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Effect of AFP and PIVKA-II secretion status on prognosis of advanced hepatocellular carcinoma patients receiving TACE combined with systemic therapy

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Abstract

Background Few biomarkers can predict the effectiveness of transcatheter arterial chemoembolization (TACE) in combination with systemic therapies for patients with advanced hepatocellular carcinoma (HCC). This study aimed to evaluate the prognostic significance of changes in alpha-fetoprotein (AFP) and prothrombin induced by vitamin K absence-II (PIVKA-II), as well as their clinical utility in patients undergoing TACE combined with immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs).

Methods This retrospective cohort study included advanced HCC patients who underwent TACE in combination with ICIs and TKIs at the Third Affiliated Hospital of Kunming Medical University between May 2021 and March 2024. Based on changes in serum AFP and PIVKA-II levels before and after treatment, patients were classified into four groups: AFP (↓) PIVKA-II (↓) (status 1), AFP (↓) PIVKA-II (↑) (status 2), AFP (↑) PIVKA-II (↓) (status 3), and AFP (↑) PIVKA-II (↑) (status 4). Kaplan-Meier analyses were conducted to compare the overall survival (OS) and progression-free survival (PFS) across the four groups. Univariate and multivariate Cox regression analyses were performed to identify potential prognostic factors for OS and PFS.

Results A total of 215 patients were included in the study. Among them, 55.3% (119/215) achieved a complete or partial response. Significant differences in OS and PFS were observed among the various AFP-PIV status groups ($P < 0.001$). Patients with elevated AFP and PIVKA-II had the poorest OS and PFS compared to the other groups. Both elevated AFP alone and elevated PIVKA-II alone were associated with an increased risk of disease progression and death. In comparison, patients with reduced levels of both AFP and PIVKA-II showed a better prognosis. The AFP-PIV status was identified as an independent risk factor for OS and PFS in patients with advanced HCC.

Conclusion In summary, the findings of this study indicate that the AFP-PIV status serves as a significant prognostic marker, independently predicting OS and PFS in advanced HCC patients undergoing TACE in combination with systemic therapy.

Keywords Hepatocellular carcinoma, AFP, PIVKA-II, TACE, Systemic therapy, Survival

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Introduction

The global burden of hepatocellular carcinoma (HCC) is projected to increase by 55% between 2020 and 2040, with significant regional variation [1]. Approximately 85% of HCC cases occur in developing countries, particularly in Eastern Asia and Northern Africa [2]. Most patients are diagnosed at an advanced stage, resulting in a 5-year survival rate of only 12% [3]. The prognosis for advanced HCC remains poor due to the rapid progression of the disease. Therefore, identifying novel prognostic markers for advanced HCC can improve treatment outcomes and enable earlier interventions.

Alpha-fetoprotein (AFP) is the most commonly used biomarker for HCC screening. As a standardized test, it is considered more objective than imaging alone and is easily accessible [4]. However, AFP has Limitations, including reduced sensitivity and specificity. Serum AFP is detectable in only about 60% of HCC patients, with detection rates dropping to approximately 20% for early-stage malignancies [5]. Protein induced by vitamin K absence II (PIVKA-II), also known as Des-gamma-carboxy prothrombin (DCP), has been suggested as a biomarker for HCC diagnosis [6]. Although PIVKA-II has proven useful in detecting HCC, its role in prognosis prediction remains largely unexplored. AFP and PIVKA-II offer distinct advantages in the diagnosis and prognosis of HCC. AFP is widely recognized for its sensitivity, while PIVKA-II is highly specific for HCC. Previous studies have shown that combining PIVKA-II and AFP improves diagnostic accuracy in HCC patients with hepatitis C virus infection [7].

Regarding prognosis, combining PIVKA-II and AFP is crucial in predicting survival and recurrence in HCC patients. The response of both AFP and PIVKA-II has been positively correlated with the radiological response in HCC patients undergoing transarterial chemoembolization (TACE) [8]. The combination of locoregional treatments and systemic therapies is increasingly recommended for advanced HCC. Therefore, accurate biomarker forecasting is essential for assessing the efficacy of TACE combined with immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs) in these patients.

In clinical practice, changes in PIVKA-II do not always align with changes in AFP for advanced HCC patients following treatment. In some cases, a decrease in serum AFP levels is not accompanied by a reduction in PIVKA-II expression, and there may even be a trend toward increased PIVKA-II levels despite a decline in AFP. The discrepancy in the changes of these two biomarkers complicates the accurate assessment of treatment efficacy in HCC patients. This raises the question of whether there is a correlation between PIVKA-II and AFP.

Therefore, we conducted this study to examine the prognostic significance of changes in AFP and PIVKA-II trends in advanced HCC patients undergoing TACE in combination with systemic therapies. Furthermore, we aimed to improve prognostic accuracy by developing novel biomarker models tailored to advanced HCC patients.

Materials and methods

Data source and study design

We retrospectively gathered clinical data from HCC patients who received TACE combined with ICIs and TKIs (triple therapy) at the Third Affiliated Hospital of Kunming Medical University between May 2021 and March 2024. All procedures were conducted in compliance with relevant guidelines and regulations. Ethical approval was obtained from the ethics committee of the Third Affiliated Hospital of Kunming Medical University. Due to the retrospective design of the study, the institutional review board waived the requirement for informed consent.

The inclusion criteria were as follows: (1) at least 18 years of age with clinical or pathological diagnosis of HCC, (2) patients with advanced unresectable HCC patients, and (3) patients who received TACE combined with targeted and anti-PD-1 therapy. The exclusion criteria were: (1) no baseline AFP or PIVKA-II levels before triple therapy, (2) no follow-up tumor marker records after treatment, (3) Barcelona Clinic Liver Cancer (BCLC) staging A, (4) no measurable lesions in the liver, (5) taking anticoagulants, and (6) patients with Child-Pugh classification C or Eastern Cooperative Oncology Group (ECOG) 3–4. To minimize selection bias, two trained investigators screened all potential participants independently. Only those who met the eligibility criteria were included in the study (Fig. 1).

In our study, TACE was performed on an as-needed basis. All procedures involved superselective catheterization and embolization, carried out by interventional physicians with over five years of experience. Chemotherapeutic and embolic agents were selected according to established guidelines. Repeat TACE was considered for patients with viable tumors or intrahepatic recurrence, as assessed by follow-up imaging. Moreover, all enrolled patients received targeted and anti-PD-1 therapy within three days following TACE. The majority of patients received a combination therapy of donafenib and tislelizumab. Some patients were treated with sorafenib combined with camrelizumab or lenvatinib in combination with tislelizumab. PD-1 inhibitors, including tislelizumab and camrelizumab, were administered at 200 mg every 3 weeks. TKIs were used according to the following regimens: lenvatinib at 12 mg/day for patients

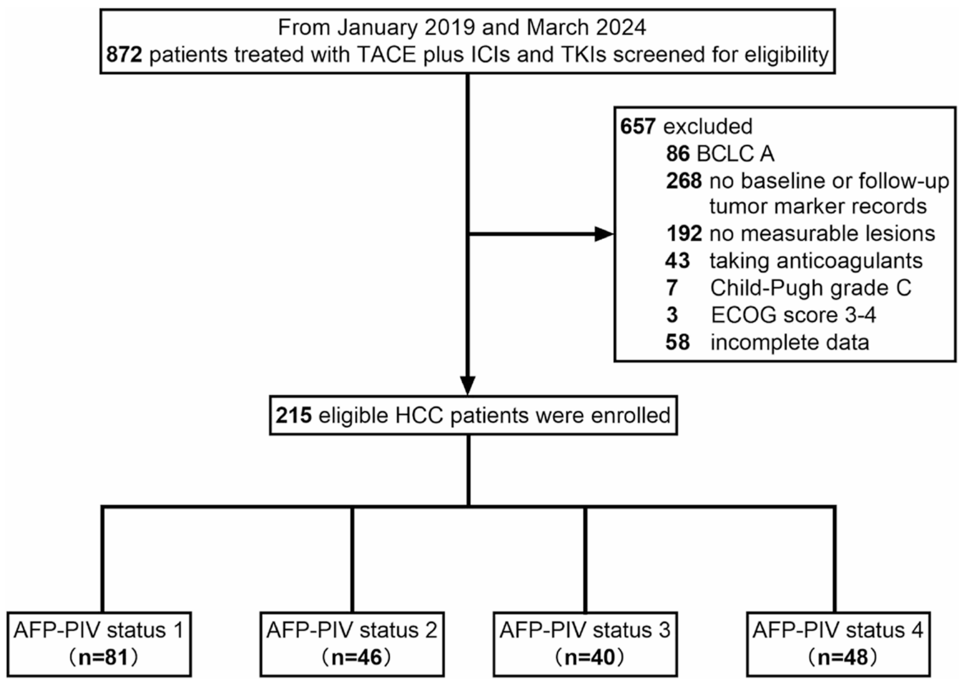

Fig. 1 Flow diagram of the study selection process

weighing ≥ 60 kg, or 8 mg/day for those weighing < 60 kg; donafenib at 0.2 g twice daily; and sorafenib at 0.4 g twice daily.

Adverse events (AEs) were evaluated according to the Common Terminology Criteria for Adverse Events v5.0. Dose interruptions or substitutions due to AEs were permitted for targeted therapies and PD-1 inhibitors. Patients continued treatment according to the planned regimen until unacceptable toxicity or disease progression occurred.

Study variables and follow-up

Pre-treatment data were collected, including age, sex, ECOG performance status, body mass index (BMI), Child-Pugh class, aetiology, presence of liver cirrhosis, BCLC staging, number of tumors, the diameter of the largest tumor, portal vein tumor thrombus (PVTT), extrahepatic metastases, types of TACE, and serum levels of AFP and PIVKA-II. Serum AFP and PIVKA-II levels were measured within 3 days before the first TACE combined with targeted and immunotherapy. Furthermore, AFP and PIVKA-II levels were measured 3 months after the initiation of triple therapy. A significant biomarker Change was defined as a variation in tumor marker levels exceeding 30% from the baseline pre-treatment values during therapeutic re-evaluation. Based on the changes in AFP and PIVKA-II levels, the AFP/PIVKA-II combined status (AFP-PIV status) was categorized as follows: AFP-PIV status 1, AFP reduction and PIVKA-II reduction; AFP-PIV status 2, AFP reduction and PIVKA-II elevation; AFP-PIV status 3, AFP elevation and PIVKA-II reduction; and AFP-PIV status 4, AFP elevation and PIVKA-II elevation.

All patients underwent abdominal imaging throughout the treatment period, including enhanced computed tomography (CT) and magnetic resonance imaging (MRI), every 4–6 weeks. An independent senior radiologist assessed the radiographic tumor response based on the Modified Response Evaluation Criteria in Solid Tumors (mRECIST) guideline. The last follow-up date was November, 2024. The relationship between AFP-PIV status and objective response rate (ORR), overall survival (OS) or progression-free survival (PFS) was further evaluated. The ORR was defined as the sum of confirmed complete (CR) and partial response (PR) rates per mRECIST criteria. The OS was defined as the time from the start of treatment until death, while PFS was calculated as the period from treatment to disease progression or death.

Statistical analyses

Using the Chi-squared test, this study analyzed the correlation between AFP-PIV status and ORR, OS or PFS. Logistic regression was used to identify potential predictors of ORR, with odds ratios (ORs) calculated for each variable. Univariate and multivariate Cox regression analyses were performed to identify potential predictors of OS and PFS, with $P < 0.05$ considered statistically significant. OS and PFS were further analyzed using the Kaplan-Meier method with the log-rank test. Hazard ratios (HRs) for OS and PFS were estimated using Cox proportional hazards regression. Kaplan-Meier curves were generated based on AFP-PIV status, and differences between groups were assessed by comparing the cumulative survival of the collected HCC patients using the log-rank test. All statistical analyses were conducted using SPSS software (version 21.0) and R software (version 4.0.5). A P-value of < 0.05 was considered statistically significant.

Results

Patient characteristics

As shown in Table 1, a total of 215 patients were enrolled in our cohort. Among these, most patients are male. More than half of the patients were aged 60 years or younger. Obesity was present in 61 (28.4%) of the patients. The majority of patients had liver cirrhosis, with nearly half classified as Child-Pugh Class B and BCLC Staging C. Low preoperative serum AFP levels (≤400 mAU/mL) were observed in 109 (50.7%) patients. In comparison, 106 (49.3%) had high AFP levels. Preoperative serum PIVKA-II levels were ≤400 mAU/mL in 52 (24.2%) patients and >400 mAU/mL in 163 (75.8%) patients. Most patients had tumor burden scores greater than 7, and some had portal vein tumor thrombus (PVTT) or extrahepatic metastases. The majority received combination therapy of donafenib with tislelizumab. Additionally, some patients were treated by sorafenib combined with camrelizumab or lenvatinib combined with tislelizumab. Comparative analysis of baseline treatment characteristics across the four AFP-PIV groups demonstrated no statistically significant differences ($P > 0.05$), suggesting comparable therapeutic profiles among these groups.

Correlation between AFP-PIV status and ORR

The ORR in 215 enrolled HCC patients was 55.3% (119/215), with 9.8% (21/215) achieving CR and 45.6% (98/215) achieving PR. For patients with AFP-PIV status 1, 64.2% (52/81) reached ORR, while only 31.2% (15/48) patients reached ORR in those AFP-PIV status 4 ($P < 0.001$). Besides, the ORR was significantly higher in patients with AFP-PIV status 2 ($P = 0.007$) and AFP-PIV status 3 ($P = 0.003$) compared to those with AFP-PIV status 4. After univariate and multivariate logistic analyses, tumor burden and AFP-PIV status were independent risk factors for ORR in advanced HCC patients (Table 2).

Effect of AFP-PIV status on OS and PFS

In the study, the median follow-up time for pateints was 24.0 (95% confidence interval [CI]: 20.8–27.2) months in AFP-PIV status 1 group, 24.0 (95% CI: 19.7–28.3) months in AFP-PIV status 2 group, 25.0 (95% CI: 21.0–29.0) months in AFP-PIV status 3 group and 23.0 (95% CI: 14.8–31.2) months in AFP-PIV status 4 group ($P = 0.78$). The median OS was 24.0 (95% CI: 18.0–30.0) months, and the median PFS was 9.0 (95% CI: 5.7–12.3) months for all patients.

As shown in Fig. 2, Kaplan-Meier analysis was conducted to compare OS and PFS between patients with AFP-PIV status 1 and those with other AFP-PIV statuses. Significant differences in OS and PFS were observed across the different AFP-PIV statuses ($P < 0.001$). The best prognosis was seen in AFP-PIV status 1 (median OS: 55.0 months, 95%CI: 26.3–83.7; median PFS: 32.0 months, 95%CI: 15.9–48.0), followed by AFP-PIV status 2 (median OS: 23.0 months, 95%CI: 8.8–27.0; median PFS: 12.0 months, 95%CI: 8.8–15.2) and AFP-PIV status 3 (median OS: 18.0 months, 95%CI: 14.2–41.8; median PFS: 9.0 months, 95%CI: 7.5–10.5). The poorest survival was observed in AFP-PIV status 4 (median OS = 7.0 months, 95%CI: 4.7–9.3; median PFS: 3 months, 95%CI: NE-NE).

A Overall survival B Progression-free survival.

Further, Kaplan–Meier survival curves were employed to evaluate the AFP-PIV status between various BCLC stages in the HCC patient cohort. As illustrated in Fig. 3, significant differences in OS and PFS were observed among patients with different AFP-PIV status, regardless of BCLC stage ($P < 0.001$). In addition, to analyze the effect of AFP-PIV status on survival for patients with a high tumor burden, we further performed Kaplan–Meier survival curves in the HCC patient cohort with tumor burden greater than 7 scores. As indicated in Fig. 4, there were also notable differences in OS and PFS amongst patients of different AFP-PIV status who had a high tumor burden ($P < 0.001$).

Independent prognostic factors in advanced HCC

In our cohort, univariate Cox analysis of OS revealed that BCLC staging, tumor burden, PVTT, extrahepatic metastases, and AFP-PIV status were significant prognostic factors in advanced HCC patients. These factors were further examined in multivariate Cox analysis, which confirmed that tumor burden, extrahepatic metastases, and AFP-PIV status were independent risk factors for OS in advanced HCC patients (Table 3).

Furthermore, univariate and multivariate Cox analyses were performed to identify prognostic factors related to PFS. As shown in Table 3, tumor burden, PVTT,

Table 1 Baseline characteristics of patients

Characteristics	AFP-PIV status (number [%])				X^2	*P*-value
	1 (*n* = 81)	2 (*n* = 46)	3 (*n* = 40)	4 (*n* = 48)		
Age, year					3.663	0.300
≤ 60	63 (77.8%)	32 (69.6%)	25 (62.5%)	32 (66.7%)		
> 60	18 (22.2%)	14 (30.4%)	15 (37.5%)	16 (33.3%)		
Sex, N					0.743	0.863
Male	73 (90.1%)	43 (93.5%)	37 (92.5%)	45 (93.8%)		
female	8 (9.9%)	3 (6.5%)	3 (7.5%)	3 (6.3%)		
BMI, kg/㎡					4.184	0.242
≤ 24	54 (66.7%)	36 (78.3%)	26 (65.0%)	38 (79.2%)		
> 24	27 (33.3%)	10 (21.7%)	14 (35.0%)	10 (20.8%)		
ECOG					0.462	0.927
0–1	71 (87.7%)	41 (89.1%)	34 (85.0%)	41 (85.4%)		
2	10 (12.3%)	5 (10.9%)	6 (15.0%)	7 (14.6%)		
Aetiology					6.032	0.737
HBV	58 (71.6%)	30 (65.2%)	29 (72.5%)	34 (70.8%)		
HCV	6 (7.4%)	5 (10.9%)	6 (15.0%)	2 (4.2%)		
Alcohol	14 (17.3%)	8 (17.4%)	4 (10.0%)	10 (20.8%)		
Others	3 (3.7%)	3 (6.5%)	1 (2.5%)	2 (4.2%)		
Liver cirrhosis					2.726	0.436
No	29 (35.8%)	12 (26.1%)	17 (42.5%)	18 (37.5%)		
Yes	52 (64.2%)	34 (73.9%)	23 (57.5%)	30 (62.5%)		
Child-Pugh Class					1.981	0.576
A	33 (40.7%)	23 (50.0%)	20 (50.0%)	19 (39.6%)		
B	48 (59.3%)	23 (50.0%)	20 (50.0%)	29 (60.4%)		
BCLC Staging					4.651	0.199
B	38 (46.9%)	23 (50.0%)	20 (50.0%)	15 (31.3%)		
C	43 (53.1%)	23 (50.0%)	20 (50.0%)	33 (68.8%)		
Tumor number, n					0.489	0.998
1	27 (33.3%)	13 (28.3%)	12 (30.0%)	16 (33.3%)		
2–4	20 (24.7%)	12 (26.1%)	10 (25.0%)	12 (25.0%)		
≥ 5	34 (42.0%)	21 (45.7%)	18 (45.0%)	20 (41.8%)		
Tumor diameter, cm					6.790	0.341
<5	21 (25.9%)	15 (32.6%)	9 (22.5%)	11 (22.9%)		
5–10	37 (45.7%)	19 (41.3%)	15 (37.5%)	15 (31.3%)		
≥ 10	23 (28.4%)	12 (26.1%)	16 (40.0%)	22 (45.8%)		
Tumor burden					4.147	0.246
≤ 7	18 (22.2%)	10 (21.7%)	5 (12.5%)	5 (10.4%)		
>7	63 (77.8%)	36 (78.3%)	35 (87.5%)	43 (89.6%)		
PVTT					5.637	0.131
Yes	30 (37.0%)	19 (41.3%)	14 (35.0%)	27 (56.3%)		
No	51 (63.0%)	27 (58.7%)	26 (65.0%)	21 (43.7%)		
Extrahepatic metastases					6.158	0.104
Yes	19 (23.5%)	16 (34.8%)	18 (45.0%)	17 (35.4%)		
No	62 (76.5%)	30 (65.2%)	22 (55.0%)	31 (64.6%)		
AFP, ng/L					0.752	0.861
< 400	41 (50.6%)	25 (54.3%)	21 (52.5%)	22 (45.8%)		
≥ 400	40 (49.4%)	21 (45.7%)	19 (47.5%)	26 (54.2%)		
PIVKA-II, mAU/ml					5.565	0.135
< 400	21 (26.9%)	16 (34.8%)	6 (15.0%)	9 (18.8%)		
≥ 400	60 (74.1%)	30 (65.2%)	34 (85.0%)	39 (81.2%)		

Table 1 (continued)

Characteristics	AFP-PIV status (number [%])				X^2	*P*-value
	1 (*n* = 81)	2 (*n* = 46)	3 (*n* = 40)	4 (*n* = 48)		
TACE types					3.010	0.390
C-TACE	51 (63.0%)	26 (56.5%)	24 (60.0%)	35 (72.9%)		
D-TACE	30 (37.0%)	20 (43.5%)	16 (40.0%)	13 (27.1%)		
Systemic therapy					4.267	0.641
Donafenib + Tislelizumab	53 (65.4%)	30 (65.2%)	23 (57.5%)	26 (54.2%)		
Sorafenib + Camrelizumab	12 (14.8%)	10 (21.7%)	10 (25.0%)	13 (27.1%)		
Lenvatinib + Tislelizumab	16 (19.8%)	6 (13.0%)	7 (17.5%)	9 (18.8%)		

BMI Body mass index, *ECOG* Eastern Cooperative Oncology Group, *HBV* Hepatitis B virus, *HCV* Hepatitis C virus, *BCLC* Barcelona Clinic Liver Cancer, *PVTT* Portal vein tumor thrombus, *AFP* Alpha-fetoprotein, *PIVKA-II* Protein induced by vitamin K absence II, *TACE* Transarterial chemoembolization, *C-TACE* Conventional TACE, *D-TACE* Drug-eluting beads TACE

extrahepatic metastases, and AFP-PIV status were significantly associated with PFS in univariate analysis. Multivariate analysis further revealed that tumor burden and AFP-PIV status were independent prognostic factors for PFS.

Discussion

In early-stage HCC, surgical resection typically leads to a significant reduction in tumor markers. However, the staged approach to treating advanced HCC requires continuous monitoring of tumor marker fluctuations to assess treatment effectiveness. These dynamic changes in tumor markers are crucial in guiding therapeutic decisions throughout the different phases of advanced HCC management. No biomarkers have been validated to consistently predict the efficacy of TACE combined with targeted and anti-PD-1 therapy in advanced HCC patients.

The present study found that the different patterns of PIVKA-II and AFP secretion during treatment were associated with the prognosis of HCC patients receiving triple therapy. We classified advanced HCC patients based on changes in serum PIVKA-II and AFP levels into four categories: A (↓) P (↓), A (↓) P (↑), A (↑) P (↓), and A (↑) P (↑). Patients with elevated levels of AFP and PIVKA-II had poorer outcomes, while those with reduced levels of both markers showed a better prognosis. In line with our findings, Sun et al. reported that reductions in AFP and PIVKA-II were positively correlated with longer OS and PFS in HCC patients undergoing anti-PD-1 immunotherapy [9]. Moreover, an elevation in either AFP or PIVKA-II alone was associated with an increased risk of disease progression and mortality. Advanced HCC patients with either AFP or PIVKA-II elevation alone had a two-fold increased risk of death and disease progression compared to those with reductions in both markers. Furthermore, we also explored the influence of various BCLC stages on survival in different AFP-PIV status. Our study suggested significant differences in OS and PFS for patients with different AFP-PIV status irrespectively of BCLC stages. In addition, the results still remained similar for HCC patients with a high tumor burden. Therefore, even without other adverse prognostic factors, the elevation of either AFP or PIVKA-II alone can significantly reduce patient survival rates, highlighting their crucial role in prognostic evaluation. These findings provide clinicians with valuable insights to develop personalized patient treatment strategies.

A previous study identified PIVKA-II as an autologous mitogen in HCC cell Lines, promoting tumor cell proliferation through activation of the Janus kinase 1 (JAK1) and signal transducer and activator of transcription 3 (STAT3) signaling pathway [10]. Furthermore, research by Suzuki et al. revealed that under hypoxic conditions, PIVKA-II secretion is suppressed due to hypophosphorylation of the mammalian target of rapamycin (mTOR), which in turn triggers epithelial-mesenchymal transition (EMT) and enhances metastatic potential in HCC [11]. Therefore, PIVKA-II does not correlate with AFP and represents distinct mechanisms of hepatocarcinogenesis, highlighting its potential as a complementary biomarker to AFP in clinical evaluations. Higher serum PIVKA-II levels have been associated with more aggressive tumor characteristics [12], and persistent elevation is often indicative of an increased risk of vascular invasion and recurrence [13, 14]. In comparison, serum AFP is a more reliable marker of tumor proliferative activity, typically showing a marked decline following extensive necrosis of hepatocellular carcinoma cells. The combined evaluation of AFP and PIVKA-II is increasingly recognized as a valuable approach in the clinical management of HCC, as these markers together improve diagnostic accuracy in most cases [15]. Moreover, in patients with locally advanced HCC, treatment-induced changes in AFP and PIVKA-II levels have shown potential in

Table 2 Logistic regression analysis for objective response rates ORR

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*	OR	95%CI	*P*
Age, year						
≤ 60	1			-		
> 60	1.108	0.613–2.004	0.733			
Sex, N						
Male	1			-		
Female	1.528	0.544–4.294	0.421			
BMI, kg/㎡						
≤ 24	1			-		
> 24	1.489	0.812–2.732	0.198			
ECOG						
0–1	1			-		
2	1.087	0.488–2.425	0.838			
Aetiology						
HBV	1			-		
HCV	0.596	0.227–1.565	0.293			
Alcohol	1.287	0.613–2.706	0.505			
Others	1.639	0.395–6.796	0.496			
Liver cirrhosis						
No	1			-		
Yes	1.286	0.734–2.256	0.379			
Child-Pugh Class						
A	1			-		
B	0.660	0.382–1.139	0.135			
BCLC Staging						
B	1			-		
	0.590	0.341–1.020	0.059			
Tumor burden						
≤ 7	1			1		
>7	0.143	0.053–0.384	<0.001	0.164	0.059–0.453	<0.001
PVTT						
No	1			1		
Yes	0.504	0.291–0.874	0.015	0.761	0.421–1.405	0.383
Extrahepatic metastases						
No	1			1		
Yes	0.561	0.316–0.998	0.049	0.654	0.342–1.250	0.199
TACE types						
C-TACE	1					
D-TACE	0.943	0.540–1.646	0.836			
Systemic therapy				-		
Donafenib + Tislelizumab	1					
Sorafenib + Camrelizumab	1.882	0.928–3.819	0.080			
Lenvatinib + Tislelizumab	1.163	0.563-2.400	0.684			
AFP-PIV status						
1	1			1		
2	0.793	0.377–1.665	0.539	0.840	0.381–1.850	0.665
3	0.929	0.424–2.038	0.885	1.173	0.509–2.703	0.709
4	0.253	0.118–0.542	<0.001	0.299	0.134–0.667	0.003

BMI Body mass index, *ECOG* Eastern Cooperative Oncology Group, *HBV* Hepatitis B virus, *HCV* Hepatitis C virus, *BCLC* Barcelona Clinic Liver Cancer, *PVTT* Portal vein tumor thrombus, *AFP* Alpha-fetoprotein, *PIVKA-II* Protein induced by vitamin K absence II, *TACE* Transarterial chemoembolization, *C-TACE* Conventional TACE, *D-TACE* Drug-eluting beads TACE

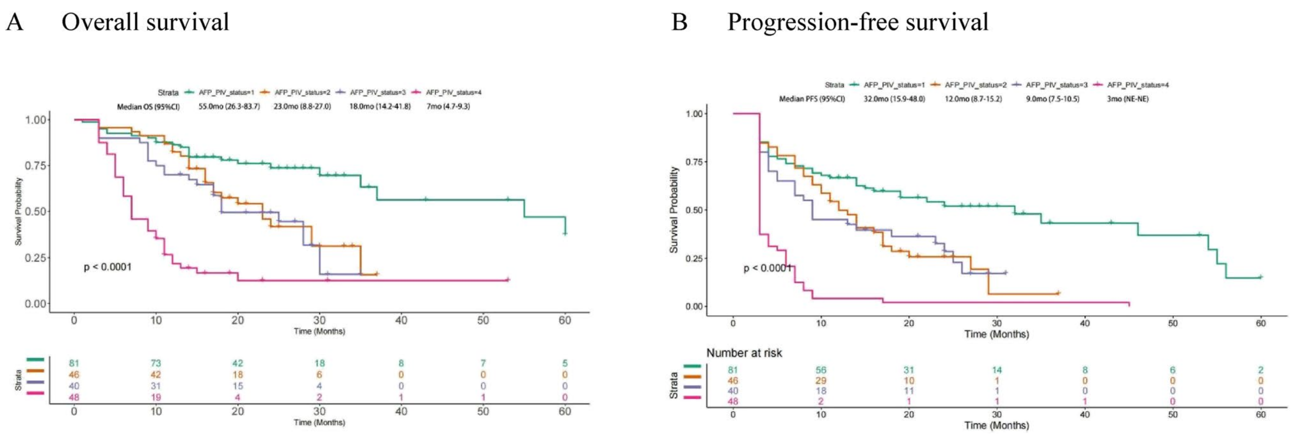

Fig. 2 Kaplan-Meier survival analysis of OS (**A**) and PFS (**B**) among different AFP-PIV status in advanced HCC patients

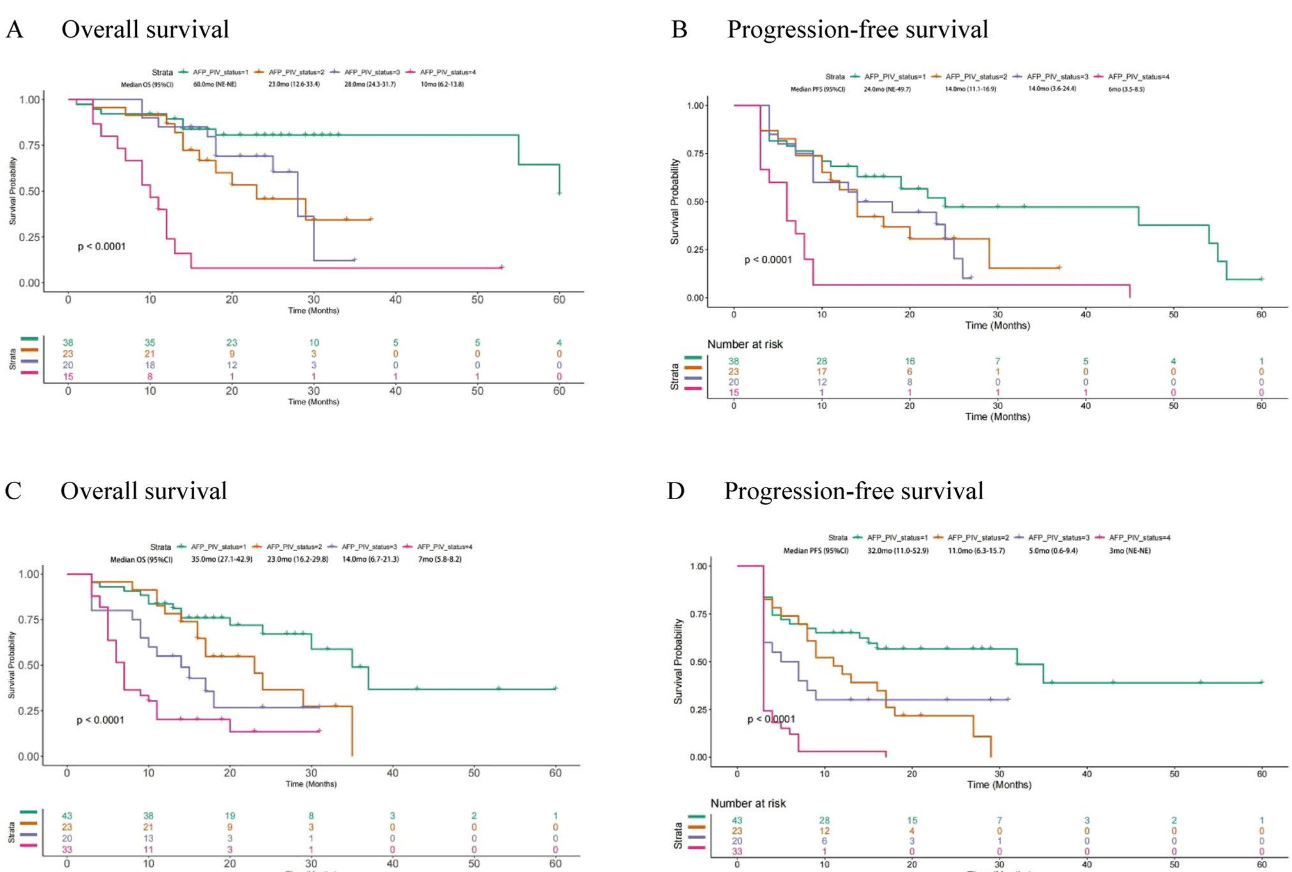

Fig. 3 Kaplan-Meier survival analysis of OS and PFS among different AFP-PIV status in HCC patients with BCLC stage B (**A**, **B**) and BCLC stage C (**C**, **D**)

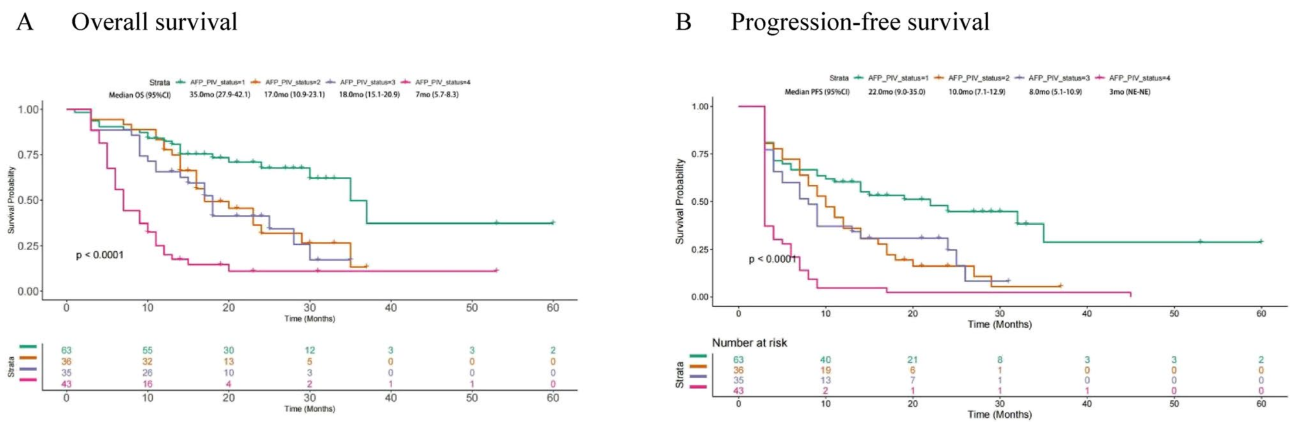

Fig. 4 Kaplan-Meier survival analysis of OS (**A**) and PFS (**B**) among different AFP-PIV status in HCC patients with a high tumor burden

predicting survival outcomes. A previous study indicates that patients who show a favorable biomarker response to TACE—reflected by reductions in AFP and PIVKA-II—tend to have longer progression-free and OS than non-responders [16].

In advanced HCC patients undergoing TACE combined with targeted therapy and anti-PD-1 immunotherapy, significant inconsistencies have been observed in the AFP and PIVKA-II levels trends, with these biomarkers sometimes displaying opposing changes. Such variability poses challenges in evaluating treatment response and prognostic outcomes. Several factors may contribute to this discrepancy. Firstly, HCC is characterized by significant intratumoral heterogeneity. Sun et al., using single-cell sequencing, demonstrated that different tumor cell subpopulations might secrete AFP and PIVKA-II. Certain subpopulations may be eliminated as treatment progresses, while others survive and continue producing specific tumor markers. Secondly, the biosynthesis of AFP and PIVKA-II is governed by distinct molecular pathways. AFP expression is primarily regulated by the Hedgehog and Notch signaling cascades, whereas PIVKA-II production is more closely linked to the Wnt/β-catenin signaling pathway [17]. Various therapeutic modalities may differentially suppress specific molecular pathways, resulting in asynchronous fluctuations in AFP and PIVKA-II levels. Moreover, alterations in the tumor microenvironment can indirectly affect biomarker expression. Following TACE, extensive tumor cell necrosis often leads to a marked decrease in AFP levels in some patients. However, PIVKA-II levels may temporarily rise due to coagulation disturbances triggered by localized ischemia, contributing to the divergent trends observed between these two biomarkers.

Several limitations of our study should be acknowledged. First, the retrospective design may introduce selection bias and further prospective validation is required. Second, the dynamic changes in AFP and PIVKA-II levels during HCC treatment are inherently complex. While our analysis highlighted characteristic patterns in these biomarkers, the underlying molecular mechanisms driving these changes remain to be fully elucidated through future research. Third, although our study is the first to underscore the prognostic value of AFP-PIV status in advanced HCC, optimal therapeutic strategies for these subgroups remain undefined. Effective treatment decisions will require the integration of multiple parameters, including imaging findings, drug sensitivity, and interventional efficacy. Future prospective studies should aim to tailor treatment regimens for patients demonstrating discordant biomarker responses to better inform clinical decision-making. Fourth, medication adherence may vary among patients due to differences in health status, socioeconomic conditions, or personal factors. Although adherence was monitored through structured follow-up, some degree of reporting inaccuracy cannot be ruled out. Lastly, various ICIs and TKIs were employed in this study. However, all agents used are recommended by established HCC treatment guidelines. This real-world approach supports the evaluation of multi-agent regimens and may allow for stratified analyses to identify the most effective combination strategies as the sample size grows.

In conclusion, we introduced an innovative approach by integrating the dynamic changes of AFP and PIVKA-II to assess their combined influence on survival outcomes in patients with advanced HCC across varying biomarker trends. This strategy offers a fresh perspective on the prognostic value of these markers and delivers meaningful insights to support clinical decision-making in the management of advanced HCC.

Table 3 Cox proportional hazards regression model analysis of OS

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P*	HR	95%CI	*P*
Age, year						
≤ 60	1			-		
> 60	1.268	0.854–1.884	0.246			
Sex, N						
Male	1			-		
Female	0.589	0.284–1.221	0.155			
BMI, kg/㎡						
≤ 24	1			-		
> 24	0.760	0.498–1.160	0.203			
ECOG						
0–1	1			-		
2	1.120	0.626–2.004	0.703			
Aetiology						
HBV	1			-		
HCV	1.557	0.863–2.809	0.141			
Alcohol	1.175	0.702–1.968	0.539			
Others	1.066	0.389–2.917	0.901			
Liver cirrhosis						
No	1			-		
Yes	1.025	0.700-1.503	0.897			
Child-Pugh Class						
A	1			-		
B	1.086	0.747–1.580	0.665			
BCLC Staging						
B	1			1		
C	1.635	1.117–2.393	0.011	0.696	0.303–1.596	0.392
Tumor burden						
≤ 7	1			1		
>7	3.305	1.715–6.369	<0.001	2.489	1.278–4.844	0.007
PVTT						
No	1			1		
Yes	1.556	1.074–2.252	0.019	1.307	0.686–2.488	0.415
Extrahepatic metastases						
No	1			1		
Yes	1.889	1.289–2.767	0.001	2.178	1.236–3.838	0.007
TACE types						
C-TACE	1					
D-TACE	0.875	0.593–1.292	0.502			
Systemic therapy				-		
Donafenib + Tislelizumab	1					
Sorafenib + Camrelizumab	1.006	0.678–1.674	0.783			
Lenvatinib + Tislelizumab	1.343	0.790–2.281	0.276			
AFP-PIV status						
1	1			1		
2	2.298	1.292–4.088	0.005	2.013	1.119–3.620	0.019
3	2.755	1.539–4.933	0.001	2.376	1.314–4.295	0.004
4	7.807	4.562–13.360	<0.001	7.234	4.189–12.495	<0.001

BMI Body mass index, *ECOG* Eastern Cooperative Oncology Group, *HBV* Hepatitis B virus; HCV, hepatitis C virus, *BCLC* Barcelona Clinic Liver Cancer, *PVTT* Portal vein tumor thrombus, *AFP* Alpha-fetoprotein, *PIVKA-II* Protein induced by vitamin K absence II, *TACE* Transarterial chemoembolization, *C-TACE* Conventional TACE, *D-TACE* Drug-eluting beads TACE

Table 4 Cox proportional hazards regression model analysis of PFS

Variables	**Univariate analysis**			**Multivariate analysis**		
	HR	**95%CI**	***P***	**HR**	**95%CI**	***P***
Age, year						
≤ 60	1			-		
> 60	1.099	0.778–1.551	0.593			
Sex, N						
Male	1			-		
Female	0.643	0.348–1.189	0.159			
BMI, kg/㎡						
≤ 24	1			-		
> 24	0.750	0.525–1.074	0.116			
ECOG						
0–1	1			-		
2	1.219	0.750–1.982	0.424			
Aetiology						
HBV	1			-		
HCV	1.254	0.729–2.156	0.414			
Alcohol	1.060	0.684–1.641	0.795			
Others	1.310	0.609–2.818	0.490			
Liver cirrhosis						
No	1			-		
Yes	1.084	0.777–1.512	0.634			
Child-Pugh Class						
A	1			-		
B	1.176	0.854–1.619	0.332			
BCLC Staging						
B	1					
C	1.359	0.987–1.872	0.060			
Tumor burden						
≤ 7	1			1		
>7	2.506	1.541–4.074	<0.001	2.018	1.230–3.311	0.005
PVTT						
No	1			1		
Yes	1.498	1.090–2.059	0.013	1.215	0.865–1.706	0.261
Extrahepatic metastases						
No	1			1		
Yes	1.414	1.010–1.979	0.044	1.296	0.908–1.851	0.153
TACE types						
C-TACE	1					
D-TACE	0.892	0.640–1.245	0.502			
Systemic therapy						
Donafenib + Tislelizumab	1					
Sorafenib + Camrelizumab	0.720	0.476–1.091	0.121			
Lenvatinib + Tislelizumab	1.261	0.824–1.930	0.286			
AFP-PIV status						
1	1			1		
2	2.017	1.272–3.196	0.003	1.951	1.229–3.099	0.005
3	2.047	1.256–3.334	0.004	1.963	1.194–3.227	0.008
4	5.909	3.746–9.323	<0.001	5.389	3.402–8.539	<0.001

BMI Body mass index, *ECOG* Eastern Cooperative Oncology Group, *HBV* Hepatitis B virus, *HCV* Hepatitis C virus, *BCLC* Barcelona Clinic Liver Cancer, *PVTT* Portal vein tumor thrombus, *AFP* Alpha-fetoprotein, *PIVKA-II* Protein induced by vitamin K absence II, *TACE* Transarterial chemoembolization, *C-TACE* Conventional TACE, *D-TACE* Drug-eluting beads TACE

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Authors' contributions
Jinfeng Bai wrote the manuscript; Rong Ding designed the study; Jinmei Zhou and Xin Zhao performed statistical analysis, Jianjie Hua, Wenqi Li and Fangfang Xiong prepared tables and figures. All authors reviewed and approved the final manuscript.

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Data availability
The datasets used during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The research was approved by the ethics committee of the third affiliated hospital of Kunming Medical University. Due to the retrospective design of the study, the institutional review board waived the requirement for informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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