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Original Research Article

ROLE AND ELEVATING PROGNOSTIC PRECISION OF PIVKA-II AS A SUPERIOR BIOMARKER IN HCC DIAGNOSIS, SURPASSING AFP

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Abstract: *The objective of this study was to evaluate the diagnostic accuracy of PIVKA-II as compared to AFP for the detection of hepatocellular carcinoma (HCC) and its potential as a devoid prognostic biomarker. With genomic discoveries, including gene mutations, epigenetic alterations, and non-coding RNAs, the context around HCC biomarkers has increased. The relevance of prognostic and predictive biomarkers is growing as they support treatment choices and evaluate clinical outcomes. These indicators are significant tools in enhancing patient care because they improve diagnosis, direct therapy, forecast outcomes, and evaluate treatment responses. Comprehensive information on the predictive value of several markers, however, is still lacking. In this study, 85 people took part, including those older than 18 with hepatocellular carcinoma in a range of clinical stages. Three groups represented the study population, comprising 85 individuals in total: group 1 consisted solely of patients with HCC, group 2 included patients with benign liver disease, and group 3 was designated as the control group. A male predominance is found in groups, except group 2. The quantity of PIVKA-II in serum was measured using an automated analyzer that was based on the CMIA. The immunoassay method was applied to determine the concentration of AFP. The statistical analyses of PIVKA-II and AFP consisted of sensitivity 90–99% and 58–81%, specificity 68–99%, and 61–98% with a 95% CI, respectively. The findings emphasize PIVKA-II's superior performance as a biomarker of cancer response when compared to AFP.*

Keywords: HCC, Prognostic Biomarker, PIVKA-II, AFP, Diagnostic Accuracy

Introduction

Traditional therapy methods have depended on a one-size-fits-all strategy, in which every patient gets the same treatment regimen regardless of their particular genetic or biochemical makeup. Efforts for personalized medical care have been prompted by the recent development of efficient technologies capable of thoroughly evaluating the genetic material, RNA, proteins, and metabolic products in patient malignancies (Gonzalez-Angulo et al., 2010). However, Targeted drug development tailored to certain biomarkers or genetic components has shown the necessity for more precise prognostic indicators to direct treatment choices. The approach is to improve the reliability of diagnosis and prognosis by developing a method using a multidimensional arrangement of biomarkers (Parthasarathy et al., 2023).

A prognostic marker is a variable that, in the dormancy of systemic medicine or when empiric therapy is used, anticipates a different result from those lacking that marker. Thus, a prognostic marker may categorize individuals into various treatment choices, including the potential for no therapy (Duffy and Crown, 2008). Markers might be straightforward measurements, like the disease's stage or tumor size, but they're frequently more complicated, like aberrant protein levels or genetic alterations (Riley et al., 2009).

Not all possible indicators end up being useful for prognosis. It takes a lot of work to perform studies that determine how much a particular marker might improve clinical prognosis (Mittal and El-Serag, 2013). In the case of hepatocellular carcinoma (HCC), early detection and accurate prognosis are crucial for timely and effective treatment.

The sixth and possibly most frequent cancer to be diagnosed is a carcinoma of the liver (hepatocellular carcinoma, or HCC), also the third fatal (fifth in males and seventh in females).Incidence has increased by more than three times in the past 30 years (1.6-6.8/100), with an average annual increase of 3%. It has a 16.6% five-year survival rate (Xu et al., 2021). 905,677 new cases were reported in 2020, increasing its incidence. Its frequency is 6.8 per 100,000 in America, 5.5 per 100,000 in the west coast of Europe, and it increases up-to seventeen percent in Asia (Koulouris et al., 2021). According to the World Health Organization, liver cancer is becoming more common, and by 2030, it is expected to be responsible for over one million fatalities per year (Steinmann et al., 2023) .The majority of HCC cases are the result of prolonged liver damage induced by the hepatitis type B or C virus. Cirrhosis of the liver, of any cause, is adeterminant for causing liver Carcinoma (Prabhakar et al., 2023).

HCC is classified according on its outcome status,as well as the degree of liver dysfunction and conventional TNM staging.Both the AASLD and the one used by the Barcelona Clinic Liver Cancer (BCLC) staging approach are advised

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by the European Association for the Study of the Liver (EASL).The BCLC grouping was modified in 2022 to better explain the future prospects and current therapies (Reig et al., 2022)

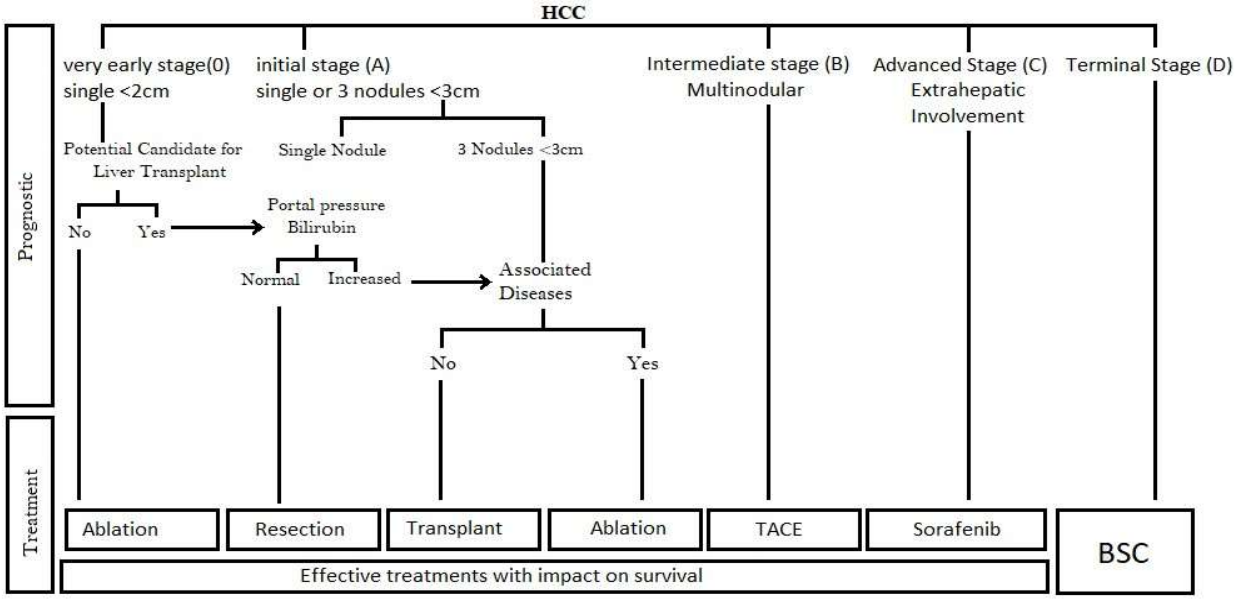

Figure 1: BCLC staging system (Barcelona-Clinic-Liver-Cancer)

For the monitoring of HCC, there are two primary groups of diagnostics that are frequently used:

1. Laboratory tests: The most often utilized serum marker for HCC surveillanceis alpha-fetoprotein (AFP) and is advised by some, but not all,HCC detection in cirrhotic patients. The precision of other indicators forms of AFP that is (AFP-L3) and des-gamma-carboxyprothrombin (DCP) has gained attention over time. Additionally, biomarkers of the gene pool, such as circulatory microRNAs, often known as "liquid biopsies," are also gaining popularity as a new way to detect early-stage HCC (Sadler et al., 2023).
2. Imaging tests: The National Institute for Health and Care Excellence now recommends ultrasonography (US) for HCC surveillance since it is secure and reasonably priced. Although CT and MRI scans offerimproved diagnostic results, they are also time and money consuming, whereas scans subject individuals to dangerous radiation. When a screening test results in positive, they sometimes serve for monitoring, but more frequently they are utilized to confirm the diagnosis (Villalba-López et al., 2023).

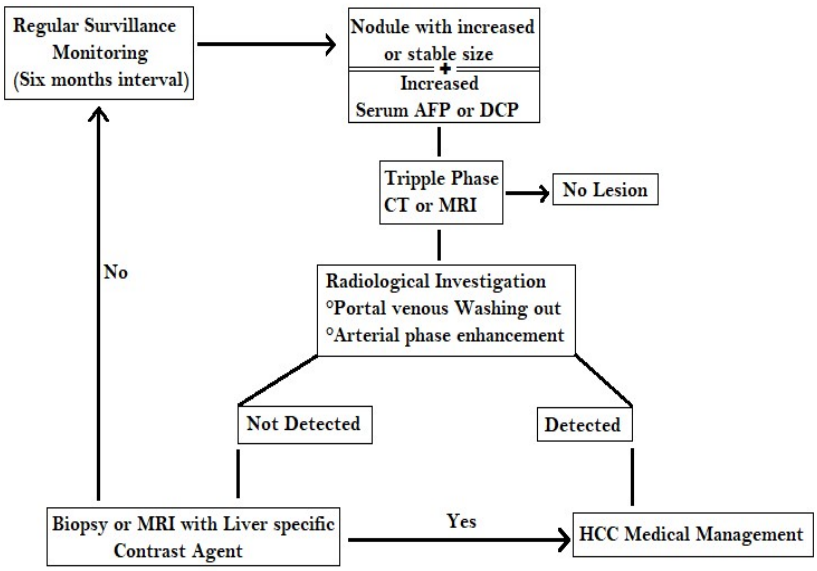

Figure 2: Current clinical practice for HCC surveillance and diagnosis

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According to further research AFP contains three glycoforms. As a non lectin lens agglutinin bound abnormality, AFP-L1 is a significant form in a number of chronic liver disorders. When compared to AFP, AFP-L3's sensitivity and specificity are both generally acceptable. Furthermore, as AFP-L3 and AFP do not correlate, the former can be employed as an independent factor for the early identification of HCC (Zhao et al., 2013).The use of AFP as a standalone screening indication for HCC is highly controversial (Desai and Guddati, 2023).

HCC has significant cellular heterogeneity, which increases the likelihood of treatment resistance and hastens the rate of recurrence. However, some patients with AFP-negative HCC require novel tumour biomarkers because of tumour heterogeneity in order to predict their prognosis in clinical settings (Suttichaimongkol et al., 2023). According to a recent study, 50% of HCC patients are AFP negative, especially those with early-stage and tiny tumours. Liebman et al. first proposed descarboxyprothrombin (DCP) in 1984. According to reports, DCP is valued higher than AFP in the evaluation of HCC (Liebman et al., 1984).

Des-gamma-carboxyprothrombin (DCP), also referred to as PIVKA-II, an immature version of prothrombin that shows no coagulative activity. It is created when patients with HCC develop abnormalities in precursor carboxylation as an aberrant protein brought up by vitamin K deficiency. The liver produces the aforementioned immature thrombin as a result of glutamate residues in the carboxyglutamic acid-rich structural region that are partially carboxylated to glutamate (Sun et al., 2023).

Patients with HCC showed considerably higher serum levels of DCP than those with cirrhosis and chronic hepatitis. When HCC is larger than 5 cm in diameter, DCP has a higher diagnostic sensitivity than AFP.By serving as an autologous growth factor, PIVKA-II might contribute to development of hepatocellular carcinoma. Additionally, high blood levels of PIVKA-II are linked to HCC growth, microvascular invasion, metastatic spread, and HCC relapse following liver transplantation or HCC nodule ablation (Gentile et al., 2017)

Methodology

A non-probabilistic sampling technique was used in this study, where convenient sampling was utilized instead of random sampling. The study had a total of 85 participants, all of whom were patients above the age of 18 and had hepatocellular carcinoma at any clinical stage. Out of the 85 participants, 63 individuals had hepatocellular carcinoma, while eight individuals who had additional liver issues entered the research. However, people who had acute inflammatory diseases, subsequent malignancies, renal and hepatic failure, Heamocoagulatory disorders, issues with vitamin K supplementation, and usage of vitamin K blocking drugs were disqualified from the study. Additionally, eight people having liver diseases but not developed HCC were enrolled. It was observed that compared to those with HCC, participants with liver disease were younger ($p < 0.005$ and $p < 0.001$, respectively). All groups, except those with various benign liver diseases, had a male majority.

The control group of the study consisted of 14 participants who had undergone full medical examinations before the testing. The average age of the participants in the control group was 60 years, and 71% of the population was male.

Table 1: Average ages of males and females in all groups

Groups	No. of individuals	Median age	Minimum	Maximum
HCC	63	62	42	84
Liver Disease	8	55	45	70
Control Group	14	58.5	45	72
Total	85	60		

PIVKA-II assay is a two-step based hybrid immunoassay for the quantitative determination of PIVKA-II. The level of PIVKA-II in serum is measured using an automated analyzer based on CMIA technology. Micro-particles covered with 3C10 antibody are used as the solid phase in PIVKA-II assay, which collects PIVKA-II. The antibody detects an epitope in the N-terminal Gla domain of PIVKA-II. The analyte-microparticle combination is detected using MCA 1-8, which identifies an epitope in the prothrombin part of the Gla motif.

For the AFP assay, an electro-chemiluminescence immunoassay is performed to find the antibodies. The sample is first treated with a biotinylated T3 antibody tagged with the ruthenium complex and a paramagnetic micro-particle coated with streptavidin. Antigen-hapten complexes occupy the vacant binding sites of the conjugated antibody, and the entire complex is bound by micro-particles of biotin and streptavidin. The antibody complexes are then moved to a measurement cell after the second round of incubation, where they are magnetized and trapped on an electrode. A buffer is used to wash the sample and unbound reagent away. Electrical estimates of the reaction's chemiluminescent reaction producing light are made. The quantity of light produced by the reaction is inversely related to how much antigen or antibody is present in the material under examination.

Results

The average age of the 43 male HCC patients included in this research was 64.5 years. There were 20 female patients, and their mean age was 59.9 years. The average age of the participants who had benign liver disease was 56.14 and people made up the control group with a mean age of 56.71 years (Figure 3)

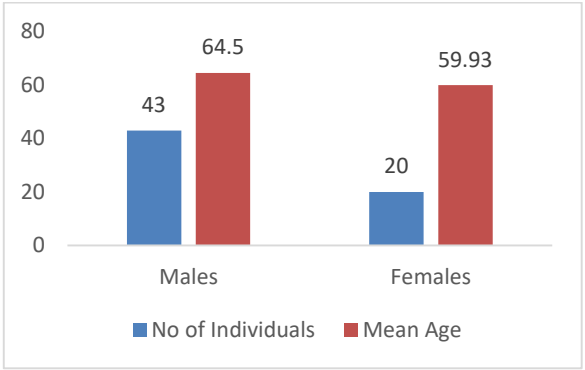

Figure 3: Bar Chart showing distribution of patients. .

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Table 2: PIVKA-II Diagnostic Evaluation:

Diagnostic Parameter	Value	95% CI
Sensitivity	97.1%	90.06% to 99.65%
Specificity	93.3%	68.05% to 99.83%
Positive Likelihood Ratio	14.57	2.19 to 96.84
Negative Likelihood Ratio	0.03	0.01 to 0.12
Disease Prevalence (*)	3.70%	
Positive Predictive Value (*)	35.89%	7.77% to 78.82%
Negative Predictive Value (*)	99.88%	99.54% to 99.97%
Accuracy (*)	**93.47%**	**85.96% to 97.69%**

Table 3: AFP Diagnostic Evaluation:

Diagnostic Parameter	Value	95% CI
Sensitivity	71.01%	58.84% to 81.31%
Specificity	87.50%	61.65% to 98.45%
Positive Likelihood Ratio	5.68	1.54 to 20.95
Negative Likelihood Ratio	0.33	0.22 to 0.50
Disease Prevalence (*)	3.70%	
Positive Predictive Value (*)	17.92%	5.59% to 44.60%
Negative Predictive Value (*)	98.74%	98.11% to 99.17%
Accuracy (*)	86.89%	77.82% to 93.24%

Table 4: Efficacy of PIVKA-II in AFP-Negative HCC Identification:

Diagnostic Parameter	Value	95% CI
Sensitivity	97.14%	90.06% to 99.65%
Specificity	93.30%	68.05% to 99.83%

Table 5: Serum Levels of AFP and PIVKA-II:

Serum Marker	HCC Mean	Control Mean	p-value
AFP	1905.2	3.98	$p < 0.01$
PIVKA-II	7607.2	25.35	$p < 0.01$

Table 2 presents a comprehensive evaluation of the diagnostic performance of PIVKA-II for hepatocellular carcinoma (HCC). The sensitivity of PIVKA-II is notably high at 97.1%, indicating its effectiveness in correctly identifying individuals with HCC. The specificity of 93.3% further underscores the test's ability to accurately exclude those without the condition. The positive likelihood ratio of 14.57 suggests a robust confirmation of HCC presence, while the extremely low negative likelihood ratio of 0.03 indicates PIVKA-II's proficiency in ruling out HCC in individuals with negative test results. The high positive predictive value (PPV) of 35.89% and exceptional negative predictive value (NPV) of 99.88% affirm the reliability of PIVKA-II in predicting both positive and negative outcomes. The overall accuracy of 93.47% further solidifies the test's diagnostic utility, positioning it in line with international standards.

Table 3 provides a detailed assessment of the diagnostic parameters for Alpha-Fetoprotein (AFP) in detecting HCC. The sensitivity of AFP, while reasonable at 71.01%, indicates its ability to identify individuals with HCC. The specificity of 87.50% suggests its capability to accurately exclude those without the condition. The positive likelihood ratio of 5.68 reflects AFP's utility in confirming the presence of HCC, while the negative likelihood ratio of 0.33 emphasizes its effectiveness in ruling out HCC in individuals with negative test results. The positive predictive value (PPV) of 17.92% and negative predictive value (NPV) of 98.74% provide insights into AFP's reliability in predicting positive and negative outcomes. The overall accuracy of 86.89% positions AFP as a diagnostic tool meeting acceptable international standards.

Table 4 explores the efficacy of PIVKA-II in identifying HCC cases that are negative for AFP. PIVKA-II demonstrates a high sensitivity of 97.14% and specificity of 93.30% in this subgroup, reaffirming its complementing role and effectiveness in identifying cases missed by AFP alone.

Table 5 compares the serum levels of AFP and PIVKA-II in individuals with HCC and the control group. The mean concentrations of AFP (1905.2 in HCC vs. 3.98 in controls) and PIVKA-II (7607.2 in HCC vs. 25.35 in controls) are significantly higher in the HCC group. The p-values, both less than 0.01, confirm the statistical significance of these differences, underscoring the diagnostic relevance of elevated AFP and PIVKA-II levels in individuals with HCC. These findings align with international standards, emphasizing the crucial role of PIVKA-II in the diagnosis of HCC.

Discussion

The results of the diagnostic evaluation for PIVKA-II and AFP, as well as the efficacy of PIVKA-II in AFP-negative HCC identification, provide valuable insights into the performance of these biomarkers in the context of hepatocellular carcinoma (HCC) detection.

PIVKA-II exhibits robust diagnostic performance, with a high sensitivity of 97.1% and specificity of 93.3%. These values suggest that PIVKA-II is highly effective in correctly

identifying individuals with HCC while minimizing false-positive results. The positive likelihood ratio of 14.57 indicates strong confirmation of HCC presence, and the extremely low negative likelihood ratio of 0.03 underscores PIVKA-II's ability to reliably rule out HCC in individuals with negative test results.

The positive predictive value (PPV) of 35.89% and negative predictive value (NPV) of 99.88% demonstrate the reliability of PIVKA-II in predicting positive and negative outcomes, respectively. The overall accuracy of 93.47% further supports the conclusion that PIVKA-II is a robust diagnostic tool for HCC, meeting international standards for diagnostic accuracy (Su et al., 2022).

AFP, while demonstrating reasonable sensitivity (71.01%) and specificity (87.50%), exhibits lower diagnostic performance compared to PIVKA-II. The positive likelihood ratio of 5.68 suggests a moderate confirmation of HCC presence, and the negative likelihood ratio of 0.33 indicates AFP's effectiveness in ruling out HCC in individuals with negative test results.

The positive predictive value (PPV) of 17.92% and negative predictive value (NPV) of 98.74% reveal the limitations of AFP in predicting positive and negative outcomes. The overall accuracy of 86.89%, while acceptable, positions AFP as a diagnostic tool with room for improvement to meet higher international standards (Sagar et al., 2021b).

The assessment of PIVKA-II's efficacy in identifying AFP-negative HCC cases demonstrates its high sensitivity (97.14%) and specificity (93.30%) in this specific subgroup. This finding emphasizes the complementary role of PIVKA-II, particularly in cases where AFP may provide false-negative results. The high sensitivity suggests that PIVKA-II is effective in capturing cases that might be missed by AFP alone, contributing to a more comprehensive diagnostic approach (Sagar et al., 2021a).

The comparison of serum levels of AFP and PIVKA-II between individuals with HCC and the control group reveals significant differences. Elevated mean concentrations of both biomarkers in the HCC group compared to the control group underscore their relevance in HCC diagnosis (Huang et al., 2017). The statistical significance ($p < 0.01$) of these differences further supports the diagnostic importance of AFP and PIVKA-II in distinguishing individuals with HCC from those without.Third and most frequent reason for cancer related mortality is HCC. As CLIP score rises, the prognosis for HCC gets worse (Gentile et al., 2017).The use of biomarkers HCC has received much research. This study explores the comparison between the sensitivity and specificity of PIVKA-II and AFP, highlighting the potential of PIVKA-II as a superior diagnostic tool for HCC.

Alpha-fetoprotein (AFP) is produced by undifferentiated liver cells. Primary liver cancer is present in 60–70% of individuals with elevated AFP levels. In HCC, particularly advanced HCC, cancer cells produce a specific amount of PIVKA, and this level is abnormally high in the serum of HCC patients. Since its initial discovery in 1963, PIVKA-II has been suggested as a diagnostic indication for HCC. Higher levels of PIVKA-II are closely linked to vascular invasion, larger tumour dimension, and worse differentiation, indicating its close association with cancer biology. As PIVKA-II is unrelated to how AFP works, it can be used to complement AFP-based diagnosis.

When used to diagnose HCC, AFP has a sensitivity of 71.01% and a specificity of 61.65% to 98.45%, depending on the cause of the HCC and the cut-off values used. However, the sensitivity drops to 59% in the early stages, which is not ideal for detecting HCC early. Compared to AFP, PIVKA-II reportedly offers higher sensitivity and specificity. However, different scientists may have varying opinions on this matter.

However, this retrospective study has a few restrictions. First, our statistical power was compromised by the limited sample size from a single center and the absence of external validation; hence, more research including more cases is needed to corroborate our findings. Second, it was impossible to eliminate selection bias and missing data in this retrospective analysis.

Conclusion

In conclusion, blood levels of AFP and PIVKA-II are trustworthy biological indicators for identifying HCC patients and determining how well they respond to therapy. PIVKA-II elevation is a better indicator of disease progression than AFP and it can be used as a benchmark for predicting patient survival. Our findings emphasize PIVKA-II's superior performance as a biomarker of cancer response when compared to AFP.

Declarations

Data Availability statement
All data generated or analyzed during the study are included in the manuscript.

Ethics approval and consent to participate
Approved by the department Concerned.

Consent for publication
Approved

Funding
Not applicable

Conflict of interest

The authors declared absence of conflict of interest.

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MOMNA RASHID BUTT
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