Observational Study

Medicine

OPEN

Cutoff values of protein induced by vitamin K absence or antagonist II for diagnosing hepatocellular carcinoma

Tyng-Yuan Jang, MD[a,b,c], Chia-Yen Dai, PhD[b,d,*]

Abstract

Protein induced by vitamin K absence or antagonist II (PIVKA-II) is a promising serum marker for hepatocellular carcinoma (HCC). There are limited data on its cutoff value in HCC for Taiwanese cirrhosis patients. This study aimed to investigate the diagnostic value of PIVKA-II levels in patients with suspected HCC. In total, 88 patients with chronic hepatitis and suspected HCC by ultrasound, elevated α-fetoprotein (AFP) or PIVKA-II levels were consecutively enrolled. Their baseline characteristics and findings on dynamic phases of computed tomography (CT) or magnetic resonance imaging (MRI) were examined. Sixty participants had cirrhosis and 34 had HCC. The median levels of PIVKA-II in non-cirrhosis and cirrhosis patients without or with HCC were 28.0, 48.0, and 847.0 mAU/mL, respectively. The optimal cutoff value of PIVKA-II in predicting HCC was 78.0 mAU/mL. Combining AFP with PIVKAII mildly increased its diagnostic performance for HCC, yielding higher specificity and positive predictive value. Significant factors predicting HCC in multivariate regression analysis were PIVKA >78.0 mAU/mL and fatty liver. Monitoring PIVKA-II level is suitable for noninvasively assessing HCC in patients with chronic hepatitis, particularly with AFP.

Abbreviations: AFP = α-fetoprotein, CHB = chronic hepatitis B, CHC = chronic hepatitis C, CT = computed tomography, HBsAg = hepatitis B surface antigen, HCC = hepatocellular carcinoma, MRI = magnetic resonance imaging, NAFLD = Nonalcoholic fatty liver disease, PIVKA-II = protein induced by vitamin K absence or antagonist II, ROC = receiver operating characteristic, UNLs = Upper normal limits.

Keywords: AFP, HCC, LC, PIVKA-II

1. Introduction

Hepatocellular carcinoma (HCC) causes many deaths in Taiwan and the world.[1] The risk factors for HCC include chronic hepatitis B (CHB) and chronic hepatitis C (CHC) infections, alcohol consumption, and nonalcoholic fatty liver disease (NAFLD).[2] CHB and CHC have been endemic in Taiwan, which cause a great health burden.[3,4]

Protein induced by vitamin K absence or antagonist II (PIVKA-II) is one of the many markers of HCC. PIVKA-II has been widely used for HCC surveys and follow-up in Japan,[5] and it has been approved by the American Food and Drug Administration. PIVKA-II has been validated in HCC with different risk factors, including CHB, CHC, NAFLD, and alcoholic hepatitis.[6,7] α-Fetoprotein (AFP) has been widely used in Taiwan; however, its sensitivity is low.[8] PIVKA-II has been gradually examined for HCC diagnosis and follow-up in Taiwan. Notably, the GALAD score (sex, age, AFP-L3, AFP, and des-gamma-carboxy prothrombin) was recently validated to detect HCC.[9] Liver cancer screening is recommended every 3 to 4 months for super-high-risk patients or every 6 months for high-risk patients by ultrasound and tumor marker measurement.[10] The cutoff value of PIVKA-II is 40 mAU/mL in diagnosing HCC.[11] However, liver cirrhosis can induce PIVKA-II elevation, and the optimal level for predicting HCC in cirrhosis patients is elusive. Therefore, we aimed to evaluate the cutoff value of PIVKA-II for HCC in Taiwanese patients with cirrhosis.

2. Methods

2.1. Patients

A total of 88 patients with chronic hepatitis suspected of having HCC (either ultrasound had liver nodules, PIVKA-II level was >40 mAU/mL, or AFP level was more than the upper limit [7.3 ng/mL]) were consecutively recruited at the

The authors have no conflicts of interest to disclose.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Supplemental Digital Content is available for this article.

[a] PhD Program of Environmental and Occupational Medicine and Graduate Institute of Clinical Medicine, Kaohsiung Medical University, Kaohsiung City, Taiwan, [b] Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, [c] Department of Internal Medicine, Pingtung Hospital, Ministry of Health and Welfare, Ping-Tung, Taiwan, [d] Department of Occupational and Environmental Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

**Correspondence: Chia-Yen Dai, Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, 100 Tzyou Road, Kaohsiung City 807, Taiwan (e-mail: daichiayen@gmail.com).*

How to cite this article: Jang T-Y and Dai C-Y. Cutoff values of protein induced by vitamin K absence or antagonist II for diagnosing hepatocellular carcinoma. Medicine 2022;101:39(e30936).

Received: 21 May 2022 / Received in final form: 31 August 2022 / Accepted: 2 September 2022

http://dx.doi.org/10.1097/MD.0000000000030936

outpatient clinic from a governmental hospital in Pingtung from September 2020 to September 2021. Patients were excluded if they were receiving known drugs that could affect the serum PIVKA-II level (e.g., warfarin or antibiotics), the PIVKA-II data were unavailable, and there was uncertainty of HCC diagnosis (Fig. 1). All patients were examined for serum PIVKA-II levels and dynamic phases of computed tomography (CT) or magnetic resonance imaging (MRI) to evaluate liver tumors. The interval between PIVKA-II examination and CT/MRI was <1 month. HCC staging was performed according to the 8th edition of the American Joint Committee on Cancer staging system. The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Committee of Kaohsiung Medical University Hospital.

2.2. Laboratory and histological analyses

Biochemical analyses were performed using a multichannel autoanalyzer (Hitachi Inc., Tokyo, Japan). Hepatitis B surface antigen (HBsAg) and AFP were examined using a standard quantitative chemiluminescent microparticle immunoassay (ARCHITECT HBsAg, Abbott Diagnostics). HCV antibodies (anti-HCV) were measured using a third-generation enzyme immunoassay (Abbott Laboratories, North Chicago, IL). Liver cirrhosis was diagnosed based on either the presence of clinical, laboratory, radiological, or endoscopic findings or evidence of portal hypertension or cirrhosis.[12] HCC surveillance was conducted by serum AFP and PIVKA-II level measurement and abdominal ultrasound examination every 3 to 6 months. HCC was diagnosed by typical dynamic imaging studies (CT or MRI) according to the guidelines of the American Association for the Study of Liver Diseases.[13] The reagents of PIVKA-II were designed for a fully automated chemiluminescence enzyme immunoassay on the LUMIPULSE G1200 system as a leading instrument (Fujirebio Diagnostics). The PIVKA-II measurement range was 5 to 75,000 mAU/mL, with the cutoff value being 40 mAU/mL. The AFP measurement range was 3.5 to 16,600 mAU/mL, with the cutoff value being 7.3 ng/mL. The fibrosis-4 index was calculated using the following formula: [age (yr) × aspartate aminotransferase (U/L)]/ [platelets (10^9/L) × alanine transaminase (U/L)$^{1/2}$].

2.3. Statistical analysis

Frequencies were compared between groups using the χ^2 test with the Yates correction or Fisher's exact test. Group means are presented as mean ± standard deviation and were compared using analysis of variance, Student's *t* test, or the nonparametric Mann–Whitney test. Stepwise logistic regression analysis was performed to assess the factors associated with high PIVKA-II levels and HCC. The area under the curve was compared using receiver operating characteristic (ROC) analysis to determine the cutoff value of the PIVKA-II and AFP levels in predicting HCC. Statistical analyses were performed using the SPSS 20 statistical package (SPSS, Chicago, IL). All statistical analyses were based on two-sided hypothesis tests, with a statistical significance set at a *P* value of <.05.

3. Results

3.1. Patient characteristics

As shown in Table 1, the mean age was 64.5 (range, 39–84) years, with men accounting for 70.5% (n = 62) of the cohort. The seropositive rates of HBsAg and anti-HCV were 50.0% (n = 44) and 13.6% (n = 12), respectively. Among the participants, 68.2% (n = 60) had cirrhosis and 38.6% (n = 34) had HCC.

3.2. Performance of pIVKA-II in HCC assessment

The upper normal limits (UNLs) of PIVKA-II and AFP were 40.0 mAU/mL and 7.3 ng/mL, respectively. Of the patients, 57.4% exceeded the UNL of PIVKA-II in the group of patients without HCC and 55.9% had an AFP level below the UNL in the group of patients with HCC. The optimal cutoff values of PIVKA-II and AFP for predicting HCC were 78.0 mAU/mL (*P* < .001; sensitivity, 79.4%; specificity, 85.2%; and accuracy, 83.0%) and 3.6 ng/mL (*P* < .001; sensitivity, 73.5%; specificity, 74.1%; and accuracy, 73.9%), respectively (Table 2). The areas under the ROC curve for predicting HCC with PIVKA-II and AFP were 0.87 (*P* < .001) and 0.81 (*P* < .001), respectively (Supplementary Figure S1, http://links.lww.com/MD/H503). A high PIVKA-II level was defined as a PIVKA-II level of 78 mAU/mL.

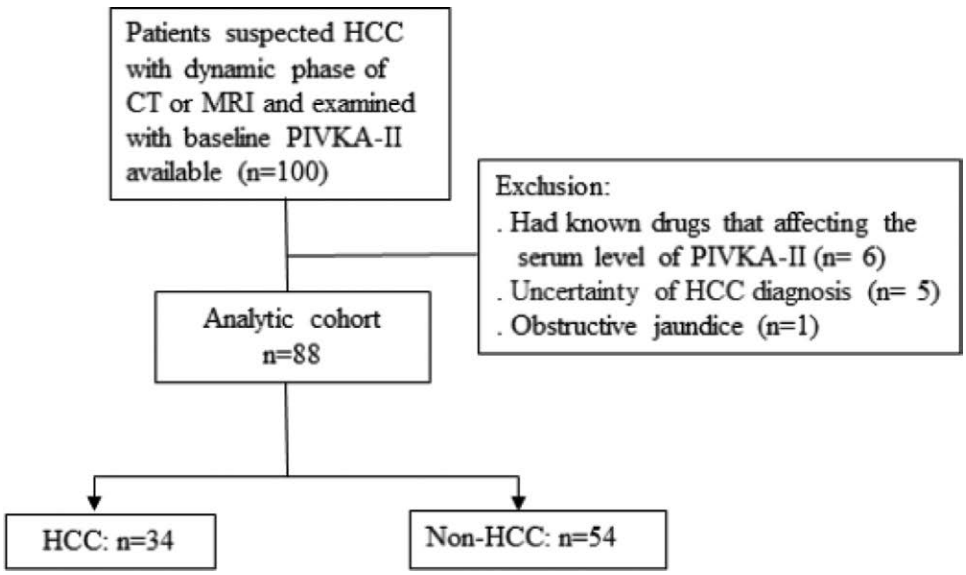

Figure 1. Patient flowchart. CHC = chronic hepatitis C, CT = computed tomography, HCC = hepatocellular carcinoma, MRI = magnetic resonance imaging, PIVKA-II = protein induced by vitamin K or antagonist II.

Combining PIVKA-II with AFP: Considering either a PIVKA-II level of >78 mAU/mL or AFP level of >3.6 ng/mL, it increased the sensitivity and negative predictive value (NPV) to 97.1% and 97.1%, respectively; considering both PIVKA-II level of >78 mAU/mL and AFP level of >3.6 ng/mL, it increased the specificity and positive predictive value (PPV) to 96.3% and 90.5%, respectively; considering either a PIVKA-II level of >78 mAU/mL or AFP level greater than or equal to the UNL (7.3 ng/mL), it increased the sensitivity and NPV to 82.4% and 89.4%, respectively; and considering both PIVKA-II level of >78 mAU/mL and AFP level greater than or equal to the UNL, it increased the specificity and PPV to 98.1% and 93.3%, respectively (Table 2). An algorithm using two sequential steps was designed to improve performance (Supplementary Figure S2, http://links.lww.com/MD/H504).

3.3. Factors associated with high pIVKA-II levels

Compared with patients without high PIVKA-II levels, patients with high PIVKA-II levels were older (67.9 vs 62.3 yr, $P = .02$) and had a higher proportion of male sex (85.7% vs 60.4%, $P = .02$), liver cirrhosis (97.1% vs 49.1%, $P < .001$), and HCC (77.1% vs 13.2 %, $P < .001$) and a lower proportion of fatty liver (28.6% vs 50.9%, $P = .048$) (Table 3). Multivariate analysis revealed that patients with high PIVKA-II levels had a higher proportion of liver cirrhosis (OR/CI, 11.93/1.37–104.24; $P = .03$) and HCC (OR/CI, 9.25/2.64–32.44; $P < .001$).

3.4. Clinical characteristics of cirrhosis patients without HCC and those with HCC

Because cirrhosis was also a crucial factor for high PIVKA-II levels, we further compared cirrhosis patients without HCC and those with HCC. Patients with HCC were older (68.4 vs 60.7 yr, $P = .01$) and had a lower proportion of fatty liver (14.7% vs 63.0%, $P < .001$) and a higher proportion of high PIVKA-II levels (79.4% vs 25.9%, $P < .001$) (Table 4). Multivariate analysis revealed that patients with HCC had a higher proportion of high PIVKA-II levels (OR/CI, 9.54/2.12–42.89, $P = .003$) and a lower proportion of fatty liver (OR/CI, 0.09/0.02–0.44, $P = .003$). The median PIVKA-II levels in patients with chronic liver disease alone, liver cirrhosis alone, and HCC were 28.0, 48.0, and 847.0 mAU/mL, respectively (Supplementary Figure S3, http://links.lww.com/MD/H505). After excluding patients with HCC, the mean PIVKA-II level was similar between patients with and without fatty liver (60.4 vs 64.1 mAU/mL, $P = .18$).

3.5. Characteristics of patients with early-stage and non-early-stage HCC

Twenty patients had early-stage HCC (tumor–node–metastasis [TNM] stage 1). Compared with patients with non-early-stage HCC, patients with early-stage HCC had a lower PIVKA-II level (601.0 vs 12,244.2 mAU/mL) (Table 5). The optimal cutoff values of PIVKA-II to predict early-stage and non-early-stage HCC were 78.0 and 137.0 mAU/mL. The areas under the ROC curve for predicting early-stage and non-early-stage HCC with PIVKA-II were 0.79 ($P < .001$) and 0.99 ($P < .001$), respectively.

Table 1

Basic characteristics of the image-diagnosed HCC cohort.

	Total (N = 88)
Age (yr, mean [SD])	64.5 (11.3)
Male gender, n (%)	62 (70.5)
BMI (kg/m^2, mean [SD])	24.6 (5.2)
Platelet count (×10^3 u/L, mean [SD])	194.8 (83.2)
AST (IU/L, mean [SD])†	45.8 (33.0)
ALT (IU/L, mean [SD])‡	39.8 (38.8)
FIB-4 (mean [SD])	3.4 (4.1)
Cretinine (mg/dL,mean [SD])	1.1 (1.0)
PIVKA-II (mAU/mL, mean [SD])	2122.5 (8741.4)
α-fetoprotein (ng/mL, mean [SD])§	895.6 (4132.2)
Fatty liver, n (%)	37 (42.0)
Liver cirrhosis, n (%)	60 (68.2)
HCC, n (%)	34 (38.6)
CHB/CHC, n/n	44/12

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CHB = chronic hepatitis B, CHC = chronic hepatitis C, FIB-4 = fibrosis-4 index, HCC = hepatocellular carcinoma, PIVKA-II = protein induced by vitamin K absence or antagonists-II, SD = standard deviation.

†Standard value: 5 to 41 IU/mL.

‡Standard value: 5 to 35 IU/mL.

§Standard value: 0 to 7.3 ng/mL.

4. Discussion

Accurate and easy-to-access noninvasive HCC diagnosis is challenging in a clinical setting. In the image diagnosis (CT or MRI) study, we demonstrated that serum PIVKA-II performed well in HCC assessment. A serum PIVKA-II level of ≥78.0 mAU/mL could predict HCC with high accuracy in this study, in which the majority of the participants had cirrhosis. Combining PIVKA-II with AFP increase the diagnostic value.

PIVKA-II is a nonfunctional prothrombin resulting from incomplete carboxylation of 10 glutamic acids located at the N-terminal portion of the molecule.[14] It is released into the circulation when vitamin K is deficient. The causes of PIVKA-II elevation include HCC, liver cirrhosis, alcoholic hepatitis,

Table 2

Accuracy of PIVKA and AFP in predicting HCC.

	HCC (n = 34)	Non-HCC (n = 54)		SEN	SPE	PPV	NPV	ACC
	n (%)	n (%)	*P* value	%	%	%	%	%
PIVKA-II >78 mAU/mL	27 (79.4)	8 (14.8)	<.001	79.4	85.2	77.1	86.8	83.0
PIVKA >40 mAU/mL	31 (91.2)	31 (57.4)	<.001	91.2	42.6	50.0	88.5	61.3
AFP >3.6 ng/mL	25 (73.5)	14 (25.9)	<.001	73.5	74.1	64.1	81.6	73.9
AFP >7.3 ng/mL	15 (44.1)	5 (9.3)	<.001	44.1	90.7	75.0	72.7	72.7
PIVKA >78 mAU/mL or AFP >3.6 ng/mL	33 (97.1)	20 (37.0)	<.001	97.1	63.0	62.3	97.1	66.1
PIVKA >78 mAU/mL and AFP >3.6 ng/mL	19 (55.9)	2 (3.7)	<.001	55.9	96.3	90.5	77.6	80.7
PIVKA >78 mAU/mL or AFP >7.3 ng/mL	28 (82.4)	12 (22.2)	<.001	82.4	77.8	70.0	89.4	79.5
PIVKA >78 mAU/mL and AFP >7.3 ng/mL	14 (41.2)	1 (1.9)	<.001	41.2	98.1	93.3	73.6	76.1

Statistical methods: χ^2 test.

ACC = accuracy, AFP =α-fetoprotein, HCC = hepatocellular carcinoma, NPV = negative predictive value, PIVKA-II = protein induced by vitamin K absence or antagonists-II, PPV = positive predictive value, SEN = sensitivity, SPE = specificity.

Table 3

Factors associated with high PIVKA level.

	PIVKA >78 (n = 35)	PIVKA < 78 (n = 53)	*P* value	Logistic regression		
				OR	95% C.I.	*P* value
Age (yr, mean [SD])	67.9 (11.0)	62.3 (11.0)	.02			
Male gender, n (%)	30 (85.7)	32 (60.4)	.02			
BMI (kg/m^2, mean [SD])	24.2 (4.1)	24.7 (5.8)	1.00			
AST (IU/L, mean [SD])	62.7 (40.4)	34.9 (21.3)	.001			
ALT (IU/L, mean [SD])	45.3 (34.4)	36.1 (41.4)	.28			
Cretinine (mg/dL, mean [SD])	1.1 (1.0)	1.1 (1.1)	.86			
Platelet count (×10^3 u/L, mean [SD])	174.7 (94.6)	208.3 (72.4)	.06			
Fatty liver, n (%)	10 (28.6)	27 (50.9)	.048			
AFP (ng/mL, mean [SD])	2242.1 (6371.3)	6.37 (14.48)	.046			
Liver cirrhosis, n (%)	34 (97.1)	26 (49.1)	<.001	11.93	1.37–104.24	.03
HCC, n (%)	27 (77.1)	7 (13.2)	<.001	9.25	2.64–32.44	<.001
CHB/CHC	10/19	18/25	.67			

Statistical methods: Student's *t* test, and stepwise logistic regression.

A high PIVKA-II level was defined as a PIVKA-II level of 78 mAU/mL.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CHB = chronic hepatitis B, CHC = chronic hepatitis C, HCC = hepatocellular carcinoma, PIVKA-II = protein induced by vitamin K absence or antagonists-II, SD = standard deviation.

Table 4

Basic characteristics of cirrhotic patients without HCC and HCC patients.

	LC w/o HCC (n = 27)	HCC (n = 34)	*P* value	Logistic regression		
				OR	95% C.I.	*P* value
Age (yr, mean [SD])	60.7 (11.9)	68.4 (11.3)	.01			
Male gender, n (%)	19 (70.4)	30 (88.2)	.11			
BMI (kg/m^2, mean [SD])	25.0 (4.4)	27.6 (9.0)	.56			
AST (IU/L, mean [SD])	45.9 (27.2)	59.3 (41.4)	.22			
ALT (IU/L, mean [SD])	43.3 (53.6)	47.3 (34.5)	.14			
Cretinine (mg/dL, mean [SD])	1.0 (0.7)	1.4 (1.5)	.06			
Platelet count (×10^3 u/L, mean [SD])	160.8 (70.4)	187.9 (87.3)	.35			
Fatty liver, n (%)	17 (63.0)	5 (14.7)	<.001	0.09	0.02–0.44	.003
AFP (ng/mL, mean [SD])	6.5 (17.5)	2309.6 (6454.4)	<.001			
PIVKA (mAU/mL, mean [SD])	87.3 (95.3)	5395.3 (13,544.7)	<.001			
PIVKA >40 mAU/mL	20 (74.1)	31 (91.2)	.09			
PIVKA >78 mAU/mL	7 (25.9)	27 (79.4)	<.001	9.54	2.12–42.89	.003
CHB/CHC	6/17	10/17	.55			

Statistical methods: Student's *t* test, the nonparametric Mann–Whitney test, and stepwise logistic regression.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CHB = chronic hepatitis B, CHC = chronic hepatitis C, HCC = hepatocellular carcinoma, PIVKA-II = Protein induced by vitamin K absence or antagonists-II, SD = standard deviation.

Table 5

The characteristics of the patients with early stage and non-early stage HCC.

	TNM stage 1 (n = 20)	TNM stage 2-4 (n = 14)	*P* value
Age (yr, mean [SD])	67.1 (12.4)	70.5 (9.7)	.46
Male gender, n (%)	17 (85.0)	12 (92.9)	.63
AST (IU/L, mean [SD])	37.4 (13.1)	93.0 (47.7)	<.001
ALT (IU/L, mean [SD])	38.6 (18.9)	59.6 (47.1)	.18
FIB-4 (mean [SD])	2.9 (1.7)	5.5 (2.8)	.01
Cretinine (mg/dL, mean [SD])	1.4 (1.5)	1.4 (1.6)	.54
Platelet count (×10^3 u/L, mean [SD])	182.7 (86.7)	195.4 (90.8)	.58
Fatty liver, n (%)	5 (25.0)	0 (0)	.06
Liver cirrhosis, n (%)	19 (95.0)	14 (100.0)	1.00
AFP (ng/mL, mean [SD])	34.6 (107.1)	5559.6 (9295.0)	.18
PIVKA (mAU/mL, mean [SD])	601.0 (904.1)	12244.2 (19,458.4)	<.001
CHB/CHC	10/4	7/2	.80

Statistical methods: Student's *t* test, or the nonparametric Mann–Whitney test.

AFP = α-Fetoprotein, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CHB = chronic hepatitis B, CHC = chronic hepatitis C, HCC = hepatocellular carcinoma, PIVKA-II = protein induced by vitamin K absence or antagonists-II, SD = standard deviation.

obstructive jaundice, hepatic adipose infiltration, liver cyst, liver abscess, pregnancy, and use of antibiotics and anticoagulants.[15,16] The PIVKA-II level is reported to be 40 mAU/mL in diagnosing HCC[15]; however, the optimal value in patients with liver cirrhosis is elusive. In Italian patients with cirrhosis, 60 mAU/mL was reported to be a cutoff value in early HCC detection,[17] but the HCC stage was not well elucidated. In a multicenter study in China, PIVKA-II at a cutoff of 45 mAU/mL was optimal for discriminating patients with HCC from those with CHB-related cirrhosis.[18] However, the methodology of PIVKA-II in different hospitals varies. In an American study, the diagnostic value of HCC was best at 125 mAU/mL.[19] In a study with mostly patients with liver cirrhosis, 78 and 137 mAU/mL were the optimal cutoff values for TNM stages 1 and 2 to 4, respectively. The serum PIVKA-II level has been correlated with the stage and microvascular invasion of HCC,[5,20] and our study corroborates previous studies.

PIVKA-II has been gradually examined in Taiwan in recent years, and there are few reports on PIVKA-II. Su et al demonstrated that there is a greater risk of HCC in the future when the PIVKA-II level is >50 mAU/mL at the time of antiviral therapy-induced viral relapse among cirrhosis Taiwanese patients with CHB.[21] However, the optimal cutoff values for

diagnosing HCC was not demonstrated in that study. AFP is the only serum marker that has been reimbursed by the National Health Insurance (NHI) for HCC surveillance before 2020.[22] PIVKA-II has been reimbursed by the NHI after September 2020. AFP had low sensitivity in diagnosing HCC,[8] and approximately 56% of patients with HCC were in the normal range in this study. By combining AFP with PIVKA-II, the diagnostic accuracy of HCC would be augmented.[23] In the study, the sequential diagram using AFP as the first step followed by PIVKA-II further provided the clinical utility in distinguishing HCC. In patients with HCC misjudged to have an AFP level of <7.3 ng/mL (n = 19), 13 patients (68.4%) could be identified by having high serum PIVKA-II levels. There were some limitations in detecting small tumors using ultrasound in patients with liver cirrhosis. If the findings of ultrasound and serum AFP and PIVKA-II measurements were considered, HCC could be detected earlier.[24] The diagnosis of early cancer was not satisfactory in Taiwan,[10] and the clinical application of PIVKA-II may improve it.

The risk factor for HCC in this study included viral hepatitis. Fatty liver accounted for 42.0%, 63.0%, 14.7%, and 28.6% of the overall cohort, cirrhosis patients without HCC, patients with HCC, and patients with an PIVKA-II level of >78 mAU/mL, respectively. Fatty liver was less prevalent in patients with HCC and high PIVKA-II levels in this study. After excluding patients with HCC, there were no differences in PIVKA-II levels between patients with and without fatty liver. The PIVKA-II level seemed not to be affected by fatty liver, but further study is needed. Fatty liver has been shown to be protective against HCC in patients with HBV.[25] Metabolic associated fatty liver disease (MAFLD) has been advocated in recent years, and the HCC surveillance rate is low in patients with MAFLD.[26] It is difficult to diagnose MAFLD in patients with HCC and liver cirrhosis because hepatic steatosis has been "burned out" and no longer evident in advanced liver disease. In addition, the surveillance of HCC by PIVKA-II in patients with NAFLD/MAFLD has been validated, especially in advanced fibrosis.[7] The role of PIVKA-II in MAFLD requires further study.

The GALAD score has been promising in recent years and has been validated in CHB, CHC, and NAFLD.[27,28] However, its role in Asian patients remains controversial[29] and requires further study. PIVKA-II has been used for decades in Japan, and there has been another method for detecting PIVKA-II (Abbott Diagnostics) in Western countries.[30] There were no significant differences between the two methodologies of PIVKA-II in predicting HCC.

The study has some limitations, including the relatively small number of cases and lack of long-term follow-up. Data on alcohol consumption and diagnosis of MAFLD were not available, but alcoholic liver disease and MAFLD were less prevalent in Asia.[31,32] Half of the patients with HCC were with more than TNM stage II in the study, which might elevate the PIVKA-II cutoff values. However, we analyzed the subgroup, and the optimal cutoff value to predict early-stage HCC was also 78.0 mAU/mL. Although the participants were enrolled at a medium-sized hospital, HCC surveillance has been kept up to date. In the present study, the optimal cutoff value for HCC in patients with liver cirrhosis was described. To the best of our knowledge, our report is the first to describe the cutoff values of PIVKA-II in Taiwan.

In conclusion, we demonstrated that the optimal value of PIVKA-II to be correlated with early-stage HCC was 78 mAU/mL and the combination with AFP may offer better diagnostic values.

This study was supported by the Ministry of Health and Welfare, Pingtung Hospital and Kaohsiung Medical University Hospital. The authors thank the secretaries of the Hepatobiliary Division in Kaohsiung Medical University Hospital.

Author contributions

Formal analysis: Tyng-Yuan Jang.
Methodology: Tyng-Yuan Jang.
Resources: Tyng-Yuan Jang.
Software: Tyng-Yuan Jang.
Visualization: Chia-Yen Dai.
Writing – original draft: Tyng-Yuan Jang.
Writing – review & editing: Chia-Yen Dai.

References

[1] Chen DS. Hepatocellular carcinoma in Taiwan. Hepatol Res. 2007;37(Suppl 2):S101–5.
[2] Janevska D, Chaloska-Ivanova V, Janevski V. Hepatocellular carcinoma: risk factors, diagnosis and treatment. Open Access Maced J Med Sci 2015;3:732–6.
[3] Yang JF, Lin CI, Huang JF, et al. Viral hepatitis infections in southern Taiwan: a multicenter community-based study. Kaohsiung J Med Sci. 2010;26:461–9.
[4] Jang TY, Liang PC, Liu TW, et al. Genotype distribution, clinical characteristics, and racial differences observed in chronic hepatitis C patients in Pingtung, Taiwan. J Chin Med Assoc. 2021;84:255–60.
[5] Kokudo N, Hasegawa K, Akahane M, et al. Evidence-based clinical practice guidelines for hepatocellular carcinoma: the Japan Society of Hepatology 2013 update (3rd JSH-HCC Guidelines). Hepatol Res. 2015;45.
[6] Unic A, Derek L, Duvnjak M, et al. Diagnostic specificity and sensitivity of PIVKAII, GP3, CSTB, SCCA1 and HGF for the diagnosis of hepatocellular carcinoma in patients with alcoholic liver cirrhosis. Ann Clin Biochem. 2018;55:355–62.
[7] Sumida Y, Yoneda M, Seko Y, et al. Surveillance of Hepatocellular carcinoma in nonalcoholic fatty liver disease. Diagnostics (Basel). 2020;10.
[8] Daniele B, Bencivenga A, Megna AS, et al. Alpha-fetoprotein and ultrasonography screening for hepatocellular carcinoma. Gastroenterology. 2004;127:S108–12.
[9] Yang JD, Addissie BD, Mara KC, et al. GALAD Score for hepatocellular carcinoma detection in comparison with liver ultrasound and proposal of GALADUS score. Cancer Epidemiol Biomarkers Prev. 2019;28:531–8.
[10] Kudo M. Management of hepatocellular carcinoma in Japan as a world-leading model. Liver Cancer. 2018;7:134–47.
[11] Seo SI, Kim HS, Kim WJ, et al. Diagnostic value of PIVKA-II and alpha-fetoprotein in hepatitis B virus-associated hepatocellular carcinoma. World J Gastroenterol. 2015;21:3928–35.
[12] Huber A, Ebner L, Heverhagen JT, et al. State-of-the-art imaging of liver fibrosis and cirrhosis: a comprehensive review of current applications and future perspectives. Eur J Radiol Open. 2015;2:90–100.
[13] Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53:1020–2.
[14] Kudo M. Biomarkers and personalized sorafenib therapy. Liver Cancer. 2014;3:399–404.
[15] Yu R, Tan Z, Xiang X, et al. Effectiveness of PIVKA-II in the detection of hepatocellular carcinoma based on real-world clinical data. BMC Cancer. 2017;17:608.
[16] Kang KH, Kim JH, Kang SH, et al. The influence of alcoholic liver disease on serum PIVKA-II levels in patients without hepatocellular carcinoma. Gut Liver. 2015;9:224–30.
[17] Saitta C, Raffa G, Alibrandi A, et al. PIVKA-II is a useful tool for diagnostic characterization of ultrasound-detected liver nodules in cirrhotic patients. Medicine. 2017;96:e7266.
[18] Ji J, Liu L, Jiang F, et al. The clinical application of PIVKA-II in hepatocellular carcinoma and chronic liver diseases: a multi-center study in China. J Clin Lab Anal. 2021:e24013.
[19] Marrero JA, Su GL, Wei W, et al. Des-gamma carboxyprothrombin can differentiate hepatocellular carcinoma from nonmalignant chronic liver disease in american patients. Hepatology. 2003;37:1114–21.
[20] Pote N, Cauchy F, Albuquerque M, et al. Performance of PIVKA-II for early hepatocellular carcinoma diagnosis and prediction of microvascular invasion. J Hepatol. 2015;62:848–54.
[21] Su TH, Peng CY, Chang SH, et al. Serum PIVKA-II and alpha-fetoprotein at virological remission predicts hepatocellular carcinoma in chronic hepatitis B related cirrhosis. J Formosan Med Assoc. 2021.
[22] Surveillance G, Diagnosis G, Staging G, et al. Management consensus guideline for hepatocellular carcinoma: 2016 updated by the Taiwan

Liver Cancer Association and the Gastroenterological Society of Taiwan. J Formosan Med Assoc. 2018;117:381–403.
[23] Alonso Lopez S, Manzano ML, Gea F, et al. A model based on noninvasive markers predicts very low hepatocellular carcinoma risk after viral response in Hepatitis C virus-advanced fibrosis. Hepatology. 2020;72:1924–34.
[24] Loglio A, Iavarone M, Facchetti F, et al. The combination of PIVKA-II and AFP improves the detection accuracy for HCC in HBV caucasian cirrhotics on long-term oral therapy. Liver Int. 2020;40:1987–96.
[25] Li J, Yang HI, Yeh ML, et al. Association between fatty liver and cirrhosis, hepatocellular carcinoma, and Hepatitis B surface antigen seroclearance in chronic Hepatitis B. J Infect Dis. 2021;224:294–302.
[26] Chen VL, Yeh ML, Yang JD, et al. Effects of cirrhosis and diagnosis scenario in metabolic-associated fatty liver disease-related hepatocellular carcinoma. Hepatol Commun. 2021;5:122–32.
[27] Schotten C, Ostertag B, Sowa JP, et al. GALAD score detects early-stage hepatocellular carcinoma in a European cohort of chronic Hepatitis B and C patients. Pharmaceuticals (Basel). 2021;14.
[28] Best J, Bechmann LP, Sowa JP, et al. GALAD score detects early hepatocellular carcinoma in an international cohort of patients with nonalcoholic steatohepatitis. Clin Gastroentero Hepatol. 2020;18:728–35 e4.
[29] Park SJ, Jang JY, Jeong SW, et al. Usefulness of AFP, AFP-L3, and PIVKA-II, and their combinations in diagnosing hepatocellular carcinoma. Medicine. 2017;96:e5811.
[30] Ryu MR, Kang ES, Park HD. Performance evaluation of serum PIVKA-II measurement using HISCL-5000 and a method comparison of HISCL-5000, LUMIPULSE G1200, and ARCHITECT i2000. J Clin Lab Anal. 2019;33:e22921.
[31] Wong SW, Ting YW, Chan WK. Epidemiology of non-alcoholic fatty liver disease-related hepatocellular carcinoma and its implications. JGH Open. 2018;2:235–41.
[32] deLemos A, Patel M, Gawrieh S, et al. Distinctive features and outcomes of hepatocellular carcinoma in patients with alcohol-related liver disease: a US multicenter study. Clin Transl Gastroenterol. 2020;11:e00139.