EVALUATION OF DIAGNOSTIC VALIDITY OF PIVKA-II FOR DIAGNOSIS OF HEPATOCELLULAR CARCINOMA IN PATIENTS OF CIRRHOSIS WITH LIVER NODULES PRESENTED IN A TERTIARY CARE HOSPITAL OF LAHORE.

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ABSTRACT

Objectives: To evaluate the diagnostic validity of PIVKA-II for Hepatocellular carcinoma in cirrhotic patients with uncertain liver nodules on Ultrasound.

Methods: This was a cross-sectional study conducted in 01-11-2020 and 31-12-2021 at Hepatitis clinic at Jinnah Hospital Lahore. Patients who fulfilled the selection criteria(n=100) were enlisted for this study. Blood samples were obtained to test for PVKA-11 and AFP in cirrhotic patients who had liver nodules that had been previously verified by ultrasound imaging. Data were entered and analyzed in SPSS ver: 21.0. Sensitivity, specificity and predictive values were calculated using CT imaging and biopsy as gold standard. ROC curve evaluating AFP, PIVKA-II, and a combination as indicators for Hepatocellular carcinoma at 95% Confidence Interval was calculated with a $p < .05$ value was taken as statistical significant.

Results: HCC was confirmed in 45 of the 100 instances, and it was invariably at an early or very early stage. At a threshold of 62.5 mAU/mL, PIVKA-II and HCC were significantly correlated (P =.015 and P =.036, respectively) in univariate and multivariate analyses. For AFP, 7.5 ng/mL was the ideal cut-off. For PIVKA-II, sensitivity was 62% and specificity was 91% , while for AFP, they are 66% and 69% respectively. The positive and negative predictive values for PIVKA-II were 81% and 74%, respectively, while for AFP sensitivity was 63% and specificity was 72%. The combination of both biomarkers improved the precision of diagnosing HCC (sensitivity = 74%, specificity = 95.5%, NPV = 81%, PPV = 92%, and AUC = 0.781).

Conclusion: PIVKA-II is a valid indicator for defining the characteristics of liver nodules in cirrhosis and when combined with AFP, it signifies superior accuracy for HCC diagnosis.

Key words: HCC, liver nodules, cirrhosis, PIVKA-II and AFP.

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Hepatocellular carcinoma (HCC) is amongst the most prevalent tumors in adults and an important cause of fatalities occurring due to cancers.[1] The survival rate with HCC is less than 15% at 5 years, despite the availability of various therapeutic modalities.[2] Late diagnosis contributes to this grim prognosis as patients are frequently not treated with any of the available modalities, including palliative medications, and are therefore ineligible for curative treatment options like surgery.[3] More than 600,000 cases of HCC are reported annually worldwide, with up to 80 percent occurring in Asia. Early stages of HCC often have minimal symptoms. The best time for therapy often ends before a specific diagnosis is made.

A major risk factor for developing HCC is chronic hepatitis, which eventually results in cirrhosis. In addition to imaging techniques, alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist II (PIVKA-II) have been extensively studied

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for HCC surveillance and therapy efficacy. Des-gamma-carboxy prothrombin, commonly known as PIVKA-II, is an aberrant precursor of prothrombin produced by liver cells and is accepted as a recognized biomarker for surveillance in the clinical guidelines of Japan and APASL.[4] At a cut-off of 42 mAU/ml, it has higher sensitivity and specificity for the diagnosis of early HCC, compared to AFP at a cut-off of 5.5 ng/ml (AUC 0.81 vs. 0, 58). As PIVKA-II and AFP are synthesized distinctly, they function as complementary indicators for HCC and when combined they yield better sensitivity and specificity. Thus, APASL recommends using combination tests for both screening and surveillance. Six months has traditionally been used as the standard time between periodic tests in many studies. Given the usability of PIVKA-II and surveillance algorithms in our local population, we believe that early detection and treatment of HCC are possible.

METHODS

100 cirrhotic patients who attended Jinnah hospital Lahore hepatitis clinic between November 2020 and October 2021 and had ultrasound evidence of cirrhosis and nodules in the liver were entered into trial after approval from the hospital ethics committee and informed consent. Within one week of ultrasound detection of liver lesions, blood samples for PVKA-11 and AFP were collected from all and stored at 70°C until testing. Patients with other liver tumors and metastases were omitted from the trial.[12] Patients with liver cirrhosis were categorized according to the Child-Pugh criteria. Following an ultrasound-based diagnosis, all patients were monitored for at least a year.[4] Nodules up to 1 cm were monitored by ultrasound until they reached >1 cm in diameter; nodules larger than 1cm with a characteristic finding of arterial enhancement and "delayed venous washout" on Tri-phasic CT abdomen were classified as HCC, and those without typical imaging features of HCC underwent liver biopsy. In 45 cases, the nodules were found to be malignant (group A), while in 55 cases they were not malignant (group B). According to BCLC (Barcelona Classification of Liver Cancer), all malignancies were discovered to be very early or early.[4] No patients were receiving anticoagulant or vitamin K treatments.

Statistical analyses: The Mann-Whitney test was applied to calculate quantitative variables (mean, standard deviation, median, and range). By utilizing the Chi-square test, an analysis of categorial variables was done. The values of AFP and PIVKA-II underwent log transformation. Boxplots and later analysis of variance were used to compare descriptive statistics for markers. When the Kolmogorov-Smirnov test indicated that the quantitative data did not have a normal distribution, the nonparametric approach was employed. Receiver operating characteristic (ROC) was created utilizing the possible cut-off values for each test in order to find the best values for these markers in HCC diagnosis. Measurements of sensitivity and specificity was done. Negative and Positive predictive values of both indicators were calculated separately and in combination to distinguish between cirrhosis patients with or without HCC. To identify predictors of HCC, univariate logistic regression analysis was employed. Variables with a P value of 0.05 or below after univariate analysis were subjected to multivariate analysis and included in the logistic model. Statistical significance was considered for a P value of 0.05 ≤. SPSS version 23.0 software was used for all statistical analyses.

RESULTS

HCC was prevalent in older patients (P=0.009). Child-Pugh class A was documented in 12 patients of HCC, whereas class B/C was present in 33 HCC patients (P = 0.002). (Table 1). Individuals with HCC had a greater prevalence of viral hepatitis, but patients without HCC had a higher prevalence of alcoholic cirrhosis. The median value of both markers in HCC patients were considerably greater (PIVKA-II=85.5 mAU/mL, range: 9.8-695 versus 32, range: 10-459, P<0.001, vs AFP 10.8 ng/mL, range: 2.8-2059 versus 5.6, range: 01.2-1538, P < 001 (Fig. 1A, B). HCC was substantially correlated with PIVKA-II scores, advanced age, viral aetiology, and Child class B or C (P = .015, P = .011, P = 0.024, and P = 0.002). Viral aetiology, PIVKA-II, and Child class B or C were all found to be highly pre-

dictive of HCC in multivariate analysis (P = 0.032, P = 0.005, and P = 0.012, respectively) (Table 2). The cut-off values of both markers were established using ROC. For PIVKA-II , 62.5 mAU/ml was an ideal cut-off, while for AFP, it was 7.5 ng/ml. (For PIVKA-II, sensitivity and specificity are 62% and 91% respectively, while for AFP, they are 66% and 69%. The PPV and NPV for PIVKA-II were 81% and 74%, respectively, while for AFP they were 63% and 72%. (Table 3). PIVKA-II had an AUROC of 0.72 (95% CI) and AFP had an AUROC of 0.738 (95% CI), respectively. When both markers were combined, they were more sensitive and specific in diagnosing HCC than either test alone, with a sensitivity of 74% and a specificity of 95.5%. The PPV was 92% while the NPV was 81%. The AUROC measured 0.781 (95% Confidence Interval 0.665-0.862). (Table 3 and Figure 2)

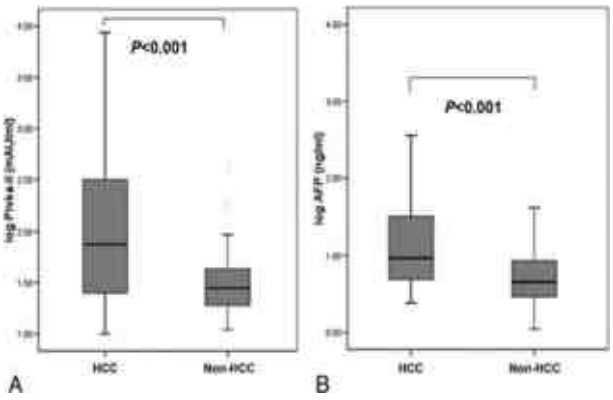

Figure 1. **(A)** *PIVKA-II values and* **(B)** *AFP serum values in cases with and without HCC. Due to the wide range of levels for both indicators (AFP and PIVKA-II), log transformation was applied to the values.*

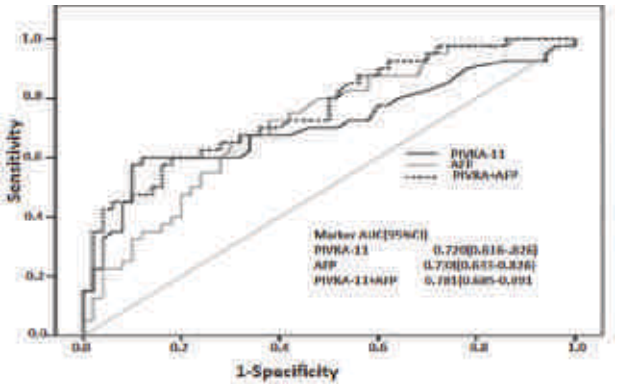

Figure 2. *ROC curve evaluating AFP, PIVKA-II, and a combination as indicators for Hepatocellular carcinoma. 95% Confidence Interval for the AUROC is shown.*

Table 1: *Demographic and clinical characteristics of patients*

Variables (n= 100)	Non HCC (n= 45)	HCC (n= 55)	P value
Age (Mean ± SD)			
Age	66.8 ± 10.1	60.9 ± 10.2	.009
Gender (freq. (%)			
Male	34 (75.5)	40 (72.7)	0.95
Female	11 (24.5)	15 (27.3)	
Etiology of Liver disease			
Viral	35 (77.8)	30 (54.5)	
NAFLD	9 (20)	15 (27.2)	.02
Alcoholic	1 (2.2)	10 (18.3)	
Child-Pugh Classification			
Child-Pugh A	12 (26.7)	32 (58.2)	.002
Child-Pugh B	33 (73.3)	23 (41.8)	
Liver nodules found at Ultrasound			
1	38 (84.44)	45 (81.8)	0.63
2 - 3	7 (15.56)	10 (8.2)	

Table 2: *Logistic analyses of predictive factors of HCC in patients with cirrhosis having Ultrasound based detected liver nodules.*

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% Confidence	P value	Odds ratio	95% Confidence	P value
PIVKA-II	1.007	1.001–1.010	.015	1.007	1.001–1.011	.036
AFP	1.000	0.999–1.012	.236	–	–	–
Age	1.058	1.013–1.114	.001	1.045	0.992–1.105	.078
Sex	0.875	0.395–2.461	.988	–	–	–
Viral etiology	2.634	1.191–7.459	.033	5.146	1.499–17.011	.007
Child–Pugh B/C	4.040	1.768–10.31	.002	4.608	1.412–14.391	.013
Number of liver nodules at Ultrasound	0.850	0.235–2.810	.660			

Table 3: Features of AFP and PIVKA-II, and combination in the detection of early HCC in patients with cirrhosis with liver nodule

Markers	Sensitivity	Specificity	PPV	NPV
AFP	66%	69%	64%	72%
PIVKA	62	91%	81%	74%
AFP + PIVKA-II	74%	95.5%	92%	81%

DISCUSSION

This trial investigated the efficacy of AFP and PIVKA-II for early detection of HCC in cases of cirrhosis with liver nodules. When it came to distinguishing between benign and malignant nodules, PIVKA-II surpassed AFP. The results are consistent with previous research.[4,5,6,7] The somewhat lesser sensitivity of PIVKA-II in this trial may have been influenced by the addition of very early/early staged HCC patients, albeit this was balanced by higher specificity (88%) and positive predictive value (80%). In spite of the fact that PIVKA-II is frequently employed in screening of HCC in several Asian nations, the evidence for its accuracy in other contexts is uncertain.[8–10] Results in terms of sensitivity and specificity were much greater when AFP and PIVKA-II were deployed in conjunction. These findings support earlier research finding suggesting that both markers act as complimentary biomarkers. Despite being the preliminary diagnostic method for cirrhotic patients, ultrasonography is still frequently unable to identify HCC.

Our research suggests that simultaneous testing of two markers, as recommended by Japanese guidelines, may help improve diagnostic accuracy. These fingers are of utmost importance for the early detection of HCC.[11-14] Recently, numerous studies have been conducted on the possible diagnostic use of non-protein serum markers (eg, exosomes and long non-coding RNAs in microvesicles).[15-18] Nevertheless, PIVKA-II and AFP are most suited for clinical evaluation and screening because they are less expensive, need very little serum, have great repeatability, and don't need any specific pretreatment. Although more large prospective trials are required to conclusively prove PIVKA-II efficacy for the early diagnosis of HCC, the routine diagnostic practice should take into account the combined use of these markers in HCC diagnosis.

CONCLUSION

PIVKA-II is a valid indicator for defining the characteristics of liver nodules in cirrhosis and when combined with AFP, it signifies superior accuracy for HCC diagnosis.

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REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBO- CAN 2012. Int J Cancer 2015;136:E359–86.
2. El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011;365: 1118–27.
3. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet 2003;362:1907–17.
4. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. Hepatology 2011;53:1020–2.
5. Marrero JA, Su GL, Wei W.Des-gamma carboxyprothrombin can differentiate hepatocellular carcinoma from nonmalignant chronic liver disease in american patients. Hepatology 2003;37:1114–21.
6. Durazo FA, Blatt LM, Corey WG.Des-gamma-carboxyprothrom- bin, alpha-fetoprotein and AFP-L3 in patients with chronic hepatitis, cirrhosis and hepatocellular carcinoma. J Gastroenterol Hepatol 2008; 23:1541–8.
7. Singal A, Volk ML, Waljee A. Meta-analysis: surveillance with ultrasound for early-stage hepatocellular carcinoma in patients with cirrhosis. Aliment Pharmacol Ther 2009;30:37–47.
8. Liaw YF, Tai DI, Chen TJ. Alpha-fetoprotein changes in the course of chronic hepatitis: relation to bridging hepatic necrosis and hepatocellular carcinoma. Liver 1986;6:133–7.
9. Chang YC, Nagasue N, Abe S. Alpha Fetoprotein producing early gastric cancer with liver metastasis: report of three cases. Gut 1991;32:542–5.
10. 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.

11. de Lope CR, Tremosini S, Forner A.Management of HCC. J Hepatol 2012;56:S75–87.
12. Baek YK, Lee JH, Jang JS, et al. Diagnostic role and correlation with staging systems of PIVKA-II compared with AFP. Hepatogastroenterology 2009;56:763–7.
13. Kokudo N, Hasegawa K, Akahane M. Evidence-based Clinical Practice Guidelines for Hepatocellular Carcinoma: The Japan Society ofHepatology 2013 update (3rd JSH-HCC Guidelines). Hepatol Res 2015;45:123–7.
14. Lok AS, Sterling RK, Everhart JE, et al. Des-gamma-carboxyprothrom- bin and alpha-fetoprotein as biomarkers for the early detection of hepatocellular carcinoma. Gastroenterology 2010;138:493–502.
15. Poté N, Cauchy F, Albuquerque M, et al. Performance of PIVKA-II for early hepatocellular carcinoma diagnosis and prediction of microvascu- lar invasion. J Hepatol 2015;62:848–54.
16. Caviglia GP, Abate ML, Petrini E, et al. Highly sensitive alpha- fetoprotein, Lens culinaris agglutinin-reactive fraction of alpha-fetopro- tein and des-gamma-carboxyprothrombin for hepatocellular carcinoma detection. Hepatol Res 2016;46:E130–5.
17. Omata M, Lesmana LA, Tateishi R, et al. Asian Pacific Association for the Study of the Liver consensus recommendations on hepatocellular carcinoma. Hepatol Int 2010;4:439–74.
18. Ertle JM, Heider D, Wichert M, et al. A combination of *a*-fetoprotein and des-*g*-carboxy prothrombin is superior in detection of hepatocellular carcinoma. Digestion 2013;87:121–31.