Diagnostic Role of Tumor Markers for Hepatocellular Carcinoma in Liver Transplantation Candidates: An Analysis Using the Korean Organ Transplantation Registry Database

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Background: This study analyzed pretransplant alpha-fetoprotein (AFP) and proteins induced by vitamin K absence or antagonist-II (PIVKA-II) in liver transplantation (LT) candidates.

Material/Methods: A total of 3273 LT recipients enrolled in the Korean Organ Transplantation Registry were divided according to hepatocellular carcinoma (HCC) status and background liver disease, and AFP and PIVKA-II were compared.

Results: In all patients, the median AFP and PIVKA-II were 6.3 ng/mL and 29 mAU/mL in the viable-HCC group and 3.3 ng/mL and 35 mAU/mL, respectively, in the no-HCC group (P<0.001 for AFP and p=0.037 for PIVKA-II). In patients with hepatitis B virus infection, they were 6.0 ng/mL and 26 mAU/mL in the HCC group and 3.2 ng/mL and 21 mAU/mL in the no-HCC group, respectively (P<0.001 and P<0.001). In patients with hepatitis C virus infection, they were 10.7 ng/mL and 37 mAU/mL in the HCC group and 2.6 ng/mL and 21 mAU/mL in the no-HCC group, respectively (P<0.001 and P=0.117). In alcoholic liver disease patients, they were 5.2 ng/mL and 61 mAU/mL in the HCC group and 6.4 ng/mL and 75 mAU/mL in the no-HCC group, respectively (P<0.001 and P=0.419). In patients with other diseases, they were 7.1 ng/mL and 32 mAU/mL in the HCC group and 3.3 ng/mL and 28 mAU/mL in the no-HCC group, respectively (P<0.001 and P=0.822).

Conclusions: The results of the present study indicate that pretransplant serum AFP and PIVKA-II were highly variably expressed in LT candidates with end-stage liver diseases; therefore, their values should be cautiously interpreted because their role in HCC diagnosis is limited.

Keywords: Hepatocellular Carcinoma • Tumor Marker • Liver Transplantation • Carcinogenesis • Viral Hepatitis • Liver Neoplasms

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Background

The hepatocellular carcinoma (HCC) tumor markers alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-II (PIVKA-II or des-gamma-carboxy prothrombin) are variably expressed in patients with HCC [1-6]. These tumor markers also can be expressed even in patients without HCC, especially in those with chronic hepatitis or liver cirrhosis. As a result, the reliability of these tumor markers for diagnosis of HCC is much lower in patients with end-stage liver diseases waiting for liver transplantation (LT) compared with the general population [3]. It was reported that alcoholic liver cirrhosis is associated with high expression of PIVKA-II in patients without HCC [7]. To assess the diagnostic role of HCC tumor markers during pretransplant recipient workup, it is necessary to analyze the expression patterns of serum AFP and PIVKA-II in LT candidates with or without HCC, regardless of background liver diseases.

Material and Methods

This was a retrospective multi-center observational study on the expression of HCC tumor markers in LT candidates. The LT database of the Korean Organ Transplantation Registry (KOTRY) was searched to identify adult patients aged 19 years or older who underwent primary LT between April 2014 and December 2020. The exclusion criteria were re-transplantation, HCC combined with other malignancy (intrahepatic cholangiocarcinoma and combined HCC-cholangiocarcinoma), and unavailability of pretransplant AFP and PIVKA-II values.

For this study, 3273 LT recipients were selected. They were divided according to the pathological diagnosis of HCC and background liver diseases. HCC status was divided into 3 groups

according to the explant liver pathology, as viable-HCC, non-viable-HCC, and no-HCC groups. Non-viable-HCC was defined as HCC showing complete pathological response following pre-transplant locoregional treatment [8]. Background liver diseases were divided into 4 groups, as hepatitis B virus (HBV)-associated liver cirrhosis, hepatitis C virus (HCV)-associated liver cirrhosis, alcoholic liver disease (ALD), and other diseases. The institutional review board of participating institutions approved this study protocol (Asan Medical Center No. 2014-0898), which waived the requirement for informed consent due to the retrospective nature of this study. This study was performed in accordance with the ethical guidelines of the World Medical Association Declaration of Helsinki 2013.

The normal cutoff values for serum AFP and PIVKA-II used in the present study were 7.5 ng/mL and 40 mAU/mL, respectively [8]. Numerical data are presented as medians with 25-75 percentiles or means with standard deviation. Continuous variables were compared using the t test, Mann-Whiney U test, or analysis of variance (ANOVA), as appropriate. The Spearman correlation coefficient (ρ [rho]) was used for correlation analysis. Receiver operating characteristic (ROC) curve analysis was used for determination of cutoff, sensitivity, and specificity. A P value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 22 (IBM, New York, NY, USA) and MedCalc version 20.010 (Ostend, Belgium).

Results

Profiles in All Patients

The number of patients with viable-HCC, non-viable-HCC, and no-HCC were 2063 (63.0%), 261 (8.0%), and 949 (29.0%),

Table 1. Patient profiles according to the status of HCC and background liver diseases.

Group	All				Viable HCC group				Non-viable HCC group				No HCC group			
	Case No.	Sex (M: F)	Age (yrs)	MELD score	Case No.	Sex (M: F)	Age (yrs)	MELD score	Case No.	Sex (M: F)	Age (yrs)	MELD score	Case No.	Sex (M: F)	Age (yrs)	MELD score
All	3273	2442: 831	55.5 ±8.5	152 ±9.3	2063	1697: 384	56.7 ±7.6	12.9 ±7.3	261	206: 55	55.7 ±7.3	11.0 ±5.8	949	557: 392	52.3 ±10.1	21.3 ±10.8
HBV	1953	1609: 344	55.9 ±7.3	13.2 ±8.2	1504	1272: 232	56.1 ±7.1	13.4 ±7.3	214	173: 41	55.7 ±6.8	10.9 ±6.2	235	154: 71	54.2 ±8.6	20.6 ±11.1
HCV	230	151: 79	58.5 ±7.5	14.5 ±7.6	188	132: 56	58.9 ±7.5	14.3 ±7.4	14	9: 5	57.0 ±7.4	11.4 ±4.1	28	10: 18	57.0 ±7.8	17.9 ±9.0
ALD	725	534: 191	53.6 ±9.3	19.8 ±10.2	233	205: 28	57.5 ±8.3	14.9 ±6.6	28	22: 6	55.7 ±9.6	11.1 ±4.1	464	307: 157	51.3 ±9.1	22.8 ±10.6
Other	365	148: 217	55.8 ±12.3	17.2 ±9.8	138	70: 68	69.4 ±9.9	13.7 ±7.4	5	2: 3	51.0 ±11.1	11.4 ±5.2	222	146: 76	53.7 ±13.1	19.4 ±10.5

HCC – hepatocellular carcinoma; MELD – model for end-stage liver disease; HBV – hepatitis B virus; HCV – hepatitis C virus; ALD – alcoholic liver disease; M – male; F – female.
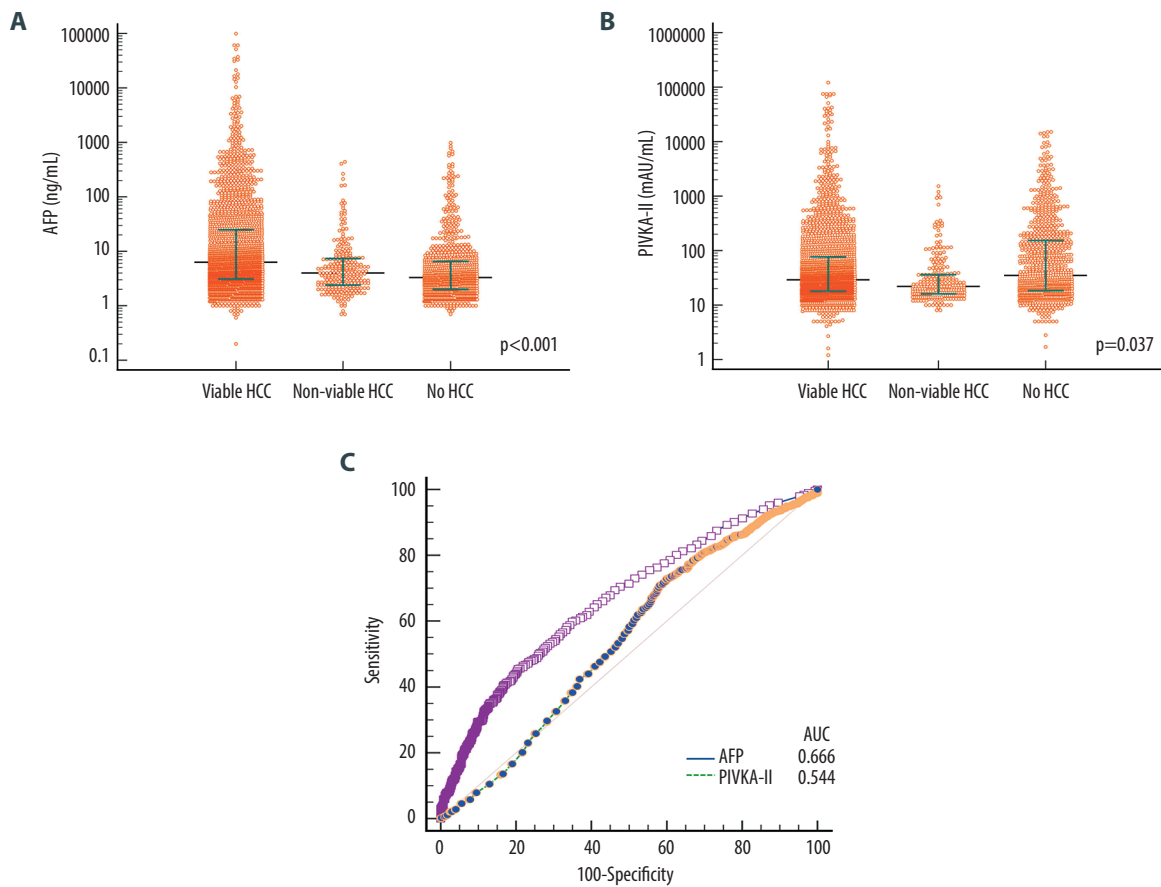
Figure 1. Comparison of alpha-fetoprotein (AFP; **A**) and protein induced by vitamin K absence or antagonist-II (PIVKA-II; **B**) levels according to the status of hepatocellular carcinoma (HCC) in all patients. Bars indicate 25-75 percentiles. **C**) Receiver operating characteristic curve analysis for diagnosis of HCC. AUC indicates the area under the curve.

respectively. Patient numbers according to the HCC status and background liver disease were summarized at **Table 1**. Deceased donor and living donor LTs were performed in 412 (12.6%) and 2861 (87.4%) patients, respectively.

The mean and median serum AFP levels were 330.7±3422.6 ng/mL and 6.3 ng/mL (25-75 percentiles: 3.1-24.9), respectively, in the viable-HCC group; 14.0±45.2 ng/mL and 4.0 ng/mL (25-75 percentiles: 2.4-7.4), respectively, in the non-viable-HCC group; and 17.8±73.8 ng/mL and 3.3 ng/mL (25-75 percentiles: 2.0-6.5), respectively, in the no-HCC group (P<0.001; viable-HCC vs no-HCC, P<0.001; viable-HCC vs non-viable-HCC, P=0.135; non-viable-HCC vs no-HCC, P=0.425; **Figure 1A**).

The mean and median serum PIVKA-II levels were 686.8±5381.3 mAU/mL and 29 mAU/mL (25-75 percentiles: 18-77), respectively, in the viable-HCC group; 65.6±167.3 mAU/mL and 22 mAU/mL (25-75 percentiles: 16-36), respectively, in the non-viable-HCC group; and 387.4±1422.9 mAU/mL and 35 mAU/mL (25-75 percentiles: 18-154), respectively, in the no-HCC group

(P=0.037; viable-HCC vs no-HCC, P=0.091; viable-HCC vs non-viable-HCC, P=0.062; non-viable-HCC vs no-HCC, P<0.001; **Figure 1B**).

Expression of AFP and PIVKA-II in the no-viable-HCC group showed equivocal findings between the viable-HCC and no-HCC groups; thus, the non-viable-HCC group was excluded from further analysis.

ROC curve analyses of AFP for HCC diagnosis showed that the area under the ROC curve (AUC) was 0.666 (P<0.001) and application of a cutoff of 7.5 ng/mL resulted in a sensitivity of 44.9% and specificity of 79.7%. ROC AUC for PIVKA-II was 0.544 (P=0.002) and application of a cutoff of 40 mAU/mL resulted in a sensitivity of 62.6% and specificity of 46.9% (**Table 2 and Figure 1C**).

The correlation analysis of AFP and PIVKA-II showed a correlation coefficient ρ of 0.229 (P<0.001) in the viable-HCC group and ρ of 0.037 (P=0.250) in the no-HCC group (**Figure 2**).

Table 2. Comparison of diagnostic predictability of tumor markers for hepatocellular carcinoma.

Group	AFP >7.5 ng/mL		PIVKA-II >40 mAU/mL	
	Sensitivity	Specificity	Sensitivity	Specificity
All	44.9%	79.7%	62.6%	46.9%
HBV	44.4%	70.6%	32.9%	73.6%
HCV	58.0%	89.3%	49.5%	64.3%
ALD	36.1%	86.2%	42.1%	62.3%
Other	47.8%	74.3%	42.0%	62.2%

AFP – alpha-fetoprotein; PIVKA-II – protein induced by vitamin K absence or antagonist-II; HBV – hepatitis B virus; HCV – hepatitis C virus; ALD – alcoholic liver disease.
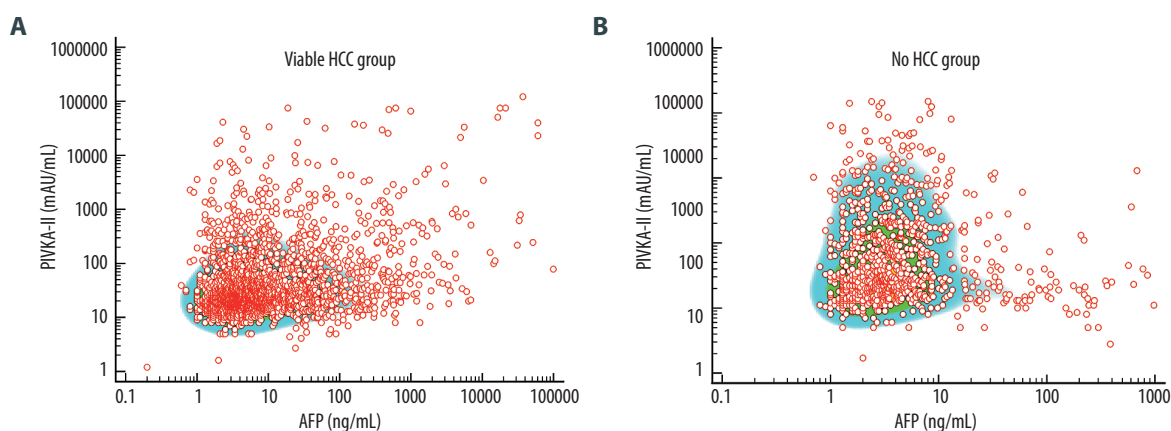
Figure 2. Scatter plots on distribution of alpha-fetoprotein (AFP) and vitamin K absence or antagonist-II (PIVKA-II) values in patients with viable (**A**) and no (**B**) hepatocellular carcinoma (HCC).

Profiles in Patients with HBV-Associated Liver Cirrhosis

In patients with HBV-associated liver cirrhosis, the mean and median AFP levels were 400.7±3905.5 ng/mL and 6.0 ng/mL (25-75 percentiles: 2.9-28.2), respectively, in the viable-HCC group; and 22.9±64.8 ng/mL and 3.2 ng/mL (25-75 percentiles: 1.7-9.6), respectively, in the no-HCC group ($P<0.001$; **Figure 3A**).

The mean and median PIVKA-II levels were 727.5±5937.7 mAU/mL and 26 mAU/mL (25-75 percentiles: 18-60), respectively, in the viable-HCC group; and 154.4±1002.1 mAU/mL and 21 mAU/mL (25-75 percentiles: 14-44), respectively, in the no-HCC group ($P<0.001$; **Figure 3B**).

ROC curve analyses of AFP for HCC diagnosis showed that the AUC was 0.636 ($P < 0.001$) and application of a cutoff of 7.5 ng/mL resulted in a sensitivity of 44.4% and specificity of 70.6%. ROC AUC for PIVKA-II was 0.585 ($P<0.001$) and application of a cutoff of 40 mAU/mL resulted in a sensitivity of 32.9% and specificity of 73.6% (**Table 2 and Figure 3C**).

Profiles in Patients with HCV-Associated Liver Cirrhosis

In patients with HCV-associated liver cirrhosis, the mean and median AFP levels were 217.3±1524.1 ng/mL and 10.7 ng/mL (25-75 percentiles: 4.6-37.4), respectively, in the viable-HCC group; and 4.0±3.4 ng/mL and 2.6 ng/mL (25-75 percentiles: 2.1-5.0), respectively, in the no-HCC group ($P<0.001$; **Figure 4A**).

The mean and median PIVKA-II levels were 290.6±1459.0 mAU/mL and 37 mAU/mL (25-75 percentiles: 18-113), respectively, in the viable-HCC group; and 132.4±228.4 mAU/mL and 21 mAU/mL (25-75 percentiles: 14-151), respectively, in the no-HCC group (p=0.117; **Figure 4B**).

ROC curve analyses of AFP for HCC diagnosis showed that the AUC was 0.809 ($P<0.001$) and application of a cutoff of 7.5 ng/mL resulted in a sensitivity of 58.0% and specificity of 89.3%. ROC AUC for PIVKA-II was 0.592 ($P=0.157$) and application of a cutoff of 40 mAU/mL resulted in a sensitivity of 49.5% and specificity of 64.3% (**Table 2 and Figure 4C**).
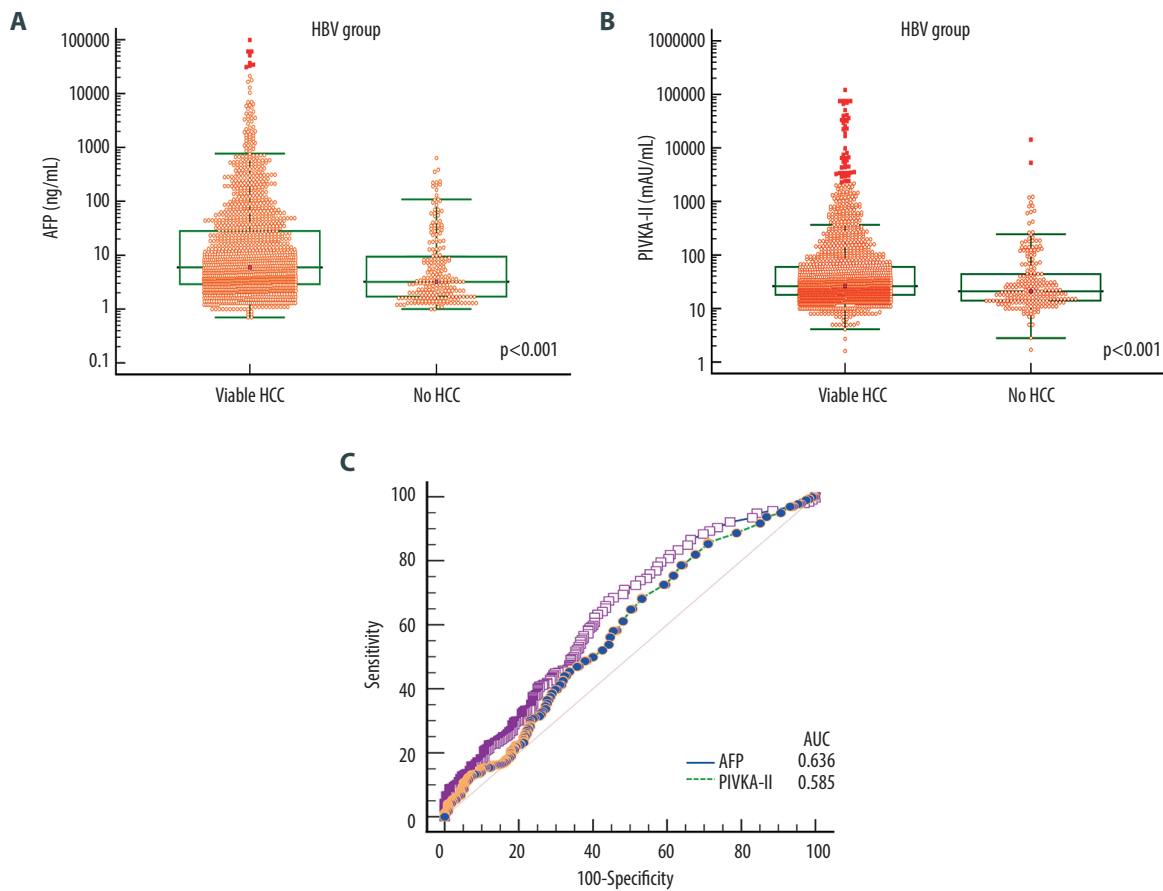
Figure 3. Comparison of alpha-fetoprotein (AFP; **A**) and protein induced by vitamin K absence or antagonist-II (PIVKA-II; **B**) levels according to viable and no hepatocellular carcinoma (HCC) in patients with hepatitis B virus (HBV)-associated liver cirrhosis. Bars indicate 25-75 percentiles. **C**) Receiver operating characteristic curve analysis of AFP and PIVKA-II for diagnosis of HCC. AUC indicates the area under the curve.

Profiles of Patients with ALD-Associated Liver Cirrhosis

In patients with ALD-associated liver cirrhosis, the mean and median AFP levels were 59.3±388.8 ng/mL and 5.2 ng/mL (25-75 percentiles: 3.4-10.7), respectively, in the viable-HCC group; and 6.4±28.7 ng/mL and 3.5 ng/mL (25-75 percentiles: 2.1-5.6), respectively, in the no-HCC group (*P*<0.001; **Figure 5A**).

The mean and median PIVKA-II levels were 825.1±3694.7 mAU/mL and 61 mAU/mL (25-75 percentiles: 26-206), respectively, in the viable-HCC group; and 420.9±1187.9 mAU/mL and 75 mAU/mL (25-75 percentiles: 25-253), respectively, in the no-HCC group (*P*=0.419; **Figure 5B**).

ROC curve analyses of AFP for HCC diagnosis showed that the AUC was 0.671 (*P*<0.001) and application of a cutoff of 7.5 ng/mL resulted in a sensitivity of 36.1% and specificity of 86.2%. ROC AUC for PIVKA-II was 0.519 (*P*=0.413) and

application of a cutoff of 40 mAU/mL resulted in a sensitivity of 42.1% and specificity of 62.3% (**Table 2 and Figure 5C**).

Profiles of Patients with Liver Cirrhosis of Other Causes

In patients with liver cirrhosis of other etiology, the mean and median AFP levels were 78.2±344.7 ng/mL and 7.1 ng/mL (25-75 percentiles: 3.5-23.6), respectively, in the viable-HCC group; and 37.9±128.3 ng/mL and 3.3 ng/mL (25-75 percentiles: 2.0-7.9) respectively in the no-HCC group (*P*<0.001; **Figure 6A**).

The mean and median PIVKA-II levels were 490.7±3680.4 mAU/mL and 32 mAU/mL (25-75 percentiles: 18-76), respectively, in the viable-HCC group; and 595.9±2132.2 mAU/mL and 28 mAU/mL (25-75 percentiles: 18-108), respectively, in the no-HCC group (*P*=0.822; **Figure 6B**).

ROC curve analyses of AFP for HCC diagnosis showed that the AUC was 0.665 (*P*<0.001) and application of a cutoff of
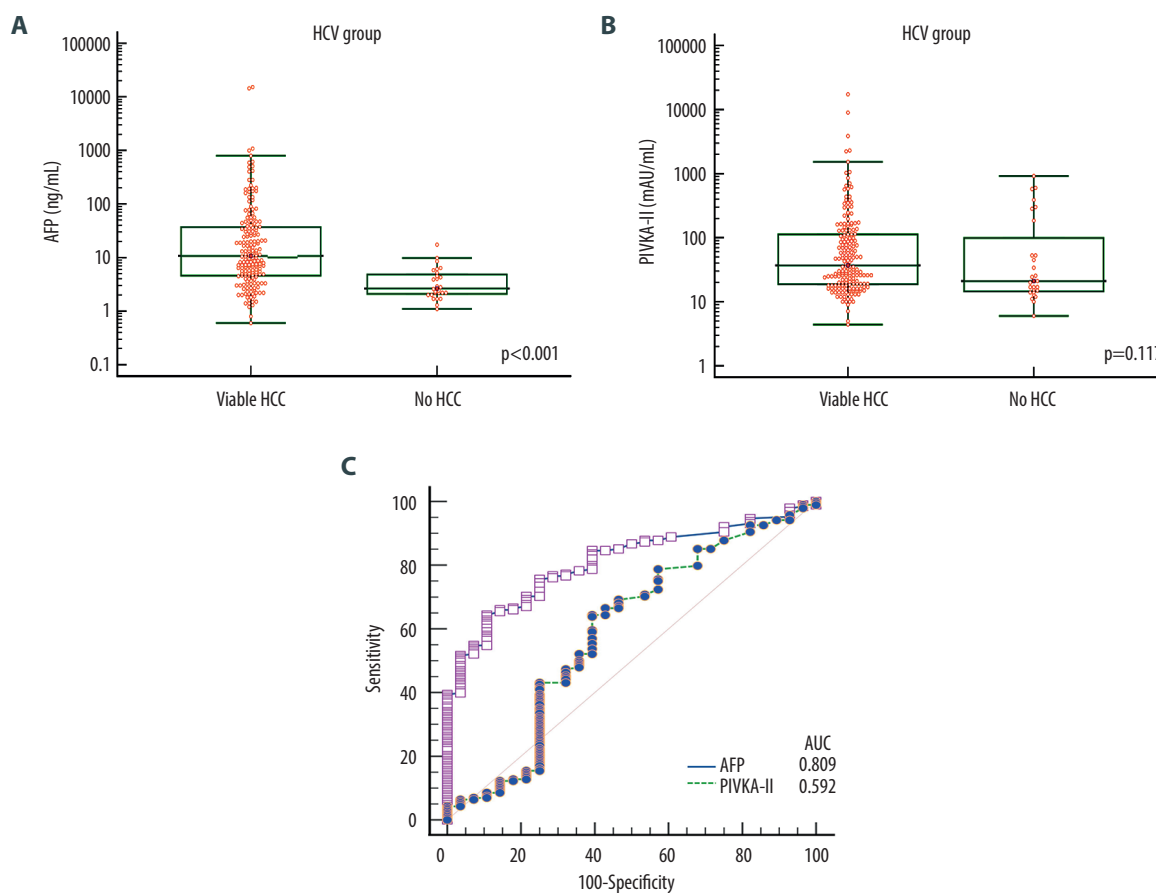
Figure 4. Comparison of alpha-fetoprotein (AFP; **A**) and protein induced by vitamin K absence or antagonist-II (PIVKA-II; **B**) levels according to viable and no hepatocellular carcinoma (HCC) in patients with hepatitis C virus (HCV)-associated liver cirrhosis. Bars indicate 25-75 percentiles. **C**) Receiver operating characteristic curve analysis of AFP and PIVKA-II for diagnosis of HCC. AUC indicates the area under the curve.

7.5 ng/mL resulted in a sensitivity of 47.8% and specificity of 74.3%. ROC AUC for PIVKA-II was 0.507 (*P*=0.819) and application of a cutoff of 40 mAU/mL resulted in a sensitivity of 42.0% and specificity of 62.2% (**Table 2 and Figure 6C**).

Comparison of AFP and PIVKA-II According to Background Liver Disease and HCC

In patients with viable HCC, median AFP and PIVKA-II levels were 6.0 ng/mL (25-75 percentiles: 2.9-28.2) and 26 mAU/mL (25-75 percentiles: 18-60), respectively, in HBV-associated liver cirrhosis; 10.7 ng/mL (25-75 percentiles: 4.6-37.4) and 37 mAU/mL (25-75 percentiles: 18-113), respectively, in HCV-associated liver cirrhosis; 5.2 ng/mL (25-75 percentiles: 3.4-10.7) and 61 mAU/mL (25-75 percentiles: 26-206), respectively, in patients with ALD-associated liver cirrhosis; and 7.1 ng/mL (25-75 percentiles: 3.5-23.6) and 32 mAU/mL (25-75 percentiles: 18-76), respectively, in patients with liver cirrhosis of other etiology (*P*=0.323 for AFP and *P*=0.141 for PIVKA-II).

In patients with no HCC, median AFP and PIVKA-II levels were 3.2 ng/mL (25-75 percentiles: 1.7-9.6) and 21 mAU/mL (25-75 percentiles: 14-44), respectively, in HBV-associated liver cirrhosis; 2.6 ng/mL (25-75 percentiles: 2.1-5.0) and 21 mAU/mL (25-75 percentiles: 14-151), respectively, in HCV-associated liver cirrhosis; 3.5 ng/mL (25-75 percentiles: 2.1-5.6) and 75 mAU/mL (25-75 percentiles: 25-253), respectively, in patients with ALD-associated liver cirrhosis; and 3.3 ng/mL (25-75 percentiles: 2.0-7.9) and 28 mAU/mL (25-75 percentiles: 18-108), respectively, in patients with liver cirrhosis of other etiology (*P*=0.788 for AFP and *P*=0.646 for PIVKA-II).

Discussion

The results of the present study revealed that pretransplant serum AFP and PIVKA-II were quite variably expressed according to the status of HCC and background liver diseases. Expression of PIVKA-II showed low diagnostic predictability
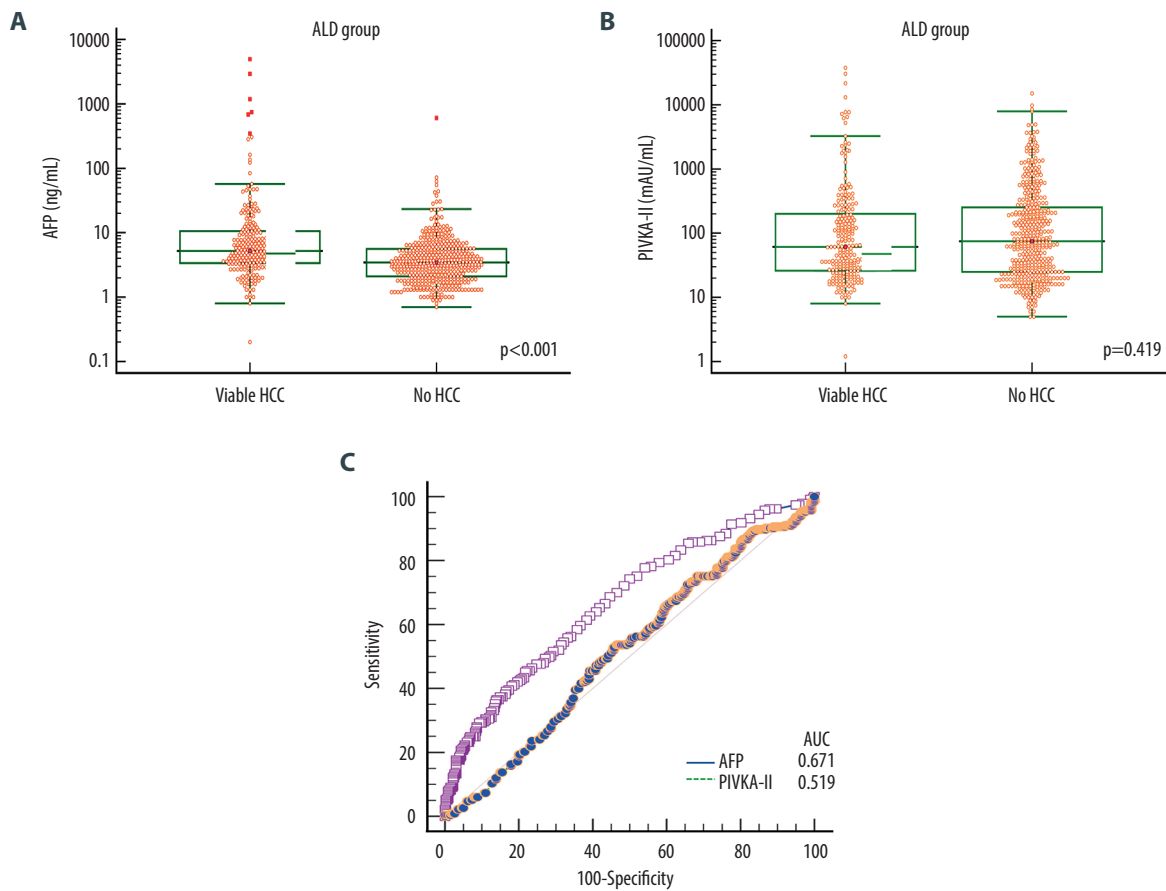
Figure 5. Comparison of alpha-fetoprotein (AFP; **A**) and protein induced by vitamin K absence or antagonist-II (PIVKA-II; **B**) levels according to viable and no hepatocellular carcinoma (HCC) in patients with alcoholic liver disease (ALD). Bars indicate 25-75 percentiles. **C**) Receiver operating characteristic curve analysis of AFP and PIVKA-II for diagnosis of HCC. AUC indicates the area under the curve.

for HCC due to its high production in the non-viral hepatitis livers without HCC.

AFP is a glycoprotein that is produced in early fetal life by the liver. It can be produced by many tumors, including HCC, hepatoblastoma, and non-seminomatous germ-cell tumors of the ovary and testis. Tumor cells synthesize fetal proteins through de-differentiation of adult hepatocytes [9]. During fetal life, AFP is synthesized at first by the yolk sac, then by the liver. Although AFP production is markedly reduced after birth, its production continues at a low level during adulthood [10]. AFP can increase temporarily in cases of liver injury or regeneration, particularly after liver resection, during fulminant viral hepatitis, or chronic viral hepatitis [11]. Serum AFP levels increase by 20-80% in patients with HCC and are closely related to aggressive tumor biology [12,13]. In 1984, PIVKA-II was found to be significantly increased in the serum of HCC patients and it could serve as a new serum marker for HCC [14]. Many studies suggested that the combined detection of PIVKA-II and AFP

may improve HCC diagnosis compared to the use of each biomarker alone [15]. The diagnostic value of PIVKA-II is controversial and it is still debated whether there is a correlation between PIVKA-II and AFP and whether PIVKA-II can completely replace or supplement the role of AFP in HCC diagnosis [15,16].

It is reported that serum AFP (>15 or 20 ng/mL) as a screening test for HCC had sensitivity between 39% and 64%, specificity between 76% and 91%, and positive predictive value between 9% and 33% [17,18]. A case-control study of 340 cirrhotic patients showed that AFP levels >20 ng/mL had sensitivity of 60% and specificity of 91% to diagnose HCC. At this threshold, 40% of all HCC patients would be missed [19]. Although the prognostic value of AFP in LT seems to be established, there is an issue regarding the cutoff value used to evaluate the level of AFP. There is no clear consensus regarding the expression level of AFP above which patients should not be eligible LT candidates [20].
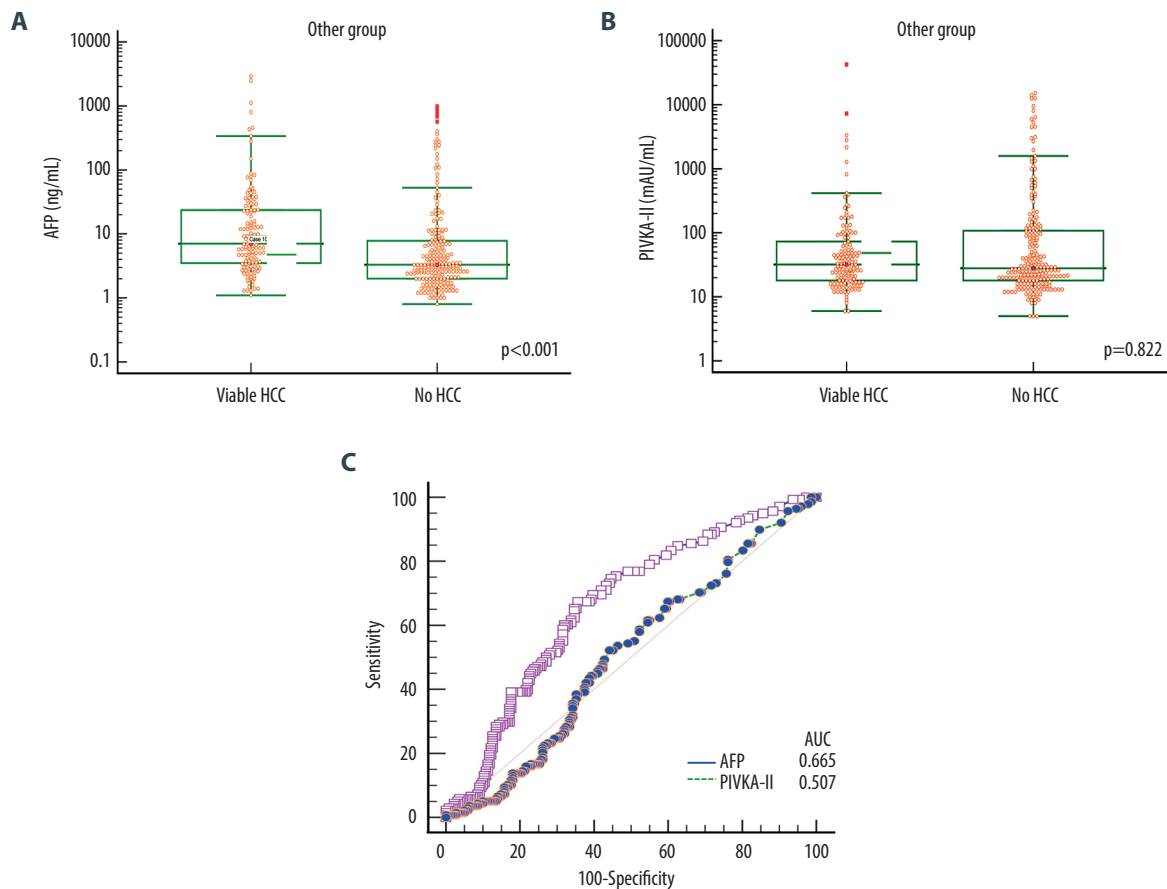
Figure 6. Comparison of alpha-fetoprotein (AFP; **A**) and protein induced by vitamin K absence or antagonist-II (PIVKA-II; **B**) levels according to viable and no hepatocellular carcinoma (HCC) in patients with liver cirrhosis of other etiology. Bars indicate 25-75 percentiles. **C**) Receiver operating characteristic curve analysis of AFP and PIVKA-II for diagnosis of HCC. AUC indicates the area under the curve.

An Italian multi-center study with 388 patients with chronic liver disease reported that the overall ROC AUC values for AFP and PIVKA-II were 0.698 ($P<0.001$) and 0.780 ($P<0.001$), respectively. ROC AUCs for AFP and PIVKA-II were 0.822 and 0.833, respectively, in chronic hepatitis B patients; 0.648 and 0.732 respectively in chronic hepatitis C patients; 0.640 and 0.806 in non-viral chronic liver disease patients. Diagnostic accuracies of AFP and PIVKA-II were 40.5-59.8% and 62.7-73.5%, and combining both markers showed 78.2% in chronic hepatitis B patients; 77% in non-viral chronic liver disease patients; and 75% in chronic hepatitis C patients. Expression of AFP was correlated with alanine transaminase in HCC patients with chronic hepatitis C and non-viral chronic liver disease, but not in chronic hepatitis B. PIVKA-II is correlated with tumor size independent of the etiology of the chronic liver disease and AFP in chronic hepatitis B patients only. The diagnostic performance of AFP and PIVKA-II is significantly influenced by the etiology and activity of chronic liver disease [21,22].

The expression patterns of PIVKA-II in patients with ALD and other non-viral liver diseases were unique in the present study, in which PIVKA-II had no role in diagnosis of HCC. A Korean study with 2528 patients without HCC revealed that ALD and antibiotics use may be confounding factors when interpreting high serum PIVKA-II levels in patients without HCC. Therefore, serum PIVKA-II levels in patients with ALD should be interpreted with caution [7]. The detailed mechanism of PIVKA-II elevation is not known yet. A Japanese study suggested that the time course for elevation of serum PIVKA-II levels in ALD was different from that of HCC. In HCC, serum PIVKA-II levels continued to increase until treatment. In contrast, its increase was transient and its levels returned to baseline in ALD [23]. To investigate the mechanism by which elevation of serum PIVKA-II in patients with ALD occurred, the effect of vitamin K on production of PIVKA-II by hepatocytes was investigated. PIVKA-II production was inhibited by addition of vitamin K in a dose-dependent manner, and elevation of serum PIVKA-II in ALD patients was suppressed by administration of vitamin K. Taken

together, these results suggest that vitamin K may have a role in the mechanism of PIVKA-II elevation in sera of these patients. However, there was no correlation observed between serum vitamin K concentration and PIVKA-II in ALD patients. This result suggests that elevation of serum PIVKA-II in ALD patients may not be due to vitamin K deficiency [23,24].

The results of the present study reveal that the expression pattern of AFP appeared to be consistently expressed in patients with viable HCC regardless of the background liver diseases. In contrast, the expression pattern of PIVKA-II seems to be more influenced by the background liver diseases. In patients with ALD and other non-viral liver diseases, PIVKA-II was paradoxically more produced in those without HCC than in those with HCC. Abnormally high expression of AFP and PIVKA-II is closely associated with the diseased livers and HCC; thus, the majority of patients showed normalization of these tumor markers after liver transplantation performing complete removal of the native liver.

This study has certain limitation. This was a retrospective multicenter cohort study in an HBV-endemic country, and the majority of HCCs in the present study had thus developed in HBV-infected livers. The severity of liver diseases and the stage of HCC were not included in analysis. Pretransplant HCC treatment was also not taken into account.

Conclusions

The results of the present study indicate that pretransplant serum AFP and PIVKA-II were highly variably expressed in LT candidates with end-stage liver diseases; thus, their values should be cautiously interpreted because their role in HCC diagnosis is limited.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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