https://doi.org/10.29309/TPMJ/2026.33.03.10063 www.theprofesional.com

ORIGINAL ARTICLE

PIVKA-II value in the diagnosis of hepatocellular carcinoma in patients with inconclusive imaging findings or AFP levels.

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ABSTRACT… Objective: To evaluate the diagnostic accuracy of Protein Induced by Vitamin K Absence-II (PIVKA-II; des-γ-carboxy prothrombin) in patients with suspected HCC who had nondiagnostic AFP or atypical imaging findings. **Study Design:** Retrospective Cross-sectional study. **Setting:** Rehman Medical Research Institute, Peshawar. **Period:** May 2018 and September 2024. **Methods:** Among 128 patients with suspected HCC the patients were 106 men and twenty two women, average age 60.3 years. Data from electronic medical records including demographics, hepatitis status, imaging results, laboratory markers and biopsy results were collected. PIVKA-II levels were analyzed and diagnostic accuracy has been calculated (sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy). The performance of PIVKA-II was evaluated by receiver operating characteristic curve analysis. **Results:** Of 128 patients, 86 (67.2%) had HCC confirmed on biopsy. PIVKA-II was abnormal in 81/128 patients (71 HCC, 10 non-HCC). Using these counts, PIVKA-II showed sensitivity 82.6%, specificity 76.2%, PPV 87.7%, NPV 68.1%, and accuracy 80.5%. AUROC was 0.776 (p = 0.002). **Conclusion:** PIVKA-II is a useful biomarker for diagnosis of HCC when AFP is non-diagnostic or imaging results are inconclusive. It demonstrates high sensitivity and reasonable specificity to justify its use for early detection and differentiation of HCC from other liver lesions. Future studies should address the limitations of this single-institution, retrospective study to confirm the clinical utility of PIVKA-II.

Key words: Biomarkers, Diagnostic Accuracy, Hepatocellular Carcinoma, PIVKA-II, AFP.

Article Citation: Abdullah M, Khan AN, Umer US, Khan MK, Safi A, Abid H. PIVKA-II value in the diagnosis of hepatocellular carcinoma in patients with inconclusive imaging findings or AFP levels. Professional Med J 2026; 33(03):405-410. https://doi.org/10.29309/TPMJ/2026.33.03.10063

INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver cancer worldwide[1] and is particularly prevalent in regions with high burdens of chronic liver disease, including hepatitis C, hepatitis B, alcoholic cirrhosis, and non-alcoholic fatty liver disease.[2] Early diagnosis is critical for initiating timely management, improving outcomes, and increasing survival.

The diagnosis of HCC can be challenging because of varied early clinical presentations.[4] Current diagnostic tools include imaging and laboratory markers, with biopsy reserved for cases that remain inconclusive. Imaging modalities such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) are widely used[5], but not all lesions display the classical features needed for a confident diagnosis.

Among blood-based markers, alpha-fetoprotein (AFP) has historically been the most utilized, though it lacks adequate sensitivity and specificity. Protein induced by vitamin K absence or antagonist-II (PIVKA-II), also known as des-γ-carboxy prothrombin (DCP), has emerged as a complementary biomarker.[6-7] PIVKA-II is an abnormal form of prothrombin resulting from impaired vitamin K-dependent carboxylation.[8] In HCC, malignant hepatocytes dysregulate this process, leading to significantly elevated serum levels, which have been linked to tumor size, vascular invasion, and poor prognosis.[9]

Several studies have demonstrated that PIVKA-II may improve early detection of HCC, including in cases where AFP is normal or only mildly elevated.[10] Reported diagnostic cutoff values vary widely (40–150 mAU/mL) depending on the assay and population studied.[11] Elevated PIVKA-II has also been associated with more aggressive tumor biology and unfavorable outcomes.

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Article received on:
04/09/2025
Date of revision:
07/10/2025
Accepted for publication:
12/11/2025

Despite its usefulness, PIVKA-II is not specific to HCC; elevations may also occur in other malignancies such as gastric, pancreatic, and cholangiocarcinoma.[12] Therefore, PIVKA-II is best interpreted in combination with AFP and imaging findings.[13] Based on this rationale, our study aimed to assess the diagnostic role of PIVKA-II in patients with suspected HCC who presented with nondiagnostic AFP or inconclusive imaging features.

METHODS

Our study population consisted of 128 suspected HCC patients using convenience sampling. These patients were 106 men and 22 women. The average age of patients had been 60.3 yrs. This study was conducted in interventional radiology department Rehman Medical Research Institute, Peshawar. Data collection period: May 2018 to September 2024. This retrospective study was approved by the Institutional Review Board (RMI/RMI-REC/ArticleApproval/120), with the requirement for individual informed consent waived. Data collected retrospectively from electronic medical record including demographics, hepatitis status, imaging results, laboratory markers and biopsy results. The gathered data have been analyzed by SPSS 26. Demographic descriptive statistics including mean and standard deviation were calculated. Diagnostic accuracy of PVKA in diagnosing HCC was calculated as sensitivity, specificity, positive predictive value, negative predictive value and accuracy. The overall performance of PVKA in the diagnosis of HCC was evaluated by receiver operating characteristic (ROC) curve analysis and AUC calculation were made. The significance of results was based on chi-square and t tests and a p-value below 0.05 is significant.

Inclusion Criteria

Adult patients (≥18 years)

Patients with focal liver lesions on imaging (ultrasound, CT, or MRI) that were suggestive but not diagnostic of HCC (i.e., inconclusive or not fulfilling LI-RADS 5 criteria).

Patients with nondiagnostic or normal AFP levels at the time of evaluation.

Patients who underwent PIVKA-II testing as part of their diagnostic workup.

Patients with histopathological confirmation available (biopsy).

Exclusion Criteria

Patients with a known prior history of HCC who had already received treatment (e.g., TACE, resection, ablation, systemic therapy).

Patients in whom histopathological confirmation was not available.

Patients with insufficient clinical or laboratory data in the medical records.

Patients with non-hepatic primary malignancies involving the liver at presentation, unless specifically included as non-HCC comparator cases.

Patients under 18 years of age.

All patients were selected on abnormal imaging or nondiagnostic alpha-fetoprotein (AFP) levels.

Definition of Inconclusive Imaging/AFP

Inconclusive imaging: Cases where contrast-enhanced CT or MRI demonstrated focal liver lesions with atypical enhancement patterns that did not fulfill LI-RADS 5 criteria for hepatocellular carcinoma (e.g., absence of classical arterial phase hyperenhancement with washout, indeterminate LI-RADS 3–4 lesions, or discordant findings between modalities).

Inconclusive AFP: Serum alpha-fetoprotein values that were within the normal reference range or elevated but below the institutional diagnostic threshold (typically <200 ng/mL), and therefore not diagnostic for HCC when considered alone.

RESULTS

We examined 128 individuals for hepatocellular carcinoma (HCC). Participants were assigned to age groups, detailed in Table-I. We collected patients' hepatitis serology data, which is a risk factor for HCC. Of these 128 patients, predominant were hepatitis C (n 87). Histopathology confirmed HCC in 86 patients (67.2%); 42 patients had non-HCC diagnoses (metastatic malignancy or benign disease).

TABLE: I

PIVKA-II diagnostic 2×2 table (using the laboratory's abnormal designation):

	HCC (Histology)	Non-HCC (Histology)
PIVKA-II abnormal (positive)	71	10
PIVKA-II normal (negative)	15	32
Total	86	42

- True positives (TP) = 71
- False positives (FP) = 10
- False negatives (FN) = 15
- True negatives (TN) = 32

Diagnostic Performance

Sensitivity = 82.6% (71/86), Specificity = 76.2% (32/42), PPV = 87.7% (71/81), NPV = 68.1% (32/47), Accuracy = 80.5% (103/128).

AUROC = 0.776 (p = 0.002).

PIVKA-II levels: 81/128 patients had abnormal PIVKA-II values (71 HCC and 10 non-HCC). Among these, 46 patients had PIVKA-II > 1600 IU. AFP was abnormal in 50 patients (all 50 had HCC); AFP was reported as 'undetermined' in 78 patients (36 HCC, 42 non-HCC).

Tables and Graphs Study Participants Demographics

TABLE-II

Summarizes the demographic characteristics of the 128 patients.

Category	Sub-category	Number of Patients
Gender	Male	106
	Female	22
Age Group	25-50 years	24
	50-75 years	96
	75-100 years	8
Hepatitis Serology	Hepatitis C positive	87
	Hepatitis B positive	26
	Negative for both	15

Correlation of PIVKA-II and AFP Levels with Diagnosis

TABLE-III

Summarizes the distribution of PIVKA-II and AFP levels in the study population and their correlation with the final diagnosis of HCC.

Bio-marker	Condition	Number of Patients	Diagnosis (HCC)	Diagnosis (Non-HCC)
PIVKA-II	Abnormal Levels	81	71	10
	> 1600 IU	46	46	0
AFP	Abnormal Levels	50	50	0
	Undeter-mined	78	36	42

PIVKA-II Diagnostic Performance Metrics

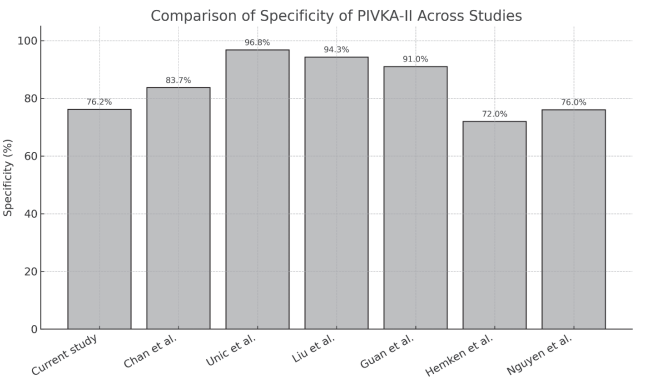
TABLE-IV

Displays the key diagnostic performance metrics for PIVKA-II in detecting hepatocellular carcinoma (HCC).

Metric	Value	
Sensitivity	82.6%	71/86
Specificity	76.2%	32/42
Positive Predictive Value (PPV)	87.7%	71/81
Negative Predictive Value (NPV)	68.1%	32/47
Accuracy	80.5%	103/128

FIGURE-1

Showing the comparative specificities of different studies.



DISCUSSION

In this retrospective cohort, PIVKA-II demonstrated a high positive predictive value (nearly 88%) and acceptable sensitivity (about 83%) and specificity (about 76%) for the diagnosis of hepatocellular

carcinoma in patients who had inconclusive imaging or nondiagnostic AFP levels. The area under the ROC curve (0.776) further supports its utility as a discriminative biomarker. Taken together, these results suggest that PIVKA-II provides clinically meaningful diagnostic information in settings where conventional diagnostic tools are insufficient.

Our findings are consistent with all those noted in prior reports assessing the diagnostic functionality of PIVKA-II for hepatocellular carcinoma (HCC) in indeterminate alpha-fetoprotein (AFP) quantities. A meta-analysis of 37 studies encompassing over 2,000 patients reported that PIVKA-II possessed a sensitivity of 89% and a specificity of 83%, much like our findings.[14]

Compared with the sensitivity rates of other studies, our sensitivity of 82.6% falls within the reported range but is slightly lower than several published values. Nguyen et al. documented a sensitivity of 91.0%, while Chan et al. and Hemken et al. reported sensitivities of 86.9% and 86.0%, respectively.
In terms of specificity, our study demonstrated a rate of 76.2%. This value is somewhat lower than those reported in several published series. For example, Chan et al. reported a specificity of 83.7%, Unic et al. observed 96.8%, and Liu et al. 94.3%. Similarly, Guan et al. documented a specificity of 91.0%. On the other hand, our findings are more comparable to the lower ranges reported by Hemken et al. (72.0%) and Nguyen et al. (76.0%), highlighting the variability across studies depending on assay method, cutoff, and patient population (FIGURE-1)

The diagnostic value of PIVKA-II can be explained by its unique pathophysiological basis. PIVKA-II is an abnormal prothrombin molecule produced when malignant hepatocytes fail to carboxylate the prothrombin precursor due to defective vitamin K metabolism. Unlike AFP, which is also elevated in non-malignant conditions such as hepatitis and cirrhosis, PIVKA-II production is more directly linked to malignant transformation and tumor biology. Elevated PIVKA-II levels correlate with tumor angiogenesis, vascular invasion, and more aggressive disease behavior. This biologically plausible link explains why PIVKA-II tends to perform better than AFP in distinguishing malignant from benign liver disease, particularly when imaging features are equivocal.

From a clinical standpoint, our results suggest that PIVKA-II is a valuable adjunct in the diagnostic algorithm for HCC. In patients with liver nodules that do not meet LI-RADS 5 imaging criteria and with AFP levels in the normal or borderline range, PIVKA-II can help guide the decision toward biopsy or closer surveillance. Furthermore, combining PIVKA-II with AFP has been shown in multiple studies to increase overall diagnostic accuracy, and future algorithms should incorporate this dual biomarker approach alongside imaging. Beyond diagnosis, PIVKA-II may also hold prognostic value, as high levels have been associated with larger tumor burden, microvascular invasion, and poorer treatment response, suggesting potential utility in risk stratification. There is also growing interest in exploring PIVKA-II in surveillance of high-risk populations, though more prospective evidence is needed before it can be adopted in that role.

Our study has several important limitations. First, it is a single-center retrospective analysis, which introduces potential selection bias, as only patients referred for biopsy after inconclusive imaging or nondiagnostic AFP were included. Second, while diagnostic metrics were carefully recalculated, the exact assay manufacturer, units, and cutoff values for PIVKA-II were not consistently documented, limiting external comparability. Third, detailed information on tumor size, BCLC stage, and vascular invasion was not uniformly available, preventing correlation of biomarker levels with disease severity. Finally, the study cohort was drawn from our region with high prevalence of hepatitis B and C, and the findings may not be generalizable to populations with different etiological backgrounds such as non-alcoholic steatohepatitis. Prospective multicenter studies using standardized assays and including comprehensive tumor staging are required to validate our findings and clarify the optimal role of PIVKA-II in clinical practice.

CONCLUSION

This study supports the potential role of PIVKA-II as a complementary biomarker in the diagnosis of hepatocellular carcinoma, particularly in patients

with inconclusive imaging or nondiagnostic AFP levels. PIVKA-II demonstrated good positive predictive value and acceptable sensitivity and specificity, reinforcing its clinical utility as an adjunct rather than a standalone test. While our findings are encouraging, prospective multicenter studies using standardized assays and clearly defined cutoffs are required to validate and refine its place within diagnostic algorithms for HCC.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1. McGlynn KA, Petrick JL, El-Serag HB. **Epidemiology of hepatocellular carcinoma.** Hepatology. 2021 Jan; 73:4-13.
2. Singh SP, Madke T, Chand P. **Global epidemiology of hepatocellular carcinoma.** Journal of Clinical and Experimental Hepatology. 2025 Mar 1; 15(2):102446.
3. Yang JD, Heimbach JK. **New advances in the diagnosis and management of hepatocellular carcinoma.** Bmj. 2020 Oct 26; 371.
4. Chartampilas E, Rafailidis V, Georgopoulou V, Kalarakis G, Hatzidakis A, Prassopoulos P. **Current imaging diagnosis of hepatocellular carcinoma.** Cancers. 2022 Aug 18; 14(16):3997.
5. Hennedige T, Venkatesh SK. **Imaging of hepatocellular carcinoma: diagnosis, staging and treatment monitoring.** Cancer Imaging. 2012; 12(3):530.
6. Guo Z, Mo H, Yuan Y, Fu W. **Diagnostic and prognostic value of combined detection of serum protein induced by Vitamin K Absence or Antagonist-II, Alpha-Fetoprotein, and Spliced Hepatitis B Virus in Hepatitis B Virus-Induced Hepatocellular Carcinoma.** Cancer Biotherapy & Radiopharmaceuticals. 2025 Jul 2; 40(9):613-21.
7. Wang SY, Su TH, Chen BB, Liu CJ, Liu CH, Yang HC, et al. **Prothrombin induced by vitamin K absence or antagonist-II (PIVKA-II) predicts complete responses of transarterial chemoembolization for hepatocellular carcinoma.** Journal of the Formosan Medical Association. 2022 Aug 1; 121(8):1579-87.
8. Dong R, Wang N, Yang Y, Ma L, Du Q, Zhang W, et al. **Review on Vitamin K deficiency and its biomarkers: Focus on the novel application of PIVKA-II in clinical practice.** Clinical Laboratory. 2018 Apr 1; 64(4):413-24.
9. Feng H, Li B, Li Z, Wei Q, Ren L. **PIVKA-II serves as a potential biomarker that complements AFP for the diagnosis of hepatocellular carcinoma.** BMC Cancer. 2021 Dec; 21(1):1-0.
10. Lee Q, Yu X, Yu W. **The value of PIVKA-Ⅱ versus AFP for the diagnosis and detection of postoperative changes in hepatocellular carcinoma.** Journal of Interventional Medicine. 2021 May 1; 4(2):77-81.
11. Ge C, Luo M, Guo K, Zhu D, Han N, Wang T, et al. **Role of PIVKA-II in screening for malignancies at a hepatobiliary and pancreatic disease center: A large-scale real-world study.** iLIVER. 2022 Dec 1; 1(4):209-16.
12. Tian S, Chen Y, Zhang Y, Xu X. Clinical value of serum AFP and PIVKA-II for diagnosis, treatment and prognosis of hepatocellular carcinoma. Journal of Clinical Laboratory Analysis. 2023 Jan;37(1):e24823.
13. Ge C, Luo M, Guo K, Zhu D, Han N, Wang T, et al. **Role of PIVKA-II in screening for malignancies at a hepatobiliary and pancreatic disease center: A large-scale real-world study.** iLIVER. 2022 Dec 1; 1(4):209-16.
14. Perne MG, Sitar-Tăut AV, Alexescu TG, Ciumărnean L, Milaciu MV, Coste SC, et al. **Diagnostic performance of extrahepatic protein induced by Vitamin K absence in the hepatocellular carcinoma: A systematic review and meta-analysis.** Diagnostics. 2023 Feb 21; 13(5):816.
15. Chan HL, Vogel A, Berg T, De Toni EN, Kudo M, Trojan J, et al. **Performance evaluation of the Elecsys PIVKA-II and Elecsys AFP assays for hepatocellular carcinoma diagnosis.** JGH Open. 2022 May; 6(5):292-300.
16. Unić A, Derek L, Duvnjak M, Patrlj L, Rakić M, Kujundžić 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.** Annals of Clinical Biochemistry. 2018 May; 55(3):355-62.
17. Liu Z, Wu M, Lin D, Li N. **Des-gamma-carboxyprothrombin is a favorable biomarker for the early diagnosis of alfa-fetoprotein-negative hepatitis B virus-related hepatocellular carcinoma.** J. Int. Med. Res. 2020; 48: 300060520902575.
18. Guan MC, Ouyang W, Liu SY, Sun LY, Chen WY, Tong XM, et al. **Alpha-fetoprotein, protein induced by vitamin K absence or antagonist-II, lens culinaris agglutinin-reactive fraction of alpha-fetoprotein alone and in combination for early detection of hepatocellular carcinoma from nonalcoholic fatty liver disease: A multicenter analysis.** Hepatobiliary & Pancreatic Diseases International. 2022 Dec 1; 21(6):559-68.
19. Hemken PM, Sokoll LJ, Yang X, Dai J, Elliott D, Gawel SH, et al. **Validation of a novel model for the early detection of hepatocellular carcinoma.** Clinical Proteomics. 2019 Dec; 16(1):2.
20. Nguyen HB, Le XT, Nguyen HH, Vo TT, Le MK, Nguyen NT, et al. **Diagnostic value of hTERT mRNA and in combination with AFP, AFP-L3%, des-γ-carboxyprothrombin for screening of hepatocellular carcinoma in liver cirrhosis patients HBV or HCV-related.** Cancer Informatics. 2022 May; 21:11769351221100730.

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1	**Muhammad Abdullah:** Design, writing.
2	**Aman Nawaz Khan:** Concept, proof reading.
3	**Ummara Siddique Umer:** Data analysis.
4	**Muhammad Kamran Khan:** Data coillection.
5	**Abdullah Safi:** Data analysis.
6	**Hadia Abid:** References.