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Diagnostic Value of Abnormal Prothrombin for Primary Liver Cancer

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Abstract: *Objective:* To investigate the diagnostic value of abnormal serum prothrombin levels in hepatocellular carcinoma (HCC). *Methods:* A total of 298 patients were diagnosed with HCC at Hunan Provincial People's Hospital between January 1, 2019, and December 31, 2024, through imaging or liver biopsy, along with 100 patients with cirrhosis, 100 patients with chronic hepatitis B virus infection, and 89 healthy controls, were included in the study. Basic demographic information, as well as levels of abnormal serum prothrombin and alpha-fetoprotein (AFP), were collected. The levels of abnormal serum prothrombin and AFP across the four groups were compared, and their diagnostic efficacy for HCC was analyzed using ROC curve analysis. *Results:* Abnormal prothrombin levels were significantly higher in the liver cancer group compared to the cirrhosis, hepatitis, and healthy control groups ($P < 0.05$). No significant differences in abnormal serum prothrombin levels were observed among the cirrhosis, hepatitis, and healthy control groups ($P > 0.05$). Serum AFP levels were significantly higher in the liver cancer group compared to the cirrhosis, hepatitis, and healthy control groups ($P < 0.05$) and were higher in the hepatitis group compared to the cirrhosis and healthy control groups ($P < 0.05$). However, no significant difference in AFP levels was found between the cirrhosis and healthy control groups ($P > 0.05$). ROC curve analysis indicated that the area under the curve (AUC) for abnormal serum prothrombin and AFP in diagnosing HCC was 0.925 (95% CI: 0.901–0.949) and 0.810 (95% CI: 0.775–0.845), respectively, with sensitivities and specificities of 84% and 75% for abnormal prothrombin and 94% and 76% for AFP. For the diagnosis of AFP-negative HCC, the AUC for abnormal serum prothrombin was 0.838 (95% CI: 0.774–0.901), with a sensitivity and specificity of 65% and 95%, respectively. *Conclusion:* Serum abnormal prothrombin levels are highly expressed in HCC patients and demonstrate strong diagnostic efficacy for HCC.

Keywords: Abnormal prothrombin; Alpha-fetoprotein; Primary liver cancer; Hepatitis B virus; Cirrhosis

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1. Introduction

Primary liver cancer is the fourth leading cause of cancer-related deaths worldwide and ranks sixth in global incidence [1]. The World Health Organization (WHO) estimates that one million people will die from liver cancer by 2030. The incidence and mortality rates of hepatocellular carcinoma (HCC) are particularly high in

China, placing the country fourth globally in terms of burden [2].

The pathological types of primary liver cancer include hepatocellular carcinoma, cholangiocellular carcinoma, and mixed hepatocellular–cholangiocyte carcinoma, with hepatocellular carcinoma accounting for more than 90% of cases. The onset of primary liver cancer is often insidious, with no apparent symptoms in the early stages. This leads many patients to present in the middle or late stages of the disease. Early diagnosis and treatment are essential for improving patient outcomes, prolonging survival, and enhancing quality of life.

In China, liver ultrasound examinations and alpha-fetoprotein (AFP) detection are commonly employed for diagnosing primary liver cancer. However, both methods have limitations. The diagnostic accuracy of liver ultrasound varies depending on the subjectivity and clinical experience of the operator. AFP also has poor sensitivity and specificity. Approximately 30% of HCC patients in China are AFP-negative [3]. Similarly, in European and American countries, only 40% to 60% of patients with HCC and 10% to 20% of patients with early HCC exhibit elevated AFP levels [4]. Moreover, AFP levels can also be elevated in other conditions, such as active hepatitis, pregnancy, and embryogenic tumors, reducing its specificity. As a result, AFP is not included in the screening indices for HCC in many countries.

Recent studies have indicated that abnormal prothrombin levels are elevated in HCC patients [5], making it a promising new serological marker for HCC screening. However, existing research on this topic is limited. This study aims to investigate the diagnostic value of abnormal prothrombin in hepatocellular carcinoma.

2. Data and methods

The study included 298 patients diagnosed with liver cancer at Hunan Provincial People's Hospital between January 1, 2019, and December 31, 2024, either through surgical treatment or liver biopsy. The liver cancer group consisted of 234 men and 64 women, with a mean age of 57.05 ± 10.965 years. Additionally, three other groups were analyzed:

(1) 100 patients with liver cirrhosis (80 men and 20 women; mean age: 55.61 ± 10.157 years),

(2) 100 patients with chronic hepatitis B (83 men and 17 women; mean age: 55.04 ± 7.808 years),

(3) 89 healthy controls (73 men and 16 women; mean age: 56.09 ± 10.002 years).

The basic demographic comparisons among the groups showed no statistically significant differences ($P > 0.05$), as summarized in **Table 1**.

Table 1. Comparison of the basic data of the four study groups

Group	*n*	Male/Female (%)	Age (years)
HCC group	298	79/21	57.05 ± 10.965
Liver cirrhosis group	100	80/20	55.61 ± 10.157
Hepatitis group	100	83/17	55.04 ± 7.808
Healthy control group	89	82/18	56.09 ± 10.002
χ^2/F		1.197	2.029
P		0.754	0.109

This study was approved by the Medical Ethics Committee of Hunan Provincial People's Hospital, and all participants provided informed consent.

2.2. Inclusion and exclusion criteria

(1) Inclusion criteria: (a) Patients aged 18 years or older; (b) Patients with a first-time diagnosis of HCC confirmed through pathological examination.

(2) Exclusion criteria: (a) Recent use of vitamin K or warfarin; (b) Presence of other malignant tumors; (c) Preoperative treatment for HCC; (d) Incomplete clinical data.

2.3. Study indicators and detection methods

Clinical data were collected for each patient, including:

(1) Preoperative demographic data: age and gender.

(2) Laboratory indicators: abnormal serum prothrombin and alpha-fetoprotein levels.

Fasting venous blood samples (5 mL) were collected, and serum PIVKA-II (abnormal prothrombin) and AFP levels were measured using an automatic immunoanalyzer (LUMIPULSE G1200, Belgium).

2.4. Statistical methods

Data analysis was performed using SPSS 26.0 statistical software. Measurement data conforming to a normal distribution were expressed as mean ± standard deviation and analyzed using a one-way analysis of variance (ANOVA). Measurement data not conforming to a normal distribution were expressed as median (first quartile–third quartile) and analyzed using the Kruskal-Wallis test. Count data were expressed as frequencies and analyzed using the χ^2 test. The diagnostic performance of abnormal prothrombin and AFP for HCC was evaluated using ROC curve analysis, which included the area under the curve (AUC), optimal cut-off points, sensitivity, and specificity. A P-value of < 0.05 was considered statistically significant.

3. Results

3.1. Comparison of abnormal serum prothrombin and alpha-fetoprotein levels

The levels of abnormal serum prothrombin and alpha-fetoprotein in the hepatocellular carcinoma (HCC) group were significantly higher than those in the liver cirrhosis, hepatitis, and healthy control groups, with statistically significant differences ($P < 0.05$). No significant difference in abnormal serum prothrombin levels was observed among the liver cirrhosis, hepatitis, and healthy control groups ($P > 0.05$).

The serum alpha-fetoprotein levels were significantly higher in the HCC group compared to the cirrhosis, hepatitis, and healthy control groups, with a statistically significant difference ($P < 0.05$). Additionally, the alpha-fetoprotein levels in the hepatitis group were higher than those in the cirrhosis and healthy control groups, also showing a statistically significant difference ($P < 0.05$). No significant difference in alpha-fetoprotein levels was found between the cirrhosis and healthy control groups ($P > 0.05$).

Table 2. Comparison of abnormal serum prothrombin and alpha-fetoprotein levels among the four groups

Group	Abnormal prothrombin (mAU/mL)	Alpha-fetoprotein (ng/mL)
HCC group	1,389.835 (140.765–12,800.1775)	214.84 (14.46–1,060.996)
Liver cirrhosis group	23.670 (17.940–37.820)	3.550 (2.032–7.530)
Hepatitis group	24.915 (18.378–36.380)	15.355 (3.888–102.903)
Healthy control group	29.130 (25.955–34.880)	4.700 (3.450–5.700)
H	318.816	200.710
P	0.000	0.000

3.2. ROC curve analysis for abnormal serum prothrombin and alpha-fetoprotein levels

The ROC curve analysis revealed that the area under the curve (AUC) for abnormal serum prothrombin and alpha-fetoprotein in distinguishing HCC from other groups (cirrhosis, hepatitis, and healthy controls) was 0.925 (95% CI: 0.901–0.949) and 0.810 (95% CI: 0.775–0.845), respectively. The sensitivity and specificity were 84% and 75% for serum prothrombin and 94% and 76% for alpha-fetoprotein, respectively.

Using the Youden index, the cut-off values were determined as 61.18 mAU/mL for abnormal serum prothrombin and 14.61 ng/mL for alpha-fetoprotein. These results are illustrated in **Figure 1**.

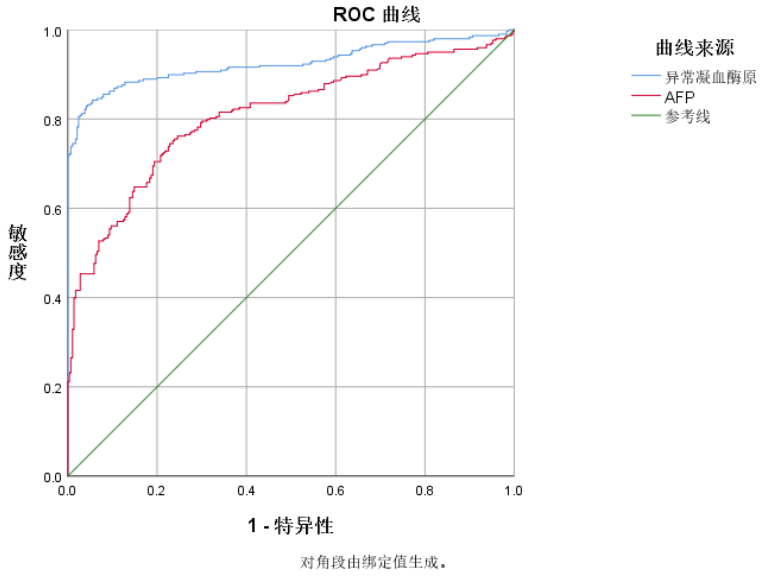

Figure 1. ROC curves of abnormal serum prothrombin and alpha-fetoprotein for the diagnosis of HCC

3.3. Diagnostic efficacy of abnormal serum prothrombin in alpha-fetoprotein-negative HCC

Within the liver cancer group, 74 cases were classified as alpha-fetoprotein-negative primary liver cancer. The ROC curve analysis for serum abnormal prothrombin in diagnosing alpha-fetoprotein-negative HCC demonstrated an AUC of 0.838 (95% CI: 0.774–0.901). The sensitivity and specificity for this subset were 65% and 95%, respectively. These findings are depicted in **Figure 2**.

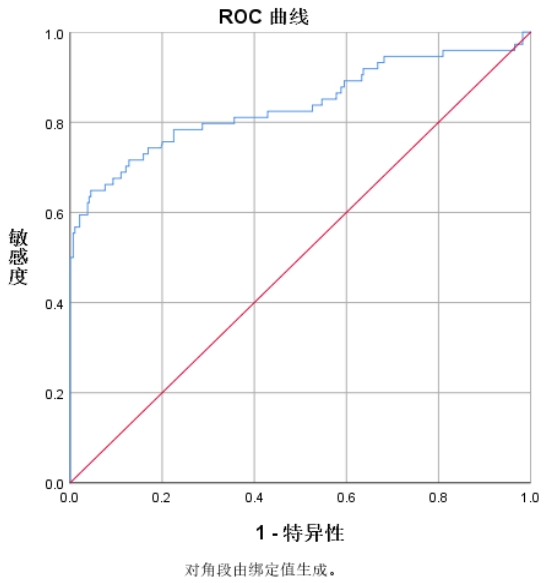

Figure 2. ROC curve of abnormal serum prothrombin for alpha-fetoprotein-negative HCC

4. Discussion

Primary liver cancer has an insidious onset, a high degree of malignancy, a short average survival period, and a poor prognosis, making it a significant threat to public health in China. Early radical surgical resection remains the most effective treatment for primary liver cancer. Therefore, early diagnosis and treatment are critical to improving patient outcomes. However, current screening methods for primary liver cancer are inadequate, necessitating the development of non-invasive, simple, and repeatable diagnostic markers.

Abnormal prothrombin, also known as PIVKA-II (protein induced by vitamin K absence or antagonist-II), is formed during prothrombin synthesis in the liver due to vitamin K deficiency. This deficiency results in incomplete carboxylation of glutamate residues, impairing the ability of prothrombin to bind calcium ions and phospholipids. Consequently, PIVKA-II is released into the bloodstream as an abnormal prothrombin variant [6,7]. Studies have identified elevated serum PIVKA-II levels in hepatocellular carcinoma (HCC) patients. This elevation may be attributed to a disruption in vitamin K metabolism, which hinders the formation of active prothrombin, or to tumor cells themselves secreting PIVKA-II. However, the specific mechanisms remain unclear [8]. These findings suggest that serum PIVKA-II could serve as a novel serological marker for primary liver cancer.

Yang *et al.* reported a 64.91% positive rate of PIVKA-II in patients with liver malignancy, which was significantly higher than other serum tumor markers. This suggests that abnormal serum prothrombin may serve as a preferred single index for the auxiliary diagnosis of liver malignancy [9]. Similarly, Liu *et al.* demonstrated that serum levels of AFP and abnormal prothrombin were significantly higher in HCC patients compared to healthy individuals. Their findings indicated that combining these markers could improve the detection rate of HCC and that PIVKA-II could serve as a supplementary marker, especially in AFP-negative cases [10].

Consistent with these findings, the current study observed significantly higher abnormal prothrombin levels in the serum of HCC patients compared to healthy controls and patients with cirrhosis or chronic hepatitis.

This indicates that PIVKA-II could be used as a promising serological marker for HCC. Furthermore, the study demonstrated that the area under the curve (AUC), sensitivity, and specificity of serum PIVKA-II for HCC diagnosis surpassed those of AFP. ROC curve analysis of PIVKA-II in AFP-negative HCC patients revealed an AUC of 0.838 (95% CI: 0.774–0.901), with sensitivity and specificity of 65% and 95%, respectively, indicating strong diagnostic efficacy.

While this study highlights the superior diagnostic performance of PIVKA-II in HCC, it does not suggest that PIVKA-II can replace AFP in clinical practice. Different serum markers have varying diagnostic utilities. PIVKA-II testing can complement AFP detection, addressing its limitations and improving the overall accuracy of liver cancer diagnosis. Future research involving multicenter, large-sample, prospective studies and the integration of multiple markers will be necessary to further confirm these findings.

Disclosure statement

The author declares no conflict of interest.

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