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Prognostic Value of Measurement of Prothrombin Induced by Vitamin K Deficiency (PIVKA2) and Alpha Feto Protein (AFP) in HCC

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Abstract:

Background: Hepatocellular carcinoma (HCC) is a major cause for alarm because it ranks third in cancer-related deaths globally and sixth in the frequency of cancer diagnoses overall. There are three main forms of HCC: viral hepatitis, chronic liver disease, and liver cirrhosis. This study aimed to evaluate the relative predictive value of measuring prothrombin time in HCC and alpha fetoprotein (AFP) and prothrombin time when vitamin K is inadequate (PIVKA2). **Methods:** In this observational research, 96 individuals undergoing therapy for liver cirrhosis at Benha University Hospital were included. Each patient was randomly assigned to one of four groups: Part I: Liver cirrhosis without HCC, and Part ꙮꙮ: HCC newly diagnosed. Classification: Group ꙮꙮ: HCC patients with metastases and Group ꙅ: HCC patients who began treatment. **Results:** The ROC analysis was used to determine the optimal cutoff value for distinguishing HCC patients from non-HCC patients. PIVKA2 demonstrated the highest sensitivity (75%) and specificity (88.89%) at 489, with an area under the curve of (0.872). **Conclusion:** PIVKA-II and AFP are both dependable biomarkers for the diagnosis and prognosis of HCC patients. In terms of the identification of patients with HCC and the prediction of the prognosis for both treated and untreated HCC, both markers exhibited comparable statistical performance. However, PIVKA2 exhibited superior sensitivity and specificity in comparison to AFP at the most optimal cut-off values.

Keywords: Alpha Feto Protein; Hepatocellular Carcinoma; Prothrombin Induced by Vitamin K Deficiency

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Introduction

The third leading cause of cancer-related death globally is hepatocellular carcinoma (HCC), which is also the sixth most diagnosed malignancy overall. Consequently, it presents a significant challenge [(1)]. In Egypt, HCC ranks as the fourth most common cancer. Multiple hospital-based studies have shown an alarming rise in the incidence of HCC. Probable causes of the uptick in incidents include: First, there must be an improvement in diagnostic tools and screening programs. Second, cirrhotic patients' survival rates have been steadily rising, which raises the risk of HCC. Thirdly, the prevalence of hepatitis C virus (HCV) infections and complications has significantly increased, making it the most prevalent cause of liver cancer in Egypt, including HCC. [(2)].

Even though the condition's management has improved in recent years, the long-term overall prognosis of HCC remains unfavorable. Consequently, it is essential to establish effective strategies for the early detection of HCC [(3)]**.** The easy-to-understand method of measuring α-fetoprotein (AFP) levels is now widely used for routine monitoring and noninvasive diagnosis of HCC, as well as for evaluating prognosis and tracing recurrence after treatment. Regrettably, AFP fails to deliver suitable diagnostic accuracy for patients with HCC. In the past, research has suggested that serum AFP has a specificity of 76–94% and a sensitivity of 39–65% in the identification of HCC. Despite this, these values are significantly deficient in terms of their clinical application [(4)].

Because the liver is undergoing regenerative and inflammatory processes, patients with nontumorous hepatic diseases may also have increased AFP serum levels. Conditions that contribute to this list include cirrhosis, acute and chronic hepatitis, and extensive hepatic necrosis [(5)]. 1984 marked the initial description of prothrombin as a biomarker that was specifically associated with HCC and was induced by vitamin K absence II (PIVKA2). A growing body of evidence indicates that PIVKA2 possesses exceptional diagnostic and prognostic capabilities for the monitoring of HCC [(6)].

While some research has found that detecting HCC with both PIVKA2 and AFP simultaneously may be more accurate than using either biomarker alone, most studies have not come to this conclusion. As a result, PIVKA2's diagnostic utility is debatable; questions remain as to whether the two tests are correlated and whether PIVKA2 can supplant or replace AFP in the diagnosis of HCC [(7)]. Additionally, there has not been enough research into the function of PIVKA2 in evaluating the curative effects of HCC or the relationship between PIVKA2 and clinicopathological findings. The importance of PIVKA2 in HCC may be better understood because of these results [(8)].

The purpose of this study was to investigate the prognostic value of measurement of PIVKA2 in comparison with AFP in HCC.

Patients and methods

The 96 patients with liver cirrhosis who began therapy between March and September 2024 at Benha University Hospital were included in this observational research. Their ages ranged from 20 to 65.

We made sure to get patients' written informed consent. A secret code and an explanation of the study's purpose were given to each patient. This study could not have begun without the green light from the Faculty of Medicine's Research Ethics Committee at Benha University.

Inclusion criteria were individuals afflicted with NASH, LC, non-alcoholic steatohepatitis (HCV), and chronic hepatitis B virus (HCV). These individuals were categorized based on a minimum of six months of seropositivity for the Hepatitis B surface antigen (HBsAg), having anti-HCV antibodies or HCV RNA

positivity, liver biochemistry, or a CT scan or ultrasonography. Liver ultrasonography and fibro scan, in addition to clinical and laboratory findings, were used to diagnose LC in patients in group I. According to the guidelines for diagnosing HCC, a multislice triphasic spiral CT scan and/or MRI were performed [(9)], The tumor's location was established using the tumour staging approach developed by the Barcelona Clinic Liver Cancer (BCLC) in group II and HCC who started treatment in group IV [(10)].

Exclusion criteria alcoholism, cancer, recent vitamin K injection, warfarin use, and other medical conditions.

Grouping: Patients were divided into four equal groups: **Group I (n=24):** with liver cirrhosis without HCC**, Group II (n=24):** with new diagnosis HCC**. Group III (n=24):** with metastasis HCC and **Group IV (n=24):** with HCC who started treatment.

All studied cases were subjected to: History taking and demographic data collection including (age, sex, occupation, history of current illness, medications and past history of any medical condition or previous hospital admission)**. Full clinical examination: General examination including** [Summary of the patient's mental and conscious status, any noticeable jaundice or paleness, The patient's anthropometric data, such as height and weight, as well as their vital signs, such as pulse, blood pressure, capillary filling time, respiratory rate, and temperature. By dividing one's weight in kilograms by one's height in meters squared, one's body mass index (BMI) was determined [(11)]], Systemic examination including (cardiovascular system, respiratory system, gastrointestinal tract (GIT) and central nervous system (CNS)), **laboratory investigations including** (complete blood count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum albumin, prothrombin time (PT), partial thromboplastin time (PTT), INR, AFP and PIVKA2), **Radiological investigations including** (pelvi - abdominal ultrasonography and CT or MRI).

We used enzyme-linked immunosorbent assays (ELISAs) to measure PIVKA2 levels in serum and AFP levels according to the protocols provided by the manufacturer. The following items were added in the specified order to 96-well plates: 100 µl of diluent (blank), standard substances, and serum samples. The plates were incubated for 16 to 24 hours at temperatures between 2 and 10 °C. Following three washes with PBST and the addition of 100 µl of enzyme-labeled antibody, the plates were placed in an incubator set at 20-30°C for one hour. Each well was then supplemented with 100 µl of substrate solution and 50 µl of stop solution following three more washing with PBST. A microplate reader was used to measure the absorbance at 450 nm for all samples, standards, and blanks. We took two readings from every sample. Electrochemiluminescence immunoassays were used to quantify serum AFP levels, and the normal value of serum PIVKA2 levels was less than 0.04 AU/mL. An electrochemical immunoluminescence analyzer (Roche Cobas E601; Roche Diagnostics; Mannheim, Germany) equipped with specialist reagents from Roche was used to measure AFP levels in the blood. Everything was done just as the manufacturer had instructed. No more than 20 ng/mL of serum AFP is acceptable.

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Statistical analysis

Software developed by SPSS 23.0 Inc. of Chicago, IL, USA, known as IBM SPSS 23.0 for Windows, was used to code, input, and analyze the data obtained. The number of observations in each category or order (n) and percentage of observations across all categories or orders (%) make up qualitative data. Data regarding measurements: middle value, outer value, dispersion, and IQR. A significant result is one with a P value of 0.05 or below; a non-significant result is one with a P value

higher than 0.05. When looking for a correlation between two qualitative variables, you can use the Chi-Square [X2] test or Fisher's exact test (f).The Kruskal-Wallis test and one-way analysis of variance (ANOVA) are applicable when examining relationships between quantitative variables belonging to more than two categories. To determine if there is a relationship between two numerical variables, researchers use tests like Pearson's and Spearman's rank correlation. To forecast the existence or nonexistence of a result from a collection of independent factors, logistic regression is a helpful tool. This model is comparable to linear regression; however, it works better with qualitative (categorical) dependent variables. To assess the specificity and sensitivity of quantitative diagnostic tests that classify patients into two categories, the receiver operating characteristic (ROC) curve is a helpful tool. Accuracy ranges from 0.90 to 1 percent, from 0.80 to 0.90 percent, from 0.70 to 0.80 percent, from 0.60 to 0.70 percent, and from 0.50 to 0.60 percent, indicating failure.

Results

Demographic data was not significantly different between the categories that were examined. The hemoglobin and platelet levels of the studied groups were statistically significantly different, with group I exhibiting a higher level of hemoglobin (P<0.001) and platelet (P<0.001), respectively. A statistically significant difference was observed when the group's kidney and liver function were examined. As compared to Group ⅓, the other groups had significantly lower levels of creatinine, total and direct bilirubin, international normalized ratio (INR), serum glutamic oxaloacetic transaminase (SGOT), and serum glutamic pyruvic transaminase (SGPT) (P=0.003, P=0.02, (P<0.001), and (P=0.003), respectively. When compared to the other groups, group I had the highest albumin level (P<0.001). **Table 1**

On comparing hemoglobin levels between the studied groups, Group I was significantly distinct from Groups II, III, and IV (P<0.001, <0.001, and <0.001, respectively). In addition, group I exhibited a statistically significant difference from Groups II, III, and IV (P<0.001, <0.001, and <0.001, respectively) when comparing platelet levels between the studied groups. When the albumin levels of the investigated groups were compared, Group I was significantly different from Groups II, III, and IV (P<0.001). When the SGPT levels of the examined groups were compared, Group I was significantly different from Group III (P=0.004). Upon comparing the SGOT levels of the investigated groups, Group I was significantly different from Group III (P=0.04). Group I exhibited a statistically significant difference from Groups II, III, and IV in terms of total bilirubin levels (P<0.001). Group I exhibited a significant difference from Groups II, III, and IV in terms of direct bilirubin levels (P<0.001). Upon comparing the INR levels of the studied groups, Group I was significantly different from Groups II, III, and IV (P<0.001), and Group II was significantly different from Group III (P<0.001). Group I exhibited a statistically significant difference from Group III in terms of creatinine levels (P=0.002). Upon comparing the AFP levels of the investigated groups, Group I was significantly different from Groups II, III, and IV (P<0.001). Additionally, group II demonstrated a statistically significant difference from Group III (P<0.001). Additionally, group III demonstrated a statistically significant difference from Group IV (P<0.001). Upon comparing the PIVKA2 levels of the investigated groups, Group I was significantly different from Groups II, III, and IV (P<0.001). It was also statistically significant (P<0.001) that Group ꝏ was different from Group ⅓. Additionally, group ꝏ and Group ㅂ were significantly different from each other (P<0.001). **Table 2**

There was a statistically significant difference between the studied groups as regards AFP and PIVKA2, as group III had the highest level of AFP and PIVKA2 when compared to the other groups (P<0.001). **Table 3**

When levels of INR and creatinine rise, so do levels of AFP, indicating a strong positive link between the three. When hemoglobin, platelets, or albumin levels drop, AFP levels rise, indicating a strong negative link between the three. Increases in SGPT, SGOT, INR, or creatinine were accompanied by corresponding increases in PIVKA2, indicating a strong positive link between the two. Hemoglobin, platelets, and albumin all had a negative connection with PIVKA2, meaning that when those levels dropped, PIVKA2 levels rose. **Table 4**

In a ROC analysis, AFP was determined to have the highest sensitivity (70.83%), specificity (76.39%), and area under the curve (0.785) when compared to other potential cutoff values for distinguishing HCC patients from non-HCC patients. In addition, PIVKA2 had the greatest results in the ROC analysis at 489 with an area under the curve of (0.872) and a sensitivity of 75%. **Table 5**

Table 6 shows that on applying univariate logistic regression analysis for predictors of HCC, male sex, low PLT, low albumin, Increased SGPT & SGOT, increased INR, increased AFP, and increased PIVKA2 were significantly associated with HCC. While on applying multivariate regression analysis, only increased AFP and PIVKA2 were found to be independent predictors for HCC.

Table 1: Demographic data, CBC, liver and kidney function tests among the studied groups

Variables			Group I (n=24)	Group II (n=24)	Group III (n=24)	Group IV (n=24)	P Value
Demographic data	**Age (years)**	**Mean ± SD**	60.2 ± 2.91	59.5 ± 3.3	58.5 ± 2.55	59.9 ± 2.84	0.16[1]
		Range	(54 – 65)	(52 – 65)	(54 – 63)	(55 – 64)	
	Sex	**Male**	21 (87.5%)	14 (58.6%)	15 (62.5%)	16 (66.7%)	0.12[2]
		Female	3 (12.5%)	10 (41.7%)	9 (37.5%)	8 (33.3%)	
CBC	**TLC (103/mm3)**	**Mean ± SD**	8.9 (4.2)	7.8 (9.4)	9.9 (3.23)	9.5 (5.5)	0.59[2]
		Range	(4.3 – 19.1)	(2.1 – 19.9)	(2.1 – 23)	(5 – 21)	
	Hb (mg/dl)	**Mean ± SD**	10.3 ± 1.21	9.07 ± 0.74	8.34 ± 1.25	8.47 ± 0.93	**<0.001*[2]**
		Range	(8.5 – 13.5)	(7.6 – 10.9)	(6.2 – 10)	(6.8 – 10.5)	
	PLT (103/mm3)	**Mean ± SD**	124 (33.8)	94 (26.5)	63 (35.5)	75 (25.5)	**<0.001*[2]**
		Range	(96 – 200)	(60 – 204)	(15 – 110)	(50 – 100)	
Liver and kidney function tests	**Albumin (g/dL)**	**Mean ± SD**	3.08 ± 0.32	2.64 ± 0.39	2.44 ± 0.41	2.51 ± 0.33	**<0.001*[1]**
		Range	(2.5 – 3.9)	(1.9 – 3.3)	(1.7 – 3)	(1.9 – 3)	
	SGPT (U/L)	**Median (IQR)**	37 (24)	44.5 (32)	68.5 (68)	47 (39.3)	**0.003*[2]**
		Range	(11 – 105)	(23 – 95)	(33 –456)	(21 – 153)	
	SGOT (U/L)	**Median (IQR)**	35 (47.8)	42.5 (27.8)	59 (56)	47.5 (44.3)	**0.02*[2]**
		Range	(16 – 100)	(19 – 100)	(25 – 450)	(27 – 142)	
	Total bilirubin (mg/dL)	**Median (IQR)**	2 (0.65)	3.3 (1)	3.8 (4.58)	3.55 (1.31)	**<0.001*[2]**
		Range	(1.2 – 3.1)	(1.9 – 5)	(1.9 – 14)	(1.9 – 5.2)	
	Direct bilirubin (mg/Dl)	**Median (IQR)**	0.95 (0.55)	1.6 (0.75)	1.95 (2.28)	1.75 (1.13)	**<0.001*[2]**
		Range	(0.5 – 2)	(0.9 – 4.2)	(1 – 11.2)	(0.9 – 4.5)	
	INR	**Mean ± SD**	1.41 ± 0.29	1.7 ± 0.25	2.08 ± 0.38	1.91 ± 0.25	**<0.001*[1]**
		Range	(1 – 1.9)	(1.2 – 2.1)	(1.5 – 3)	(1.4 – 2.4)	
	Creatinine (mg/dL)	**Mean ± SD**	1.53 ± 0.49	1.85 ± 0.58	2.33 ± 0.89	1.88 ± 0.95	
		Range	(0.8 – 3.1)	(1 – 3.5)	(1.5 –4.5)	(1.1 – 4.3)	**0.003*[1]**

Data was presented as Mean ± SD, range, Median (IQR). *: significant as P value ≤ 0.05, 1One way ANOVA test, [2]Fisher exact test. TLC=Total leucocytic count, HB: hemoglobin, PLT: platelets, SGPT: Serum glutamic pyruvic transaminase, SGOT=Serum glutamic oxaloacetic transaminase, INR=International normalized ratio.

Table 2: post-HOC analysis of LFT and KFT, platelets and AFP and PIVKA2 parameters

		Post-Hoc analysis P-value		
		Group II	**Group III**	**Group IV**
Hb	**Group I**	**<0.001****	**<0.001****	**<0.001****
	Group II	-	0.08	0.21
	Group III	-	-	0.97
PLT	**Group I**	**<0.001****	**<0.001****	**<0.001****
	Group II	-	**<0.001****	**0.003***
	Group III	-	-	0.29
Albumin	**Group I**	**<0.001****	**<0.001****	**<0.001****
	Group II	-	0.25	0.61
	Group III	-	-	0.92
SGPT	**Group I**	0.49	**0.004***	0.28
	Group II	-	0.06	0.94
	Group III	-	-	0.18
SGOT	**Group I**	0.83	**0.04***	0.23
	Group II	-	0.08	0.71
	Group III	-	-	0.48
Total bilirubin	**Group I**	**<0.001****	**<0.001****	**<0.001****
	Group II	-	0.14	0.72
	Group III	-	-	0.37
Direct bilirubin	**Group I**	**<0.001****	**<0.001****	**<0.001****
	Group II	-	0.15	0.97
	Group III	-	-	0.37
INR	**Group I**	**0.005***	**<0.001****	**<0.001****
	Group II	-	**<0.001****	0.09
	Group III	-	-	0.22
Creatinine	**Group I**	0.47	**0.002***	0.37
	Group II	-	0.12	0.99
	Group III	-	-	0.17
AFP	**Group I**	**<0.001****	**<0.001****	**<0.001****
	Group II	-	**<0.001****	0.52
	Group III	-	-	**<0.001****
PIVKA2	**Group I**	**<0.001****	**<0.001****	**<0.001****
	Group II	-	**<0.001****	0.23
	Group III	-	-	**<0.001****

Data was presented as *Significant: P ≤0.05, **Highly significant: P <0.001. Hb: haemoglobin, PLT: platelet count, AFP: Alpha fetoprotein, PIVKA2: Prothrombin induced by vitamin K absence 2. SGPT: Serum glutamic pyruvic transaminase, SGOT: Serum glutamic oxaloacetic transaminase, INR: International normalized ratio and INR: International normalized ratio.

Table 3: The expression level of different markers among the studied groups

Variables		**Group I (n=24)**	**Group II (n=24)**	**Group III (n=24)**	**Group IV (n=24)**	**P Value**
AFP (ng/ml)	**Median (IQR)**	11.5 (15.3)	316.5 (188.8)	1033.5 (720.3)	382.5 (181.3)	**<0.001***
	Range	(2 – 50)	(150 – 800)	(433 – 2400)	(203 – 704)	
PIVKA2 (mAU/ml)	**Median (IQR)**	37.6 (12.4)	208.5 (94.8)	866.1 (490.2)	280.5 (126)	**<0.001***
	Range	(12.5 – 82)	(155 – 503)	(245 – 1469)	(145 – 501)	

Data was presented as Median (IQR) or range. *: significant as P value ≤ 0.05.AFP: Alpha fetoprotein, PIVKA2: Prothrombin induced by vitamin K absence 2.

Table 4: Correlation of different markers with different parameters among the studied groups

Variables	AFP		PIVKA2	
	r	***P***	***r***	***P***
Age	-0.163	0.11[1]	-0.015	0.88[1]
TLC	-0.002	0.99[2]	0.008	0.94[2]
Hb	-0.367	**<0.001[2]**	-0.294	**0.004[2]**
PLT	-0.442	**<0.001[2]**	-0.615	**<0.001[2]**
Albumin	-0.358	**<0.001[2]**	-0.442	**<0.001[2]**
SGPT	0.083	0.42[2]	0.394	**0.001[2]**
SGOT	0.014	0.89[2]	0.344	**0.005[2]**
Total bilirubin	0.078	0.45[2]	0.123	0.23[2]
Direct bilirubin	0.117	0.26[2]	0.186	0.07[2]
INR	0.418	**<0.001[1]**	0.495	**<0.001[1]**
Creatinine	0.245	**0.02[2]**	0.336	**0.001[1]**

Data was presented as numbers. *[1]Pearson correlation, [2]Spearman rank correlation test. TLC: Total leucocytic count, Hb: haemoglobin, PLT: platelets, SGPT: Serum glutamic pyruvic transaminase, SGOT: Serum glutamic oxaloacetic transaminase, INR: International normalized ratio. *: significant as P value ≤ 0.05.

Table 5: ROC curve analysis (Receiver operation curve) of different markers in detecting HCC diagnosis

Variables	Cut point	Sensitivity (%)	Specificity (%)	PPV (%)	NPP (%)	AUC (%)
AFP	731	70.83%	76.39%	50%	88.71%	0.785
PIVKA2	489	75%	88.89%	69.23%	91.43%	0.872

Data was presented as frequency (%). HCC: Hepatocellular carcinoma, PPV: Positive Predictive Value, AUC: area under the curve, NPP: Negative Predictive Value, AFP: Alpha fetoprotein, PIVKA2: Prothrombin induced by vitamin K absence 2.

Table 6: Logistic regression analysis for predictors of HCC

Variables	Univariate analysis		Multivariate analysis	
	P value	Odds (CI 95%)	P value	Odds (CI 95%)
Age	0.31	1.09 (0.93 – 1.28)	-	-
Male sex	**0.03**	4.2 (1.14 – 15.42)	0.09	0.14 (0.02 – 1.31)
TLC	0.81	0.99 (0.89 – 1.09)	-	-
Hb	**0.01**	0.59 (0.39 – 0.89)	0.09	0.68 (0.43 – 1.06)
PLT	**<0.001**	0.97 (0.95 – 0.98)	0.07	0.98 (0.96 – 1.01)
Albumin	**0.02**	0.21 (0.05 – 0.78)	0.11	0.15 (0.01 – 1.48)
SGPT	**0.009**	1.03 (1.01 – 1.05)	0.24	0.94 (0.85 – 1.04)
SGOT	**0.01**	1.02 (1.01 – 1.04)	0.95	1.01 (0.92 – 1.11)
Total bilirubin	0.32	0.91 (0.74 – 1.11)	-	-
Direct bilirubin	0.36	0.89 (0.69 – 1.14)	-	-
INR	**<0.001**	1.68 (1.31 – 3.16)	0.45	1.72 (0.12 – 2.91)
Creatinine	0.12	1.73 (0.86 – 3.48)	-	-
AFP	**0.02**	1.01 (1.002 – 1.02)	**0.02**	1.01 (1.002 – 1.03)
PIVKA2	**0.002**	1.02 (1.01 – 1.04)	**0.01**	1.14 (1.01 – 1.29)

Data was presented as numbers. TLC: Total leucocytic count, Hb: haemoglobin, PLT: platelets, SGPT: Serum glutamic pyruvic transaminase, SGOT: Serum glutamic oxaloacetic transaminase, INR: International normalized ratio. AFP: Alpha fetoprotein, PIVKA2: Prothrombin induced by vitamin K absence 2. *: significant as P value ≤ 0.05.

Discussion

Hepatocellular carcinoma (HCC) ranks first among primary liver cancers. Most HCC cases are caused by viral hepatitis, chronic liver disease, or liver cirrhosis. There are now many more options for treating early-stage lesions, but for late-stage HCC, there are very few. A depressing outlook is the consequence of the late diagnosis of most HCC. In order to improve the prognosis for people diagnosed with HCC, it is crucial to have screening programs that are both effective and accurate [12].

We did not find any statistically significant differences in age or sex across the groups we examined. Regardless, the platelet counts differed significantly among the groups, with group I having the largest quantity (P<0.001). The values of SGPT, total bilirubin, direct bilirubin, and creatinine were lowest in group VI compared to the other groups (P<0.001, P=0.02, P=0.04, P=0.02, and P<0.001, respectively). There was a similar disparity when looking at INR and creatinine levels. The INR was lowest in group I (P<0.001) when contrasted with the other groups.

Furthermore, Hadi et al. [8] found that compared to the non-HCC groups (LC and NCHR), those with HCC exhibited much more severe liver damage. People without HCC had far higher albumin levels, while those with HCC had much higher total bilirubin, ALT, and the international normalized ratio (INR). Our study found that when comparing the levels of AFP and PIVKA2 across the diverse groups, Group ꝏ stood out with a statistically significant difference (P<0.001). The most elevated values of these markers were seen in Group ꝏ.

This was also observed in Tian et al. [6] Findings from the 470 people who comprised the sample include: Here were just a few of the many types of patients included in this study: 101 healthy individuals serving as controls, A total of 145 people have been diagnosed with HCC, 57 with BLD, 55 with CGC, 112 with OGTLM, other gastrointestinal malignancies that have spread to the liver, and many more. The HCC group outperformed the other four groups with significantly higher blood AFP and PIVKA-II levels ($p <–0.01$) after evaluating all five groups. Within the HC and BLD groups, PIVKA-II levels did not change significantly ($p>0.05$), but between the CGC and BLD groups, a significant difference was noted. In addition, PIVKA-II outperformed AFP as a predictor of surgical responsiveness, and all markers demonstrated a notable decrease in blood levels following surgery in comparison to pre-surgery values ($p < 0.05$).

Conforming to our findings, Lee et al. [13] When comparing the control group to those with chronic hepatitis B and primary liver cancer, we discovered that 158 patients with cancer and 62 patients with chronic hepatitis B without cancer had significantly higher detection values for AFP and PIVKA2. The p-values for the two groups were 0.002 and <0.001, respectively.

Our results showed that AFP and both INR (r=0.225, P=0.03) and creatinine (r=0.214, P=0.04) were positively correlated. Although AFP and platelets were significantly inversely related (r=-0.252, P=0.01). A favorable connection of 0.227 (P=0.03) and 0.357 (P<0.001) between PIVKA2 and INR and creatinine was also found. The connection between PIVKA2 and platelets was negative and statistically significant (r=-0.291, P=0.004). Additionally, there is a strong positive association between AFP and PIVKA2 (r=0.792, P<0.001).

Supporting our results, Hadi et al. [8] examined the inter-group relationship between tumor markers and blood parameters, and found that PIVKA2 and AFP levels were positively correlated with the severity of BCLC staging, Child-Pugh score, total bilirubin, ALT, and INR tests. There was an inverse relationship between the two indicators and albumin levels.

Regarding Feng et al. [7], PIVKA2 expression levels were found to have significant correlations with a number of clinicopathological variables, such as tumor size, tumor stage, tumor metastasis, degree of differentiation, and complications. Following surgical resection, PIVKA2 expression dropped.

At 20, AFP showed the greatest performance among the receiver operating characteristic (ROC) tests conducted to determine the optimal cutoff value for differentiating HCC patients from non-HCC patients. Its sensitivity was 73.61%, specifically 79.17%, and the area under the curve was 0.743. Furthermore, when ROC analysis was conducted on PIVKA2, it exhibited the highest levels of sensitivity (81.94%) and specificity (87.5%) at 58.3 with an area under the curve of (0.891).

Similarly, Tian et al. [6] A comparison was made between the diagnostic acuity of AFP, PIVKA-II, and AFP-PIVKA-II. When looking at HCC in comparison to BLD, the AUC values for AFP were 0.903 (0.862 - 0.944), for PIVKA-II it was 0.945 (0.915 - 0.975), and for the total impact it was 0.975 (0.956 - 0.994). While 38.91 mAU/ml was determined to be the most accurate PIVKA-II cutoff, the most accurate AFP cutoff was 5.6 ng/ml. Both the AFP and PIVKA-specificity II tests were highly sensitive (96.5% sensitivity and 98.2% specificity), but each test alone was only 76.6% sensitive and 98.2% specific. The area under the curve (AUC) for AFP was 0.901 (0.861 - 0.940), for PIVKA-II it was 0.938 (0.907 - 0.970), and for both combined it was 0.972 (0.954 - 0.991) when comparing HCC and HCs simultaneously. The PIVKA-II cutoff was 49.74 mAU/ml, while the ideal AFP cutoff was 6 ng/ml. Diagnostic specificities for AFP and PIVKA II when used together were 75.9% and 98%, respectively. Along with the diagnostic's 86.2% accuracy, it has a sensitivity level of 91.0%. Combining AFP and PIVKA-II for evaluation improved their diagnostic efficacy.

In contrast, Hadi et al. [8] Compared to PIVKA2 or AFP alone, the combined AUROC score of HCC and NMHR was higher (95% CI, 0.856 to 0.950, $p < 0.0001$). While PIVKA2 had a greater area under the curve (0.905, 95% CI, 0.849 to 0.945, $p < 0.0001$), AFP exhibited a lower area (0.869, 95% CI, 0.807 to 0.916, $p < 0.0001$). It was determined statistically that they were identical. The AUROC curves for PIVKA2, AFP, and the combination were 0.904, 0.865, and 0.898, respectively, after a p-value of less than 0.0001. With 95% CIs ranging from 0.797 to 0.917 for AFP and from 0.842 to 0.947 for PIVKA2, the two variables were similar. Consistent with earlier research, there was no change. The ideal concentrations of PIVKA2 (36.7 mAU/mL; Youden index J: 0.7211) and AFP (14.2 ng/mL; Youden index J: 0.6850) for distinguishing HCC from NMHR were determined by our research. At these concentrations, PIVKA2 was 90% sensitive and 82.10% specific, whereas AFP was 75% sensitive and 93.50% specific.

The limitations of the study were that it was a small sample size, single center study and shorter follow up.

Conclusion

PIVKA2 and AFP are dependable indicators for HCC patients when it comes to diagnosis and prognosis. When it came to identifying HCC patients and forecasting the prognosis of both treated and non-treated HCC patients, both indicators performed statistically similarly. Still, at the sweet spot for cut-off values, PIVKA2 showed more sensitivity and specificity than AFP.

As a result, the study suggested that a larger sample size, additional multicenter collaboration, and extended follow-up periods are required to evaluate the prognosis and survival after HCC treatment, as well as to observe the correlation between changes in serum PIVKA-II and AFP. Additionally, the study emphasized the need to further

investigate the biological mechanisms of tumors.

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Conflicts of interest

No conflicts of interest

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