High conversion rate and survival benefits of transarterial chemoembolization with targeted immunotherapy in initially unresectable hepatocellular carcinoma: efficacy, safety, and optimal patient selection

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KEY WORDS

hepatocellular carcinoma, immunotherapy, optimal population, targeted therapy

ABSTRACT

INTRODUCTION Primary liver cancer ranks among the most prevalent malignancies globally.

AIM We aimed to evaluate the efficacy and safety of transarterial chemoembolization (TACE) combined with targeted immunotherapy in initially unresectable hepatocellular carcinoma (uHCC), and identify patients most likely to benefit from this approach.

MATERIALS AND METHODS We retrospectively analyzed 68 uHCC patients treated with TACE with targeted immunotherapy at the Nanjing Drum Tower Hospital (April 2020–July 2024). Tumor response was assessed using the modified Response Evaluation Criteria in Solid Tumors. Progression-free survival (PFS) and overall survival rates were estimated with the Kaplan–Meier analysis. Logistic and Cox regression models were used to identify the predictors of response and survival.

RESULTS The objective response rate was 57.4%, and the disease control rate amounted to 89.7%. Median PFS was 13.8 months (95% CI, 8.7–19), with 6- and 12-month PFS rates of 73.1% and 52.5%, respectively. Surgical conversion occurred in 52.9% of the patients, with 94.6% achieving R0 resection; 47.2% had major pathologic response. Multivariable analysis showed that fewer than 3 tumors (hazard ratio [HR], 6.35; $P = 0.01$) and absence of major vascular invasion (HR, 3.89; $P = 0.03$) independently predicted favorable response, while the male sex (HR, 0.27; $P < 0.001$), China Liver Cancer (CNLC) stage Ib–IIa (HR, 6.05; $P < 0.001$), and proton density fat fraction (PDFF) below 6.5% ($P = 0.03$) predicted longer PFS. Grade 3 adverse events occurred in 52.9% of the patients, with no grade 4–5 events. All were manageable.

CONCLUSIONS TACE with targeted immunotherapy yields high response and surgical conversion rates with acceptable toxicity in uHCC. Patients with CNLC stage Ib–IIa, fewer than 3 tumors, no major vascular invasion, and low PDFF derive the greatest benefit, supporting this approach as an effective conversion strategy.

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INTRODUCTION Primary liver cancer ranks among the most prevalent malignancies globally, with China bearing a particularly heavy burden, where it is the fourth most common cancer and the second leading cause of cancer-related mortality.[1] Hepatocellular carcinoma (HCC), accounting for 75%–85% of liver cancer cases, remains a major public health challenge. For HCC patients, surgical resection offers the best chance for long-term survival.[2,3] However, due to its insidious progression, approximately 70% of the them are diagnosed at intermediate-to-advanced stages, making curative resection impossible because of anatomical or tumor-related constraints.

Conversion therapy, a strategy aimed at downstaging initially unresectable HCC (uHCC) to enable surgical resection, has emerged as a transformative approach. By integrating systemic therapies (targeted agents, immune checkpoint inhibitors [ICIs]) with local modalities, this combination

has demonstrated superior tumor response rates and survival outcomes than monotherapy, enabling surgical resection in a subset of patients.[4-7] Transarterial chemoembolization (TACE) combined with targeted immunotherapy has become a mainstream approach for intermediate--to-advanced HCC.[8-11] Clinical evidence highlights its efficacy: a phase II trial (TACTICS-L)[12] showed that patients receiving TACE with lenvatinib and programmed cell death protein (PD)-1 inhibitors achieved significantly higher objective response rates (ORRs) and conversion rates than those treated with TACE alone, along with prolonged median progression-free survival (PFS). The CHANCE2201 study[13] further demonstrated improved median overall survival (OS) and PFS in triple-therapy cohorts, as compared with targeted immunotherapy alone. Although the number of adverse events (AEs) increased, they remained manageable. Notwithstanding these advances, treatment efficacy is still suboptimal in a substantial patient subset, highlighting the critical need for precise patient selection to optimize therapeutic responses.

Proton density fat fraction (PDFF), a quantitative magnetic resonance imaging (MRI) biomarker derived from in-phase (IP) and out-of-phase (OP) PDFF sequences (1/2 – OP/2IP), has emerged as a valuable tool in hepatic disease assessment. Beyond quantifying hepatic steatosis, PDFF correlates with HCC lipid metabolic characteristics, fatty acid degradation subtypes, and tumor microenvironment features.[14] This metric also aids in evaluating liver functional reserve, guiding treatment selection, and monitoring treatment-related toxicity during conversion therapy.

AIM Despite the promise of conversion therapy for uHCC, optimal patient selection criteria and long-term prognostic indicators remain poorly defined.[7,15,16] This retrospective study evaluated the efficacy and safety of TACE-based combined targeted immunotherapy in uHCC patients. Through patient stratification based on tumor response and long-term follow-up, we aimed to identify key biomarkers and clinical characteristics that predict favorable conversion outcomes and sustained survival benefits, thereby informing precision oncology strategies for HCC management.

MATERIALS AND METHODS **Inclusion and exclusion criteria** This retrospective study included uHCC patients who received TACE combined with targeted immunotherapy at our hospital from April 2020 to July 2024. A total of 92 patients were initially screened. Of them, 24 were excluded due to incomplete clinical data (n = 10), concurrent malignancies (n = 6), or loss to follow-up (n = 8). Ultimately, 68 patients met the inclusion criteria and were enrolled in the final analysis. Inclusion criteria were as follows: 1) diagnosis of HCC on pathologic and imaging examinations according to the Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (2022 edition)[17]; 2) China Liver Cancer (CNLC) stage Ib–IIIa; 3) at least 1 measurable target lesion according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST)[18]; 4) no previous treatment for HCC; 5) a history of at least 1 course of TACE combined with targeted immunotherapy; 6) liver function lower than or equal to 7 points according to the Child–Pugh classification; and 7) Eastern Cooperative Oncology Group performance status score of 0–1. Exclusion criteria comprised: 1) a history of or currently active other malignant tumors; 2) receiving radiotherapy during treatment period; 3) incomplete clinical data; and 4) a lack of complete follow-up data.

Treatment regimen TACE was performed by experienced interventional radiologists. The Seldinger method was used to puncture the femoral artery, and a Rösch hepatic catheter was inserted. The catheter tip was placed in the superior mesenteric artery and celiac artery for angiography, respectively. The location, number, size, and blood supply of the tumor lesions were determined in combination with imaging examinations. Subsequently, superselective intubation was performed to the main feeding artery of the lesion for perfusion chemotherapy with raltitrexed or oxaliplatin. Then, a microcatheter was used for superselective intubation to the tumor-feeding branch. After angiographic confirmation, an appropriate amount of emulsion of epirubicin hydrochloride / idarubicin and lipiodol was injected for embolization treatment. Depending on the specific characteristics of the tumor, an appropriate number of embolic microspheres or gelatin sponge microspheres were used as adjuvants. After the operation, the catheter and catheter sheath were removed, the femoral artery puncture site was compressed and bandaged, and the patient was transferred back to the department. Targeted therapy and immunotherapy were sequentially carried out after TACE, which was repeated as needed.

The targeted therapy drugs and regimens were as follows. For patients with body weight over 60 kg, 12 mg of lenvatinib mesylate was administered orally once a day, and for those whose body weight was 60 kg or less, 8 mg was given orally once daily. For donafenib tosylate tablets, 200 mg was administered orally twice a day. For apatinib mesylate, a dose of 250 mg was taken orally once a day. For sorafenib tosylate tablets, 400 mg was administered orally twice daily. If drug-related adverse reactions occurred during the treatment, the drug dosage was adjusted, or the medication was suspended according to the drug-related instructions.

Intravenous infusion of the following monoclonal antibody drugs selected for immunotherapy was given every 3 weeks: camrelizumab (200 mg), tislelizumab (200 mg), or sintilimab (200 mg).

Data collection and follow-up Clinical data of the patients were extracted from an electronic

TABLE 1 Treatment process of patients with initially unresectable hepatocellular carcinoma

Parameter	Value
Treatment method	
Treatment cycles of transarterial chemoembolization	2 (2–3)
Treatment cycles of immunotherapy	2 (2–4)
Types of immunotherapy drugs, n (%)	
Camrelizumab	38 (55.9)
Tislelizumab	28 (41.2)
Sintilimab	2 (2.9)
Types of targeted drugs, n (%)	
Donafenib	33 (48.5)
Lenvatinib	31 (45.7)
Apatinib	2 (2.9)
Sorafenib	2 (2.9)

Data are presented as median (interquartile range) unless indicated otherwise.

TABLE 2 Overall efficacy of transarterial chemoembolization combined with targeted immunotherapy in patients with initially unresectable hepatocellular carcinoma

Treatment outcome	Total (n = 68)
Complete remission	5 (7.4)
Partial remission	34 (50)
Stable disease	22 (32.3)
Progressive disease	7 (10.3)
Objective response rate, %	57.4
Disease control rate, %	89.7
Median progression-free survival, mo	13.8 (95% CI, 8.7–19)
6-month progression-free survival rate, %	73.1
12-month progression-free survival rate, %	52.5
Median overall survival, mo	–
18-month survival rate, %	85.1
24-month survival rate, %	63.9

Data are presented as numbers (percentages) unless indicated otherwise.

medical record system, and they included basic information (sex, age, hepatitis B virus surface antigen [HBsAg], liver cirrhosis, and albumin-bilirubin [ALBI] grade), tumor characteristics (number of tumors, maximum tumor diameter, and CNLC stage), and laboratory test indicators (routine blood tests before and early after treatment, including neutrophil count, lymphocyte count, platelet count, etc.; blood biochemical indicators, such as alanine aminotransferase, aspartate aminotransferase, total bilirubin, albumin; α-fetoprotein, and des-γ-carboxy prothrombin). Peripheral blood inflammatory markers, such as neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio, were calculated based on these data.

The efficacy of the treatment was evaluated according to the mRECIST standard, and the ORR and disease control rate (DCR) were calculated. Tumor response was categorized as complete remission (CR), partial remission (PR), stable disease (SD), or progressive disease (PD). PFS was defined as the time from the start of treatment to tumor progression, death, or the last follow-up. OS was defined as the time from the start of treatment to death or the last follow-up. The patients were followed up through an electronic medical record system, telephone, and outpatient visits. The follow-up deadline was December 1, 2024, or until the patient was lost to follow-up or died. Treatment-related AEs during the treatment period were recorded according to the Common Terminology Criteria for Adverse Events, version 5.0.

Statistical analysis Statistical analyses were performed using SPSS Statistics software, version 27.0 (IBM, Armonk, New York, United States). Continuous variables were compared using the *t* test (independent or paired samples, as appropriate) for normally distributed data, and the Mann–Whitney test for non-normally distributed data. Data conforming to a normal distribution were expressed as mean (SD), while non-normally distributed continuous variables were presented as median and interquartile range (IQR). Variables with statistical significance in the univariate analysis were included in the multivariable logistic regression and Cox regression models to explore potential predictors of treatment response and survival. Kaplan–Meier survival curves were generated, and the log-rank test was used to compare PFS and OS between the groups. Given the limited sample size, these multivariable analyses were conducted in an exploratory manner to minimize the risk of model overfitting. A 2-sided *P* value below 0.05 was considered significant.

Ethics This study adhered to the Declaration of Helsinki and was approved by the Ethics Committee of the Nanjing Drum Tower Hospital, Affiliated Hospital of Nanjing University Medical School (2021-049-01).

RESULTS **Baseline characteristics** From April 2020 to July 2024, a total of 68 uHCC patients (52 men [76.5%]), subjected to TACE combined with targeted immunotherapy were included. Baseline characteristics of the participants are shown in **TABLE 1**. Mean (SD) age was 57.9 (11.9) years. A total of 50 patients were positive for HBsAg (73.6%). Forty-seven individuals (69.1%) had an ALBI grade 2 liver function. The overall tumor burden of the patients was relatively high. Mean (SD) maximum tumor diameter was 10.1 (3.1) cm, and the patients in CNLC stage IIa, IIb, and IIIa accounted for 82.4% in total.

Treatment and efficacy The median number of TACE treatments received by the patients was 2, as was the median number of cycles of immunotherapy cycles. The main immunotherapy drugs used were camrelizumab, tislelizumab, and sintilimab; the targeted drugs included donafenib, lenvatinib, apatinib, and sorafenib (**TABLE 2**). As

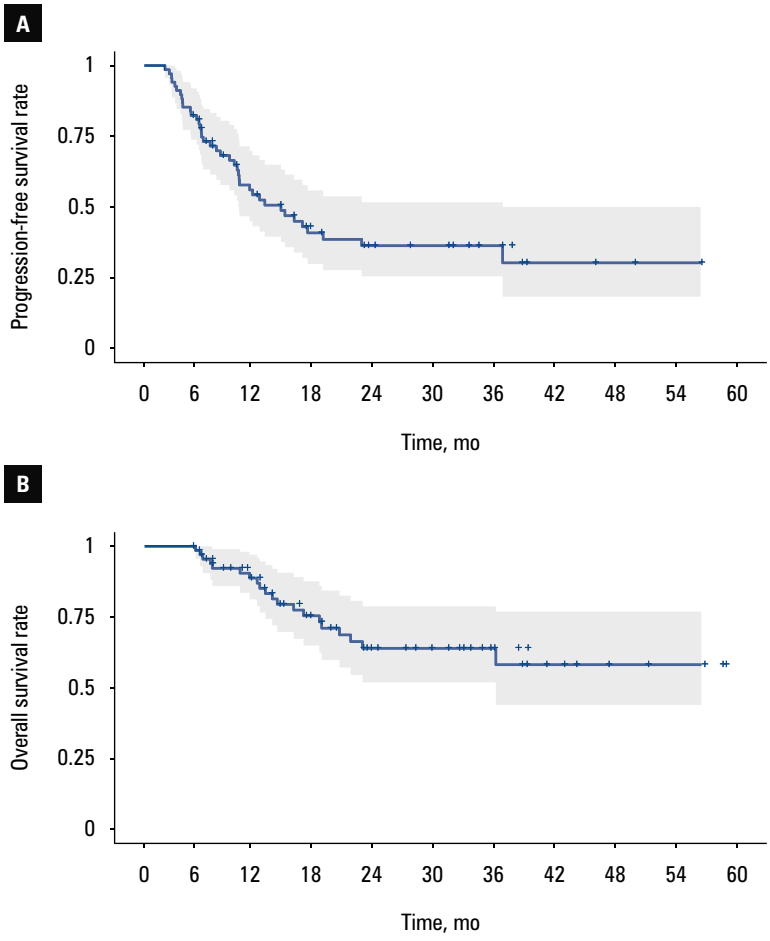

FIGURE 1 Kaplan–Meier curves of progression-free survival (**A**) and overall survival (**B**) rates of all patients

of December 1, 2024, according to the mRECIST standard, 5 patients achieved clinical CR, 34 individuals achieved clinical PR, 22 patients had clinical SD, and 7 participants had clinical PD. The ORR of the patients was 57.4%, and the DCR was 89.7%. As analyzed by the Kaplan–Meier method, the median PFS of the patients was 13.8 (95% CI, 9.6–not available [NA]) months. This indicates that the upper bound of the 95% CI had not been reached by the end of follow-up. The median (IQR) follow-up was 26.3 (15–40.5) months. At the time of data cutoff (December 1, 2024), 38 patients (55.9%) were still alive and therefore censored, while 30 participants (44.1%) had died. The PFS rates at 6 and 12 months were 73.1% and 52.5% respectively, and the survival rates at 18 and 24 months were 85.1% and 63.9%, respectively (FIGURE 1; TABLE 2).

Characteristics of the optimal therapeutic population To identify the characteristics of patients who would benefit from this therapy, we conducted a Cox regression analysis of PFS. The result indicated that male sex (hazard ratio [HR], 0.27; 95% CI, 0.13–0.57; P <0.001) and CNLC stage Ib–IIa (HR, 6.05; 95% CI, 2.27–16.14; P <0.001) were independent influencing factors for PFS (TABLE 3).

We also observed differences in OS and PFS between the individuals who achieved remission (CR and PR) and those who did not (SD and PD). To determine the factors associated with treatment remission, univariate and multivariable logistic regression analyses were performed. The results of multivariable logistic regression showed that 3 tumors or more / fewer than 3 tumors (HR, 6.35; 95% CI, 1.54–26.22; P = 0.01) and having / not having major vascular invasion (HR, 3.89; 95% CI, 1.11–13.71; P = 0.03) were independent risk factors for poor treatment response (TABLE 4).

Prognostic analysis of the patients undergoing surgery A total of 36 patients underwent hepatectomy (surgical conversion rate, 52.9%), with other 2 patients receiving liver transplant. Median (IQR) conversion time for the surgical patients was 2.67 (2–3.8) months, mean (SD) operation time was 5.1 (1.1) hours, median (IQR) intraoperative blood loss was 500 (200–1275) ml, the R0 resection rate reached 94.64%, and median (IQR) postoperative hospital stay was 16 (12–20) days (TABLE 5). The surgical methods included laparoscopic hepatectomy, robot-assisted resection, and open resection. Except for 1 individual, whose pathologic condition was unknown due to surgery performed in another hospital, there were complete data on the remission rates of 35 patients. Seventeen (47.2%) achieved a major pathologic response (pathologic remission rate ≥70%), and 6 (16.7%) achieved a complete pathologic remission (TABLE 5). Median OS was 17.93 (95% CI, 12.93–NA) months in the nonsurgical group, whereas it had not been not reached in the surgical group (P <0.001) by the end of follow-up, indicating substantially longer survival among the individuals who underwent surgery (FIGURE 2A). Median relapse-free survival (RFS) of the patients who underwent hepatectomy was 34.63 months (95% CI, 9–NA; FIGURE 2B).

Univariate and multivariable Cox proportional-hazards regression models were used to analyze the factors affecting postoperative RFS of the patients who underwent hepatectomy. A multivariable analysis of these factors showed that male sex (HR, 0.13; 95% CI, 0.02–0.74; P = 0.02) and residual viable tumor cell rate of 30% or lower (HR, 0.19; 95% CI, 0.04–0.83; P = 0.03) were independent influencing factors for the RFS in the surgical patients (TABLE 6).

Predictive role of magnetic resonance imaging proton density fat fraction in the efficacy of transarterial chemoembolization combined with targeted immunotherapy MRI-PDFF is a noninvasive MRI technique that can accurately assess the accumulation of triglycerides in the liver, and has high precision and good reproducibility in the diagnosis of nonalcoholic fatty liver disease. Previous studies have confirmed that the MRI-PDFF value is closely related to the severity of hepatic steatosis[19]. In this group, 46 patients underwent MRI-PDFF dual-echo to collect signals when water

TABLE 3 Univariate and multivariable analyses of progression-free survival

Clinical characteristics	Progression-free survival			
	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Sex (man/woman)	0.32 (0.18–0.72)	0.004[a]	0.27 (0.13–0.57)	<0.001
Age, y (≥60/<60)	0.62 (0.31–1.23)	0.17	–	–
HBsAg (positive/negative)	1.02 (0.48–2.16)	0.96	–	–
Liver cirrhosis (present/absent)	1.51 (0.8–2.85)	0.21	–	–
ALBI before treatment (grade 2/grade 1)	1.82 (0.76–4.34)	0.18	–	–
Number of tumors (<3/≥3)	0.64 (0.33–1.28)	0.21	–	–
Maximum tumor diameter, cm (≥10/<10)	1.26 (0.67–2.37)	0.48	–	–
CNLC stage (Ib–IIa/IIb–IIIa)	5.19 (2.02–13.37)	<0.001	6.05 (2.27–16.14)	<0.001
NLR (decrease/increase)	0.46 (0.24–0.9)	0.024	0.4 (0.34–1.35)	0.27
PLR (decrease/increase)	0.6 (0.31–1.16)	0.13	–	–
AFP, ng/ml (≥400/<400)	0.84 (0.31–2.29)	0.74	–	–
DCP, mAU/ml (≥400/<400)	1.82 (0.44–7.49)	0.41	–	–

A *P* value <0.05 was deemed significant.

Abbreviations: AFP, α-fetoprotein; ALBI, albumin-bilirubin; CNLC, China Liver Cancer; DCP, des-γ-carboxy prothrombin; HBsAg, hepatitis B virus surface antigen; HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio

and fat were IP and OP, respectively, so as to calculate the percentage of fat signal intensity. Using 6.5 as the cutoff value, an analysis was conducted to compare PFS in subgroups with different PDFF values (**TABLE 7**). PFS of the population with a PDFF value lower than 6.5 was better than that of the population with a PDFF value higher than 6.5 ($P = 0.03$).

Adverse events Common treatment-related AHEs that were recorded during follow-up are outlined in **TABLE 8**, and they occurred in 97.1% of the patients. The incidence of grade 3 AEs was 52.9%, and no grade 4–5 AEs were recorded. AEs, such as abdominal pain, fever, and nausea, which were caused by the postoperative embolization syndrome associated with TACE, were all grade 1–2. After local chemotherapy, 38.24% of the patients developed leukopenia. AEs related to immunotherapy and targeted therapy included hypertension (26.47%), hand-foot syndrome (25%), proteinuria (22.06%), and skin rash (20.59%). All patients with grade 3 AEs improved after dose reduction, drug discontinuation, and symptomatic treatment. Subsequently, this study analyzed the changes in ALBI scores of 68 individuals before and after receiving triple therapy. The average ALBI score before treatment was –2.45 (0.3), and after treatment, it was –2.3 (0.4; $P = 0.02$; **FIGURE 3**).

DISCUSSION This study evaluated clinical application of TACE combined with targeted immunotherapy in initially uHCC. It aimed to systematically explore the therapeutic efficacy of this combined treatment method (including, among others, tumor remission), safety, surgical conversion potential, and accurately identify the characteristics of the patient population most eligible for this combined treatment. The findings provide valuable theoretical and practical guidance for optimizing clinical management strategies and enhancing treatment effectiveness for uHCC.

We demonstrated that TACE combined with targeted immunotherapy regimen had remarkable therapeutic effects, achieving ORR of 57.4%, DCR of 89.7%, and a surgical conversion rate of 52.9%. These results strongly indicate that this combined treatment has significant beneficial effects for certain uHCC patients. Comparative analysis with previous research found that the ORR and DCR in our study were at relatively high levels,[16,20-22] highlighting the superior advantages of this combined approach in controlling tumor progression. Consistent with our findings that intensifying treatment beyond TACE alone may translate into better outcomes, prior studies have reported that TACE combined with [^{125}I] iodine seed insertion (TACE-I) demonstrated better efficacy and survival rates than TACE alone. In a single-center retrospective cohort, TACE-I yielded considerably higher response rates (CR, 59% vs 22%; total response, 92.3% vs 58.5%), as well as prolonged PFS (13 vs 7 mo) and OS (23 vs 15 mo) without excess toxicity.[23] Moreover, a recent meta-analysis pooling 5 studies demonstrated that TACE-I was associated with improved ORR and longer PFS and OS relative to TACE, with a comparable safety profile.[24] Although heterogeneity and potential publication bias were noted for some end points, the direction of benefit remained robust. Together, these data support the rationale of multimodal strategies, by either augmenting locoregional control (eg, brachytherapy) or combining TACE with systemic agents, to achieve deeper tumor responses and better survival rates in patients with inoperable HCC. This dual-pronged approach could partly explain the PFS-OS dissociation observed in our cohort, where earlier progression did not necessarily translate into early death given effective postprogression management.

Notably, some studies did not even report the crucial surgical conversion rate metric.[2,21,25] For initially uHCC patients, the surgical conversion rate of 52.9% obtained in this study is extremely remarkable. Compared with other common treatment regimens, such as neoadjuvant therapy, this is undoubtedly a prominent advantage of this combined treatment regimen. The main reason for the differences in research results can be attributed to the significant dissimilarities in the characteristics of the patient

TABLE 4 Univariate and multivariable logistic regression analyses of factors affecting treatment response

Clinical characteristics	Treatment response			
	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Sex (man/woman)	2.06 (0.66–6.4)	0.21	–	–
Age, y (≥60/<60)	2.49 (0.89–6.97)	0.08	2.53 (0.8–8.01)	0.16
HBsAg (positive/negative)	1.1 (0.37–3.27)	0.86	–	–
Liver cirrhosis (present/absent)	0.61 (0.23–1.60)	0.31	–	–
ALBI before treatment (grade 2/grade 1)	0.42 (0.14–1.26)	0.12	–	–
Number of tumors (≥3/<3)	2.79 (0.92–8.47)	0.07	6.35 (1.54–26.22)	0.01
Maximum tumor diameter, cm (≥10/<10)	0.89 (0.34–2.32)	0.81	–	–
Major vascular invasion (present/absent)	2.46 (0.91–6.64)	0.08	3.89 (1.11–13.71)	0.03
AFP, ng/ml (≥400/<400)	0.84 (0.31–2.29)	0.74	–	–
DCP, mAU/ml (≥400/<400)	1.82 (0.44–7.49)	0.41	–	–
NLR (decrease/increase)	0.8 (0.29–2.24)	0.68	–	–
PLR (decrease/increase)	0.61 (0.23–1.65)	0.34	–	–

Abbreviations: see **TABLE 3**

TABLE 5 Surgical and postoperative pathological characteristics of the patients after conversion therapy

Condition	Total (n = 36)
Conversion time, mo	2.67 (2–3.8)
Operation time, h, mean (SD)	5.1 (1.1)
Intraoperative blood loss, ml	500 (200–1275)
R0 resection rate, %	94.64
Postoperative hospital stay, d	16 (12–20)
Major pathological response	17 (47.2)
Pathological complete response	6 (16.7)

Data are presented as number (percentage) or median (interquartile range) unless indicated otherwise.

populations included in each study. Some studies recruit patients with varied characteristics, such as different tumor stages, underlying health conditions, and genetic backgrounds, and these factors have a substantial and complex impact on treatment outcomes.

During an in-depth examination of the optimal patient population eligible for this combined treatment regimen, through rigorous data analysis and statistical processing, multiple key influencing factors were observed. CNLC stage of Ib–IIa and the male sex were clearly identified as important factors influencing PFS. Specifically, stage Ib–IIa patients who are initially inoperable usually have larger tumors, and the predicted remaining liver volume is insufficient to maintain normal liver function, which is determined unresectable from a surgical perspective. However, after TACE combined with targeted immunotherapy, these patients can often achieve an ideal PFS state. Men generally derive greater benefits from this combined treatment than women. This phenomenon may be related to their better tolerance of the combined treatment,[26] enabling them to more effectively cope with the adverse reactions caused by the drugs during treatment process and maintain normal metabolism and immune response mechanisms of the body, thus ensuring smooth treatment progress and efficacy. These key factors provide clinicians with valuable reference points for developing personalized treatment plans and evaluating patient prognosis.

In this study, the treatment remission rate of the patients with CNLC stage IIb–IIIa was relatively low. These individuals typically have a heavy tumor burden, with large tumors that have likely invaded surrounding tissues or blood vessels. This situation not only greatly increases the complexity and technical difficulty of the treatment but also notably elevates the risk of micrometastases of tumor cells. In addition, tumor microenvironment in CNLC stage IIIa patients is more complex, containing various immunosuppressive cells and cytokines that interfere with immunotherapy effectiveness.[27] These factors make it difficult for immune cells to effectively recognize and attack tumor cells. At the same time, tumor cell heterogeneity of stage IIIa patients is also greater, and the sensitivity of different tumor cell subsets to treatment may vary considerably, which undoubtedly makes it challenging to completely control tumor progression through this combined treatment. In terms of treatment response, further analysis showed that patients with fewer than 3 tumor lesions and without major vascular invasion obtained more benefits from this combined treatment method (markedly higher CR or PR rates).

In our study, 46 patients were examined and analyzed using the MRI-PDFF dual-echo technique. This method leverages the diverse physical properties of water and fat in tissues during MRI scanning.[7,14,16] In an external magnetic field, hydrogen protons in water and fat have very different precession frequencies due to their distinct chemical environments. Signals are collected respectively in the IP and OP of water and fat, and as the signals of water and fat are superimposed on each other in the IP state, they partially cancel one another out in the OP state. Through precise processing of the signals collected in these 2 different echo states and calculating the percentage of the fat signal intensity in the total signal intensity, the PDFF value at the baseline can be accurately measured. Using 6.5 as the critical value, an in-depth analysis was conducted on the relationship between different PDFF value groups of the patient population and the PFS rate. The results showed that the PFS rate of the group with

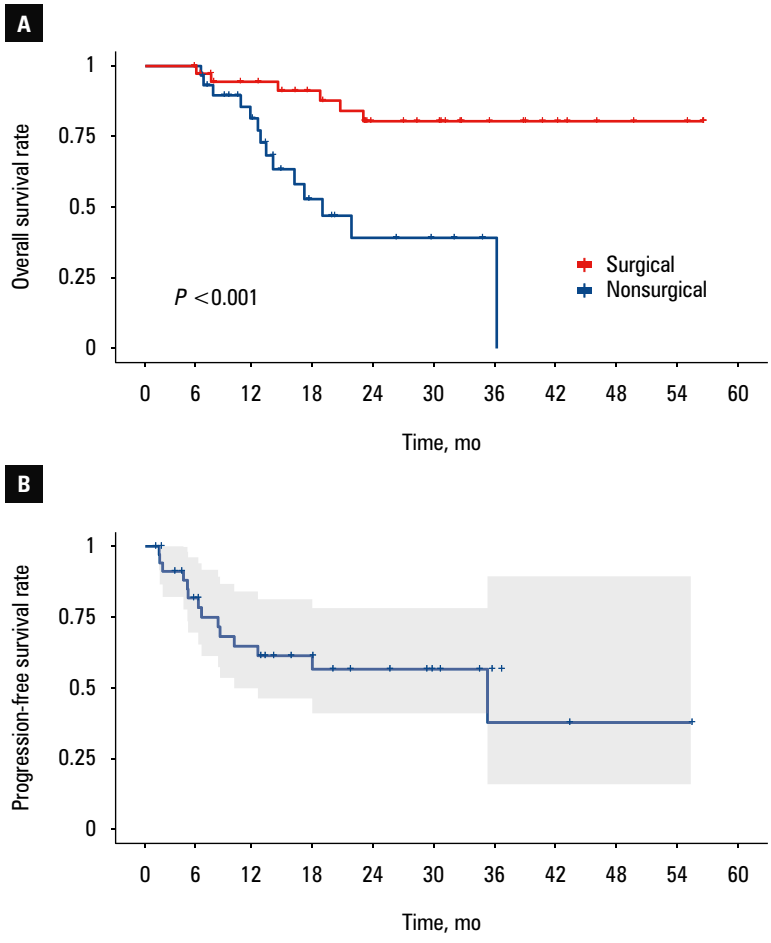

FIGURE 2 Kaplan–Meier curves of overall survival rate for the surgical and nonsurgical groups (**A**) and progression-free survival rate for the patients receiving hepatectomy (**B**)

TABLE 6 Univariate and multivariable analyses of recurrence-free survival of the surgical patients

Clinical characteristic	Recurrence-free survival			
	Univariate analysis		Multivariable analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Male sex	0.29 (0.08–1.04)	0.06	0.13 (0.02–0.74)	0.02
Age ≥60 y	0.81 (0.21–3.15)	0.77	–	–
Number of tumors <3	1.39 (0.18–11.04)	0.98	–	–
Maximum tumor diameter ≥10 cm	0.98 (0.28–3.41)	0.98	–	–
CNLC stage, Ib–IIb	0.1 (0.01–0.81)	0.03	0.12 (0.01–1.16)	0.07
Efficacy reaching PR or CR	1.4 (0.27–7.12)	0.69	–	–
Preoperative AFP decrease to 20 ng/ml	0.27 (0.07–1.01)	0.052	0.89 (0.17–4.82)	0.9
RVTCs ≤30%	0.26 (0.08–0.85)	0.03	0.19 (0.04–0.83)	0.03

A *P* value <0.05 was deemed significant.

Abbreviations: CR, complete remission; PR, partial remission; RVTCs, residual viable tumor cells; others, see **TABLE 3**

a PDFF value lower than 6.5 was considerably better than that of the group with a PDFF value higher than 6.5 ($P = 0.03$). The likely mechanism behind this difference is the close internal relationship between liver fat content (quantitatively reflected by the PDFF value) and the overall metabolic microenvironment of the body. A lower PDFF value may mean a lower degree of fat accumulation in the liver, a relatively better metabolic state of the body,[28] and a more sufficient liver function reserve, enabling the body to better tolerate various burdens related to the treatment process. At the same time, this good metabolic state is also conducive to maintaining normal immune function of the body, so that the growth and spread of tumor cells are inhibited to a certain extent, and finally manifest as a higher PFS rate. Conversely, higher PDFF values may indicate abnormal fat metabolism in the liver. This creates a microenvironment that potentially favors tumor cell proliferation, invasion, and metastasis. At the same time, it may also have a negative impact on the normal function of immune cells, weakening the body's immune surveillance and its ability to kill tumor cells, thus leading to a relatively lower PFS rate.

In terms of safety assessment, most of the AEs observed in this study were mild (grade 1–2), and higher-grade events (grade 3 and above) could be effectively managed through appropriate clinical interventions. This result indicates that the overall safety of TACE combined with targeted immunotherapy is within an acceptable range. Patients can tolerate treatment-related side effects to a certain extent, and this characteristic is an important consideration for clinicians when making treatment decisions. Through a detailed analysis of the ALBI scores before and after treatment at the baseline,[29] it can be clearly concluded that this combined treatment would have a certain degree of negative impact on the liver function of the patients, which is why liver reserve function must be taken into account when screening and including individuals for treatment to ensure its safety and effectiveness.

Despite obtaining important findings, our work has some limitations that cannot be ignored. First, as a single-center retrospective study, the sample size was relatively limited, which may have introduced selection bias and affected the generalizability of the findings. Accordingly, the multivariable analyses should be interpreted with caution and considered exploratory rather than confirmatory. Moreover, patient populations across different medical centers may vary in disease characteristics, genetic backgrounds, and treatment practices, which could further limit the external validity of our results. Our study included various targeted drugs and ICIs with different efficacy profiles and safety characteristics,[5,22,25,30,31] which may have affected the consistency of our treatment analysis. In addition, the mechanisms of action of different drugs, their metabolic pathways in the body, and synergistic effects with

TABLE 7 Comparison of treatment response between the high and low proton density fat fraction groups

Clinical characteristic	Remission group (n = 26)	Nonremission group (n = 20)	*P* value
PDFF ≤6.5%	22 (66.7)	11 (33.3)	0.03
PDFF >6.5%	4 (30.8)	9 (69.2)	

Data are presented as mean (SD).

Abbreviations: PDFF, proton density fat fraction

TABLE 8 Adverse events related to treatment

Adverse event	Any grade	Grade 1–2	Grade 3
Abdominal pain	42 (61.76)	42 (61.76)	0
Fever	27 (39.71)	27 (39.71)	0
Nausea	16 (23.35)	16 (23.35)	0
Elevation of alanine aminotransferase	49 (72.07)	40 (58.82)	9 (13.24)
Elevation of aspartate aminotransferase	49 (72.07)	37 (54.41)	12 (17.65)
Elevation of total bilirubin	25 (36.76)	25 (36.76)	0
Hand-foot syndrome	17 (25)	16 (23.53)	1 (1.47)
Telangiectasia	10 (14.71)	8 (11.76)	2 (2.94)
Skin rash	14 (20.59)	11 (16.18)	3 (4.41)
Hypertension	18 (26.47)	17 (25)	1 (1.47)
Hypothyroidism	8 (11.76)	8 (11.76)	0
Proteinuria	15 (22.06)	14 (20.59)	1 (1.47)
Decrease in platelets	28 (41.18)	25 (36.76)	3 (4.41)
Decrease in white blood cells	26 (38.24)	22 (32.35)	4 (5.88)

Data are presented as numbers (percentages).

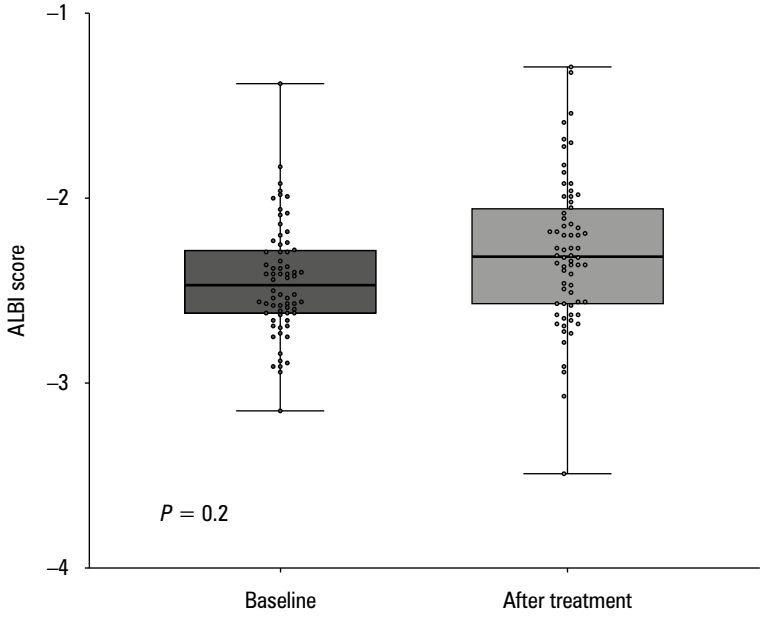

FIGURE 3 Changes in albumin-bilirubin (ALBI) scores after transarterial chemoembolization combined with targeted therapy and immunotherapy. Boxes indicate the interquartile range, bars designate the median, whiskers indicate the minimal and maximal values, and dots represent individual patients.

TACE treatment are all different, making it extremely difficult to accurately evaluate the specific contribution of each drug in the combined treatment. In addition, the maximum follow-up was 56.3 months, and the median OS has not yet been reached, making it impossible to analyze the 5-year survival rate. This prevents comprehensive analysis of factors affecting OS and limits our ability to accurately evaluate the long--term prognosis of the patients. Extended follow--up is crucial for observing the recurrence of tumors, distant metastasis, and long-term adverse reactions caused by the treatment.

To address these limitations, future research should focus on conducting multicenter, large--sample prospective studies. Such analyses can more rigorously verify the results of our study and appropriately explore the differences in the therapeutic efficacy of different combinations of targeted and immune drugs in the treatment of uHCC. Multicenter studies can include a more extensive patient population, effectively reduce the influence of selection bias, and improve the reliability and general applicability of the results. Follow-up should be extended to better evaluate the combined treatment's impact on long-term patient survival, including tumor recurrence rates, distant metastasis, and quality of life. In addition, other biomarkers that can accurately predict the treatment response need to be further explored. By detecting specific gene markers, protein markers, or immune cell subsets, sensitivity of patients to TACE combined with targeted immunotherapy could be predicted. This would provide a solid scientific basis for clinicians to formulate personalized treatment plans, enabling doctors to optimize strategies according to the individual characteristics of patients and provide more precise and effective options for individuals with uHCC, thus further improving treatment effects and quality of life of patients.

CONCLUSIONS TACE combined with targeted drugs and ICIs has a good therapeutic effect on some patients with initially uHCC, achieving relatively high ORR, DCR, and surgical conversion rate. However, the treatment effects vary among patients at different stages. Those with CNLC stage Ib–IIa can achieve an ideal PFS after combined conversion treatment. However, the treatment remission rate of IIb–IIIa stage patients is low. Individuals with fewer than 3 tumor lesions and without major vascular invasion can benefit more from the combined treatment. The PDFF value of the liver is related to the PFS rate. The population with a PDFF value lower than 6.5 has a better PFS rate. The overall safety profile is acceptable, with most AEs being mild (grade 1–2), and higher-grade events remaining controllable. However, the treatment has a certain negative impact on the liver function, so liver reserve function needs to be considered. Due to the limitations of this study, further research is needed to verify and improve its results.

ARTICLE INFORMATION

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REFERENCES

1 Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024; 74: 229-263.

2 Zeng Z, Yang B, Liao ZY. Current progress and prospect of immune checkpoint inhibitors in hepatocellular carcinoma. Oncol Lett. 2020; 20: 45.

3 Himes BT, Peterson TE, de Mooij T, et al. The role of extracellular vesicles and PD-L1 in glioblastoma-mediated immunosuppressive monocyte induction. Neuro Oncol. 2020; 22: 967-978.

4 Zhu XD, Huang C, Shen YH, et al. Downstaging and resection of initially unresectable hepatocellular carcinoma with tyrosine kinase inhibitor and anti-PD-1 antibody combinations. Liver Cancer. 2021; 10: 320-329.

5 Takeda H, Nishijima N, Nasu A, et al. Long-term antitumor effect of lenvatinib on unresectable hepatocellular carcinoma with portal vein invasion. Hepatol Res. 2019; 49: 594-599.

6 Zhu XD, Huang C, Shen YH, et al. Hepatectomy after conversion therapy using tyrosine kinase inhibitors plus anti-PD-1 antibody therapy for patients with unresectable hepatocellular carcinoma. Ann Surg Oncol. 2023; 30: 2782-2790.

7 Kloeckner R, Galle PR, Bruix J. Local and regional therapies for hepatocellular carcinoma. hepatology. 2021; 73 Suppl 1: 137-149.

8 Yin L, Liu R, Li W, et al. Deep learning-based CT radiomics predicts prognosis of unresectable hepatocellular carcinoma treated with TACE-HAIC combined with PD-1 inhibitors and tyrosine kinase inhibitors. BMC Gastroenterol. 2025; 25: 24.

9 Hatzidakis A, Müller L, Krokidis M, et al. Local and regional therapies for hepatocellular carcinoma and future combinations. Cancers (Basel). 2022; 14: 2469.

10 Ji J, Zhou C, Yan LL, et al. Transarterial chemoembolization plus tyrosinkinase inhibitors and PD-1 inhibitors for spontaneously ruptured hepatocellular carcinoma. Cardiovasc Intervent Radiol. 2024; 47: 299-309.

11 Chen QF, Jiang XY, Chen MS, et al. A metrology informatics investigation of conversion therapy in hepatocellular carcinoma: 2014–2023. Ann Surg Open. 2025; 6: e562.

12 Kudo M, Ueshima K, Saeki I, et al. A phase 2, prospective, multicenter, single-arm trial of transarterial chemoembolization therapy in combination strategy with lenvatinib in patients with unresectable intermediate-stage hepatocellular carcinoma: TACTICS-L trial. Liver Cancer. 2023; 13: 99-112.

13 Jin ZC, Chen JJ, Zhu XL, et al. Immune checkpoint inhibitors and anti-vascular endothelial growth factor antibody/tyrosine kinase inhibitors with or without transarterial chemoembolization as first-line treatment for advanced hepatocellular carcinoma (CHANCE2201): a target trial emulation study. EClinicalMedicine. 2024; 72: 102622.

14 Kupczyk PA, Kurt D, Endler C, et al. MRI proton density fat fraction for estimation of tumor grade in steatotic hepatocellular carcinoma. Eur Radiol. 2023; 33: 8974-8985.

15 Vogel A, Meyer T, Sapisochin G, et al. Hepatocellular carcinoma. Lancet. 2022; 400: 1345-362.

16 Hatanaka T, Yata Y, Naganuma A, et al. Treatment strategy for intermediate-stage hepatocellular carcinoma: transarterial chemoembolization, systemic therapy, and conversion therapy. Cancers (Basel). 2023; 15: 1798.

17 Bureau of Medical Administration, National Health Commission of the People's Republic of China. [Standardization for diagnosis and treatment of hepatocellular carcinoma (2022 edition)]. Zhonghua Gan Zang Bing Za Zhi. 2022; 30: 367-388.

18 Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Semin Liver Dis. 2010; 30: 52-60.

19 Zhang L, Mai X, Li B, et al. Fat fraction quantification by MRI predicts diagnosis and prognosis of HBV-related steatohepatitic hepatocellular carcinoma. Eur Radiol. 2025; 35: 3144-3157.

20 Duan X, Li H, Kuang D, et al. Transcatheter arterial chemoembolization plus apatinib with or without camrelizumab for unresectable hepatocellular carcinoma: a multicenter retrospective cohort study. Hepatol Int. 2023; 17: 915-926.

21 Dawood ZS, Brown ZJ, Alaimo L, et al. Comparison of tumor response and outcomes of patients with hepatocellular carcinoma after multimodal treatment including immune checkpoint inhibitors – a systematic review and meta-analysis. HPB (Oxford). 2024; 26: 618-629.

22 He M, Li Q, Zou R, et al. Sorafenib plus hepatic arterial infusion of oxaliplatin, fluorouracil, and leucovorin vs sorafenib alone for hepatocellular carcinoma with portal vein invasion: a randomized clinical trial. JAMA Oncol. 2019; 5: 953-960.

23 Wang YB, Zhang W, Bao L, et al. Transarterial chemoembolization with insertion of radioactive seeds for hepatocellular carcinoma. Wideochir Inne Tech Maloinwazyjne. 2023; 18: 645-654.

24 Zhu R, Mao K, Lu XZ, et al. Transarterial chemoembolization with ^{125}I seed insertion for unresectable hepatocellular carcinoma: a metaanalysis. Wideochir Inne Tech Maloinwazyjne. 2025; 20: 30-35.

25 Xie D, Sun Q, Wang X, et al. Immune checkpoint inhibitor plus tyrosine kinase inhibitor for unresectable hepatocellular carcinoma in the real world. Ann Transl Med. 2021; 9: 652.

26 Fan W, Zhu B, Chen S, et al. Survival in patients with recurrent intermediate-stage hepatocellular carcinoma: sorafenib plus TACE vs TACE alone randomized clinical trial. JAMA Oncol. 2024; 10: 1047-1054.

27 Yau T, Kang YK, Kim TY, et al. Efficacy and safety of nivolumab plus ipilimumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib: the CheckMate 040 randomized clinical trial. JAMA Oncol. 2020; 6: e204564.

28 Simon TG, Wilechansky RM, Stoyanova S, et al. Aspirin for metabolic dysfunction-associated steatotic liver disease without cirrhosis: a randomized clinical trial. Jama. 2024; 331: 920-929.

29 Toyoda H, Johnson PJ. The ALBI score: From liver function in patients with HCC to a general measure of liver function. JHEP Rep. 2022; 4: 100557.

30 Llovet JM, De Baere T, Kulik L, et al. Locoregional therapies in the era of molecular and immune treatments for hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol. 2021; 18: 293-313.

31 Leone P, Solimando AG, Fasano R, et al. The evolving role of immune checkpoint inhibitors in hepatocellular carcinoma treatment. Vaccines (Basel). 2021; 9: 532.