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Clinical performance of GAAD score, alpha-fetoprotein, and PIVKA-II in diagnosing hepatocellular carcinoma in the Vietnamese cohort

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Abstract

Objective Alpha-fetoprotein (AFP), PIVKA-II, and GAAD have been studied effectively for the early diagnosis of hepatocellular carcinoma (HCC), creating an opportunity for effective treatment, thereby improving the survival outcomes. However, evidence was scarce in Vietnam, where patients were largely diagnosed at advanced stages with poor prognosis.

Methods A retrospective study was conducted at a single-center in Vietnam to investigate clinical application of standard cutoffs GAAD (2.57), AFP (20 ng/mL), and PIVKA-II (28.4 ng/mL). Receiver operating characteristic (ROC) analysis and area under the curve (AUC) values were calculated for all markers.

Results Among 2611 participants, there were 128 (4.9%) diagnosed with HCC. In HCC cases, 91.41% were aged ≥ 50 with a male to female ratio of 3.9. There were 58.59% with cirrhosis and 63.28% with hepatitis, dominated by hepatitis B (52.34%). GAAD score attained 98.33% of AUC, sensitivity of 86.7%, and specificity of 98.4%. GAAD was more effective than PIVKA-II and AFP in screening HCC patients. A strategy of combining PIVKA-II and AFP overcame limitations of these two biomarkers used alone, denoted by higher values of sensitivity (84.4%) and specificity (96.0%).

Conclusion This study in Vietnam revealed the performance of GAAD and PIVKA-II plus AFP in the HCC screening strategy. These strategies appeared effective for HCC patients regardless of tumor size (≤ 2 cm) or patient age (≥ 50). Further study is encouraged to confirm these findings.

Keywords Hepatocellular carcinoma, GAAD score, PIVKA-II, Des gamma carboxy prothrombin, Alpha-fetoprotein.

1 Introduction

Playing as a global health problem, hepatocellular carcinoma (HCC) accounted for more than 90% of tumors derived from the liver, of which, cirrhosis was found in 85% of cases [1]. According to Globocan 2022, liver cancer was attributable to over 865,269 new cases

and 757,948 deaths related to cancer worldwide [2]. Despite ranking at 6th in incidence, liver cancer obtained a significant mortality rate, positioning at 3rd in cancer death databases [2]. The situation was more notable in Vietnam, where it was recorded as the 2nd in incidence and leading in mortality among cancer types [3]. Apparently, the condition affected three times more males than females [4].

HCC patients faced a high mortality rate due to a low 18% of five-year survival probability [1]. In Vietnam, HCC was poor prognosis with median of survival time was only 10.0 months [5]. Due to the variety of HCC presentations, depending on hepatocyte differentiation, tumor stages, and cirrhotic status, the early diagnosis and survival prognosis was not without challenges. American Association for the Study of Liver Diseases (AASLD) [6] has recommended combining abdominal ultrasound (AUS) and alpha fetoprotein (AFP) in HCC surveillance strategy, which improves early detection, curative treatment, especially survival rates of HCC patients [7]. Indeed, the strategy attained a higher sensitivity (varied from 60% to 74.1%), but a lower specificity (84%) compared to single use of AUS or AFP, and it was consistent across studies [8, 9]. Unfortunately, the previous study indicated that one in three patients might not be detected by this strategy (AUS + AFP) [10].

Several biomarkers have been studied to continue enhancing the quality of HCC surveillance. Protein induced by vitamin K absence or antagonist-II (PIVKA-II), also known as des gamma carboxy prothrombin (DCP), had been studied for long time. In 2016, a comprehensive meta-analysis of 38 studies revealed that PIVKA-II alone in HCC diagnosis was worthy of attention, with sensitivity and specificity of 66% and 88%, respectively (AUC = 0.9002) [11]. The developing PIVKA-II cutoff of 28.4 ng/mL was promising in clinical diagnosis, showing sensitivity of 86.9% and specificity of 83.7% by Elecsys PIVKA-II assay [12].

Taking into account the different HCC risks by males and females, GALAD (gender, AFP, Lens-culinaris AFP [AFP-L3], and PIVKA-II), and GAAD (gender, age, AFP, and PIVKA-II) have emerged as new diagnostic tools in high-risk patients [13, 14]. With the threshold of 2.57, GAAD performed a high sensitivity of 70.1% and strong specificity of 93.7% in detecting early-stage HCC, surpassing the performance of AFP or PIVKA-II alone in the same study [14]. Also, GAAD in combination with AUS was shown as the most cost-effective approach for HCC patients in the early stages with chronic HBV status [15]. Overall, the mushrooming of those studies would be the foundation to derive promising tools in the HCC diagnostic approach.

Contributing to the HCC surveillance, prognostic factors play a role in the long-term management of HCC patients. The increased AFP, as the current common biomarker, has shown a strong correlation with poor HCC survival in several studies. However, up to 30% of advanced patients adopted a normal AFP, requiring other biomarkers in replacement [16]. With updated studies, some new biomarkers have been marked as potentially useful in predicting HCC recurrence or worse survival, such as tumor-associated lymphatic vessel density (LVD), which is obtained under microscopy [17] or portal venous coefficient (PVC) and hepatic arterial coefficient (HAC) measured by CT scans [18]. Additionally, the emergence of the genetic era has unveiled the genetic and epigenetic alterations underlying HCC progression, showing the distinction characteristics and prognosis between genetic subtypes. In combination with those characteristics, patients with hepatitis B or C (HBV/HCV) are classified into six subgroups (G3-6), with different

genetic alterations (chromosomal instability or single-gene variants such as *AXIN1*, *TP53*, *IGF2*, *PIK3CA*, *CDKN2A*, *CTNNB1*) that help explain the underlying progression of tumor derivation and predict prognosis [19].

In Vietnam, a comprehensive study reported that HCC incidence increased from 2010 to 2016, together with over 40% of advanced stage diagnosis, which was inappropriate for the surgical or locoregional therapy [20]. In 2020, the Health Ministry published "Guidelines for the diagnosis and treatment of hepatocellular carcinoma", generally recommended the use of AUS combined with AFP, AFP-L3, or PIVKA-II in screening HCC in high-risk patients every 3–6 months [21]. From 2023, our medical center, named MEDIC Medical Center (MEDIC) at Ho Chi Minh City, Vietnam, has adopted GAAD (Roche Diagnostics International Ltd.) in HCC clinical management. However, lack of report regarding GAAD in HCC diagnosis in Vietnam. This study evaluated the performance of GAAD and other markers in predicting HCC condition, to establish strong evidence of their implications in the Vietnamese population.

2 Materials and methods

2.1 Data collection

The study was conducted on subjects undergoing health check-ups at MEDIC, Ho Chi Minh City, Vietnam, particularly patients with chronic liver disease who had scheduled regular visits. Data was retrospectively collected from September 2023 to December 2024.

Eligible recruitment included subjects aged 18 years or older with sufficient data regarding age, sex, viral hepatitis status, liver elastography using FibroScan 502 (Echosens), HCC biomarkers (AFP, PIVKA-II, and GAAD Score), and imaging tests confirming the HCC diagnosis. HCC was diagnosed using the guidelines of the Vietnamese Health Ministry in 2020 (3129/QĐ-BYT). The FibroScan reported the fibrosis score, with F4 indicating cirrhosis.

Exclusion criteria were applied to those with insufficient data, missing information, or without a definitive diagnosis. Additionally, subjects with a history of HCC, undergoing HCC treatment, HCC recurrence, end-stage kidney disease, use of vitamin K antagonists, under other cancer treatments, or having acute hepatitis were also removed from the study.

2.2 Biomarkers analysis

Briefly, serum samples were collected according to the ISO-certified MEDIC testing protocol. AFP and PIVKA-II concentrations were detected by electrochemiluminescence immunoassay on the Cobas E801 machine according to the manufacturer's instructions (Roche Diagnostics, GmbH, Mannheim, Germany), processing all tests according to ISO 15,189 standards. GAAD scores were automatically calculated and reported using Navify's algorithm.

The standard cutoffs used in the study to determine the HCC screening positive were 2.57 for GAAD score, 20 ng/mL for AFP concentration, and 28.4 ng/mL for PIVKA-II level.

2.3 Statistical analysis

Participants' characteristics were summarized, and comparisons were statistically displayed. As continuous variables, values were summarized into mean and standard deviation (SD) for normal distribution or median and their values at the 25th and 75th percentiles for non-normal distribution. Categorical variables were displayed as a count number and a percentage. To compare, the Chi-square test was applied to categorical variables, the t-test was applied to continuous variables (normal distribution), or using the Mann-Whitney U Test instead (non-normal distribution). *P*-value < 0.05 denotes statistical significance.

Clinical performance of GAAD, AFP, and PIVKA-II in screening for HCC were calculated and compared via receiver operating characteristic (ROC) analysis and area under the curve (AUC) values. Additionally, the combination of AFP and PIVKA-II was also considered in separating analysis. The *p*-value of comparison between AUCs under 0.05 was considered significant level.

Sensitivity and specificity together with 95% confidence intervals (CIs) of those markers were calculated using Wald method. All statistical tests were under SAS 9.4.

3 Results

A total of 2,611 participants were eligible and included in the final analysis. Of these, 128 (4.9%) patients were diagnosed with HCC, and 2,483 (95.1%) were confirmed as non-cancer cases (Fig. 1).

3.1 Study participant characteristics

Table 1 displayed study participants' characteristics stratified by their HCC status. Overall, 66.07% of participants were aged 50 years or older, with a median age of 56 (IQR: 46–65) years. Males were observed more than females (54.35% vs. 45.65%). Only 14.21% were denoted with cirrhosis. Hepatitis occurred in 64.73% of participants, among which

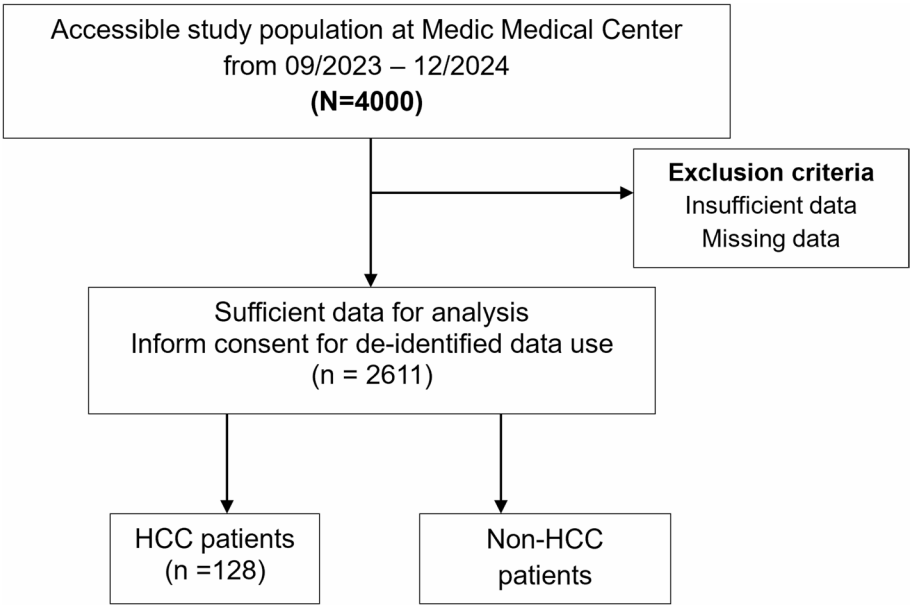


Fig. 1 Study recruitment flow chart

Table 1 Study participants' characteristics

	Total	Non-HCC patients	HCC patients	*p*-value
	2611 (100.0)	2483 (95.10)	128 (4.9)	
Age (years) (median, 25th-75th)	56 (46–65)	55 (45–64)	63 (56–72)	**< 0.001**
< 50	886 (33.93)	875 (35.24)	11 (8.59)	**< 0.001**
≥ 50	1725 (66.07)	1608 (64.76)	117 (91.41)	
Sex (n, %)				
Female	1192 (45.65)	1166 (46.96)	26 (20.31)	**< 0.001**
Male	1419 (54.35)	1317 (53.04)	102 (79.69)	
Cirrhosis (n, %)				
Yes	371 (14.21)	296 (11.92)	75 (58.59)	**< 0.001**
No	2237 (85.68)	2184 (87.96)	53 (41.41)	
Hepatitis B and C (n, %)				
HBV	1348 (51.63)	1281 (51.59)	67 (52.34)	0.6261
HCV	320 (12.26)	308 (12.40)	12 (9.38)	
Concurrent HBV/HCV	22 (0.84)	20 (0.81)	2 (1.56)	
non-HBV/HCV	921 (35.27)	874 (35.20)	47 (36.72)	
Fibroscan (n, %)				
F0	527 (20.18)	527 (21.22)	0 (0)	**< 0.001**
F1	985 (37.73)	981 (39.51)	4 (3.13)	
F2	423 (16.20)	408 (16.43)	15 (11.72)	
F3	305 (11.68)	271 (10.91)	34 (26.56)	
F4	371 (14.21)	296 (11.92)	75 (58.59)	
PIVKA-II (ng/mL) (median, 25th-75th)	15.60 (13.80–18.00)	15.50 (13.80–17.60)	56.50 (27.30–297.00)	**< 0.001**
AFP (ng/mL) (median, 25th-75th)	2.85 (2.13–4.13)	2.74 (2.10–3.87)	8.32 (4.55–40.20)	**< 0.001**
GAAD scores (median, 25th-75th)	0.35 (0.17–0.75)	0.33 (0.16–0.67)	5.05 (3.11–8.10)	**< 0.001**
GAAD categories (n, %)				
High risk (> 2.57)	150 (5.74)	39 (1.57)	111 (86.72)	**< 0.001**
Low risk (≤ 2.57)	2456 (94.06)	2439 (98.23)	17 (13.28)	

Comparison between groups was conducted by Chi-square test for categorical variables, Mann-Whitney U Test for continuous variables with non-normal distribution (age, PIVKAII, AFP, GAAD score). P-value < 0.05 denotes statistical significance

HBV (51.63%) accounted for a higher portion than HCV (12.26%), which were added by 0.84% of concurrent infection.

Over 25% of subjects were scored Fibroscan with F3 to F4. The medians for PIVKA-II, AFP, and GAAD were 15.60 (IQR: 13.80–18.00), 2.85 (IQR: 2.13–4.13), 0.35 (IQR: 0.17–0.75), respectively. At the GAAD cutoff of 2.57, only 5.74% of participants were categorized as high-risk for HCC, while almost all individuals (94.06%) were low risk.

Comparing HCC to non-HCC patients, HCC patients were found to be older (91.41% vs. 64.76% ≥ 50 years old), largely dominated by males (79.69% vs. 53.04%), more diagnosed with cirrhosis (58.59% vs. 11.92%), and more advanced fibrosis score F3 (26.56% vs. 10.91%) or F4 (58.59% vs. 11.92%). Furthermore, HCC patients had over three times higher levels of PIVKA-II (56.50 vs. 15.50 ng/mL) and AFP (8.32 vs. 2.74 ng/mL). In terms of GAAD score, the median of HCC patients was more 15-fold higher than that of non-HCC (5.05 vs. 0.33), resulting in 86.72% of HCC patients in the high-risk group (all *p-values* < 0.001). There was no significant difference in hepatitis/non-hepatitis status between the two subject groups (*p-value* = 0.6261).

3.2 Tumors of 128 HCC-patients

Most of the HCC patients were detected with a single tumor (80%), while 6% were from two, 2% were from three, and 12% had four or more tumors. Among 128 HCC patients,

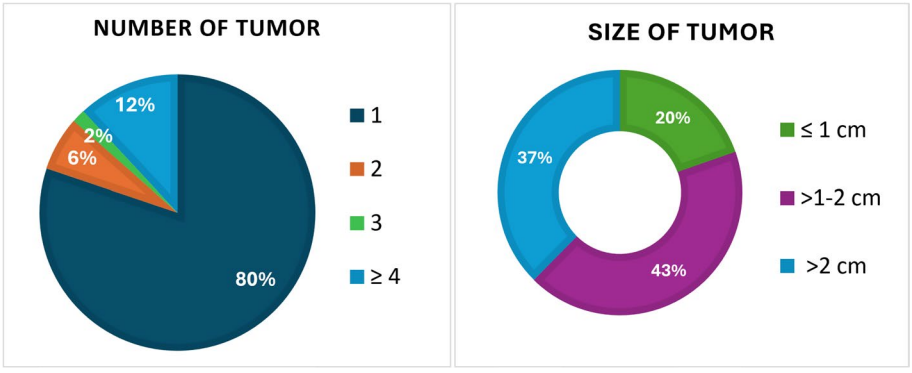
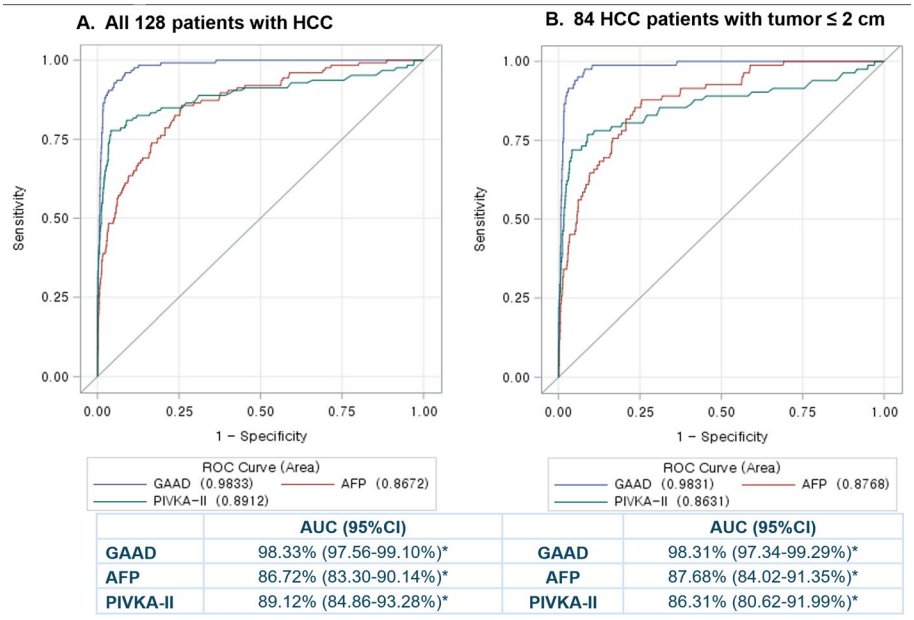


Fig. 2 Number and size of tumor in 128 patients with HCC



	AUC (95%CI)		AUC (95%CI)
GAAD	98.33% (97.56-99.10%)*	GAAD	98.31% (97.34-99.29%)*
AFP	86.72% (83.30-90.14%)*	AFP	87.68% (84.02-91.35%)*
PIVKA-II	89.12% (84.86-93.28%)*	PIVKA-II	86.31% (80.62-91.99%)*

Fig. 3 Receiver operating characteristic (ROC) plots of GAAD score, AFP, and PIVKA-II in the general study population **A** and in patients with tumors ≤ 2 cm **B**. The area under the curves (AUC) was calculated for each diagnosis marker and compared between them; the *p*-value < 0.05 denotes a significant difference between the AUC of markers. **p*-values for GAAD vs. AFP and GAAD vs. PIVKA-II < 0.001

63% had tumors with a maximum size of 2 centimeters (cm), while 37% had tumors exceeding a dimension of 2 cm (Fig. 2).

3.3 Performance of biomarkers in predicting HCC

Figure 3 showed the ROC plots of GAAD score, AFP, and PIVKA-II in predicting HCC. Across all possible thresholds, AUC values showed good classification between HCC and non-HCC patients performed by GAAD (AUC 98.33%, 95%CI: 97.56–99.10), followed by PIVKA-II (AUC 89.12%, 95%CI: 84.86–93.28) ($p < 0.001$) and AFP (AUC 86.72%, 95%CI: 83.30-90.14). GAAD demonstrated more effectively than the two other models (Fig. 3A). The performances of these models were in the same trend for the subgroup of tumor sizes ≤ 2 cm (Fig. 3B).

Using the standard cutoff of 2.57 for GAAD score, sensitivity and specificity were respectively obtained as 86.7% and 98.4%, which surpassed AFP and PIVKA-II in

Table 2 The performance of GAAD score, AFP, PIVKA-II, and PIVKA-II combined with AFP in predicting HCC patients using standard cutoffs

	Total	Age ≥ 50 (Years old)	Tumor size ≤ 2 cm
	N = 2611	*N* = 1725	*N* = 2567
GAAD score ≥ 2.57			
Sensitivity	0.867 (0.808–0.926)	0.863 (0.801–0.926)	0.869 (0.797–0.941)
Specificity	0.984 (0.979–0.989)	0.980 (0.973–0.986)	0.984 (0.979–0.989)
Accuracy	0.979 (0.973–0.984)	0.972 (0.964–0.980)	0.981 (0.975–0.986)
Positive predictive value (PPV)	0.740 (0.669–0.810)	0.754 (0.681–0.827)	0.652 (0.564–0.740)
Negative predictive value (NPV)	0.993 (0.989–0.996)	0.990 (0.985–0.995)	0.996 (0.993–0.998)
AFP ≥ 20ng/mL			
Sensitivity	0.328 (0.247–0.410)	0.299 (0.216–0.382)	0.286 (0.189–0.382)
Specificity	0.989 (0.985–0.993)	0.989 (0.984–0.994)	0.989 (0.985–0.993)
Accuracy	0.956 (0.949–0.964)	0.943 (0.932–0.954)	0.966 (0.959–0.973)
Positive predictive value (PPV)	0.60 (0.485–0.715)	0.673 (0.546-0.800)	0.462 (0.326–0.597)
Negative predictive value (NPV)	0.966 (0.959–0.973)	0.951 (0.941–0.961)	0.976 (0.970–0.982)
PIVK-II ≥ 28.4 ng/mL			
Sensitivity	0.727 (0.649–0.804)	0.735 (0.655–0.815)	0.679 (0.579–0.778)
Specificity	0.970 (0.963–0.977)	0.965 (0.956–0.974)	0.970 (0.963–0.977)
Accuracy	0.958 (0.950–0.966)	0.949 (0.939–0.960)	0.960 (0.953–0.968)
Positive predictive value (PPV)	0.554 (0.478–0.629)	0.601 (0.521–0.682)	0.432 (0.347–0.516)
Negative predictive value (NPV)	0.986 (0.981–0.990)	0.980 (0.974–0.987)	0.989 (0.985–0.993)
PIVKA-II ≥ 28.4 ng/mL or AFP ≥ 20ng/mL			
Sensitivity	0.844 (0.781–0.907)	0.838 (0.771–0.904)	0.821 (0.740–0.903)
Specificity	0.960 (0.952–0.968)	0.956 (0.946–0.966)	0.960 (0.952–0.968)
Accuracy	0.954 (0.946–0.962)	0.948 (0.937–0.958)	0.956 (0.948–0.964)
Positive predictive value (PPV)	0.522 (0.454–0.590)	0.580 (0.506–0.654)	0.411 (0.336–0.485)
Negative predictive value (NPV)	0.992 (0.988–0.995)	0.988 (0.982–0.993)	0.994 (0.991–0.997)

screening for HCC. The combination of PIVKA-II ≥ 28.4 ng/mL and AFP ≥ 20ng/mL seemed to overcome the disadvantage of each biomarker when individually applied, denoted by higher values of sensitivity and specificity of 84.4% and 96.0%, respectively (Table 2). Further stratification analyses were conducted in subgroups of age (≥ 50 years old) and tumor size (≤ 2 cm), and the results were shown in the same pattern as the overall analysis.

4 Discussion

A total of 128 (4.9%) individuals were diagnosed with HCC. They were 91.41% from 50 years or older (median age of 63), had a male to female ratio of 3.9, about 58.59% of cirrhosis, and 63.28% of hepatitis. Among HCC patients, 52.34% were HBV, while 9.38% were HCV and 1.56% were both HBV and HCV infections. In this study, the GAAD score (AUC = 98.33%) demonstrated the highest sensitivity of 86.7% and specificity of 98.4%, which was more effective than other models (PIVKA-II and AFP) in screening HCC patients. A strategy of combining PIVKA-II and AFP overcame limitations of these two biomarkers used alone, denoted by higher values of sensitivity (84.4%) and specificity (96.0%). The performances of those biomarkers were consistent by tumor size (≤ 2 cm) and age subgroup (≥ 50 years old) analyses.

Previously, a study in Northern Vietnam revealed that HCC patients had a median age of 57 years old and the ratio of male/female patients was 8.9 to 1 [22], which was significantly different compared to our study. Also, that study displayed a higher proportion of HBV infection (81.3%) compared to 53.9% in our probands [22]. Our study, located in

the Southern area, revealed different characteristics compared to those of the Northern area. So far, one study reported varying characteristics regarding HBV infection and primary liver cancer between the Northern and Southern regions in Vietnam [23], which could explain the controversy between studies.

AFP was one of the most common markers in diagnosing HCC, with varied sensitivity and specificity by the cutoff used [24]. Nevertheless, AFP faced debates because of its poor performance in HCC detection as well as nonspecific elevations across hepatic and non-hepatic conditions [25]. Accordingly, the sensitivity and specificity of AFP in screening HCC conditions ranged 17–60% and 90-99.4%, respectively, depended on AFP cutoff values. The sensitivity was shown to be highest by 60% for a cutoff of 20 ng/mL [25]. From a meta-analysis, the AFP threshold of 20–100 ng/mL showed the summary sensitivity of 0.61 (95%CI 0.60–0.62) and specificity of 0.86 (95%CI 0.86–0.87). Combining AFP with other biomarkers helped improve its sensitivity but reduced its specificity [8, 9]. The AFP specificity was significantly improved (99.0%) as a higher AFP threshold was applied (400 ng/mL or 200 ng/mL) [24]. In this study, to discriminate HCC and non-HCC patients, the AFP analysis reported the value of AUC (95% CI) at 86.72% (83.30-90.14); however, AFP did not yield good performance in our cases at cutoff 20ng/mL with sensitivity of only 32.8%, but with high specificity at 98.9%. To note that, the median AFP level in our patients was 8.32 (IQR: 4.55–40.20) ng/mL, which was significantly lower than the standard cutoff (20 ng/mL). Evidence showed that bigger tumors generally had higher AFP values; therefore, the sensitivity of AFP decreased from 52% to 25% for tumors under 3 cm in diameter [26]. According to our cases, about 80% had one tumor and over 63% had tumors with a maximum size of 2 cm. Moreover, studies showed that the AFP-negative condition could exist in 50% of HCC patients, which was mainly in early and small HCC tumors. Furthermore, up to 30% of advanced patients did not with AFP elevation [16], which could help explain the poor AFP levels in our study samples, leading to its poor performance.

Some studies showed PIVKA-II was comparable to, or effective complementary use with AFP [27, 28]. Nevertheless, the recommendation for PIVKA-II was still limited to HCC risk stratification rather than HCC surveillance, approved by the US Food and Drug Administration (FDA). Whether PIVKA-II capacity to replace or complement AFP in detecting HCC was controversial. In 2023, a consensus statement of experts from Asia-Pacific region highlighted the role of PIVKA-II in patients with AFP-negative, and that 100% agreement for the beneficial use of PIVKA-II in AFP-negative cases [10]. Our study supported the advantage of PIVKA-II in detecting HCC, with an AUC (95% CI) was 89.12% (84.86–93.28). Using the threshold of 28.4 ng/mL, our study showed high sensitivity (72.7%) and specificity (97.0%) for PIVKA-II, which was more effective than AFP alone. As discussed above, our patients had a significantly low level of AFP compared to the standard cutoff; hence, we believed that PIVKA-II had been well-performed in our study sample. Interestingly, our study showed that the combination of AFP and PIVKA-II was a better strategy, showing improved sensitivity (84.4%) and good specificity (96%) compared to that of each biomarker. Indeed, a recent study revealed that the combination had notable performance (sensitivity of 92% and specificity of 82%), which was even higher than ours [12]. Also, PIVKA-II in the combined strategy with AFP was proven to be a good prognostic indicator in liver transplantation at pre-operation [10].

By incorporating multiple parameters such as clinical and serum biomarkers into algorithms for early HCC detection, different models were studied [29]. A study by Hou et al. showed that, using a cutoff of 2.57 in differentiating all-stage HCC with chronic liver diseases, GAAD score (Cobas) attained an AUC of 95.4%, sensitivity of 85.2%, and specificity of 90.1%. In comparison, higher values were recorded for late-stage HCC (AUC: 98.3%, sensitivity: 95.1%, and specificity: 90.1%) [30]. In the same study, GALAD (Cobas) was shown to have a similar benefit to GAAD in screening for HCC [30]. Consistently, in 2024, a study in China showed that GAAD attained an AUC of 95.6% in all-stage HCC, higher value observed for late-stage HCC (99.7%) [31]. Also using 2.57 cutoff, GAAD sensitivity was 77.3% for all-stage, 67.3% for the early stage, and driving up to 93.9% for late-stage HCC, with a specificity of 99.3% [31]. Those studies denoted the advantage of GAAD in late-stage compared to early-stage HCC. Interestingly, GAAD and GALAD algorithms had comparable performance, independent of HBV status, cirrhosis condition, and study region, suggesting that AFP-L3 in GALAD seems to have a negligible role in HCC diagnosis [31]. Our study evaluated GAAD in detecting HCC; the outcome was in line with previous reports. Accordingly, our GAAD score achieved the highest AUC value (98.33%) among investigated biomarkers (GAAD, AFP, and PIVKA-II), which was not inferior to other AUCs in previous studies. Our study showed the performance of GAAD with 86.7% sensitivity and 98.4% specificity, independent of age and tumor size. The results of this study were not stratified by HCC stage; instead, we assessed all-stage HCC patients. As results, the sensitivity and specificity of GAAD in this study were higher as compared to those of previous reports, values corresponding to all-stage HCC. Overall, the GAAD score was the most promising biomarker in our study to predict HCC patients. Adding to current knowledge, a strategy of applying GAAD with AUS in HCC surveillance in China showed that GAAD plus AUS was a cost-effective strategy [15], suggesting the application in a screening scheme for high-risk populations in the future.

This was the first study in Southern Vietnam to evaluate the GAAD score on HCC screening. Accessing a large cohort of patients, our study was believed to be representative of our area's population. However, some limitations were not eliminated from our study. This study was retrospective recruitment so that some information was not available for study analysis, leading to large number of patients excluded from a primary cohort. Our study could suffer from selection bias, which might affect the study population representation. We tried to minimize it by prolonging the study time frame to 15 months to maximize our study sample sizes. Based on the study purpose, we only considered potential variables related to HCC surveillance strategy, preventing the exclusion of people missing unnecessary information. In addition, all participants with specific conditions that seemed to confound the study results were excluded. Furthermore, clinical presentations related to HCC were not obtained, deep analysis for study subgroups by patients' manifestations was limited. Further study with strong design, larger sample size, prospective data collection, and involving disease manifestations would be encouraged to confirm our results in Vietnamese population as well as to perform deeper stratification analyses for those biomarkers in specific groups.

In conclusion, our study was the first study in Vietnam to reveal the performance of GAAD and PIVKA-II plus AFP in the HCC screening strategy. These strategies appeared

effective for all HCC patients coming to our department, regardless of tumor size (≤ 2 cm) or patient age (≥ 50). Further research is encouraged to confirm these findings.

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Author contributions
Conceptualization and method: T.TTP and H.TP; Data acquisition, curation, and analysis: D.TH and T.BN; Interpretation: T.TTP and H.TP; Drafting and revising manuscript: T.TTP; Final approval: all authors approved the final version to be published.

Data availability
All data underlying the results were available as part of the article.

Declarations

Competing interests
The authors declare no competing interests.

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