less than 1 indicated a better prognostic factor correlation. A P value less than 0.05 was considered to indicate a statistically significant difference. Finally, meta-analysis techniques were applied to synthesize relevant literature and validate the findings related to OS, PFS, and prognostic risk factors. Additionally, survival prognostic models were constructed to enhance predictive accuracy. To validate a model, the receiver operating characteristic (ROC) curve was plotted and the area under the curve (AUC) was maximized for predictive accuracy, ensuring the model's discriminative power and calibration aligned with observed outcomes.

Results

Basic characteristics of patients

Initially, 226 patients were enrolled at our hospital from December 21, 2018, to January 15, 2023. After applying the inclusion and exclusion criteria, 174 patients with advanced HCC were included in the study. Of these, 122 patients were treated with TACE + TKIs + PD-1, and 52 patients were in the TACE + TKIs group (*Figure 1*). We collected baseline data for both groups, and no statistically significant differences were found in terms of age, gender, AFP levels, ECOG performance status, tumor size, Child-Pugh classification, hepatic vein invasion, BCLC stage, extrahepatic metastasis, number of tumors, cirrhosis status, number of TACE sessions, hepatitis B infection, albumin, and gamma-glutamyl transferase levels (P>0.05), as detailed in *Table 1*.

Clinical efficacy

The disease control rate (DCR) in the TACE + TKIs + PD-1 group was significantly higher than that in the TACE + TKIs group (82.8% *vs.* 57.7%, P<0.001). The ORR was also higher in the TACE + TKIs + PD-1 group compared to the TACE + TKIs group, with rates of 37.7% versus 28.9%, respectively; however, this difference was not statistically significant (P=0.26), as detailed in *Table 2*.

Table 1 Baseline information of patients

Characteristics	TACE + TKIs + PD-1 (n=122), n (%)	TACE + TKIs (n=52), n (%)	χ^2 value	P
Age (years)			1.008	0.32
<60	65 (53.3)	32 (61.5)		
≥60	57 (46.7)	20 (38.5)		
Gender			0.502	0.48
Male	68 (55.7)	32 (61.5)		
Female	54 (44.3)	20 (38.5)		
BCLC			0.343	0.56
Stage B	83 (68.0)	33 (63.5)		
Stage C	39 (32.0)	19 (36.5)		
Tumor size (cm)			0.28	0.60
≥2	64 (52.5)	25 (48.1)		
<2	58 (47.5)	27 (51.9)		
AFP (ng/mL)			1.889	0.17
≥400	33 (27.0)	9 (17.3)		
<400	89 (73.0)	43 (82.7)		
ECOG PS			1.492	0.22
1	93 (76.2)	35 (67.3)		
0	29 (28.8)	17 (32.7)		
Child-Pugh class			0.014	0.91
B	41 (33.6)	17 (32.7)		
A	81 (66.4)	35 (67.3)		
Hepatic vein invasion			0.04	0.84
Yes	38 (31.1)	17 (32.7)		
No	84 (68.9)	35 (67.3)		
Extrahepatic metastasis			0.05	0.82
Yes	18 (14.8)	7 (13.5)		
No	104 (85.2)	45 (86.5)		
Tumor number			0.633	0.43
≤3	60 (49.2)	29 (55.8)		
>3	62 (50.8)	23 (44.2)		
Hepatic cirrhosis			0.054	0.82
Yes	116 (95.1)	49 (94.2)		
No	6 (4.9)	3 (5.8)		
TACE times			1.615	0.20
≤3	77 (63.1)	38 (73.1)		
>3	45 (36.9)	14 (26.9)		

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	TACE + TKIs + PD-1 (n=122), n (%)	TACE + TKIs (n=52), n (%)	χ^2 value	P
Hepatitis B			0.676	0.41
Yes	102 (83.6)	46 (88.5)		
No	20 (16.4)	6 (11.5)		
ALB (g/L)			0.15	0.70
<30	88 (72.1)	36 (69.2)		
≥30	34 (27.9)	16 (30.8)		
ALT (U/L)			0.567	0.45
≥40	89 (73.0)	35 (67.3)		
<40	33 (27.0)	17 (32.7)		

ALB and ALT were dichotomized into binary variables based on the presence or absence of abnormalities, and both were displayed as percentages. TACE, transarterial chemoembolization; TKIs, tyrosine kinase inhibitors; PD-1, programmed cell death protein 1; ALB, albumin; ALT, alanine aminotransferase; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2 Recent efficacy

Tumor response	TACE + TKIs + PD-1 (n=122), n (%)	TACE + TKIs (n=52), n (%)	χ^2	P
CR	11 (9.0)	3 (5.8)		
PR	35 (28.7)	12 (23.1)		
SD	55 (45.1)	15 (28.8)		
PD	21 (17.2)	22 (42.3)		
ORR (CR + PR)	46 (37.7)	15 (28.9)	1.257	0.26
DCR (CR + PR + SD)	101 (82.8)	30 (57.7)	12.34	<0.001

TACE, transarterial chemoembolization; TKIs, tyrosine kinase inhibitors; PD-1, programmed cell death protein 1; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

AEs

Adverse reactions were observed in 159 patients (91.4%), of which 55 (34.6%) were grade 3 or higher treatment-related AEs. The incidence of overall AEs and grade ≥3 AEs was 91.8% and 34.4% in the TACE + TKIs + PD-1 group, respectively, and 90.4% and 25% in the TACE + TKIs group. The safety profiles of the TACE + TKIs + PD-1 and TACE + TKIs groups were comparable, indicating a similar tolerability. Common AEs in the TACE + TKIs + PD-1 group included rash and fatigue, while those in the TACE + TKIs group included abdominal pain, elevated transaminases, and fatigue. Additionally, rash developed in 52 patients (29.9%) overall, with 45 (36.9%) in the TACE + TKIs + PD-1 group and 7 (13.5%) in the TACE + TKIs group. As delineated in *Table 3*, neither cohort experienced mortality attributable to the treatments administered.

Survival analysis

The final follow-up for this study was conducted until May 22, 2024, with a median follow-up duration of 19.7 months from the initial TACE treatment until death or withdrawal from the study. The median OS in the TACE + TKIs + PD-1 group was significantly better than that in the TACE + TKIs group, with respective medians of 20.8 months [95% confidence interval (CI): 13.6–28.0] and 14.7 months (95% CI: 11.6–17.8). This represents a prolongation of 6.1 months in OS for the TACE + TKIs + PD-1

Table 3 Adverse events

Adverse events	Total (n=174)	TACE + TKIs + PD-1 (n=122)	TACE + TKIs (n=52)	P
Overall				
Any grade	159 (91.4)	112 (91.8)	47 (90.4)	0.76
Grade ≥3	55 (31.6)	42 (34.4)	13 (25.0)	0.22
Abdominal pain				
Any grade	104 (59.8)	70 (57.4)	34 (65.4)	0.32
Grade ≥3	0	0	0	
Decreased appetite				
Any grade	58 (33.3)	39 (32.0)	19 (36.5)	0.56
Grade ≥3	7 (4.0)	5 (4.1)	2 (3.8)	0.94
Platelet count decreased				
Any grade	30 (17.2)	22 (18.0)	8 (15.4)	0.67
Grade ≥3	8 (4.6)	5 (4.1)	3 (5.8)	0.63
Diarrhea				
Any grade	45 (25.9)	34 (27.9)	11 (21.2)	0.35
Grade ≥3	7 (4.0)	6 (4.9)	1 (1.9)	0.36
Elevated aminotransferase				
Any grade	102 (58.6)	74 (60.7)	28 (53.8)	0.40
Grade ≥3	35 (20.1)	25 (20.5)	10 (19.2)	0.85
Fatigue				
Any grade	74 (42.5)	56 (45.9)	18 (34.6)	0.17
Grade ≥3	10 (5.7)	8 (6.6)	2 (3.8)	0.48
Fever				
Any grade	37 (21.3)	30 (24.6)	7 (13.5)	0.10
Grade ≥3	15 (8.6)	11 (9.0)	4 (7.7)	0.78
Hypertension				
Any grade	37 (21.3)	23 (18.9)	14 (26.9)	0.23
Grade ≥3	18 (10.3)	12 (9.8)	6 (11.5)	0.74
Liver abscesses				
Any grade	2 (1.1)	2 (1.6)	0	0.35
Grade ≥3	2 (1.1)	2 (1.6)	0	
Nausea				
Any grade	35 (20.1)	25 (20.5)	10 (19.2)	0.85
Grade ≥3	22 (12.6)	15 (12.3)	7 (13.5)	0.83
Proteinuria				
Any grade	6 (3.4)	6 (4.9)	0	0.10
Grade ≥3	0	0	0	

Table 3 (*continued*)

Table 3 (*continued*)

Adverse events	Total (n=174)	TACE + TKIs + PD-1 (n=122)	TACE + TKIs (n=52)	P
Pruritus				
Any grade	17 (9.8)	13 (10.7)	4 (7.7)	0.55
Grade ≥3	6 (3.4)	6 (4.9)	0	0.10
Rash				
Any grade	52 (29.9)	45 (36.9)	7 (13.5)	0.002
Grade ≥3	13 (7.5)	10 (8.2)	3 (5.8)	0.58
Vomiting				
Any grade	17 (9.8)	12 (9.8)	5 (9.6)	0.96
Grade ≥3	2 (1.1)	2 (1.6)	0	0.35

TACE, transarterial chemoembolization; TKIs, tyrosine kinase inhibitors; PD-1, programmed cell death protein 1.

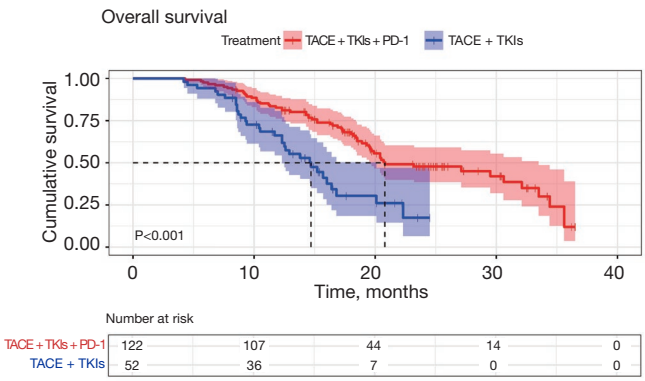

Figure 2 OS survival curves for different treatment regimens. TACE, transarterial chemoembolization; TKIs, tyrosine kinase inhibitors; PD-1, programmed cell death protein 1; OS, overall survival.

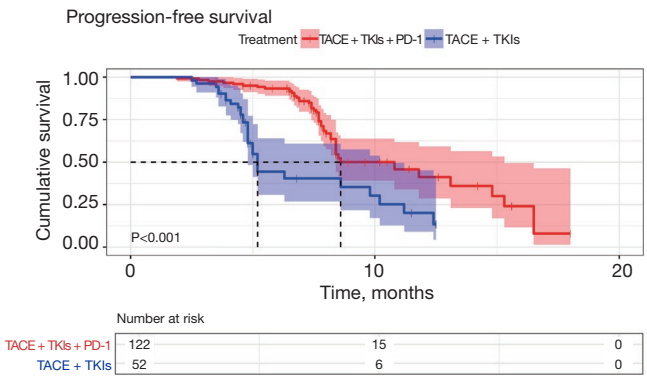

Figure 3 PFS survival curves for different treatment regimens. TACE, transarterial chemoembolization; TKIs, tyrosine kinase inhibitors; PD-1, programmed cell death protein 1; PFS, progression-free survival.

group compared to the TACE + TKIs group (P<0.001) (*Figure 2*). The median PFS was also significantly better in the TACE + TKIs + PD-1 group, with medians of 8.6 months (95% CI: 6.6–10.6) versus 5.2 months (95% CI: 4.8–5.6) for the TACE + TKIs group, amounting to a prolongation of 3.4 months in PFS for the TACE + TKIs + PD-1 group (P<0.001) (*Figure 3*). Using the BCLC staging system for subgroup analysis, patients with BCLC-B stage HCC had longer OS than those with BCLC-C stage, and this difference was statistically significant, as shown in *Figure 4*. Subgroup analyses comparing BCLC-B versus BCLC-C stages revealed that the TACE + TKIs + PD-1 treatment modality was superior to TACE + TKIs in both stages, as depicted in *Figures 5,6*.

Risk factor analysis

For OS, univariate analysis indicated that treatment options, BCLC stage, tumor size, AFP levels, ECOG PS, extrahepatic metastasis, and tumor number were correlated with OS (P<0.05). Subsequent multivariate analysis identified treatment options (TACE + TKIs + PD-1 *vs.* TACE + TKIs) (HR =0.311, 95% CI: 0.192–0.503, P<0.001), BCLC stage (B *vs.* C) (HR =0.367, 95% CI: 0.235–0.574, P<0.001), and ECOG-PS (1 *vs.* 0) (HR =1.974, 95% CI: 1.059–3.678, P=0.03) as independent prognostic factors affecting OS. Regarding PFS, univariate analysis demonstrated that treatment options, BCLC stage, and extrahepatic metastasis were all associated with PFS (P<0.05). Multivariate analysis revealed treatment

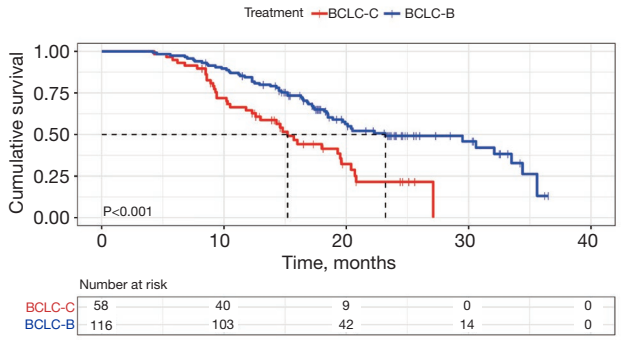

Figure 4 OS survival curves of BCLC-B and BCLC-C subgroups. OS, overall survival; BCLC, Barcelona Clinic Liver Cancer.

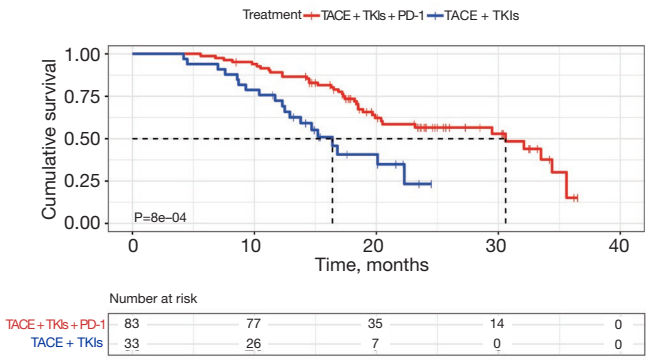

Figure 5 OS survival curves of different treatment regimens in BCLC-B stage. OS, overall survival; BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor; PD-1, programmed cell death protein 1.

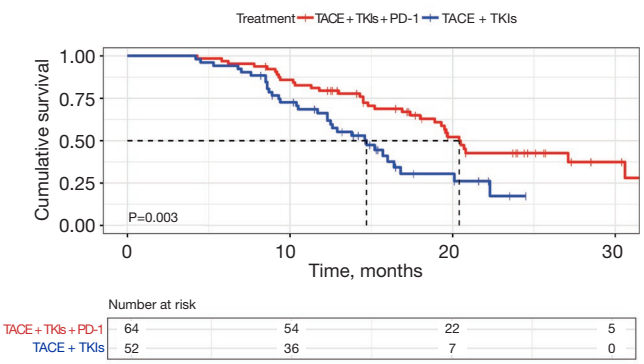

Figure 6 OS survival curves of different treatment regimens in BCLC-C stage. OS, overall survival; BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor; PD-1, programmed cell death protein 1.

options (TACE + TKIs + PD-1 *vs.* TACE + TKIs) (HR =0.352, 95% CI: 0.221–0.559, P<0.001) and the presence of extrahepatic metastasis (yes *vs.* no) (HR =2.034, 95% CI: 1.201–3.444, P=0.008) as the independent prognostic factors affecting PFS, as detailed in *Tables 4,5*.

Risk factor validation—meta-analysis

As of January 20, 2024, an extensive literature search was conducted in PubMed, Embase, Cochrane Library, and Clinical Trials, as well as other relevant databases, to identify studies that evaluated the efficacy of combining TACE with TKIs and PD-1 inhibitors versus TACE with TKIs alone for the treatment of unresectable HCC. Two researchers independently performed literature screening, data extraction, and quality assessment, and conducted the meta-analysis using RevMan 5.4, Stata 17.0, and R software. Results: a total of 10 studies (33-42) involving 1,744 patients were included in the meta-analysis. The meta-analysis results demonstrated that the combination of TACE with TKIs and PD-1 inhibitors significantly improved OS with a HR of 0.551 (95% CI: 0.488–0.623) (*Figure 7*), and PFS with an HR of 0.525 (95% CI: 0.465–0.591) (*Figure 8*). The meta-analysis of prognostic factors indicated that BCLC stage, treatment modality, tumor size, tumor number, AFP levels, Child-Pugh score, extrahepatic metastasis, and cirrhosis were risk factors for OS (*Figure 9*). Additionally, treatment modality, PS score, Child-Pugh score, vascular invasion, extrahepatic metastasis, and cirrhosis were identified as risk factors for PFS (*Figure 10*). The comprehensive analysis conducted in this study discerned those therapeutic strategies, the BCLC staging system, and the ECOG PS grading were pivotal determinants of OS, independent of other variables. Furthermore, the study delineated that therapeutic approaches and the presence of extrahepatic metastases were significant predictors of PFS, operating independently. The congruence of these outcomes with the synthesized evidence from the meta-analysis corroborates their validity.

Modeling and validation for predicting long-term survival in patients with advanced HCC

We developed a predictive model for long-term survival in patients with advanced HCC using the Cox proportional hazards model (*Figure 11*). Each predictor was converted

Table 4 Prognostic risk factors for OS

Variable	N	Univariate analysis			Multivariate analysis		
		P	HR	95% CI	P	HR	95% CI
Treatment options (TACE + TKIs + PD-1/TACE + TKIs)	122/52	<0.001	0.405	0.258–0.634	<0.001	0.311	0.192–0.503
Age (≥60/<60 years)	77/97	0.60	1.117	0.74–1.686			
Gender (male/female)	100/74	0.78	0.941	0.622–1.425			
BCLC (B/C)	116/58	<0.001	0.445	0.289–0.684	<0.001	0.367	0.235–0.574
Tumor size (≥2/<2 cm)	89/85	0.04	1.554	1.027–2.351			
AFP (≥400/<400 ng/mL)	42/132	0.02	1.631	1.065–2.498			
ECOG PS (1/0)	128/46	0.03	1.799	1.049–3.087	0.03	1.974	1.059–3.678
Child-Pugh class (B/A)	58/116	0.16	1.352	0.891–2.053			
Hepatic vein invasion (yes/no)	55/119	0.26	1.275	0.833–1.951			
Extrahepatic metastasis (yes/no)	25/149	0.04	1.694	1.019–2.814			
Tumor number (>3/≤3)	89/85	0.04	1.555	1.03–2.349			
Hepatic cirrhosis (yes/no)	165/9	0.59	1.294	0.501–3.343			
TACE times (>3/≤3)	59/115	0.24	0.761	0.484–1.197			
Hepatitis B (yes/no)	148/26	0.25	1.45	0.771–2.727			
ALB (<30/≥30 g/L)	118/56	0.42	1.199	0.773–1.859			
ALT (≥40/<40 U/L)	124/50	0.60	1.129	0.716–1.782			

TACE, transarterial chemoembolization; TKIs, tyrosine kinase inhibitors; PD-1, programmed cell death protein 1; OS, overall survival; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; ALB, albumin; ALT, alanine aminotransferase; AFP, alpha-fetoprotein; HR, hazard ratio; CI, confidence interval.

into a scoring system, which was then integrated into a total score with the aim of enhancing clinical decision-making accuracy. This model was constructed from retrospective cohort study data, encompassing variables such as treatment options, tumor stage, and ECOG PS, to estimate the 1-, 2-, and 3-year survival probabilities for patients. To ensure the model's reliability and generalizability, we employed an internal validation approach. The concordance statistic (C-index) was calculated to be 0.676, indicating a moderate level of predictive accuracy. Additionally, we developed receiver operating characteristic (ROC) curves to forecast the OS at the 1-, 2-, and 3-year milestones, utilizing RStudio as the computational platform. The AUC values were 0.706, 0.775, and 0.741 (*Figures 12,13*), respectively, demonstrating satisfactory predictive performance of the model.

Treatment cases

The following is a 43-year-old male patient diagnosed with HCC. He was treated with TACE combined with TKIs and ICIs, demonstrating remarkable efficacy (*Figure 14*). *Figure 14A* presents a T1-weighted MRI of the patient prior to treatment, while *Figure 14B* displays a T2-weighted MRI of the same, with the tumor exhibiting a maximum transverse diameter of 125.22 mm and a maximum longitudinal diameter of 106.24 mm. *Figure 14C* illustrates the image during the TACE procedure. *Figure 14D* depicts the T1-weighted MRI following treatment with TACE, TKIs, and ICIs, and *Figure 14E* shows the T2-weighted MRI post-treatment, with the tumor dimensions reduced to a maximum transverse diameter of 43.74 mm and a maximum longitudinal diameter of 34.40 mm. These findings significantly demonstrate the excellent efficacy of the triple therapy regimen.

Discussion

In recent years, while the armamentarium for systemic

Table 5 Prognostic risk factors for PFS

Variable	N	Univariate analysis			Multivariate analysis		
		P	HR	95% CI	P	HR	95% CI
Treatment options (TACE + TKIs + PD-1/TACE + TKIs)	122/52	<0.001	0.376	0.24–0.589	<0.001	0.352	0.221–0.559
Age (≥60/<60 years)	77/97	0.36	0.824	0.547–1.241			
Gender (male/female)	100/74	0.72	0.928	0.615–1.40			
BCLC (B/C)	116/58	0.03	0.624	0.411–0.946			
Tumor size (≥2/<2 cm)	89/85	0.28	1.259	0.831–1.907			
AFP (≥400/<400 ng/mL)	42/132	0.14	1.382	0.902–2.117			
ECOG PS (1/0)	128/46	0.08	1.611	0.938–2.766			
Child-Pugh class (B/A)	58/116	0.64	1.103	0.728–1.671			
Hepatic vein invasion (yes/no)	55/119	0.33	1.233	0.806–1.887			
Extrahepatic metastasis (yes/no)	25/149	0.04	1.708	1.028–2.838	0.008	2.034	1.201–3.444
Tumor number (>3/≤3)	89/85	0.12	1.388	0.918–2.100			
Hepatic cirrhosis (yes/no)	165/9	0.97	0.98	0.396–2.430			
TACE times (>3/≤3)	59/115	0.12	0.696	0.441–1.1			
Hepatitis B (yes/no)	148/26	0.64	1.162	0.615–2.195			
ALB (<30/≥30 g/L)	118/56	0.65	0.903	0.58–1.406			
ALT (≥40/<40 U/L)	124/50	0.33	1.254	0.797–1.974			

TACE, transarterial chemoembolization; TKIs, tyrosine kinase inhibitors; PD-1, programmed cell death protein 1; PFS, progression-free survival; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; CI, confidence interval; ALB, albumin; ALT, alanine aminotransferase.

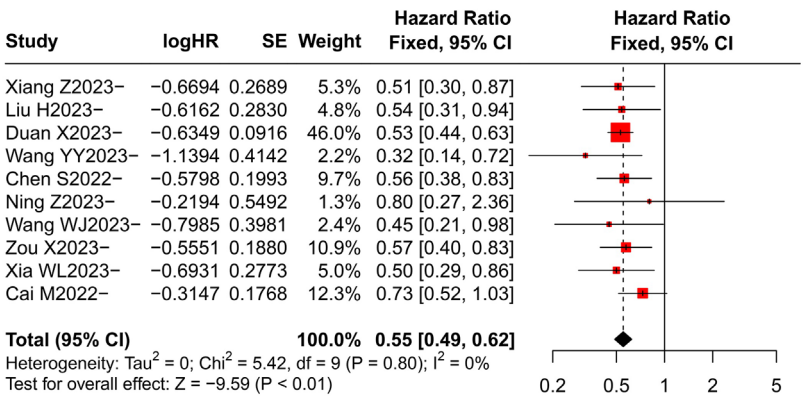

Figure 7 OS meta-forest plot. OS, overall survival; SE, standard error; CI, confidence interval.

treatment of HCC has expanded, optimal treatment options for patients with advanced HCC remain elusive. This study evaluated the efficacy and safety of combining TACE with TKIs and PD-1 inhibitors in a population of patients with advanced HCC. We explored the prognostic factors associated with treatment outcomes, developed a predictive model, and validated its accuracy.

TACE is a widely used intervention for intermediate-

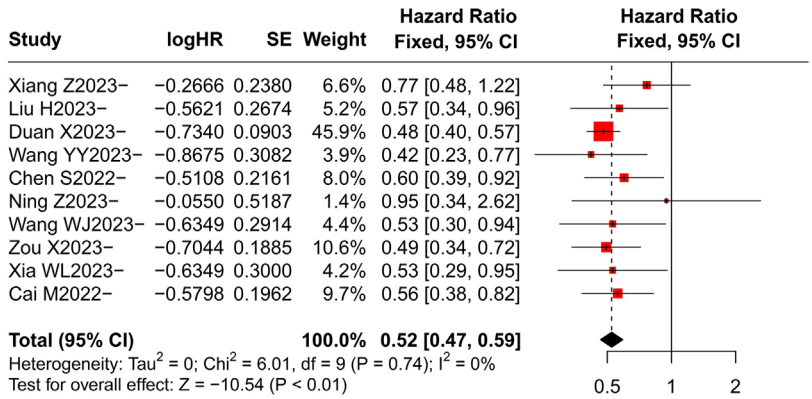

Figure 8 PFS meta-forest plot. PFS, progression-free survival; SE, standard error; CI, confidence interval.

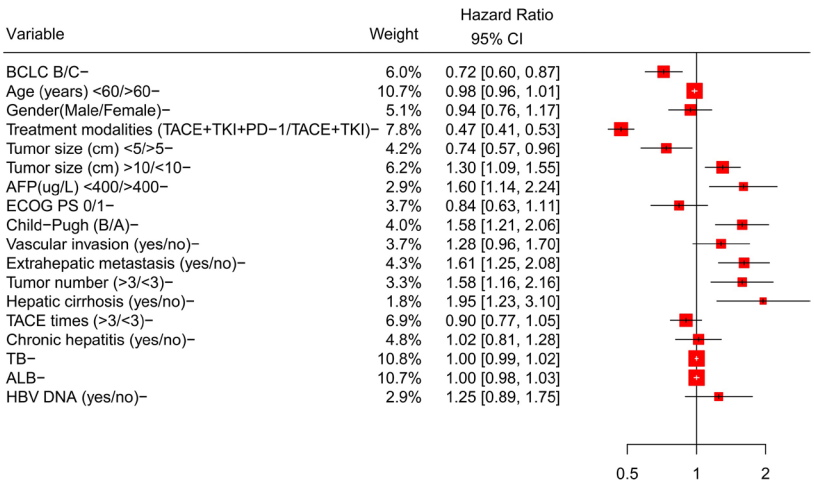

Figure 9 OS risk factor meta-forest plot. OS, overall survival; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor; PD-1, programmed cell death protein 1; AFP, alpha-fetoprotein; ECOG PS, Eastern Cooperative Oncology Group performance status; TB, total bilirubin; ALB, albumin; HBV, hepatitis B virus.

and advanced-stage HCC, leveraging a local therapeutic effect by infusing embolic agents with chemotherapeutic drugs to occlude the tumor-supplying blood vessels (43). However, TACE faces limitations in treating intermediate and advanced HCC. The extensive collateral circulation in large HCC tumors can undermine the effectiveness of embolization, necessitating higher doses of embolic agents that may increase liver burden and postoperative adverse reactions. Additionally, TACE-induced alterations in the tumor microenvironment can lead to upregulation of various cytokines. These changes promote neovascularization and the proliferation and differentiation of tumor cells, potentially accelerating tumor recurrence and metastasis (44). Consequently, patients may develop resistance to TACE following multiple treatments. Given these challenges, there is a pressing need to investigate novel therapeutic strategies to impede HCC progression.

Targeted therapy represents a novel strategy for impeding tumor growth and metastasis by targeting specific molecular pathways, demonstrating significant clinical efficacy. Sorafenib, for instance, impedes tumor vascularization by targeting vascular endothelial growth factor receptors (VEGFR) and platelet-derived growth factor receptors (PDGFR), thereby inhibiting vasculogenesis and tumor cell proliferation through the Raf/MAPK/ERK signaling pathway, achieving a dual inhibitory effect (45,46).

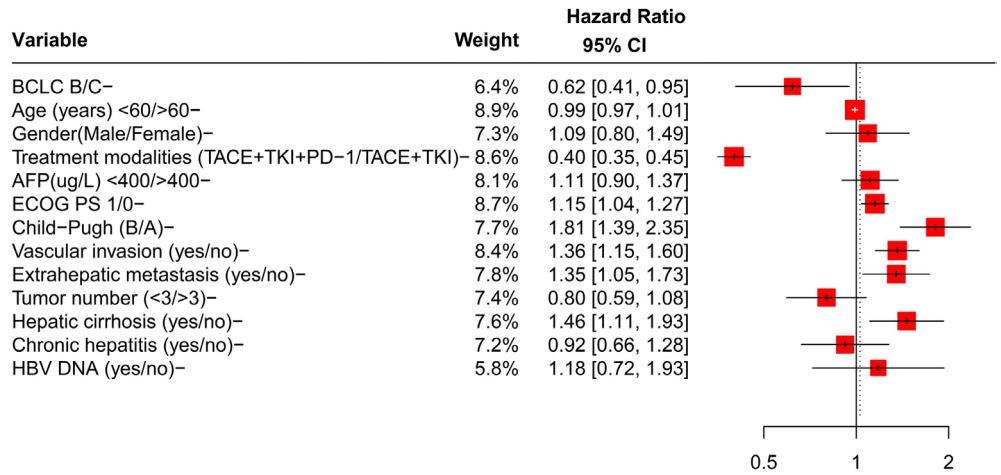

Figure 10 PFS risk factor meta-forest plot. PFS, progression-free survival; CI, confidence interval; BCLC, Barcelona Clinic Liver Cancer; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor; PD-1, programmed cell death protein 1; AFP, alpha-fetoprotein; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus.

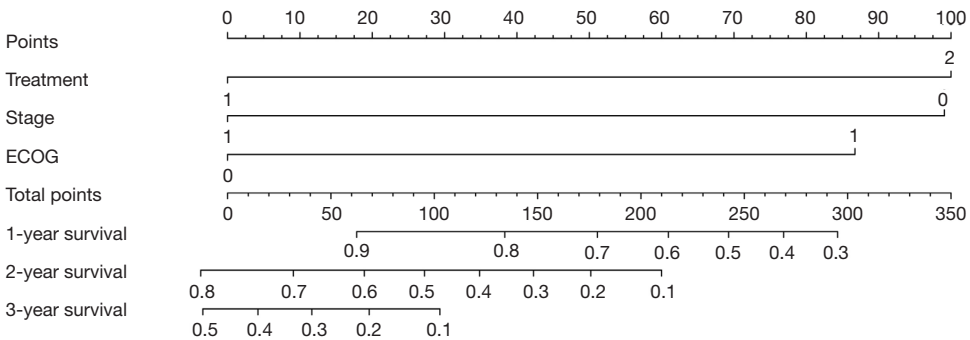

Figure 11 Long-term survival prediction model (nomogram). Treatment: 1 is TACE + TKIs + PD-1, 2 is TACE + TKIs; Stage: 1 is BCLC Stage B, 0 is BCLC Stage C. ECOG, Eastern Cooperative Oncology Group; TACE, transarterial chemoembolization; TKIs, tyrosine kinase inhibitors; PD-1, programmed cell death protein 1; BCLC, Barcelona Clinic Liver Cancer.

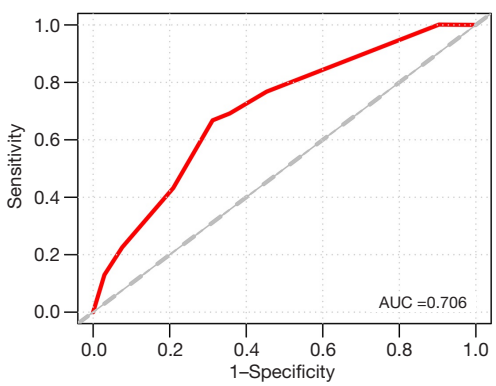

Figure 12 1-year survival ROC. ROC, receiver operating characteristic; AUC, area under the curve.

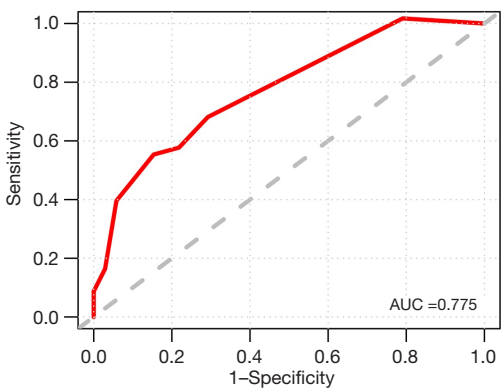

Figure 13 2-year survival ROC. ROC, receiver operating characteristic; AUC, area under the curve.

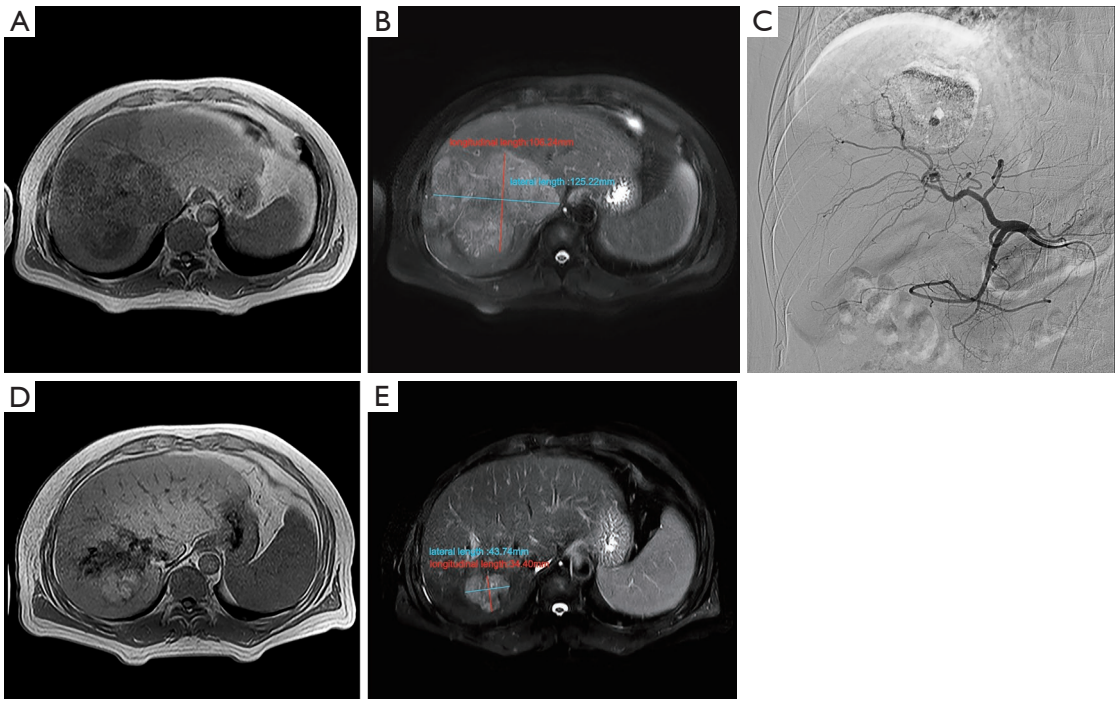

Figure 14 Comparison chart of the patient's treatment effects before and after TACE + TKI + PD-1 therapy. (A,B) Pre-treatment magnetic resonance imaging results. The liver has smooth edges, with a slightly widened hepatic fissure. The right lobe of the liver is relatively enlarged in volume, containing clusters of slightly long T1 and compressed T2 mixed signals. The lesion exhibits a high signal on DWI sequences and shows inhomogeneous, mild-to-moderate enhancement during all phases of dynamic contrast-enhanced imaging. The lesion boundary is indistinct, with the largest cross-sectional dimensions measuring approximately 109 mm in width, 116 mm in height, and 129 mm in depth. Adjacent structures, including the middle hepatic vein and right hepatic vein, as well as the left and right branches of the portal vein, are compressed and shifted. The lumen of the hepatic segment of the inferior vena cava is dilated, with a diameter of about 25 mm at its widest point, showing uneven and mildly intensified signals within the lumen. The portal vein and the middle and right hepatic veins display filling defects. The intrahepatic bile ducts are poorly visualized, with no obvious dilatation of the common bile duct. The gallbladder has a regular shape, a smooth wall, and a non-uniform signal within the lumen. No significant abnormal enhancement is observed in the gallbladder wall or lumen on dynamic enhanced scans. The pancreas, spleen, and both kidneys exhibit regular morphology with no obvious abnormal signal or enhancement. The bilateral adrenal glands also show no significant abnormal signal or enhancement. Multiple lymph nodes are noted in the porta hepatis and retroperitoneum, with the largest measuring approximately 11 mm in short diameter and showing homogeneous enhancement. (C) Imaging during the second TACE procedure. (D,E) Post-treatment magnetic resonance imaging results. The liver edge remains smooth, with a slightly widened hepatic fissure. The right lobe of the liver is relatively enlarged, containing a mass with mixed T1 and T2 signals. Scattered patchy signals of slightly high intensity are noted in the posterior aspect of the DWI sequence. The lesion shows no enhancement in the arterial phase of dynamic contrast-enhanced scanning, with low signals, and minimal ring-shaped linear enhancement at the lesion margins in the portal and equilibrium phases. The largest cross-sectional area is approximately 100 mm × 66 mm × 84 mm. The adjacent middle hepatic vein, right hepatic vein, and portal vein exhibit compression and migration-like changes, with corresponding filling defects in the portal vein and middle and right hepatic veins. The local lumen of the inferior vena cava shows uneven and mildly intensified signals, with a length of about 35 mm. The intrahepatic bile ducts are poorly visualized, with no obvious dilatation of the common bile duct. The gallbladder maintains a regular shape, a smooth wall, and a non-uniform signal within the lumen. No significant abnormal enhancement is observed in the gallbladder wall or lumen. The pancreas shows a regular morphology with no obvious abnormal signals or foci of abnormal enhancement. The spleen and both kidneys also exhibit regular morphology with no significant abnormal signals or enhancement on enhancement scans. No obvious abnormal signals or enhancement are detected in the adrenal regions. Multiple lymph nodes are noted in the hilar area and retroperitoneum, with the largest measuring approximately 11 mm in short diameter and showing homogeneous enhancement. TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor; PD-1, programmed cell death protein 1; DWI, diffusion-weighted imaging.

Despite this, the SHARP trial reported an ORR of only 2% for sorafenib as monotherapy (47). Additionally, sorafenib monotherapy is associated with adverse effects such as diarrhea, rash, fatigue, hand-foot skin reactions, hypertension, and appetite loss, which has led to its frequent use in combination with TACE to enhance therapeutic efficacy in HCC (48,49). Lenvatinib is an oral multi-TKI that targets VEGFR1–3, fibroblast growth factor receptors 1–4 (FGFR1–4), PDGFR, RET, and c-Kit, thereby inhibiting tumor cell proliferation, differentiation, invasion, migration, and tumor angiogenesis (50,51). A meta-analysis of advanced HCC patients treated with sorafenib combined with TACE versus TACE alone indicated superior ORR, DCR, and both 6-month and 1-year OS rates for the combination therapy (52). A Phase III randomized clinical trial conducted in China, known as the LAUNCH trial, has demonstrated the therapeutic superiority of lenvatinib in combination with TACE. The median OS and PFS were significantly longer in the lenvatinib plus TACE group, with durations of 17.8 and 10.6 months, respectively, compared to the lenvatinib monotherapy group. Additionally, the ORR was notably higher in the combination therapy group, at 45.9%, versus 20.8% in the lenvatinib-only group. These findings underscore the potential of the lenvatinib-TACE combination in enhancing survival outcomes for patients with HCC, particularly those who have failed multiple prior treatments (15). Additionally, a randomized, multicenter, prospective trial organized in Japan, known as the TACTICS study, has demonstrated that the median PFS in the group treated with TACE plus sorafenib was significantly longer than that in the group treated with TACE alone (25.2 *vs.* 13.5 months; P=0.006), thereby confirming the efficacy of combining TACE with targeted therapy (53).

In recent years, immunotherapy has emerged as a promising treatment for advanced tumors. Notably, therapies targeting the PD-1 pathway have been approved for first-line treatment of advanced solid tumors with defects in mismatch repair or high microsatellite instability. However, in the context of HCC, monotherapy with ICIs has generally demonstrated modest efficacy, with a meta-analysis reporting an ORR of only 13.2% to 21.4% for advanced HCC (54). A notable exception is the combination regimen studied in the Mbrave150 trial, which showed an ORR of 33.2% for the atezolizumab plus bevacizumab treatment in advanced HCC (55). The EMERALD-1 study results have indicated that the combination of TACE with immunotherapy can extend the PFS from 8.2 months (95% CI: 6.9–8.5) to 9.0 months (95% CI: 7.0–10.9) compared with TACE alone, highlighting the beneficial effects of the combined therapy (56). The suboptimal response to ICI monotherapy in HCC may be attributed to the liver's unique immunosuppressive microenvironment. This environment is characterized by the accumulation of immunosuppressive cells and the depletion of effector T-lymphocytes, which contribute to the development of a hepatic suppressive immune context during liver metastasis and potentially underlie resistance to immunotherapy (57).

The combination of TACE with TKIs and ICIs may address the limitations of single-modality treatments. TACE induces ischemic necrosis of the tumor's immunogenic cells, leading to the release of tumor antigens and an increase in PD-L1 and inflammatory cytokine expression, which can enhance the recognition of the tumor by ICIs (58). TKIs target the tumor microenvironment, antagonizing neovascularization and disrupting the hypoxic milieu, thereby reducing chemotherapeutic drug resistance (59). Additionally, TKIs inhibit tumor cell proliferation and differentiation, regulate immunosuppressive signaling pathways, and promote T-cell response and infiltration at the tumor site, reducing TACE side effects and enhancing ICI immunotherapeutic activity (60). This multimodal approach compensates for the individual shortcomings of TACE, TKIs, and ICIs, potentially improving outcomes for patients with intermediate- and advanced-stage HCC. A retrospective study (61) reported that the median OS for the TACE + TKIs + PD-1 group was significantly better than that for the TACE + TKIs and TACE groups, with mOS values of 24.1 months (95% CI: 15.1–33.1), 14.9 months (95% CI: 10.7–19.1), and 11.4 months (95% CI: 8.4–14.5), respectively. The median PFS in the TACE + TKIs + PD-1 group was 10.6 months (95% CI: 6.5–14.7), surpassing the 6.7 months (95% CI: 5.5–7.9) observed in the TACE + TKIs group. Another study (36) found that the combination of TACE, lenvatinib, and a PD-1 inhibitor was superior to TACE plus lenvatinib alone in terms of OS (23.5 *vs.* 18.3 months, P<0.001) and PFS (7.5 *vs.* 4.3 months, P<0.001). These findings underscore the clinical benefits of combining TACE with TKIs and ICIs for the treatment of HCC.

In this study, the combination of TACE with TKIs and PD-1 inhibitors resulted in significantly improved median OS and PFS compared to TACE plus TKIs alone. The TACE + TKIs + PD-1 group also achieved a higher DCR and ORR, underscoring the therapeutic benefits of this combined approach. However, the incidence of rash in

the TACE + TKIs + PD-1 group was significantly higher, indicating a need for vigilance regarding skin-related AEs, while other AEs did not differ significantly between groups, suggesting a favorable safety profile. The study's stratification by BCLC stage revealed that patients with BCLC-B stage had significantly better median OS than those with BCLC-C stage, highlighting the prognostic significance of clinical staging in the management of HCC. Subgroup analysis using BCLC staging further demonstrated that the median OS of patients receiving TACE combined with TKIs and ICIs was superior to that of the TACE plus TKIs group alone, evidencing the multidimensional clinical efficacy of triple therapy. Multifactorial analysis identified BCLC-C stage and an ECOG PS of 1 as independent risk factors for OS, while extrahepatic metastasis emerged as an independent risk factor for PFS. These findings were corroborated by meta-analyses, which aligned with the outcomes of our study. Additionally, another study has indicated that a tumor single nodule diameter greater than 5 cm is a risk factor for OS (33). In our study, a tumor diameter greater than 2 cm was not identified as a risk factor; this suggests that the prognostic relevance of tumor nodule size may be more accurately gauged using a cutoff of 5 cm. Ultimately, a predictive model for long-term survival, informed by the multifactorial analysis of OS, was developed. Validation of this model indicated good performance, suggesting its potential utility in the clinical setting for comprehensive patient assessment in conjunction with existing diagnostic and therapeutic strategies.

In summary, this study thoroughly investigated the synergistic effects of TACE when used in conjunction with ICIs and TKIs. Preliminary results suggest that this integrated therapeutic strategy has the potential to significantly improve survival rates in patients, particularly in those who have failed multiple traditional treatments, where the efficacy is notably pronounced. Furthermore, the findings of this study are expected to provide guiding recommendations for clinical practice and foster the development of personalized treatment strategies. Nonetheless, there are still several knowledge gaps within the current field, including the long-term efficacy of different treatment combinations, optimization of patient selection criteria, and management of treatment-related side effects. Future clinical trials and multicenter studies should be conducted, such as prospective studies on the combined use of TACE with new targeted drugs. Looking ahead over the next 5 years, significant changes are anticipated in the field of liver tumor treatment, with the development of new drugs and the optimization of treatment regimens becoming increasingly widespread. As precision medicine continues to advance, personalized treatment strategies based on genomics and molecular characteristics will play an increasingly pivotal role in the comprehensive management of liver cancer.

Limitations

The limitations of this study are as follows: Principally, it is a retrospective analysis conducted at a single institution, featuring a relatively small participant cohort and a short follow-up period. This design is prone to certain inherent biases that, despite all efforts, may not be entirely mitigated. Second, the heterogeneity in the types of TKIs used, influenced by patients' economic status and tolerance levels, affects the uniformity of the treatment regimen. Consequently, future research should employ large-sample, prospective, multicenter randomized controlled trials to provide a more precise assessment.

Conclusions

In conclusion, the findings of this study suggest that the TACE + TKIs + PD-1 treatment regimen offers superior long-term survival and immediate efficacy compared to TACE + TKIs alone. While the overall safety profile is favorable, this regimen may increase the risk of rash. The survival prediction model developed in this study demonstrates high accuracy, potentially offering valuable insights for clinical prognostication.

Acknowledgments

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Lu'an Hospital of Traditional Chinese Medicine Affiliated to Anhui University of Traditional Chinese Medicine (No. LASZYY-LL-2024016) and individual consent for this retrospective analysis was waived.

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