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Original Article

Expression and diagnostic value of abnormal prothrombin and osteopontin in hepatocellular carcinoma with cirrhosis

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Abstract: Objective: To investigate the expression levels of prothrombin induced by vitamin K absence-II (PIVKA-II) and osteopontin (OPN) in patients with hepatocellular carcinoma (HCC) and cirrhosis, and to evaluate their potential as markers for cirrhosis severity. Methods: This retrospective study included 84 patients with HCC and cirrhosis treated at the Liver Disease Center of the 904th Hospital from January 2021 to December 2023, forming the cirrhosis group. Fifty healthy individuals undergoing routine physical examinations during the same period comprised the control group. We compared cirrhosis-related indicators and serum levels of PIVKA-II and OPN between the two groups and analyzed the relationships between these biomarkers, liver cancer-related indicators, Child-Pugh grades, tumor size, and their diagnostic value using receiver operating characteristic (ROC) curve analysis. Results: The cirrhosis group showed significantly higher levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), prothrombin time (PT), total bilirubin (TBIL), alpha-fetoprotein (AFP), OPN, and PIVKA-II compared to the control group (all $P < 0.05$). Conversely, levels of hemoglobin (Hb), white blood cells (WBC), platelets (PLT), and albumin (ALB) were significantly lower (all $P < 0.05$). Serum levels of OPN, PIVKA-II, AFP, TBIL, PT, and Child-Pugh scores were positively correlated, with correlation coefficients (r values) of 0.678, 0.634, 0.529, 0.617, 0.479, 0.551, 0.620, and 0.054, respectively (all $P < 0.05$). These markers were negatively correlated with ALB levels, with r values of -0.480 and -0.533 (both $P < 0.05$). Additionally, higher PIVKA-II and OPN levels were associated with larger tumors (> 3 cm) and more advanced cirrhosis stages ($P < 0.05$). Over a two-year follow-up, 12 patient deaths were recorded, with deceased patients showing higher levels of PIVKA-II, OPN, and AFP than those in the control group. ROC curve analysis revealed that AFP had a sensitivity of 98.8% and specificity of 82.0% in diagnosing HCC with cirrhosis. OPN achieved a sensitivity of 93.82% and a specificity of 88.0% for diagnosing cirrhosis, while PIVKA-II showed a sensitivity of 98.8% and a specificity of 80.0%. Conclusion: Serum levels of PIVKA-II and OPN correlate significantly with HCC presence, cirrhosis severity, Child-Pugh grading, and patient prognosis. Their combined diagnostic use enhances detection rates of HCC with cirrhosis and holds substantial clinical value, recommending their incorporation into clinical practice.

Keywords: Hepatocellular carcinoma with cirrhosis, prothrombin induced by vitamin K absence-II, osteopontin, diagnostic efficacy, cirrhosis grading

Introduction

Hepatocellular carcinoma (HCC) is a major malignancy within the digestive system and is the focus of ongoing global research and medical scrutiny [1, 2]. According to the World Health Organization, there is a rising incidence of HCC worldwide, particularly in developing nations [3, 4]. Studies indicate that the incidence of HCC is shaped by genetic predispositions, lifestyle choices, dietary patterns, and environmental pollutants, positioning it as a significant public health issue [5, 6]. The prognosis of HCC largely hinges on the stage at diagnosis; early detection markedly enhances patient survival. Currently, alpha-fetoprotein (AFP) is the predominant serum marker for HCC diagnosis, but its sensitivity and specificity are inadequate for

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Table 1. Comparison of general data between the two groups

Category	Cirrhosis group (n=80)	Control group (n=50)	t/χ^2	P
Age	57.4±11.5	56.8±12.0	1.578	0.074
Gender (Male/Female)	43/37	24/26	0.407	0.523
ALT (U/L)	69.4±18.2	23.0±6.2	14.523	< 0.001
AST (U/L)	57.5±14.3	13.9±4.0	17.611	< 0.001
Hb (g/L)	12.2±1.9	14.3±2.2	5.580	0.031
WBC ($\times 10^9$)	5.4±1.2	6.8±1.3	6.532	0.022
PLT ($\times 10^9$)	128.6±33.2	315.4±46.2	25.680	< 0.001
PT (s)	16.9±3.7	12.3±1.3	7.843	0.017
ALB (g/L)	35.4±9.5	48.6±10.0	7.868	0.012
TBIL (μmol/L)	63.4±15.2	12.4±3.3	12.054	< 0.001
AFP (μg/mL)	14.8±3.2	6.8±1.8	13.004	< 0.001
PIVKA-II (mAu/L)	25.6±2.9	104.67±22.7	17.882	< 0.001
OPN (ng/mL)	129.74±32.80	68.36±19.13	24.558	< 0.001

ALT: alanine aminotransferase, AST: aspartate aminotransferase, Hb: hemoglobin, WBC: white blood cells, PLT: platelets, ALB: albumin, PT: prothrombin time, TBIL: total bilirubin, AFP: alpha-fetoprotein, OPN: osteopontin, PIVKA-II: prothrombin induced by vitamin K absence-II.

Table 2. Correlation analysis of serum PIVKA-II, OPN and liver related indexes in patients with hepatocellular carcinoma cirrhosis

Category	PIVKA-II		OPN	
	r	P	r	P
AFP	0.678	0.041	0.479	0.030
TBIL	0.634	0.036	0.551	0.021
PT	0.529	0.042	0.620	0.013
Child-Pugh grading	0.617	0.026	0.0542	0.027
ALB	-0.480	0.039	-0.533	0.035

ALB: albumin, PT: prothrombin time, TBIL: total bilirubin, AFP: alpha-fetoprotein, OPN: osteopontin, PIVKA-II: prothrombin induced by vitamin K absence-II.

clinical demands. As a result, the search for more effective biomarkers, such as prothrombin induced by vitamin K absence-II (PIVKA-II) and osteopontin (OPN), is imperative [7, 8]. PIVKA-II, an inactive protein produced under vitamin K deficiency found in HCC tissues, and OPN, involved in the activation of hepatic stellate cells and variably expressed in liver lesions, are underexplored in clinical settings despite their diagnostic potential [9]. Previous research has largely focused on the diagnostic efficacy of PIVKA-II and OPN in detecting HCC, with limited exploration of their prognostic capabilities [10]. This study reaffirms their diagnostic value, aligning them with AFP, and explores their potential to predict patient outcomes post-treatment, thus broadening their applicability in diagnosis, treatment, and prognosis, and opening new avenues for early HCC detection.

Methods and materials

General information

We conducted a retrospective analysis of eighty-four patients diagnosed with HCC and cirrhosis treated at the Liver Disease Center of the 904th Hospital from January 2021 to December 2023, who constituted the cirrhosis group. Inclusion criteria: 1. Age > 18 years old; 2. Diagnosis and treatment of HCC with cirrhosis according to established guidelines [11]; 3. Availability of complete clinical data; 4. Good compliance and cooperation; 5. Primary diagnosis of HCC.

Exclusion criteria were: 1. Age > 70 years old; 2. Presence of other malignant tumors; 3. Prior treatment for HCC; 4. Significant cardiac or renal dysfunction. Fifty healthy individuals who underwent routine physical examinations during the same period were selected as the control group, with the main inclusion criterion being the absence of liver disease, confirmed by abdominal ultrasound, CT, or relevant blood tests. The study was approved by the Ethics Committee of the 904th Hospital.

Treatment measures

Patients with primary liver cancer (PLC) underwent transcatheter arterial chemoembolization. The modified Seldinger technique was employed to access the right femoral artery, introduce arterial sheathing, and positioning

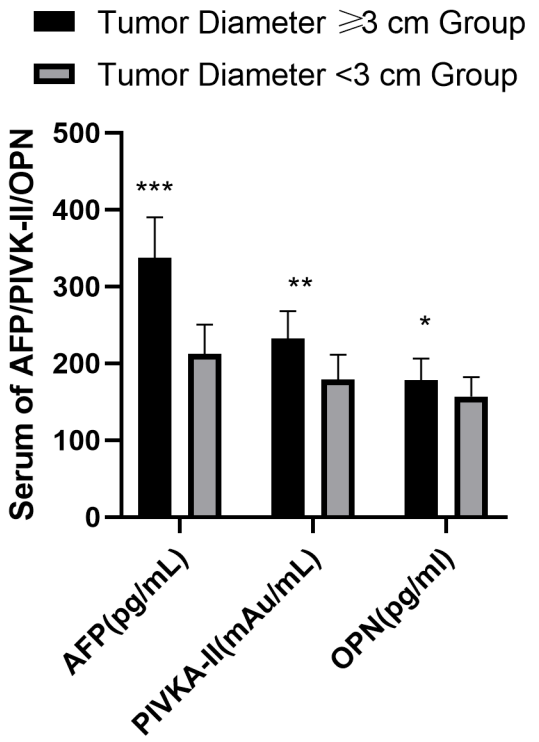

Figure 1. Expression of serum AFP, PIVKA-II, OPN and liver tumor size. Compared with tumor diameter < 3 cm, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. AFP: alpha-fetoprotein, OPN: osteopontin, PIVKA-II: prothrombin induced by vitamin K absence-II.

the catheter within the tumor-supplying artery. A mixture of oxaliplatin (50 mg), cisplatin (150 mg), and epirubicin (30 mg) was administered through the catheter. The selected dose of ethiodized oil ensured complete tumor staining disappearance, marking the endpoint of embolization. Additionally, a combination therapy of docetaxel and oxaliplatin was adopted. Patients received 3 mg/m^2 docetaxel intravenously over 15 minutes followed by 130 mg/m^2 oxaliplatin 45 minutes later, repeated every three weeks. Docetaxel dosage adjustments were based on creatinine clearance levels: 100% of the dose every 3 weeks if > 65 ml/min, 75% every 4 weeks if 55-65 ml/min, and 50% every 4 weeks if 25-54 ml/min. Drug resistance was assessed at baseline and during each treatment cycle.

Outcome measures

Routine examinations for all participants included complete blood count (hemoglobin, white blood cells, platelets), coagulation profile (prothrombin time), and liver function tests (ALB, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), prothrombin time (PT)) using an automated biochemical analyzer (Roche, Switzerland). Serum levels of PIVKA-II and AFP were measured through chemiluminescent microparticle immunoassay. Blood collection involved drawing 5 mL of fasting venous blood early in the morning, followed by centrifugation at 3,500 rpm for 5 minutes with a radius of 10 cm. Serum AFP was assessed using the Centaur XP automatic immunoassay analyzer (Siemens, Germany); PIVKA-II levels were measured using the G1200 analyzer (Lumipulse, Fujirebio, Japan).

Statistical analysis

Data were analyzed using SPSS software version 26.0. Continuous variables were presented as mean ± SEM and analyzed using the t-test for normally distributed data, with independent sample t-tests for comparisons between groups. Categorical variables were expressed as percentages and analyzed using the chi-square test (χ^2). Spearman's correlation analysis was used to examine relationships between serum levels of PIVKA-II, OPN, and other liver-related indicators. A *p*-value of less than 0.05 was considered statistically significant.

Results

Comparison of baseline data between the two groups

No significant differences were observed in age and gender between the two groups (both P > 0.05). The cirrhosis group exhibited significantly elevated levels of ALT, AST, PT, TBIL, AFP, PIVKA-II, and OPN, and decreased levels of hemoglobin, platelets, and total protein compared to the control group (all P < 0.05). See **Table 1**.

Correlation analysis of serum PIVKA-II and OPN with liver-related indicators

Serum levels of OPN, PIVKA-II, AFP, TBIL, PT, and Child-Pugh scores were positively correlated, with correlation coefficients (r values) of 0.678, 0.634, 0.529, 0.617, 0.479, 0.551, 0.620, and 0.054, respectively (all P < 0.05).

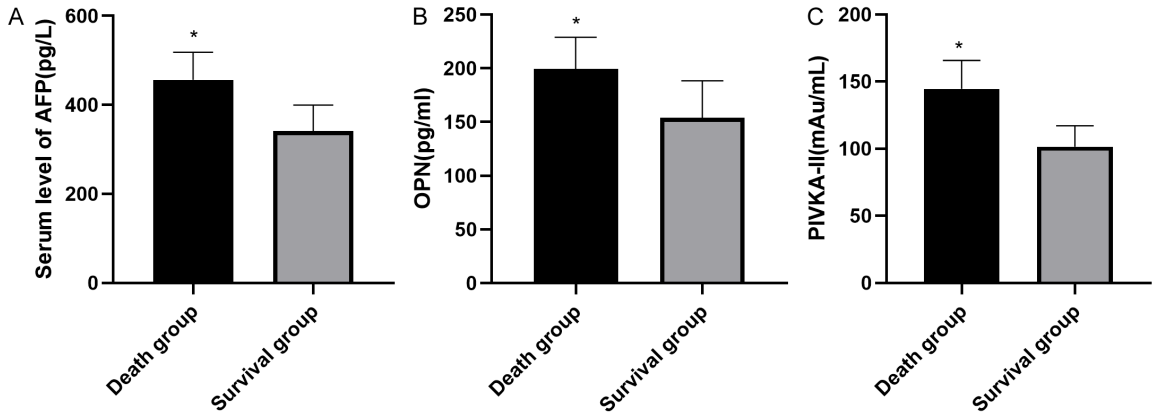

Figure 2. The expression levels of AFP, PIVKA-II and OPN were compared in the deceased patients and the surviving patients between the two groups. A: The efficacy of serum AFP in predicting death; B: The efficacy of serum OPN in predicting death; C: Predictive efficacy of bid PIVKA-II for patient death. AFP: alpha-fetoprotein, OPN: osteopontin, PIVKA-II: prothrombin induced by vitamin K absence-II. *Compared with the survival group, $P < 0.05$.

Table 3. Serum AFP, PIVKA-II and OPN levels in two groups predicting the diagnostic efficacy of death in patients with cirrhosis

Detection index	Sensitivity	Specificity	AUC (95% CI)
AFP	88.24%	83.33%	0.915 (0.834-0.929)
OPN	83.82%	75.0%	0.841 (0.735-0.947)
PIVKA-II	97.26%	91.67%	0.951 (0.8776-0.993)

AFP: alpha-fetoprotein, OPN: osteopontin, PIVKA-II: prothrombin induced by vitamin K absence-II.

These markers negatively correlated with ALB, with r values of -0.480 and -0.533 (both $P < 0.05$). See **Table 2**.

Relationship between serum levels of AFP, PIVKA-II, OPN, and liver tumor size

Patients were categorized based on tumor size: 47 with tumors ≥ 3 cm and 33 with tumors < 3 cm. Those with larger tumors had higher serum levels of AFP, PIVKA-II, and OPN (all $P < 0.05$). During the study period, 12 deaths occurred, with deceased patients showing higher levels of these biomarkers compared to survivors. See **Figures 1** and **2**.

Predictive efficacy of serum biomarkers in mortality prediction

The study determined cutoff values for AFP, OPN, and PIVKA-II at 410.8 pg/mL, 186.0 pg/mL, and 127.7 mAu/mL, respectively. PIVKA-II showed superior sensitivity and specificity in predicting mortality among patients with HCC and cirrhosis compared to AFP and OPN (all $P < 0.05$). See **Table 3** and **Figure 3**.

Serum levels of PIVKA-II and OPN across different Child-Pugh grades

Among the patients, 34 were classified as Child-Pugh grade A, 36 as grade B, and 14 as grade C. Higher Child-Pugh grades were associated with increased serum levels of PIVKA-II and OPN (all $P < 0.05$). See **Figure 4**.

Diagnostic performance of serum biomarkers in HCC with cirrhosis

Cutoff values were established for diagnosing HCC with cirrhosis: 59.8 pg/mL for AFP, 47.7 pg/mL for OPN, and 57.01 mAu/mL for PIVKA-II. See **Table 4** and **Figure 5**.

Discussion

PLC is a major malignant tumor of the digestive tract that occurs worldwide [12, 13]. Surgical resection remains the preferred treatment [14], but due to the late presentation of symptoms and the prevalence of chronic liver conditions such as cirrhosis, only about 20% of patients qualify for surgery [15]. Therefore, early and precise diagnosis is vital for improving patient outcomes. Liver biopsy, despite being a primary diagnostic tool for PLC, is invasive; hence, imaging and monitoring of AFP are more com-

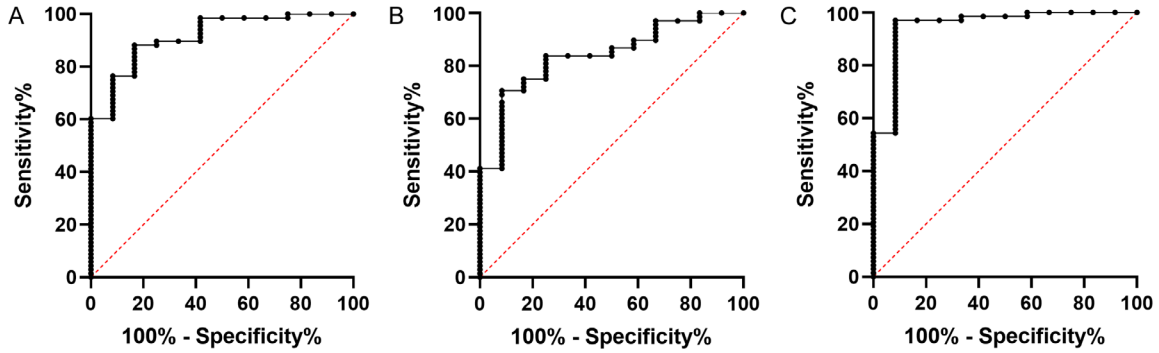

Figure 3. Serum AFP (A), PIVKA-II (B) and OPN (C) levels predicted the diagnostic efficacy of death in patients with cirrhosis. AFP: alpha-fetoprotein, OPN: osteopontin, PIVKA-II: prothrombin induced by vitamin K absence-II.

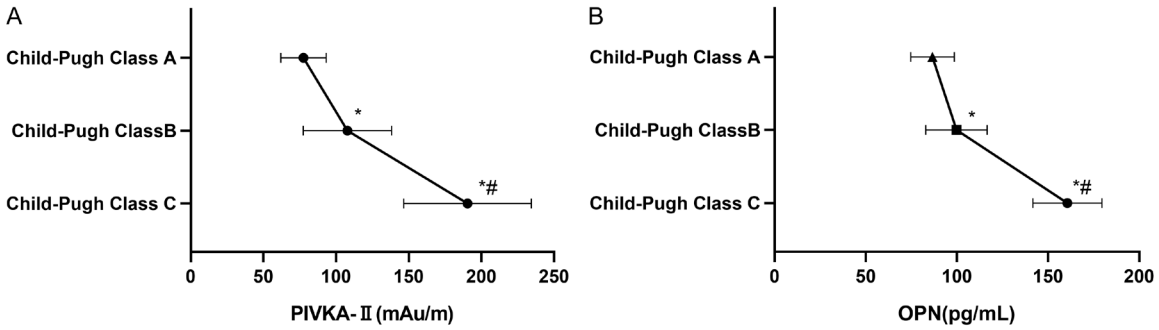

Figure 4. Relationship between serum PIVKA-II and OPN levels in patients with Child-Pugh classification. A: The relationship between serum PIVKA-II and grade. *indicates $P < 0.05$ compared with Grade A and Grade C; #indicates $P < 0.05$ compared with Grade C and Grade B. B: The relationship between serum OPN and grade. *indicates $P < 0.05$ compared with Grade B and Grade C; #indicates $P < 0.05$, comparing Grade C with Grade B. AFP: alpha-fetoprotein, OPN: osteopontin, PIVKA-II: prothrombin induced by vitamin K absence-II.

monly used. AFP, a glycoprotein produced by hepatocytes and yolk sac cells during embryonic development, is markedly increased in response to liver damage and serves as a critical clinical marker for PLC [16]. High AFP levels (≥ 400 μg/L) indicate malignant liver lesions, while mild elevations (< 400 μg/L) call for continued monitoring. Nevertheless, nearly 30% of PLC patients may exhibit normal serum AFP levels [17]. Moreover, AFP detection proves less effective in populations predominantly affected by alcohol- and fat-related liver cancer, with early-stage positivity rates dipping below 20%. As a result, AFP is increasingly viewed as unreliable for screening in many regions, driving the search for more sensitive and specific biomarkers. This retrospective study reviews patient data and serum biomarkers to investigate the diagnostic and prognostic potential of PIVKA-II and OPN for liver cancer.

Previous studies typically find lower levels of liver enzyme markers (ALT and AST), platelet counts, and total protein in healthy individuals [17]. In contrast, this study observes that these indicators are elevated in patients with HCC and cirrhosis compared to healthy controls, likely due to liver damage from HCC and cirrhosis which leads to increased enzyme release into the bloodstream. Cirrhosis also disrupts the portal venous system, leading to obstructed blood flow, splenic enlargement, increased spleen activity, and consequently, reduced platelet counts. These findings support those of previous research [18]. Furthermore, studies have shown correlations between PIVKA-II and OPN levels and various HCC and cirrhosis markers (AFP, TBIL, PT, and ALB), substantiating the results of this study [19]. OPN, a member of the SIBLING family located on chromosome 4, is a secretory calcium-binding phosphorylated glycoprotein with diverse biological roles, includ-

Table 4. Diagnostic efficacy of serum AFP, PIVKA-II and OPN levels in liver cancer cirrhosis

Detection index	Sensitivity	Specificity	AUC (95% CI)
AFP	98.8%	82.0%	0.962 (0.933-0.991)
OPN	93.82%	88.0%	0.902 (90.851-0.953)
PIVKA-II	98.8%	80.0%	0.873 (0.814-0.933)

AFP: alpha-fetoprotein, OPN: osteopontin, PIVKA-II: prothrombin induced by vitamin K absence-II.

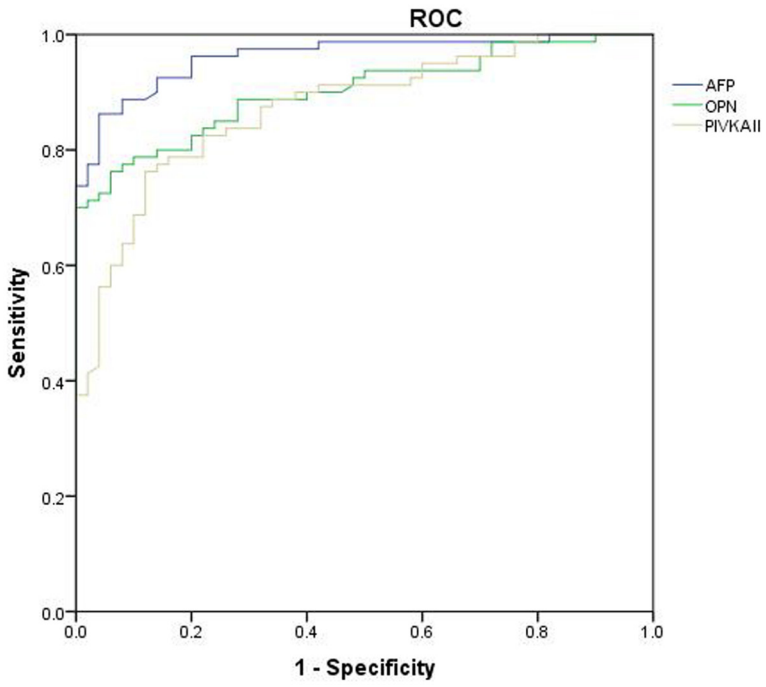

Figure 5. Diagnostic efficacy of serum AFP, PIVKA-II and OPN levels in liver cancer cirrhosis. AFP: alpha-fetoprotein, OPN: osteopontin, PIVKA-II: prothrombin induced by vitamin K absence-II.

ing early stages of malignant tumor development. It is particularly linked to the development and metastasis of HCC and has shown a detection rate over 90% for hepatitis B-related liver cancer, highlighting its diagnostic potential [20-22]. This study suggests that OPN's diagnostic value rivals that of AFP, historically the primary marker for liver cancer.

Individuals with vitamin K deficiency, those taking warfarin, or those exposed to benzene may exhibit elevated levels of PIVKA-II. Treatment with dicoumarol - a propyl coumarin zymogen - can cause decarboxylation coagulation abnormalities due to its ineffective binding with calcium ions to phospholipids, leading to functional deficits. Measuring PIVKA-II can preemptively indicate vitamin K deficiency before coagulation tests or bleeding occur. While PIVKA-II is uncommon in healthy individuals, it may be present in those with liver diseases or malignancies, even in the absence of vitamin K deficiency [23]. Research has established PIVKA-II as an effective marker for diagnosing HCC, demonstrating higher sensitivity and specificity than AFP, thus improving liver cancer detection rates [24, 25]. Authoritative guidelines from organizations such as the Asian Pacific association for the study of the Liver and Japan Society of Hepatology now recommend PIVKA-II as a critical biomarker for liver cancer screening, contributing to both diagnosis and prognosis assessments. This study supports these findings, indicating that PIVKA-II possesses superior diagnostic value compared to AFP, corroborating previous research [26, 27]. The enhanced diagnostic performance of PIVKA-II, OPN, and AFP observed in this study may be linked to the advanced stages of the diseases in the patient cohort. These results indicate that PIVKA-II and OPN potentially match AFP in their diagnostic effectiveness for HCC and cirrhosis.

Our analysis of the predictive efficacy of serum levels of AFP, PIVKA-II, and OPN for mortality in patients with liver cirrhosis shows that all three biomarkers have comparable predictive value. This observation aligns with the fact that these markers are released from hepatocytes into the bloodstream during liver damage, with higher expressions correlating with more advanced liver disease. Such findings affirm the robust predictive value of AFP, PIVKA-II, and OPN for patient prognosis, echoing previous research [28, 29].

This study has a few limitations, its small sample size and variability in patient condition

severity, necessitating further validation with a larger dataset. Moreover, while this study highlights the individual diagnostic efficacy of the biomarkers, the potential synergistic effects of their combined use remain unexplored. Exploring this combined predictive impact could further refine our conclusions and improve diagnostic accuracy. Lastly, the follow-up time of patients in this study is relatively short, and additional follow-up studies are needed to consolidate the predictive effect of serum markers on the long-term prognosis of patients with liver cancer.

In summary, serum levels of PIVKA-II and OPN correlate with liver cancer cirrhosis indicators, Child-Pugh classification, and patient prognosis. Utilizing a combined diagnostic approach can enhance the detection rate of liver cancer cirrhosis, offering significant clinical value.

Disclosure of conflict of interest

None.

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