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# The Use of AFP and PIVKA II for Screening Hepatocellular Carcinoma in Patients with Viral Cirrhosis

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**Abstract** Hepatocellular carcinoma is the most common form of liver cancer. Secondary prevention of HCC is based on the introduction of screening programs for the detection of hepatocellular carcinoma. This article highlights the results of screening hepatocellular carcinoma among patients with cirrhosis of the liver of viral etiology using AFP and PIVKA II. Blood sampling for this study was carried out on the day of admission of the patient to hospital treatment at the Research Institute of Virology. Whole blood was collected from patients and collected in pre-labeled EDTA vacuum tubes. The exact volume was drawn into the test tube, avoiding overfilling of the test tubes. Not later than 2 minutes from the moment of filling, the contents of the tube were mixed by gentle inversion, avoiding foaming. Within 1 hour from the moment of sampling, centrifugation of blood samples was carried out in order to separate the plasma. Of 60 patients with cirrhosis of HCV etiology, 6 patients had PIVKA II and AFP was higher than normal. In 5 of them, a mass was visualized on ultrasound and in 1 on MSCT. An isolated increase in PIVKA II was found in 8 patients, in 4 of them a mass was detected on ultrasound, and in 4 it was detected using MSCT. In 5 patients in this group, an isolated increase in AFP was observed. In 1 of them, a mass was found on ultrasound, and 2 of 4 patients without a mass on ultrasound subsequently underwent MSCT examination, however, no mass was found, 2 patients refused further research. The introduction into routine practice of the determination of tumor markers in patients with cirrhosis of viral etiology will make it possible to detect hepatocellular carcinoma in the early stages, which will improve the survival rate and quality of life of patients.

**Keywords** HBV, HCV, HDV, Hepatocellular carcinoma, Cirrhosis AFP, PIVKA II, Screening

## 1. Introduction

Hepatocellular carcinoma is the most common form of liver cancer. Secondary prevention of hepatocellular carcinoma is based on the introduction of screening programs to directly detect the hepatocellular carcinoma itself [1]. A number of cohort studies and the creation of models have demonstrated that screening for hepatocellular carcinoma is cost-effective and contributes to the improvement of early detection of tumor processes, therapy and survival, if the detection of tumors, cure rates and survival, with access to screening is higher than 34% of patients from risk groups [2-6]. In fact, access to screening for risk groups does not exceed 20% [7].

Patient categories and screening methods are discussed in many publications, the main of which are the joint guidelines of the European Organization for Research and Treatment of Cancer and the American Association for the Study of Liver Diseases recommendations [8-11]. One of the widespread methods of screening for hepatocellular carcinoma is ultrasound liver, despite the fact that the sensitivity of the method varies, according to different authors, from 33 to 96% [12]. The identification of reliable serum biomarkers is of paramount importance in the diagnosis of liver cancer, especially for the early detection and screening of hepatocellular carcinoma. [13,14]. Serum tumor markers are most suitable for clinical routine assessment and population screening because these tests require very small amounts of serum, are cheap, have high reproducibility, and do not require specific pretreatment [15].

## 2. Materials and Methods

The study was carried out at the Research Institute of Virology. Blood sampling was carried out in patients with cirrhosis of viral etiology at the Research Institute of Virology. The criteria for inclusion in the group of patients with cirrhosis of HBV, HBV + HDV and HCV etiology without hepatocellular carcinoma were age over 18 years,

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patient consent to participate in the study, and the presence of markers of viral hepatitis. The exclusion criteria were age under 18 years of age and refusal to study, histologically confirmed hepatocellular carcinoma.

Blood sampling for this study was carried out on the day of admission of the patient to hospital treatment at the Research Institute of Virology.

Whole blood was collected from patients and collected in pre-labeled EDTA vacuum tubes. The exact volume was drawn into the test tube, avoiding overfilling of the test tubes. Not later than 2 minutes from the moment of filling, the contents of the tube were mixed by gentle inversion, avoiding foaming. Within 1 hour from the moment of sampling, centrifugation of blood samples was carried out in order to separate the plasma. The primary tube with blood was centrifuged at 10,000 rpm for 5 min. At least 1 ml of serum was taken and transferred into 3 separate labeled Eppendorf tubes with a volume of 2 ml, while at least 200 µl of plasma was taken into each tube. Aliquots of blood serum samples with a volume of 200 µl were stored at a temperature not exceeding -80° until the moment of the study. If necessary, the samples were transported in a special thermal container on dry ice.

The AFP-IFA-BEST set by Vector Best (Russia) was used to determine the AFP level. All samples were affixed to a Biotek spectrophotometer by ELISA. The PIVKA II 100 test kit from Maglumi (China) was used to determine the PIVKA II level. Determination of the PIVKA II level was carried out on a Maglumi 800 (Snibe). The analyzes were performed according to the instructions of the manufacturers.

## 3. Results and Discusion

The aim of the study was the early detection of hepatocellular carcinoma, for which screening was carried out among patients with cirrhosis of HBV, HCV, HBV + HDV etiology for hepatocellular carcinoma. The screening program included 151 patients with viral hepatitis cirrhosis. using tumor markers PIVKA II and AFP. The distribution by sex, age and etiological characteristics is presented in Table 1.

**Table 1.** Characteristics of the examined patients

| Data | Cirrhosis HBV etiology (*n* = 31) | Cirrhosis HBV+HDV etiology (*n* = 60) | Cirrhosis HCV etiology (n = 60) |
|---|---|---|---|
| Age (years) | 55,43± 4,22 | 53,38 ± 3,88 | 55,83 ± 3,56 |
| Sex: male<br>women | 19(61%)<br>12(39%) | 46,5(60%)<br>53,5(40%) | 33(55%)<br>27(45%) |

Among the patients, 64.23% of cases were diagnosed with Child-Pugh class B cirrhosis, 30.46% with Child-Pugh class A cirrhosis and 5.31% of cases with Child-Pugh class C cirrhosis. The distribution of CPU classes according to Child-Pugh is shown in Figure 1.

The results of screening 151 patients for hepatocellular carcinoma are shown in Figure 2.

Of 31 patients with cirrhosis of HBV etiology, 4 had PIVKA II and AFP higher than normal. The presence of a mass in 3 patients was confirmed by ultrasound and in 1 patient, the formation was not visualized by ultrasound, but was confirmed by MSCT. Of 4 patients with an isolated increase in PIVKA II-in 2, a volumetric lesion was detected on ultrasound, and in 2 patients a volumetric lesion was detected on MSCT. There was no isolated increase in AFP in this group.

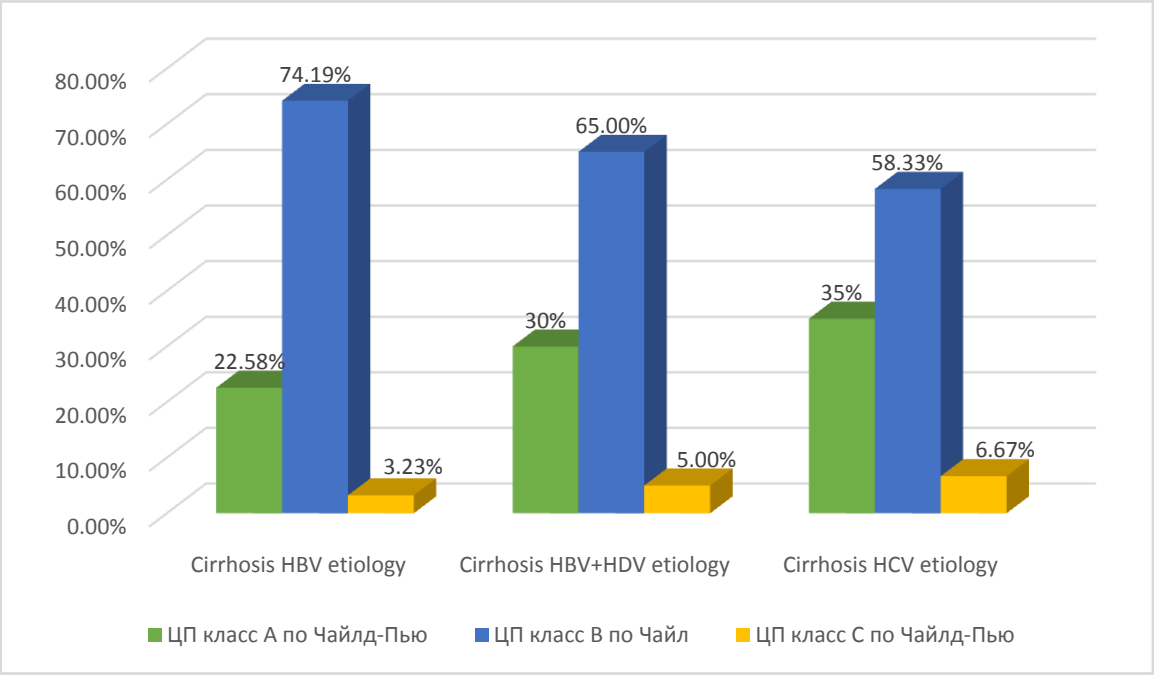


**Figure 1.** Distribution of patients in the study groups according to the Child-Pugh classification

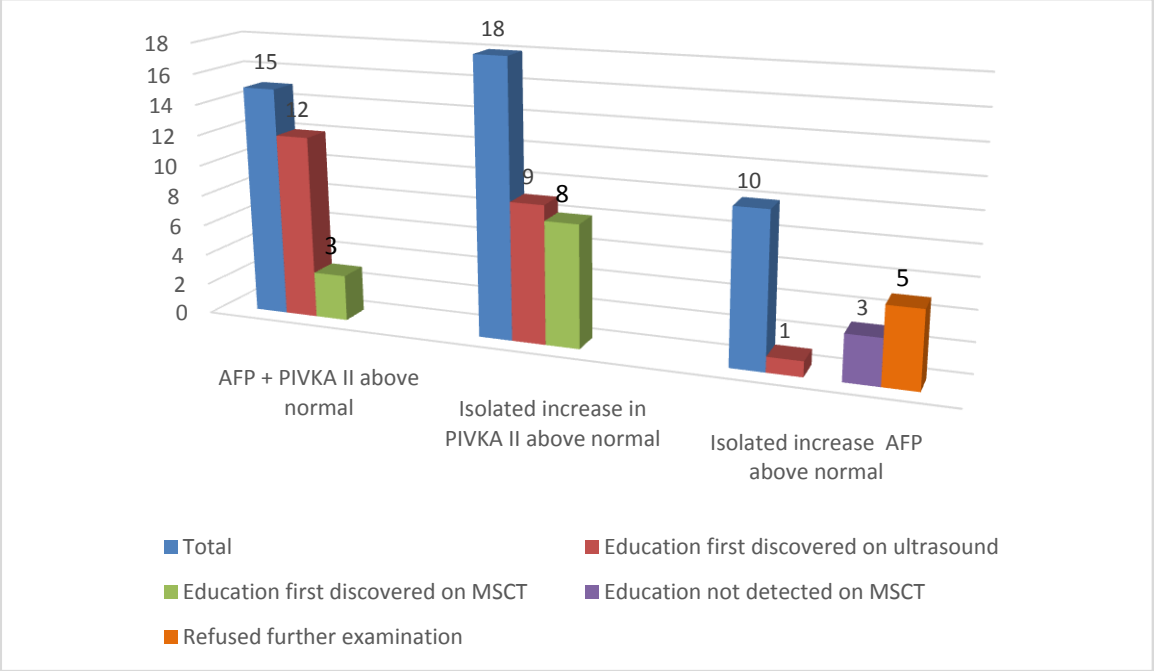


**Figure 2.** Results of screening for hepatocellular carcinoma among patients with cirrhosis of viral etiology

Of 60 patients with cirrhosis of HCV etiology, 6 patients had PIVKA II and AFP was higher than normal. In 5 of them, a mass was visualized on ultrasound and in 1 on MSCT. An isolated increase in PIVKA II was found in 8 patients, in 4 of them a mass was detected on ultrasound, and in 4 it was detected using MSCT. In 5 patients in this group, an isolated increase in AFP was observed. In 1 of them, a mass was found on ultrasound, and 2 of 4 patients without a mass on ultrasound subsequently underwent MSCT examination, however, no mass was found, 2 patients refused further research.

Of 60 patients with cirrhosis of HBV + HDV etiology, 5 had PIVKA II and AFP levels above normal. Of these, 4 patients had a volumetric lesion visualized on ultrasound and in 1 patient a volumetric lesion was detected by MSCT. In 5 patients with a PIVKA II level higher than normal, in 3 ultrasound scans were found space-occupying lesions, in 2 patients a space-occupying lesion was found on MSCT. Out of 5 patients with an isolated increase in AFP, 1 patient with an isolated increased AFP level was found on ultrasound, in 1 patient, no masses were detected on MSCT, and 3 patients refused further research.

In a comparative analysis, the average size of the tumor node detected by ultrasound / MSCT in the group of patients who underwent screening was significantly less than the average size of hepatocellular carcinoma in patients who were hospitalized at the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology with hepatocellular carcinoma in the outcome of viral hepatitis B and amounted to 31.59 ± 11.68 mm. versus 105.13 ± 46.17 mm ($p < 0.001$).

The results of our research show that hepatocellular carcinoma is not always visualized on ultrasound and therefore additional research methods are required as a screening. The simplest, minimally invasive and relatively inexpensive method is the determination of tumor markers. Elevated AFP levels in cirrhosis do not always favor hepatocellular carcinoma. As can be seen from our study, with an increased level of AFP in masses, they are not detected on MSCT. PIVKA II showed the best result in determining hepatocellular carcinoma, however, given that an isolated increase in AFP was observed in a patient with a formation visualized by ultrasound, the most reliable combination of AFP + PIVKA II, as diagnostic tumor markers of hepatocellular carcinoma and can be recommended for screening hepatocellular carcinomas in patients with HBV, HCV and HDV infections.

## 4. Conclusions

The introduction into routine practice of the determination of tumor markers in patients with cirrhosis of viral etiology will make it possible to detect hepatocellular carcinoma in the early stages, which will improve the survival rate and quality of life of patients.

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