Journal of Hepatocellular Carcinoma

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Early PIVKA-II Response Associated with Treatment Efficacy and Survival Outcomes for Patients with Advanced Hepatocellular Carcinoma Receiving Immune Checkpoint Inhibitors and Targeted Therapy

Zheng-Kang Fang[1,2], Yu-Ting Xiao[1], Xia Feng[1], Zhe-Jin Shi[1,3], Si-Yu Liu[4], Yang Yu[5], Li-Ming Jin[1], Dong-Sheng Huang[1], Cheng-Wu Zhang[1], Jun-Wei Liu[1], Lei Liang[1]

[1]Department of General Surgery, Cancer Center, Hepatobiliary & Pancreatic Surgery and Minimally Invasive Surgery, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou, Zhejiang, People's Republic of China; [2]Department of Postgraduate Training Base Alliance, Wenzhou Medical University, Wenzhou, Zhejiang, People's Republic of China; [3]Department of the second School of Clinical Medicine, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, People's Republic of China; [4]Department of Laboratory Medicine, the Key Laboratory of Imaging Diagnosis and Minimally Invasive Interventional Research of Zhejiang Province, Zhejiang University Lishui Hospital, Lishui, Zhejiang, People's Republic of China; [5]Department of Urology, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, People's Republic of China

Correspondence: Lei Liang, Department of General Surgery, Cancer Center, Hepatobiliary and Pancreatic Surgery and Minimal Invasive Surgery, Zhejiang Provincial People's Hospital, Affiliated People's Hospital, Hangzhou Medical College, Hangzhou, Zhejiang, 310014, People's Republic of China, Email liangl1992@hotmail.com; Jun-Wei Liu, Email liujunwei@hmc.edu.cn

Background & Aims: Prothrombin induced by vitamin K absence-II (PIVKA-II) levels have been reported to correlate with hepatocellular carcinoma (HCC) prognosis, but its utility for assessing early treatment response remains underexplored. This study evaluated early PIVKA-II changes for predicting response and survival in HCC patients undergoing immune checkpoint inhibitors (ICIs) and targeted therapy.

Methods: Eighty-two HCC patients were enrolled. Serum PIVKA-II levels were measured at baseline and after the first treatment cycle. Patients were stratified based on early PIVKA-II dynamics into a biochemical response group (≥50% reduction, n=40) and a non-response group (<50% reduction, n=42). Logistic regression and Cox proportional hazards models were used to identify predictors of objective response rate (ORR), progression-free survival (PFS), and overall survival (OS).

Results: Time-dependent ROC analysis established ≥50% PIVKA-II decline as the early response threshold. The PIVKA-II response group had a significantly higher proportion of patients with Child-Pugh A, a lower incidence of extrahepatic metastasis, and significantly higher ORR (82.5% vs 38.1%, P<0.001). Median PFS and OS were not reached in the PIVKA-II responder group, compared to 8.9 months and 16.7 months, respectively, in the non-responder group (both P < 0.001). Multivariate analysis confirmed early PIVKA-II response as an independent predictor of PFS (HR=0.687, P<0.001) and OS (HR=0.709, P<0.001). Notably, in AFP-negative patients, an early PIVKA-II response was predictive of ORR and was associated with significantly longer PFS and OS.

Conclusion: Early PIVKA-II response effectively predicts treatment response and prognosis in advanced HCC patients receiving ICI and targeted therapy, especially in AFP-negative patients.

Keywords: hepatocellular carcinoma, PIVKA-II, target therapy, immune checkpoint inhibitors, objective response rate

Introduction

Hepatocellular carcinoma (HCC) represents the third leading cause of cancer-related deaths worldwide, with an estimated 900,000 new cases annually.[1] Although current surveillance strategies are widely implemented, over half of HCC cases present with advanced-stage disease at diagnosis, exhibiting a median overall survival (OS) under 12 months in the

Received: 2 August 2025
Accepted: 30 September 2025
Published: 2 October 2025

absence of treatment.[2] Currently, the treatment of advanced HCC has evolved into a comprehensive therapeutic system primarily consisting of targeted therapy, immunotherapy, and local interventional therapy.[3] Targeted agents exert antitumor effects by inhibiting key signaling pathways, including vascular endothelial growth factor receptor. However, monotherapy demonstrates only a 10%-20% objective response rate (ORR) and frequently encounters acquired resistance issues.[4] Immune checkpoint inhibitors (ICIs) activate T-cell immune responses through PD-1/PD-L1 pathway blockade, yet their single-agent ORR remains at 15%-20%.[5]

In recent years, combination ICIs and targeted therapy have emerged as the first-line standard treatment for advanced HCC. The latest IMbrave150 study data revealed that the atezolizumab plus bevacizumab regimen achieved a median OS of 21.1 months (95% CI: 18.0–24), median progression-free survival (PFS) of 7.1 months (95% CI: 6.1–9.6), and improved ORR to 34%.[6] Regarding local therapies, interventional approaches such as transarterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC) maintain significant therapeutic value for advanced patients with preserved liver function.[7,8] Recent clinical data reveal that HAIC combined with targeted immunotherapy achieves remarkable short-term efficacy, with ORR and disease control rate (DCR) reaching 70.4% and 88.9% respectively, while the 6-, 12-, and 18-month overall survival rates were 100%, 88.2%, and 76.4% respectively.[9,10] Additionally, real-world studies of TACE-HAIC combined with tyrosine kinase inhibitors and PD-1 inhibitors also reported encouraging outcomes, with ORR and DCR reaching 67.7% and 90.3% respectively. The overall median OS was 18.2 months (95% CI 16.24–20.16), and median PFS was 9.2 months (95% CI 7.24–11.16).[11] Although comprehensive treatment strategies have significantly improved outcomes for advanced HCC patients, critical challenges, including interpatient response heterogeneity and secondary resistance, remain major clinical obstacles.[12] Consequently, developing more precise efficacy-predictive biomarkers to guide clinical decision-making and exploring more effective therapeutic strategies to extend survival in advanced HCC patients have become key research priorities.

Alpha-fetoprotein (AFP), as one of the earliest discovered and most widely used biomarkers, holds significant value in clinical practice. Previous studies have demonstrated that baseline AFP levels and post-treatment serum AFP decline correlate with tumor response in HCC patients undergoing various systemic therapies.[13,14] However, clinical practice has revealed that approximately 40% of HCC patients exhibit AFP-negative expression, a limitation that has prompted researchers to actively explore more reliable alternative or complementary biomarkers. Protein induced by vitamin K absence or antagonist-II (PIVKA-II) has emerged as a novel serum biomarker for HCC, demonstrating unique predictive value in recent clinical studies.[15] Its biological basis is closely associated with abnormalities in the coagulation cascade, where the deficiency of gamma-carboxylated glutamic acid domains leads to the production of abnormal prothrombin.[16] This molecular process is linked to malignant phenotypes such as tumor angiogenesis and cellular proliferation. Multiple cohort studies demonstrated that elevated PIVKA-II levels showed a significant positive correlation with tumor aggressiveness, with high-level groups exhibiting higher rates of microvascular invasion and poorer clinical outcomes.[17] Moreover, its concentration increases exponentially with tumor stage progression, reaching 92% sensitivity for advanced HCC cases, whereas AFP showed only 58% sensitivity in such cases.[18] Notably, existing research predominantly focuses on the prognostic value of PIVKA-II expression levels in HCC patients, while limited studies investigate its role in predicting therapeutic response through longitudinal monitoring following systemic treatments. Furthermore, the exclusion of AFP-negative patients in most studies may introduce selection bias, potentially leading to systematic underestimation of PIVKA-II's biological significance in this subgroup.

Therefore, this study aims to comprehensively analyze the predictive role of early-phase PIVKA-II level changes in patients with advanced HCC undergoing combined ICIs and targeted therapy, to improve the accuracy of treatment efficacy evaluation and prognosis prediction, thereby facilitating the development of personalized treatment strategies.

Methods

Patients

A retrospective analysis of patients with advanced HCC who received combination therapy with ICIs and targeted agents at Zhejiang Provincial People's Hospital between July 2020 and May 2024. Inclusion criteria: (1) age ≥ 18 years at diagnosis, (2) Eastern Cooperative Oncology Group performance status (ECGO PS) score 0–1, (3) HCC diagnosis

confirmed by NCCN guidelines, (4) Barcelona Clinic Liver Cancer (BCLC) stage B or C, (5) presence of ≥ 1 measurable intrahepatic target lesion on contrast-enhanced computerized tomography (CT) or magnetic resonance imaging (MRI), (6) completion of ≥ 4 cycle of ICIs and targeted therapy. Exclusion criteria: (1) No baseline or post-treatment PIVKA-II values were obtained, (2) history of other active malignancies within 5 years, (3) Child-Pugh grade C, (4) current use of therapeutic anticoagulation, (5) with obstructive jaundice, (6) incomplete clinical or follow-up data.

Treatment Protocols

In this study, all patients received ICIs and targeted therapy. Among them, sorafenib was administered orally at 400 mg per day based on body weight, lenvatinib at 8 or 12 mg per day, and sintilimab or tislelizumab at fixed doses of 200 mg. Moreover, atezolizumab (1200 mg) combined with bevacizumab (15 mg/kg body weight) was administered in 3-week cycles. TACE was performed using the Seldinger technique. A chemotherapeutic emulsion consisting of epirubicin (10 mg/m^2), cisplatin (100 mg/m^2), and lipiodol (2–5 mL) was infused into tumor-feeding arteries, followed by additional pure lipiodol (up to 20 mL) to achieve embolization.[19] TACE is typically administered 1 to 2 times, with an interval of 3 to 4 weeks between treatments. For HAIC, the FOLFOX regimen was utilized, consisting of oxaliplatin (130 mg/m^2, 2-hour infusion), leucovorin (200 mg/m^2, 2-hour infusion), followed by 5-fluorouracil (400 mg/m^2 bolus + 2400 mg/m^2 continuous infusion over 46–48 hours). HAIC is generally performed 2–4 times, with an interval of 3 weeks between each session. The selection of targeted agents and immunotherapeutic regimens was individualized based on patients' financial status, physical condition, and clinicians' judgment.

Patients Follow-up

The patient's baseline data include: age at diagnosis, sex, hepatitis B virus (HBV) infection status, ECOG PS, Child-Pugh grade, albumin-bilirubin (ALBI) grade,[20] neutrophil/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR), liver cirrhosis, BCLC stage, macrovascular invasion, extrahepatic metastasis, with TACE, with HAIC, AFP reduction, PIVKA-II reduction, baseline AFP and PIVKA-II levels. Based on the previous related research-defined cut-off value, the independent variable was categorized as a binary variable.[18,21–23] All data were collected from the medical record system and followed up via telephone or outpatient visits.

Treatment efficacy was evaluated after 4 treatment cycles following initiation of ICIs combined with targeted therapy. Tumor progression and new lesion development were monitored through contrast-enhanced abdominal CT or MRI scans performed cyclically. Serum PIVKA-II levels were measured at two predefined time points: (1) baseline assessment (obtained within 7 days before treatment initiation); (2) post-treatment assessment (collected at 3–4 weeks after the first treatment). Prior studies established that a ≥ 50% decrease in post-treatment serum PIVKA-II levels relative to baseline serves as the cutoff threshold.[22] Accordingly, this study defined early PIVKA-II response as a ≥50% reduction in serum PIVKA-II levels compared to baseline levels after the first cycle (3–4 weeks) of ICIs combined with targeted therapy.

Outcome Assessment

Tumor response was assessed and collected after 4 cycles using the Modified Response Evaluation Criteria in Solid Tumors (mRECIST). Complete response (CR) was defined as the absence of intra-tumoral arterial enhancement in all target lesions. Partial response (PR) was defined as a reduction of ≥ 30% in the sum of the longest diameters of arterial-enhancing target lesions compared to baseline. Progressive disease (PD) was defined as an increase of ≥ 20% in the longest diameters of target lesions or the appearance of new lesions. Stable disease (SD) was defined as neither reaching the required reduction for PR nor attaining the necessary progression for PD.[24] ORR was defined as the proportion of HCC patients demonstrating either CR or PR. PFS was calculated from treatment initiation until radiologically confirmed disease progression, death, or last documented follow-up. OS was measured from treatment commencement to death from any cause or final follow-up assessment.

Statistical Analysis

Continuous variables were presented as medians (with ranges), while categorical variables were described in terms of counts (and proportions). The chi-square test and Fisher's exact test were used to compare categorical variables between

groups, and the correlation between early PIVKA-II response and ORR was analyzed. Potential predictors of ORR were screened using logistic regression analysis. PFS and OS were analyzed using Kaplan-Meier curves and Log rank tests, with hazard ratios (HR) calculated via the Cox proportional hazards model. Clinically significant factors identified in univariate analysis ($P < 0.1$) were further subjected to multivariate analysis. In the AFP-negative subgroup at baseline, we evaluated the diagnostic performance of PIVKA-II using receiver operating characteristic (ROC) curve analysis, calculating the area under the curve (AUC) and determining the optimal cut-off value, while reporting sensitivity and specificity. Additionally, PFS and OS were compared using Kaplan-Meier survival curves and Log rank tests. $P < 0.05$ was set as statistical significance. Data processing and statistical analysis were both conducted using IBM SPSS 27.0 and R version 4.3.0 software.

Results

Clinical Characteristics

A total of 82 eligible patients with advanced HCC, with baseline characteristics detailed in Table 1. The median age of the cohort was 60 years (range: 27–91), with a male predominance (87.8%). The distribution of targeted therapies was as

Table 1 Baseline Characteristics of Patients with Advanced Hepatocellular Carcinoma Receiving Combined Immune Checkpoint Inhibitors and Targeted Therapy

Variables (n, %)	All Patients (n =82)	Early PIVKA-II Non-Response (n =42)	Early PIVKA-II Response (n =40)	P
Sex, male	72 (87.8)	39 (92.8)	33 (82.5)	0.273
Age, ≥ 50 years	72 (87.8)	36 (85.7)	36 (90.0)	0.799
Hepatitis, HBV	62 (75.6)	33 (78.6)	29 (72.5)	0.522
PS, 0	48 (58.5)	25 (59.5)	23 (57.4)	0.852
Child-Pugh, A	59 (71.9)	23 (54.8)	36 (90.0)	< 0.001
ALBI grade				
1	24 (29.2)	5 (11.9)	19 (47.5)	< 0.001
≥ 2	58 (70.7)	37 (88.1)	21 (52.5)	
NLR, ≥ 2.96	41 (50.0)	26 (61.9)	15 (37.5)	0.027
LMR, < 4.4	66 (80.4)	37 (88.1)	29 (72.5)	0.075
Cirrhosis, with	62 (75.6)	34 (80.1)	28 (70.0)	0.248
Baseline AFP levels, ≥ 400ng/mL	34 (41.4)	23 (54.8)	11 (27.5)	0.012
Baseline PIVKA-II levels, ≥ 400mAU/mL	59 (71.9)	33 (78.6)	26 (65.0)	0.171
BCLC				
B stage	23 (28.1)	5 (11.9)	18 (45.0)	< 0.001
C stage	59 (71.9)	37 (88.1)	22 (55.0)	
Extrahepatic metastasis, yes	39 (47.5)	28 (66.7)	11 (27.5)	< 0.001
Macrovascular invasion, yes	48 (58.5)	29 (69.0)	19 (47.5)	0.048
TACE, with	49 (59.8)	29 (69.0)	20 (50.0)	0.079
HAIC, with	27 (32.9)	10 (23.8)	17 (42.5)	0.072
AFP reduction, ≥ 50%	30 (36.5)	10 (23.8)	20 (50.0)	0.014
Target type				0.902
Sorafenib	6 (7.2)	3 (7.1)	3 (7.3)	
Lenvatinib	56 (68.7)	28 (66.7)	28 (70.7)	
Bevacizumab	20 (24.1)	11 (26.2)	9 (22.0)	
ICIs type				0.944
Tislelizumab	43 (51.8)	22 (51.2)	21 (52.5)	
Sintilimab	20 (24.1)	10 (23.3)	10 (25.0)	
Atezolizumab	20 (24.1)	11 (25.6)	9 (22.5)	

Abbreviations: PIVKA-II, prothrombin induced by vitamin K absence-II; ICIs, immune checkpoint inhibitors; AFP, alpha-fetoprotein; ECGO PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; ALBI, albumin- bilirubin; NLR, neutrophil/lymphocyte ratio; LMR, lymphocyte/monocyte ratio; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy.

follows: lenvatinib (68.7%), bevacizumab (24.1%), and sorafenib (7.2%). Immunotherapy regimens included tislelizumab (51.8%), sintilimab (24.1%), and atezolizumab (24.1%). The median baseline levels of AFP and PIVKA-II were 128.9 ng/mL and 3019.9 mAU/mL, respectively. Based on the predefined criteria for early PIVKA-II response, patients were stratified into non-responder (n=42) and responder (n=40) groups. The responder group exhibited better liver function reserve, with a significantly higher proportion of Child-Pugh grade A (90.0% vs 54.8%, $P < 0.001$) and ALBI grade 1 (47.5% vs 11.9%, $P < 0.001$). Notably, the responder group had a significantly higher proportion of patients with ≥50% AFP decline (50.0% vs 23.8%, $P = 0.014$), suggesting a potential biological link between PIVKA-II response and AFP dynamics. In contrast, the non-responder group displayed more aggressive tumor features: a higher rate of extrahepatic metastasis (66.7% vs 27.5%, $P < 0.001$), vascular invasion (69.0% vs 47.5%, $P = 0.048$). This group also had a significantly higher proportion of patients with baseline AFP ≥400 ng/mL (54.8% vs 27.5%, $P = 0.012$) and NLR ≥2.96 (61.9% vs 37.5%, $P = 0.027$). Importantly, the responder group had a significantly lower proportion of BCLC C stage patients (55.0% vs 88.1%, $P < 0.001$), which may be the primary driver of differences in tumor stage-related variables between the two groups. However, no significant differences were observed in age, sex distribution, ECOG performance status, HBV infection rate, or cirrhosis, suggesting that PIVKA-II response differences may primarily be associated with tumor biological behavior and disease progression.

Tumor Response

According to mRECIST criteria, 3 patients (3.7%) achieved CR, 46 patients (56.0%) achieved PR, while SD and PD were observed in 24 patients (29.3%) and 9 patients (11.0%), respectively. Following combination therapy, the ORR was achieved in 59.8% patients, while the disease control rate (DCR) was observed in 89.0% patients. Of particular significance, curative-intent hepatectomy was successfully performed in 19 patients, resulting in a surgical conversion rate of 23.1%. The distribution of changes in intrahepatic target lesions relative to baseline is depicted in Table 2. The results showed that the response group exhibited significantly higher rates of tumor PR and SD than the non-response group, while a higher PD rate was observed in the non-response group. Additionally, the early PIVKA-II responder group achieved an ORR of 82.5%, while the non-response group showed a significantly lower ORR of only 38.1% ($P < 0.001$). Similar results were observed for DCR (97.5% vs 81.0%, $P = 0.041$).

Defining the Cut-off Value for Early PIVKA-II Response

The ROC curve analysis was used to determine the optimal cut-off values for predicting treatment responses. For predicting ORR, a PIVKA-II reduction of ≥54.3% showed an AUC of 0.81 (95% CI 0.756–0.892) with sensitivity of 0.63 and specificity of 0.88. Similarly, a PIVKA-II reduction of ≥52.3% demonstrated predictive value for DCR (AUC = 0.74 (95% CI 0.701–0.797), with sensitivity of 0.61 and specificity of 0.84. Based on these consistent thresholds around a 50% reduction, this study adopted a PIVKA-II level reduction of ≥50% to define early PIVKA-II response.

Table 2 The Distribution of Tumor Response

Variables (N, %)	All (N=82)	Early PIVKA-II Non-Response (N=42)	Early PIVKA-II Response (N=40)	P
CR	3 (3.7)	0 (0.0)	3 (7.5)	0.112
PR	46 (56.0)	16 (38.1)	30 (75.0)	0.001
SD	24 (29.3)	18 (42.9)	6 (15.0)	0.007
PD	9 (11.0)	8 (19.0)	1 (2.5)	0.030
ORR (CR+PR)	49 (59.8)	16 (38.1)	33 (82.5)	< 0.001
DCR (CR+PR+SD)	73 (89.0)	34 (81.0)	39 (97.5)	0.041

Abbreviations: PIVKA-II, prothrombin induced by vitamin K absence-II; ORR, objective response rate; DCR disease control rate; CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease.

Association of Early PIVKA-II Response with ORR

Univariate logistic regression analysis revealed that Child-Pugh class B (P < 0.001), extrahepatic metastasis, BCLC stage C, ≥50% reduction in AFP levels, and early PIVKA-II response were significantly associated with the ORR. Multivariate analysis confirmed that ≥ 50% reduction in AFP levels (OR = 0.817, 95% CI 0.255–0.851, P = 0.020), and early PIVKA-II response (OR=0.739, 95% CI 0.236–0.863, P = 0.021) were independent predictors of treatment response (Table 3).

Association of Early PIVKA-II Response with Survival Outcomes

The median follow-up duration was 18.9 months (range: 5.3–54.9 months). By the end of follow-up, 7 patients (17.5%) in the early PIVKA-II responder group and 23 patients (54.7%) in the non-response group had died. Kaplan-Meier analysis demonstrated significantly prolonged PFS in response compared to non-response group (median not reached vs 8.9 months, P < 0.001) (Figure 1a). Similarly, the response group showed significantly superior OS benefit versus non-response group (median not reached vs 16.7 months, P < 0.001) (Figure 1b). Univariate and multivariate Cox regression analysis confirmed Early PIVKA-II response as the independent predictors of PFS (HR = 0.687, 95% CI 0.226–0.884, P < 0.001) (Table 4). Accordingly, the results also confirmed Early PIVKA-II response as the independent predictor of OS (HR = 0.709, 95% CI 0.224–0.869, P < 0.001) (Table 5).

Subgroup Analysis of AFP-Negative Patients

To further evaluate the predictive value of early PIVKA-II response, the AFP-negative cohort was stratified into response (n = 19) and non-response (n = 11) groups. Fisher's exact test revealed significantly higher ORR in the response group compared to the non-response group (79.0% vs 27.3%, P = 0.009). Notably, the response group had an obviously higher DCR than the non-response group, although no statistical significance was observed (94.7% vs 72.1%, P = 0.126). Then, the ROC analysis demonstrated that early PIVKA-II response had superior predictive power for ORR than AFP (AUC = 0.751, 95% CI 0.605–0.811, sensitivity = 0.830, specificity = 0.670, P = 0.022). Kaplan-Meier analysis showed significantly prolonged PFS in the response versus the non-response group (median not reached vs 9.4 months, P < 0.001) (Figure 2a). Similarly, the responder group exhibited significantly better OS outcomes (median not reached vs

Table 3 Univariate and Multivariate Logistic Regression Analysis of Risk Factors for Objective Response Rate

Variables (N, %)	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P	OR (95% CI)	P
Sex, male vs female	0.331 (0.066–1.668)	0.180		
Age, ≥50 vs < 50 years	1.571 (0.417–5.924)	0.504		
Hepatitis, HBV vs others	0.941 (0.370–2.392)	0.899		
PS, 0 vs 1	1.154 (0.470–2.834)	0.755		
Child-Pugh, B vs A	0.383 (0.133–1.103)	0.175		
ALBI grade, ≥ 2 vs 1	1.177 (1.062–2.507)	0.017	NS	
NLR, ≥ 2.96 vs <2.96	0.488 (0.198–1.198)	0.117		
LMR, <4.4 vs ≥4.4	0.425 (0.124–1.457)	0.174		
Cirrhosis, with vs without	0.941 (0.370–2.392)	0.899		
Baseline AFP levels, ≥400 vs < 400 ng/mL	0.515 (0.208–1.276)	0.152		
Baseline PIVKA-II levels, ≥400 vs <400 mAU/mL	0.418 (0.145–1.210)	0.108		
BCLC, C vs B stage	1.308 (1.101–1.938)	0.038	1.085 (1.017–1.774)	0.035
TACE/HAIC, with vs without	0.870 (0.379–0.978)	0.041	0.781 (0.412–0.951)	0.047
AFP reduction, ≥50% vs <50%	0.933 (0.234–0.928)	0.002	0.817 (0.255–0.851)	0.020
PIVKA-II reduction, ≥50% vs <50%	0.821 (0.145–0.896)	< 0.001	0.739 (0.236–0.863)	0.021

Abbreviations: PIVKA-II, prothrombin induced by vitamin K absence-II; ICIs, immune checkpoint inhibitors; AFP, alpha-fetoprotein; ECGO PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; ALBI, albumin- bilirubin; NLR, neutrophil/lymphocyte ratio; LMR, lymphocyte/monocyte ratio; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; OR, odds ratio; NS, no significance.

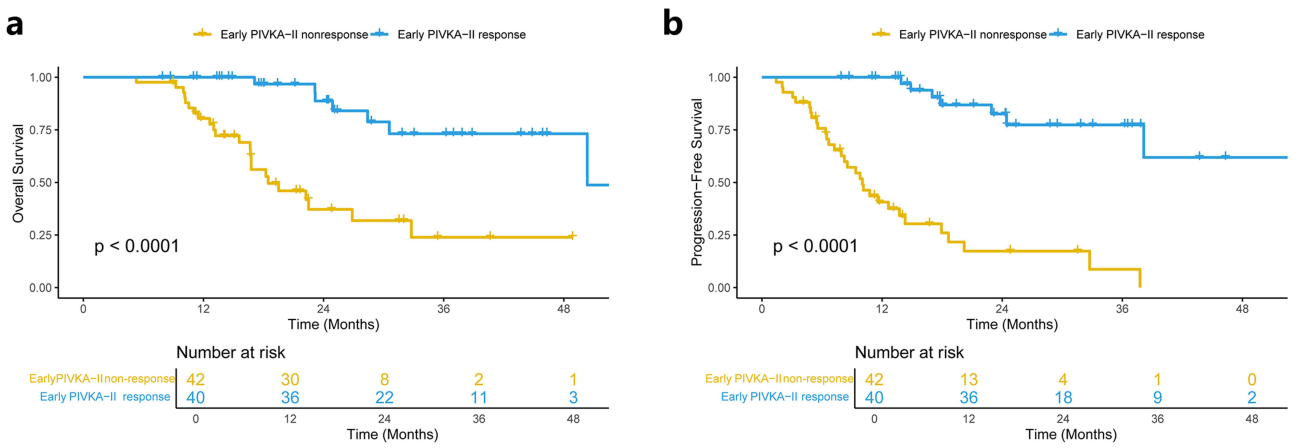

Figure 1 The K-M curves comparisons of overall survival and progression-free survival between patients with early PIVKA-II response and non-response. (**A**) Overall survival, (**B**) Progression-free survival. PIVKA-II, prothrombin induced by vitamin K absence-II.

18.5 months, P < 0.001) (Figure 2b). These findings confirm that early PIVKA-II response maintains significant correlations with ORR, PFS, and OS in the AFP-negative cohort.

Discussion

In recent years, with advances in targeted therapy and immunotherapy, the treatment paradigm for advanced HCC has undergone a revolutionary transformation. Combination therapies represented by immune checkpoint ICIs plus anti-angiogenic targeted agents have become the new standard of care for first-line treatment of advanced HCC, significantly improving patient survival outcomes.[25] However, two major challenges persist in clinical practice: significant heterogeneity in treatment response among patients and the inevitable development of secondary resistance during therapy. Serum tumor biomarkers play a crucial role in the HCC diagnostic and monitoring system.[16] Among them, AFP, the most widely used biomarker, has been well-validated for its correlation with treatment efficacy prediction and long-term

Table 4 Univariate and Multivariate Cox-Regression Analysis of Progression-Free Survival

Variables (N, %)	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P	HR (95% CI)	P
Sex, male vs female years	1.756 (0.540–5.716)	0.053	NS	
Age, ≥50 vs < 50	0.662 (0.276–1.589)	0.356		
Hepatitis, HBV vs others	0.908 (0.456–1.808)	0.784		
PS, 0 vs 1	0.825 (0.432–1.574)	0.559		
Child-Pugh, B vs A	1.417 (1.060–2.636)	0.005	NS	
ALBI grade, ≥ 2 vs 1	3.122 (1.807–4.518)	0.002	1.296 (1.065–2.152)	0.035
NLR, ≥ 2.96 vs <2.96	2.075 (1.061–4.060)	0.033	NS	
LMR, <4.4 vs ≥4.4	2.123 (0.826–5.452)	0.118		
Cirrhosis, with vs without	0.908 (0.456–1.808)	0.784		
Baseline AFP levels, ≥400 vs < 400 ng/mL	1.700 (0.883–3.272)	0.112		
Baseline PIVKA-II levels, ≥400 vs <400 mAU/mL	1.564 (0.716–3.414)	0.262		
BCLC, C vs B stage	2.807 (1.162–6.779)	0.022	1.160 (1.030–1.855)	0.032
TACE/HAIC, with vs without	0.641 (0.335–1.229)	0.081	0.879 (0.354–0.929)	0.043
AFP reduction, ≥50% vs <50%	0.901 (0.328–0.961)	0.003	0.842 (0.393–0.929)	0.004
PIVKA-II reduction, ≥50% vs <50%	0.784 (0.134–0.905)	< 0.001	0.687 (0.226–0.884)	< 0.001

Abbreviations: PIVKA-II, prothrombin induced by vitamin K absence-II; ICIs, immune checkpoint inhibitors; AFP, alpha-fetoprotein; ECGO PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; ALBI, albumin- bilirubin; NLR, neutrophil/lymphocyte ratio; LMR, lymphocyte/monocyte ratio; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; HR, hazard ratio; NS, no significance.

https://doi.org/10.2147/JHC.S552528

Table 5 Univariate and Multivariate Cox-Regression Analysis of Risk Factors for Overall Survival

Variables (N, %)	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P	HR (95% CI)	P
Sex, male vs female	2.509 (0.595–10.581)	0.210		
Age, ≥50 vs < 50 years	0.574 (0.219–1.507)	0.260		
Hepatitis, HBV vs others	0.913 (0.389–2.143)	0.835		
PS, 0 vs 1	1.233 (0.601–2.530)	0.567		
Child-Pugh, B vs A	2.023 (1.395–2.378)	0.004	1.159 (1.073–1.914)	0.024
ALBI grade, ≥ 2 vs 1	4.891 (1.474–16.227)	0.009	NS	
NLR, ≥ 2.96 vs <2.96	2.422 (1.123–5.233)	0.024	NS	
LMR, <4.4 vs ≥4.4	2.054 (0.714–5.909)	0.182		
Cirrhosis, with vs without	0.761 (0.357–1.623)	0.480		
Baseline AFP levels, ≥400 vs < 400 ng/mL	2.008 (0.954–4.226)	0.606		
Baseline PIVKA-II levels, ≥400 vs <400 mAU/mL	1.963 (0.801–4.808)	0.140		
BCLC, C vs B stage	2.211 (0.892–5.484)	0.087	1.163 (1.025–2.070)	0.005
TACE/HAIC, with vs without	0.872 (0.272–0.906)	0.012	0.887 (0.310–0.951)	0.011
AFP reduction, ≥50% vs <50%	0.846 (0.341–0.960)	0.021	0.873 (0.392–0.906)	0.019
PIVKA-II reduction, ≥50% vs <50%	0.756 (0.163–0.888)	< 0.001	0.709 (0.224–0.869)	< 0.001

Abbreviations: PIVKA-II, prothrombin induced by vitamin K absence-II; ICIs, immune checkpoint inhibitors; AFP, alpha-fetoprotein; ECGO PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; ALBI, albumin- bilirubin; NLR, neutrophil/lymphocyte ratio; LMR, lymphocyte/monocyte ratio; TACE, transarterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy; HR, hazard ratio; NS, no significance.

prognosis in combined ICIs and targeted therapy.[26,27] In contrast, research on PIVKA-II has lagged, with most studies focusing only on the association between baseline levels and prognosis. Therefore, this study focuses on the early dynamic changes of PIVKA-II in the context of ICI-based combination therapy, systematically evaluating its predictive value for treatment response and prognosis.

Currently, there is no unified standard for defining early PIVKA-II response. Based on a previous study, a serological response of a ≥70% decline in PIVKA-II was defined as significantly associated with better prognosis.[28] Another research demonstrated that a ≥50% decline in PIVKA-II effectively predicted the efficacy of anti-PD-1 therapy in HCC patients.[22] Through ROC curve analysis, the present study ultimately established a ≥50% decline in PIVKA-II levels at 3–4 weeks of treatment compared to baseline as the criterion for early response. This threshold showed optimal balance in predicting ORR (AUC=0.73, P<0.001) and was significantly correlated with patient prognosis.

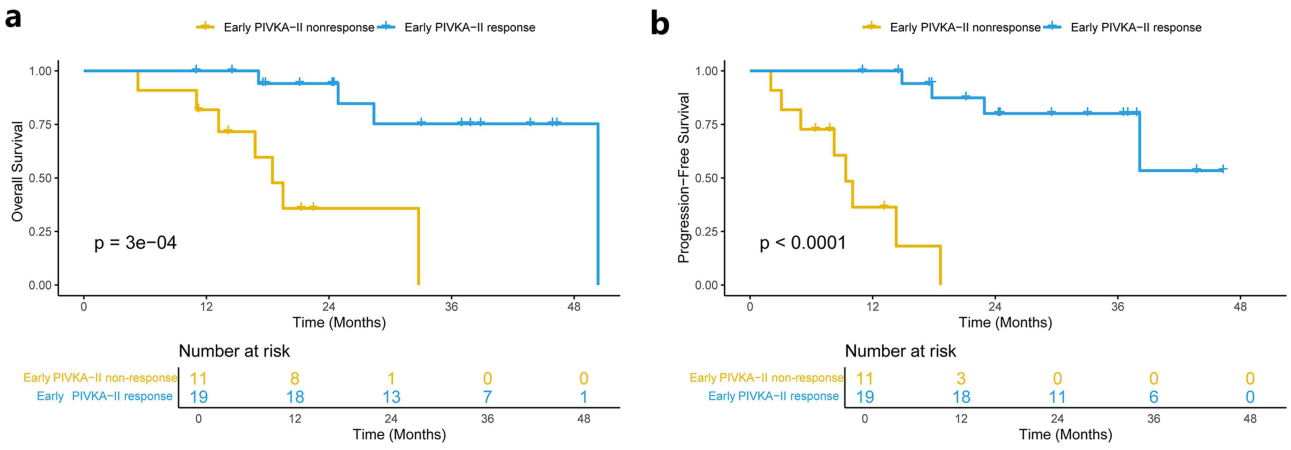

Figure 2 The K-M curves comparisons of overall survival and progression-free survival between AFP-negative patients with early PIVKA-II response and non-response. (**A**) Overall survival, (**B**) Progression-free survival. AFP, alpha-fetoprotein; PIVKA-II, prothrombin induced by vitamin K absence-II.

The study results demonstrated that the early PIVKA-II response group achieved a significantly higher ORR of 82.5% compared to 38.1% in the non-response group. A similar trend was observed in DCR (97.5% vs 81.0%, P=0.041). Notably, the dynamic changes in PIVKA-II showed strong concordance with imaging assessments based on mRECIST criteria, confirming its reliability as a complementary biomarker to radiological evaluation. Survival analysis revealed that patients with early PIVKA-II response had significantly prolonged PFS and OS compared to the non-response group ($P < 0.001$). Multivariate Cox regression analysis further validated that early PIVKA-II response was an independent predictor of PFS and OS. These findings suggest that integrating dynamic biomarker monitoring into clinical practice can significantly improve the accuracy and clinical utility of prognostic assessment.

Particularly noteworthy is that in AFP-negative patients (accounting for 36.6% of the study population), early PIVKA-II response maintained excellent predictive performance for ORR (AUC = 0.751, 95% CI 0.605–0.811, sensitivity = 0.830, specificity = 0.670, P = 0.022). Survival analysis revealed significantly prolonged PFS and OS in the early PIVKA-II response group compared to the non-response group ($P < 0.001$). These findings provide a novel biomarker strategy for precision therapy in advanced HCC, offering a new dimension for individualized efficacy assessment.

The profound and rapid decline in PIVKA-II observed in responders likely reflects a massive and immediate cytoreductive effect of the combination therapy, leading to a shutdown of its production by viable tumor cells. This rapid biochemical response appears to precede and more accurately predict the subsequent anatomical changes seen on imaging, positioning it as a valuable early indicator of tumor cell kill. Based on the excellent predictive performance of early PIVKA-II response in evaluating therapeutic efficacy and prognosis in advanced HCC patients, we propose a potentially effective standardized treatment pathway: for the good-response group (PIVKA-II decline ≥50%), it is recommended to maintain the current immune-combined targeted therapy regimen while appropriately extending imaging assessment intervals to 10–12 weeks. Concurrently, PIVKA-II should be monitored every 3 weeks, alongside close observation of clinical symptoms, to ensure sustained treatment efficacy and reduce patient burden. And for the suboptimal-response group (PIVKA-II decline <50%), immediate intervention is required, including: prompt imaging reassessment (contrast-enhanced CT or MRI) and multidisciplinary team discussion for treatment adjustment. Intensified targeted therapy, such as increasing the dosage of anti-angiogenic drugs or switching to second-line targeted agents.[4] Immunotherapy optimization, including switching immune checkpoint inhibitors or considering dual immune-combination regimens.[29] Combination with local therapies, such as TACE, HAIC, stereotactic body radiotherapy, or local ablation, to enhance treatment response.[30] This decision-making framework, guided by early dynamic PIVKA-II monitoring, achieves dual optimization: precisely identifying treatment-sensitive patients to avoid excessive testing and enabling early intervention for potentially resistant cases, thereby improving overall prognosis. Translation adapted for clarity and academic rigor while preserving the original intent.

Our study has several limitations that should be acknowledged. First, as a retrospective study, it is subject to selection bias. This is particularly relevant given our inclusion criterion requiring patients to have completed at least four treatment cycles. This introduces an "immortal time bias", as patients who experienced early progression or death were excluded, likely leading to an overestimation of the response rates and survival outcomes in our cohort. Secondly, a major limitation is the heterogeneity of treatment regimens. A significant portion of patients received concurrent local therapies such as TACE or HAIC in addition to systemic treatment. As our own multivariate analysis showed that local therapy was an independent predictor of survival, it is difficult to definitively disentangle its effect from that of the systemic therapy. Therefore, the observed PIVKA-II decline may reflect the combined efficacy of both local and systemic treatments rather than the systemic therapy alone. Future studies should stratify patients by treatment modality to isolate the predictive value of PIVKA-II for specific regimens. Additionally, the therapeutic decision-making algorithm we proposed requires further validation through multicenter prospective cohort studies to confirm its reliability. Finally, future research directions should include expanding sample sizes, establishing multicenter collaborations, developing multi-omics predictive models, and creating adaptive treatment pathways based on dynamic biomarker monitoring to further optimize individualized therapeutic strategies.

Conclusion

The results of this study demonstrated that an early decline in PIVKA-II levels serves as a strong predictor of treatment response and survival outcomes. The early PIVKA-II response group showed significantly higher ORR and markedly prolonged PFS and OS compared to non-responders. Most notably, this biomarker retained high predictive accuracy even in AFP-negative patients, highlighting its particular clinical relevance. These findings support the use of early, dynamic PIVKA-II monitoring as a practical tool for timely assessment of treatment efficacy, facilitating early intervention in non-responding patients and aiding personalized therapeutic strategies. Further prospective studies are warranted to validate these results and integrate PIVKA-II into standardized response-guided treatment algorithms.

Abbreviations

HCC, Hepatocellular carcinoma; PIVKA-II, prothrombin induced by vitamin K absence-II; ICIs, immune checkpoint inhibitors; AFP, alpha-fetoprotein; ECGO PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; ALBI, albumin- bilirubin; NLR, neutrophil/lymphocyte ratio; LMR, lymphocyte/monocyte ratio; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; DCR disease control rate; CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease; ROC, receiver operating characteristic; AUC, area under the ROC curve; HR, hazard ratios; CI, confidence interval.

Data Sharing Statement

Upon reasonable request, the corresponding author (Dr. Lei Liang) can provide access to the datasets employed and examined in the ongoing research.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of the Zhejiang Provincial People's Hospital and complied with the Declaration of Helsinki 1975 (Ethical number: QT2025173). Informed consent was waived due to the retrospective nature of the study, with assurance that data were either anonymized or kept confidential.

Acknowledgment

Zheng-Kang Fang, Yu-Ting Xiao, Xia Feng, and Zhe-Jin Shi contributed equally to this work. The patients participating in this study are sincerely acknowledged.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Funding for the study was provided by the National Natural Science Foundation of China (No. 82302915 and 82203403), the Zhejiang Provincial Natural Science Foundation of China (No. LQ23H160049), and the fund of Medical and Health Research Projects in Zhejiang Province (No. 2024KY764).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660

2. Pinter M, Fulgenzi CAM, Pinato DJ, et al. Systemic treatment in patients with hepatocellular carcinoma and advanced liver dysfunction. *Gut*. 2025;74(7):1178–1188. doi:10.1136/gutjnl-2025-334928
3. Wang JM, Qiu GG, Liu ZD, et al. Treatment for unresectable hepatocellular carcinoma patients: options and management after complete response. *ILIVER*. 2025;4(1):100145. doi:10.1016/j.iliver.2025.100145
4. Yang X, Yang C, Zhang S, et al. Precision treatment in advanced hepatocellular carcinoma. *Cancer Cell*. 2024;42(2):180–197. doi:10.1016/j.ccell.2024.01.007
5. Vogel A, Meyer T, Sapisochin G, et al. Hepatocellular carcinoma. *Lancet*. 2022;400(10360):1345–1362. doi:10.1016/S0140-6736(22)01200-4
6. Finn RS, Galle PR, Ducreux M, et al. Efficacy and safety of atezolizumab plus bevacizumab versus sorafenib in hepatocellular carcinoma with main trunk and/or contralateral portal vein invasion in IMbrave150. *Liver Cancer*. 2024;13(6):655–668. doi:10.1159/000539897
7. Kudo M, Ren Z, Guo Y, et al. Transarterial chemoembolisation combined with lenvatinib plus pembrolizumab versus dual placebo for unresectable, non-metastatic hepatocellular carcinoma (LEAP-012): a multicentre, randomised, double-blind, Phase 3 study. *Lancet*. 2025;405(10474):203–215. doi:10.1016/S0140-6736(24)02575-3
8. Yang DL, Ye L, Zeng FJ, et al. Multicenter, retrospective GUIDANCE001 study comparing transarterial chemoembolization with or without tyrosine kinase and immune checkpoint inhibitors as conversion therapy to treat unresectable hepatocellular carcinoma: survival benefit in intermediate or advanced, but not early, stages. *Hepatology*. 2025;82(2):357–369. doi:10.1097/HEP.0000000000001229
9. Wang Z, Song S, Zhang L, et al. Hepatic arterial infusion chemotherapy combined with immune checkpoint inhibitors and molecular targeted therapies for advanced infiltrative hepatocellular carcinoma: a single-center experience. *Front Immunol*. 2024;15:1474442. doi:10.3389/fimmu.2024.1474442
10. Lu YC, Yang YC, Ma D, et al. FOLFOX-HAIC combined with targeted immunotherapy for initially unresectable hepatocellular carcinoma: a real-world study. *Front Immunol*. 2024;15:1471017. doi:10.3389/fimmu.2024.1471017
11. Pang B, Zuo B, Huang L, et al. Real-world efficacy and safety of TACE-HAIC combined with TKIs and PD-1 inhibitors in initially unresectable hepatocellular carcinoma. *Int Immunopharmacol*. 2024;137:112492. doi:10.1016/j.intimp.2024.112492
12. Yang DL, Peng N, Nong JL, et al. Survival benefit of hepatectomy after complete or partial response to conversion therapy in unresectable hepatocellular carcinoma (GUIDANCE003): a multicenter study. *Liver Cancer*;2025. 1–17. doi:10.1159/000546052
13. Tian J, Pan S, Wang Y, et al. Early alpha-fetoprotein response predicts sustained tumor response following immune checkpoint inhibitors combined with targeted therapy in liver cancer. *Biomedicines*. 2024;12(12):2769. doi:10.3390/biomedicines12122769
14. Shao YY, Lin ZZ, Hsu C, et al. Early alpha-fetoprotein response predicts treatment efficacy of antiangiogenic systemic therapy in patients with advanced hepatocellular carcinoma. *Cancer*. 2010;116(19):4590–4596. doi:10.1002/cncr.25257
15. Kudo M. Urgent global need for PIVKA-II and AFP-L3 measurements for surveillance and management of hepatocellular carcinoma. *Liver cancer*. 2024;13(2):113–118. doi:10.1159/000537897
16. Kim DY, Toan BN, Tan CK, et al. Utility of combining PIVKA-II and AFP in the surveillance and monitoring of hepatocellular carcinoma in the Asia-Pacific region. *Clin Mol Hepatol*. 2023;29(2):277–292. doi:10.3350/cmh.2022.0212
17. Dong L, Qiu X, Gao F, et al. Protein induced by vitamin K absence or antagonist II: experience to date and future directions. *Biochim Biophys Acta Rev Cancer*. 2023;1878(6):189016. doi:10.1016/j.bbcan.2023.189016
18. Guarneri V, Loggi E, Ramacieri G, et al. Diagnostic performance of PIVKA-II in Italian patients with hepatocellular carcinoma. *Cancers*. 2025;17(2):167. doi:10.3390/cancers17020167
19. Gao ZY, Jin LM, Fang ZK, et al. Survival benefit of adjuvant TACE for patients with hepatocellular carcinoma and child-pugh B7 or B8 after hepatectomy. *BMC Cancer*. 2024;24(1):1241.
20. Xie YM, Lu W, Cheng J, et al. Naples prognostic score is an independent prognostic factor in patients undergoing hepatectomy for hepatocellular carcinoma. *J Hepatocell Carcinoma*. 2023;10:1423–1433. doi:10.2147/JHC.S414789
21. Zhu HF, Feng JK, Xiang YJ, et al. Combination of alpha-fetoprotein and neutrophil-to-lymphocyte ratio to predict treatment response and survival outcomes of patients with unresectable hepatocellular carcinoma treated with immune checkpoint inhibitors. *BMC Cancer*. 2023;23(1):547. doi:10.1186/s12885-023-11003-0
22. Sun X, Mei J, Lin W, et al. Reductions in AFP and PIVKA-II can predict the efficiency of anti-PD-1 immunotherapy in HCC patients. *BMC Cancer*. 2021;21(1):775. doi:10.1186/s12885-021-08428-w
23. Peng Z, Fan W, Liu Z, et al. Adjuvant transarterial chemoembolization with sorafenib for portal vein tumor thrombus: a randomized clinical trial. *JAMA Surgery*. 2024;159(6):616–624. doi:10.1001/jamasurg.2024.0506
24. Llovet JM, Lencioni R. Lencioni R: mRECIST for HCC: performance and novel refinements. *J Hepatol*. 2020;72(2):288–306. doi:10.1016/j.jhep.2019.09.026
25. Parikh ND, Tayob N, Singal AG. Blood-based biomarkers for hepatocellular carcinoma screening: approaching the end of the ultrasound era? *J Hepatol*. 2023;78(1):207–216. doi:10.1016/j.jhep.2022.08.036
26. Hu X, Chen R, Wei Q, et al. The landscape of alpha fetoprotein in hepatocellular carcinoma: where are we? *Int J Biol Sci*. 2022;18(2):536–551. doi:10.7150/ijbs.64537
27. Zhang N, Yang X, Piao M, et al. Biomarkers and prognostic factors of PD-1/PD-L1 inhibitor-based therapy in patients with advanced hepatocellular carcinoma. *Biomark Res*. 2024;12(1):26. doi:10.1186/s40364-023-00535-z
28. Zhang T, Li W, Chen Q, et al. Prognostic significance of early alpha fetoprotein and des-gamma carboxy prothrombin responses in unresectable hepatocellular carcinoma patients undergoing triple combination therapy. *Front Immunol*. 2024;15:1508028. doi:10.3389/fimmu.2024.1508028
29. Llovet JM, Pinyol R, Yarchoan M, et al. Adjuvant and neoadjuvant immunotherapies in hepatocellular carcinoma. *Nat Rev Clin Oncol*. 2024;21(4):294–311. doi:10.1038/s41571-024-00868-0
30. Kudo M, Aoki T, Ueshima K, et al. Achievement of complete response and drug-free status by atezolizumab plus bevacizumab combined with or without curative conversion in patients with transarterial chemoembolization-unsuitable, intermediate-stage hepatocellular carcinoma: a multicenter proof-of-concept study. *Liver Cancer*. 2023;12(4):321–338. doi:10.1159/000529574