Journal of Clinical and Translational Hepatology **2025**
DOI: 10.14218/JCTH.2025.00377

Review Article

Protein Induced by Vitamin K Absence or Antagonist II in Primary Liver Cancer: Basic Research Insights and Clinical Applications

Xin Zhang[1,2#], Rong Wang[1,2#], Bin Niu[1,2#] and Liaoyun Zhang[1,2*]

[1]*The First Clinical Medical School, Shanxi Medical University, Taiyuan, Shanxi, China;* [2]*Department of Infectious Diseases, First Hospital of Shanxi Medical University, Taiyuan, Shanxi, China*

Received: July 28, 2025 | **Revised:** September 27, 2025 | **Accepted:** October 11, 2025 | **Published online:** October 28, 2025

Abstract

Hepatocellular carcinoma (HCC) is the most common subtype of primary liver cancer and continues to be a major cause of cancer-related mortality, particularly in regions of China with a high hepatitis B virus prevalence. Early-stage diagnosis remains challenging due to its asymptomatic onset and the limited sensitivity of conventional biomarkers, which together contribute to delayed detection, suboptimal therapeutic outcomes, and poor prognosis. These limitations underscore the urgent need for reliable, sensitive, and specific biomarkers to enable timely detection and targeted intervention. Protein induced by vitamin K absence or antagonist-II, an abnormal prothrombin variant generated under vitamin K deficiency or antagonism, has emerged as a promising candidate with diagnostic and therapeutic relevance in HCC. This review critically examines the molecular and biological characteristics of protein induced by vitamin K absence or antagonist-II, evaluates its clinical utility in HCC diagnosis and management, and delineates the current limitations hindering its broader application. Furthermore, future perspectives are proposed to guide translational research and clinical implementation. Collectively, this review aims to provide a comprehensive theoretical framework to advance precision diagnosis and individualized treatment strategies for HCC.

Citation of this article: Zhang X, Wang R, Niu B, Zhang L. Protein Induced by Vitamin K Absence or Antagonist II in Primary Liver Cancer: Basic Research Insights and Clinical Applications. J Clin Transl Hepatol 2025. doi: 10.14218/JCTH.2025.00377.

Introduction

According to the latest global cancer statistics, hepatocellular carcinoma (HCC) is the sixth most frequently diagnosed malignancy and the third leading cause of cancer-related mortality worldwide, accounting for more than 750,000 deaths annually.[1] In its early stages, HCC is typically asymptomatic, and approximately 80% of cases are diagnosed at an advanced stage, when curative treatment options are no longer feasible. Advanced-stage HCC is often characterized by extensive intrahepatic and extrahepatic tumor dissemination, resulting in poor therapeutic efficacy and a dismal five-year overall survival rate of approximately 14.1%.[2] Thus, early diagnosis and timely intervention are essential for enhancing clinical outcomes.[3] However, conventional surveillance methods, such as abdominal ultrasonography combined with alpha-fetoprotein (AFP) testing, have limited sensitivity, particularly in patients with AFP-negative HCC (AFP-NHCC), resulting in a high rate of missed diagnoses.[4] Abnormal prothrombin, also known as protein induced by vitamin K absence or antagonist-II (PIVKA-II), was first identified in 1984 as an abnormal prothrombin variant and proposed as a potential biomarker for HCC.[5] Evidence indicates that its expression is closely associated with tumor differentiation, neovascularization, and invasiveness, underscoring its potential as a biomarker reflecting tumor biology. Importantly, the diagnostic accuracy of PIVKA-II exceeds that of AFP alone, particularly in AFP-NHCC populations.[6] This review critically evaluates the distinctive diagnostic utility of PIVKA-II, both as an independent marker and in combination with other emerging biomarkers. It further explores its potential role in improving early detection and guiding personalized treatment strategies. Collectively, this review aims to provide a robust theoretical basis for the integration of PIVKA-II into precision oncology approaches for HCC.

Biological significance and characteristics of PIVKA-II

Mechanism of formation and molecular characteristics

The indirect synthesis of PIVKA-II was first reported by Hemker *et al*. in 1963,[7] and was subsequently validated by Nilehn and Ganrotin.[8] Subsequent research has established a close association between PIVKA-II and abnormalities in vitamin K metabolism. Under physiological conditions, vitamin K-dependent γ-glutamyl carboxylase catalyzes the γ-carboxylation

Keywords: Hepatocellular carcinoma; Protein induced by vitamin K absence or antagonist-II; PIVKA-II; Diagnosis; Prognosis; Biomarker; Des-γ-carboxy prothrombin; DCP.

[#]Contributed equally to this work.

[*]**Correspondence to:** Liaoyun Zhang, Department of Infectious Disease, First Hospital of Shanxi Medical University, 85 Jiefang South Road, Taiyuan, Shanxi 030001, China. ORCID: https://orcid.org/0000-0002-7666-7368. Tel: +86-13603518852, E-mail: zlysgzy@163.com.

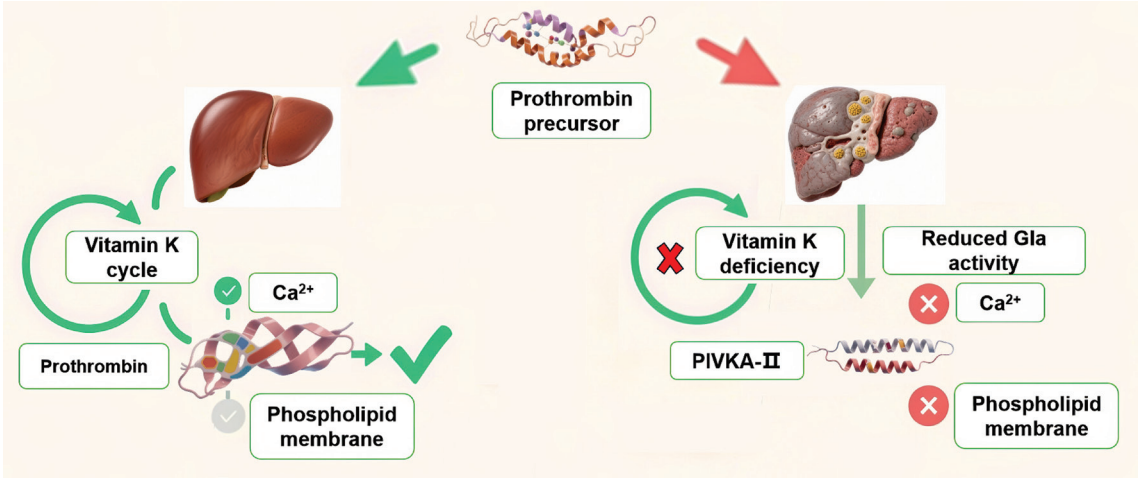

Fig. 1. Biological significance and characteristics of PIVKA-II. PIVKA-II, protein induced by vitamin K absence or antagonist-II.

of glutamic acid residues within the *γ*-carboxylated glutamic acid (Gla) domain of prothrombin precursors, which represents a critical step in the post-translational activation of prothrombin into functional thrombin.[7] In cases of vitamin K deficiency or exposure to vitamin K antagonists such as warfarin, carboxylase activity is inhibited, resulting in the secretion of incompletely carboxylated prothrombin precursors into the bloodstream.[9] These undercarboxylated molecules, collectively referred to as PIVKA-II, lack normal coagulation activity and accumulate abnormally in circulation. Previous studies have demonstrated that the carboxylation process follows a defined spatial and sequential pattern.[10] Specifically, the ten Gla residues undergo modification in a three-dimensional progression from the interior to the exterior of the molecule, with the order of carboxylation being glutamic acid residues at positions 26, 25, 16, 29, 20, 19, 14, 32, 7, and 6 from the N-terminus. Disruption of this sequence impairs complete carboxylation, thereby contributing to the pathological accumulation of PIVKA-II.

PIVKA-II, also known as des-*γ*-carboxy prothrombin (DCP), is an aberrant isoform of prothrombin characterized by defective *γ*-carboxylation within its Gla domain. In physiologically active prothrombin, the Gla domain contains ten fully carboxylated glutamic acid residues, which enable the protein to bind calcium ions and interact with phospholipid membranes. This is an essential step for anchoring prothrombin to the surface of injured blood vessels.[11] In contrast, PIVKA-II contains incompletely carboxylated Gla residues, resulting in markedly reduced calcium-binding capacity and a failure to adopt the functional conformation required for coagulation activity.[12] Site-directed mutagenesis studies have demonstrated that carboxylation at positions 16, 26, and 29 is critical for maintaining procoagulant function. Loss of *γ*-carboxylation at these key sites reduces the coagulation activity of PIVKA-II to less than 1% of that of native prothrombin.[11] Moreover, structural analyses have revealed that the conformational flexibility of the Gla domain in PIVKA-II is significantly diminished, which disrupts the spatial organization of the kringle and protease domains and further compromises its biological function (Fig. 1).[13] Collectively, these findings clarify the molecular basis of PIVKA-II dysfunction; however, the dynamic regulation of domain interactions and their pathological implications remain incompletely defined, underscoring the need for further structural and functional studies.

The mechanism of PIVKA-II production in HCC

Since the initial report by Liebman in 1984 demonstrating the presence of PIVKA-II in the serum of patients with HCC,[5] serum PIVKA-II levels have been extensively utilized as a clinically valuable biomarker for HCC diagnosis.[14] Despite its widespread clinical application, the molecular mechanisms underlying the aberrant production of PIVKA-II in HCC remain incompletely understood. It is generally accepted that PIVKA-II is produced in HCC under conditions of vitamin K deficiency or impaired vitamin K utilization, highlighting its close pathophysiological association with vitamin K metabolism. Hypoxia is characteristic of HCC tissues, and hypoxic stress has been shown to impair vitamin K uptake. Moreover, concentrations of vitamin K1 and specific vitamin K2 subtypes, particularly menaquinone-7 and menaquinone-8, are markedly reduced in HCC tissues, thereby contributing to defective *γ*-carboxylation.[15] PIVKA-II synthesis is further associated with the liver-like differentiation phenotype of HCC cells, as its expression is highly specific to primary HCC, while remaining negligible in both normal liver and metastatic liver lesions.[16] Taken together, the aberrant production of PIVKA-II in HCC is thought to involve a multistep process, including enhanced synthesis of prothrombin precursors under hypoxic conditions, localized depletion of vitamin K, and reduced activity of *γ*-glutamyl carboxylase. As a result, a proportion of newly synthesized prothrombin precursors fail to be fully carboxylated, leading to the accumulation and release of undercarboxylated prothrombin PIVKA-II into the circulation.

The mechanism of the progression of HCC triggered by PIVKA-II

PIVKA-II has been shown to directly contribute to the malignant behavior of HCC by activating multiple oncogenic signaling pathways. Specifically, PIVKA-II can bind to the cell surface receptor tyrosine kinase c-Met at the Tyr1234/1235 phosphorylation sites, thereby activating the c-Met-Janus kinase 1-signal transducer and activator of transcription 3 pathway, which promotes HCC cell proliferation.[17,18] Further investigations have revealed that PIVKA-II also stimulates phosphorylation of the epidermal growth factor receptor, leading to activation of the Ras-Raf-MEK-ERK-MAPK signaling cascade, a critical driver of tumor invasion and metastasis.[19] In the context of angiogenesis, PIVKA-II binds to the kinase insert domain receptor (KDR, also known as vascular

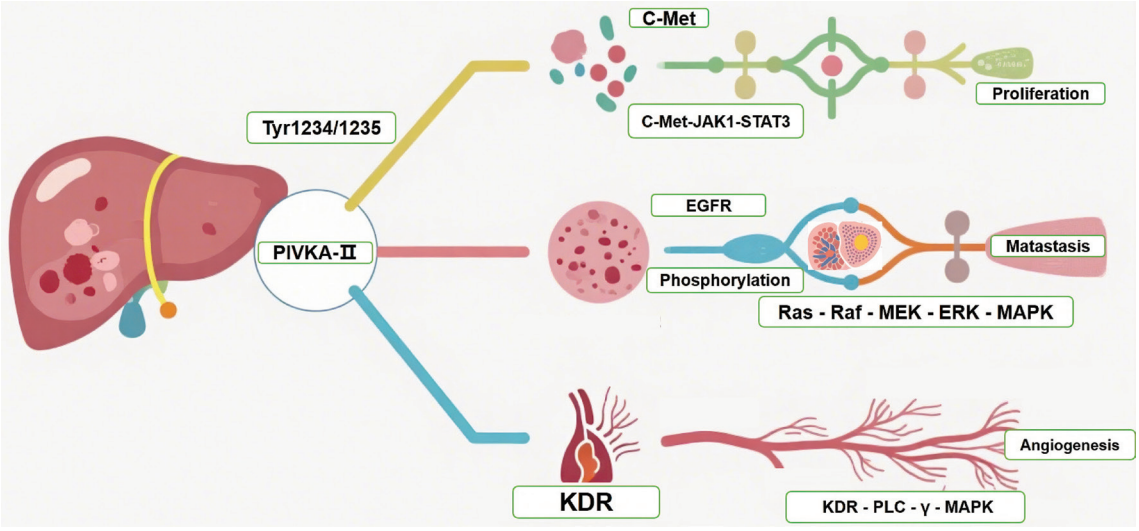

Fig. 2. PIVKA-II promotes HCC progression. PIVKA-II, protein induced by vitamin K absence or antagonist-II; HCC, Hepatocellular carcinoma; EGFR, the epidermal growth factor receptor; KDR, the kinase insert domain receptor; PLC, phospholipase C.

endothelial growth factor receptor-2), thereby initiating the KDR-phospholipase C-γ-MAPK signaling axis (Fig. 2). This pathway enhances endothelial cell proliferation and migration, which establishes a pro-angiogenic microenvironment that facilitates both intrahepatic and extrahepatic tumor dissemination. Thus, the pro-metastatic potential of PIVKA-II is closely associated with its ability to drive vascular remodeling and tumor cell motility through receptor-mediated signaling.

Specialized variant

Beyond the conventional forms of PIVKA-II, increasing attention has focused on a structurally distinct variant known as next-generation des-γ-carboxy prothrombin (NX-DCP), which offers novel insights into the molecular heterogeneity of this biomarker. NX-DCP contains fewer Gla residues and can be specifically detected using monoclonal antibodies such as P-11 or P-16.[20] This structural distinction is clinically relevant because it reduces the false-positive elevations frequently observed with conventional PIVKA-II in patients receiving vitamin K antagonists, or those with vitamin K deficiency, obstructive jaundice, or alcohol-related liver disease.[21] Both NX-DCP and the NX-DCP ratio (PIVKA-II/NX-DCP, cut-off 1.5) have demonstrated higher specificity in distinguishing HCC-related elevations, and their levels are strongly correlated with microvascular invasion and larger tumor burden.[20,22,23] Immunohistochemical analyses further revealed that NX-DCP exhibits stronger staining at vascular invasion sites than either AFP or conventional PIVKA-II.[24] Nevertheless, its wider clinical adoption remains constrained by inter-assay variability, the absence of standardized thresholds, and the relatively high cost of antibody-based assays. These findings demonstrate that NX-DCP not only improves the diagnostic and prognostic accuracy of PIVKA-II in HCC but also serves as a valuable target for future clinical research and therapeutic exploration.

Overall, PIVKA-II represents a distinctive molecular entity linking disrupted vitamin K metabolism with hepatocarcinogenesis. Its biochemical origin lies in incomplete γ-carboxylation of prothrombin precursors; however, in HCC, this process is further amplified by hypoxia, vitamin K depletion, and impaired γ-glutamyl carboxylase activity, highlighting a disease-specific vulnerability of hepatic metabolic pathways. Beyond serving merely as an abnormal by-product, PIVKA-II acquires pathological significance by activating receptor-mediated oncogenic and pro-angiogenic signaling pathways, thereby directly contributing to tumor progression. The identification of variants such as NX-DCP highlights both the molecular heterogeneity of this biomarker and its potential to enhance diagnostic specificity. Nevertheless, the relative role of PIVKA-II as a driver versus a surrogate of malignancy, the mechanisms governing variant formation, and the integration of these pathways into the broader metabolic and microenvironmental context of HCC remain incompletely elucidated. Addressing these questions will be critical for transforming PIVKA-II from a diagnostic biomarker into a mechanistically informed therapeutic target.

PIVKA-II as an HCC biomarker

Early detection of HCC

PIVKA-II is increasingly recognized as a complementary biomarker for HCC monitoring[25,26] and is referenced in the European Association for the Study of the Liver (EASL) guidelines for HCC management.[27] The 2021 Clinical Practice Guidelines of the Japanese Society of Hepatology set a threshold of ≥40 mAU/mL to define abnormal PIVKA-II levels warranting further imaging,[26] while the Taiwan Liver Cancer Association emphasizes its ability to improve sensitivity in high-risk populations.[28]

PIVKA-II has been systematically evaluated in multiple studies for its diagnostic sensitivity and specificity. In a European cohort, a PIVKA-II threshold of >37 mAU/mL yielded a sensitivity of 80% and specificity of 76%, outperforming the diagnostic performance of AFP.[29] A multi-center analysis further demonstrated that PIVKA-II exhibits particularly high diagnostic efficacy in patients with advanced or metastatic disease. For tumors ≥ 5 cm in diameter, the sensitivity and specificity reached 92.55% and 87.18%, respectively, compared to 73.74% and 61.77% for tumors < 5 cm.[30] Notably, the diagnostic performance of PIVKA-II varies according to the underlying etiology of HCC. In hepatitis B virus (HBV)-related cirrhosis, the serum PIVKA-II level > 50 mAU/mL is associated with a 1.74-fold increased risk of HCC development.[31] In hepatitis C virus-related cirrhosis, PIVKA-II

demonstrates robust diagnostic utility, with a specificity of 95.12% and sensitivity of 77.46% for predicting the four-year cumulative incidence of HCC.[32,33] In alcoholic cirrhosis, cases of PIVKA-II levels below 20 ng/mL have demonstrated both sensitivity and specificity around 80% as a diagnostic indicator.[34] Moreover, emerging evidence supports the diagnostic value of PIVKA-II in non-cirrhotic HCC, including HCC associated with non-alcoholic fatty liver disease (NAFLD), where it exhibits strong serological performance.[35]

The 2021 Clinical Practice Guidelines of the Japanese Society of Hepatology explicitly recommend PIVKA-II as a primary screening biomarker for AFP-NHCC.[26] Similarly, the 2024 edition of the Chinese Diagnosis and Treatment Guidelines for Primary Liver Cancer emphasizes the role of PIVKA-II as a supplementary diagnostic tool in high-risk individuals with AFP-NHCC.[25] AFP, although traditionally employed as a standard biomarker for HCC, exhibits substantial limitations in sensitivity for AFP-NHCC, resulting in underdiagnosis within this clinically significant subset. In contrast, PIVKA-II has emerged as a promising alternative capable of addressing these diagnostic shortcomings. Lin *et al*. reported that serum PIVKA-II levels were significantly elevated in AFP-NHCC patients, with a diagnostic cutoff of 40.00 mAU/mL yielding a sensitivity of 84.62% and specificity of 90.38%.[36] A multi-center study involving 1,034 Chinese patients with HBV-related HCC further validated the diagnostic performance of PIVKA-II. When assessed independently, it achieved an area under the curve (AUC) of 0.856 for AFP-NHCC, with a sensitivity of 74.3% and specificity of 89.1%. Notably, in early-stage AFP-NHCC (tumor diameter ≤ 3 cm), PIVKA-II maintained a sensitivity of 68.5% and specificity of 91.2%.[37] However, other findings suggest that sensitivity may decline to 56% in tumors < 2 cm, highlighting the persistent challenge of detecting very early-stage disease.[38] Importantly, a prospective cohort study conducted in Western populations revealed that elevated PIVKA-II levels frequently precede radiographic evidence of tumor progression in AFP-NHCC patients.[39] This observation underscores the potential of PIVKA-II as a predictive biomarker for subclinical disease progression. Overall, serum PIVKA-II testing provides a practical solution to the diagnostic limitations of AFP, particularly in AFP-NHCC. Beyond its diagnostic utility, PIVKA-II also contributes to earlier detection, more accurate staging, and prognostic evaluation. As such, it represents an essential component in the refinement of HCC diagnostic and monitoring paradigms.

Although PIVKA-II has demonstrated promise as a biomarker, its sensitivity and specificity remain suboptimal when used alone for the early detection of HCC. Both the American Association for the Study of Liver Diseases (AASLD) and EASL acknowledge that combining PIVKA-II with conventional diagnostic tools enhances diagnostic accuracy beyond that achievable with single markers.[27,40] Consequently, recent research has increasingly focused on the combined use of PIVKA-II with additional serum biomarkers. Despite variations in assay methodologies, patient populations, and underlying disease etiologies—factors that contribute to heterogeneity in study outcomes—most investigations converge on a key conclusion: integrating PIVKA-II with complementary biological markers and clinical parameters significantly improves diagnostic performance. Such combinatorial strategies offer a practical means to overcome the inherent limitations of single-marker approaches, thereby enhancing both sensitivity and specificity in early HCC diagnosis.

To enhance the diagnostic accuracy of HCC, a series of quantitative scoring models have been developed, integrating demographic variables such as gender and age with serum biomarkers, including PIVKA-II. In 2014, a multi-center study introduced the GALAD model, which incorporates gender, age, AFP, the percentage of AFP-L3 (an isoform of AFP), and PIVKA-II. The diagnostic equation is defined as: $Z = -10.08 + 0.09 \times \text{age} + 1.67 \times \text{gender}$ (1 for males, 0 for females) $+ 2.34 \times \log(\text{AFP}) + 0.04 \times \text{AFP-L3} + 1.33 \times \log(\text{PIVKA-II})$. The primary strength of this model lies in its ability to dynamically reflect tumor biological behavior,[41] and it has demonstrated high diagnostic sensitivity and specificity for HCC.[42] In a large-scale multi-center study, Hou *et al*. evaluated the GALAD model's predictive accuracy for early-stage HCC, yielding an AUC of 0.914, with a sensitivity of 57.6% and a specificity of 85%. Importantly, its diagnostic efficacy remained robust across different etiological backgrounds, including HBV, hepatitis C virus, and non-viral liver diseases.[43] However, a prospective Chinese study noted a marginally reduced performance in non-viral etiologies, suggesting that etiology-specific threshold adjustments may be warranted.[44] Numerous research groups have independently validated the GALAD model in international cohorts and concurrently developed optimized derivatives. Among these are the C-GALAD,[45]AALP,[46] and GAADPB[47] models. Simplified adaptations such as GAAD, GAAP, and ASAP omit AFP-L3 while retaining comparable diagnostic performance. For example, Piratvisuth *et al*. reported that the GAAD model achieved a sensitivity of 71.8% and specificity of 90.0% for early HCC detection,[48] whereas Liu *et al*. demonstrated that the GAAP model attained an AUC of 0.914 in HBV-related HCC.[49] Similarly, a prospective cohort by Maneenil *et al*. found the ASAP model to have an AUC of 0.898 for HCC prediction.[50] Expanding the scope to global application, Fan and colleagues conducted an extensive international study spanning five continents, 29 countries, and 968 research centers to develop the aMAP model. The Z-score is calculated as follows: $Z = \{[0.06 \times \text{age} + 0.89 \times \text{gender} + 0.48 \times (0.66 \times \log_{10}\text{total bilirubin} - 0.085 \times \text{albumin}) - 0.01 \times \text{platelet count}] + 7.4\} / 14.77 \times 100$. The aMAP model exhibited strong predictive capability across various diverse ethnicities and liver disease etiologies, with AUC values ranging from 0.82 to 0.87.[51] Additionally, a prospective cohort led to the development of the HES V2.0 model, which outperformed both the GALAD and ASAP models in identifying HCC.[52] Collectively, these models exemplify a strategic integration of serum biomarkers such as PIVKA-II with demographic and biochemical variables to generate numerical risk scores. This approach not only enhances the sensitivity and specificity of early HCC diagnosis but also facilitates dynamic risk stratification and personalized prognostic assessment, thereby guiding clinical decision-making and improving patient outcomes (Table 1).[41,43–52]

In addition to the aforementioned scoring models, several studies have proposed streamlined yet effective biomarker combinations that further enhance diagnostic performance in early HCC, particularly in specific etiological contexts. Wang *et al*. demonstrated that integrating the γ-glutamyl transferase to aspartate aminotransferase ratio with PIVKA-II and AFP significantly improved diagnostic accuracy for HBV-related early HCC. This composite model achieved an AUC of 0.925, surpassing that of conventional single-modality imaging techniques.[53] Similarly, Chen *et al*. reported that combining AFP and PIVKA-II yielded the highest diagnostic performance, with an AUC of 0.965, highlighting the synergistic value of dual-marker strategies.[54] With regard to NAFLD, a growing body of evidence indicates that nearly 50% of HCC cases in this population arise in the absence of cirrhosis and are frequently associated with increased tumor burden. In this high-risk subgroup, Mi *et al*. found that combining PIVKA-II levels with platelet count markedly enhanced screening accuracy. The combined approach demonstrated excellent

Table 1. PIVKA-II combined with other indicators in a diagnostic model for HCC

Model	Researcher	Cohort model	Study type	Diagnostic performance	Cut-off value	References
GALAD, 2014	Philip J. Johnson	331 HCC + 339 chronic	Multicenter prospective cohort study	Training set AUC = 0.97, validation set AUC = 0.95	NA	41
GALAD, 2025	Jinlin Hou	1558 cirrhosis (109 developed HCC)	Multicenter prospective cohort study	AUC = 0.78, SEN = 62%, SPE = 82%	PIVKA-II = 40 mAU/mL	43
GALAD, 2025	Henry L Y Chan	297 HCC + 709 chronic	Multicenter prospective cohort study	AUC = 0.914, SEN = 57.6%, SPE = 85%	PIVKA-II = 28.4 ng/ml	44
C-GALAD, 2024	Chenjun Huang	822 HCC + 2137 chronic	Multicenter retrospective and prospective cohort study	Training set AUC = 0.952; Internal validation AUC = 0.912; External validation AUC = 0.927	PIVKA-II = 40 mAU/mL	45
AALP, 2023	Tianying Ren	395 HCC + 846 chronic	Cross-sectional study	AUC = 0.939, SEN = 81%, SPE = 95%	PIVKA-II = 40 mAU/mL	46
GAADPB, 2022	Lanjuan Li	155 HCC + 269 chronic + 87 healthy	Randomized controlled trial	Training set AUC = 0.941, validation set AUC = 0.896	PIVKA-II = 40 mAU/mL	47
GAAD, 2023	Teerha Piratvisuth	675 HCC + 1039 chronic	Prospective cohort study	Training set AUC = 0.907, validation set AUC = 0.914	PIVKA-II = 28.4 ng/mL	48
GAAP, 2020	Miaoxia Liu	434 HCC + 422 chronic + 27 liver metastasis	Single-center cohort study	AUC = 0.914, SEN = 88%, SPE = 80%	PIVKA-II = 40 mAU/mL	49
ASAP, 2024	Chongkonrat Maneenil	174 HCC + 477 chronic	Single-center prospective cohort study	AUC = 0.898, SEN = 88.7%, SPE = 81.7%	NA	50
aMAP, 2020	Rong Fan	13088 CHB + 3566 CHC + 720 non-viral hepatitis	Multicenter prospective observational cohorts or randomized controlled trials	AUC = 0.82–0.87	NA	51
HES V2.0, 2025	Hashem B El-Serag	125 HCC + 2206 cirrhosis	Prospective and retrospective cohort study	AUC = 0.77	NA	52

HCC, hepatocellular carcinoma; PIVKA-II, protein induced by vitamin K absence or antagonist-II; AUC, area under the curve; SEN, sensitivity; SPE, specificity; CHB, chronic hepatitis B; CHC, chronic hepatitis C.

sensitivity and specificity across multiple risk strata, achieving a maximum diagnostic accuracy of 91%.[35]

Collectively, these findings underscore a critical limitation of relying solely on serum PIVKA-II levels for early HCC detection. While PIVKA-II remains a robust biomarker, its diagnostic sensitivity and specificity are suboptimal when used in isolation, particularly across diverse clinical contexts. The development and implementation of multi-parametric diagnostic models allow the integration of complementary biological signals, the fine-tuning of diagnostic thresholds, and the minimization of false-negative rates. Such strategies not only address diagnostic blind spots but also provide more precise and individualized evidence to inform clinical decision-making regarding early detection and therapeutic intervention in HCC.

Distinguishing HCC from intrahepatic cholangiocarcinoma (ICC)

Primary liver cancer encompasses a spectrum of malignancies arising from hepatocytes or epithelial cells of the intrahepatic bile ducts and periductal glands, including HCC, ICC, and combined hepatocellular-cholangiocarcinoma (HCC-ICC).[55] Although ICC is less prevalent than HCC, it is characterized by an aggressive clinical course and poor prognosis. Its incidence has increased markedly in recent years, yet its precise etiological mechanisms remain poorly understood. Accurate differentiation between HCC and ICC is therefore critical for guiding first-line treatment and optimizing patient outcomes.[56] In a multicenter study, Bu *et al*. reported that at the commonly recommended threshold of 40.00 mAU/mL, the serum PIVKA-II positivity rate among ICC patients was 30.12%,[30] suggesting a potential but limited diagnostic role for PIVKA-II in ICC. To address diagnostic challenges arising from overlapping biomarker profiles, Si *et al*. developed a clinically applicable nomogram that integrates multiple serum indicators, including PIVKA-II, AFP, carbohydrate antigen (CA) 19-9, and CA125, significantly improving diagnostic accuracy in distinguishing HCC from ICC.[57] Subsequent analysis by the same research group revealed a synergistic interaction between PIVKA-II and HBV status: elevated PIVKA-II levels in HBV-positive patients were more indicative of HCC, whereas low PIVKA-II levels combined with the presence of elevated CA19-9 favored a diagnosis of ICC. Similarly, Huang *et al*. proposed a PIVKA-II-based composite diagnostic model, further confirming the clinical utility of the marker in differentiating HCC from ICC.[58] Despite accumulating clinical evidence

supporting the role of PIVKA-II in distinguishing subtypes of primary liver cancers, the mechanistic basis underlying its differential expression in HCC and ICC remains incompletely understood. Continued investigation is warranted to elucidate the biological determinants of PIVKA-II specificity, with the ultimate goal of refining diagnostic strategies and improving the precision of liver cancer classification in clinical practice.

Efficacy assessment and prognosis analysis

PIVKA-II has emerged as a clinically important biomarker for HCC, demonstrating value not only in early diagnosis but also in predicting treatment efficacy and prognosis.

The management of HCC has entered a phase of increasing therapeutic diversification, encompassing liver transplantation, hepatic resection, ablation therapy, endovascular intervention, radiotherapy, and systemic anticancer treatments. Within this evolving landscape, PIVKA-II serves as a valuable indicator of tumor biology and treatment response. The AASLD associates high serum levels (≥400 mAU/mL) with increased tumor burden and vascular invasion,[40] whereas the EASL recognizes biomarker dynamics as supportive indicators of immunotherapy response.[27] The Korean Liver Cancer Association further incorporates preoperative PIVKA-II elevation into the MoRAL score to guide transarterial chemoembolization strategies.[59] Several predictive models have reinforced the clinical value of PIVKA-II. Wu *et al*. demonstrated that combining PIVKA-II with computed tomography radiomics and laboratory parameters, including AFP, enabled accurate preoperative assessment of tumor grade, with an AUC of 0.926.[60] Similarly, Xu developed a nomogram incorporating PIVKA-II and tumor burden scores to predict microvascular invasion, thereby optimizing surgical decision-making.[61] Feng further substantiated the diagnostic utility of PIVKA-II in AFP-NHCC, reporting an AUC of 0.76 and strong associations with tumor size, differentiation, and metastasis.[62] A systematic review corroborated the predictive value of the combined product of PIVKA-II and AFP (P*A ≥ 1,600) as a robust marker of tumor invasiveness in early-stage HCC, aiding in treatment selection between surgical resection and radiofrequency ablation.[63] Moreover, studies have shown that integrating PIVKA-II levels with tumor burden subclassification systems enhances prognostic stratification in HCC patients undergoing transarterial chemoembolization, with PIVKA-II concentrations ≥ 150 mAU/mL independently predicting poorer overall survival.[64] Dynamic changes in PIVKA-II also carry significant prognostic implications across therapeutic modalities. Sun reported that HCC patients receiving anti-PD-1 therapy who achieved >50% reductions in PIVKA-II had higher objective response rates.[65] In patients treated with atezolizumab plus bevacizumab, baseline PIVKA-II levels ≥ 186 mAU/mL were associated with shorter survival.[66] Unome similarly observed that patients who failed to achieve a decline in PIVKA-II levels (ΔPIVKA-II ≥ 0%) within three months after treatment exhibited significantly reduced survival.[67] Emerging evidence also implicates elevated PIVKA-II expression in resistance to targeted therapies. Cui revealed that PIVKA-II can antagonize the inhibitory effect of gefitinib in HCC by enhancing epidermal growth factor receptor and c-Met signaling, thereby contributing to therapeutic resistance.[68] In patients undergoing sorafenib therapy, Nakano reported that high baseline PIVKA-II levels predicted significantly decreased survival, with persistent PIVKA-II elevation during treatment correlating with disease progression.[69] Likewise, Saeki proposed that in the setting of lenvatinib administration, a failure to achieve a ≥40% decline in PIVKA-II within one month could serve as an early indicator of non-responsiveness, emphasizing the importance of dynamic biomarker monitoring.[70] In a multimodal therapeutic approach combining stereotactic body radiotherapy, immunotherapy, and targeted therapy, Zhang found that patients exhibiting early PIVKA-II reductions of ≥70% attained a median progression-free survival of 15.6 months, with concurrent AFP dynamics further enhancing the identification of high-risk subgroups.[71] Furthermore, Chen demonstrated that in AFP-NHCC, the combination of PIVKA-II and gene mutation profiles outperformed AFP alone as a biomarker for therapeutic response monitoring.[38] Beyond efficacy prediction, PIVKA-II levels have been associated with immunotherapy safety profiles. Chon reported that patients with elevated baseline PIVKA-II were more susceptible to grade ≥3 adverse events, such as hypertension, and exhibited increased rates of treatment discontinuation.[66] Finally, Unome highlighted that persistently elevated PIVKA-II levels were associated with accelerated hepatic functional decline, necessitating timely adjustments in therapeutic regimens.[67]

A growing body of evidence has substantiated the high sensitivity of PIVKA-II for pre-treatment diagnosis and pathological grading of HCC, while also underscoring its strong predictive value for postoperative recurrence and long-term survival. Given the inherently poor prognosis and high aggressiveness of HCC, with overall survival ranging from less than three months to over 60 months, accurate prognostic biomarkers are of paramount clinical importance. The AASLD notes that rising PIVKA-II levels after liver transplantation often signal recurrence,[40] whereas the Taiwan Liver Cancer Association recommends its use as a surveillance marker following curative therapy.[28] The Korean Liver Cancer Association links an increase in PIVKA-II after surgery with an early recurrence, especially in cases of microvascular invasion.[59] In a multicenter retrospective study, Zhu demonstrated that postoperative serum PIVKA-II levels were significantly higher in the recurrence group than in the non-recurrence group, and that PIVKA-II outperformed AFP in prediction, particularly among patients with preoperative PIVKA-II negativity.[72] Supporting this, Devillers and colleagues reported in liver transplant recipients that patients with baseline PIVKA-II ≤ 90 mAU/mL and AFP ≤ 8 ng/mL achieved a five-year recurrence-free survival of 100%, underscoring the prognostic utility of dual-biomarker stratification.[73] Zhu further confirmed that after radical resection, median PIVKA-II levels were significantly higher in the non-recurrence group (84.62 vs. 18.76 mAU/mL), and that its diagnostic accuracy, as measured by AUC, was markedly superior to AFP.[72] In a complementary study, Yangdemonstrated that the integration of modified Response Evaluation Criteria in Solid Tumors with dynamic changes in PIVKA-II, specifically an 80% postoperative reduction, enabled accurate prediction of major pathological response and was significantly associated with recurrence-free survival.[74] Additionally, patients with PIVKA-II declines after radiofrequency ablation had lower recurrence rates and longer disease-free survival.[75] In a prospective study, Wang reported that patients with baseline PIVKA-II levels below 26 mAU/mL were more likely to achieve complete remission after transarterial intervention, and that persistent post-treatment declines in PIVKA-II levels were associated with favorable clinical outcomes.[76] Further findings by Gan corroborated these results, showing that patients achieving complete remission after arterial intervention had significantly lower PIVKA-II levels than those with partial remission or progressive disease.[77] Collectively, these findings affirm the potential of PIVKA-II as a reliable biomarker for post-treatment surveillance in HCC, providing critical insights to guide and refine clinical management strategies aimed at improving patient prognosis (Table 2).[38,60–77]

Table 2. PIVKA-II in HCC efficacy assessment and prognostic analysis

Researcher	Time	Treatment	Predicted outcome	Cut-off value	References
Meng Wu	2025	Hepatic resection in 108 HCC	PIVKA-II, combined with CT imaging, histology, and AFP, constructed a model to predict pathological grading, AUC = 0.926	NA	60
Ya-Dan Xu	2025.	Hepatic resection in 605 HCC	PIVKA-II combined with columnar maps of tumor load score predicted preoperative microvascular invasion and guided the choice of treatment options, AUC = 0.804	NA	61
Honglei Feng	2021.	Hepatic resection in 89 HCC	PIVKA-II levels were broadly correlated with clinicopathological features representing tumor cell dissemination and/or poor prognosis, $P < 0.01$. PIVKA-II can be used to evaluate the efficacy of hepatic resection for HCC	NA	62
Ros Wade	2023	Hepatic resection/radiofrequency ablation	PIVKA-II with AFP product ≥ 1600 predicts early HCC invasiveness and guides procedure selection	PIVKA-II * AFP = 1,600	63
Haruki Kimura	2017	Transarterial chemoembolization in 125 HCC	PIVKA-II ≥ 150 mAU/mL is associated with poorer overall survival and accurately predicts prognosis in conjunction with the tumor load subclassification system	PIVKA-II = 150 mAU/mL	64
Xuqi Sun	2021	235 HCC received PD-1 blockade therapy	The objective remission rate was significantly improved in patients with a >50% decrease in PIVKA-II after treatment	ΔPIVKA-II > 50%	65
Young Eun Chon	2023	121 HCC treated with atilizumab + Bevacizumab	Patients with baseline PIVKA-II ≥ 186 mAU/mL had shorter median survival, and patients with high baseline PIVKA-II were more likely to experience grade ≥ 3 adverse events (e.g., hypertension) and had increased rates of treatment interruption	PIVKA-II ≥ 186 mAU/mL	66
Shinji Unome	2022	Systemic antitumor therapy with atilizumab/bevacizumab in 69 HCC	Patients with no decline in PIVKA-II (Δ ≥ 0%) within 3 months of treatment had poorer median survival and faster deterioration of liver function	NA	67
Shuxiang Cui	2015	Basic research, gefitinib-targeted therapy in HCC cell lines	PIVKA-II antagonizes gefitinib efficacy by upregulating the EGFR/c-Met pathway, leading to treatment failure	NA	68
Masahito Nakano	2013	96 HCC treated with sorafenib targeted therapy	Patients with high baseline PIVKA-II had a short median survival of less than 11.6 months, with persistent elevations during treatment, suggesting tumor progression	NA	69
Issei Saeki	2020	70 HCC treated with targeted therapy with lenvatinib	Failure to decrease PIVKA-II by ≥40% within 1 month of treatment allows early identification of non-responders	ΔPIVKA-II by ≥40%	70
Teng Zhang	2024	115 HCC treated with stereotactic radiotherapy combined with immunotherapy and targeted therapy	Early PIVKA-II decline ≥ 70% Median progression-free survival of patients 15.6 months	ΔPIVKA-II decline ≥ 70%	71
Muh-Hwa Yang	2025	Combination therapy for 61 AFP-NHCC	PIVKA-II, combined with mutation profiling, replaces AFP as an efficacy monitoring marker	PIVKA-II = 600 mAU/mL	38
WenFeng Zhu	2024	Hepatic resection in 198 HCC	Postoperative PIVKA-II levels were significantly higher in the recurrent group than in the nonrecurrent group, with a diagnostic recurrence AUC = 0.883	NA	72
Monique J C Devillers	2023	121 HCC after liver transplantation (15 recurrences)	PIVKA-II can be used as a predictor of microvascular infiltration in exosomes 100% recurrence-free survival at 5 years in patients with PIVKA-II ≤ 90 mAU/mL and AFP ≤ 8 ng/mL	PIVKA-II ≤ 90 mAU/mL	73
Bin Song	2025	Hepatic Resection or Liver Transplantation in 112 HCC	PIVKA-II dynamic decline predicts pathologic remission and recurrence-free survival	NA	74
Zusheng Yu	2021	98 HCC treated with radiofrequency ablation	Patients with reduced PIVKA-II levels had lower recurrence rates and longer disease-free survival	NA	75
Sungyin Wang	2022	46 HCC treated with transarterial intervention	Patients with baseline PIVKA-II < 26 mAU/mL were more likely to achieve complete remission, and sustained decline after treatment was associated with a favorable prognosis	PIVKA-II < 26 mAU/mL	76
Dan Gou	2025	Transarterial intervention in 93 HCC + 101 healthy	PIVKA-II levels were significantly lower in patients in complete remission than in patients in partial remission or progression	NA	77

HCC, hepatocellular carcinoma; PIVKA-II, protein induced by vitamin K absence or antagonist-II; AFP, alpha-fetoprotein; AUC, area under the curve; PD-1, programmed cell death-1; AFP-NHCC, alpha-fetoprotein-negative hepatocellular carcinoma.

Comparative analysis of PIVKA-II and other biomarkers

Following the discussion of the clinical value of PIVKA-II, it is essential to compare it directly with other established and emerging biomarkers to more comprehensively evaluate its potential across diverse clinical contexts. AFP remains the most widely used biomarker for HCC; however, its sensitivity in early-stage disease is limited, with approximately 30%–40% of patients testing negative for AFP.[78] In such cases, PIVKA-II serves as a valuable complementary marker. Unlike PIVKA-II, AFP performs poorly in HCC arising from alcoholic liver disease or NAFLD,[35] and its levels are easily confounded by non-tumor factors, which reduces diagnostic accuracy and limits its utility for monitoring therapeutic response.[79] AFP-L3, a glycosylated isoform of AFP, achieves approximately 95.05% specificity when AFP is only mildly elevated; however, its sensitivity remains inferior to that of PIVKA-II.[80] Persistently high AFP-L3 levels are strongly associated with recurrence and poor prognosis after curative treatment; however, its dynamic changes are heavily influenced by overall AFP concentrations, making it more suitable as an auxiliary indicator.[81] Glypican-3 (GPC3), a tumor-associated antigen, demonstrates high sensitivity at the tissue level and reflects tumor burden. Nonetheless, its specificity is relatively low (29.2%),[82] which limits its ability to distinguish malignant from benign lesions as precisely as PIVKA-II, and its diagnostic value for early or small tumors remains inadequate. Circulating GPC3 is, therefore, more often used as an adjunct to imaging rather than a stand-alone screening tool. For instance, stratifying patients into high- and low-risk groups using a serum threshold of 0.124 ng/mL yields three-year overall survival rates of 38.0% and 62.9%, respectively (P = 0.011), underscoring its ability to reflect tumor biology but not other key prognostic determinants, such as liver function or treatment modality.[36] The neutrophil-to-lymphocyte ratio (NLR), though not tumor-specific, represents a simple, inexpensive, and reproducible marker of systemic inflammation with prognostic value in HCC.[83] It has demonstrated clinical utility in preoperative risk stratification and postoperative management of patients undergoing liver resection.[84] Importantly, across multiple etiological contexts, including alcoholic liver disease, NAFLD, and HBV infection, NLR has been shown to dynamically reflect disease activity in unresectable HCC.[85] Taken together, AFP and PIVKA-II remain the cornerstones of routine screening and surveillance; AFP-L3 enhances specificity in patients with intermediate AFP levels; GPC3 provides supplementary diagnostic and therapeutic insights; and NLR offers complementary prognostic information. Through this head-to-head comparison, PIVKA-II demonstrates relative advantages in early detection, applicability across diverse etiological backgrounds, and monitoring of treatment responses, thereby reinforcing its central role in the clinical management of HCC.

Nevertheless, several important challenges remain. The diagnostic performance of PIVKA-II varies across tumor sizes, disease etiologies, and geographic populations, highlighting the absence of consensus on optimal thresholds and assay standardization. Its limited specificity in distinguishing HCC from ICC further underscores the need for composite diagnostic models. At the mechanistic level, the reasons why PIVKA-II is selectively elevated in HCC but less so in ICC remain unclear, thereby constraining efforts to refine biomarker-based classification strategies. From a clinical standpoint, harmonized cut-off values, standardized assay methodologies, and validation across diverse populations are urgently required. In summary, PIVKA-II has evolved from a serological anomaly into a cornerstone biomarker for the diagnosis, prognosis, and monitoring of HCC. However, it should not be regarded as a stand-alone indicator; its greatest value lies in integration with complementary serum markers, imaging modalities, and clinical parameters to advance precision oncology. Future efforts integrating biological insights with clinical validation will determine whether PIVKA-II remains a supportive biomarker or emerges as a transformative element in HCC management.

Shortcomings and future prospects

Detection method

In 1985, Motohara pioneered an enzyme-linked immunosorbent assay (ELISA)-based method for PIVKA-II detection, achieving a sensitivity of 0.13 U/mL[2]. Currently, immunoassay techniques remain the cornerstone of PIVKA-II quantification, encompassing ELISA, chemiluminescent enzyme immunoassay (CLEIA), and electrochemiluminescent immunoassay. Guariglia compared a novel ELISA platform (AssayGenie) and the conventional CLEIA system (Fujirebio), revealing a strong correlation in serum PIVKA-II measurements among HCC patients. Both assays also demonstrated independent prognostic value for patient survival. Notably, ELISA exhibited superior cost-effectiveness, making it more suitable for routine clinical application.[75,86] In parallel, Jabor assessed the biological variability of PIVKA-II in healthy individuals using an automated electrochemiluminescent immunoassay platform (Roche Elecsys) and verified that its analytical performance met established clinical standards.[87] Nonetheless, conventional PIVKA-II assays remain susceptible to confounding factors such as vitamin K deficiency, anticoagulant therapy (e.g., warfarin), and underlying liver conditions (e.g., cirrhosis), which may result in false-positive or false-negative findings. Additionally, inter-method variability poses interpretative challenges. For instance, median PIVKA-II concentrations measured by CLEIA (197 mAU/mL) were markedly higher than those obtained by ELISA (118 ng/mL), potentially affecting clinical decision-making and diagnostic accuracy.[86] To overcome these limitations and further improve the sensitivity and specificity of PIVKA-II detection, the development of advanced sensor technologies and next-generation assay platforms represents a promising direction for future research, with the potential to enhance serological support for diagnosis, prognosis, and therapeutic monitoring.

PIVKA-II in non-HCC diseases

PIVKA-II, although well established as a biomarker for HCC, can also be affected by a spectrum of non-HCC conditions, including hepatic disorders, gallbladder cancer, pancreatic cancer, and chronic kidney disease. These findings suggest the potential to define novel diagnostic thresholds and prognostic associations beyond HCC. Honda *et al*. reported that in patients with non-HCC liver diseases such as hepatitis B, hepatitis C, and autoimmune hepatitis, serum PIVKA-II levels correlated significantly with Child-Pugh scores, bone metabolism (e.g., low-carboxylated osteocalcin), and muscle function assessed by the SARC-F score. These findings imply that multisystemic diseases may indirectly modulate PIVKA-II concentrations through alterations in vitamin K metabolism and suggest that PIVKA-II assessment could aid in evaluating both disease severity and bone–muscle metabolic status in liver disease.[88] Maruyama further demonstrated that hepatic hemangiomas were associated with elevated serum PIVKA-II levels, which correlated with both lesion size and coagulation abnormalities. This elevation was attributed to increased production of prothrombin precursors, driven by

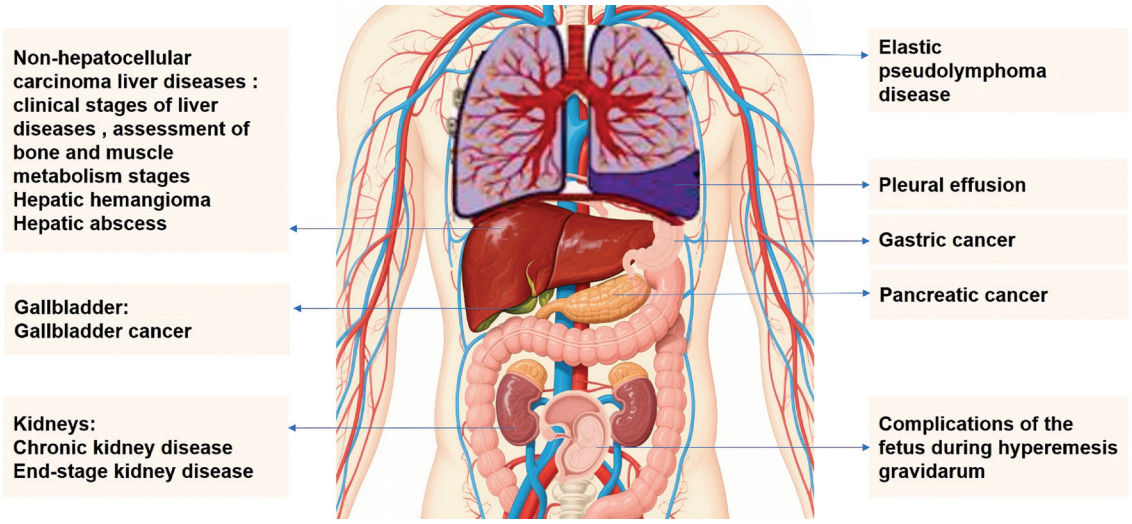

Fig. 3. PIVKA-II in non-HCC diseases. PIVKA-II, protein induced by vitamin K absence or antagonist-II; HCC, Hepatocellular carcinoma.

enhanced coagulation-fibrinolysis activity within the hemangioma.[89] Hsu *et al*. further reported that although abscess size was not correlated with PIVKA-II levels, the biomarker may have predictive value for treatment response in suppurative liver abscesses, which is an association warranting further validation.[90]

With the continued advancement of clinical research, the application of PIVKA-II testing has expanded beyond hepatic pathology, demonstrating promising diagnostic and prognostic utility in a range of extrahepatic malignancies and non-hepatic diseases, including renal disorders. This broadening scope not only enhances the clinical value of PIVKA-II but also introduces novel molecular targets and research directions for multidisciplinary diagnostic and therapeutic strategies. Liu *et al*. reported that patients with gallbladder cancer had significantly higher serum PIVKA-II levels than those with benign gallbladder disease or healthy controls, with concentrations positively correlating with both TNM stage and tumor differentiation. These findings support its role as a biomarker for tumor burden and aggressiveness.[91] Kudo reported a case of gastric cancer with co-expression of PIVKA-II and AFP, suggesting that certain gastrointestinal tumors may secrete PIVKA-II through mechanisms of 'liver-like differentiation'.[92] Expanding on this, Wang demonstrated that PIVKA-II, when combined with CA19-9 and CEA, achieved a high positive detection rate (94.59%) for pancreatic cancer, indicating its potential value in complementing conventional markers.[93] Tartaglione further confirmed that PIVKA-II levels were significantly higher in patients with pancreatic ductal adenocarcinoma than in those with benign pancreatic conditions and that its diagnostic performance surpassed CA19-9, the current standard marker.[94] Farina extended these findings, showing that elevated PIVKA-II in patients with pancreatic ductal adenocarcinoma was associated with epithelial-mesenchymal transition, thereby implicating it in tumor progression and metastatic potential.[95] Beyond malignancy, Nyvad reported that chronic kidney disease is frequently accompanied by elevated PIVKA-II levels, attributed to disruptions in vitamin K metabolism.[96] Similarly, Caluwé documented widespread vitamin K deficiency in patients with end-stage renal disease, resulting in concomitant elevations of both PIVKA-II and desphospho-uncarboxylated matrix Gla protein, thereby underscoring the systemic impact of vitamin K-dependent biomarker dysregulation in renal pathology.[97] Aleksiev observed elevated PIVKA-II levels in patients with pleural effusion; however, its diagnostic specificity for distinguishing benign from malignant etiologies remains limited, thereby constraining its utility in pleural disease stratification.[98] A high prevalence of vitamin K deficiency has also been reported in ICU patients, significantly influencing PIVKA-II levels. As highlighted in the review by Paulus, vitamin K deficiency leads to increased PIVKA-II concentrations, reinforcing its role as a sensitive indicator of vitamin K status in critically ill populations.[99] Miyamoto further established PIVKA-II as a highly sensitive biomarker for diagnosing elastic pseudohypoparathyroidism, a rare disorder characterized by multiple coagulation factors, in which vitamin K supplementation may provide therapeutic benefit.[100] In obstetric complications, Ouchi demonstrated that dynamic monitoring of vitamin K deficiency via PIVKA-II, combined with timely vitamin K supplementation, may contribute to preventing fetal complications associated with severe hyperemesis gravidarum, underscoring its clinical relevance beyond hepatic and oncologic contexts (Fig. 3).[101]

In clinical practice, accurate interpretation of PIVKA-II levels requires a comprehensive, multidisciplinary assessment that integrates patient history, imaging findings, and additional tumor biomarkers. Dynamic monitoring of serum PIVKA-II is essential to evaluate temporal trends and should be conducted in parallel with liver function tests and, when indicated, pathological biopsy results. Such an integrative approach is critical to exclude potential confounding factors, including disturbances in vitamin K metabolism, biliary tract disorders, chronic hepatic injury, and other non-malignant conditions that may contribute to elevated PIVKA-II levels. This strategy significantly mitigates the risk of misdiagnosis or missed diagnosis stemming from isolated abnormal test results, thereby enhancing the diagnostic precision and clinical reliability in the context of HCC detection and management.

Future prospects

The rapid evolution of information technology has facilitated the integration of PIVKA-II with artificial intelligence (AI) and deep learning, offering novel strategies to address long-standing challenges in the early diagnosis and prognostic as-

sessment of HCC. Zhu *et al*. introduced a diagnostic platform based on electro-hydrodynamic dielectric digital microfluidics capable of quantitatively detecting serum biomarkers, including PIVKA-II, thereby providing a rapid, cost-effective, and clinically accessible tool for early HCC detection, particularly in primary healthcare settings.[102] Building on this, Wang *et al*. developed a machine learning-based risk prediction model incorporating PIVKA-II and other serum markers to enhance diagnostic accuracy.[103] Similarly, Yang *et al*. created an online predictive calculator using PIVKA-II for HCC detection in patients with chronic hepatitis B, supporting timely clinical intervention.[104] Li further advanced the field by designing a non-invasive diagnostic model powered by an AI neural network system, integrating PIVKA-II as a key feature to distinguish early-stage HCC from cirrhosis with high fidelity.[105] Collectively, these AI-driven approaches have improved both the sensitivity and specificity of early HCC diagnosis and facilitated more personalized treatment strategies. The integration of PIVKA-II into next-generation digital platforms represents a transformative step toward biomarker-driven early warning and precision diagnostics for HCC.

Despite substantial advances in PIVKA-II quantification through immunoassays, several challenges persist. Analytical variability across platforms, susceptibility to confounding factors—such as vitamin K deficiency, anticoagulant therapy, and chronic liver diseases—and inconsistent cut-off standardization continue to limit diagnostic reliability. Moreover, elevated PIVKA-II levels in non-HCC conditions complicate interpretation and emphasize the need for multidisciplinary assessment integrating clinical history, imaging, and complementary biomarkers. These limitations caution against reliance on PIVKA-II as a stand-alone marker but also suggest the potential for novel applications in assessing multisystemic disease severity and prognosis. Looking forward, incorporation of PIVKA-II into AI- and machine learning-based diagnostic models, together with next-generation biosensing technologies, holds promise for improving sensitivity, specificity, and early detection of HCC. However, mechanistic understanding of its regulation in both hepatic and extrahepatic contexts, standardization across diverse populations, and rigorous clinical validation remain unresolved challenges. Addressing these issues will be essential to fully realize the role of the biomarker in precision oncology and broader clinical applications.

Conclusions

PIVKA-II has emerged as a pivotal serum biomarker with significant translational potential in both fundamental research and clinical management of HCC. Mechanistic studies have elucidated the role of PIVKA-II in tumorigenesis, including its interactions with the tumor microenvironment, promotion of angiogenesis, and modulation of immune responses, offering critical insights into early diagnostic strategies and the development of targeted therapies. A growing body of clinical evidence has substantiated the utility of PIVKA-II in diverse aspects of HCC care, including population-based screening, diagnosis, staging, prognosis evaluation, and postoperative surveillance. Particularly noteworthy is its diagnostic superiority in AFP-NHCC cases and its ability to differentiate HCC from ICC, thereby augmenting diagnostic precision in clinical settings. Despite considerable progress, current research on PIVKA-II has not fully addressed its role in the immune microenvironment and metabolic reprogramming of HCC. In addition, its clinical validation remains limited in non-HBV-related populations. Key areas requiring further investigation include inter-population variability in diagnostic sensitivity and specificity, optimization of biomarker panels for combinatorial use, and deeper exploration of the role of PIVKA-II in the context of immunotherapies and molecularly targeted interventions. Future research should prioritize the integration of multi-omics profiling, AI-assisted diagnostic frameworks, and large-scale, multicenter clinical validation to enhance generalizability and clinical utility. The convergence of AI and deep learning with dynamic PIVKA-II profiling holds the potential to revolutionize early detection, pathological grading, and individualized therapeutic strategies for HCC. Monitoring the dynamic changes of PIVKA-II within intelligent diagnostic platforms may not only broaden its clinical applicability but also catalyze the expansion of the molecular biomarker repertoire for comprehensive disease monitoring and precision oncology.

Funding

Key R&D Projects of the Department of Science and Technology of Shanxi Province (201903D421056).

Conflict of interest

The authors have no conflicts of interest related to this publication.

Author contributions

Manuscript writing (XZ) and critical revision (RW, BN, LZ). All authors have approved the final version and publication of the manuscript.

References

[1] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, *et al*. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024;74(3):229–263. doi:10.3322/caac.21834, PMID:38572751.
[2] Motohara K, Endo F, Matsuda I. Effect of vitamin K administration on acarboxy prothrombin (PIVKA-II) levels in newborns. Lancet 1985;2(8449):242–244. doi:10.1016/s0140-6736(85)90291-0, PMID:2862419.
[3] Yu D, Chen H, Wang L. Emerging Trends in Neoadjuvant Immunotherapy for Hepatocellular Carcinoma: A Focus on Liver Transplant Candidates. Cancer Rep (Hoboken) 2025;8(7):e70244. doi:10.1002/cnr2.70244, PMID:40682511.
[4] Zhang S, Gao C, Wang Y, Chen L, Gao S. Evaluating the combined diagnostic power of alpha-fetoprotein and protein induced by vitamin K absence or antagonist-II for hepatocellular carcinoma. J Gastrointest Oncol 2025;16(3):1157–1175. doi:10.21037/jgo-2024-863, PMID:40672067.
[5] Liebman HA, Furie BC, Tong MJ, Blanchard RA, Lo KJ, Lee SD, *et al*. Des-gamma-carboxy (abnormal) prothrombin as a serum marker of primary hepatocellular carcinoma. N Engl J Med 1984;310(22):1427–1431. doi:10.1056/NEJM198405313102204, PMID:6201741.
[6] Kim DY, Toan BN, Tan CK, Hasan I, Setiawan L, Yu ML, *et al*. Utility of combining PIVKA-II and AFP in the surveillance and monitoring of hepatocellular carcinoma in the Asia-Pacific region. Clin Mol Hepatol 2023;29(2):277–292. doi:10.3350/cmh.2022.0212, PMID:36710606.
[7] Hemker HC, Veltkamp JJ, Hensen A, Loeliger EA. Nature of Prothrombin Biosynthesis: preprothrombinaemia in vitamin K-Deficiency. Nature 1963;200:589–590. doi:10.1038/200589a0, PMID:14082242.
[8] Niléhn JE, Ganrot PO. Plasma prothrombin during treatment with Dicumarol. I. Immunochemical determination of its concentration in plasma. Scand J Clin Lab Invest 1968;22(1):17–22. doi:10.3109/00365516809160730, PMID:4178912.
[9] Uehara S, Gotoh K, Handa H, Honjo K, Hirayama A. Process of carboxylation of glutamic acid residues in the gla domain of human des-gamma-carboxyprothrombin. Clin Chim Acta 1999;289(1-2):33–44. doi:10.1016/s0009-8981(99)00152-7, PMID:10556651.
[10] Furie B, Furie BC. Molecular basis of vitamin K-dependent gamma-carboxylation. Blood 1990;75(9):1753–1762. PMID:2184900.
[11] Ratcliffe JV, Furie B, Furie BC. The importance of specific gamma-carboxyglutamic acid residues in prothrombin. Evaluation by site-specific mutagenesis. J Biol Chem 1993;268(32):24339–24345. PMID:8226983.
[12] Stenflo J. Vitamin K and the biosynthesis of prothrombin. II. Structural comparison of normal and dicoumarol-induced bovine prothrombin. J Biol Chem 1972;247(24):8167–8175. PMID:4118353.
[13] Pozzi N, Chen Z, Gohara DW, Niu W, Heyduk T, Di Cera E. Crystal structure of prothrombin reveals conformational flexibility and mechanism of

activation. J Biol Chem 2013;288(31):22734–22744. doi:10.1074/jbc.M113.466946, PMID:23775088.
[14] Wan Y, Geng X, Liu Q, Lu S, Liu Y, Wang T, *et al*. CTSE inhibits anti-tumor T cell response by promoting des-γ-carboxy prothrombin releasing in hepatocellular carcinoma. Cell Death Dis 2025;16(1):434. doi:10.1038/s41419-025-07753-3, PMID:40467555.
[15] Miyakawa T, Kajiwara Y, Shirahata A, Okamoto K, Itoh H, Ohsato K. Vitamin K contents in liver tissue of hepatocellular carcinoma patients. Jpn J Cancer Res 2000;91(1):68–74. doi:10.1111/j.1349-7006.2000.tb00861.x, PMID:10744046.
[16] Suzuki M, Shiraha H, Fujikawa T, Takaoka N, Ueda N, Nakanishi Y, *et al*. Des-gamma-carboxy prothrombin is a potential autologous growth factor for hepatocellular carcinoma. J Biol Chem 2005;280(8):6409–6415. doi:10.1074/jbc.M406714200, PMID:15582995.
[17] Gao J, Feng X, Inagaki Y, Song P, Kokudo N, Hasegawa K, *et al*. Des-γ-carboxy prothrombin and c-Met were concurrently and extensively expressed in hepatocellular carcinoma and associated with tumor recurrence. Biosci Trends 2012;6(4):153–159. doi:10.5582/bst.2012.v6.4.153, PMID:23006961.
[18] Zhang YS, Chu JH, Cui SX, Song ZY, Qu XJ. Des-γ-carboxy prothrombin (DCP) as a potential autologous growth factor for the development of hepatocellular carcinoma. Cell Physiol Biochem 2014;34(3):903–915. doi:10.1159/000366308, PMID:25200250.
[19] Yue P, Gao ZH, Xue X, Cui SX, Zhao CR, Yuan Y, *et al*. Des-γ-carboxyl prothrombin induces matrix metalloproteinase activity in hepatocellular carcinoma cells by involving the ERK1/2 MAPK signalling pathway. Eur J Cancer 2011;47(7):1115–1124. doi:10.1016/j.ejca.2011.01.017, PMID:21349701.
[20] Dong L, Qiu X, Gao F, Wang K, Xu X. Protein induced by vitamin K absence or antagonist II: Experience to date and future directions. Biochim Biophys Acta Rev Cancer 2023;1878(6):189016. doi:10.1016/j.bbcan.2023.189016, PMID:37944832.
[21] Saito M, Yano Y, Hirano H, Momose K, Mouri K, Hishimoto A, *et al*. The serum level of NX-DCP-R, but not DCP, is not increased in alcoholic liver disease without hepatocellular carcinoma. Cancer Biomark 2016;16(1):171–180. doi:10.3233/CBM-150553, PMID:26600398.
[22] Kurokawa T, Yamazaki S, Mitsuka Y, Moriguchi M, Sugitani M, Takayama T. Prediction of vascular invasion in hepatocellular carcinoma by next-generation des-r-carboxy prothrombin. Br J Cancer 2016;114(1):53–58. doi:10.1038/bjc.2015.423, PMID:26679378.
[23] Zhou Z, Liu Q, Liu J, Li W, Cao S, Xu J, *et al*. Research progress of protein induced by vitamin K absence or antagonist II in liver transplantation for hepatocellular carcinoma. Heliyon 2024;10(9):e30622. doi:10.1016/j.heliyon.2024.e30622, PMID:38726103.
[24] Yamazaki S, Takayama T, Kurokawa T, Shimamoto N, Mitsuka Y, Yoshida N, *et al*. Next-generation des-r-carboxy prothrombin for immunohistochemical assessment of vascular invasion by hepatocellular carcinoma. BMC Surg 2020;20(1):201. doi:10.1186/s12893-020-00862-0, PMID:32928172.
[25] Department of Medical Administration, National Health Commission of the People's Republic of China. Guideline for diagnosis and treatment of primary liver cancer (2024). Zhonghua Xue Ye Xue Za Zhi 2024;23(4):429–478. doi:10.3760/cma.j.cn115610-20240415-00203.
[26] Kudo M, Kawamura Y, Hasegawa K, Tateishi R, Kariyama K, Shiina S, *et al*. Management of Hepatocellular Carcinoma in Japan: JSH Consensus Statements and Recommendations 2021 Update. Liver Cancer 2021;10(3):181–223. doi:10.1159/000514174, PMID:34239808.
[27] European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatocellular carcinoma. J Hepatol 2025;82(2):315–374. doi:10.1016/j.jhep.2024.08.028, PMID:39690085.
[28] Lee IC, Wang HW, Teng W, Lin TJ, Chen CH, Lai HC, *et al*. Taiwan Liver Cancer Association Management Consensus Guidelines for Intermediate Stage Hepatocellular Carcinoma. Clin Mol Hepatol 2025;31(4):1213–1232. doi:10.3350/cmh.2025.0724, PMID:40755008.
[29] Guarneri V, Loggi E, Ramacieri G, Serra C, Vukotic R, Vitale G, *et al*. Diagnostic Performance of PIVKA-II in Italian Patients with Hepatocellular Carcinoma. Cancers (Basel) 2025;17(2):167. doi:10.3390/cancers17020167, PMID:39857948.
[30] Bu H, Luo W, Tao W, Dong C, Wang M, Ye X, *et al*. A Large-Scale Retrospective Study of Serum Des-Gamma-Carboxy Prothrombin as a Diagnostic Marker of HCC: Effect of Liver Function on Specificity. J Clin Lab Anal 2025;39(10):e70025. doi:10.1002/jcla.70025, PMID:40230049.
[31] Su TH, Peng CY, Chang SH, Tseng TC, Liu CJ, Chen CL, *et al*. Serum PIVKA-II and alpha-fetoprotein at virological remission predicts hepatocellular carcinoma in chronic hepatitis B related cirrhosis. J Formos Med Assoc 2022;121(3):703–711. doi:10.1016/j.jfma.2021.08.003, PMID:34452785.
[32] Caviglia GP, Fariselli P, D'Ambrosio R, Colombatto P, Degasperi E, Ricco G, *et al*. Development and Validation of a PIVKA-II-Based Model for HCC Risk Stratification in Patients With HCV-Related Cirrhosis Successfully Treated With DAA. Aliment Pharmacol Ther 2025;61(3):538–549. doi:10.1111/apt.18409, PMID:39569574.
[33] Degasperi E, Perbellini R, D'Ambrosio R, Uceda Renteria SC, Ceriotti F, Perego A, *et al*. Prothrombin induced by vitamin K absence or antagonist-II and alpha foetoprotein to predict development of hepatocellular carcinoma in Caucasian patients with hepatitis C-related cirrhosis treated with direct-acting antiviral agents. Aliment Pharmacol Ther 2022;55(3):350–359. doi:10.1111/apt.16685, PMID:34738664.
[34] Beale G, Chattopadhyay D, Gray J, Stewart S, Hudson M, Day C, *et al*. AFP, PIVKAII, GP3, SCCA-1 and follisatin as surveillance biomarkers for hepatocellular cancer in non-alcoholic and alcoholic fatty liver disease. BMC Cancer 2008;8:200. doi:10.1186/1471-2407-8-200, PMID:18638391.
[35] Mi K, Ye T, Zhu L, Pan CQ. Risk-stratified hepatocellular carcinoma surveillance in non-cirrhotic patients with MASLD. Gastroenterol Rep (Oxf) 2025;13:goaf018. doi:10.1093/gastro/goaf018, PMID:39980834.
[36] Lin Y, Ma Y, Chen Y, Huang Y, Lin J, Xiao Z, *et al*. Diagnostic and prognostic performance of serum GPC3 and PIVKA-II in AFP-negative hepatocellular carcinoma and establishment of nomogram prediction models. BMC Cancer 2025;25(1):721. doi:10.1186/s12885-025-14025-y, PMID:40247208.
[37] Ji J, Wang H, Li Y, Zheng L, Yin Y, Zou Z, *et al*. Diagnostic Evaluation of Des-Gamma-Carboxy Prothrombin versus α-Fetoprotein for Hepatitis B Virus-Related Hepatocellular Carcinoma in China: A Large-Scale, Multicentre Study. PLoS One 2016;11(4):e0153227. doi:10.1371/journal.pone.0153227, PMID:27070780.
[38] Chen SC, Ho HL, Liu CA, Hung YP, Chiang NJ, Chen MH, *et al*. PIVKA-II as a surrogate biomarker for therapeutic response in Non-AFP-secreting hepatocellular carcinoma. BMC Cancer 2025;25(1):199. doi:10.1186/s12885-025-13568-4, PMID:39905360.
[39] Sagar VM, Herring K, Curbishley S, Hodson J, Fletcher P, Karkhanis S, *et al*. The potential of PIVKA-II as a treatment response biomarker in hepatocellular carcinoma: a prospective United Kingdom cohort study. Oncotarget 2021;12(24):2338–2350. doi:10.18632/oncotarget.28136, PMID:34853657.
[40] Singal AG, Llovet JM, Yarchoan M, Mehta N, Heimbach JK, Dawson LA, *et al*. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology 2023;78(6):1922–1965. doi:10.1097/HEP.0000000000000466, PMID:37199193.
[41] Johnson PJ, Pirrie SJ, Cox TF, Berhane S, Teng M, Palmer D, *et al*. The detection of hepatocellular carcinoma using a prospectively developed and validated model based on serological biomarkers. Cancer Epidemiol Biomarkers Prev 2014;23(1):144–153. doi:10.1158/1055-9965.EPI-13-0870, PMID:24220911.
[42] Marsh TL, Parikh ND, Roberts LR, Schwartz ME, Nguyen MH, Befeler A, *et al*. A Phase 3 Biomarker Validation of GALAD for the Detection of Hepatocellular Carcinoma in Cirrhosis. Gastroenterology 2025;168(2):316–326.e6. doi:10.1053/j.gastro.2024.09.008, PMID:39293548.
[43] Hou J, Berg T, Vogel A, Piratvisuth T, Trojan J, De Toni EN, *et al*. Comparative evaluation of multimarker algorithms for early-stage HCC detection in multicenter prospective studies. JHEP Rep 2025;7(2):101263. doi:10.1016/j.jhepr.2024.101263, PMID:39897614.
[44] Chan HLY, Hu Y, Malinowsky K, Madin K, Kroeniger K, Hou J, *et al*. Prospective appraisal of clinical diagnostic algorithms for hepatocellular carcinoma surveillance in Chinese patients with chronic hepatitis B infection. Sci Rep 2024;14(1):28996. doi:10.1038/s41598-024-80257-w, PMID:39578653.
[45] Huang C, Xiao X, Tong L, Gao Z, Ji J, Zhou L, *et al*. Risks and Clinical Predictors of Hepatocellular Carcinoma in Chinese Populations: A Real-World Study of 10,359 Patients in Six Medical Centers. J Hepatocell Carcinoma 2024;11:411–425. doi:10.2147/JHC.S447700, PMID:38435681.
[46] Ren T, Hou X, Zhang X, Chen D, Li J, Zhu Y, *et al*. Validation of combined AFP, AFP-L3, and PIVKA II for diagnosis and monitoring of hepatocellular carcinoma in Chinese patients. Heliyon 2023;9(11):e21906. doi:10.1016/j.heliyon.2023.e21906, PMID:38028013.
[47] Li L, Lu F, Chen P, Song H, Xu W, Guo J, *et al*. Validation of the GALAD model and establishment of a new model for HCC detection in Chinese patients. Front Oncol 2022;12:1037742. doi:10.3389/fonc.2022.1037742, PMID:36620588.
[48] Piratvisuth T, Hou J, Tanwandee T, Berg T, Vogel A, Trojan J, *et al*. Development and clinical validation of a novel algorithmic score (GAAD) for detecting HCC in prospective cohort studies. Hepatol Commun 2023;7(11):e0317. doi:10.1097/HC9.0000000000000317, PMID:37938100.
[49] Liu M, Wu R, Liu X, Xu H, Chi X, Wang X, Zhan M, *et al*. Validation of the GALAD Model and Establishment of GAAP Model for Diagnosis of Hepatocellular Carcinoma in Chinese Patients. J Hepatocell Carcinoma 2020;7:219–232. doi:10.2147/JHC.S271790, PMID:33123501.
[50] Maneenil C, Sripongpun P, Chamroonkul N, Tantisaranon P, Jarumanokul R, Samaeng M, *et al*. Comparative performance of the GAAD and ASAP scores in predicting early-stage hepatocellular carcinoma. Gastroenterol Rep (Oxf) 2025;13:goaf074. doi:10.1093/gastro/goaf074, PMID:40746370.
[51] Fan R, Papatheodoridis G, Sun J, Innes H, Toyoda H, Xie Q, *et al*. aMAP risk score predicts hepatocellular carcinoma development in patients with chronic hepatitis. J Hepatol 2020;73(6):1368–1378. doi:10.1016/j.jhep.2020.07.025, PMID:32707225.
[52] El-Serag HB, Jin Q, Tayob N, Salem E, Luster M, Alsarraj A, *et al*. HES V2.0 outperforms GALAD for detection of HCC: A phase 3 biomarker study in the United States. Hepatology 2025;81(2):465–475. doi:10.1097/HEP.0000000000000953, PMID:38899967.
[53] Wang Q, Chen Q, Zhang X, Lu XL, Du Q, Zhu T, *et al*. Diagnostic value of gamma-glutamyltransferase/aspartate aminotransferase ratio, protein induced by vitamin K absence or antagonist II, and alpha-fetoprotein in hepatitis B virus-related hepatocellular carcinoma. World J Gastroenterol 2019;25(36):5515–5529. doi:10.3748/wjg.v25.i36.5515, PMID:31576097.
[54] Chen ZJ, Wang XK, Han CY, He YF, Liang TY, Mo ST, *et al*. Diagnostic value of alpha-fetoprotein and prothrombin induced by vitamin K absence-II in serum, bile, and feces in hepatocellular carcinoma. World J Gastrointest Oncol 2025;17(5):105311. doi:10.4251/wjgo.v17.i5.105311, PMID:40487934.
[55] Moris D, Palta M, Kim C, Allen PJ, Morse MA, Lidsky ME. Advances in the treatment of intrahepatic cholangiocarcinoma: An overview of the current and future therapeutic landscape for clinicians. CA Cancer J Clin 2023;73(2):198–222. doi:10.3322/caac.21759, PMID:36260350.
[56] Ren S, Li Q, Liu S, Qi Q, Duan S, Mao B, *et al*. Clinical Value of Machine Learning-Based Ultrasomics in Preoperative Differentiation Between Hepa-

tocellular Carcinoma and Intrahepatic Cholangiocarcinoma: A Multicenter Study. Front Oncol 2021;11:749137. doi:10.3389/fonc.2021.749137, PMID:34804935.
[57] Si YQ, Wang XQ, Pan CC, Wang Y, Lu ZM. An Efficient Nomogram for Discriminating Intrahepatic Cholangiocarcinoma From Hepatocellular Carcinoma: A Retrospective Study. Front Oncol 2022;12:833999. doi:10.3389/fonc.2022.833999, PMID:35480111.
[58] Huang C, Xu X, Wang M, Xiao X, Cheng C, Ji J, *et al*. Serum N-glycan fingerprint helps to discriminate intrahepatic cholangiocarcinoma from hepatocellular carcinoma. Electrophoresis 2021;42(11):1187–1195. doi:10.1002/elps.202000392, PMID:33570803.
[59] Korean Liver Cancer Association (KLCA) and National Cancer Center (NCC) Korea. 2022 KLCA-NCC Korea practice guidelines for the management of hepatocellular carcinoma. Clin Mol Hepatol 2022;28(4):583–705. doi:10.3350/cmh.2022.0294, PMID:36263666.
[60] Wu M, Yu H, Pang S, Liu A, Liu J. Application of CT-based radiomics combined with laboratory tests such as AFP and PIVKA-II in preoperative prediction of pathologic grade of hepatocellular carcinoma. BMC Med Imaging 2025;25(1):51. doi:10.1186/s12880-025-01588-2, PMID:39962429.
[61] Xu YD, Wang FH, Chen KL, Tang Y, Zhang Q, Han H, *et al*. The value of clinical indicators combined with imaging tumor burden score in predicting microvascular invasion of hepatocellular carcinoma. Clin Hemorheol Microcirc 2025;89(1):123–135. doi:10.3233/CH-242407, PMID:39911121.
[62] 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;21(1):401. doi:10.1186/s12885-021-08138-3, PMID:33849479.
[63] Wade R, South E, Anwer S, Sharif-Hurst S, Harden M, Fulbright H, *et al*. Ablative and non-surgical therapies for early and very early hepatocellular carcinoma: a systematic review and network meta-analysis. Health Technol Assess 2023;27(29):1–172. doi:10.3310/GK5221, PMID:38149643.
[64] Kimura H, Ohkawa K, Miyazaki M, Sakakibara M, Imanaka K, Tamura T, *et al*. Subclassification of patients with intermediate-stage (Barcelona Clinic Liver Cancer stage-B) hepatocellular carcinoma using the up-to-seven criteria and serum tumor markers. Hepatol Int 2017;11(1):105–114. doi:10.1007/s12072-016-9771-0, PMID:27766479.
[65] Sun X, Mei J, Lin W, Yang Z, Peng W, Chen J, *et al*. Reductions in AFP and PIVKA-II can predict the efficiency of anti-PD-1 immunotherapy in HCC patients. BMC Cancer 2021;21(1):775. doi:10.1186/s12885-021-08428-w, PMID:34218801.
[66] Chon YE, Cheon J, Kim H, Kang B, Ha Y, Kim DY, *et al*. Predictive biomarkers of survival in patients with advanced hepatocellular carcinoma receiving atezolizumab plus bevacizumab treatment. Cancer Med 2023;12(3):2731–2738. doi:10.1002/cam4.5161, PMID:35997637.
[67] Unome S, Imai K, Takai K, Miwa T, Hanai T, Nishigaki Y, *et al*. Changes in ALBI Score and PIVKA-II within Three Months after Commencing Atezolizumab Plus Bevacizumab Treatment Affect Overall Survival in Patients with Unresectable Hepatocellular Carcinoma. Cancers (Basel) 2022;14(24):6089. doi:10.3390/cancers14246089, PMID:36551574.
[68] Cui SX, Zhang YS, Chu JH, Song ZY, Qu XJ. Des-gamma-carboxy prothrombin (DCP) antagonizes the effects of gefitinib on human hepatocellular carcinoma cells. Cell Physiol Biochem 2015;35(1):201–212. doi:10.1159/000369688, PMID:25591763.
[69] Nakano M, Tanaka M, Kuromatsu R, Nagamatsu H, Sakata K, Matsugaki S, *et al*. Efficacy, safety, and survival factors for sorafenib treatment in Japanese patients with advanced hepatocellular carcinoma. Oncology 2013;84(2):108–114. doi:10.1159/000342650, PMID:23147476.
[70] Saeki I, Yamasaki T, Yamashita S, Hanazono T, Urata Y, Furutani T, *et al*. Early Predictors of Objective Response in Patients with Hepatocellular Carcinoma Undergoing Lenvatinib Treatment. Cancers (Basel) 2020;12(4):779. doi:10.3390/cancers12040779, PMID:32218295.
[71] Zhang T, Li W, Chen Q, He W, Sun J, Li D, *et al*. Prognostic significance of early alpha fetoprotein and des-gamma carboxy prothrombin responses in unresectable hepatocellular carcinoma patients undergoing triple combination therapy. Front Immunol 2024;15:1508028. doi:10.3389/fimmu.2024.1508028, PMID:39726604.
[72] Zhu W, Wang W, Zheng W, Chen X, Wang X, Xie J, *et al*. Diagnostic performance of PIVKA-II in identifying recurrent hepatocellular carcinoma following curative resection: a retrospective cohort study. Sci Rep 2024;14(1):8416. doi:10.1038/s41598-024-59174-5, PMID:38600210.
[73] Devillers MJC, Pluimers JKF, van Hooff MC, Doukas M, Polak WG, de Man RA, *et al*. The Role of PIVKA-II as a Predictor of Early Hepatocellular Carcinoma Recurrence-Free Survival after Liver Transplantation in a Low Alpha-Fetoprotein Population. Cancers (Basel) 2023;16(1):4. doi:10.3390/cancers16010004, PMID:38201435.
[74] Yang C, Chen Y, Sheng L, Wang Y, Zhang X, Yang Y, *et al*. Prediction of Pathologic Response in Unresectable Hepatocellular Carcinoma After Downstaging with Locoregional and Systemic Combination Therapy. J Hepatocell Carcinoma 2025;12:43–58. doi:10.2147/JHC.S499597, PMID:39835161.
[75] Yu Z, Li G, Yuan N, Ding W. Comparison of ultrasound guided versus CT guided radiofrequency ablation on liver function, serum PIVKA-II, AFP levels and recurrence in patients with primary hepatocellular carcinoma. Am J Transl Res 2021;13(6):6881–6888. PMID:34306439.
[76] 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. J Formos Med Assoc 2022;121(8):1579–1587. doi:10.1016/j.jfma.2022.01.005, PMID:35078686.
[77] Gan D, Wang Y, Yang X, Huang J, Zhang L, Guo B, *et al*. Diagnostic value of TAP, PIVKA-II, and AFP in hepatocellular carcinoma and their prognostic value for patients treated with transarterial chemoembolization. Lab Med 2025;56(3):297–304. doi:10.1093/labmed/lmae104, PMID:39749461.
[78] Wang Q, Sun L, Zhang G, Chen Z, Li G, Jin R. A novel nomogram based on machine learning predicting overall survival for hepatocellular carcinoma patients with dynamic α-fetoprotein level changes after local resection. Oncol Lett 2025;29(6):310. doi:10.3892/ol.2025.15056, PMID:40342725.
[79] Chen J, Wu M, Gong J, Liu Z, He G, Zhu H, *et al*. Influence of Alanine Transaminase Levels on Alpha-Fetoprotein for Predicting Hepatocellular Carcinoma in Patients with Hepatitis B Infection. Biomed Res Int 2020;2020:2043715. doi:10.1155/2020/2043715, PMID:33490235.
[80] Luo L, Wang X, Peng X, Zhong R, Xuan X, Lin H, *et al*. Analysis of the optimal patterns of serum alpha fetoprotein (AFP), AFP-L3% and protein induced by vitamin K absence or antagonist-II (PIVKA-II) detection in the diagnosis of liver cancers. PeerJ 2025;13:e19712. doi:10.7717/peerj.19712, PMID:40708828.
[81] Okamura J, Tamai H. Lens culinaris-agglutinin-reactive fraction of alpha-fetoprotein is a prognostic biomarker in atezolizumab plus bevacizumab for hepatocellular carcinoma. Eur J Gastroenterol Hepatol 2025;37(9):1055–1062. doi:10.1097/MEG.0000000000002979, PMID:40359294.
[82] Ozturk Y, Purnak T, Simsek H, Sokmensuer C. Predicting hepatocellular carcinoma development in advanced fibrosis or cirrhosis due to chronic hepatitis B: The role of glypican-3, heat shock protein 70, CD34, and glutamine synthetase. Hepatol Forum 2025;6(3):99–104. doi:10.14744/hf.2025.2025.0002, PMID:40686594.
[83] Peng J, Chen H, Chen Z, Tan J, Wu F, Li X. Prognostic value of neutrophil-to-lymphocyte ratio in patients with hepatocellular carcinoma receiving curative therapies: a systematic review and meta-analysis. BMC Cancer 2025;25(1):571. doi:10.1186/s12885-025-13972-w, PMID:40158082.
[84] Liu F, Xiang Y, Xu H, Xu X. Preoperative serum inflammatory markers in the prognostic assessment of hepatocellular carcinoma resection in stages I/II. Front Mol Biosci 2025;12:1640390. doi:10.3389/fmolb.2025.1640390, PMID:40894075.
[85] Ishikawa T, Sato R, Natsui H, Iwasawa T, Ogawa M, Kobayashi Y, *et al*. Efficacy of Durvalumab-Tremelimumab Treatment in Combination With Locoregional Therapy in Unresectable Hepatocellular Carcinoma: A Preliminary Study. Cancer Diagn Progn 2025;5(5):591–596. doi:10.21873/cdp.10473, PMID:40900880.
[86] Guariglia M, Gaia S, Rolle E, Abate ML, Carucci P, Caviglia GP. Analytical and clinical evaluation of a novel ELISA assay for the measurement of serum PIVKA-II in patients with hepatocellular carcinoma of viral-etiology. Minerva Biotechnol Biomol Res 2024;36(4):181–187. doi:10.23736/s2724-542x.24.03116-x.
[87] Jabor A, Kubíček Z, Časenská J, Vacková T, Filová V, Franeková J. Biological variation of PIVKA-II in blood serum of healthy subjects measured by automated electrochemiluminescent assay. Pract Lab Med 2024;39:e00389. doi:10.1016/j.plabm.2024.e00389, PMID:38576474.
[88] Honda T, Ichikawa T, Yamashima M, Yamamichi S, Koike M, Nakano Y, *et al*. PIVKA-II is associated with liver function, bone metabolism, and muscle function in patients with liver disease. Biomed Rep 2024;20(1):2. doi:10.3892/br.2023.1690, PMID:38222867.
[89] Maruyama S, Matono T, Koda M. Elevated Serum Protein Induced by Vitamin K Absence or Antagonist II Levels in Patients with Hepatic Hemangiomas. Int J Mol Sci 2025;26(8):3681. doi:10.3390/ijms26083681, PMID:40332214.
[90] Hsu CC, Jang TY. Improvement of serum PIVKA level after the treatment of liver abscess. J Formos Med Assoc 2025. doi:10.1016/j.jfma.2025.04.022, PMID:40280781.
[91] Liu Y, Wu Y, He S. Clinical Value of Abnormal Prothrombin and Carbohydrate Antigen 125 in the Diagnosis of Patients With Gallbladder Cancer. Am Surg 2025;91(4):608–613. doi:10.1177/00031348241312119, PMID:39754532.
[92] Kudo M, Takamine Y, Nakamura K, Shirane H, Uchida H, Kasakura S, *et al*. Des-gamma-carboxy prothrombin (PIVKA-II) and alpha-fetoprotein-producing IIc-type early gastric cancer. Am J Gastroenterol 1992;87(12):1859–1862. PMID:1280406.
[93] Wang M, Bu H, Luo W, Zeng X, Chen G, He Y, *et al*. CA19-9, CEA and PIVKA-II as a novel panel of serum markers for diagnosis of pancreatic cancer. Clin Biochem 2025;137:110902. doi:10.1016/j.clinbiochem.2025.110902, PMID:40024361.
[94] Tartaglione S, Pecorella I, Zarrillo SR, Granato T, Viggiani V, Manganaro L, *et al*. Protein Induced by Vitamin K Absence II (PIVKA-II) as a potential serological biomarker in pancreatic cancer: a pilot study. Biochem Med (Zagreb) 2019;29(2):020707. doi:10.11613/BM.2019.020707, PMID:31223261.
[95] Farina A, Tartaglione S, Preziosi A, Mancini P, Angeloni A, Anastasi E. PANC-1 Cell Line as an Experimental Model for Characterizing PIVKA-II Production, Distribution, and Molecular Mechanisms Leading to Protein Release in PDAC. Int J Mol Sci 2024;25(6):3498. doi:10.3390/ijms25063498, PMID:38542466.
[96] Nyvad J, Christensen KL, Andersen G, Reinhard M, Nørgaard BL, Madsen JS, *et al*. PIVKA-II but not dp-ucMGP is associated with aortic calcification in chronic kidney disease. BMC Nephrol 2024;25(1):426. doi:10.1186/s12882-024-03876-5, PMID:39604863.
[97] Caluwé R, Verbeke F, De Vriese AS. Evaluation of vitamin K status and rationale for vitamin K supplementation in dialysis patients. Nephrol Dial Transplant 2020;35(1):23–33. doi:10.1093/ndt/gfy373, PMID:30590803.
[98] Aleksiev V, Markov D, Bechev K. Tumor Markers in Pleural Fluid: A Comprehensive Study on Diagnostic Accuracy. Diagnostics (Basel) 2025;15(2):204. doi:10.3390/diagnostics15020204, PMID:39857088.
[99] Paulus MC, Drent M, Kouw IWK, Balvers MGJ, Bast A, van Zanten ARH. Vitamin K: a potential missing link in critical illness-a scoping review. Crit Care 2024;28(1):212. doi:10.1186/s13054-024-05001-2, PMID:38956732.

[100] Miyamoto S, Shinkuma S, Yada K, Hamada K, Ogawa K, Nogami K, *et al*. PIVKA-II as a biomarker in pseudoxanthoma elasticum-like disorder with multiple coagulation factor deficiency: implications for vitamin K therapy. Br J Dermatol 2025;193(1):171–173. doi:10.1093/bjd/ljaf078, PMID:40036623.
[101] Ouchi N, Kuwabara Y, Yonezawa M, Ogawa J, Kasano S, Kato M, *et al*. Prolonged prothrombin time in hyperemesis gravidarum as an indicator of vitamin K deficiency. J Obstet Gynaecol Res 2025;51(1):e16198. doi:10.1111/jog.16198, PMID:39746218.
[102] Zhu W, Qian H, Cao S, Xia W, Wang X, Jin J, *et al*. A new platform of electrowetting-on-dielectric digital microfluidics for rapid detection of early-stage Hepatocellular Carcinoma(HCC) specific biomarker. Anal Chim Acta 2025;1336:343533. doi:10.1016/j.aca.2024.343533, PMID:39788685.
[103] Wang YY, Yang WX, Du QJ, Liu ZH, Lu MH, You CG. Construction and evaluation of a liver cancer risk prediction model based on machine learning. World J Gastrointest Oncol 2024;16(9):3839–3850. doi:10.4251/wjgo.v16.i9.3839, PMID:39350987.
[104] Yang T, Xing H, Wang G, Wang N, Liu M, Yan C, *et al*. A Novel Online Calculator Based on Serum Biomarkers to Detect Hepatocellular Carcinoma among Patients with Hepatitis B. Clin Chem. 2019;65(12):1543–1553. doi:10.1373/clinchem.2019.308965, PMID:31672853.
[105] Li B, Li B, Guo T, Sun Z, Li X, Li X, *et al*. Artificial neural network models for early diagnosis of hepatocellular carcinoma using serum levels of α-fetoprotein, α-fetoprotein-L3, des-γ-carboxy prothrombin, and Golgi protein 73. Oncotarget 2017;8(46):80521–80530. doi:10.18632/oncotarget.19298, PMID:29113322.