PIVKA-II and GAAD in HCC Screening for AFP-Negative CHB Patients

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Project Aims & Objectives

Aim

To assess the clinical value and diagnostic performance of the GAAD **(Gender, Age, AFP, DCP)** algorithm in the early detection and screening of hepatocellular carcinoma (HCC) in high-risk chronic hepatitis B (CHB) patients with AFP-negative status (<20 ng/mL)1.

Objectives

Evaluate the sensitivity and specificity of the GAAD score compared to individual markers (AFP and PIVKA-II) in HCC screening among CHB patients with AFP < 20 ng/mL.

Determine the optimal cut-off value for GAAD in this population and its effectiveness in early-stage HCC detection.

Analyze the characteristics of HCC cases detected via GAAD, including tumor stage and detection rates missed by traditional methods.

Provide clinical recommendations for integrating GAAD into routine HCC screening protocols for AFP-negative patients.

Project Background/Methods

Background

HCC is a leading cancer with high mortality, especially in Vietnam, where CHB infection is prevalent.

Routine screening in CHB patients uses AFP and ultrasound, but sensitivity is limited (especially in AFP-negative cases).

Novel biomarkers (PIVKA-II) and statistical algorithms (GAAD) combining AFP, PIVKA-II, age, and gender may improve detection rates.

There is limited evidence on the effectiveness of these combinations in Vietnamese CHB patients with AFP < 20 ng/mL.

Methods

Study design: Cross-sectional descriptive study combining **retrospective and prospective** data collection.

Study period: January 2022 – July 2024

Setting: National Hospital of Tropical Diseases (Vietnam)

Biomarker assessment:

AFP and PIVKA-II measured using **Elecsys (COBAS E601/E801)** system

GAAD score calculated using **Roche GAAD software**, integrating AFP, PIVKA-II, age, and gender

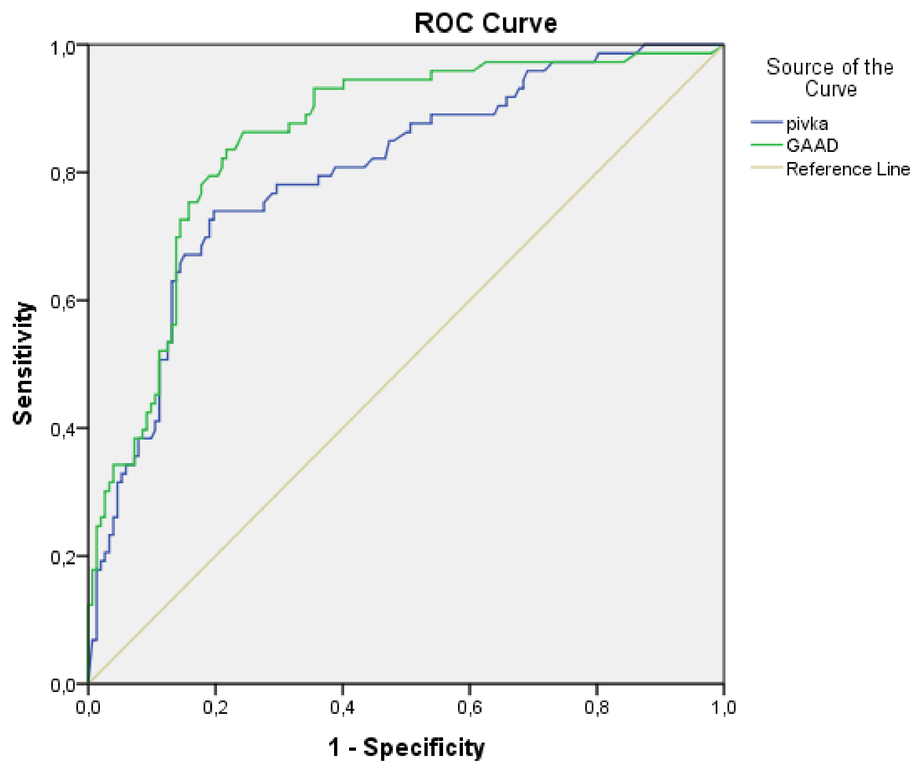
Ethics approval: Approved by Institutional Review Board of the National Hospital of Tropical Diseases

Charts and Figures

Characteristic	HCC (n = 73)	No HCC (n = 152)	p-value
Gender			
Male	62 (84.9%)	106 (69.7%)	0.014*
Female	11 (15.1%)	46 (30.3%)	
Age			
≤ 40	3 (4.1%)	38 (25.0%)	
41 - 70	59 (80.8%)	106 (69.7%)	
> 70	11 (15.1%)	8 (5.3%)	
(χ ± SD)	61.1 ± 9.8	50.6 ± 12.6	

* Chi-square test (χ^2)

	Cut-off	AUC (95%CI)	Sen (%)	Spec (%)	PPV (%)	NPV (%)
PIVKA-II	21.45	0.800 (0.737-0.862)	74.0	80.3	73.9	86.8
GAAD	1.09	0.854 (0.800-0.907)	86.3	75.7	86.3	75.6



Analysis

Study population: 225 patients with chronic hepatitis B (CHB), regularly followed at the National Hospital of Tropical Diseases, all with AFP < 20 ng/mL and complete AFP, PIVKA-II tests.

Inclusion criteria: CHB patients with AFP < 20 ng/mL, confirmed or excluded HCC diagnosis via imaging (CT/MRI) or histopathology in accordance with Vietnam Ministry of Health guidelines.

Biomarker cut-offs:

- AFP: 20 ng/mL
- PIVKA-II: 28.4 ng/mL
- GAAD: calculated using Roche software, proposed cut-off determined at 1.09

Statistical analysis: Conducted with SPSS v20.0. ROC curves, AUC, sensitivity, specificity, PPV, and NPV were calculated to evaluate diagnostic accuracy.

Results

HCC Diagnosis: 73/225 patients (32.4%) diagnosed with HCC despite AFP < 20 ng/mL.

Mean age (HCC vs non-HCC): 61.1 vs 50.6 years (p < 0.001)

Male predominance: 84.9% in HCC group (p < 0.05)

Tumor Characteristics:

74% with single nodule; 24.7% had tumors <2cm.

52.1% detected in early or very early stage (Barcelona staging).

13.3% of HCC cases were missed on initial ultrasound but later confirmed by CT/MRI.

Biomarker Levels (mean ± SD):

AFP: 7.8 ± 5.2 ng/mL (HCC), 4.8 ± 3.9 ng/mL (non-HCC)

PIVKA-II: 1116.6 ± 3035 ng/mL (HCC), 146.6 ± 1017 ng/mL (non-HCC)

GAAD score: 4.5 ± 3.4 (HCC), 1.23 ± 1.9 (non-HCC), p < 0.001

Positive detection rates in HCC group: PIVKA-II: 65.8%; GAAD ≥1.09: 57.5%

The area under the curve (AUC) of PIVKA-II is 0.800. The optimal cut-off for hepatocellular carcinoma (HCC) diagnosis is 21.45 ng/mL with a sensitivity of 74.0% and specificity of 80.3%.

The AUC of GAAD is 0.854, higher than that of PIVKA-II. The optimal cut-off for HCC diagnosis is 1.09 with a sensitivity of 86.3% and specificity of 75.7%.

7 cases (9.6%) GAAD(+)/PIVKA-II(−), of which 6 were early-stage HCC.

Conclusion

The study confirms that the GAAD algorithm delivers superior diagnostic accuracy for hepatocellular carcinoma screening in chronic hepatitis B patients with AFP <20ng/mL compared to AFP or PIVKA-II alone. At the proposed optimal cut-off (GAAD ≥1.09), the algorithm achieved a sensitivity of 86.3% and an AUC of 0.854, outperforming PIVKA-II in this high-risk, hard-to-detect group.

Incorporating the GAAD score into routine HCC surveillance protocols may enhance early cancer detection and reduce missed diagnoses, especially for patients with negative AFP and PIVKA-II results or inconclusive imaging. Further studies are recommended to validate these findings in broader and multi-center cohorts, but current data support the clinical application of GAAD as a practical, sensitive, and cost-effective tool to advance early HCC screening in Vietnam's CHB population

Next step

Future studies will focus on validating the GAAD algorithm in larger cohorts across multiple centers to further confirm its utility in the early detection of hepatocellular carcinoma (HCC) in chronic hepatitis B patients. Additionally, we aim to explore the integration of GAAD with other biomarkers and imaging techniques to refine screening protocols and improve diagnostic accuracy in various clinical settings.

Acknowledgements

We would like to express our sincere gratitude to Roche Vietnam for their financial support and for providing the GAAD scoring software used in this research.

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