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Role of Protein Induced by Vitamin K Absence II in Comparison to Alpha-Feto Protein in Hepatocellular Carcinoma

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Abstract:

Background: One of the most prevalent primary liver cancers in the world, hepatocellular carcinoma (HCC) is frequently linked to cirrhosis and chronic liver disease. Because widely used biomarkers like alpha-fetoprotein (AFP) have poor sensitivity and specificity, especially in early-stage disease, early identification of HCC is still difficult. Des-gamma-carboxy prothrombin (DCP), or protein generated by vitamin K absence or antagonist-II (PIVKA-II), has become a promising diagnostic for the detection and monitoring of HCC. The diagnostic performance of PIVKA-II alone or in conjunction with AFP has been assessed in a number of studies, indicating that the evaluation of both markers together may enhance the early diagnosis and monitoring of HCC. This study highlights the clinical benefit of combining both biomarkers in the diagnosis and surveillance of hepatocellular carcinoma and summarizes the available data addressing the role of PIVKA-II in comparison to AFP.

Keywords: Hepatocellular carcinoma, PIVKA-II, Des-gamma-carboxy prothrombin, Alpha-fetoprotein, Biomarkers, Liver cancer diagnosis.

Introduction:

The most prevalent primary liver cancer and a significant global health burden is hepatocellular carcinoma (HCC). It typically appears in conjunction with long-term liver conditions such alcoholic liver disease, non-alcoholic fatty liver disease, hepatitis B virus (HBV), and hepatitis C virus (HCV). Because many patients are discovered at advanced stages of the disease, the prognosis for HCC remains dismal despite advancements in diagnostic and therapy methods. Therefore, improving patient outcomes and survival rates requires early identification and monitoring of high-risk groups (1).

Although alpha-fetoprotein (AFP) has long been utilized as a serum biomarker for HCC diagnosis and surveillance, its inferior sensitivity and specificity, particularly in early-stage tumors, continue to restrict its diagnostic accuracy. Des-gamma-carboxy prothrombin (DCP), also known as protein induced by vitamin K absence or antagonist-II (PIVKA-II), has recently become a promising biomarker for the identification of HCC. The combination of both biomarkers may greatly increase the sensitivity of HCC diagnosis and surveillance, as several studies have shown that PIVKA-II may perform better diagnostically than AFP in specific clinical scenarios (2).

PIVKA-II as a Biomarker:

Weitz et al. (3) identified PIVKA-II, also called des-gamma-carboxyprothrombin (DCP), as a protein induced by vitamin K absence or antagonist II. PIVKA-II is an aberrant byproduct of liver carboxylation during the formation of thrombogen that functions as an autologous mitogen for HCC cell lines.

Without vitamin K, PIVKA-II cannot undergo the typical carboxylation of glutamic acid residues to become prothrombin, which causes it to build up and then be released into the plasma (4).

Cui et al. (5) reported sensitivity and specificity of PIVKA-II (cut-off value of 40 mAU/ml) in discriminating between HCC and cirrhosis to be 51.7 and 86.7 %, respectively, while the combined test of PIVKA-II and AFP showed a sensitivity of 78.3 %, which is higher than that of PIVKA-II (51.7 %) and AFP alone (56.7 %). Other investigations have comparable sensitivity and specificity.

In a different investigation, PIVKA-II demonstrated a sensitivity of 53.3% and specificity of 85.6%. The combined tests of PIVKA-II and AFP demonstrated a sensitivity of 78.3%, which is more than that of PIVKA-II (53.3%) and AFP alone (58.3%). However, in a meta-analysis by Hu et al. PIVKA-II was not statistically better than AFP, however the combined measurement of PIVKA-II and AFP was superior to AFP alone. In general, PIVKA-II's diagnostic sensitivity was higher than AFP when HCC tumor size was [5 cm], but it was lower than AFP when HCC tumor size was [3 cm] (6).

According to Hashimoto et al., PIVKA-II rose in hepatitis C virus-related HCC and AFP increased in non-alcoholic steatohepatitis-related HCC (NASH-HCC) (7). They proposed that the etiology may influence AFP and PIVKA-II sensitivity (7). PIVKA-II is more likely to be higher in patients with more advanced HCC, such as bigger tumors, vascular invasion, or metastases, according to Masahiro et al., who also reported that the treatment approach was a major predictor for survival in patients with PIVKA-II [100 mAU]. For living donor liver transplantation (LDLT), PIVKA-II is therefore being considered as a potential option for new recipient selection criteria. Currently, LDLT is typically performed using the Milan selection criteria (single nodule B5 cm or B3 nodules, all B3 cm) (8).

For LDLT instances that don't meet the Milan criteria, PIVKA-II has been used. Vascular invasion, however, indicated a poor prognosis following liver transplantation for HCC. It is crucial to rule out patients with vascular invasion in addition to the Milan criteria. As a result, the PIVKA-II value is used by several research teams. Kyushu University researchers established new standards, which include a tumor size of at least 5 cm and a PIVKA-II level of at least 300 mAU/ml. In addition to a PIVKA-II level of B400 mAU/ml and B10 nodules, all of which were not [5 cm] in size, the Kyoto University research team included the quantity of tumor nodules in their criterion. Furthermore, these investigations revealed a relationship between the existence of microvascular invasion in resected HCC and a greater level of PIVKA-II (9).

Comparison with Alpha-fetoprotein (AFP):

The usefulness of AFP and PIVKA-II in the diagnosis of HCC was evaluated in a study by Kobeissy et al. In terms of ethnic group (African, European, Asian, and American patients), etiology (mixed-type HCC, hepatitis C virus (HCV)-related, and hepatitis B virus (HBV)-related), and sample size of cases, subgroup analysis showed that PIVKA-II had higher AUC values than AFP. According to this study, PIVKA-II is a more accurate biomarker than AFP for detecting and monitoring HCC. The data indicate that PIVKA-II outperforms AFP in detecting HCC across varied racial groups and sample sizes, as well as in cases of HBV-related, HCV-related, or mixed-etiology HCC (10).

The goal of Xing et al.'s systematic review and meta-analysis was to evaluate how well PIVKA-II and alpha-fetoprotein (AFP) performed in the diagnosis of HCC. PIVKA-II outperformed AFP in terms of the AUC for both small HCC (< 3 cm), according to subgroup analysis. This meta-analysis reveals that PIVKA-II is better than AFP in terms of the accuracy for identifying HCC, regardless of tumor size, patient ethnic group, or HCC etiology (11).
In a large, multi-center study conducted in China, Ji et al. (12) sought to assess how well des-gamma-carboxy prothrombin (DCP) identified hepatitis B virus-related HCC. For DCP and AFP, blind parallel detections were performed. The diagnostic efficacy was assessed using the area under the receiver operating characteristic curve (AUC).

When it came to monitoring early HCC [AUC 0.837 (95% CI: 0.771–0.903) vs. 0.650 (0.555–0.745)] and AFP-negative HCC [AUC: 0.856 (0.798–0.914)] as well as differentiating HCC from LC (accuracy: 92.9% vs.64.71%). Shorter disease-free life and worse clinical behaviors were linked to higher DCP levels. DCP shows better performance in HCC surveillance, early diagnosis, treatment response, and recurrence monitoring in the

HBV-related population, in addition to being complimentary to AFP in identifying AFP-negative HCC and ruling out AFP-positive non-HCC (liver cirrhosis) (12).

Poté et al. compared the effectiveness of α-fetoprotein (AFP) and PIVKA-II serum levels for early-stage HCC detection in a case-control study. At a cut-off of 42 mAU/ml, PIVKA-II showed a sensitivity of 77% and a specificity of 82% for the diagnosis of early HCC, compared to 61% and 50% for AFP at a cut-off of 5.5 ng/ml (AUC 0.81 vs. 0.58, respectively). Microvascular invasion (MVI) was substantially correlated with high PIVKA-II tissue expression ($p = 0.001$). PIVKA-II could be utilized as a predictive biomarker of MVI and was more effective than AFP in the identification of early HCC (2).

In order to diagnose chronic hepatitis, cirrhosis, and HCC, Morota et al. compared the sensitivity and specificity of α-fetoprotein (AFP) with protein generated by the lack of vitamin K or antagonist-II (PIVKA-II). A total of 229 serum samples from normal people and patients with cirrhosis, HCC, and chronic hepatitis were assessed. When compared to AFP, PIVKA-II demonstrated better sensitivity and specificity for HCC (13).

The assessment of PIVKA-II and AFP in the diagnosis of HCC in India was examined in a study by Sharma et al. PIVKA-II and AFP levels were assessed for each patient using ELISA. The results showed that AFP had 72.9% sensitivity and 65.8% specificity at a cutoff level of 13.02 ng/ml, whereas PIVKA-II had 80% sensitivity and 92.1% specificity at a cutoff level of 9.2 ng/ml. For the diagnosis of HCC in the Indian population, PIVKA-II was found to be more sensitive and specific than AFP (14).

Clinical Utility of Combined Biomarker Assessment:

In a study by Kim et al. who wanted to explore the clinical usefulness and value of PIVKA-II in the Asia-Pacific area for the surveillance and treatment monitoring of HCC, its benefits and limits, and next steps required to increase its use. They discovered that PIVKA-II in conjunction with AFP and US will be clinically beneficial in the Asia-Pacific area for surveillance, particularly for individuals with minor and AFP-negative HCC, and more so for forecasting treatment results in HCC patients (15).

The effectiveness of PIVKA-II by itself and in conjunction with AFP for HCC screening in the Chinese population is assessed by Yu et al. At a cutoff of 40 mAU/mL, PIVKA-II's sensitivity and specificity were 74.6% and 67.8%, while at a cutoff of 200 mAU/mL, they were 64.2% and 89.7%. At a cutoff of 20 ng/mL, AFP's sensitivity and specificity were 76.7% and 65.0%, while at a cutoff of 195.23 ng/mL, they were 60.4% and 88.9%. The sensitivity and specificity of the two markers combined were 91.1% and 41.0%, respectively. This demonstrated that when employed as a single marker for HCC screening, PIVKA-II was just as effective as AFP, and the combination of two biomarkers produced better results (16).

A multi-center case-controlled study was conducted to examine the clinical value of measuring alpha fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) simultaneously for the detection of hepatocellular carcinoma (HCC) in Chinese patients, primarily due to hepatitis B virus infection. The results showed that even for tiny tumors, the combination of DCP and AFP produced a higher Youden score and a sensitivity of almost 90%. The simultaneous measurement of AFP and DCP could provide a greater sensitivity in detecting Chinese HCC patients, especially for tiny tumors (17).

Choi et al. assess the diagnostic utility of prothrombin induced by vitamin K absence-II (PIVKA-II) and α-fetoprotein (AFP)-L3 in hepatocellular carcinoma (HCC). In patients with low AFP levels, AFP-L3 with a cut-off value of 5% demonstrated sensitivity of 71.1% and specificity of 83.8%, whereas PIVKA-II with a cut-off value of 40 AU/L demonstrated sensitivity of 57.9% and specificity of 95.9%. In the low AFP group, the combination of AFP-L3 and PIVKA-II improved the sensitivity and specificity to 92.1% and 79.7%, respectively. In the low AFP group, combined markers identified 81.8% of early-stage HCC (Union for International Cancer Control Stage I), 86.7% of tiny tumors (less than 2 cm), and 91.7% of single HCC tumors. In individuals with or without elevated AFP levels, the combined measurement of AFP-L3 and PIVKA-II may enhance the diagnostic value for HCC identification (18).

In a European cohort, the combined analysis of AFP and des-γ-carboxy prothrombin (DCP) was assessed. Patients with HCC had higher levels of AFP and DCP than controls ($p < 0.0001$). When AFP and DCP were

combined, the sensitivity increased from 28.7% for AFP (cutoff 400 ng/ml; AFP at cutoff 10 ng/ml: 54.9%) to 78.0% utilizing cutoffs of 10 ng/ml for AFP and 5 ng/ml for DCP (DCP alone, cutoff 5 ng/ml: 63.4%). The sensitivity rose from 20% for AFP (cutoff 400 ng/ml; AFP at cutoff 10 ng/ml: 38%) to 55% in combination (DCP alone, cutoff 5 ng/ml: 47%) among patients in the early stages. According to the findings, AFP by itself is insufficient for the serological detection of HCC in European patients, but AFP with DCP can boost sensitivity even in patients in the early stages of the disease (19).

A study by Ishida et al. assessed the diagnostic efficacy of two tumor markers, alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP), a combination of these tests, for patients developing hepatocellular carcinoma (HCC) during long-term follow-up for HCV-related liver illness. They showed that the combination tests for DCP at 40 mAU/ml and AFP at 100 ng/ml produced the best sensitivity at 0.84 with a specificity of 0.50. When AFP, AST, LD, hemoglobin, prothrombin time, and male ratio were used as variables in a multivariate logistic regression model, the diagnostic performance was considerably better (sensitivity 0.85, specificity 0.74) than when AFP and DCP were used alone or in combination (20).

A study by Yoon et al. who investigated the sensitivity and specificity of PIVKA-II, alone or in conjunction with alpha-fetoprotein (AFP), for the identification of HCC during surveillance, and to assess whether PIVKA-II was a significant risk factor for patient survival. The AFP and PIVKA-II sensitivity rates were found to be 57.5% (61/106) and 51.9% (55/106), respectively. AFP and PIVKA-II had specificities of 88.0% and 97.0%, respectively. They came to the conclusion that, particularly when combined with AFP, PIVKA-II can be utilized as a tumor marker for the early diagnosis of HCC in individuals with persistent HBV infection (21).

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