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The value of PIVKA-II versus AFP for the diagnosis and detection of postoperative changes in hepatocellular carcinoma

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ABSTRACT

Objective: To explore the diagnostic value of abnormal prothrombin II (PIVKA-II) and alpha-fetoprotein (AFP) in primary hepatocellular carcinoma (HCC).
Methods: From 2018 0.01 to 2020.01, there were 158 patients with primary liver cancer caused by chronic hepatitis B (male 116, women 42) and 62 patients with chronic hepatitis B (male 34, female 28). The levels of serum PIVKA-II and AFP were measured, and the results were statistically analyzed.
Results: The value of PIVKA-IIin liver cancer group was distinctly higher than that in chronic viral hepatitis B group, the difference is statistically significant ($P < 0.05$). So does the value of AFP. Draw the subject working characteristic curve (ROC curve), the area under the curve of AFP and PIVKA-II is 0.799 and 0.836, and that of the combination of AFP and PIVKA-II is 0.854, the sensitivity is 57.6%,68.4%,72.2%,respectively, the specificity is 93.5%, 98.4%, 96.8%, respectively. After operation or interventional therapy, the value of PIVKA-II in liver cancer group was clearly lower than that before treatment, and the difference was statistically significant.
Conclusion: In the diagnostic value of primary liver cancer, PIVKA-II combined with AFP is higher than PIVKA-II, while AFP has the lowest benefit. We also find that PIVKA-II has higher disease monitoring value than AFP.

1. Background

Primary liver cancer is the fourth most common malignant tumor and the second leading cause of tumor-related deaths in China, making it a serious threat to the health of the population.[1] Primary hepatocellular carcinoma has an insidious onset and lacks clinical symptoms in the early stage. Liver ultrasound (US) and serum alpha-fetoprotein (AFP) are often used for the early screening of liver cancer. Among them, the serological detection of AFP is an important diagnostic method and, while AFP is generally considered a specific marker for the detection of primary liver cancer, other factors such as pregnancy, gonad embryoma, active hepatitis, and secondary liver cancer need to be excluded. The positive rate of liver cancer detection is less than 70%, with a 30% missed detection rate when used alone.[2] Since its first discovery by Libert in 1984,[3] the protein induced by vitamin K deficiency or antagonist II (PIVKA-II), also known as Des-γ-carboxyprothrombin (DCP), has been gradually accepted as a specific serum biomarker for liver cancer and is included in the Japanese Society of Hepatology (JSH) guidelines.[4] The purpose of the present study was to evaluate the clinical contribution of PIVKA-II as a new biomarker for the diagnosis of liver cancer and to compare it to AFP.

1.1. Data

From January 2018 to January 2020, data from 257 patients with primary liver cancer (male, 189; female, 68) and 314 patients with chronic hepatitis B (male 206, female 108) at Wenzhou People's Hospital were collected. Primary liver cancer was diagnosed pathologically or clinically according to the Standard for Diagnosis and Treatment of Primary Liver Cancer, version 2019. Chronic hepatitis B was diagnosed by five indicator test for hepatitis B and HBV-DNA load. After excluding patients with coagulation disorders, vitamin K uptake disorders, vitamin K blocker use, acute inflammatory diseases, and kidney and liver failure, this study finally enrolled a total of 158 patients with primary liver cancer and 62 patients with chronic hepatitis B (see Figs. 1 and 2). The basic information of the patients in each group is shown in Table 1.

1.2. Methods

Peripheral venous blood samples were collected from fasted patients, who had not had any prior treatment and showed no acute inflammation during blood collection. The blood samples of the selected cases were

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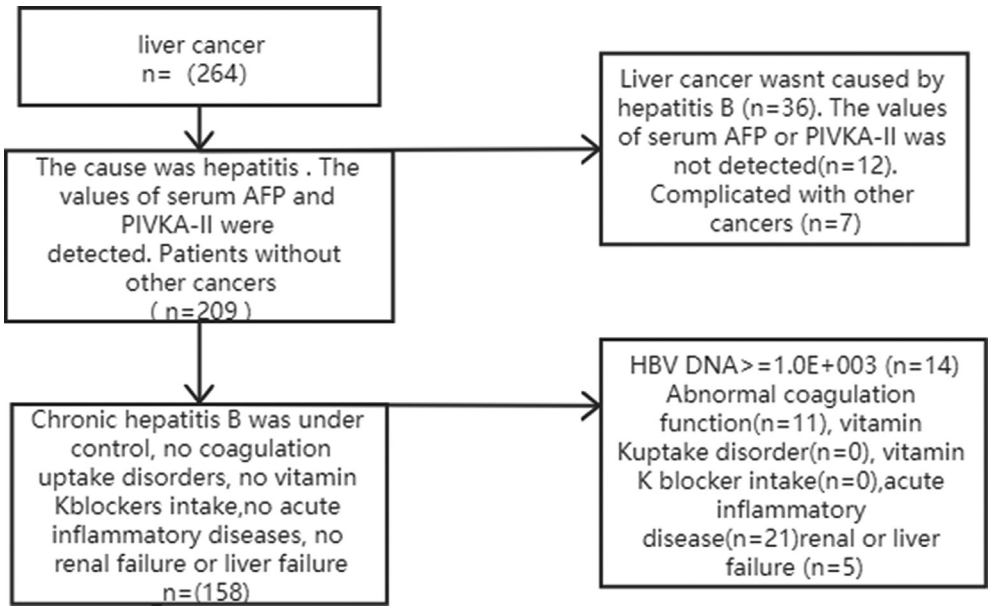

Fig. 1. Flowchart of liver cancer patient included definition.

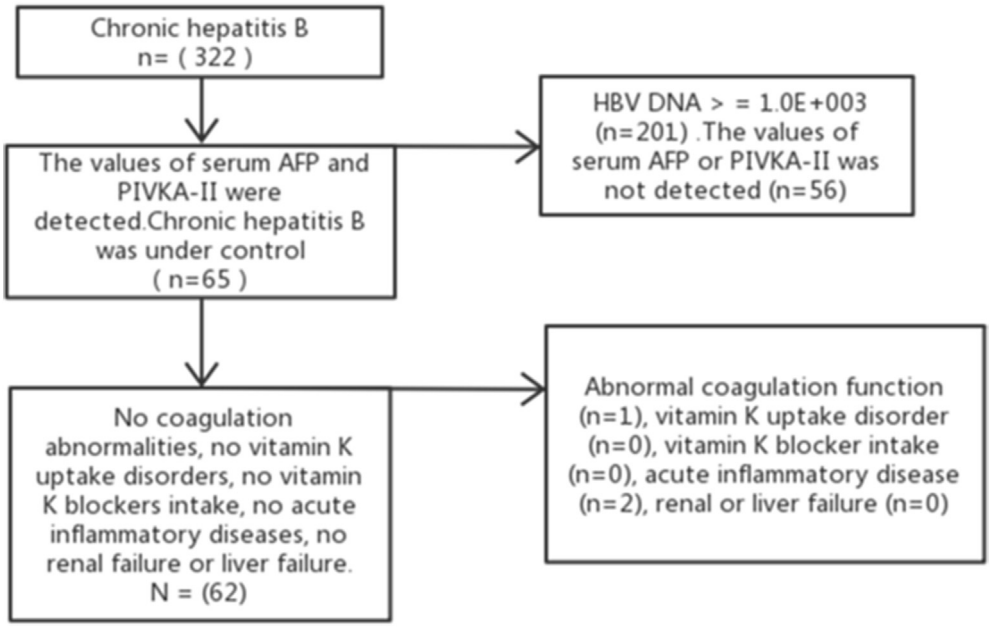

Fig. 2. Flowchart of patients with chronic hepatitis B included definition.

Table 1
Basic characteristics of two groups.

Variable	Primary liver cancer group	Chronic hepatitis B group
Age,years		
<40	7	8
40–70	118	48
>70	33	6
Sex		
Male	116	34
Female	42	28
AFP(ng/ml) [X ± S]	2429.87 ± 9775.11	11.16 ± 48.63
PIVKA-II(mAU/ml)[X ± S]	3406.85 ± 9780.04	27.08 ± 46.15

analyzed on an ARCHITECT PLUS i2000SR system after centrifugation for 10 min. In this study, the threshold PIVKA-II and AFP concentrations for the diagnosis of liver cancer were 40 mAU/mL and 10 ng/mL, respectively. Cases with concentrations exceeding this threshold were diagnosed with liver cancer. The positive rate for the combined diagnosis was determined based on at least one test value exceeding the threshold. Other laboratory tests were performed to rule out clinical conditions that might affect the serum levels of the measured parameters (i.e., severe renal or liver failure, inflammation).

1.3. Ethical approval

The study was approved by the ethics committee of Wenzhou people's Hospital. All clinical practices and observations were conducted in accordance with the Declaration of Helsinki. Informed consent was

Table 2
Detection of AFP and PIVKA- II in serum of patients in two groups.

Groups	Number of cases	AFP(ng/ml) [X ± S]	PIVKA-II(mAU/ml) [X ± S]
Primary liver cancer	158	2429.87 ± 9775.11	3406.85 ± 9780.04
Chronic hepatitis B	62	11.16 ± 48.63	27.08 ± 46.15
t		3.110	4.344
p value		0.002	0.000

obtained from each patient before the study was conducted.

1.4. Patient consent

Written informed consent was obtained from patients for publication of these case reports and any accompanying images.

2. Results

2.1. Basic data

In the primary liver cancer group, 104 cases had PIVKA-II concentrations above the threshold value, while 89 cases had AFP concentrations above the threshold. A total of 117 cases of liver cancer were detected by both measures. In the chronic hepatitis B group, four cases had AFP concentrations above the threshold, compared to one patient for PIVKA-II. Using independent sample t-test, $t'_{AFP} = 3.110$ ($P = 0.002$) and $t'_{PIVKA\text{-}II} = 4.344$ ($P = 0.000$), The detection value of the liver cancer group was significantly greater than that of the chronic hepatitis B virus group (see Table 2).

2.2. ROC curve analysis and threshold values for single and combined detection using AFP and PIVKA-II

The ROC curves of AFP, PIVKA-II, and AFP combined with PIVKA-II in the primary liver cancer group are shown in Fig. 3 and Table 3. In this group, the AUC of AFP combined with PIVKA-II was the highest, while the AUC of AFP was the lowest. The Youden index was the highest for an AFP concentration of 9.10 ng/mL and PIVKA-II concentration of 34.92 mAU/mL. In this study, the sensitivity of AFP, PIVKA-II, and AFP combined with PIVKA-II were 57.6%, 68.4%, and 72.2%, respectively, while the specificities were 93.5%, 98.4%, and 96.8%, respectively (Table 4).

Table 3
AUC in evaluating PIVKA-II and AFP in the diagnosis of Primary Hepatocellular carcinoma.

Variable	AUC	SE	P	95%CI
AFP	0.799	0.30	0.000	0.740–0.859
PIVKA-II	0.836	0.26	0.000	0.785–0.888
AFP combined with PIVKA-II	0.854	0.25	0.000	0.805–0.903

Table 4
Sensitivity and Specificity of each variable and their Combination.

		Combination PIVKA –II
Sensitivity		
AFP	57.6%	72.2%
PIVKA –II	68.4%	
Specificity		
AFP	93.5%	96.8%
PIVKA –II	98.4%	

2.3. Evaluation of the value of PIVKA-II in disease surveillance

A total of 84 patients in the primary liver cancer group were treated with surgery or interventional therapy. Throughout treatment, the AFP and PIVKA-II levels declined. After treatment, the AFP and PIVKA-II levels decreased compared to those before treatment. Paired sample t-tests were showed no significant difference between the groups, but the decrease in PIVKA-II was statistically significant when there was no grouping (Table 5, Fig. 4 and 5).

3. Discussion

Abnormal PIVKA-II results from an inability to convert the prothrombin precursor in the liver into prothrombin to provide clotting activity due to vitamin K deficiency or vitamin K muggers and is released into the blood. The only structural difference between abnormal PIVKA-II and prothrombin is that the glutamic acid residue distributed on the N-terminal of the molecule is not carboxylated, so it cannot bind calcium

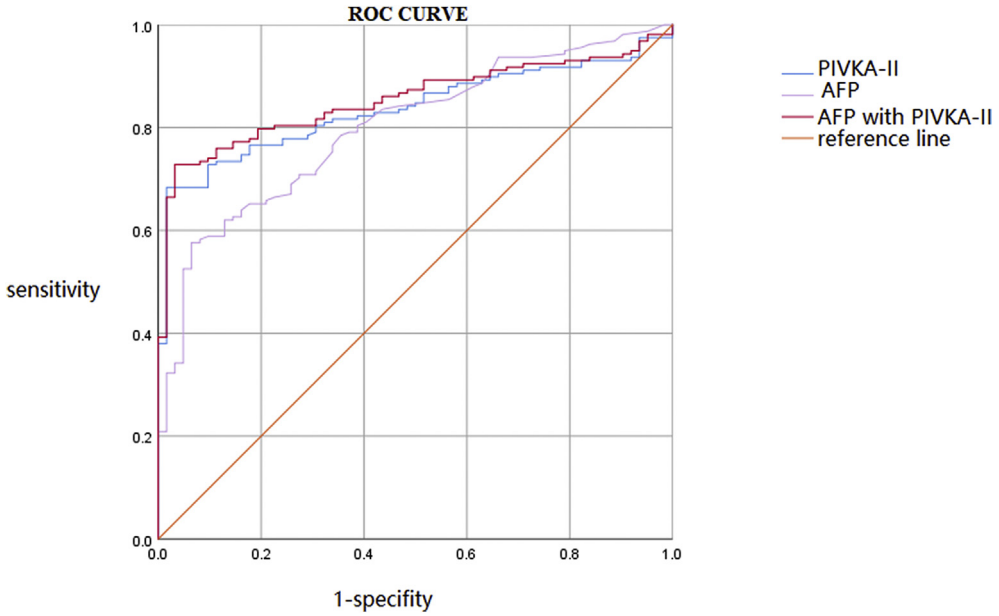

Fig. 3. ROC curve of single and combined detection of PIVKA-II and AFP in the diagnosis of primary liver cancer.

Table 5
Values of AFP and PIVKA-II before and after treatment of each group.

Category	Treatment			
	Microwave Ablation	Surgery	Intervention	Total
Cases NO.	23	35	26	84
AFP value before treatment [X ± S](ng/ml)	1712.04 ± 4276.58	3319.94 ± 14652.55	3932.60 ± 902.20	6026.52 ± 29095.55
AFP value after treatment [X ± S](ng/ml)	903.71 ± 2731.61	851.69 ± 3139.30	3850.77 ± 883.43	1497.71 ± 4754.08
t	1.678	1.098	1.131	1.661
p value	0.1075	0.282	0.273	0.100
DCP value before treatment [X ± S](mAU/ml)	3237.60 ± 809.40	5059.65 ± 923.76	17198.72 ± 3945.66	3598.01 ± 11454.90
DCP value after treatment [X ± S](mAU/ml)	549.82 ± 137.46	5217.74 ± 952.62	9691.22 ± 2223.32	1346.06 ± 5020.38
t	1.819	1.621	0.053	2.244
p value	0.074	0.108	0.311	0.027

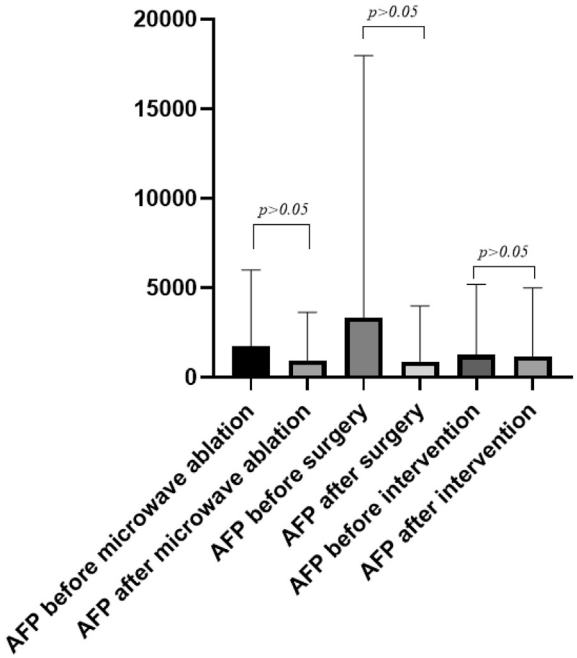

Fig. 4. The value of AFP in each group before and.

ions and phospholipids and loses its clotting activity. PIVKA-II in patients with liver cancer is believed to be produced by cancer cells; that is, it is the product of liver cancer itself.[5] AFP is produced by undifferentiated hepatocytes and is the most commonly used tumor marker for the detection of primary liver cancer; however, its levels also increase in acute hepatitis and acute attack of chronic hepatitis. Hepatitis B virus load affects AFP detection; thus, the diagnostic sensitivity and specificity of this marker are not satisfactory. The results of the present study showed that higher sensitivity, specificity, and AUC for PIVKA-II in primary liver cancer compared to those for AFP. Increasing numbers of studies on the diagnosis of primary liver cancer at home and abroad have shown a higher clinical value of PIVKA-II than that of AFP. The Chinese Standard for the Diagnosis and Treatment of Primary Liver Cancer (2019 edition) states that abnormal prothrombin can also be used as a marker

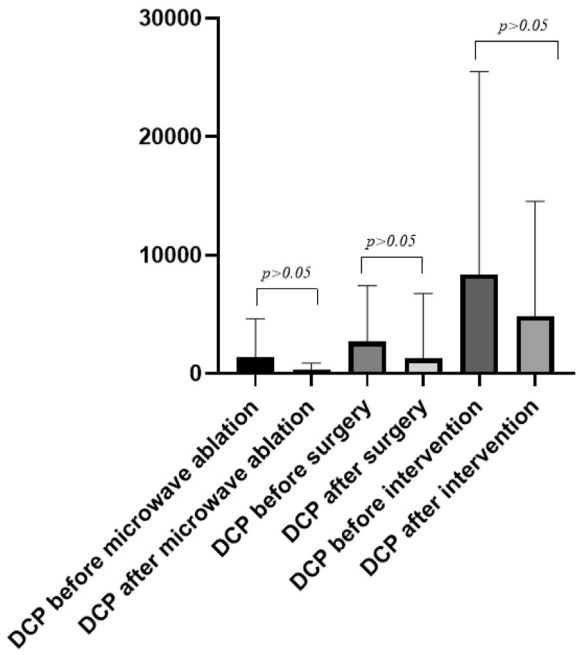

Fig. 5. The value of DCP in each group before and after treatment and the difference between groups after treatment and the difference between groups. Note:PIVKA-II also called DCP.

for the early diagnosis of liver cancer, especially in patients with negative serum AFP findings.[6–9] This study also observed decreased AFP and PIVKA-II levels after operation or interventional therapy. Subgroup analysis showed no significant differences among groups. However, as the number of cases was small, the decrease in PIVKA-II was statistically significant when not grouped. A decrease in PIVKA-II concentration showed prognostic value, as also reported by Yang et al.[10] however, the study was limited by the number of cases and related indicators; thus, additional research is required. In addition, due to the limited number of cases, comparative analysis of healthy cases and other causes of liver disease or a comparative analysis of primary liver cancer by stages were performed; therefore, a more accurate conclusion could not be drawn. Additional relevant cases need to be collected for analysis.

4. Conclusion

In this study, PIVKA-II was superior to AFP for the diagnosis of primary liver cancer, with the combination of the two markers showing the best effect. PIVKA-II may also be useful for monitoring the prognosis of liver cancer.

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Declaration of competing interest

The authors declare that they have no conflicts of interests to this work. We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

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