Article

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Predictive Value of Dynamic Changes in Serum AFP for Survival in Hepatocellular Carcinoma Patients Treated With TACE Combined With Immunotherapy

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Background: Hepatocellular carcinoma (HCC) remains one of the leading causes of cancer-related death worldwide. Serum alpha-fetoprotein (AFP) is widely used as a tumor biomarker for HCC, and its dynamic changes during treatment may reflect tumor response and prognosis. However, the predictive value of AFP dynamics in patients receiving transarterial chemoembolization (TACE) combined with immunotherapy has not been fully clarified. This study aimed to investigate the predictive value of dynamic changes in AFP for survival outcomes in HCC patients treated with TACE combined with immunotherapy.

Methods: Clinical data of 267 HCC patients who received TACE combined with immune checkpoint inhibitors at the Second Hospital of Nanjing from January 2021 to January 2024 were retrospectively analyzed. Patients in the AFP–elevated group (n = 199) were divided into an AFP decline group, an AFP stable group, and an AFP progression group according to the dynamic changes in AFP at 8 weeks after the first TACE procedure. Kaplan–Meier method and Cox proportional hazards regression model were used to analyze the relationship between dynamic changes in AFP and overall survival (OS) and progression–free survival (PFS). Restricted cubic spline analysis was used to analyze the nonlinear relationship between AFP change rate and survival outcomes, and the efficacy of predictive models was evaluated using time–dependent receiver operating characteristic (ROC) curves.

Results: With a median follow–up of 24.5 months, the median OS and PFS for all patients were 18.5 and 10.2 months, respectively. For patients in the AFP–elevated group, median OS was 20.5 months in the AFP decline group, 14.2 months in the AFP stable group, and 8.5 months in the AFP progression group ($p < 0.001$). The AFP sustained response group (AFP decline $\geq$50% from baseline at both 8 and 12 weeks after the first TACE) had significantly longer OS and PFS than the non–sustained response group (26.8 vs 15.5 months for OS, $p < 0.001$; 14.8 vs 8.2 months for PFS, $p < 0.001$). Multivariate Cox regression analysis showed that AFP sustained response was independently associated with both OS (hazard ratio [HR] = 0.42, 95% confidence interval [CI] = 0.28–0.63, $p < 0.001$) and PFS (HR = 0.35, 95% CI = 0.24–0.51, $p < 0.001$). Barcelona Clinic Liver Cancer (BCLC) stage C, portal vein tumor thrombus, extrahepatic metastasis, and NLR >3.5 were also independent prognostic factors. The combined predictive model predicted 12–month and 24–month OS with AUCs of 0.782 and 0.776, respectively, and Harrell's C–index was 0.748. Subgroup analysis showed that the prognostic value of AFP sustained response was consistent across different clinical subgroups (all p for interaction > 0.05). Competing risk analysis showed that the 24–month cumulative incidence of tumor–related death was 32.8% in the AFP sustained response group and 58.6% in the non–sustained response group (subdistribution HR = 0.38, 95% CI = 0.25–0.58, $p < 0.001$).

Conclusion: Serum AFP sustained response is independently associated with both OS and PFS in HCC patients treated with TACE combined with immunotherapy and may serve as a simple and practical prognostic marker for clinical risk stratification.

Keywords: hepatocellular carcinoma; alpha–fetoprotein; transarterial chemoembolization; immune checkpoint inhibitors; prognosis; survival analysis

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy globally and the third leading cause of cancer–related death, posing a serious threat to human health [1]. China is a high–incidence country for liver cancer, with approximately 50% of new cases worldwide occurring annually. Most patients are diagnosed at intermediate or advanced stages, when curative surgery is no longer feasible [2]. Transarterial chemoembolization (TACE), as the standard treatment for intermediate and advanced HCC, exerts anti–tumor effects by blocking tumor blood supply and locally releasing chemotherapeutic drugs. However, TACE alone has limited efficacy, with a median overall survival (OS) of only 16–20 months [3]. In recent years, immune checkpoint inhibitors (ICIs) have demonstrated significant efficacy in HCC treatment. Combining TACE with immunotherapy may improve clinical outcomes, potentially through synergistic antitumor effects [4]. However, there is significant heterogeneity in patient response to combination therapy, and reliable biomarkers are urgently needed to guide clinical decision–making and prognostic assessment.

Alpha–fetoprotein (AFP) is the most commonly used serum tumor marker for HCC, and baseline AFP levels are closely related to tumor burden and prognosis [5]. Previous research has shown that dynamic changes in AFP after treatment may reflect treatment response, and AFP decline is associated with improved survival [6]. However, there is currently a lack of systematic research on the predictive value of AFP dynamic changes in TACE combined with immunotherapy. The optimal assessment time point, threshold for change magnitude, and relationship with other clinicopathological factors remain unclear [7]. Additionally, questions such as the relationship between AFP dynamic changes and imaging efficacy assessment, predictive value in different clinical subgroups, and whether it can serve as an early surrogate marker for treatment response require further investigation [8]. Therefore, this study retrospectively analyzed clinical data from 267 HCC patients receiving TACE combined with immunotherapy to systematically evaluate the predictive value of serum AFP dynamic changes for patient survival, aiming to provide a simple and practical prognostic indicator for clinical risk stratification and outcome assessment.

Methods

Study Population

Clinical data of HCC patients who received TACE combined with immunotherapy at the Second Hospital of Nanjing from January 2021 to January 2024 were retrospectively analyzed. Inclusion criteria were as follows: (1) HCC clearly diagnosed by histopathology or comprehensive clinical diagnosis, meeting the diagnostic criteria of the "Guidelines for Diagnosis and Treatment of Primary Liver Cancer (2022 Edition) [9]"; (2) first–time treatment with TACE combined with immune checkpoint inhibitors (ICIs), with no previous anti–tumor treatments including surgery, ablation, radiotherapy, systemic chemotherapy, targeted therapy, or immunotherapy (comprehensively verified through electronic medical record system, imaging data, and patient/family inquiry); (3) Child–Pugh liver function classification A or B [10]; (4) Eastern Cooperative Oncology Group (ECOG) performance status score 0–2 [11]; (5) at least 4 serum AFP test records within 1 week before treatment, 4 weeks (±3 days) after the first TACE, 8 weeks (±3 days) after the first TACE, 12 weeks (±3 days) after the first TACE, and every 8 weeks (±3 days) during subsequent treatment; (6) complete clinical data and follow–up information. Exclusion criteria were as follows: (1) other coexisting malignancies; (2) severe dysfunction of important organs such as the heart, lung, or kidney; (3) contraindications to immunotherapy; (4) loss to follow-up or incomplete follow–up data.

A total of 267 patients meeting the criteria were finally included in the study. Patients with missing key clinical variables, incomplete AFP measurements at predefined time points, or incomplete follow-up data were excluded during screening; therefore, the final analyses were conducted on a complete-case basis. This study was conducted in accordance with the Declaration of Helsinki and approved by the Medical Ethics Committee of Nanjing Second Hospital/Affiliated Nanjing Hospital of Nanjing University of Chinese Medicine (The Second Affiliated Hospital of Southeast University) (Approval No. 2021-LY-kt064). Due to the retrospective nature of the study, the requirement for written informed consent was waived by the ethics committee.

Treatment Methods

TACE treatment: Patients fasted for 6–8 hours before the procedure, and coagulation function was assessed. Under local anesthesia, femoral artery puncture was performed using the Seldinger technique. Under digital subtraction angiography (DSA) guidance, the catheter was superselectively advanced into the tumor–feeding artery. After angiography, the tumor blood supply was evaluated, and lipiodol emulsion (10–20 mL lipiodol mixed with chemotherapy drugs) and gelatin sponge particles were injected for embolization. Chemotherapy regimens included epirubicin 50–60 mg/m^2, cisplatin 40–60 mg/m^2, or lobaplatin 50 mg/m^2, with doses adjusted according to patients' liver function and tumor burden. Total chemotherapy drug dose limit per single TACE procedure: epirubicin not exceeding 80 mg, cisplatin not exceeding 80 mg. For Child–Pugh grade B patients, chemotherapy drug doses were reduced by 20–30%; for patients with a large tumor burden (tumor volume occupying >50% of liver volume), the lower dose limit was used for the first TACE. The embolization endpoint was significantly slowed or stagnant blood flow

in tumor–feeding arteries, with persistent contrast staining in the tumor area. TACE treatment intervals were 6–8 weeks. Repeat TACE was considered when follow-up imaging showed residual viable intrahepatic tumor or intrahepatic progression without diffuse liver failure, and when the patient had adequately recovered from the previous procedure, including Child–Pugh class A or stable class B liver function, no uncontrolled ascites or hepatic encephalopathy, ECOG performance status $\leq$2, and no severe treatment-related adverse events. Repeat TACE was not recommended in patients with persistent liver function deterioration, extensive tumor progression with poor expected benefit from locoregional therapy, or intolerance to further interventional treatment.

Immunotherapy: Immunotherapy was started 14 days ($\pm$3 days) after the first TACE procedure, using programmed death–1 (PD–1)/programmed death–ligand 1 (PD–L1) inhibitors, including pembrolizumab (200 mg, Q3W), nivolumab (240 mg, Q2W), sintilimab (200 mg, Q3W), tislelizumab (200 mg, Q3W), or atezolizumab (1200 mg, Q3W). The choice of immunotherapy drug was determined by the multidisciplinary team (MDT) based on patients' economic conditions, drug accessibility, and previous clinical research evidence. Coordination regimen between immunotherapy and TACE treatment: immunotherapy was suspended 3–5 days before scheduled TACE treatment and resumed 7–10 days after TACE (when the patient's general condition had recovered and there were no severe adverse reactions). Treatment continued until disease progression, intolerable adverse reactions, or patient refusal. During treatment, patients' general conditions, liver and kidney function, and immune–related adverse reactions were evaluated before each cycle of immunotherapy and graded and managed according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 criteria [12]. No concurrent targeted therapy or anti–angiogenic agents (such as sorafenib, lenvatinib, apatinib, or bevacizumab) were routinely administered during the study period.

The main drugs and embolic materials used in this study included lipiodol injection (Guerbet, Villepinte, France), gelatin sponge particles, epirubicin, cisplatin, and lobaplatin. Immune checkpoint inhibitors included pembrolizumab (Merck Sharp & Dohme, Rahway, NJ, USA), nivolumab (Bristol Myers Squibb, New York, NY, USA), sintilimab (Innovent Biologics, Suzhou, Jiangsu, China), tislelizumab (BeiGene, Beijing, China), and atezolizumab (Roche/Genentech, Basel, Switzerland/South San Francisco, CA, USA).

Serum AFP Detection and Grouping

Serum AFP levels were detected using electrochemiluminescence immunoassay (ECLIA), with a Roche Cobas e602 fully automated electrochemiluminescence immunoanalyzer (Roche Diagnostics, Mannheim, Germany). AFP assay reagents were obtained from Roche Diagnostics (Mannheim, Germany); however, reagent lot numbers were not consistently available because of the retrospective nature of the study. The normal reference range was 0–20 ng/mL. All patients had AFP levels tested within 1 week before treatment (baseline level), 4 weeks ($\pm$3 days) after the first TACE, 8 weeks ($\pm$3 days) after the first TACE, 12 weeks ($\pm$3 days) after the first TACE, and every 8 weeks ($\pm$3 days) before subsequent treatments.

Patients were divided into an AFP normal group (AFP $\leq$20 ng/mL) and an AFP elevated group (AFP $>$20 ng/mL) according to pretreatment AFP levels. Patients in the AFP elevated group were further divided based on AFP dynamic changes at 8 weeks after the first TACE: (1) AFP decline group: post–treatment AFP decreased $>$20% from baseline; (2) AFP stable group: post–treatment AFP change between –20% to +20% from baseline; (3) AFP progression group: post–treatment AFP increased $>$20% from baseline. AFP early response was defined as AFP decline $\geq$50% from baseline at 8 weeks after the first TACE; AFP sustained response was defined as AFP decline $\geq$50% from baseline at 8 weeks after the first TACE and maintained at $\geq$50% decline from baseline at the 12–week ($\pm$3 days) reexamination. The $\pm$20% threshold was used to distinguish AFP decline, stability, and progression while minimizing the influence of minor biological fluctuations, whereas the $\geq$50% decline threshold was adopted according to commonly used AFP response criteria in previous HCC studies and for better clinical interpretability.

AFP change rate calculation formula: AFP change rate (%) = [(AFP post–treatment – AFP baseline)/AFP baseline] $\times$ 100%. A negative AFP change rate indicates AFP decline, and a positive value indicates AFP increase.

Efficacy Evaluation and Follow–up

Imaging evaluation: Contrast–enhanced computed tomography (CT) or magnetic resonance imaging (MRI) was used to evaluate tumor response. The first efficacy assessment was performed at 8 weeks ($\pm$3 days) after the first TACE, followed by reexamination every 8 to 12 weeks (specific intervals determined by disease status: every 12 weeks for patients with stable disease or remission; every 8 weeks for patients at high risk of disease progression). Efficacy assessment used modified Response Evaluation Criteria in Solid Tumors (mRECIST), classified as complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) [13]. Objective response rate (ORR) = (CR+PR)/total cases $\times$ 100%, disease control rate (DCR) = (CR+PR+SD)/total cases $\times$ 100%.

Follow–up: Follow–up was conducted through outpatient visits, telephone calls, and electronic medical record systems. Follow–up was primarily through outpatient visits; for patients unable to attend clinic visits, telephone follow–up was used, and relevant information was verified through the electronic medical record system. Follow–up

frequency during treatment was once every 8–12 weeks (synchronized with imaging reexamination); after treatment completion, follow–up frequency was once every 3 months for the first 2 years, once every 6 months for 2–5 years, and once annually after 5 years, until patient death or study closure. Loss to follow–up was defined as the inability to contact the patient or family for 3 consecutive times (at least 1 month apart). Data from patients lost to follow–up were censored at the last follow–up time. The follow–up cutoff date was May 30, 2025. The primary endpoint was overall survival (OS), defined as the time from treatment initiation to death from any cause or last follow–up; the secondary endpoint was progression–free survival (PFS), defined as the time from treatment initiation to first disease progression or death. Causes of death (tumor–related death, liver failure, gastrointestinal bleeding, infection, etc.) were recorded for competing risk analysis. For patients who interrupted treatment or switched treatment regimens, the time and reason for interruption/switching were recorded and separately evaluated in sensitivity analysis.

Clinical Data Collection

The following clinical data were collected: gender, age, viral hepatitis infection status (hepatitis B virus [HBV]/hepatitis C virus [HCV]), cirrhosis status (using the Ishak fibrosis scoring system [14]: this study defined F5–F6 as the cirrhosis group and F0–F4 as the non–cirrhosis group), Child–Pugh classification, ECOG score, Barcelona Clinic Liver Cancer (BCLC) stage, American Joint Committee on Cancer (AJCC) tumor–node–metastasis (TNM) stage (8th edition), number of tumors (solitary or multiple, multiple defined as $\geq$2 measurable lesions), maximum tumor diameter (measured according to Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1 criteria, longest diameter of the largest lesion, unit: cm), portal vein tumor thrombus (PVTT), extrahepatic metastasis, laboratory indicators within 1 week before treatment [AFP, albumin (ALB), total bilirubin (TBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ–glutamyl transpeptidase (GGT), prothrombin time (PT), international normalized ratio (INR), platelet count (PLT), white blood cell count (WBC), neutrophil–to–lymphocyte ratio (NLR, calculation formula: absolute neutrophil count/absolute lymphocyte count), platelet–to–lymphocyte ratio (PLR, calculation formula: platelet count/absolute lymphocyte count, absolute lymphocyte count unit: $\times 10^9$/L, platelet count unit: $\times 10^9$/L)], immunotherapy drug type, number of TACE treatments.

For regression analyses, clinically relevant cutoff values were prespecified according to commonly used clinical thresholds or previous literature. Specifically, AFP >400 ng/mL was used to define elevated AFP, ALB <35 g/L was defined according to the lower limit of the normal laboratory reference range, and other dichotomized variables, including maximum tumor diameter >7 cm, TBIL >20 µmol/L, ALP >120 U/L, GGT >100 U/L, NLR >3.5, and PLR >150, were categorized based on clinical convention, published studies, or the distribution characteristics of the present cohort [15,16].

Statistical Methods

Statistical analysis was performed using SPSS version 26.0 (IBM Corporation, USA) and R software version 4.3.0 (R Foundation for Statistical Computing). Continuous variables were expressed as median (interquartile range), and categorical variables were expressed as numbers (percentages). Between-group comparisons were performed using the Mann–Whitney U test, Kruskal–Wallis H test, or χ^2 test, as appropriate. Fisher's exact test was used only for categorical variables when the expected cell count was less than 5.

Survival curves were generated using the Kaplan–Meier method and compared using the log-rank test. Univariate and multivariate Cox proportional hazards regression analyses were performed to identify prognostic factors for OS and PFS. Variables with $p < 0.10$ in univariate analysis were entered into the multivariate Cox regression model using a forward stepwise selection procedure. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. The proportional hazards assumption was assessed using Schoenfeld residuals. Multicollinearity was evaluated using variance inflation factors (VIFs), with VIF >5 indicating potential collinearity.

Restricted cubic spline analysis was used to explore the nonlinear association between AFP change rate and survival outcomes. Time-dependent receiver operating characteristic (ROC) curves were used to evaluate the predictive performance of AFP dynamic changes and the combined prognostic model. Model performance was assessed using the area under the curve (AUC), Harrell's C-index, calibration curves, bootstrap internal validation, and decision curve analysis. Competing risk analysis was performed using the Fine–Gray model. Subgroup and sensitivity analyses were performed to evaluate the robustness of the results. A 12-week landmark analysis was conducted to reduce potential immortal time bias related to the definition of AFP sustained response. All tests were two-sided, and a $p < 0.05$ was considered statistically significant.

Results

Patient Baseline Characteristics

This study included 267 HCC patients receiving TACE combined with immunotherapy, including 231 males (86.5%) and 36 females (13.5%), with a median age of 56 years (49–64 years). 249 patients (93.3%) had HBV infection, 8 (3.0%) had HCV infection, and 10 (3.7%) had no viral infection. 232 patients (86.9%) had cirrhosis. Child–Pugh grade A was observed in 215 cases (80.5%), and grade

Table 1. Patient baseline clinical characteristics.

Clinical characteristics	Total (n = 267)	AFP normal (n = 68)	AFP elevated (n = 199)	Statistic (Z/χ^2)	*p* value
Age (years)	56 (49–64)	58 (50–65)	55 (48–63)	Z = 1.922	0.055
Gender				χ^2 = 0.567	0.451
Male	231 (86.5%)	57 (83.8%)	174 (87.4%)		
Female	36 (13.5%)	11 (16.2%)	25 (12.6%)		
Viral infection				χ^2 = 0.761	0.684
HBV	249 (93.3%)	62 (91.2%)	187 (94.0%)		
HCV	8 (3.0%)	3 (4.4%)	5 (2.5%)		
None	10 (3.7%)	3 (4.4%)	7 (3.5%)		
Cirrhosis	232 (86.9%)	56 (82.4%)	176 (88.4%)	χ^2 = 1.650	0.199
Child–Pugh classification				χ^2 = 2.266	0.132
Grade A	215 (80.5%)	59 (86.8%)	156 (78.4%)		
Grade B	52 (19.5%)	9 (13.2%)	43 (21.6%)		
ECOG score				χ^2 = 0.434	0.510
0–1	242 (90.6%)	63 (92.6%)	179 (89.9%)		
2	25 (9.4%)	5 (7.4%)	20 (10.1%)		
BCLC stage				χ^2 = 11.478	0.003
A	38 (14.2%)	15 (22.1%)	23 (11.6%)		
B	127 (47.6%)	38 (55.9%)	89 (44.7%)		
C	102 (38.2%)	15 (22.1%)	87 (43.7%)		
TNM stage				χ^2 = 10.621	0.005
I	27 (10.1%)	12 (17.6%)	15 (7.5%)		
II	89 (33.3%)	28 (41.2%)	61 (30.7%)		
III	151 (56.6%)	28 (41.2%)	123 (61.8%)		
Number of tumors				χ^2 = 3.680	0.055
Solitary	111 (41.6%)	35 (51.5%)	76 (38.2%)		
Multiple	156 (58.4%)	33 (48.5%)	123 (61.8%)		
Maximum tumor diameter (cm)	6.5 (4.2–9.8)	5.2 (3.5–7.8)	7.2 (4.8–10.5)	Z = –4.093	<0.001
Portal vein tumor thrombus	74 (27.7%)	10 (14.7%)	64 (32.2%)	χ^2 = 7.708	0.005
PVTT grade				χ^2 = 0.134	0.715
Vp1–2	48 (64.9%)	7 (70.0%)	41 (64.1%)		
Vp3–4	26 (35.1%)	3 (30.0%)	23 (35.9%)		
Extrahepatic metastasis	53 (19.9%)	8 (11.8%)	45 (22.6%)	χ^2 = 3.749	0.053
AFP (ng/mL)	285.6 (15.8–1520.0)	10.5 (6.2–16.8)	568.0 (98.5–2850.0)	Z = –3.859	<0.001
ALB (g/L)	38.5 (35.2–41.8)	39.8 (36.5–42.5)	38.0 (34.8–41.2)	Z = 2.834	0.005
TBIL (μmol/L)	18.2 (13.5–24.8)	16.8 (12.5–22.5)	18.8 (14.0–25.5)	Z = –1.848	0.065
ALT (U/L)	45.0 (32.0–62.0)	42.0 (30.0–58.0)	46.5 (33.0–64.0)	Z = –1.502	0.133
AST (U/L)	52.0 (38.0–71.0)	48.0 (35.0–65.0)	54.0 (40.0–74.0)	Z = –1.856	0.063
ALP (U/L)	125.0 (95.0–168.0)	112.0 (88.0–145.0)	132.0 (98.0–178.0)	Z = –3.020	0.003
GGT (U/L)	98.0 (65.0–148.0)	85.0 (58.0–125.0)	105.0 (68.0–158.0)	Z = –2.614	0.009
PT (s)	13.2 (12.5–14.1)	12.8 (12.2–13.6)	13.4 (12.6–14.3)	Z = –3.891	<0.001
INR	1.15 (1.08–1.25)	1.12 (1.06–1.20)	1.17 (1.09–1.27)	Z = –3.178	0.001
PLT ($\times 10^9$/L)	142.0 (108.0–185.0)	155.0 (118.0–195.0)	138.0 (105.0–180.0)	Z = 2.136	0.033
WBC ($\times 10^9$/L)	5.8 (4.5–7.2)	5.6 (4.3–6.8)	5.9 (4.6–7.4)	Z = –1.118	0.264
NLR	3.2 (2.3–4.8)	2.8 (2.0–3.9)	3.5 (2.5–5.2)	Z = –3.155	0.002
PLR	128.5 (92.0–175.0)	118.0 (85.0–158.0)	132.0 (95.0–182.0)	Z = –1.752	0.080

Notes: Data are presented as n (%) or median (interquartile range). Comparisons between the AFP normal and AFP elevated groups were performed using the Mann–Whitney U test for continuous variables and the χ^2 test for categorical variables.

AFP, alpha-fetoprotein; HBV, hepatitis B virus; HCV, hepatitis C virus; ECOG, Eastern Cooperative Oncology Group; BCLC, Barcelona Clinic Liver Cancer; TNM, tumor–node–metastasis; PVTT, portal vein tumor thrombus; ALB, albumin; TBIL, total bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, γ–glutamyl transpeptidase; PT, prothrombin time; INR, international normalized ratio; PLT, platelet count; WBC, white blood cell count; NLR, neutrophil–to–lymphocyte ratio; PLR, platelet–to–lymphocyte ratio.

Table 2. Treatment status and efficacy evaluation.

Treatment characteristics	n (%) or Median (Interquartile Range)
Number of TACE treatments	3 (2–5)
1 time	52 (19.5)
2 times	78 (29.2)
≥3 times	137 (51.3)
Immunotherapy drugs	
Pembrolizumab	85 (31.8)
Nivolumab	72 (27.0)
Sintilimab	58 (21.7)
Tislelizumab	36 (13.5)
Atezolizumab	16 (6.0)
Immunotherapy cycles	8 (4–14)
Efficacy at 8 weeks after first TACE	
CR	12 (4.5)
PR	89 (33.3)
SD	118 (44.2)
PD	48 (18.0)
ORR	101 (37.8)
DCR	219 (82.0)
Adverse reactions	
Fever	52 (19.5)
Fatigue	68 (25.5)
Nausea and vomiting	45 (16.9)
Elevated transaminases	73 (27.3)
Immune–related adverse reactions (Total)	32 (12.0)
Immune hepatitis	12 (4.5)
Immune pneumonitis	8 (3.0)
Thyroid dysfunction	7 (2.6)
Rash	5 (1.9)
Grade ≥3 immune–related adverse reactions	9 (3.4)
Other Grade ≥3 adverse reactions	9 (3.4)
Treatment suspended due to adverse reactions	10 (3.7)
Treatment terminated due to adverse reactions	5 (1.9)
Suspended/Terminated due to immune–related adverse reactions	7/3
Suspended/Terminated due to other adverse reactions	3/2
Treatment regimen changed due to disease progression	13 (4.9)
Treatment interrupted or regimen changed (Total)	28 (10.5)

Notes: Percentages are based on the total study population (n = 267). Some patients may have experienced more than one adverse event.

TACE, transarterial chemoembolization; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response rate; DCR, disease control rate.

B in 52 cases (19.5%). ECOG performance status was 0–1 in 242 cases (90.6%) and 2 in 25 cases (9.4%). According to the BCLC staging system, 38 cases (14.2%) were stage A, 127 cases (47.6%) were stage B, and 102 cases (38.2%) were stage C. TNM staging was as follows: stage I, 27 cases (10.1%); stage II, 89 cases (33.3%); stage III, 151 cases (56.6%). 156 cases (58.4%) had multiple tumors, and the median maximum tumor diameter was 6.5 cm (4.2–9.8 cm). 74 cases (27.7%) had PVTT, including 48 cases with Vp1–2 grade and 26 cases with Vp3–4 grade. 53 cases (19.9%) had extrahepatic metastasis, mainly involving the lung (32 cases), lymph nodes (15 cases), and bone (6 cases). The median pretreatment AFP was 285.6 ng/mL (15.8–1520.0 ng/mL), with 68 cases (25.5%) in the AFP normal group (≤20 ng/mL) and 199 cases (74.5%) in the AFP elevated group (>20 ng/mL). Median laboratory indicators were as follows: ALB 38.5 g/L (35.2–41.8 g/L), TBIL 18.2 μmol/L (13.5–24.8 μmol/L), ALT 45.0 U/L (32.0–62.0 U/L), AST 52.0 U/L (38.0–71.0 U/L), ALP 125.0 U/L (95.0–168.0 U/L), GGT 98.0 U/L (65.0–148.0 U/L), PT 13.2 s (12.5–14.1 s), INR 1.15 (1.08–1.25), PLT 142.0 $\times$ 10^9/L (108.0–185.0 $\times$ 10^9/L), WBC 5.8 $\times$ 10^9/L (4.5–7.2 $\times$ 10^9/L), NLR

Table 3. Radiologic response according to AFP dynamics in the AFP-elevated group.

Analysis group	Subgroup	CR	PR	SD	PD	ORR, n (%)	χ^2 for ORR	*p* value for ORR	DCR, n (%)	χ^2 for DCR	*p* value for DCR
AFP dynamic change at 8 weeks	AFP decline group (n = 125)	8	55	50	12	63 (50.4)	24.984	<0.001	113 (90.4)	44.540	<0.001
	AFP stable group (n = 38)	1	8	21	8	9 (23.7)			30 (78.9)		
	AFP progression group (n = 36)	0	3	11	22	3 (8.3)			14 (38.9)		
AFP sustained response	Yes (n = 65)	7	34	21	3	41 (63.1)	26.495	<0.001	62 (95.4)	15.764	<0.001
	No (n = 134)	2	32	61	39	34 (25.4)			95 (70.9)		

Notes: This table includes only patients in the AFP-elevated group (baseline AFP >20 ng/mL, n = 199). AFP sustained response was defined as an AFP decline of ≥50% from baseline at both 8 and 12 weeks after the first TACE. ORR was defined as CR + PR, and DCR was defined as CR + PR + SD. The χ^2 values and *p* values refer to comparisons of ORR and DCR among the corresponding AFP subgroups.

3.2 (2.3–4.8), PLR 128.5 (92.0–175.0) (Table 1). After eligibility screening, there were no missing data for any variables included in the final analyses; therefore, all 267 patients were included in the descriptive, survival, and regression analyses.

Treatment Status and Efficacy Evaluation

All patients received TACE combined with immunotherapy. The median number of TACE treatments was 3 (2–5), including 52 cases (19.5%) undergoing 1 treatment, 78 cases (29.2%) undergoing 2 treatments, and 137 cases (51.3%) undergoing 3 or more treatments. Immunotherapy drugs included pembrolizumab in 85 cases (31.8%), nivolumab in 72 cases (27.0%), sintilimab in 58 cases (21.7%), tislelizumab in 36 cases (13.5%), and atezolizumab in 16 cases (6.0%). The median number of immunotherapy cycles was 8 (4–14 cycles). Efficacy assessment at 8 weeks after the first TACE was as follows: CR in 12 cases (4.5%), PR in 89 cases (33.3%), SD in 118 cases (44.2%), PD in 48 cases (18.0%); ORR was 37.8% (101/267), while DCR was 82.0% (219/267). Among patients in the AFP–elevated group, radiologic response according to mRECIST differed significantly across AFP dynamic subgroups ($p < 0.001$). In the AFP decline group, 8 patients achieved CR, 55 achieved PR, 50 had SD, and 12 had PD, corresponding to an ORR of 50.4% and a DCR of 90.4%. In the AFP stable group, 1 patient achieved CR, 8 achieved PR, 21 had SD, and 8 had PD, with an ORR of 23.7% and a DCR of 78.9%. In the AFP progression group, no patient achieved CR, 3 achieved PR, 11 had SD, and 22 had PD, with an ORR of 8.3% and a DCR of 38.9%. In addition, patients with AFP sustained response showed significantly higher ORR and DCR than those without sustained response [63.1% (41/65) vs 25.4% (34/134) and 95.4% (62/65) vs 70.9% (95/134), respectively; both $p < 0.001$], indicating good concordance between favorable AFP dynamics and radiologic tumor response.

Common adverse reactions during treatment included fever in 52 cases (19.5%), fatigue in 68 cases (25.5%), nausea and vomiting in 45 cases (16.9%), and elevated transaminases in 73 cases (27.3%). Immune–related adverse reactions occurred in 32 cases (12.0%), specifically including: immune hepatitis 12 cases (4.5%), immune pneumonitis 8 cases (3.0%), thyroid dysfunction 7 cases (2.6%), rash 5 cases (1.9%), among which grade ≥3 immune–related adverse reactions occurred in 9 cases (3.4%). Other grade ≥3 adverse reactions occurred in 9 cases (3.4%), including severe transaminase elevation in 5 cases, severe nausea and vomiting in 2 cases, and severe fatigue in 2 cases. Treatment was suspended due to adverse reactions in 10 cases (3.7%), and terminated due to adverse reactions in 5 cases (1.9%), of which 7 cases were suspended, and 3 cases were terminated due to immune–related adverse reactions; 3 cases were suspended and 2 cases were terminated due to other adverse reactions. The treatment regimen was changed due to disease progression in 13 cases (4.9%). A total of 28 cases (10.5%) interrupted treatment or changed regimens, including: 5 cases terminated treatment due to adverse reactions, 13 cases changed treatment regimen due to disease progression, and 10 cases interrupted treatment for personal reasons (Table 2).

Among patients in the AFP-elevated group (n = 199), ORR and DCR differed significantly across AFP dynamic subgroups. The AFP decline group showed the highest ORR and DCR, whereas the AFP progression group had the poorest radiologic response. In addition, patients with AFP sustained response had significantly higher ORR and DCR than those without sustained response (both $p < 0.001$), indicating good concordance between favorable AFP dynamics and radiologic tumor response (Table 3).

AFP Dynamic Changes

Among the 199 patients in the AFP-elevated group, patients were classified based on AFP dynamic changes at 8 weeks after the first TACE into the AFP decline group (125 cases, 62.8%), the AFP stable group (38 cases, 19.1%), and the AFP progression group (36 cases, 18.1%). In the AFP decline group, the median AFP change rate was –58.5% (–76.2% to –35.8%); in the AFP stable group, the median change rate was –5.2% (–12.5% to 8.6%); in the AFP progression group, the median change rate was +68.5% (+35.2% to +142.8%).

At 4 weeks after the first TACE, 89 patients (44.7%) in the AFP-elevated group had an AFP decline of >20%,

Table 4. AFP dynamic changes.

AFP dynamic changes	n (%)	Median AFP change rate (%)
AFP elevated group (baseline >20 ng/mL)	199 (74.5)	
4 weeks after first TACE		–32.5 (–58.2 to +15.8)
AFP decline >20%	89 (44.7)	
AFP decline ≥50%	52 (26.1)	
8 weeks after first TACE		
AFP decline group	125 (62.8)	–58.5 (–76.2 to –35.8)
AFP stable group	38 (19.1)	–5.2 (–12.5 to 8.6)
AFP progression group	36 (18.1)	+68.5 (+35.2 to +142.8)
AFP early response (at 8 weeks)	82 (41.2)	–72.8 (–85.6 to –62.5)
AFP sustained response (at 8 and 12 weeks)	65 (32.7)	–76.5 (–88.2 to –65.8)†
AFP normal group (baseline ≤20 ng/mL)	68 (25.5)	
AFP elevation after treatment	8 (11.8)	

Notes: AFP sustained response was defined as an AFP decline ≥50% from baseline at both 8 and 12 weeks after the first TACE. †The reported AFP change rate for the AFP sustained response subgroup refers to the 12-week AFP change rate relative to baseline.

Table 5. Survival analysis of patients with different AFP groupings.

Comparison	Subgroup	Median OS (months)	Median PFS (months)	*p* for OS	*p* for PFS
Overall cohort	Total (n = 267)	18.5 (16.2–20.8)	10.2 (9.1–11.3)	—	—
AFP status	AFP normal group (n = 68)	23.8 (20.5–27.1)	12.8 (10.5–15.1)	0.002	0.011
	AFP elevated group (n = 199)	16.8 (14.5–19.1)	9.5 (8.2–10.8)		
AFP dynamic changes	AFP decline group (n = 125)	20.5 (17.8–23.2)	11.5 (10.0–13.0)	<0.001	<0.001
	AFP stable group (n = 38)	14.2 (11.5–16.9)	7.8 (6.2–9.4)		
	AFP progression group (n = 36)	8.5 (6.2–10.8)	4.2 (3.0–5.4)		
AFP early response	Yes (n = 82)	24.2 (21.0–27.4)	13.2 (11.0–15.4)	<0.001	<0.001
	No (n = 117)	14.8 (12.5–17.1)	7.8 (6.5–9.1)		
AFP sustained response	Yes (n = 65)	26.8 (23.2–30.4)	14.8 (12.5–17.1)	<0.001	<0.001
	No (n = 134)	15.5 (13.2–17.8)	8.2 (7.0–9.4)		

Notes: Data are presented as median survival time with 95% confidence interval. *p* values were calculated using the log-rank test for Kaplan–Meier survival comparisons between subgroups within each comparison category. No *p* value is presented for the overall cohort because it does not represent a between-group comparison.

OS, overall survival; PFS, progression–free survival.

and 52 patients (26.1%) achieved an AFP decline of ≥50%. The median AFP change rate at 4 weeks after the first TACE was –32.5% (–58.2% to +15.8%).

82 cases (41.2%) achieved AFP early response (AFP decline ≥50% from baseline at 8 weeks after the first TACE), of which 65 cases (32.7%) maintained AFP sustained response (maintained ≥50% decline at week 12). Among patients in the AFP normal group, 8 cases (11.8%) had AFP elevation to >20 ng/mL during treatment (Table 4).

Survival Analysis

As of May 30, 2025, the median follow–up time was 24.5 months (19.2–32.8 months). The median OS for all patients was 18.5 months (95% CI: 16.2–20.8 months), with a 12–month OS rate of 68.2%, a 24–month OS rate of 42.3%, and a 36–month OS rate of 28.5%. The median PFS was 10.2 months (95% CI: 9.1–11.3 months), with a 12–month PFS rate of 46.8% and a 24–month PFS rate of 22.5%.

158 patients (59.2%) died, including 132 cases (83.5%) from tumor–related death, 18 cases (11.4%) from liver failure, 5 cases (3.2%) from gastrointestinal bleeding, and 3 cases (1.9%) from infection.

The median OS in the AFP normal group was 23.8 months (95% CI: 20.5–27.1 months), and in the AFP elevated group was 16.8 months (95% CI: 14.5–19.1 months), with a statistically significant difference between the two groups ($p = 0.002$).

In the AFP elevated group, the median OS was 20.5 months (95% CI: 17.8–23.2 months) in the AFP decline group, 14.2 months (95% CI: 11.5–16.9 months) in the AFP stable group, and 8.5 months (95% CI: 6.2–10.8 months) in the AFP progression group, with statistically significant differences among the three groups ($p < 0.001$).

Table 6. Univariate cox regression analysis for OS.

Variable	HR	95% CI	*p* value
Age >60 years	1.08	0.78–1.49	0.645
Gender (Male vs Female)	0.92	0.61–1.38	0.685
HBV infection	1.12	0.68–1.85	0.652
Cirrhosis	1.28	0.82–2.00	0.278
Child–Pugh grade B vs A	2.38	1.68–3.37	<0.001
ECOG 2 vs 0–1	1.85	1.22–2.80	0.003
BCLC stage C vs A–B	2.82	2.05–3.88	<0.001
TNM stage III vs I–II	2.45	1.75–3.43	<0.001
Multiple tumors vs solitary	1.42	1.06–1.90	0.018
Maximum tumor diameter >7 cm	1.85	1.38–2.48	<0.001
PVTT	2.28	1.68–3.09	<0.001
Extrahepatic metastasis	2.15	1.55–2.98	<0.001
AFP >400 ng/mL	1.58	1.18–2.12	0.002
AFP dynamic changes (Progression vs Decline)	3.25	2.18–4.85	<0.001
AFP early response	0.38	0.26–0.55	<0.001
AFP sustained response	0.32	0.22–0.47	<0.001
ALB <35 g/L	1.48	1.05–2.08	0.024
TBIL >20 µmol/L	1.42	1.03–1.96	0.032
ALP >120 U/L	1.52	1.12–2.06	0.008
GGT >100 U/L	1.45	1.08–1.95	0.015
NLR >3.5	1.68	1.25–2.26	0.006
PLR >150	1.38	1.01–1.88	0.042
Number of TACE treatments ≥3	0.68	0.50–0.92	0.012

Table 7. Multivariate cox regression analysis for OS.

Variable	HR	95% CI	*p* value
BCLC stage C vs A–B	2.15	1.42–3.25	<0.001
PVTT	1.68	1.18–2.39	0.004
Extrahepatic metastasis	1.85	1.28–2.67	0.001
AFP sustained response	0.42	0.28–0.63	<0.001
NLR >3.5	1.52	1.12–2.06	0.007

Notes: All variables passed the Schoenfeld residuals test ($p > 0.05$), satisfying the proportional hazards assumption. The number of TACE treatments was not included in the multivariate model due to potential time-dependent bias.

The median OS in the AFP early response group was 24.2 months (95% CI: 21.0–27.4 months), compared to 14.8 months (95% CI: 12.5–17.1 months) in the non–early response group ($p < 0.001$). Similarly, PFS was significantly longer in the AFP early response group compared with the non–early response group (13.2 vs 7.8 months, $p < 0.001$). The median OS in the AFP sustained response group was 26.8 months (95% CI: 23.2–30.4 months), compared to 15.5 months (95% CI: 13.2–17.8 months) in the non–sustained response group ($p < 0.001$). Patients with AFP sustained response also showed significantly improved PFS compared with those without sustained response (14.8 vs 8.2 months, $p < 0.001$) (Table 5).

Univariate and Multivariate Cox Regression Analysis for OS

Univariate Cox regression analysis showed that Child–Pugh classification ($p < 0.001$), ECOG score ($p = 0.003$), BCLC stage ($p < 0.001$), TNM stage ($p < 0.001$), number of tumors ($p = 0.018$), maximum tumor diameter ($p < 0.001$), PVTT ($p < 0.001$), extrahepatic metastasis ($p < 0.001$), AFP level ($p = 0.002$), AFP dynamic changes ($p < 0.001$), AFP early response ($p < 0.001$), AFP sustained response ($p < 0.001$), ALB ($p = 0.024$), TBIL ($p = 0.032$), ALP ($p = 0.008$), GGT ($p = 0.015$), NLR ($p = 0.006$), PLR ($p = 0.042$), and number of TACE treatments ($p = 0.012$) were associated with OS.

Multivariate Cox regression analysis showed that BCLC stage C (HR = 2.15, 95% CI: 1.42–3.25, $p < 0.001$), PVTT (HR = 1.68, 95% CI: 1.18–2.39, $p = 0.004$), extrahepatic metastasis (HR = 1.85, 95% CI: 1.28–2.67, $p = 0.001$), AFP sustained response (HR = 0.42, 95% CI: 0.28–0.63, $p < 0.001$), and NLR >3.5 (HR = 1.52, 95% CI: 1.12–2.06, $p = 0.007$) were independent prognostic factors for OS. Although several variables were significantly associated with OS in the univariate analysis, only these factors remained independently significant after forward stepwise multivariable adjustment. Variables not retained in the final model lost statistical significance after adjustment, overlapped with related clinical factors, or were excluded because of potential time-dependent bias. All variables included in the multivariate analysis were verified by

Table 8. Univariate and multivariate cox regression analysis for PFS.

Variable	Univariate HR	95% CI	*p* value	Multivariate HR	95% CI	*p* value
Age >60 years	1.05	0.77–1.44	0.742	—	—	—
Gender (Male vs Female)	0.95	0.64–1.40	0.784	—	—	—
HBV infection	1.09	0.67–1.78	0.731	—	—	—
Cirrhosis	1.24	0.81–1.90	0.316	—	—	—
Child–Pugh grade B vs A	2.06	1.45–2.93	<0.001	—	—	—
ECOG 2 vs 0–1	1.68	1.14–2.49	0.008	—	—	—
BCLC stage C vs A–B	2.74	1.97–3.81	<0.001	2.28	1.58–3.29	<0.001
TNM stage III vs I–II	2.31	1.66–3.21	<0.001	—	—	—
Multiple tumors vs solitary	1.39	1.08–1.81	0.012	—	—	—
Maximum tumor diameter >7 cm	1.79	1.37–2.35	<0.001	—	—	—
PVTT	2.21	1.64–2.98	<0.001	1.85	1.32–2.59	<0.001
Extrahepatic metastasis	2.04	1.50–2.79	<0.001	2.08	1.48–2.92	<0.001
AFP >400 ng/mL	1.49	1.12–1.99	0.006	—	—	—
AFP progression	2.96	2.04–4.31	<0.001	—	—	—
AFP early response	0.41	0.29–0.58	<0.001	—	—	—
AFP sustained response	0.30	0.21–0.44	<0.001	0.35	0.24–0.51	<0.001
ALB <35 g/L	1.29	0.93–1.80	0.124	—	—	—
TBIL >20 μmol/L	1.26	0.93–1.72	0.132	—	—	—
ALP >120 U/L	1.39	1.06–1.83	0.018	—	—	—
GGT >100 U/L	1.27	0.96–1.68	0.094	—	—	—
NLR >3.5	1.43	1.07–1.91	0.015	1.68	1.25–2.26	0.001
PLR >150	1.22	0.91–1.64	0.181	—	—	—
Number of TACE treatments ≥3	0.72	0.53–0.97	0.028	—	—	—

Notes: Variables with $p < 0.10$ in univariate analysis were entered into the multivariate Cox regression model using a forward stepwise procedure. Variables not retained in the final model lost statistical significance after adjustment, overlapped with other prognostic factors, or were excluded because of potential time-dependent bias. All variables included in the multivariate model passed the Schoenfeld residuals test ($p > 0.05$), indicating that the proportional hazards assumption was satisfied.

the Schoenfeld residuals test and satisfied the proportional hazards assumption ($p > 0.05$). The detailed results of univariate and multivariate Cox regression analyses are shown in Tables 6,7, respectively.

In addition, multicollinearity diagnostics showed that the VIF values for BCLC stage, PVTT, extrahepatic metastasis, AFP sustained response, and NLR were 1.84, 1.52, 1.47, 1.21, and 1.18, respectively, indicating no significant multicollinearity among variables included in the final model.

Univariate and Multivariate Cox Regression Analysis for PFS

Univariate Cox regression analysis showed that Child–Pugh grade B ($p < 0.001$), ECOG 2 points ($p = 0.008$), BCLC stage C ($p < 0.001$), TNM stage III ($p < 0.001$), multiple tumors ($p = 0.012$), maximum tumor diameter >7 cm ($p < 0.001$), PVTT ($p < 0.001$), extrahepatic metastasis ($p < 0.001$), AFP >400 ng/mL ($p = 0.006$), AFP progression ($p < 0.001$), AFP early response ($p < 0.001$), AFP sustained response ($p < 0.001$), ALP >120 U/L ($p = 0.018$), NLR >3.5 ($p = 0.015$), and number of TACE treatments ≥3 ($p = 0.028$) were associated with PFS.

Multivariate Cox regression analysis showed that BCLC stage C (HR = 2.28, 95% CI: 1.58–3.29, $p < 0.001$), PVTT (HR = 1.85, 95% CI: 1.32–2.59, $p < 0.001$), extrahepatic metastasis (HR = 2.08, 95% CI: 1.48–2.92, $p < 0.001$), AFP sustained response (HR = 0.35, 95% CI: 0.24–0.51, $p < 0.001$), and NLR >3.5 (HR = 1.68, 95% CI: 1.25–2.26, $p = 0.001$) were independent prognostic factors for PFS. Similarly, although multiple variables were significant in the univariate analysis for PFS, only these factors remained independently significant in the final multivariate model after forward stepwise adjustment. Variables not retained in the final model did not remain independently significant after adjustment or overlapped with other prognostic factors. All variables included in multivariate analysis were verified by the Schoenfeld residuals test and satisfied the proportional hazards assumption ($p > 0.05$) (Table 8).

Relationship Between AFP Change Rate and Survival Outcomes

Among the 199 patients in the AFP-elevated group (baseline AFP >20 ng/mL), the AFP change rate at 8 weeks after the first TACE relative to baseline was used for subsequent continuous-variable analyses of survival outcomes.

Table 9. Time–dependent ROC curve analysis of predictive models.

Predictive model	AUC for 12–month OS	AUC for 24–month OS
AFP sustained response	0.685 (0.625–0.745)	0.680 (0.618–0.742)
Combined predictive model	0.782 (0.728–0.836)	0.776 (0.720–0.832)
DeLong test	Z = 4.28, $p < 0.001$	Z = 4.65, $p < 0.001$
C–index	0.748 (0.712–0.784)	
Calibration metrics		
Mean absolute error	0.042	0.038
Brier score	0.168	0.182
Calibration slope	0.96	0.94
Decision curve analysis (threshold probability 30%)		
Combined model net benefit	0.285	
AFP sustained response net benefit	0.158	

AUC, area under the curve.

Restricted cubic spline analysis showed a nonlinear relationship between AFP change rate and OS (p for nonlinearity < 0.001). Three knots were set at the 10th, 50th, and 90th percentiles, corresponding to AFP change rates of –76.8%, –28.5%, and +52.3%, respectively. Analysis results showed that the greater the AFP decline, the longer the OS. When AFP declined >50%, OS improvement was most pronounced, and the HR curve tended to plateau; when AFP increased >30%, the risk of death increased significantly (HR >2.0).

Using the same AFP-elevated cohort and the 8-week AFP change rate, the optimal cutoff value for AFP change rate to predict 12–month OS was determined to be –48.5% by a Youden index (sensitivity: 72.8%, specificity: 68.5%, Youden index: 0.413). Using this cutoff value to group patients, the median OS was 25.6 months (95% CI: 22.3–28.9 months) in the AFP decline ≥48.5% group and 14.2 months (95% CI: 12.1–16.3 months) in the AFP decline <48.5% group, with a statistically significant difference between the two groups (log–rank $p < 0.001$).

Establishment and Validation of Predictive Model

Based on multivariate Cox regression analysis results, a predictive model including BCLC stage, PVTT, extrahepatic metastasis, AFP sustained response, and NLR was established. The regression coefficients of the final model were as follows: BCLC stage C, $\beta = 0.765$; PVTT, $\beta = 0.519$; extrahepatic metastasis, $\beta = 0.615$; AFP sustained response, $\beta = -0.868$; and NLR >3.5, $\beta = 0.419$. Accordingly, the linear predictor was calculated as: risk score = 0.765 × (BCLC stage C) + 0.519 × (PVTT) + 0.615 × (extrahepatic metastasis) – 0.868 × (AFP sustained response) + 0.419 × (NLR >3.5), with each variable coded as 1 for presence and 0 for absence. Time–dependent ROC curve analysis showed that the model predicted 12–month OS with an AUC of 0.782 (95% CI: 0.728–0.836) and predicted 24–month OS with an AUC of 0.776 (95% CI: 0.720–0.832). AFP sustained response alone predicted 12–month OS with an AUC of 0.685 (95% CI: 0.625–0.745) and predicted 24–month OS with an AUC of 0.680 (95% CI: 0.618–0.742). DeLong test showed that the AUC of the combined predictive model was significantly higher than that of AFP sustained response alone (12 months: Z = 4.28, $p < 0.001$; 24 months: Z = 4.65, $p < 0.001$).

The model's Harrell's C–index was 0.748 (95% CI: 0.712–0.784). Bootstrap internal validation (1000 resamples) and calibration curves showed good agreement between predicted survival probabilities and actual observed outcomes, with a mean absolute error of 0.042 and Brier score of 0.168 for 12–month OS prediction; mean absolute error of 0.038 and Brier score of 0.182 for 24–month OS prediction. Calibration slopes were close to 1 (12 months: 0.96, 24 months: 0.94), indicating good model calibration.

Decision curve analysis showed that the combined predictive model had high clinical net benefit within the threshold probability range of 10%–70%. When the threshold probability was 30%, the net benefit of the combined model was 0.285, while the net benefit of AFP sustained response alone was 0.158, suggesting that the combined model has greater clinical utility for decision–making (Table 9).

Subgroup Analysis

In the AFP-elevated group (n = 199), subgroup analysis was performed according to BCLC stage, Child–Pugh classification, PVTT, extrahepatic metastasis, and immunotherapy drug type to evaluate the prognostic value of AFP sustained response across different subgroups. Results showed that AFP sustained response was associated with better OS in all subgroups: BCLC stage A–B (HR = 0.38, 95% CI: 0.22–0.65, $p < 0.001$), BCLC stage C (HR = 0.46, 95% CI: 0.28–0.77, $p = 0.003$); Child–Pugh grade A (HR = 0.40, 95% CI: 0.26–0.62, $p < 0.001$), grade B (HR = 0.48, 95% CI: 0.23–1.00, $p = 0.050$); without PVTT (HR = 0.38, 95% CI: 0.24–0.60, $p < 0.001$), with PVTT (HR = 0.52, 95% CI: 0.28–0.95, $p = 0.033$); without extrahepatic metastasis (HR = 0.39, 95% CI: 0.26–0.59, $p < 0.001$), with extrahepatic metastasis (HR = 0.55, 95% CI: 0.25–1.21, $p =$

Table 10. Prognostic value of AFP sustained response in different subgroups (AFP elevated group, n = 199).

Subgroup	n	HR	95% CI	*p* value
BCLC stage				
Stage A–B	112	0.38	0.22–0.65	<0.001
Stage C	87	0.46	0.28–0.77	0.003
p for interaction				0.512
Child–Pugh classification				
Grade A	156	0.4	0.26–0.62	<0.001
Grade B	43	0.48	0.23–1.00	0.05
p for interaction				0.683
PVTT				
Without	135	0.38	0.24–0.60	<0.001
With	64	0.52	0.28–0.95	0.033
p for interaction				0.358
Extrahepatic metastasis				
Without	154	0.39	0.26–0.59	<0.001
With	45	0.55	0.25–1.21	0.136
p for interaction				0.428
Immunotherapy drug				
Anti–PD–1	183	0.41	0.28–0.61	<0.001
Anti–PD–L1	16	0.52	0.18–1.52	0.228
p for interaction				0.425

Notes: Only patients in the AFP-elevated group (n = 199) were included in this analysis. AFP sustained response was defined as an AFP decline ≥50% from baseline that was maintained at both 8 weeks and 12 weeks after the first TACE.

0.136). Interaction tests showed no significant differences in the prognostic value of AFP sustained response across different BCLC stages (p for interaction = 0.512), Child–Pugh classification (p for interaction = 0.683), PVTT (p for interaction = 0.358), and extrahepatic metastasis (p for interaction = 0.428) subgroups, suggesting that the prognostic value of AFP sustained response is not affected by these clinical characteristics. The prognostic value of AFP sustained response was similar among different immunotherapy drug type subgroups (p for interaction = 0.425) (Table 10).

Sensitivity Analysis

After excluding 28 patients (10.5%) who interrupted treatment or changed regimens, AFP sustained response remained an independent prognostic factor for OS (HR = 0.40, 95% CI: 0.26–0.61, $p < 0.001$). After excluding 15 patients (5.6%) with follow–up time <3 months, the results were consistent with the overall analysis (HR = 0.41, 95% CI: 0.27–0.62, $p < 0.001$). When using different AFP change rate cutoff values to define AFP response, as the stringency of the standard increased (from 10% to 50%), the HR showed a monotonically decreasing trend, and the association strength between AFP response and OS gradually increased: 10% cutoff (HR = 0.52, 95% CI: 0.36–0.75, $p < 0.001$), 30% cutoff (HR = 0.46, 95% CI: 0.32–0.66, $p < 0.001$), 50% cutoff (HR = 0.42, 95% CI: 0.28–0.63, $p < 0.001$), consistent with the biological dose–response relationship.

To further address potential immortal time bias related to the definition of AFP sustained response at both 8 and 12 weeks, a 12–week landmark analysis was additionally performed. Only patients who were alive and progression–free at 12 weeks after the first TACE and had available AFP measurements at both 8 and 12 weeks were included in the landmark cohort. Survival time was recalculated from the 12–week landmark time point. In the landmark cohort, AFP sustained response remained significantly associated with improved survival outcomes. The landmark Cox analysis showed that AFP sustained response was still an independent protective factor for OS (HR = 0.49, 95% CI: 0.32–0.76, $p = 0.001$) and PFS (HR = 0.44, 95% CI: 0.30–0.66, $p < 0.001$), supporting the robustness of the primary findings.

Competing risk analysis was performed using the Fine–Gray model, with tumor–related death treated as the primary outcome event and non–tumor–related deaths (including liver failure, gastrointestinal bleeding, infection; a total of 26 cases, accounting for 16.5% of total deaths) as competing events. Results showed that the cumulative incidence of tumor–related death at 12 months was 18.5% (95% CI: 10.2%–28.6%) in the AFP sustained response group and 32.8% (95% CI: 22.1%–44.5%) at 24 months; in the non–sustained response group, it was 42.3% (95% CI: 34.5%–50.6%) at 12 months and 58.6% (95% CI: 50.2%–66.8%) at 24 months. The cumulative incidence of tumor–related death in the AFP sustained response group was significantly lower than that in the non–sustained response group (subdistribution HR = 0.38, 95% CI: 0.25–0.58, $p < 0.001$). There was no significant difference in the cumulative incidence of non–tumor–related death between the two groups (subdistribution HR = 0.72, 95% CI: 0.38–1.36, $p = 0.312$), indicating that AFP sustained response was primarily associated with a lower risk of tumor-related death rather than non-tumor-related death (Table 11).

Discussion

As the most commonly used serum tumor marker for HCC, dynamic changes in AFP can reflect tumor burden and treatment response in real time [17]. Previous studies mainly focused on AFP changes in TACE alone or systemic therapy. This study is the first to systematically evaluate the predictive value of AFP dynamic changes in TACE combined with immunotherapy, a novel combination regimen [18,19]. Compared with the previously reported AFP decline rate of 40–50% after TACE alone [20], 62.8% of patients in this study achieved AFP decline >20% at 8 weeks after the first TACE, and 41.2% achieved early response (decline ≥50%), suggesting that the addition of immunotherapy may be associated with greater early antitumor activity and a higher likelihood of AFP decline. This is consistent with a recent multicenter study reporting that the

Table 11. Sensitivity analysis results.

Sensitivity analysis	HR	95% CI	*p* value
Excluding patients who interrupted treatment or changed regimens (n = 239)	0.4	0.26–0.61	<0.001
Excluding patients with follow–up time <3 months (n = 252)	0.41	0.27–0.62	<0.001
AFP change rate cut-off 10%	0.52	0.36–0.75	<0.001
AFP change rate cut-off 30%	0.46	0.32–0.66	<0.001
AFP change rate cut-off 50% (original standard)	0.42	0.28–0.63	<0.001
12–week landmark analysis for OS	0.49	0.32–0.76	0.001
12–week landmark analysis for PFS	0.44	0.30–0.66	<0.001
Competing risk analysis			
Tumor–related death (primary outcome)	0.38	0.25–0.58	<0.001
Non–tumor–related death (competing event)	0.72	0.38–1.36	0.312
Cumulative incidence in AFP sustained response group			
12–month tumor–related death	18.5% (10.2%–28.6%)		
24–month tumor–related death	32.8% (22.1%–44.5%)		
Cumulative incidence in non–sustained response group			
12–month tumor–related death	42.3% (34.5%–50.6%)		
24–month tumor–related death	58.6% (50.2%–66.8%)		

Notes: Non–tumor–related deaths included 18 cases of liver failure, 5 cases of gastrointestinal bleeding, and 3 cases of infection, totaling 26 cases, accounting for 16.5% of total deaths (158 cases). For the 12–week landmark analysis, only patients who were alive and progression–free at 12 weeks after the first TACE and had AFP measurements available at both 8 and 12 weeks were included. Survival outcomes were recalculated from the 12–week landmark time point.

AFP response rate of TACE combined with immunotherapy was approximately 15–20% higher than that of TACE alone [21]. In addition, our analysis showed that favorable AFP dynamics were significantly associated with better radiologic response by mRECIST, with higher ORR and DCR observed in the AFP decline and sustained response groups, further supporting the potential utility of AFP dynamics as an early response-associated marker.

Several biological explanations may account for the observed association between AFP dynamics and treatment outcomes. TACE may reduce AFP-producing tumor burden through ischemic necrosis and local cytotoxic effects [22]. ICIs may contribute to antitumor activity by restoring antitumor immune responses [23,24]. In addition, TACE-induced tumor antigen release has been proposed as a potential mechanism that may enhance the activity of immunotherapy [22]. Our clinical findings are consistent with these proposed mechanisms, although the present study was not designed to directly investigate the underlying mechanisms.

This study used restricted cubic spline analysis to reveal the nonlinear relationship between AFP change rate and OS, showing that OS improvement was most significant when AFP declined by >50%, while the risk of death increased significantly when AFP increased by >30%. This finding is similar to research results in the field of targeted therapy. A previous study reported that an AFP decline of >50% during sorafenib treatment was associated with better survival outcomes [25]. However, this study further clarified the importance of "sustained response", namely that patients who maintained AFP decline ≥50% at both 8 weeks and 12 weeks had the best prognosis (median OS 26.8 months), emphasizing the necessity of dynamic monitoring [26]. This may be because AFP decline at a single time point may be affected by detection errors, tumor heterogeneity, or temporary treatment effects, while sustained response may better capture persistent treatment-associated tumor control [27]. Notably, the predefined ≥50% AFP decline threshold was highly consistent with the Youden–derived optimal cutoff of –48.5% identified in our analysis, supporting the clinical and statistical validity of this response definition.

Notably, 25.5% of patients in this study had normal baseline AFP (≤20 ng/mL), and this group had a median OS of 23.8 months, superior to the AFP-elevated group. This suggests that AFP–negative HCC may have different biological behaviors, possibly related to differences in tumor differentiation, gene mutation spectrum, or immune microenvironment [28]. For AFP–negative patients, imaging evaluation remains the primary method for monitoring efficacy, whereas the value of other potential markers such as des–gamma–carboxy prothrombin (DCP), Golgi protein 73 (GP73), or circulating tumor deoxyribonucleic acid (DNA) warrants further exploration [29].

The combined predictive model established in this study integrates five independent prognostic factors: BCLC stage, PVTT, extrahepatic metastasis, AFP sustained response, and NLR. The AUCs for predicting 12–month and 24–month OS were 0.782 and 0.776, respectively, significantly superior to AFP sustained response alone. This is consistent with a previous study emphasizing the importance of comprehensive prognostic assessment [30]. NLR,

as a marker of systemic inflammatory response, is associated with tumor progression and immunosuppressive microenvironment when elevated, and has been shown to have prognostic value in various malignancies [31]. In this study, NLR >3.5 was an independent risk factor for OS and PFS, suggesting that inflammatory status may affect immunotherapy efficacy [32]. To improve transparency and clinical utility, we additionally reported the full regression coefficients and the corresponding risk score formula of the final model, which may facilitate individualized risk estimation in routine practice.

Subgroup analysis showed that the prognostic value of AFP sustained response was consistent across different BCLC stages, Child–Pugh classifications, PVTT, and extrahepatic metastasis status, with no significant interactions, supporting its robustness and broad applicability as a predictive biomarker [33]. This finding has important clinical implications, suggesting that dynamic AFP monitoring may aid patient stratification across different clinical contexts. However, in the extrahepatic metastasis subgroup, the prognostic value of AFP sustained response appeared less pronounced and did not reach statistical significance. This may be partly attributable to the relatively small sample size of this subgroup and to the more complex patterns of disease progression observed in patients with extrahepatic metastasis [34].

This study used 8 weeks after the first TACE as the primary assessment time point for AFP dynamic changes based on the following considerations: first, tumor response to treatment is generally established by 8 weeks, and AFP levels tend to stabilize by this timepoint; second, this time point is synchronized with the first imaging efficacy assessment, facilitating clinical implementation; third, this time point precedes the traditional 12–week assessment, which may enable earlier identification of patients with treatment failure [35]. In this study, 44.7% of patients showed AFP decline >20% at 4 weeks post–procedure, suggesting that earlier AFP monitoring may have predictive value, but these potential benefits should be balanced against detection costs and clinical utility.

From a clinical application perspective, AFP dynamic monitoring has the advantages of being non–invasive, convenient, and repeatable, and can serve as an important complement to imaging assessment [36]. For patients with AFP sustained response, continued benefit from the current regimen may be more likely, whereas patients with AFP progression or stable AFP levels may warrant closer monitoring and further clinical evaluation. Whether AFP dynamics should be used to guide treatment modification requires prospective validation. The decision curve analysis of this study showed that the combined predictive model had high clinical net benefit within the threshold probability range of 10%–70%, supporting its value in clinical decision–making [37].

This study has certain limitations. First, as a single–center retrospective study, there may be selection bias and information bias; second, the follow–up time is relatively short (median 24.5 months), and long–term survival data require further follow–up; third, other emerging biomarkers such as circulating tumor DNA or tumor–infiltrating lymphocytes were not included for combined analysis; fourth, there may be differences in efficacy among different immunotherapy drugs, and the sample size of this study limited the statistical power of subgroup analyses. In addition, because the AFP sustained response was defined based on AFP measurements at both 8 and 12 weeks, potential immortal time bias could not be completely excluded; therefore, a 12–week landmark analysis was performed in the sensitivity analysis, and the results remained consistent with the primary findings. Although model performance was evaluated using multiple complementary metrics, including time–dependent ROC analysis, DeLong test, Harrell's C–index, calibration, and decision curve analysis, additional indices, such as net reclassification improvement and integrated discrimination improvement, were not assessed in the current study and should be considered in future validation analyses. Future multicenter prospective studies are needed to validate the predictive value of AFP dynamic changes and explore their combined application with other biomarkers to establish a more precise prognostic assessment system.

This study systematically evaluated the predictive value of serum AFP dynamic changes in HCC patients treated with TACE combined with immunotherapy. Results showed that AFP sustained response (AFP decline ≥50% from baseline continuously at 8 weeks and 12 weeks after the first TACE) is an independent prognostic factor for OS and PFS. The median OS in the AFP sustained response group yielded 26.8 months, significantly superior to 15.5 months in the non–sustained response group. This finding suggests that AFP sustained response may be a simple and practical prognostic marker for clinical risk stratification, although its role in treatment decision-making requires further prospective validation.

Conclusion

Serum AFP sustained response after TACE combined with immunotherapy is significantly associated with improved survival outcomes in hepatocellular carcinoma. Dynamic monitoring of AFP may serve as a convenient and clinically meaningful biomarker for treatment evaluation and prognostic stratification.

Availability of Data and Materials

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

Author Contributions

CYX and SZ contributed equally to this work. CYX, SZ, and MX designed the research study. CYX, SZ, BC, WJ, and JY collected and organized the clinical data. JL, CD, and SMZ contributed to data verification, literature review, and statistical analysis. CYX and SZ drafted the manuscript. BC, WJ, JY, JL, CD, SMZ, and MX contributed to critical revision of the manuscript for important intellectual content. MX supervised the study. All authors gave final approval of the version to be published. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work in accordance with the ICMJE authorship criteria.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Medical Ethics Committee of the Second Hospital of Nanjing (Approval No. 2021-LY-kt064). Because of the retrospective nature of the study, the requirement for written informed consent was waived by the ethics committee.

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Conflict of Interest

The authors declare no conflict of interest.

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