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# Clinical utility of protein induced by vitamin K absence in patients with chronic hepatitis B virus infection

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**Abstract.** Hepatitis B virus (HBV) is a leading cause of hepatocellular carcinoma (HCC). α-fetoprotein (AFP) is a common tumor marker for the diagnosis of HCC, although not for protein induced by the absence of vitamin K or antagonist-II (PIVKA-II). The present study aimed to evaluate the role of PIVKA-II in the diagnosis of HCC in HBV-infected Vietnamese patients. A total of 166 consecutive HBV-infected Vietnamese patients were enrolled, including 41 HCC, 43 liver cirrhosis (LC), 26 chronic hepatitis (CH) and 56 asymptomatic carriers (ASC). AFP was examined using ELISA, while PIVKA-II was analyzed using Eitest PIVKA-II. The cut-off level of AFP and PIVKA-II was 20 ng/ml and 40 mAU/ml, respectively. Although the markers, AFP (344±356 ng/ml) and PIVKA-II (16,200±25,386 mAU/ml), were the highest in the HCC groups, only PIVKA-II in HCC was significantly higher compared to the other groups (P<0.001). The univariate analysis demonstrated that age over 50, male, genotype C, AFP and PIVKA-II were risk factors of LC and HCC. Results of the receiver operating characteristics (ROC) analysis showed that PIVKA-II was more sensitive to HCC compared to AFP. Moreover, PIVKA-II was strongly correlated with the portal venous thrombosis in HCC, as opposed to AFP. Results of the multivariate analysis demonstrated that PIVKA-II was the strongest independent risk factor of LC and HCC. In conclusion, PIVKA-II is likely to be a better marker for the diagnosis of HCC in chronic HBV-infected Vietnamese patients.

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*Key words:* hepatitis B virus, hepatocellular carcinoma, protein induced by vitamin K absence or antagonist-II, Vietnam

## Introduction

Vietnam is one of the countries in the Western part of the Pacific-Ocean, with a high rate of hepatitis B virus (HBV) infection and hepatocellular carcinoma (HCC). At present, the prevalence of HBV infection in Vietnam is more than 8%, and in some regions it may be up to 25% (1-4). Vietnamese HBV strains share characteristics of mutations in the core promoter and enhancement II region of the X gene in its genome, similar to HBV strains from China, Hong Kong and Japan. These mutations are risk factors for the development of severe liver diseases and HCC (5-8). HBV is the leading cause of HCC in Vietnam, with an incidence only less than that of lung and stomach cancer in males (9,10). Recently, the Vietnamese government has made serious efforts to persuade individuals, particularly parents of neonates, to join the HBV vaccination program nationwide. However, partly due to the living standards and the differences in medical services available in the cities and countryside, and partly due to lack of awareness, not all newborn babies have been vaccinated at present. Serum α-fetoprotein (AFP) is used as a routine test, although magnetic resonance imaging (MRI) and computed tomography (CT) scans are only available in large cities or in major provincial hospitals. Additionally, MRI and CT scans are expensive for ordinary Vietnamese individuals. Ultrasound (US) examination was introduced in Vietnam over 20 years ago, however, good operators are working only in big hospitals at present.

The above reasons render HCC a major health problem in Vietnam, with an incidence >15/100,000 population (10,11). Several HCC patients present in hospitals when the conditions are irreversible, while a number of patients have liver tumor of a diameter >5 cm. Multiple tumors within a liver parenchyma or liver cirrhosis (LC) are extremely severe and may result in multi-organ metastasis. Liver tumor resection, transcatheter arterial chemoembolization (TACE), percutaneous ethanol injection (PEIT) and radiofrequency ablation (RFA) are the key methods for the treatment of HCC in Vietnam. However, early diagnosis of a liver tumor remains a challenge. Similar to other countries in the world, the serum AFP test, ultrasound examination or the combination thereof are common methods

for screening HCC at present. However, ultrasound depends on the skill of the operator, the body mass index of patients and is limited in differentiating HCC from non-neoplastic nodules. In addition, varying sensitivity and specificity of AFP has been observed in different population studies, thus several patients are likely to be lost (12-18). At present, newer and better markers are required for the detection, surveillance and post-therapy follow-up of HCC. AFP is currently the only tumor marker used in the clinical diagnosis of HCC in Vietnam. However, few studies are available regarding the development of new clinically applied markers for the detection of HCC in Vietnamese patients (19). Moreover, none of those studies have focused on protein induced by vitamin K absence or antagonist-II (PIVKA-II). Since Liebman *et al* first reported a high level of PIVKA-II in HCC patients (20), several clinical studies have been conducted to evaluate the role of PIVKA-II in different patient populations worldwide (21-31). Although several studies have reported heterogeneous results in assessing the role of PIVKA-II in HCC patients, a number of these studies have proven PIVKA-II to be a better tumor marker when compared to AFP, in diagnosis as well as regarding tumor size, progression of disease, vascular invasion and differentiating cancer lesions from non-malignant diseases (31-36). The present study is the first to evaluate the role of PIVKA-II in the diagnosis of HCC in HBV-infected Vietnamese patients.

## Materials and methods

*Patients*. A total of 166 consecutive chronic HBV-infected patients (139 male and 27 female, mean age 39.8±16.4 years) from 15 different provinces in Northern Vietnam were enrolled in the study [41 HCC, 43 LC, 26 chronic hepatitis B (CH) and 56 asymptomatic carriers (ASC)]. The patients with a previous medical history of antiviral treatment and HCC therapy or co-infection with hepatitis C virus (HCV), human immunodeficiency virus (HIV) were excluded. The HCC lesions developed in patients with LC. This study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Ethnics Committee of Bach Mai Hospital, Hanoi, Vietnam.

*Clinical diagnostic criteria*. Chronic HBV infection was confirmed based on the medical history of the HBV status or positive HBV surface antigen (HBsAg) test was carried out twice in the serum for at least 6 months. HCC confirmation was based on the pathophysiologic examination or two-imaging modality with typical findings of liver tumor that included the characteristics of a high density mass in the arterial phase and a low density mass in the portal phase on dynamic CT scan or MRI. The final diagnosis was evaluated by two different histologists or radiologists unaware of additional clinicobiochemical information on patients. LC and CH was diagnosed based on clinical examination and biochemical test in combination with ultrasound, CT scan and MRI, with or without upper gastrointestinal endoscopy. ASC was evaluated by chronic HBV infection, without any clinical signs/symptoms or abnormality of a biochemical test and US examination.

*AFP, PIVKA-II, HBV-DNA and HBV genotype tests*. The sera of collected patients were stored at -40˚C until use for further examinations at the Kobe University Graduate School of Medicine. The AFP levels were evaluated using the Microwell ELISA. The AFP test (Hope Laboratories, Pacoima, CA, USA) and PIVKA-II levels were examined using Eitest PIVKA-II (Eisai Co., Ltd. Tokyo, Japan), according to the manufacturer's instructions. HBV-DNA was extracted from 200 $\mu$l of sera, using a QIAamp DNA blood mini kit (QIAGEN GmbH, Hilden, Germany), following the manufacturer's instructions. The HBV-DNA levels were confirmed by real-time PCR with a set of primers and TaqMan probe located in the S gene, as previously described (32) and HBV genotype was classified by PCR-RFLP, as previously reported (33).

*Statistical analysis*. The Chi-square, Fisher's exact and Mann-Whitney U tests (Wilcoxon rank-sum test), Kruskal-Wallis one-way analysis of variance, receiver operating characteristic (ROC), univariate and multivariate analyses were carried out to analyze the data using the Stata software 8.0 (StataCorp LP, College Station, TX, USA). $P<0.05$ was considered to indicate a statistically significant difference.

## Results

*Clinical characteristics of the patient population*. Table I shows the characteristics of the study population. The mean age of the patients was 39.8±16.4 years (range, 17-75), with the mean age in the ASC group being the youngest (22.8±7.3 years) and it was significantly younger compared to the other groups ($P<0.0001$). The mean age in the LC and the HCC groups (50.8±12.4 and 49.8±12.4 years, respectively) was also higher (42.6±13.5 years) compared to the CH group ($P<0.05$). The male to female ratio showed no difference in the LC, CH and ASC groups (38/5, 20/6 and 42/14, respectively), although it was significantly higher (39/2) in the HCC, compared to the CH and ASC groups ($P<0.05$ and $P<0.01$). The positive prevalence for HBV e antigen (HBeAg) in CH (3.8%) was significantly lower compared to the other groups ($P<0.05$, $P<0.01$ and $P<0.001$). However, the positive prevalence of anti-HBe antibody in CH was higher compared to the ASC group (69.2 vs. 35.7%, $P<0.01$).

The prevalence of the HBV genotype B in the CH and ASC was significantly higher compared to the LC and HCC groups (88.5, 80.4, 60.5 and 56.1%, respectively) ($P<0.05$ and $P<0.01$), whereas the prevalence of HBV genotype C in the LC (39.5%) and HCC (43.9%) groups was higher compared to the CH (11.5%) and ASC (19.6%) groups. Together with the status of HBeAg and anti-HBe, the HBV-DNA level in CH (4.4±1.7 log copies/ml) was significantly lower compared to the other groups ($P<0.05$, $P<0.01$ and $P<0.001$). The HBV-DNA level was the highest in the LC (6.2±1.8 log copies/ml), although not significantly, compared to the HCC (5.8±1.9 log copies/ml) and ASC (5.4±2.3 log copies ml) groups. The AFP level was the highest in the HCC group, showing no significant difference compared to the LC and CH groups. The PIVKA-II level was significantly higher in the HCC compared to the other groups, while the PIVKA-II level in the LC was higher compared to the CH and ASC groups ($P<0.05$ and $P<0.001$).

*Characteristics of AFP and PIVKA-II in HCC*. The comparison of sensitivity and specificity in AFP and PIVKA-II is

Table I. Characteristics of population study.

| Characteristics | Total (n=166) | Clinical diagnosis | | | |
|---|---|---|---|---|---|
| | | HCC (n=41) | LC (n=43) | CH (n=26) | ASC (n=56) |
| Age (years) | 39.8±16.4 (17-75) | 49.8±11.0[a,d] (28-74) | 50.8±12.4[a,d] (18-75) | 42.6±13.5[a,d] (17-70) | 22.8±7.3[d] (19-51) |
| Gender (m/f) | 139/27 | 39/2[a,b] | 38/5 | 20/6[a] | 42/14[b] |
| HBeAg (+) | 114 (68.7%) | 9[a,b] (22%) | 14[b] (32.6%) | 1[a-c] (3.8%) | 28[b,c] (50%) |
| Anti-HBe (+) | 86 (51.8%) | 20 (48.8%) | 27[b] (62.8%) | 18[b] (69.2%) | 20[b] (35.7%) |
| Genotype | | | | | |
| B | 117 (70.5%) | 23[a,b] (56.1%) | 26[a] (60.5%) | 23[a,b] (88.5%) | 45[a] (80.4%) |
| C | 49 (29.5%) | 18[a,b] (43.9%) | 17[a] (39.5%) | 3[a,b] (11.5%) | 11[a] (19.6%) |
| HBV-DNA (log copies/ml) | 5.5±2.1 (2.6-9.7) | 5.8±1.9[b] (2.6-9.5) | 6.2±1.8[c] (2.6-8.8) | 4.4±1.7[a-c] (2.6-8.9) | 5.4±2.3[a] (2.6-9.7) |
| AFP (ng/ml) | 150±279 (0-901) | 344±356[d] (0-894) | 152±285[d] (0-863) | 143±261[d] (0.1-901) | 10.4±31.6[d] (0-179) |
| PIVKA-II (mAU/ml) | 6,780±19,332 (4-75,000) | 16,201±25,386[c,d] (15-75,000) | 10,576±25,794[a,c] (9-75,000) | 184±431[a,d] (4-1,965) | 31.5±8.5[c,d] (17-59) |

[a]P<0.05; [b]P<0.01; [c]P<0.001; [d]P<0.0001. HCC, hepatocellular carcinoma; LC, liver cirrhosis; CH, chronic hepatitis; ASC, asymptomatic carrier; HBeAg, hepatitis B virus e antigen; anti-Hbe, antibody to hepatitis B virus e antigen; HBV, hepatitis B virus; AFP, α-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II.

Table II. Sensitivity and specificity for the detection of HCC using different cut-off levels of AFP and PIVKA-II.

| AFP (ng/ml) | Sensitivity (%) | Specificity (%) | PIVKA-II (mAU/ml) | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|
| ≥20 | 63.4[a] | 69.6 | ≥40 | 87.8[a] | 62.4 |
| ≥50 | 56.1[b] | 80.0 | ≥100 | 80.5[b] | 79.2 |
| ≥100 | 51.2[c] | 86.4 | ≥200 | 78.0[c] | 82.4 |
| ≥200 | 46.3[d] | 88.8 | ≥400 | 75.6[d] | 87.2 |
| ≥400 | 46.3 | 92.0 | ≥800 | 63.4 | 89.6 |

[a]P=0.01; [b]P=0.018; [c]P=0.011; [d]P=0.007. AFP, α-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II.

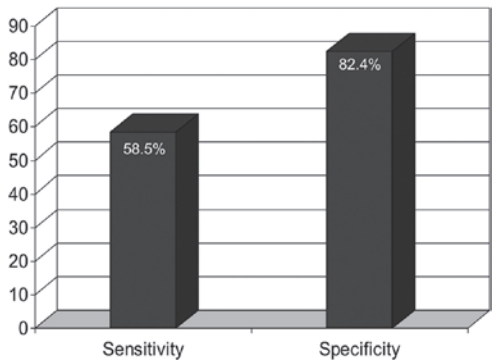


Figure 1. Sensitivity and specificity in the detection of hepatocellular carcinoma (HCC) when the combined cut-off levels used are over 40 mAU/ml prothrombin induced by vitamin K absence or antagonist-II (PIVKA-II) and over 20 ng/ml of α-fetoprotein (AFP).

shown in Table II. The levels of AFP and PIVKA-II showed a gradual increase from the cut-off level (AFP 20 ng/ml and PIVKA-II 40 mAU/ml) to 2.5, 5, 10 and 20 times over the cut-off level of each marker. At each compared level, the sensitivity of PIVKA-II was significantly higher compared to the AFP (P=0.01, P=0.018, P=0.011 and P=0.007), while the specificity of AFP was higher compared to PIVKA-II, although this difference was not significant (P>0.05). The significance of the combination of these two markers was also examined and compared. Fig. 1 shows that the combination of the two markers had a significantly higher specificity than either AFP (P=0.018) or PIVKA-II (P<0.001), and a significantly lower sensitivity compared to PIVKA-II alone (P=0.003), although not significantly lower compared to AFP (P>0.05).

The characteristics of liver tumor in association with AFP and PIVKA-II in 41 HCC patients are shown in Table III. Portal vein thrombosis was present in 36.6% (15/41) of patients, with several liver tumors located in the right (53.6%) or in both the left and right lobes (34.2%), while few tumors were presented in the left lobe (12.2%). In the present study, the liver tumors had a diameter <3 cm, while the number of patients with a diameter

Table III. Characteristics of HCC in association with AFP and PIVKA-II.

| Characteristics | No. (%) | AFP (ng/ml) | PIVKA-II (mAU/ml) |
|---|---|---|---|
| Portal vein thrombosis | | | |
| Present | 15 (36.6) | 427±342 | 32,860±29,954[a] |
| Absent | 26 (63.4) | 297±362 | 6,590±16,312[a] |
| Localization | | | |
| Left lobe | 5 (12.2) | 472±431 | 13,532±29,633 |
| Right lobe | 22 (53.6) | 347±368 | 15,628±25,990 |
| Both | 14 (34.2) | 295±324 | 18,055±24,791 |
| Tumor no. | | | |
| Single | 20 (48.8) | 351±384 | 12,496±24,021[b] |
| Multiple (≥2) | 21 (51.2) | 338±337 | 19,729±26,720[b] |
| Tumor size (cm) | | | |
| >3-5 | 12 (29.3) | 290±410 | 12,631±22,967 |
| >5 | 29 (70.7) | 367±367 | 17,678±26,565 |

HCC, hepatocellular carcinoma; AFP, α-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II. [a]P=0.0025; [b]P=0.0782.

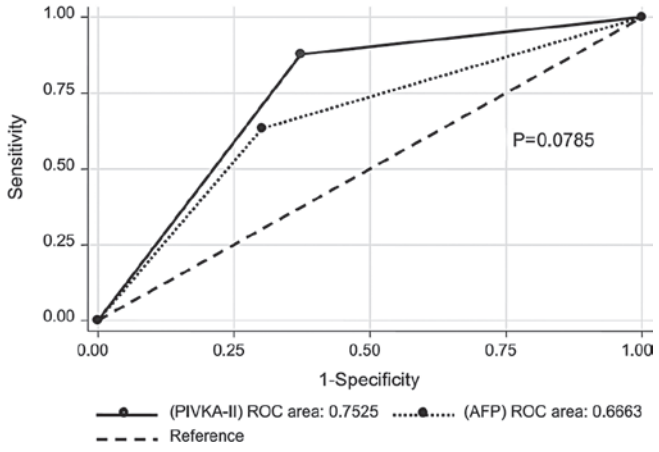


Figure 2. ROC analysis curves for comparing protein induced by vitamin K absence or antagonist-II (PIVKA-II) and α-fetoprotein (AFP) in detection of hepatocellular carcinoma (HCC) in hepatitis B virus (HBV) infected Vietnamese. Cut-off level for PIVKA-II of 40 mAU/ml and for AFP of 20 ng/ml is shown.

of liver tumor <5 cm was ~70.7%. AFP showed no significant association with any tumor characteristics, including portal thrombosis, tumor localization, number or size. By contrast, the PIVKA-II level in HCC patients with portal vein thrombosis was significantly higher compared to patients without portal vein thrombosis (32,860±29,954 vs. 6,590±16,312 mAU/ml, P=0.0025). In addition, PIVKA-II was correlated with multiple tumors as compared to single tumors (12,496±24,021 vs. 19,729±26,7207 mAU/ml, P=0.087). To further compare AFP and PIVKA-II, ROC was applied to analyze the data (Fig. 2). The analysis demonstrated that PIVKA-II was the better marker compared to AFP in HBV-infected Vietnamese patients. The area under ROC (AUC) of PIVKA-II was higher compared to AFP (0.7525 vs. 0.6663, P=0.0785).

*Univariate and multivariate analyses of risk factors for LC and HCC*. The risk factors of LC and HCC are shown in Tables IV and V using univariate and multivariate analyses. In Table IV, age (≥50 years), gender (male), HBV genotype C, HBV-DNA (≥5.0 log copies/ml), AFP (≥20 ng/ml) and PIVKA-II (≥40 mAU/ml) were the risk factors of LC by univariate analysis. By multivariate analysis, however, only age (≥50 years) and PIVKA-II (≥40 mAU/ml) were the independent risk factors of LC, although not for AFP (≥20 ng/ml). Similar findings are shown in the data of Table V, i.e., the variables age (≥50 years), gender (male), HBV genotype C, AFP (≥20 ng/ml) and PIVKA-II (≥40 mAU/ml) were the risk factors of HCC by univariate analysis. However, by multivariate analysis, only PIVKA-II (≥40 mAU/ml) was the independent risk factor of HCC. Nevertheless, the odds ratio of AFP was relatively high, 2.1 (0.92-4.9) and P=0.076.

## Discussion

Screening is crucial to the early diagnosis of cancer. At present, there are different methods and medications to cure cancer patients, however, the earlier the diagnosis the better the clinical outcomes. The combination of ultrasound and serum AFP test is the most common method to screen HCC due to its being cost-effective, non-invasive and available globally. However, these tests are limited regarding clinical practice (12-18,34,36), thus a number of patients are lost. Moreover, differentiating cancer lesions from nodules in cirrhotic patients is challenging. At present, a new HCC surveillance method is urgently required to identify cost-effective and easy to use novel biomarkers suitable for clinical activity that may replace the serum AFP test, particularly in the diagnosis of HCC in cirrhotic patients at an early stage of liver tumor (11,17,18,35). PIVKA-II is one of the novel candidate markers for the detection of HCC. In a physiological process, glutamic acids located in the N-terminal of the prothrombin precursor are converted to

Table IV. Univariate and multivariate analysis of the LC risk factors.

| | Univariate (n=166) | | Multivariate (n=166) | |
|---|---|---|---|---|
| Factors | OR (95% CI) | P-value | OR (95% CI) | P-value |
| Age (years) | | | | |
| ≥50 | 9.6 (4.4-21.2) | <0.0001 | 5.7 (2.2-15.0) | <0.001 |
| <50 | 1 | | 1 | |
| Gender | | | | |
| Male | 3.5 (1.4-8.9) | 0.007 | 2.2 (0.68-7.2) | 0.182 |
| Female | 1 | | 1 | |
| HBeAg | | | | |
| Positive | 0.69 (0.4-1.3) | 0.268 | 0.52 (0.2-1.5) | 0.227 |
| Negative | 1 | | 1 | |
| Genotype | | | | |
| C | 3.5 (1.7-7.1) | 0.001 | 2.6 (0.95-7.0) | 0.064 |
| B | 1 | | 1 | |
| HBV-DNA (log copies/ml) | | | | |
| ≥5 | 2.3 (1.2-4.3) | 0.012 | 2.1 (0.79-5.7) | 0.133 |
| <5 | 1 | | 1 | |
| AFP (ng/ml) | | | | |
| ≥20 | 3.3 (1.7-6.3) | <0.0001 | 1.5 (0.6-3.7) | 0.396 |
| <20 | 1 | | 1 | |
| PIVKA-II (mAU/ml) | | | | |
| ≥40 | 12.2 (5.9-25.3) | <0.0001 | 8.8 (3.7-20.9) | <0.0001 |
| <40 | 1 | | 1 | |

LC, liver cirrhosis; OR, odds ratio; CI, confidence interval; HBeAg, hepatitis B virus e antigen; HBV, hepatitis B virus; AFP, α-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II.

γ-carboxyl glutamic acids by vitamin K-dependent carboxylase. PIVKA-II is produced when this pathway is disturbed in the absence of vitamin K, or when a vitamin K antagonist is used. Liebman *et al* first reported PIVKA-II in 1984 (20). PIVKA-II has since been considered a specific marker for the detection of liver cancer in HCC patients, and is studied worldwide. Most recently, PIVKA-II has also been demonstrated to be highly present in advanced gastric cancer patients (37,38).

Wang *et al* reported that the sensitivity of PIVKA-II in detecting HCC was superior to AFP in patients with liver tumor of a diameter >3 cm, as well as in patients with liver tumor size 2-3 or <2 cm (28). However, a study comprising Japanese patients showed that the sensitivity and utility of PIVKA-II for the diagnosis of HCC was lower compared to AFP in the case of a small liver tumor (<3 cm), but higher compared to AFP in case of a large tumor (>5 cm) (23). Durazo *et al* conducted a study in the American population focusing on HBV-infected ethnic Asians, and found that PIVKA-II had the highest sensitivity and positive predicting value compared to AFP and AFP-L3 (39. Thus, the authors recommended that PIVKA-II be used as the main serum test for HCC detection (39). Another American study comprising mainly non-hispanic white, HCV-infected patients, also reported PIVKA-II to be more sensitive and specific compared to AFP when differentiating HCC from non-malignant chronic liver diseases (29). By contrast, results obtained from the HALT-C trial group in different American ethnicities demonstrated AFP to be more sensitive compared to PIVKA-II or APF-L3 in the detection of early or very early stages of HCC with a new cut-off level of 10.9 ng/ml (24,25), while another study found neither AFP nor PIVKA-II to be optimal for the detection of HCC but served a complementary role to ultrasound in the detection of early HCC (25). In addition, the combination of AFP and PIVKA-II may increase the sensitivity up to 91% (25). In the present study on HBV-infected Vietnamese patients and HCC tumors >3 cm, the data have shown that PIVKA-II has a significantly higher sensitivity compared to AFP at different analyzed serum levels (Table II), although the combination of these tumor markers only enhances the specificity (Fig. 1) as previously reported in a study on American subjects (25). The decreased sensitivity when combining PIVKA-II to AFP in the present study was consistent with the results obtained from a recent study on Indian patients (31). The results of the present study have again shown that the liver tumor markers, AFP and PIVKA-II, are likely to be affected by etiologies of liver diseases, patient demographics, stages of liver disease and the characteristics of the HCC tumor. Thus, in the future, large-scale population studies are required worldwide to examine the role of liver tumor markers.

The number of tumors, liver tumor size and vascular invasion indicate a poor prognosis of HCC patients (40-45). When compared to AFP and AFP-L3, PIVKA-II is a good

Table V. Univariate and multivariate analysis of the HCC risk factors.

| | Univariate (n=166) | | Multivariate (n=166) | |
|---|---|---|---|---|
| Factors | OR (95% CI) | P-value | OR (95% CI) | P-value |
| Age (years) | | | | |
| ≥50 | 3.3 (1.6-6.8) | 0.001 | 1.6 (0.7-3.8) | 0.301 |
| <50 | 1 | | 1 | |
| Gender | | | | |
| Male | 4.9 (1.1-21.5) | 0.037 | 3.1 (0.6-15.9) | 0.179 |
| Female | 1 | | 1 | |
| HBeAg | | | | |
| Positive | 0.54 (0.23-1.3) | 0.140 | 0.47 (0.2-1.4) | 0.176 |
| Negative | 1 | | 1 | |
| Genotype | | | | |
| C | 2.4 (1.1-4.9) | 0.022 | 2.0 (0.76-5.3) | 0.159 |
| B | 1 | | 1 | |
| HBV-DNA (log copies/ml) | | | | |
| ≥5 | 1.2 (0.6-2.6) | 0.563 | 1.02 (0.4-2.7) | 0.955 |
| <5 | 1 | | 1 | |
| AFP (ng/ml) | | | | |
| ≥20 | 4.1 (1.9-8.7) | <0.0001 | 2.1 (0.92-4.9) | 0.076 |
| <20 | 1 | | 1 | |
| PIVKA-II (mAU/ml) | | | | |
| ≥40 | 11.9 (4.4-32.6) | <0.0001 | 7.4 (2.6-21.3) | <0.0001 |
| <40 | 1 | | 1 | |

HCC, hepatocellular carcinoma; OR, odds ratio; CI, confidence interval; HBeAg, hepatitis B virus e antigen; HBV, hepatitis B virus; AFP, α-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist-II.

predictor for portal vein thrombosis and microvascular invasion (26,27,30). The present study reports that the level of AFP and PIVKA-II in HCC patients with portal vein thrombosis is higher compared to HCC patients without portal vein thrombosis. However, a statistically significant difference was only found for PIVKA-II (32,860±29,954 vs. 6,590±16,312 mAU/ml, P=0.0025), as opposed to AFP (427±342 vs. 297±362 ng/ml, P>0.05). Demonstrating a certain percentage of sensitivity (Table II), PIVKA-II was found to be a better marker compared to AFP as it is a strong independent factor for predicting LC and HCC in HBV-infected Vietnamese patients (Tables IV and V), while ROC analysis demonstrates that the area under the ROC of PIVKA-II in the present study is also higher compared to AFP (0.7525 vs. 0.6663, P=0.0785). In contrast to a previous study (28), findings of the present study have shown that PIVKA-II is not more strongly correlated to liver tumor size than AFP, partly due to the HCC patients in the study having a tumor size of more than 3 cm, with approximately 70.7% of them with a liver tumor size of more than 5 cm. In addition, PIVKA-II and AFP levels in the present study were also relatively high in patients with LC and CH (Table I).

In conclusion, the data in this first cross-sectional study on examining the role of PIVKA-II in HBV-infected Vietnamese patients indicate that PIVKA-II is likely to be a good marker in the detection of HCC, the prediction of portal vein thrombosis, as well as complementing the ultrasound in clinical utility for screening HCC. However, further studies are required to determine whether PIVKA-II is a better marker for the diagnosis of HCC in chronic HBV-infected Vietnamese patients.

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