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GALAD score and a proposal for GALADUS model for detecting hepatocellular carcinoma in Vietnamese patients with chronic liver disease

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Abstract. – OBJECTIVE: The GALAD score, a serum biomarker-based model, predicts the likelihood of hepatocellular carcinoma (HCC) in patients with chronic liver disease. We evaluated the performance of the GALAD score compared to that of liver ultrasound in detecting HCC.

PATIENTS AND METHODS: This study recruited a group of 136 patients with HCC and a control group of 436 patients with cirrhosis or chronic hepatitis B or hepatitis C. The performance of the GALAD score and ultrasound in detecting HCC in these patients was analyzed using the area under the receiver operating characteristic curve (AUC). The sensitivity and specificity of the optimal GALAD score were compared to those of ultrasound.

RESULTS: The AUC of the GALAD score for detecting HCC was 0.940 [95% confidence interval (CI) 0.92-0.96], higher than that of ultrasound [0.939 (0.91-0.96), $p < 0.001$]. At a threshold of 1.24, the GALAD score had a sensitivity of 91.2% and a specificity of 81.9% for detecting HCC. The AUC of the GALAD score for early HCC detection was 0.75 (95% CI 0.71-0.80, $p < 0.001$; threshold 1.13, sensitivity 87.5%, specificity 67.8%, $p < 0.001$). The combination of GALAD and ultrasound (GALADUS score) showed further improvement, achieving an AUC of 0.97 (95% CI 0.96-0.99; cut-off point 1.37, sensitivity 95.6%, specificity 89.2%, $p < 0.001$).

CONCLUSIONS: In our study, the GALADUS score showed improved performance compared to the GALAD score. Therefore, we suggest that the performance of the GALAD score should be reconsidered and that it should be evaluated in combination with ultrasound for HCC detection.

Key Words:
Hepatocellular carcinoma, AFP, AFP-L3, DCP, Hepatitis, Cirrhosis.

Abbreviations

AASLD; American Association for the Study of Liver Diseases; AFP, α-fetoprotein; AFP-L3, α-fetoprotein-L3; ALT, alanine aminotransferase; APASL, Asian Pacific Association for the Study of the Liver; AST, aspartate aminotransferase; AUC, area under the curve; BCLC, Barcelona clinic liver cancer; CT Scan, computed tomography scan; DCP, Des-carboxy-prothrombin; EASL, European Association for the Study of the Liver; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MRI, magnetic resonance imaging; US, ultrasound.

Introduction

According to GLOBOCAN[1] 2020, liver cancer is the primary cause of new cancer cases in Vietnam. Hepatocellular carcinoma (HCC), the predominant form of liver cancer worldwide, can be triggered by a variety of causes, such as cirrhosis and chronic hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. Most HCC patients are diagnosed at an advanced stage when effective treatment options are limited[2]. For high-risk individuals, HCC surveillance is advised to guarantee early detection[3], as it has been linked to better outcomes for HCC patients[4-6].

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The most common and affordable HCC surveillance diagnostic is liver ultrasonography. The American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of the Liver (EASL), and the Asian Pacific Association for the Study of the Liver (APASL) have all advised biannual liver sonography[7-10]. An HCC surveillance study employing blood α-fetoprotein (AFP) levels and ultrasonography is now being conducted on a sizable cohort of Vietnamese patients suffering from chronic liver disease. However, reports[4] state that the US has a 40-80% sensitivity for HCC identification. There are some reasons why detecting an early-stage HCC is difficult with liver ultrasound: (1) the detection of small lesions by ultrasound is not easy; (2) the density of liver cells is disturbed in patients with cirrhosis, making it difficult to detect liver tumors using ultrasound images; (3) the gas, as a strong reflector that prevents transmission of ultrasound waves and creates reverberation artifacts, inhibits diagnostic information from being obtained. In addition, the physiological gas within the bowel will further prevent accurate interpretation[11]; (4) the quality of liver ultrasound as a surveillance test is often limited due to the high prevalence of obesity and metabolic liver disease[12]. It is reported[4,13,14] that up to 30-40% of tumors found during ultrasonography surveillance are not in the early stages of HCC. Hepatic inflammation affects the level of AFP in the serum. In individuals with chronic viral hepatitis, in particular, elevated hepatocyte death and regeneration are frequently observed in the presence of elevated AFP in the absence of HCC. The erroneous elevation of AFP in patients with gonadal malignancies or pregnant women restricts the test's usefulness as a surveillance tool[15].

Recently, a statistical model for determining the likelihood that a given patient with chronic liver disease has HCC was proposed: the GALAD score. It has been demonstrated[16,17] that the GALAD score, which is derived from gender, age, AFP-L3, AFP, and des-carboxyprothrombin (DCP), is a very accurate model for identifying HCC. Vietnam has not frequently assessed the GALAD score's performance, although it has been validated in the UK, Germany, Japan, and Hong Kong. Additionally, a different GALADUS score that combines the ultrasound results with the GALAD model has been proposed. It seems that the GALADUS score outperforms the GALAD score by a small margin. Consequently, the outcome of an ultrasound examination for a patient can be included in the scoring system[18,19], whether the result is positive or negative. Furthermore, it is yet unknown how well the GALAD score performs in comparison to ultrasound.

Therefore, we aimed to evaluate the performance of the GALAD score compared to that of liver ultrasound in detecting HCC in Vietnamese patients with liver cirrhosis and hepatitis. In addition, we assessed a scoring model (GALADUS) combining the GALAD score and liver ultrasound results.

Patients and Methods

The retrospective study was conducted in Bach Mai Hospital or Hanoi Medical University Hospital between October 2019 and August 2021. This study was approved by the Hanoi Department of Science and Technology. Patients provided written informed consent.

Candidates for HCC surveillance, i.e., patients with cirrhosis, chronic hepatitis B, or chronic hepatitis C without HCC, were included in the control group. Either (1) they supplied stored serum for measuring AFP, AFP-L3%, and DCP, or (2) they were tested for AFP, AFP-L3%, and DCP as part of their routine clinical care. These patients had to have a negative result from a liver biopsy, magnetic resonance imaging (MRI), or multiphasic contrast-enhanced computed tomography (CT) in order to rule out HCC, or they had to be monitored for a minimum of six months following the GALAD score assessment.

Patients with cirrhosis or chronic hepatitis B who were also diagnosed with HCC made up the HCC group. These patients either (1) underwent routine clinical care testing for AFP, AFP-L3%, and DCP, or (2) provided stored serum for AFP, AFP-L3%, and DCP measurements at the time of tumor diagnosis.

Exclusion criteria: (1) a confirmed diagnosis of other associated cancers, (2) patients using warfarin were excluded because it can elevate the DCP level in the absence of HCC, (3) missing case data (Figure 1).

Clinical Information

Clinical characteristics of patients were obtained closest to the time of blood collection within a maximum period of three months. Cirrhosis was defined according to (1) histology, (2) ultrasound outcomes, (3) CT results, or (4) MRI results.

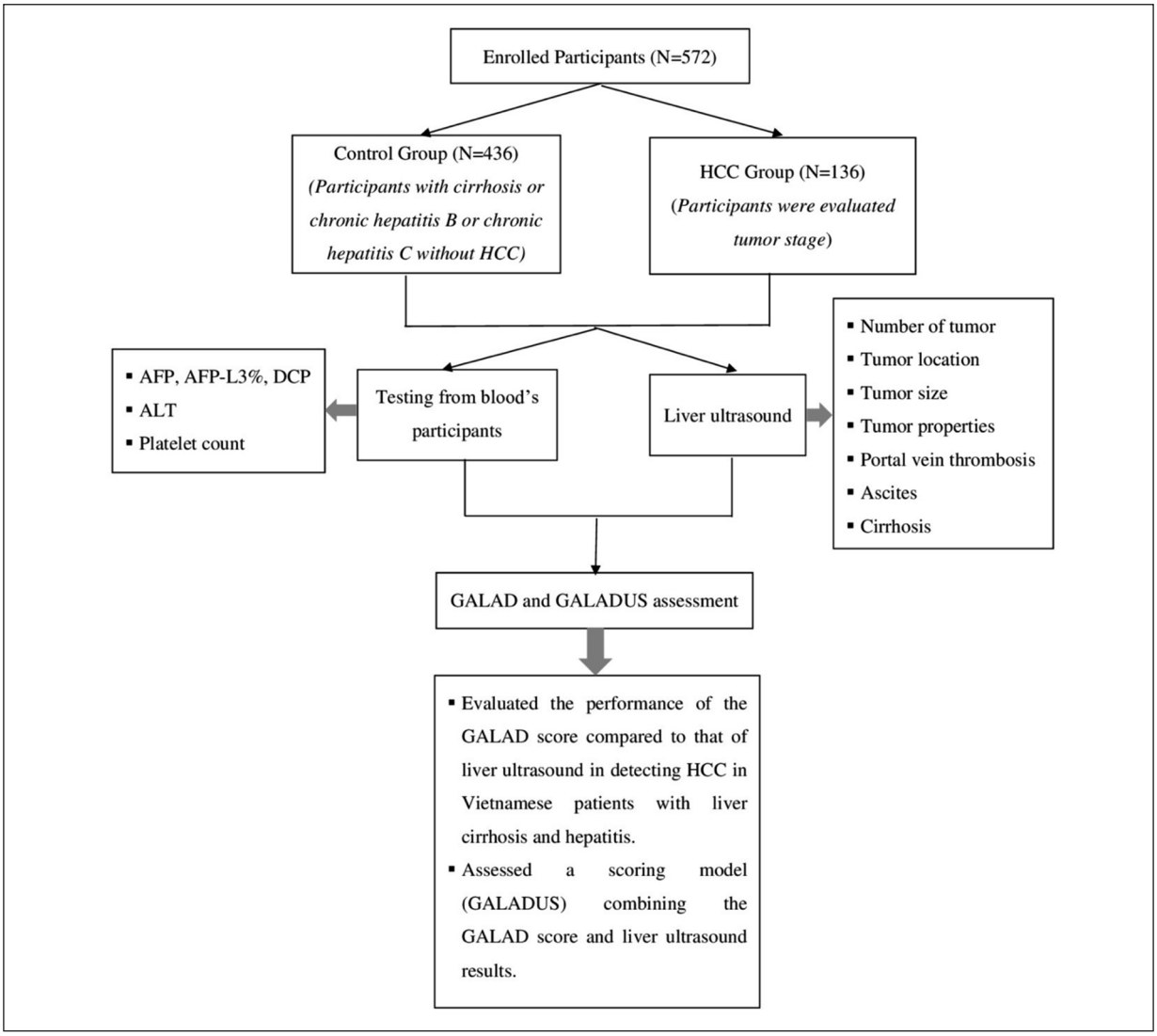

Figure 1. Flow diagram of the study.

Based on quantitative detection of HBV DNA and hepatitis B surface antigen positivity, HBV infection, the fundamental cause of liver disease, was established. HCV RNA or anti-HCV was used to test for HCV infection in cases of chronic liver disease. The diagnosis of HCC was made by CT or MRI of the liver or biopsy according to the guidelines of the Vietnam Ministry of Health. Specifically, the hepatic lesion was diagnosed according to one of the following three criteria: (1) typical image of HCC on contrast-enhanced CT scan or contrast-enhanced abdominal MRI combining AFP $\geq$ 400 ng/ml; or (2) typical image of HCC on contrast-enhanced CT scan or contrast-enhanced abdominal MRI combining elevated AFP (but less than 400 ng/ml) and HBV and/or HCV infection. A liver biopsy may be performed to confirm the diagnosis if the clinician considers it necessary. All cases that do not meet the above criteria should undergo a liver tumor biopsy, which may need to be performed multiple times to obtain a conclusive diagnosis. If the biopsy is still negative, follow-up and repeat imaging and biomarker tests every two months are necessary); or (3) histological evidence of HCC. In addition, typical images from contrast-enhanced CT or contrast-enhanced abdominal MRI may show tumor(s) with superior hepatic artery and wash-out in the portal vein. An MRI scan with gadoxetate disodium (gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid; Gd-EOB-DTPA) contrast agent is recommended to

increase the likelihood of diagnosis of HCC. CT scans of a patient with a right liver tumor and cirrhosis are shown in Figure 2.

Ultrasound results at the time of blood collection were abstracted from medical records in order to compare the performance of GALAD and ultrasound. A positive ultrasound result was defined by the presence of a solid hepatic lesion. Serum biomarkers, AFP, AFP-L3%, and DCP, were measured using an immunoanalyzer (μTAS-Wako i30, Wako Pure Chemical Industries, Ltd, Osaka, Japan).

The GALAD score was calculated using the formula: $-10.08 + 1.67 \times$ [Gender (1 for male, 0 for female)] $+ 0.09 \times$ [Age] $+ 0.04 \times$ [AFP-L3%] $+ 2.34 \times \log$[AFP] $+ 1.33 \times \log$[DCP][16].

Statistical Analysis

The Chi-square test was employed to compare categorical variables, while the Wilcoxon rank-

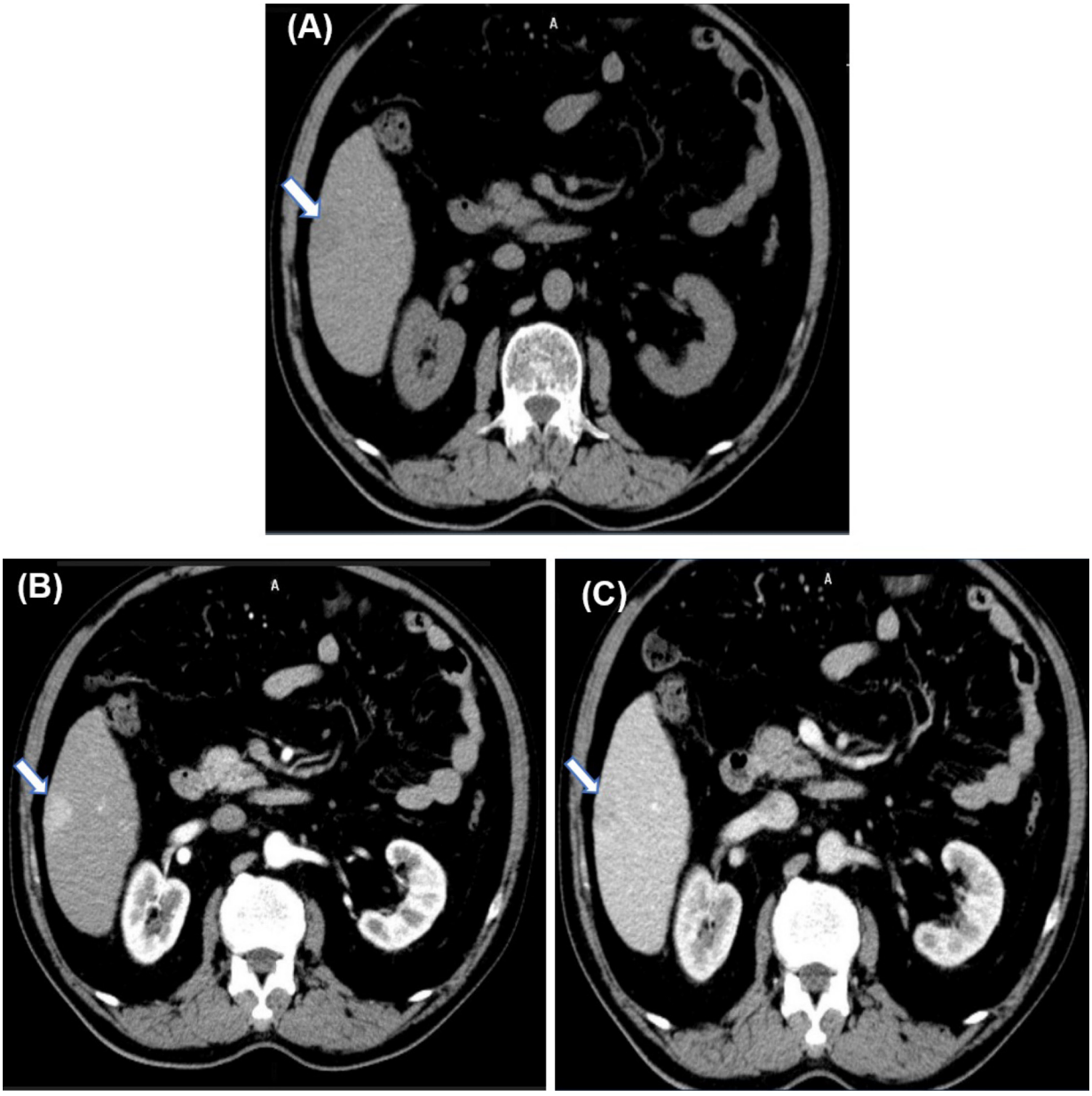

Figure 2. CT scans of a patient with right liver tumor and cirrhosis. The patient was diagnosed with hepatocellular carcinoma. Normal liver size, irregular margins. Parenchyma subsegment VI has hypoattenuating mass, size 21 × 17 mm. Unenhanced phase (**A**), Enhancement in arterial phase (**B**) and washing out in venous phase (**C**).

sum test was utilized to compare continuous variables. The efficacy of the GALAD score in identifying HCC was evaluated by computing the area under the receiver operating characteristic curve (AUC). The performance of the GALAD score was also examined through subgroup analyses by gender, age, AFP level, etiologies, ascites, Child-Pugh score, alanine transaminase (ALT) level, and tumor stage.

The best GALAD cutoffs were determined using Youden's index, and the resulting sensitivity, specificity, and 95% confidence intervals (CI) were computed and compared with liver ultrasonography data[20]. Using multivariate logistic regression analysis with all the variables in the GALAD score and liver ultrasound, the GALADUS score was also computed by combining the GALAD and liver ultrasound for the purpose of detecting HCC. Statistical analyses were carried out with SPSS Statistics version 16.0 (SPSS Inc., Chicago, IL, USA). $p < 0.05$ was the threshold for statistical significance.

Results

Characteristics of the Patients

A total of 572 patients were eligible (136 with HCC and 436 controls), and Table I summarizes their clinical and demographic features. In the HCC group, the percentage of males was higher at 92.7% compared to the control group at 70.2% ($p < 0.01$). In comparison to the control group, the HCC group was older (58.09

Table I. Clinical characteristics of patients with HCC (the HCC group) and the control group.

	HCC group (N = 136)	Control group (N = 436)	*p*-value
Age, years, mean (SD)	58.09 (11.3)	49.86 (12.7)	< 0.01
Age < 60 years	71 (17.3%)	340 (82.7%)	
Age ≥ 60 years	65 (40.4%)	86 (59.6%)	
Gender			< 0.01
Female	10 (7.1%)	130 (92.9%)	
Male	126 (29.2%)	306 (70.8%)	
Child-Pugh score			< 0.01
A	103 (28.9%)	254 (71.1%)	
B-C	33 (13.0%)	174 (87.0%)	
Etiology			
HCV infection	8 (19.5%)	33 (80.5%)	0.635
HBV infection	111 (23.4%)	363 (76.6%)	0.755
Cirrhosis	84 (38.9%)	132 (61.1%)	< 0.01
Platelet count (IQR)	194.5 (129.1-247.7)	187.5 (125.0-231.0)	0.228
ALT, median	49	34	< 0.01
ALT < 40	44 (14.9%)	251 (85.1%)	
ALT ≥ 40	87 (33.6%)	172 (66.4%)	
AFP, median	120.4	2.3	< 0.01
AFP < 20	44 (10.2%)	387 (89.8%)	
AFP ≥ 20	87 (64.0%)	49 (36.0%)	
DCP, median	1,233.0	16.0	< 0.01
AFP-L3, median	11.1	< 0.5	< 0.01
Ascites			< 0.01
0 (no ascites)	100 (20.4%)	390 (79.6%)	
1 (controlled ascites)	28 (38.4%)	45 (61.6%)	
2 (refractory ascites)	8 (88.9%)	1 (11.1%)	
GALAD_Z, mean (SD)	6.6 (3.1, 10.9)	-1.68 (-3.2, 0.3)	< 0.01
Ultrasound detection of lesion			< 0.01
Negative	7 (1.7%)	405 (98.3%)	
Positive	129 (80.6%)	31 (19.4%)	
Tumor stage			
Very early (BCLC O)	8 (5.9%)		
Early (BCLC A)	32 (23.5%)		
Non-early (BCLC B-D)	96 (70.6%)		

AFP, α-fetoprotein; AFP-L3, α-fetoprotein-L3; ALT, alanine aminotransferase; BCLC, Barcelona Clinic Liver Cancer; DCP, Des-carboxyprothrombin; HBV, hepatitis B virus; HCV, hepatitis C virus.

vs. 49.86 years, $p < 0.01$). In the control group, HBV was the most common cause of liver disease (91.7%) and the leading cause of HCC (93.2%). In the control group (61.1%), the percentage of patients with cirrhosis was higher than in the HCC group (38.9%, $p < 0.01$). Less than half of the HCC patients had very early (n = 8, 5.9%) or early-stage (n = 32, 23.5%) HCC at diagnosis.

Performance of GALAD in Detecting HCC Compared to the Performance of Liver Ultrasound

In comparison to ultrasound (0.939, 95% CI 0.91-0.96, $p < 0.001$), the AUC of the GALAD score for HCC detection was 0.940 (95% CI 0.92-0.96; Table II; Figure 3). The GALAD score had a 91.2% sensitivity and an 81.9% specificity for HCC detection at an ideal cutoff of 1.24.

In the subgroups of gender, age, AFP level, and HCC etiology, the AUC of GALAD stayed high (Table II; Figure 4). For example, the AUC of the GALAD score was 0.948 (Figure 4A), 0.909 (Figure 4B), or 0.896 (Figure 4C) for the detection of HCC in patients with cirrhosis, HBV infection, or HCV infection, respectively. For negative tumor detection based on AFP at a cutoff of -0.51, the GALAD score had a sensitivity of 95.4% and a specificity of 76.0%; the AUC of the GALAD score was higher than that of ultrasound (0.91 *vs.* 0.80, $p < 0.001$).

The GALAD score's AUC remained high at 0.75 (95% CI 0.73-0.80) when the analysis was restricted to early-stage HCC [Barcelona Clinic Liver Cancer (BCLC) 0-A] (Figure 4B). When it came to the identification of early-stage HCC, the AUC of the GALAD score was lower than that of ultrasound (0.75 *vs.* 0.86, $p < 0.001$), but it was higher than ultrasound (0.95 *vs.* 0.90, $p < 0.001$; Table II).

A Proposal for GALADUS Score

Subsequently, we assessed whether the liver ultrasound and GALAD score combined could enhance the detection of HCC more than either test alone. When GALAD and liver ultrasonography were combined, the model's performance was greatly enhanced.

The following is the equation for calculating the GALADUS score: GALADUS is equal to -12.79 + 0.09*age + 1.74*(male, 0 for female) + 2.44*log10(AFP) + 0.04*AFPL3 + 1.39*log10(DCP) + 3.56*(one positive ultrasound, zero negative).

As shown in Figure 5A, the AUC of the GALADUS score for the detection of HCC was 0.97 (95% CI 0.96-0.99). Table III shows that the sensitivity was 96% and the specificity was 89% at the GALADUS cutoff of 1.37. The AUC of the GALADUS score remained high at 0.808 (95% CI 0.79-0.95); cutoff -0.19, sensitivity 97%, specificity 69%; Figure 5B) when the analysis was restricted to early-stage HCC (BCLC 0-A).

Discussion

This study confirmed, for the first time, the excellent performance of the GALAD score in detecting HCC in a Vietnamese patient cohort. Firstly, it was demonstrated that the GALAD score performed better than ultrasound. In addition, the GALAD score demonstrated strong performance in identifying early-stage HCC, including AFP-negative tumors. The GALAD score was unaffected by gender, age group, the underlying cause of the HCC, or the degree of liver dysfunction; however, patients with poorly managed ascites or Child-Pugh class B or C cirrhosis had difficulties with the ultrasound. The exceptional performance of the GALAD score was verified in a separate multicenter cohort of patients with cirrhosis and early-stage HCC, proving the usefulness of the GALAD score as a superior tool for HCC detection. Ultimately, we employed the GALADUS score – a combination of the GALAD score and liver ultrasonography – to identify HCC. It performed better than either the GALAD score or the liver ultrasonography alone, albeit the slight advantage in AUC between GALADUS and GALAD may not have any practical significance.

Data[16] from a single UK center was used to create the GALAD score in the beginning. It involved a statistical model that used objective measurements, specifically serological tumor markers, to estimate the risk of HCC in specific patients with chronic liver diseases. The GALAD score's AUC for identifying all HCCs was 0.97; for identifying early-stage HCC, it was 0.96, and for identifying advanced-stage HCC, it was 0.98. The GALAD score in a German cohort reached 90% specificity and 92% sensitivity at the cutoff of -0.63. Later on, a more extensive study[21] involving multiple centers across multiple continents validated the GALAD score. In this study, participants with chronic liver disease (4,404) and

Table II. Performance of GALAD compared to that of ultrasound in subgroup analyses.

Subgroup	GALAD Cutoff	Sensitivity (95% CI)		Specificity (95% CI)		AUC (95% CI)†			
		GALAD	Ultrasound	GALAD	Ultrasound	GALAD	*p*-value	Ultrasound	*p*-value
Overall	1.24	0.91 (0.84, 0.95)	0.95 (0.89, 0.98)	0.81 (0.78, 0.85)	0.93 (0.90, 0.95)	0.940 (0.92, 0.96)	< 0.001	0.939 (0.91, 0.96)	< 0.001
Age									
Age < 60 years	1.8	0.90 (0.80, 0.97)	0.94 (0.85,0.98)	0.93 (0.90, 0.96)	0.95 (0.92, 0.97)	0.97 (0.95, 0.99)	< 0.001	0.95 (0.91, 0.98)	< 0.001
Age ≥ 60 years	5.47	0.58 (0.45, 0.70)	0.95 (0.86, 0.99)	0.93 (0.85, 0.97)	0.85 (0.76, 0.91)	0.82 (0.76, 0.89)	< 0.001	0.90 (0.85, 0.95)	< 0.001
Gender									
Female	-0.017	1.00 (0.65, 1.00)	0.9 (0.54, 0.99)	0.87 (0.80, 0.92)	0.95 (0.89, 0.98)	0.97 (0.94, 1.00)	< 0.001	0.92 (0.81, 1.00)	< 0.001
Male	1.80	0.87 (0.80, 0.92)	0.95 (0.89, 0.98)	0.81 (0.76, 0.85)	0.92 (0.88, 0.95)	0.92 (0.90, 0.95)	< 0.001	0.94 (0.91, 0.96)	< 0.001
Etiology									
HCV	0.66	1.00 (0.60, 1.00)	1.00 (0.60, 1.00)	0.85 (0.67, 0.94)	0.85 (0.67, 0.94)	0.91 (0.82, 1.00)	< 0.001	0.94 (0.90, 0.98)	< 0.001
HBV	1.77	0.90 (0.82, 0.95)	0.94 (0.87, 0.97)	0.87 (0.83, 0.90)	0.95 (0.92, 0.97)	0.95 (0.93, 0.97)	< 0.001	0.94 (0.91, 0.97)	< 0.001
AFP									
AFP < 20	-0.51	0.95 (0.83, 0.99)	0.95 (0.83, 0.99)	0.76 (0.71, 0.80)	0.93 (0.90, 0.95)	0.91 (0.87, 0.95)	< 0.001	0.80 (0.74, 0.85)	< 0.001
AFP ≥ 20	5.56	0.86 (0.76, 0.92)	0.95 (0.87, 0.98)	0.84 (0.70, 0.92)	0.90 (0.77, 0.96)	0.90 (0.85, 0.95)	< 0.001	0.92 (0.86, 0.98)	< 0.001
Ascites									
0 (no ascites)	1.13	0.91 (0.83, 0.95)	0.95 (0.88, 0.98)	0.85 (0.80, 0.88)	0.93 (0.90, 0.95)	0.94 (0.92, 0.96)	< 0.001	0.94 (0.91, 0.97)	< 0.001
1 and 2 (controlled and refractory ascites)	4.2	0.83 (0.67, 0.93)	0.94 (0.80, 0.99)	0.89 (0.77, 0.96)	0.93 (0.81, 0.98)	0.92 (0.86, 0.98)	< 0.001	0.94 (0.88, 1.00)	< 0.001
Child-Pugh score									
A	1.13	0.90 (0.82, 0.95)	0.95 (0.88, 0.98)	0.81 (0.76, 0.86)	0.91 (0.87, 0.94)	0.93 (0.90, 0.95)	< 0.001	0.93 (0.90, 0.96)	< 0.001
B-C	2.04	0.97 (0.82, 1.00)	0.94 (0.78, 0.99)	0.88 (0.83, 0.92)	0.95 (0.90, 0.97)	0.97 (0.95, 0.99)	< 0.001	0.95 (0.89, 0.99)	< 0.001
ALT									
< 40	0.60	0.95 (0.83, 0.99)	0.95 (0.83, 0.99)	0.88 (0.83, 0.92)	0.94 (0.90, 0.96)	0.96 (0.93, 0.99)	< 0.001	0.95 (0.91, 0.99)	< 0.001
≥ 40	3.97	0.76 (0.65, 0.84)	0.84 (0.86, 0.98)	0.89 (0.83, 0.93)	0.91 (0.85, 0.94)	0.91 (0.87, 0.94)	< 0.001	0.92 (0.89, 0.96)	< 0.001
Tumor stage									
Early (O-A)	1.13	0.87 (0.72, 0.95)	0.68 (0.64, 0.72)	0.95 (0.82, 0.99)	0.77 (0.73, 0.8)	0.75 (0.71, 0.80)	< 0.001	0.86 (0.81, 0.91)	< 0.001
Non-early (B-D)	3.25	0.86 (0.78, 0.92)	0.88 (0.85, 0.91)	0.95 (0.88, 0.98)	0.85 (0.82, 0.88)	0.95 (0.93, 0.97)	< 0.001	0.90 (0.87, 0.93)	< 0.001

†For calculating AUC, the continuous GALAD score was used (whereas for sensitivity and specificity, we used the GALAD cutoff). AFP, α-fetoprotein; ALT, alanine aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus.

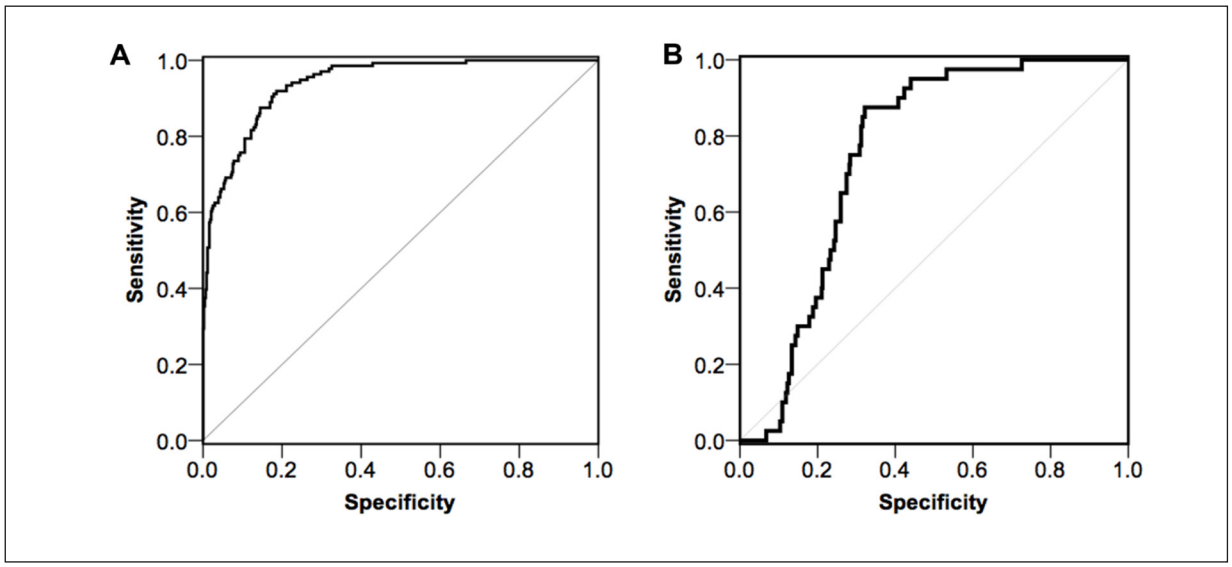

Figure 3. The ROC of GALAD scores for HCC diagnosis in each subgroup. The ROC of GALAD score for detecting HCC, AUC 0.94 (**A**); the ROC of GALAD score for detecting early-stage HCC, AUC 0.75 (**B**).

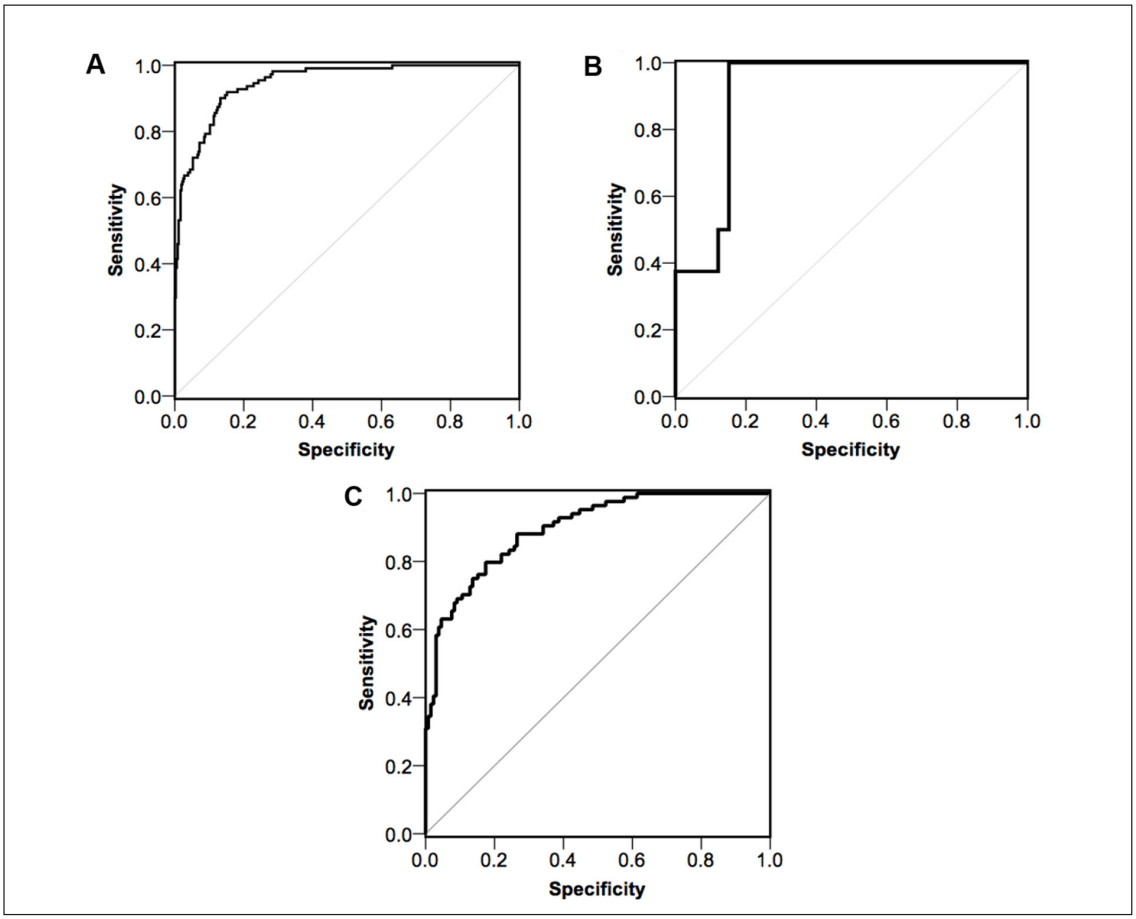

Figure 4. The ROC of GALAD scores for HCC diagnosis in each subgroup with different etiologies. The ROC of GALAD scores for HCC diagnosis in patients with hepatitis B infection, AUC 0.948 (**A**); the ROC of GALAD scores for HCC diagnosis in patients with hepatitis C infection, AUC 0.909 (**B**); the ROC of GALAD scores for HCC diagnosis in patients with cirrhosis, AUC 0.896 (**C**).

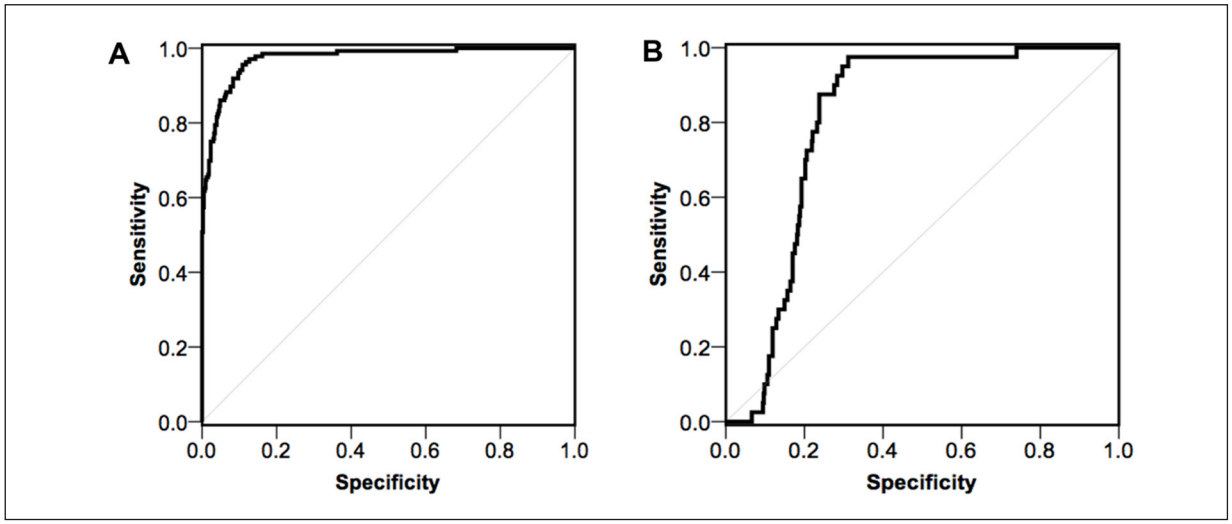

Figure 5. The ROC of GALADUS scores for HCC diagnosis. The ROC of the GALADUS score for detecting HCC, AUC 0.973 (**A**); the ROC of the GALADUS score for detecting early-stage HCC, AUC 0.808 (**B**).

HCC (2,430) were enrolled from Germany, Japan, and Hong Kong. For the German and Japanese validation cohorts, the overall AUCs of GALAD for HCC detection were 0.94 (95% CI 0.93-0.96) and 0.93 (95% CI 0.92-0.94), respectively. In the German cohort[17], the GALAD score yielded a sensitivity of 88% and a specificity of 88% at the cutoff of -0.68. An additional investigation[22] in-

Table III. Performance of GALADUS in subgroup analyses.

Subgroup	GALADUS Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	*p*-value
Overall	1.37	0.96 (0.90, 0.98)	0.89 (0.85, 0.92)	0.97 (0.96, 0.99)	< 0.001
Age					
Age < 60 years	-1.41	0.97 (0.84, 1.00)	0.89 (0.81, 0.95)	0.97 (0.95, 0.99)	< 0.001
Age ≥ 60 years	0.34	0.82 (0.72, 0.90)	0.91 (0.83, 0.96)	0.82 (0.76, 0.89)	< 0.001
Gender					
Female	1.03	1.00 (0.65, 1.00)	0.97 (0.92, 0.99)	0.99 (0.98, 1.00)	< 0.001
Male	1.35	0.96 (0.90, 0.98)	0.85 (0.81, 0.89)	0.96 (0.95, 0.98)	< 0.001
Etiology					
HCV	-0.53	0.94 (0.83, 0.99)	0.85 (0.68, 0.95)	0.91 (0.82, 1.00)	< 0.001
HBV	-1.68	1.00 (0.62, 1.00)	1.00 (0.82, 1.00)	0.95 (0.93, 0.97)	< 0.001
AFP					
AFP < 20	-1.18	0.89 (0.77, 0.96)	0.81 (0.74, 0.86)	0.91 (0.87, 0.95)	< 0.001
AFP ≥ 20	3.91	0.69 (0.56, 0.80)	1.00 (0.28, 1.00)	0.90 (0.85, 0.95)	< 0.001
Ascites					
0 (no ascites)	-0.18	0.95 (0.87, 0.99)	0.91 (0.84, 0.96)	0.97 (0.95, 0.99)	< 0.001
1 (controlled ascites)	-0.27	0.95 (0.75, 0.97)	0.85 (0.72, 0.94)	0.96 (0.92, 1.00)	< 0.001
2 (refractory ascites)	-0.20	1.00 (0.42, 1.00)	1.00 (0.70, 1.00)	1.00 (1.00, 1.00)	< 0.001
Child-Pugh score					
A	-0.85	0.92 (0.84, 0.97)	0.84 (0.76, 0.90)	0.93 (0.90, 0.95)	< 0.001
B-C	0.42	0.83 (0.64, 0.94)	0.96 (0.86, 1.00)	0.97 (0.95, 0.99)	< 0.001
ALT					
< 40	-1.01	0.95 (0.82, 0.99)	0.86 (0.78, 0.91)	0.96 (0.93, 0.99)	< 0.001
≥ 40	0.38	0.84 (0.73, 0.91)	0.95 (0.86, 0.99)	0.91 (0.87, 0.94)	< 0.001
Tumor stage					
Early (O-A)	-0.19	0.97 (0.85, 1.00)	0.69 (0.65, 0.73)	0.81 (0.77, 0.85)	< 0.001
Non-early (B-D)	1.37	0.99 (0.93, 1.00)	0.83 (0.79, 0.86)	0.97 (0.96, 0.98)	< 0.001

AFP, α-fetoprotein; ALT, alanine aminotransferase; HBV, hepatitis B virus; HCV, hepatitis C virus.

volving 98 Italian patients, 44 with chronic liver disease and 54 with HCC, found that the overall AUC of GALAD for the detection of HCC was 0.98.

The best GALAD score for detecting HCC was found in a prior study[23], with an AUC of 0.976, sensitivity of 96.3%, and specificity of 84.1%. In comparison to other individual markers, the GALAD score for diagnosing HCC had the highest AUC in the German (0.94), Japanese (0.93), and British (0.97) groups, according to Berhane et al[17]. Yang et al[19] examined 180 patients with cirrhosis or hepatitis B and 111 patients with HCC. They found that the AUC of the GALAD score was 0.95, significantly higher than the ultrasound's (0.82, $p < 0.01$).

Yang et al[19] demonstrated that the AUC of the GALADUS score for HCC detection in the context of the GALADUS model was 0.98. Specificity was 91% and sensitivity was 95% at the GALADUS cutoff of -0.179. For the early-stage HCC group, the AUC of the GALADUS score stayed high at 0.97 (best cutoff -0.5, sensitivity 88%, and specificity 94%). The AUC of the GALADUS model was 0.98 for HCC overall and 0.97 for early-stage disease, according to Roberts[24]. The GALADUS score's AUC for HCC detection in our investigation was 0.97 (cutoff 1.37, sensitivity 96%, specificity 89%). The AUC of the GALADUS score held steady at 81% (sensitivity 97%, specificity 69%, cutoff -0.19). Compared to GALAD or ultrasound alone, the GALADUS score model's AUC, sensitivity, and specificity were superior.

Liver ultrasonography is a routine HCC surveillance test that is approved by multiple societies, such as the Asian-Pacific Association for the Study of the Liver (APASL), the European Association for the Study of the Liver (EASL), and the American Association for the Study of Liver Diseases (AASLD). Nevertheless, as a surveillance test for HCC, ultrasonography has a number of significant drawbacks. The sonographer's proficiency is crucial to the performance of the surveillance ultrasound. Furthermore, it can be difficult to identify early HCC nodules, especially in individuals who have noduled cirrhosis of the liver.

The purpose of our study was to investigate the necessity of combining ultrasound and measurements of AFP, AFP-L3%, and DCP for early HCC surveillance testing. Vietnamese patients with severe liver disease have often been evaluated using the GALAD score. Nonetheless, we discovered that in our investigation, there were more patients with non-early-stage HCC than with early-stage HCC. Actually, the majority of Vietnamese patients with HCC are typically found in a late stage. This might be the result of Vietnamese people's propensity to put off routine medical exams.

Limitations

One of the study's limitations is that we did not examine data collected when patients had testing and ultrasounds at the three- and six-month follow-ups. It may be possible to ascertain the score's longer-term value through such an investigation.

Conclusions

We demonstrated that for the purpose of detecting HCC, the GALAD score performs better than ultrasound. In addition to ultrasound, the GALAD score can be useful in the detection of hepatitis and cirrhosis in patients. Additionally, we tested the GALADUS score, which combines the results of the liver ultrasound and the GALAD score. The GALADUS score was found to be superior to the GALAD score or the ultrasound alone. Prior to being widely used in clinical practice, future research should compare the cost-effectiveness of GALAD or GALADUS *vs.* liver ultrasonography with or without AFP.

Conflict of Interest

The authors declare that they have no conflict of interests.

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Authors' Contribution

Conception, design and study supervision: P.C.P., P.V.T., M.T.K. and N.T.L.; development of methodology: P.V.T., N.T.L., V.T.T.Q., N.T.H.M. and N.D.L.; performing research and analyzing data: N.T.L., V.T.T.Q., N.T.H.M. and N.D.L.; acquisition of data (acquired and managed patients, provided facilities, etc.): N.T.L., V.T.T.Q., N.T.H.M., N.D.L., N.V.D., N.Q.H., D.Q.L., L.V.N. and D.T.T.; writing, review, and/or revision of the manuscript: N.M.D., V.T.T.Q., P.C.P. and P.V.T. All authors have read and agreed to the published version of the manuscript.

Ethics Approval
The Ethics Committee of Bach Mai Hospital approved the study and authorized its conduct (Approval No.: 1508/QĐ-BM; date of approval: June 17th, 2020).

Data Availability
The corresponding author can provide the datasets used and analyzed in this study upon reasonable request.

Informed Consent
Individual patient consent for inclusion in the study was obtained. All participants gave their written informed consent prior to the serum being taken from them, following a detailed explanation of the study's objectives. Throughout the study, the patients had the freedom to withdraw from the study at any time.

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References

1) Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021; 71: 209-249.
2) Yang JD, Mannalithara A, Piscitello AJ, Kisiel JB, Gores GJ, Roberts LR, Kim WR. Impact of surveillance for hepatocellular carcinoma on survival in patients with compensated cirrhosis. Hepatology 2018; 68: 78-88.
3) Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, Tateishi R, Han KH, Chawla YK, Shiina S, Jafri W, Payawal DA, Ohki T, Ogasawara S, Chen PJ, Lesmana CRA, Lesmana LA, Gani RA, Obi S, Dokmeci AK, Sarin SK. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int 2017; 11: 317-370.
4) Yang JD, Kim WR. Surveillance for hepatocellular carcinoma in patients with cirrhosis. Clin Gastroenterol Hepatol 2012; 10: 16-21.
5) Yang JD, Harmsen WS, Slettedahl SW, Chaiteerakij R, Enders FT, Therneau TM, Orsini L, Kim WR, Roberts LR. Factors that affect risk for hepatocellular carcinoma and effects of surveillance. Clin Gastroenterol Hepatol 2011; 9: 617-623.
6) Singal AG, Pillai A, Tiro J. Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis. PLoS Med 2014; 11: e1001624.
7) European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012; 56: 908-943.
8) Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology 2011; 53: 1020-1022.
9) Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, Tateishi R, Han KH, Chawla YK, Shiina S, Jafri W, Payawal DA, Ohki T, Ogasawara S, Chen PJ, Lesmana CRA, Lesmana LA, Gani RA, Obi S, Dokmeci AK, Sarin SK. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int 2017; 11: 317-370.
10) Tan CH, Low SC, Thng CH. APASL and AASLD Consensus Guidelines on Imaging Diagnosis of Hepatocellular Carcinoma: A Review. Int J Hepatol 2011; 2011: 519783.
11) Goudie A. Detection of intraperitoneal free gas by ultrasound. Australas J Ultrasound Med 2013; 16: 56-61.
12) Yang JD. Detect or not to detect very early stage hepatocellular carcinoma? The western perspective. Clin Mol Hepatol 2019; 25: 335-343.
13) Singal AG, Conjeevaram HS, Volk ML, Fu S, Fontana RJ, Askari F, Su GL, Lok AS, Marrero JA. Effectiveness of hepatocellular carcinoma surveillance in patients with cirrhosis. Cancer Epidemiol Biomarkers Prev 2012; 21: 793-799.
14) Atiq O, Tiro J, Yopp AC, Muffler A, Marrero JA, Parikh ND, Murphy C, McCallister K, Singal AG. An assessment of benefits and harms of hepatocellular carcinoma surveillance in patients with cirrhosis. Hepatology 2017; 65: 1196-1205.
15) Kakisaka K, Kataoka K, Onodera M, Suzuki A, Endo K, Tatemichi Y, Kuroda H, Ishida K, Takikawa Y. Alpha-fetoprotein: A biomarker for the recruitment of progenitor cells in the liver in patients with acute liver injury or failure. Hepatol Res 2015; 45: E12-E20.
16) Johnson PJ, Pirrie SJ, Cox TF, Berhane S, Teng M, Palmer D, Morse J, Hull D, Patman G, Kagebayashi C, Hussain S, Graham J, Reeves H, Satomura S. The detection of hepatocellular carcinoma using a prospectively developed and validated model based on serological biomarkers. Cancer Epidemiol Biomarkers Prev 2014; 23: 144-153.
17) Berhane S, Toyoda H, Tada T, Kumada T, Kagebayashi C, Satomura S, Schweitzer N, Vogel A,

Manns MP, Benckert J, Berg T, Ebker M, Best J, Dechêne A, Gerken G, Schlaak JF, Weinmann A, Wörns MA, Galle P, Yeo W, Mo F, Chan SL, Reeves H, Cox T, Johnson P. Role of the GALAD and BALAD-2 Serologic Models in Diagnosis of Hepatocellular Carcinoma and Prediction of Survival in Patients. Clin Gastroenterol Hepatol 2016; 14: 875-886.

18) Best J, Bechmann LP, Sowa JP, Sydor S, Dechêne A, Pflanz K, Bedreli S, Schotten C, Geier A, Berg T, Fischer J, Vogel A, Bantel H, Weinmann A, Schattenberg JM, Huber Y, Wege H, von Felden J, Schulze K, Bettinger D, Thimme R, Sinner F, Schütte K, Weiss KH, Toyoda H, Yasuda S, Kumada T, Berhane S, Wichert M, Heider D, Gerken G, Johnson P, Canbay A. GALAD Score Detects Early Hepatocellular Carcinoma in an International Cohort of Patients With Nonalcoholic Steatohepatitis. Clin Gastroenterol Hepatol 2020; 18: 728-735.

19) Yang JD, Addissie BD, Mara KC, Harmsen WS, Dai J, Zhang N, Wongjarupong N, Ali HM, Ali HA, Hassan FA, Lavu S, Cvinar JL, Giama NH, Moser CD, Miyabe K, Allotey LK, Algeciras-Schimnich A, Theobald JP, Ward MM, Nguyen MH, Befeler AS, Reddy KR, Schwartz M, Harnois DM, Yamada H, Srivastava S, Rinaudo JA, Gores GJ, Feng Z, Marrero JA, Roberts LR. GALAD Score for Hepatocellular Carcinoma Detection in Comparison with Liver Ultrasound and Proposal of GALADUS Score. Cancer Epidemiol Biomarkers Prev 2019; 28: 531-538.

20) Youden WJ. Index for rating diagnostic tests. Cancer 1950; 3: 32-35.

21) Berhane S, Toyoda H, Tada T, Kumada T, Kagebayashi C, Satomura S, Nora S, Arndt V, Michael PM, Julia B, Thomas B, Maria E, Jan B, Alexander D, Guido G, Joerg FS, Arndt W, Marcus AW, Peter G, Winnie Y, Frankie M, Stephen LC, Helen R, Trevor C, Johnson P. Role of the GALAD and BALAD-2 serologic models in diagnosis of hepatocellular carcinoma and prediction of survival in patients. Clin Gastroenterol Hepatol 2016, 14: 875-886.

22) Caviglia GP, Abate ML, Petrini E, Gaia S, Rizzetto M, Smedile A. Highly sensitive alpha-fetoprotein, Lens culinaris agglutinin-reactive fraction of alpha-fetoprotein and des-gamma-carboxyprothrombin for hepatocellular carcinoma detection. Hepatol Res 2016; 46: E130-E135.

23) Singal AG, Pillai A, Tiro J. Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis. PLoS Med 2014; 11: e1001624.

24) Roberts LR. Current Status of the GALAD and BALAD Biomarker Models for Hepatocellular Carcinoma. Gastroenterol Hepatol (N Y) 2019; 15: 672-675.