Glosains: Jurnal Sains Global Indonesia
Volume 7, Issue 1, 177-186
e_ISSN: 2798-4311
https://glosains.staiku.ac.id
DOI: doi.org/10.59784/glosains.v7i1.658

Serum PIVKA-II as a Preoperative Predictor of Microvascular Invasion and Tumor Proliferation in HBV-Related Hepatocellular Carcinoma

Irfansyah[1]* Universitas Indonesia, Indonesia
Wifanto S. Jeo[2] Universitas Indonesia, Indonesia
Nur Rahadiani[3] Universitas Indonesia, Indonesia

***Corresponding author:**
Irfansyah, Universitas Indonesia, Indonesia. ✉dokteripan@gmail.com

Article Info :
Article history:
Received: February 14th, 2026
Revised: March 4th, 2026
Accepted: March 10th, 2026

Keywords:
hepatocellular carcinoma; serum PIVKA-II; microvascular invasion; tumor proliferation; hepatitis B virus.

Abstract

Background: Hepatocellular carcinoma (HCC) contributes significantly to cancer-related mortality worldwide, particularly in hepatitis B–endemic regions such as Indonesia. The need for reliable preoperative biomarkers remains a major gap, especially to predict microvascular invasion (MVI) and tumor proliferation. PIVKA-II was specifically selected over AFP because of its superior ability to reflect tumor-invasive biology through MET and JAK/STAT pathway activation.
Objective: This study aimed to assess whether serum PIVKA-II levels can predict MVI and Ki-67 proliferation index.
Methods: A retrospective study was conducted on 20 patients with HBV-related HCC who underwent liver resection at Cipto Mangunkusumo Hospital (2017–2025). Serum PIVKA-II was categorized as high (>40 mAU/mL) or low (≤40 mAU/mL). MVI was identified histologically; Ki-67 expression was categorized as high (>20%) or low (≤20%) using immunohistochemistry.
Results: PIVKA-II levels showed a significant relationship with AFP (p = 0.033) and BCLC stage (p = 0.038). ROC analysis showed that PIVKA-II had fair discriminative ability (AUC = 0.703) in predicting vascular invasion, with a sensitivity of 87.5% and specificity of 75%. There was a significant relationship between high PIVKA-II levels and the occurrence of vascular invasion (p = 0.032; RR = 2.33). However, PIVKA-II did not show good predictive ability for tumor cell proliferation (Ki-67) (AUC = 0.484), and no significant relationship was found between them (p = 0.530).
Conclusion: PIVKA-II is a useful preoperative biomarker for predicting microvascular invasion in HBV-related HCC. Its lack of association with Ki-67 indicates that additional markers are needed to assess tumor proliferative behavior. These findings support the integration of PIVKA-II into preoperative risk assessment.

To cite this article: Irfansyah, Jeo, W. S., & Rahadiani, N. (2026). Serum PIVKA-II as a Preoperative Predictor of Microvascular Invasion and Tumor Proliferation in HBV-Related Hepatocellular Carcinoma. *Glosains: Jurnal Sains Global Indonesia*, *7*(1), 177-186. https://doi.org/10.59784/glosains.v7i1.658

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related mortality, with over 865,000 new cases and 757,000 deaths recorded in 2022 (Adams et al., 2024; Alawyia & Constantinou, 2023). A significant share of these cases arises in Asia, where hepatitis B virus (HBV) infection continues to be the primary underlying cause (Alqahtani & Colombo, 2020; Cardoso & Machado, 2024). Indonesia is among the countries with the highest burden of HBV-related HCC, reflecting ongoing challenges in early detection and timely treatment (Hu, 2024; Jasirwan et al., 2020).

Despite advancements in imaging, surgical techniques, and systemic therapy, the overall prognosis remains unfavorable, largely because of delayed diagnosis, high rates of early recurrence, and the scarcity of definitive curative therapies (Adams et al., 2024; Lai & Chung, 2024; Toh et al., 2023). Microvascular invasion (MVI) and high tumor proliferative activity,

typically assessed using Ki-67 expression, are well-established pathological predictors of recurrence and survival (Feng et al., 2017; Roayaie et al., 2009). However, both parameters can only be confirmed postoperatively, limiting their value for preoperative risk stratification. Crucially, preoperative knowledge of MVI status directly influences surgical planning: patients at high MVI risk may benefit from wider anatomical resection margins or may be deprioritized for liver transplantation under the Milan criteria. Yet no reliable non-invasive predictor is currently embedded in routine preoperative workup.

Serum biomarkers provide non-invasive, accessible, and cost-effective tools to support clinical decision-making. Alpha-fetoprotein (AFP), although widely used, has limited sensitivity for early-stage or biologically aggressive HCC (Kim et al., 2019; Lim & Singal, 2019; Tzartzeva et al., 2018). Protein Induced by Vitamin K Absence or Antagonism-II (PIVKA-II) has shown enhanced diagnostic and prognostic utility, especially in identifying vascular invasion and aggressive tumor characteristics (Hotta et al., 2016; Tsukamoto et al., 2018). Mechanistically, PIVKA-II has been shown to activate MET and JAK/STAT signaling pathways, promoting angiogenesis, cellular migration, and endothelial invasion, thereby contributing directly to a more invasive tumor phenotype. However, evidence evaluating PIVKA-II in Indonesian HBV-associated HCC populations remains scarce. AFP demonstrates a sensitivity of approximately 41–65% and specificity of 80–94% for HCC detection, varying widely by cutoff and population, and performs particularly poorly (sensitivity <50%) in early-stage tumors and HBV-driven disease. PIVKA-II, also known as des-gamma-carboxyprothrombin (DCP), was specifically chosen in this study because it reflects tumor-invasive biology independent of hepatic synthetic function, offering mechanistically grounded predictive potential that AFP cannot provide. The cited evidence specifically includes studies on PIVKA-II's diagnostic accuracy for MVI detection and its prognostic value for post-resection survival, providing multi-dimensional support for its selection as the primary biomarker in this study (Poté et al., 2015; Saitta et al., 2016; Si et al., 2020).

Prior studies evaluating PIVKA-II's predictive value for MVI have predominantly been conducted in Chinese or Japanese cohorts. Ma et al. (2018) demonstrated that PIVKA-II independently predicted MVI in a Chinese HCC cohort (HR 3.77; $p = 0.014$), and Poté et al. (2015) confirmed its predictive performance in a European series (AUC 0.72; $p < 0.001$). However, both studies focused on mixed HCC etiologies, limiting their direct applicability to HBV-endemic settings. Critically, no published study has specifically examined PIVKA-II's predictive performance for both MVI and Ki-67 proliferative index simultaneously in an Indonesian HBV-related HCC cohort, a population with distinct epidemiological, genetic, and clinical characteristics. This gap motivates the present study, which is the first to address this intersection in the Indonesian context.

Understanding whether PIVKA-II can predict key pathological prognostic markers such as MVI and Ki-67 expression may enhance preoperative risk stratification and guide treatment planning, particularly in resource-limited settings. Therefore, this study aims to evaluate the relationship between preoperative serum PIVKA-II levels, vascular invasion, and Ki-67 proliferative index in Indonesian patients with HBV-related HCC, and to assess its association with clinical characteristics. More specifically, the study pursues two interrelated aims: (1) to assess the predictive performance of PIVKA-II for MVI and Ki-67 expression using ROC analysis; and (2) to characterize the association between PIVKA-II levels and clinical characteristics of the study population.

METHOD

Study Design and Setting

This was a retrospective observational study conducted at Cipto Mangunkusumo National Referral Hospital, Jakarta, Indonesia. The study included patients treated between April 2017 and October 2025. All procedures followed institutional ethical guidelines. Data were extracted from electronic medical records, laboratory information systems, and histopathology reports. Cases with missing preoperative PIVKA-II values or incomplete histopathological assessment (MVI or Ki-67) were excluded from the analysis; no imputation of missing data was applied.

Target Population and Sampling Method

The study population included all patients diagnosed with HCC and confirmed hepatitis B infection who received curative liver resection at our center. Participants were recruited through consecutive sampling, whereby every eligible patient treated within the study timeframe was enrolled, as long as they fulfilled the established inclusion criteria. During the study period, a total of 27 HBV-related HCC patients underwent liver resection at our center. Of these, 7 were excluded due to incomplete PIVKA-II data (n = 4) or unavailable postoperative histopathology reports (n = 3), yielding a final analytic cohort of 20 patients. This exclusion process may introduce selection bias, which is acknowledged as a study limitation.

The Inclusion Criteria

1. Diagnosis of HCC with confirmed hepatitis B infection (HBsAg positive).
2. Underwent curative liver resection
3. Had complete preoperative serum PIVKA-II data collected within ≤30 days prior to surgery.
4. Had available postoperative histopathological evaluation, including MVI and Ki-67 proliferative index.
5. Age ≥18 years.

The Exclusion Criteria

Patients who received vitamin K supplementation or warfarin therapy, as these may alter PIVKA-II levels. In this cohort, no patients met this exclusion criterion (0 patients were receiving vitamin K supplementation or anticoagulation therapy at the time of PIVKA-II measurement). In total, 20 patients fulfilled the eligibility criteria and were subsequently included in the final analysis. No *a priori* sample size calculation was performed, as this study represents a complete consecutive cohort within the defined study period rather than a pre-planned sample. The small sample size (n = 20) constitutes a recognized limitation and reduces statistical power, particularly for subgroup analyses. This is addressed further in the limitations section.

Variables and Operational Definitions

A. The Independent Variable

1. Serum PIVKA-II level
   Categorized as:
   a) High: >40 mAU/mL
   b) Low: ≤40 mAU/mL

This threshold was adopted based on manufacturer-recommended reference ranges (Fujirebio LUMIPULSE) and is consistent with cut-offs used in prior studies evaluating PIVKA-II as a predictor of MVI (Ma et al., 2018; Poté et al., 2015). It does not represent a data-derived optimal threshold for this specific cohort.

B. Dependent Variables

1. MVI
   a) Defined as presence of tumor emboli within endothelial-lined vascular spaces on histopathology.
   b) Reported as present or absent.
2. Ki-67 proliferative index
   a) Measured using immunohistochemistry.
   b) Categorized as:
      1) High proliferation: >20% nuclear staining
      2) Low proliferation: ≤20%

C. Other Clinical Variables

1. Age (years)
2. Sex
3. Liver enzymes (AST, ALT)
4. Alpha-fetoprotein (AFP)
5. Tumor number (solitary vs multifocal)
6. Tumor size (cm)
7. Tumor margin (well-defined vs infiltrative)

8. BCLC stage

Measurement Procedures

A. Serum PIVKA-II Measurement

Blood samples were analyzed using a Chemiluminescent Enzyme Immunoassay (CLEIA) on the LUMIPULSE G1200 system (Fujirebio Inc.), processed at a certified external laboratory. Results were reported in mAU/mL.

B. Histopathological Assessment

Resected tumor specimens were evaluated by consultant pathologists using standardized criteria. Pathologists were blinded to PIVKA-II results during histopathological assessment to minimize interpretation bias. Assessment was performed independently by two consultant pathologists; discordant cases were resolved by consensus.

1. MVI**:** Identified using routine hematoxylin–eosin staining.
2. Ki-67**:** Evaluated using immunohistochemical staining; proliferative index calculated as the percentage of positive tumor cell nuclei.

Study Outcomes

The primary outcomes included the predictive performance of PIVKA-II in predicting MVI and Ki-67 status, evaluated through ROC curve analysis (AUC, sensitivity, specificity) and bivariate association tests.

Statistical Analysis

1. Bivariate Analysis
   a) Chi-square or Fisher's exact test was used to assess associations between PIVKA-II and categorical variables (MVI, Ki-67, clinical characteristics).
   b) A p-value <0.05 was regarded as statistically significant.
2. Diagnostic Performance
   a) Receiver Operating Characteristic (ROC) curve analysis was performed to assess the ability of PIVKA-II to predict MVI and Ki-67 status. All statistical analyses were performed using SPSS version 26.0. The cutoff value of 40 mAU/mL was applied as a pre-specified threshold based on established literature rather than being derived empirically from the ROC curve of this cohort. For reference, the Youden index–derived optimal threshold from this dataset's ROC analysis is reported alongside the pre-specified cutoff to provide full transparency.
   b) The area under the curve (AUC), along with sensitivity, specificity, and optimal threshold values was determined.
3. Definitions
   a) AUC values were interpreted as:
      - 0.5 = no discriminative ability
      - 0.7–0.8 = fair
      - 0.8–0.9 = good
      - 0.9 = excellent

RESULTS AND DISCUSSION

Results

Most patients (75%) exhibited elevated serum PIVKA-II levels (>40 mAU/mL). The proportion of patients with AFP concentrations >20 ng/mL was significantly greater in the high PIVKA-II group (66.7%) compared to the low PIVKA-II group (0%) (p = 0.033). A statistically significant difference was likewise observed in BCLC stage distribution: all individuals classified as BCLC stage B or C (100%) were exclusively in the high PIVKA-II group, whereas all patients in the low PIVKA-II group (100%) were categorized as BCLC stage 0 or A (p = 0.038). No significant associations were identified between PIVKA-II levels and other baseline characteristics, including age, sex, ALT, AST, tumor number, tumor size, or tumor margin. Table 1 summarizes the overall sociodemographic and clinical characteristics, as well as their distribution according to PIVKA-II category. No clinical or pathological variables demonstrated significant associations with microvascular invasion or tumor proliferative activity (Ki-67).

Table 1. Sociodemographic and Clinical Characteristics Overall and by PIVKA-II Category

Variable	Total	PIVKA-II High (>40 mAU/mL)	PIVKA-II Low (≤40 mAU/mL)	p-value[a]
	n	%	n	%
Age				
≤50 years	5	25.0	11	73.3
>50 years	15	75.0	4	26.7
Sex				
Male	15	75.0	11	73.3
Female	5	25.0	4	26.7
ALT				
≤40 U/L	8	40.0	8	53.3
>40 U/L	12	60.0	7	46.7
AST				
≤40 U/L	8	40.0	10	66.7
>40 U/L	12	60.0	5	33.3
AFP				
≤20 ng/mL	10	50.0	10	66.7
>20 ng/mL	10	50.0	5	33.3
Tumor Number				
Single	8	40.0	11	73.3
Multiple	12	60.0	4	26.7
Tumor Size				
≤5 cm	8	40.0	10	66.7
>5 cm	12	60.0	5	33.3
Tumor Margin				
Well-defined	13	65.0	7	46.7
Poorly defined	7	35.0	8	53.3
BCLC Stage				
0 + A	11	55.0	9	60.0
B + C	9	45.0	6	40.0

[a]Fisher exact/Chi square test

Further analysis revealed a significant relationship between serum PIVKA-II levels and microvascular invasion. Of the 16 patients with microvascular invasion, 14 (87.5%) exhibited elevated PIVKA-II levels. Individuals in the high PIVKA-II group had a 2.33-fold higher risk of microvascular invasion compared with those in the low PIVKA-II group (RR 2.33; 95% CI 0.79–6.89), and this association was statistically significant ($p = 0.032$). It is important to note that the wide 95% confidence interval (0.79–6.89) crosses 1.0, indicating substantial uncertainty around the point estimate. This reflects the limited statistical precision inherent to the small sample size and should be interpreted with caution; the association is statistically significant at the $p < 0.05$ threshold, but the true magnitude of risk elevation remains imprecisely estimated.

In contrast, no significant correlation was identified between PIVKA-II levels and tumor proliferative activity as assessed by Ki-67 expression ($p = 0.530$). Although all four patients with high Ki-67 expression were categorized within the high PIVKA-II group, the difference was not statistically significant. The relationships among PIVKA-II levels, microvascular invasion, and tumor proliferation are presented in Table 2.

Table 2. Association of Tumor Proliferation and Vascular Invasion with PIVKA-II category

Variable	PIVKA-II High (>40 mAU/mL)	PIVKA-II Low (≤40 mAU/mL)	p-value[a]	RR (95% CI)
Vascular Invasion				
Present	14 (93.3)	2 (40.0)	**0.032**	2.33 (0.79–6.89)
Absent	1 (6.7)	3 (60.0)		
Tumor Proliferation (Ki-67)				
High	4 (26.7)	0 (0.0)	0.530	N/A
Low	11 (73.3)	5 (100.0)		

[a]Fisher's exact test. N/A: Not applicable (risk ratio not estimable due to zero cells)

The predictive value of PIVKA-II for microvascular invasion and tumor proliferation was assessed through ROC curve analysis (Figure 1). The results demonstrated an AUC of 0.703 (95% CI: 0.375–1.000) for microvascular invasion, reflecting fair discriminative ability, and 0.484 (95% CI: 0.375–1.000) for tumor proliferation, indicating poor discriminative performance. The diagnostic characteristics of PIVKA-II at a threshold of 40 mAU/mL for predicting microvascular invasion and tumor proliferation are summarized in Table 3.

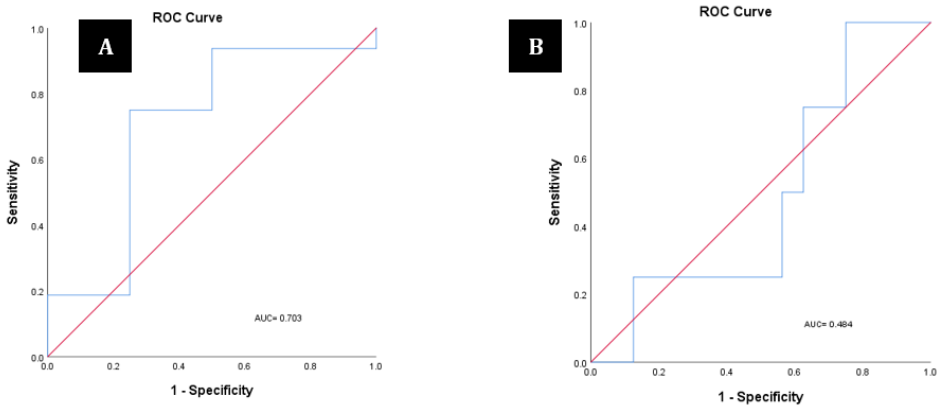

Figure 1. ROC curves that demonstrate PIVKA-II's diagnostic efficacy in anticipating (A) vascular invasion and (B) tumor cell proliferation

Table 3. Diagnostic Performance of PIVKA-II (cut-off 40 mAU/mL) for Predicting Vascular Invasion and Tumor Cell Proliferation (Ki-67 Expression)

Parameter	PIVKA-II – Vascular Invasion (%) (95% CI)	PIVKA-II – Ki-67 Expression (%) (95% CI)
Sensitivity	87.5 (63.9 – 96.5)	100 (51.0 – 100)
Specificity	75.0 (30.1 – 95.4)	31.3 (14.2 – 55.6)
Positive Predictive Value (PPV)	93.3 (70.2 – 98.8)	26.7 (10.9 – 51.9)
Negative Predictive Value (NPV)	60.0 (23.1 – 82.4)	100 (56.6 – 100)
Diagnostic Accuracy	85.0 (63.9 – 94.8)	45.0 (25.8 – 65.8)

Table 3 presents the diagnostic performance of PIVKA-II at a cut-off value of 40 mAU/mL in predicting microvascular invasion and tumor cell proliferation as assessed by Ki-67 expression. Overall, PIVKA-II demonstrates stronger diagnostic performance for microvascular invasion compared to Ki-67 expression.

In predicting microvascular invasion, PIVKA-II showed a high sensitivity of 87.5% (95% CI: 63.9–96.5), indicating a strong ability to correctly identify patients with microvascular invasion. The specificity was 75.0% (95% CI: 30.1–95.4), reflecting a moderate ability to correctly classify patients without microvascular invasion. The positive predictive value (PPV) was notably high at 93.3% (95% CI: 70.2–98.8), suggesting that most patients with elevated PIVKA-II levels

indeed had microvascular invasion. However, the negative predictive value (NPV) was lower at 60.0% (95% CI: 23.1–82.4), indicating that a negative result does not fully exclude the presence of microvascular invasion. The overall diagnostic accuracy reached 85.0% (95% CI: 63.9–94.8), supporting the clinical utility of PIVKA-II as a relatively reliable predictor of microvascular invasion.

In contrast, for predicting tumor cell proliferation based on Ki-67 expression, PIVKA-II achieved a sensitivity of 100% (95% CI: 51.0–100), meaning all cases with high Ki-67 expression were detected. However, specificity was low at 31.3% (95% CI: 14.2–55.6), indicating a high rate of false-positive results among patients without high Ki-67 expression. This is reflected in the low PPV of 26.7% (95% CI: 10.9–51.9). Conversely, the NPV was 100% (95% CI: 56.6–100), suggesting that a negative PIVKA-II result effectively rules out high proliferative activity. Despite this, the overall diagnostic accuracy was only 45.0% (95% CI: 25.8–65.8), indicating limited reliability in predicting Ki-67 expression.

Discussion

The results indicate that elevated PIVKA-II levels were significantly correlated with the presence of vascular invasion, while no significant relationship was found between PIVKA-II levels and Ki-67 expression. These results highlight the differential biological implications of PIVKA-II in tumor aggressiveness. MVI is broadly acknowledged as a critical factor contributing to early recurrence and reduced survival following hepatic resection or liver transplantation. In this study, high serum PIVKA-II levels were significantly associated with MVI ($p = 0.038$), consistent with previous international evidence. ROC analysis demonstrated fair discriminative ability of PIVKA-II, with an AUC of 0.703. These findings parallel those of Ma et al. (2018) who reported that PIVKA-II independently predicts MVI (HR 3.77; $p = 0.014$)10 and Poté et al. (2015) likewise reported a significant association between PIVKA-II levels and vascular invasion ($p < 0.001$). Collectively, these reinforce the value of PIVKA-II as a preoperative marker of invasive tumor biology. At the molecular level, PIVKA-II has been shown to promote angiogenesis, migration, and endothelial invasion by activating MET signaling and JAK/STAT pathways. These mechanisms plausibly explain its strong association with vascular infiltration observed in clinical studies and support its role as a surrogate marker of invasive phenotype rather than mere tumor mass or burden.

In contrast, PIVKA-II did not demonstrate a significant association with tumor proliferative activity (Ki-67) ($p = 0.530$). Although a higher proportion of Ki-67–high cases was observed in the elevated PIVKA-II group, the difference was not statistically meaningful, and ROC analysis confirmed poor discriminatory accuracy. These findings diverge from those of Ma et al. (2018) who observed that elevated PIVKA-II correlated with higher Ki-67 levels. Variations in sample size, ethnicity, tumor biology, and Ki-67 cut-off points likely contribute to this discrepancy. While differences in ethnicity, tumor biology, and Ki-67 cut-off values are plausible contributing factors, this explanation remains speculative in the absence of comparative genomic or molecular data from our cohort. Future studies should include molecular subtyping to test whether these factors systematically modify the PIVKA-II/Ki-67 relationship.

Other studies evaluating Ki-67 in HCC have shown heterogeneous prognostic significance. King et al. (1998) reported a moderate association between Ki-67 and pathological aggressiveness, though findings remain inconsistent across populations. This reinforces the concept that angiogenesis-driven pathways (captured by PIVKA-II) do not universally correlate with proliferative pathways captured by Ki-67. No significant associations were identified between PIVKA-II levels and other clinical parameters such as age, sex, liver enzymes, AFP, tumor size, or tumor number. This aligns with previous literature suggesting that PIVKA-II reflects tumor-specific biological behavior more than patient-related factors.

Clinically, these findings suggest that PIVKA-II may serve as an effective biomarker for predicting MVI in HBV-related HCC, thereby aiding in surgical decision-making, especially in settings where advanced imaging modalities are limited. Identifying patients at higher risk for MVI may influence the choice of anatomical resection, surgical margins, perioperative strategies, and intensity of postoperative surveillance. For example, patients with elevated preoperative PIVKA-II (>40 mAU/mL) may be candidates for wider anatomical resection to achieve safer margins, may require closer postoperative surveillance intervals, or in the transplant context may warrant reassessment of eligibility under extended criteria given the higher MVI probability.

This study has several limitations, such as a limited sample size, a retrospective study design, and the use of institution-specific Ki-67 cut-off values. Despite these, the study provides valuable data in an underrepresented population and supports the growing evidence for PIVKA-II as a preoperative predictive biomarker for vascular invasion in HCC. Additional limitations include: (1) selection bias arising from the resection-only cohort, which excludes patients who were ineligible for surgery and may represent a more aggressive disease spectrum; (2) the single-center design limits generalizability to other Indonesian hospitals or HBV-endemic settings with different patient profiles; and (3) the absence of external or prospective validation of the 40 mAU/mL cut-off in this specific population.

Future research should pursue prospective, multicenter validation studies across multiple Indonesian tertiary centers to confirm the predictive performance and optimal cut-off of PIVKA-II for MVI in HBV-related HCC. Multimodal models incorporating radiologic features (e.g., contrast-enhanced MRI), molecular biomarkers, and combined AFP+PIVKA-II panels should be explored to improve preoperative risk stratification beyond what either marker achieves in isolation.

CONCLUSION

This study confirms that high serum PIVKA-II levels are significantly associated with MVI in HBV-related HCC, achieving the objective of identifying a biomarker capable of predicting aggressive tumor features before surgery. These findings advance current knowledge by supporting the clinical value of PIVKA-II in preoperative risk stratification, particularly when imaging and routine markers are insufficient. However, PIVKA-II showed no association with Ki-67 expression, suggesting that proliferative behavior requires additional or alternative markers. Further research with larger populations is warranted to validate the cutoff values and strengthen its integration into clinical decision-making algorithms. ROC analysis demonstrated fair discriminative ability for MVI prediction (AUC = 0.703; 95% CI 0.491–0.915), with sensitivity of 87.5% and specificity of 75% at the prespecified threshold of 40 mAU/mL. However, the assertion of definitive clinical utility should be regarded as preliminary; external validation with a prospective, multicenter design is required before PIVKA-II can be formally recommended as a clinical decision tool for MVI prediction.

ACKNOWLEDGEMENT

The author(s) wish to thank the medical, surgical, and pathology staff of Cipto Mangunkusumo Hospital for their assistance in data acquisition and clinical support. The authors also acknowledge the Department of Surgery and the Department of Anatomical Pathology, Faculty of Medicine Universitas Indonesia, for providing institutional support throughout the study.

AUTHOR CONTRIBUTION STATEMENT

All authors contributed significantly to this study. Irfansyah conceptualized the study, designed the methodology, and was involved in data analysis and interpretation. Wifanto S. Jeo contributed to the study's design, supported the analysis, and critically reviewed the manuscript. Nur Rahadiani participated in data collection, interpretation of results, and contributed to drafting the manuscript. All authors read and approved the final manuscript for submission.

REFERENCES

Adams, A. M., Kaseb, A. O., & Tran Cao, H. S. (2024). Hepatocellular carcinoma. In *Transplant Oncology: A Frontier in Multidisciplinary Cancer Care*. https://doi.org/10.1016/B978-0-443-21901-6.00003-3

Alawyia, B., & Constantinou, C. (2023). Hepatocellular Carcinoma: a Narrative Review on Current Knowledge and Future Prospects. In *Current Treatment Options in Oncology* (Vol. 24, Number 7). https://doi.org/10.1007/s11864-023-01098-9

Alqahtani, S. A., & Colombo, M. (2020). Viral hepatitis as a risk factor for the development of hepatocellular carcinoma. In *Hepatoma Research* (Vol. 6). https://doi.org/10.20517/2394-5079.2020.49

Cardoso, M. F., & Machado, M. V. (2024). The Changing Face of Hepatitis Delta Virus Associated Hepatocellular Carcinoma. In *Cancers* (Vol. 16, Number 22). https://doi.org/10.3390/cancers16223723

Feng, L. H., Dong, H., Lau, W. Y., Yu, H., Zhu, Y. Y., Zhao, Y., Lin, Y. X., Chen, J., Wu, M. C., & Cong, W. M. (2017). Novel microvascular invasion-based prognostic nomograms to predict survival outcomes in patients after R0 resection for hepatocellular carcinoma. *Journal of Cancer Research and Clinical Oncology*, *143*(2). https://doi.org/10.1007/s00432-016-2286-1

Hotta, M., Kashiwabara, M., Arai, M., Takasaki, H., Yamahatsu, K., Ueda, J., Yoshida, H., Makino, H., Naitoh, Z., & Uchida, E. (2016). A Case of Alpha-fetoprotein and Des-gamma-carboxy Prothrombin-Producing Gastric Carcinoma Mimicking Hepatocellular Carcinoma. *International Journal of Gastroenterology Disorders & Therapy*, *3*(1). https://doi.org/10.15344/2393-8498/2016/121

Hu, S. S. (2024). Epidemiology and current management of cardiovascular disease in China. *Journal of Geriatric Cardiology*, *21*(4). https://doi.org/10.26599/1671-5411.2024.04.001

Jasirwan, C. O. M., Fahira, A., Siregar, L., & Loho, I. (2020). The alpha-fetoprotein serum is still reliable as a biomarker for the surveillance of hepatocellular carcinoma in Indonesia. *BMC Gastroenterology*, *20*(1). https://doi.org/10.1186/s12876-020-01365-1

Kim, M. N., Kim, B. K., Kim, S. U., Park, J. Y., Ahn, S. H., Han, K. H., & Kim, D. Y. (2019). Longitudinal assessment of alpha-fetoprotein for early detection of hepatocellular carcinoma in patients with cirrhosis. *Scandinavian Journal of Gastroenterology*, *54*(10). https://doi.org/10.1080/00365521.2019.1673478

King, K. L., Hwang, J. J., Chau, G. Y., Tsay, S. H., Chi, C. W., Lee, T. G., Wu, L. H., Wu, C. W., & Lui, W. Y. (1998). Ki-67 expression as a prognostic marker in patients with hepatocellular carcinoma. *Journal of Gastroenterology and Hepatology (Australia)*, *13*(3). https://doi.org/10.1111/j.1440-1746.1998.01555.x

Lai, Y. W., & Chung, C. H. (2024). Epidemiology of Hepatocellular Carcinoma in Taiwan. *Clinics and Practice*, *14*(2). https://doi.org/10.3390/clinpract14020044

Lim, J., & Singal, A. G. (2019). An Official Learning Resource of AASLD surveillance and Diagnosis of Hepatocellular Carcinoma. *Clinical Liver Disease*, *13*(1).

Ma, X. L., Zhu, J., Wu, J., Tian, L., Gao, Y. Y., Zhang, C. Y., Zhou, Y., Dai, Q., Wang, B. L., Pan, B. S., Zhou, J., Fan, J., Yang, X. R., & Guo, W. (2018). Significance of PIVKA-II levels for predicting microvascular invasion and tumor cell proliferation in Chinese patients with hepatitis B virus-associated hepatocellular carcinoma. *Oncology Letters*, *15*(6). https://doi.org/10.3892/ol.2018.8375

Poté, N., Cauchy, F., Albuquerque, M., Voitot, H., Belghiti, J., Castera, L., Puy, H., Bedossa, P., & Paradis, V. (2015). Performance of PIVKA-II for early hepatocellular carcinoma diagnosis and prediction of microvascular invasion. *Journal of Hepatology*, *62*(4). https://doi.org/10.1016/j.jhep.2014.11.005

Roayaie, S., Blume, I. N., Thung, S. N., Guido, M., Fiel, M. I., Hiotis, S., Labow, D. M., Llovet, J. M., & Schwartz, M. E. (2009). A System of Classifying Microvascular Invasion to Predict Outcome After Resection in Patients With Hepatocellular Carcinoma. *Gastroenterology*, *137*(3). https://doi.org/10.1053/j.gastro.2009.06.003

Saitta, C., Raffa, G., Casuscelli, F., Brancatelli, S., Alibrandi, A., Raimondo, G., & Pollicino, T. (2016). PIVKA-II is a useful tool for the diagnosis of early hepatocellular carcinoma. *Digestive and Liver Disease*, *48*. https://doi.org/10.1016/j.dld.2015.12.076

Si, Y. Q., Wang, X. Q., Fan, G., Wang, C. Y., Zheng, Y. W., Song, X., Pan, C. C., Chu, F. L., Liu, Z. F., Lu, B. R., & Lu, Z. M. (2020). Value of AFP and PIVKA-II in diagnosis of HBV-related hepatocellular carcinoma and prediction of vascular invasion and tumor differentiation. *Infectious Agents and Cancer*, *15*(1). https://doi.org/10.1186/s13027-020-00337-0

Toh, M. R., Wong, E. Y. T., Wong, S. H., Ng, A. W. T., Loo, L. H., Chow, P. K. H., & Ngeow, J. (2023). Global Epidemiology and Genetics of Hepatocellular Carcinoma. *Gastroenterology*, *164*(5). https://doi.org/10.1053/j.gastro.2023.01.033

Tsukamoto, M., Nitta, H., Imai, K., Higashi, T., Nakagawa, S., Okabe, H., Arima, K., Kaida, T., Taki, K., Hashimoto, D., Chikamoto, A., Ishiko, T., Beppu, T., & Baba, H. (2018). Clinical significance of half-lives of tumor markers α-fetoprotein and des-γ-carboxy prothrombin after hepatectomy for hepatocellular carcinoma. *Hepatology Research*, *48*(3). https://doi.org/10.1111/hepr.12942

Tzartzeva, K., Obi, J., Rich, N. E., Parikh, N. D., Marrero, J. A., Yopp, A., Waljee, A. K., & Singal, A. G. (2018). Surveillance Imaging and Alpha Fetoprotein for Early Detection of Hepatocellular Carcinoma in Patients With Cirrhosis: A Meta-analysis. *Gastroenterology*, *154*(6). https://doi.org/10.1053/j.gastro.2018.01.064