




# The Index sAGP is Valuable for Distinguishing Atypical Hepatocellular Carcinoma from Atypical Benign Focal Hepatic Lesions

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**Purpose:** The differential diagnosis of atypical hepatocellular carcinoma (aHCC) and atypical benign focal hepatic lesions (aBFHL) usually depends on pathology. This study aimed to develop non-invasive approaches based on conventional blood indicators for the differential diagnosis of aHCC and aBFHL.

**Patients and Methods:** Hospitalized patients with pathologically confirmed focal hepatic lesions and their clinical data were retrospectively collected, in which patients with HCC with serum alpha-fetoprotein (AFP) levels of  $\leq 200$  ng/mL and atypical imaging features were designated as the aHCC group ( $n = 224$ ), and patients with benign focal hepatic lesions without typical imaging features were designated as the aBFHL group ( $n = 178$ ). The performance of indexes (both previously reported and newly constructed) derived from conventional blood indicators by four mathematical operations in distinguishing aHCC and aBFHL was evaluated using the receiver operating characteristic (ROC) curve and diagnostic validity metrics.

**Results:** Among ten previously reported derived indexes related to HCC, the index GPR, the ratio of  $\gamma$ -glutamyltransferase (GGT) to platelet (PLT), showed the best performance in distinguishing aHCC from aBFHL with the area under ROC curve (AUROC) of 0.853 (95% CI 0.814–0.892), but the other indexes were of little value (AUROCs from 0.531 to 0.700). A new derived index, sAGP [(standardized AFP + standardized GGT)/standardized PLT], was developed and exhibited AUROCs of 0.905, 0.894, 0.891, 0.925, and 0.862 in differentiating overall, BCLC stage 0/A, TNM stage I, small, and AFP-negative aHCC from aBFHL, respectively.

**Conclusion:** The sAGP index is an efficient, simple, and practical metric for the non-invasive differentiation of aHCC from aBFHL.

**Keywords:** atypical hepatocellular carcinoma, differential diagnosis, conventional blood indicator, derived index, sAGP

## Introduction

Primary hepatic carcinoma (PHC) is one of the common malignancies, with an estimated 906,000 new cases and 830,000 deaths in 2020, ranking as the sixth most frequent cancer and the third leading cause of cancer-related death worldwide.<sup>1</sup> Due to difficulties in early diagnosis, 60% of patients with PHC have progressed to intermediate or advanced stages at the time of diagnosis, and the majority lose the opportunity for radical surgery, resulting in an overall 5-year survival rate of  $< 10\%$ .<sup>2</sup> In contrast, early diagnosis followed by effective treatment can significantly change the course of the disease and improve prognosis, resulting in an overall 5-year survival rate of  $> 70\%$ .<sup>3</sup> Therefore, early diagnosis of PHC is important.

Hepatocellular carcinoma (HCC) accounts for 90% of PHC. At present, the clinical diagnosis of HCC mainly depends on serum alpha-fetoprotein (AFP) and imaging examination. In the Asia-Pacific guidelines for the management of hepatocellular carcinoma,  $\text{AFP} \geq 200$  ng/mL is used as a criterion for HCC surveillance.<sup>4</sup> However, up to 30% of HCC

patients do not present with elevated serum AFP levels.<sup>5</sup> In addition, approximately 40% of patients with hepatitis and 30% of patients with cirrhosis have elevated AFP levels, even exceeding 200ng/mL.<sup>6</sup>

Imaging examination is an important tool in the diagnosis of HCC. The typical imaging features of HCC are hyper-enhancement during the arterial phase followed by washout during the portal and late phases. However, 5–41% of HCC do not have these typical features, while some benign focal hepatic lesions (BFHL) are radiologically difficult to distinguish from atypical HCC, which leads to the requirement for pathological examination to clarify the diagnosis.<sup>7</sup> Unfortunately, preoperative pathological examination requires liver biopsy to obtain tissue specimens. Liver biopsy, in addition to causing pain to the patient, may cause bleeding, infection, needle track tumor seeding, and injury (pneumothorax, hemothorax, and injury to the gallbladder, bowel, or kidney). Therefore, non-invasive diagnostic approaches are important for patients with focal hepatic lesions but whose imaging examinations are difficult to diagnose qualitatively. Here, we defined the HCC and BFHL with AFP < 200ng/mL and uncertain imaging diagnosis as atypical HCC (aHCC) and atypical BFHL (aBFHL), respectively.

In recent years, some studies have found that routine laboratory indicators alone or in combination are of certain value in the clinical practice of HCC.<sup>8,9</sup> Given the limited value of single routine laboratory indicators, a number of indexes based on a combination of routine laboratory indicators have been derived by four arithmetic operations, and their diagnostic and prognostic performances for HCC have been evaluated, including inflammation-related derived indexes, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune inflammatory index (SII), lymphocyte-to-monocyte ratio (LMR),<sup>10–12</sup> and liver function-related derived indexes, such as  $\gamma$ -glutamyltransferase to aspartate aminotransferase ratio (GGT/AST),  $\gamma$ -glutamyltransferase to alanine aminotransferase ratio (GGT/ALT),  $\gamma$ -glutamyltransferase to alkaline phosphatase ratio (GGT/ALP),  $\gamma$ -glutamyltransferase-to-platelet ratio (GPR), fibrinogen-to-prealbumin ratio (FPR), and fibrinogen-to-albumin ratio (FAR).<sup>13–16</sup> These derived indexes are potentially valuable for the diagnosis and prognosis of HCC.<sup>17</sup>

The differential diagnostic value of these derived indexes for aHCC and aBFHL is unclear. We speculate that they may be of good value in distinguishing aHCC from aBFHL, as the above findings suggest that conventional clinical indicators contain important clinical information about HCC. Therefore, in the present study, we evaluated the performance of the above reported derived indexes for differentiating aHCC from aBFHL and, more importantly, tried to derive new indexes with better performance to distinguish aHCC from aBFHL.

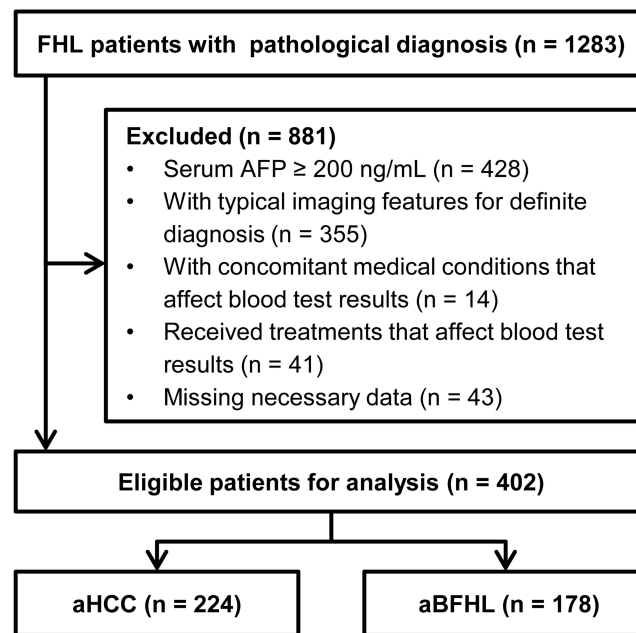
## Materials and Methods

### Patients and Data Collection

Patients with focal hepatic lesions (FHL) who were hospitalized at the First Affiliated Hospital of Nanchang University from January 2015 to December 2020 and had a pathological diagnosis were retrospectively collected. The clinical and pathological data of each patient were obtained from the electronic medical records, including demographics data, results of first laboratory tests and imaging examinations before treatment after admission to hospital, and pathological results of FHL. Patients with the following conditions were excluded: (1) serum AFP levels >200 ng/mL; (2) typical imaging features on CT scans allowing for a definite diagnosis (3) concomitant medical conditions that may affect the results of laboratory blood tests; (4) received therapies that may affect the results of laboratory blood tests; (5) missing necessary data, including AFP, GGT, and contrast-enhanced CT/MRI scan. [Figure 1](#) shows the flowchart of patient selection.

### Data Processing and Statistical Analysis

Patients with aHCC were staged according to the Barcelona Clinic Liver Cancer (BCLC) staging system 2022<sup>18</sup> and the eighth version of the Tumor, Node, Metastases (TNM) staging system.<sup>19</sup> The reported derived indexes were calculated according to the algorithms in the literature: NLR, PLR, LMR, SII, GGT/AST, GGT/ALT, GGT/ALP, FPR, FAR, GPR, as well as Child-Pugh score and grade. The best reported derived indexes were used to derive new indexes with better diagnostic performance. In this process, the indicators were standardized using the upper limit of their normal range (ie, the ratio of the original value to the upper limit) and marked with the prefix “s” in order to improve the generalization ability of the new indexes in applications.



**Figure 1** Flowchart of patient selection.

**Abbreviations:** FHL, focal hepatic lesion; AFP, alpha-fetoprotein; aHCC, atypical hepatocellular carcinoma; aBFHL, atypical benign focal hepatic lesion.

Measurement variables were presented as the mean  $\pm$  standard deviation (SD) if normally distributed or median (M) (interquartile range, IQR) if non-normally distributed and compared between the two groups using Student's *t*-test or Mann–Whitney *U*-test. Categorical variables were presented as count and percentage and compared between the two groups using Pearson's Chi-squared test.  $P < 0.05$  was considered statistically significant. The diagnostic performance of indexes was evaluated using the area under the receiver operating characteristic (ROC) curve (AUROC) and sensitivity, specificity, accuracy, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio. Statistical software SPSS 25.0 (IBM, Chi, USA) and MedCalc 22.0 (MedCalc Software Ltd, Ostend, BE) were used for data analyses.

## Results

### Demographic and Clinical Data of Patients

A total of 402 patients were enrolled in this study, including 224 cases of aHCC and 178 cases of aBFHL. The demographic and clinical characteristics of patients are shown in Table 1. Clinical tumor staging data were available in 212 aHCC patients, of which 23 (10.8%), 164 (77.4%), 11 (5.2%), and 14 (6.6%) cases were in BCLC stages 0, A, B, and C, respectively, and 180 (84.9%), 10 (4.7%), 16 (7.5%), and 6 (2.8%) cases were in TNM stages I, II, III, and IV, respectively. The majority of aHCC were hepatitis B virus-associated HCC, with an 84.4% (189/224) positive rate of hepatitis B virus serum markers. Patients with aBFHL included 109 cases of cavernous hemangioma, 19 cases of angiomyolipoma, 21 cases of focal nodular hyperplasia, and 29 cases of other diseases.

### Diagnostic Performance of Reported Derived Indexes for aHCC

Previously reported derived indexes that were related to HCC included the inflammation-related (NLR, PLR, LMR, SII) and the liver function-related (GGT/AST, GGT/ALT, GGT/ALP, GPR, FPR, FAR). The diagnostic performance of these derived indexes for aHCC was analyzed using the ROC curve (Figure 2), and the results showed that GPR had the best diagnostic performance, with an AUROC of 0.853 (95% CI: 0.814–0.892), whereas the AUROCs of other derived indexes were below 0.8 (Table 2).

**Table 1** Demographic and Clinical Characteristics of the Patients

	Result [Mean ± SD, n (%) or M (IQR)]				P
	n	aHCC	n	aBFHL	
<b>Age (years)</b>	224	56.0 ± 10.2	178	46.8 ± 11.5	< 0.001 <sup>a</sup>
<b>Sex</b>	224		178		< 0.001 <sup>b</sup>
Male		204 (91.1)		61 (34.3)	
Female		20 (8.9)		117 (65.7)	
<b>Blood tests</b>					
WBC (*10 <sup>9</sup> /L)	224	5.0 (3.9–6.4)	178	5.2 (4.1–6.4)	0.332 <sup>c</sup>
RBC (*10 <sup>12</sup> /L)	224	4.5 ± 0.6	178	4.5 ± 0.5	0.816 <sup>a</sup>
HGB (g/L)	224	140.0 (128.0–151.8)	178	131.0 (122.0–142.3)	< 0.001 <sup>c</sup>
PLT (*10 <sup>9</sup> /L)	224	155.2 ± 80.0	178	221.6 ± 72.0	< 0.001 <sup>a</sup>
NEUT (*10 <sup>9</sup> /L)	224	2.8 (2.1–3.7)	178	3.0 (2.3–3.9)	0.308 <sup>c</sup>
LYM (*10 <sup>9</sup> /L)	224	1.5 ± 0.7	178	1.7 ± 0.5	0.044 <sup>a</sup>
MON (*10 <sup>9</sup> /L)	224	0.4 (0.3–0.5)	178	0.4 (0.3–0.5)	0.031 <sup>c</sup>
ALB (g/L)	224	41.4 (38.1–44.3)	178	44.2 (41.7–46.3)	< 0.001 <sup>c</sup>
TBIL (μmol/L)	224	13.7 (9.3–17.5)	178	9.4 (7.0–12.5)	< 0.001 <sup>c</sup>
DBIL (μmol/L)	224	3.8 (2.9–6.1)	178	2.4 (1.7–3.4)	< 0.001 <sup>c</sup>
ALT (U/L)	224	31.0 (23.0–45.0)	178	16.0 (11.0–27.0)	< 0.001 <sup>c</sup>
AST (U/L)	224	34.5 (27.0–49.8)	178	20.7 (18.0–25.3)	< 0.001 <sup>c</sup>
GGT (U/L)	224	48.5 (28.0–88.8)	178	21.0 (14.0–34.0)	< 0.001 <sup>c</sup>
ALP (U/L)	224	100.5 (81.3–127.0)	178	76.0 (59.8–94.3)	< 0.001 <sup>c</sup>
PA (g/L)	143	210.3 ± 69.7	107	268.7 ± 72.6	< 0.001 <sup>a</sup>
CR (μmol/L)	224	74.2 ± 15.4	178	62.3 ± 14.4	< 0.001 <sup>a</sup>
BUN (mmol/L)	224	5.4 ± 1.5	178	5.0 ± 1.4	0.004 <sup>a</sup>
PT (s)	221	11.8 (11.1–12.7)	178	10.9 (10.4–11.6)	< 0.001 <sup>c</sup>
APTT (s)	221	28.4 (26.3–32.5)	178	27.6 (25.3–29.8)	< 0.001 <sup>c</sup>
FBG (g/L)	221	2.5 (2.1–3.2)	173	2.4 (2.1–2.9)	0.198 <sup>c</sup>
AFP (ng/mL)	224	8.6 (3.2–42.6)	178	2.4 (1.6–3.4)	< 0.001 <sup>c</sup>
<b>Child-Pugh grade</b>	221		178		0.004 <sup>b</sup>
A		209 (94.6)		175 (98.3)	
B		12 (5.4)		2 (1.1)	
C		0 (0.0)		1 (0.6)	

**Notes:** <sup>a</sup>Student's *t*-test. <sup>b</sup>Pearson's Chi-squared test. <sup>c</sup>Mann-Whitney *U*-test.

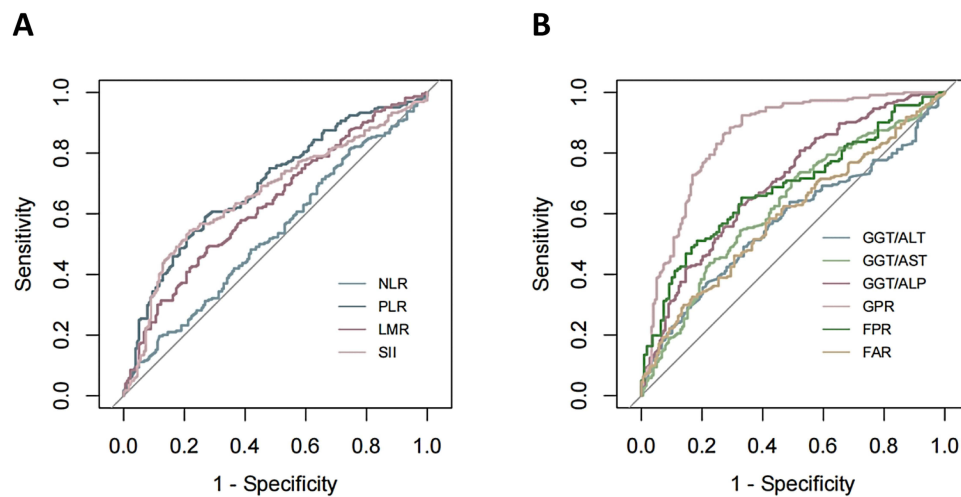
**Abbreviations:** aHCC, atypical hepatocellular carcinoma; aBFHL, atypical benign focal hepatic lesions; WBC, white blood cell; RBC, red blood cell; HGB, hemoglobin; PLT, platelet; LYM, lymphocyte; MON, monocyte; NEUT, neutrophil; ALB, albumin; TBIL, total bilirubin; DBIL, direct bilirubin; ALT, alanine aminotransaminase; AST, aspartate aminotransaminase; GGT,  $\gamma$ -glutamyltransferase; ALP, alkaline phosphatase; PA, prealbumin; CR, creatinine; BUN, blood urea nitrogen; PT, prothrombin time; APTT, activated partial thromboplastin time; FBG, fibrinogen; AFP, alpha fetoprotein.

## A New Derived Index and Its Diagnostic Performance for aHCC

Among the reported derived indexes, GPR showed the greatest AUROC for the diagnosis of aHCC. Therefore, we combined the indicators of GPR with other indicators to construct new derived indexes to outperform GPR in terms of diagnostic performance, and the results showed that the AUROC of AGP [(AFP+GGT)/PLT] was the greatest among the new derived indexes and higher than those of GPR and AFP (Figure 3A). For better generalization of AGP, the three indicators in AGP (ie, AFP, GGT, and PLT) were standardized using the upper limit of normal range, and a standardized AGP, sAGP [(standardized AFP + standardized GGT) to standardized PLT ratio], was obtained, which further improved the diagnostic performance (Figure 3A). Based on the ROC curve analysis, the optimal cutoff values for sAGP, GPR, and AFP to diagnose aHCC were 1.92, 0.13, and 4.37, respectively. According to these cutoff values, the metrics of diagnostic validity for aHCC were calculated and are shown in Figure 3B.

## Diagnostic Performances of sAGP for Early, Small, and AFP-Negative aHCC

The AUROCs and diagnostic validity metrics of sAGP were calculated for aHCC subtypes, including early aHCC (BCLC stage 0/A, *n* = 187, and TNM stage I, *n* = 180), small aHCC (tumor diameter <3 cm, *n* = 65), and AFP-negative



**Figure 2** Receiver operating characteristic curves of derived indexes reported previously for the diagnosis of atypical hepatocellular carcinoma. **(A)** Inflammation-related derived indexes; **(B)** Liver function-related derived indexes.

**Abbreviations:** NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; SII, systemic immune inflammatory index; ALT, alanine aminotransaminase; AST, aspartate aminotransaminase; GGT,  $\gamma$ -glutamyltransferase; ALP, alkaline phosphatase; GPR,  $\gamma$ -glutamyltransferase-to-platelet ratio; FPR, fibrinogen-to-prealbumin ratio; FAR, fibrinogen-to-albumin ratio.

(AFP < 20 ng/mL, n = 146) aHCC, and the results showed that sAGP performed well in diagnosing various subtypes of aHCC and better than GPR and AFP (Figure 4).

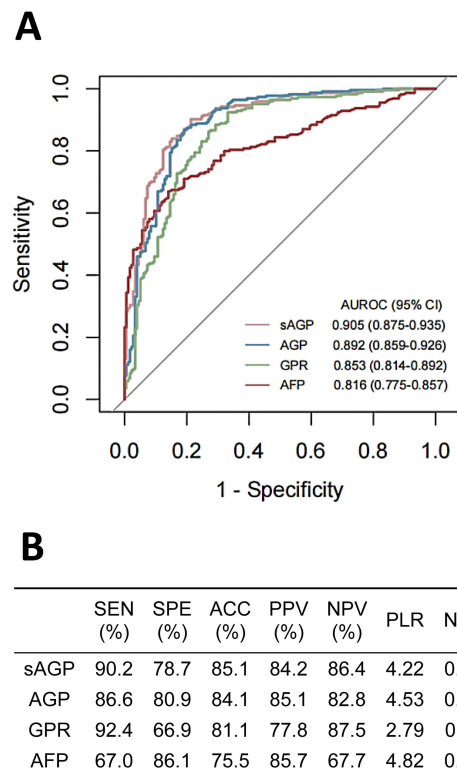
## Discussion

In this study, we investigated indexes derived from conventional laboratory blood indicators for the differential diagnosis of HCC and BFHL that are atypical on imaging. We evaluated the diagnostic value of previously reported ten derived indexes and found that only GPR had an AUROC greater than 0.8 in differentiating aHCC from aBFHL. In order to improve the diagnostic performance, the new index sAGP was derived by the combination of AFP with the two indicators (GGT and PLT) in GPR and showed good diagnostic performance for aHCC (AUROC = 0.905). More importantly, sAGP also performed well in diagnosing early-stage, small, and AFP-negative aHCC. These results suggest that sAGP is a valuable index for the clinical diagnosis of aHCC.

**Table 2** Reported Derived Indexes for the Diagnosis of Atypical Hepatocellular Carcinoma

Indexes	Result [M (IQR)]				P	AUROC (95% CI)
	n	aHCC	n	aBFHL		
NLR	224	1.92 (1.47–2.60)	178	1.86 (1.37–2.51)	0.286	0.531 (0.474–0.588)
PLR	224	95.77 (69.94–134.66)	178	135.42 (102.63–176.94)	< 0.001	0.694 (0.643–0.746)
LMR	223	3.75 (2.75–4.92)	178	4.38 (3.43–5.98)	< 0.001	0.628 (0.574–0.683)
SII	224	259.58 (167.01–425.72)	178	394.68 (290.17–553.68)	< 0.001	0.666 (0.613–0.719)
GGT/ALT	224	1.66 (0.96–2.53)	178	1.27 (0.99–1.98)	0.014	0.572 (0.516–0.627)
GGT/AST	224	1.39 (0.89–2.11)	178	0.95 (0.69–1.50)	< 0.001	0.626 (0.571–0.681)
GGT/ALP	224	0.46 (0.30–0.83)	178	0.29 (0.20–0.45)	< 0.001	0.700 (0.649–0.751)
GPR	224	0.38 (0.19–0.74)	178	0.10 (0.07–0.17)	< 0.001	0.853 (0.814–0.892)
FAR	221	0.06 (0.05–0.08)	173	0.05 (0.05–0.07)	0.002	0.591 (0.536–0.647)
FPR	141	0.01 (0.01–0.02)	107	0.01 (0.01–0.01)	< 0.001	0.682 (0.616–0.747)

**Abbreviations:** aHCC, atypical hepatocellular carcinoma; aBFHL, atypical benign focal hepatic lesions; AUROC, area under the receiver operating characteristic curve; CI, interval confidence; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; SII, systemic immune inflammatory index; ALT, alanine aminotransaminase; AST, aspartate aminotransaminase; GGT,  $\gamma$ -glutamyltransferase; ALP, alkaline phosphatase; GPR,  $\gamma$ -glutamyltransferase to platelet ratio; FPR, fibrinogen to prealbumin ratio; FAR, fibrinogen to albumin ratio.



**Figure 3** Diagnostic performance of sAGP, AGP, GPR, and AFP in differentiating atypical hepatocellular carcinoma from atypical benign focal hepatic lesion. **(A)** Receiver operating characteristic curves; **(B)** Diagnostic validity metrics.

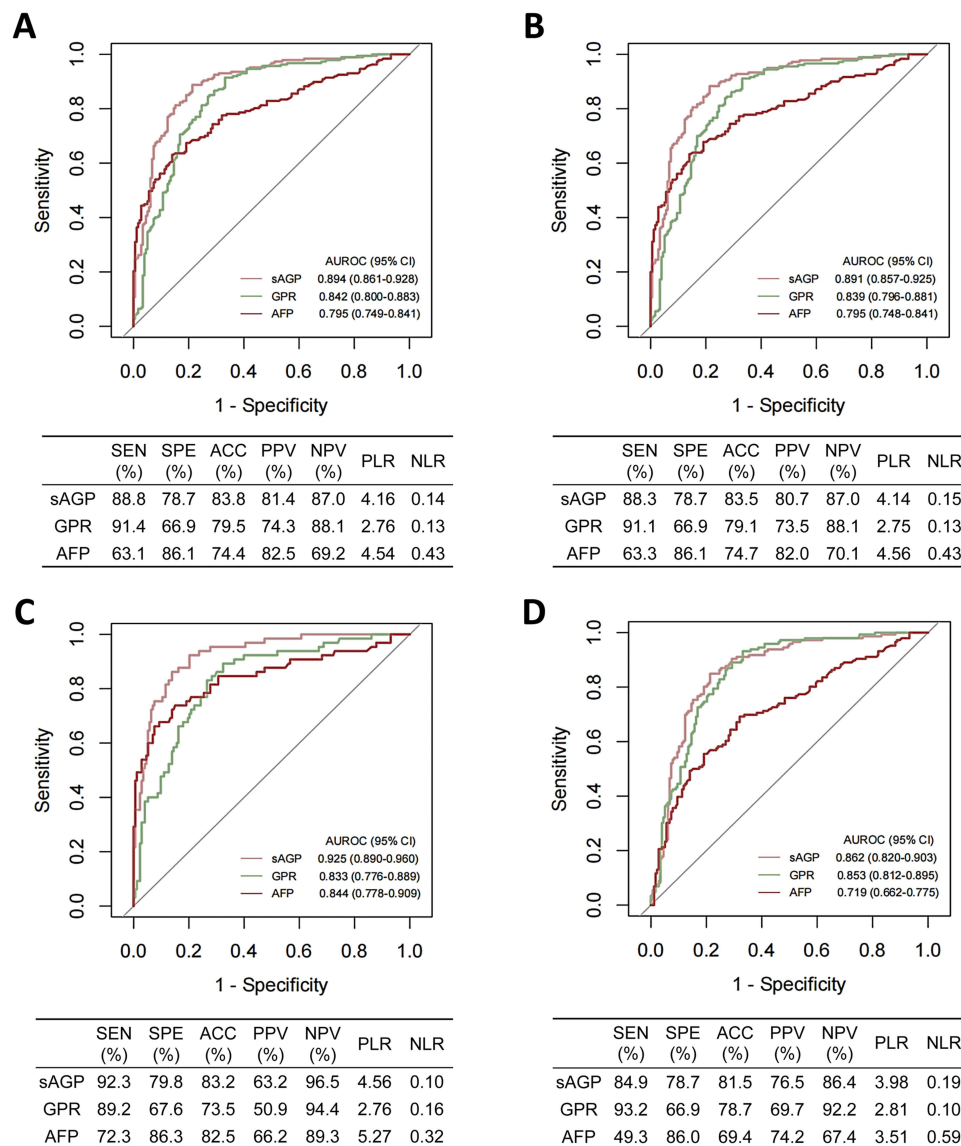
**Abbreviations:** AUROC, area under the receiver operating characteristic curve; CI, confidence interval; sAGP, (standardized  $\alpha$ -fetoprotein + standardized  $\gamma$ -glutamyltransferase) to standardized platelet count ratio; AGP, ( $\alpha$ -fetoprotein +  $\gamma$ -glutamyltransferase) to platelet count ratio; GPR,  $\gamma$ -glutamyltransferase-to-platelet ratio; AFP,  $\alpha$ -fetoprotein; SEN, sensitivity; SPE, specificity; ACC, accuracy; PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; NLR, negative likelihood ratio.

To our knowledge, this study is the first time to differentiate aHCC and BFHL based on conventional laboratory indicators. Similar studies previously reported are mainly based on imaging methods, particularly ultrasound. A machine learning model based on ultrasonography features for discriminating aHCC from hepatic focal nodular hyperplasia showed an AUROC of 0.86, sensitivity of 76.6%, and specificity of 80.5%.<sup>20</sup> Based on contrast-enhanced ultrasound images, a computer-aided diagnostic approach that extracted spatio-temporal semantics of the images achieved better performance in distinguishing aHCC from focal nodular hyperplasia, with an average accuracy 94.40%, specificity 93.62%, and sensitivity 94.76%.<sup>21</sup> Compared to these imaging-based methods, index sAGP derived from AFP, GGT, and PLT has outstanding advantages in terms of cost, convenience, and practicality, making it easy to apply at all levels of hospitals.

The index GPR, the ratio of GGT to PLT, showed the best diagnostic performance among the ten derived indexes. When HCC occurs, cancer cells synthesize large amounts of GGT, and intrahepatic bile duct obstruction also induces large amounts of GGT production by hepatocytes; meanwhile, inflammation around cancerous tissue contributes to increased permeability of hepatocyte membranes, making serum GGT levels elevated.<sup>22</sup> PLT is often reduced in HCC patients due to decreased production of hormone thrombopoietin (TPO) in the damaged liver and increased platelet destruction through phagocytosis in the enlarged spleen. Thrombocytopenia can also affect the growth and metastasis of HCC.<sup>23,24</sup> GPR integrates both GGT and PLT by ratio to widen the difference between HCC and control, thus providing better diagnostic performance for HCC. Huang et al<sup>15</sup> found that the AUROCs of GPR were 0.884, 0.914, and 0.859 for discriminating AFP-negative HCC, AFP-negative HCC with tumor size <3 cm, AFP-negative HCC with BCLC-A stage from healthy controls, respectively. GPR can also be used for risk assessment and prognostic evaluation of HCC.<sup>25,26</sup>

When AFP was integrated into the index GPR, the new index sAGP was developed and showed good diagnostic performance for aHCC (AUROC = 0.905). AFP is the most widely used tumor marker for the diagnosis of HCC, but it is only elevated in 60–70% of HCC patients. Serum AFP levels are often low or normal in patients with small and high-differentiated HCC, which





**Figure 4** Receiver operating characteristic curves and diagnostic validity metrics of sAGP in the diagnosis of aHCC subgroups. **(A)** Early BCLC stage (0/A) aHCC vs aBFHL; **(B)** Early TNM stage (I) aHCC vs aBFHL; **(C)** Small aHCC (tumor diameter < 3 cm) vs aBFHL; **(D)** AFP-negative aHCC (AFP < 20 ng/mL) vs aBFHL.

**Abbreviations:** AUROC, area under the receiver operating characteristic curve; CI, confidence interval; sAGP, (standardized  $\alpha$ -fetoprotein + standardized  $\gamma$ -glutamyltransferase) to standardized platelet count ratio; GPR,  $\gamma$ -glutamyltransferase-to-platelet ratio; AFP,  $\alpha$ -fetoprotein; SEN, sensitivity; SPE, specificity; ACC, accuracy; PPV, positive predictive value; NPV, negative predictive value; PLR, positive likelihood ratio; NLR, negative likelihood ratio.

poses a problem for the clinical diagnosis of HCC without typical image features.<sup>27</sup> When the cut-off value was 200 ng/mL, the sensitivity and specificity of AFP in diagnosing HCC were 22.4% and 99.4%, respectively.<sup>28</sup> However, in the present study, AFP was valuable to some extent in differentiating aHCC from aBFHL, with an AUROC of 0.816 for the diagnosis of aHCC and a sensitivity of 67.0% and a specificity of 86.1% at the optimal cut-off value of 4.37 ng/mL. The good diagnostic performance of sAGP also indicates the importance of AFP in discriminating of aHCC from aBFHL. In fact, this importance of AFP was easy to understand, since AFP levels were significantly higher in aHCC than in aBFHL (median: 8.6 vs 2.4 ng/mL,  $p < 0.001$ ), although AFP levels were low or even normal in aHCC.

However, there are some limitations in this study. First, this study is retrospective and some data is missing, which may introduce bias. Prospective studies are needed to confirm the findings. Second, this is a single-center study, and the results should be validated in an external patient cohort. Third, the patients in this study are all pathologically confirmed

and thus mainly surgical patients, resulting in a small proportion of advanced HCC in the cohort, which differs from the distribution of HCC cases in the real world.

In conclusion, we derived the index sAGP from three blood indicators (AFP, GGT, and PLT) conventionally used in clinical practice using four arithmetic operations. This index exhibited good performance in the differentiation of aHCC (including early-stage, small, and AFP-negative aHCC) from aBFHL, outperforming previously reported derived indexes and AFP. Due to its low cost, convenience, and practicality, sAGP has great potential for clinical applications. However, multicenter and prospective studies are needed to further confirm the diagnostic value of sAGP for aHCC.

## Patient Consent Statement

The Ethics Committee of the First Affiliated Hospital of Nanchang University waived the requirement for informed consent because this study was a retrospective investigation that did not require additional patient participation, and the medical records can be used for medical research without informed consent while ensuring that patients' personal information is not disclosed. We confirm that the patient's personal information has not been disclosed and will be kept confidential.

## Ethical Statement

This study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University and conducted in accordance with the requirements of the Declaration of Helsinki.

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## Disclosure

The authors report no conflicts of interest in this work.

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