Radiology

ORIGINAL RESEARCH • GASTROINTESTINAL IMAGING

APS (Age, Platelets, 2D Shear-Wave Elastography) Score Predicts Hepatocellular Carcinoma in Chronic Hepatitis B

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Supported by the National Key R&D Program of China (grant 2017YFC0112000), National Natural Science Foundation of China (grants 81430038, 81601503, and 81901942), Science and Technology Program of Guangzhou (grant 201704020164), Science and Technology Planning Project of Guangdong Province (grant 2017B090901034), and Guangdong Basic and Applied Basic Research Foundation (grant 2019A1515011095).

Conflicts of interest are listed at the end of this article.

Radiology 2021; 000:1–10 • https://doi.org/10.1148/radiol.2021204700 • Content codes: GI MR

Background: Two-dimensional (2D) shear-wave elastography (SWE) has been considered to be useful in predicting hepatocellular carcinoma (HCC) development in patients with chronic hepatitis B (CHB).

Purpose: To develop a risk model using 2D SWE to predict HCC in patients with CHB and to compare its predictive value with that of other models.

Materials and Methods: Patients with biopsy-proven CHB who underwent US and 2D SWE between April 2011 and December 2015 were enrolled in this study. After 2D SWE and biopsy were performed, the patients received regular follow-up for the detection of HCC. The scoring system was developed by dividing the parameters of the Cox proportional hazards model by the smallest parameter and simplifying the assigned points to integers. The predictive performance of the new score was compared with that of other scores.

Results: Among the 654 patients (mean age, 37 years; range, 30–43 years; 510 men), 26 developed HCC. The variables of age, platelet count, and liver stiffness measurement at 2D SWE were weighted to develop the so-called APS score, with a cutoff of 60 showing the best discrimination for HCC risk. The APS score (area under the receiver operating characteristic curve [AUC], 0.89) was superior to that of the Chinese University HCC prediction score constructed from age, albumin level, bilirubin level, hepatitis B virus (HBV) DNA level, and cirrhosis (AUC, 0.70; $P = .005$) and slightly higher than that of the guide with age, gender, HBV DNA level, core promoter mutations, and cirrhosis, or GAG-HCC score (AUC, 0.82; $P = .052$). In patients who underwent transient elastography, the AUC of the APS score was 0.79, compared with 0.82 for the modified risk estimation for HCC in CHB, or mREACH-B, score ($P = .05$). The APS score performed better in patients regardless of whether antiviral treatment was used, inflammation grade was low or high, or alanine aminotransferase levels were normal or high (all $P > .05$).

Conclusion: The APS score based on only the patient's baseline liver stiffness measurement at two-dimensional shear-wave elastography, age, and platelet count is valuable for predicting hepatocellular carcinoma in patients with chronic hepatitis B.

Online supplemental material is available for this article.

Hepatitis B virus (HBV) infection is one of the most common causes of end-stage liver diseases, such as liver cirrhosis, liver failure, and hepatocellular carcinoma (HCC) (1). Previous reports show that more than 400 million people globally are chronically infected with HBV, with more than 90 million chronic hepatitis B (CHB) infections in China (2,3), and the risk of HCC is a lifelong concern for patients with CHB (4). To date, liver cirrhosis has been the most well-known risk factor for HCC development (5,6). However, patients without clinical cirrhosis remain at risk for HCC (7). The most effective and efficient method for HCC surveillance remains controversial. Furthermore, differentiation of high-risk from low-risk patients is important clinically because high-risk patients require prompt antiviral treatment (AVT) and close follow-up, whereas low-risk patients do not require treatment.

Current clinical scores using serologic indicators—such as the guide with age, gender, HBV DNA level, core promoter mutations, and cirrhosis score (hereafter, GAG-HCC) (8); HCC prediction score constructed from cirrhosis, age, male sex, and diabetes (hereafter, CAMD) (9); and Chinese University HCC prediction score constructed from age, albumin level, bilirubin level, HBV DNA level, and cirrhosis (hereafter, CU-HCC) (10) models—to predict the development of HCC show area under the receiver operating characteristic curves (AUCs) ranging from approximately 0.7 to 0.8 at 3- and 5-year follow-ups (8–10). Only decompensated cirrhosis evaluated with use of clinical features or ascites that were depicted on conventional US scans was considered in the scoring models mentioned earlier. Furthermore, conventional US depends on experiences and subjective suggestions

Abbreviations

2D = two-dimensional, ALT = alanine aminotransferase, AUC = area under the receiver operating characteristic curve, AVT = antiviral treatment, CHB = chronic hepatitis B, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, LSM = liver stiffness measurement, PLT = platelet count, SWE = shear-wave elastography, TE = transient elastography

Summary

A hepatocellular carcinoma (HCC) prediction score constructed from age, platelet count, and liver stiffness measurement at two-dimensional shear-wave elastography, or APS score, higher than 60 is predictive of higher risk of HCC development in patients with chronic hepatitis B.

Key Results

- In an evaluation of 654 patients with chronic hepatitis B without cirrhosis, 26 developed hepatocellular carcinoma (HCC) over a median follow-up of 66 months.
- The 5-year predictive performance of the HCC prediction score constructed from age, platelet count, and liver stiffness measurement at two-dimensional shear-wave elastography, or APS score, was superior to the Chinese University HCC prediction score constructed from age, albumin level, bilirubin level, hepatitis B virus (HBV) DNA level, and cirrhosis (area under the receiver operating characteristic curve [AUC], 0.89 vs 0.70; $P = .005$), and slightly better than the guide with age, gender, HBV DNA level, core promoter mutations, and cirrhosis, or GAG-HCC score (AUC, 0.82; $P = .05$).

in the evaluation of liver fibrosis and cirrhosis. Thus, early cirrhosis may be missed at conventional US. This limitation may decrease the performances of HCC prediction when using the scoring models mentioned earlier if the presence or absence of cirrhosis is misclassified.

Liver stiffness measurement (LSM) obtained using transient elastography (TE) is a good prognostic method for HCC development in the absence of cirrhosis and has been incorporated to improve the prediction performance of HCC scoring systems, such as the HCC prediction score constructed from LSM, age, serum albumin level, and HBV DNA level, or LSM-HCC (11), and the modified risk estimation for HCC in CHB score (hereafter, mREACH-B), which is constructed from LSM, gender, age, alanine aminotransferase (ALT) level, and hepatitis B e antigen positivity (12). However, TE is performed with self-standing dedicated equipment and specific probes, and the system does not provide B-mode anatomic images or the ability to perform liver surveillance (13). Two-dimensional (2D) shear-wave elastography (SWE) is based on shear waves implemented with use of a conventional US system. Previous studies indicated excellent diagnostic performance for staging liver fibrosis in patients with CHB (13), and 2D SWE is significantly superior to TE in depicting liver fibrosis, especially in patients with stage F3 and F4 fibrosis (14). A few studies have suggested that 2D SWE may be useful in predicting HCC development (15,16). Whether 2D SWE can be a useful component of a risk score to predict HCC, especially in patients without clinical cirrhosis, remains to be clarified. Thus, the purpose of this retrospective study was to evaluate the performance of a risk score refined with 2D SWE in predicting HCC development in patients with CHB without clinical cirrhosis.

Materials and Methods

Patients and Study Procedures

This retrospective study was approved by the institutional ethics review board and complied with the Declaration of Helsinki. Informed consent was obtained from every patient. Between April 2011 and December 2015, 811 patients with CHB who were consecutively admitted to our hospital to undergo liver biopsy and 2D SWE were considered for this study. CHB was diagnosed when the hepatitis B surface antigen and HBV DNA were present in the serum for more than 6 months. The exclusion criteria were coinfection with other hepatitis viruses (eg, hepatitis C, hepatitis D, or hepatitis E virus); 2D SWE measurement failure or an invalid value; loss to follow-up; HCC at enrollment or a history of HCC; diagnosis of clinical cirrhosis within 1 month after the 2D SWE examination; and incomplete laboratory test data. Clinical cirrhosis was diagnosed as follows: *(a)* platelet count (PLT) less than 100×10^9/L and US findings suggestive of cirrhosis, including a blunted, nodular liver edge accompanied by splenomegaly (>12 cm), or *(b)* evidence of clinical signs of portal hypertension, such as ascites, esophageal or gastric varices, and hepatic encephalopathy (17).

Clinical and Laboratory Evaluation

Blood samples were obtained on the day of the liver biopsy procedure. The following data were collected from all patients: age, sex, weight, height, ALT level, aspartate aminotransferase level, total bilirubin level, serum albumin level, hemoglobin level, PLT, prothrombin time, HBV DNA loads, and hepatitis B e antigen. Body mass index was calculated as body weight divided by height squared.

Patient Follow-up

After enrollment, the patients underwent periodic surveillance with US and laboratory work-up, including routine blood chemistry serum HBV DNA loads and α-fetoprotein measurements, every 3 or 6 months to screen for the development of HCC and hepatic decompensation. HCC was diagnosed following pathologic confirmation or using at least one imaging technique (contrast-enhanced CT, contrast-enhanced MRI, or contrast-enhanced US) for nodules at least 1 cm in diameter in patients with cirrhosis (18). The evaluation was conducted by two authors (J.J. and M.W., each with 5 years of experience in HCC management) by assessing the electronic medical records of patients or through telephone interviews. Both were blinded to the patients' laboratory LSM and liver biopsy results. A final decision was made at consultation to resolve any discrepancies between the two readers.

LSM with 2D SWE

Within 3 days of liver biopsy, 2D SWE was performed at the same location as liver biopsy to avoid sampling error. Two radiologists (Z.H. and J.Z., each with 8 years of experience in performing liver US examinations and at least 3 months of experience in performing 2D SWE examinations) performed the procedures independently and obtained measurements following the crite-

ria suggested by the Society of Radiologists in Ultrasound Liver Elastography (19). The radiologists were blinded to the patients' clinical information and pathologic results. An Aixplorer US system (SuperSonic Imagine) was used and equipped with a convex broadband probe (SC6–1, 1–6 MHz). With use of a 4 cm × 3 cm box, 2D SWE of the right liver lobe was performed with a depth of 1–2 cm under the liver capsule in a parenchymal area, which is free of large vessels (Fig E1 [online]). Five 2D SWE images were obtained for each patient. The measurements were classified as failed when less than 60% or less than two-thirds of a signal was obtained in the 2D SWE box for all acquisitions. Patients with failed 2D SWE measurements (n = 11) were excluded from the analysis.

LSM with TE

Some of the patients underwent TE on the same day after 2D SWE was performed. LSM was performed with use of a TE device (FibroScan, Echosens) according to the instructions and training provided by the manufacturer. The details of the technique and examination procedure followed the 2017 European Federation of Societies for Ultrasound in Medicine and Biology guidelines (13). In our study, only TE values with at least 10 validated measurements and a success rate of 60% were considered reliable. The ratio of interquartile range to LSM was less than or equal to 0.3. Liver stiffness is expressed in kilopascals.

Liver Biopsy

Percutaneous liver biopsy was performed in the right liver lobe using a 16-gauge disposable needle under US guidance. Liver biopsy specimens were fixed in formalin and embedded in paraffin. Then, specimens were stained with hematoxylin-eosin and Masson trichrome solutions. All liver tissue samples were evaluated by an experienced hepatopathologist who was blinded to the patients' clinical histories and 2D SWE and US scores. Liver fibrosis was evaluated using the METAVIR scoring system, as follows: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis and few septa; F3, numerous septa without cirrhosis; and F4, cirrhosis. Substantial fibrosis was defined as a score of F2 or higher, and severe fibrosis was defined as a score of F3 or higher.

Statistical Analysis

The data for LSM and other clinical parameters are expressed as means ± standard deviations, medians with ranges, or numbers with percentages, as appropriate. Differences among continuous and categorical variables were examined for statistical significance with use of the Student t test (or the Mann-Whitney U test) and the χ^2 test (or Fisher exact test), respectively. The patients were censored at the time of HCC development or at their last follow-up. Cumulative HCC incidence was analyzed using the Kaplan-Meier method and compared with the log-rank test. Hazard ratios and corresponding 95% CIs were used, where indicated. Variables were selected with a stepwise approach. To develop a scoring model with good performance, we first randomly split the data set into a training set and a testing set with a stratified approach. To address the imbalance problem, we applied the synthetic minority oversampling technique, or SMOTE (20), in the training set and built a Cox proportional hazards model. The model performance was assessed with the testing set. Then, we developed the scoring system by dividing the parameters of the Cox proportional hazards model by the smallest parameter and simplified the assigned points to integers. For this scoring system, we obtained the optimal cutoff value based on the Youden index and categorized all participants into high-risk and low-risk groups. The cumulative incidence of HCC between the two groups was compared with time-dependent receiver operating characteristic curves. In addition, we also compared our scores with other published scores. All statistical analyses were performed by using R software (version 3.5.3, the R Foundation). Two-sided $P < .05$ was considered to indicate statistically significant difference.

Results

Baseline Characteristics and Cumulative Probability of HCC

The baseline characteristics of the enrolled patients are presented in Table 1. Among the 654 patients with CHB in the final analytic cohort, the median age was 37 years (interquartile range, 30–43 years), and there were 144 women (22%) and 510 men (78%). All patients had well-preserved liver function (Child-Pugh class A). At enrollment, 151 patients (23%) had previous or ongoing use of an antiviral agent, whereas 274 patients (42%) received AVT after enrollment. During follow-up, 229 patients did not receive AVT (Fig 1). All 654 patients underwent liver biopsy and 2D SWE, and 302 (46%) underwent both TE and 2D SWE prior to biopsy. The median LSM at 2D SWE was 7.8 kPa (interquartile range, 6.1–11 kPa). During the follow-up period (median, 66 months [interquartile range, 40–76 months]), 26 patients developed HCC, of which 15 were diagnosed following imaging and 11 following pathologic confirmation. The 1-, 3-, and 5-year cumulative incidences of HCC were 0.2%, 2%, and 5%, respectively.

Multivariable Analysis of Factors Associated with the Development of HCC

Table 2 shows the analysis with the Cox proportional hazards model concerning the parameters associated with HCC. The cutoff values were chosen according to the guidelines that 7.1 kPa and 11.5 kPa referred to fibrosis stages F2 (substantial liver fibrosis) and F4 (liver cirrhosis), respectively (21,22). They were chosen to define three strata of 2D SWE because these values had the highest sum of sensitivity and specificity.

Univariable analyses showed that older age, diabetes, higher aspartate aminotransferase levels, lower PLT, prolonged prothrombin time, and a 2D SWE value above 7.1 kPa were associated with HCC. An LSM higher than 11.5 kPa was associated with a higher risk of HCC. In the multivariable analysis, the following were found to be independent risk factors for the development of HCC: older age, lower PLT, and an LSM at 2D SWE above 7.1 kPa or 11.5 kPa (Table 2).

Table 1: Baseline Characteristics of Enrolled Patients

Variable	All Patients (n = 654)	Patients with TE Examination (n = 302)	P Value*
Clinical data			
Age (y)	37 (30–43)	38 (31–44)	.55
Sex†			.88
Male	510 (78)	236 (78)	
Female	144 (22)	66 (22)	
Body mass index (kg/m²)	22.04 (20.05–24.27)	22.38 (20.49–24.46)	.30
Antiviral treatment†	425 (65)	198 (66)	.81
Diabetes†	43 (7)	24 (8)	.43
Fibrosis test			
Liver stiffness at 2D SWE (kPa)	7.8 (6.1–11)	7.6 (6–10.5)	.45
Liver stiffness at TE (kPa)	7.0 (5.3–11.8)	7.0 (5.3–11.8)	>.99
Biochemical parameter			
Aspartate aminotransferase (IU/L)	32 (25–46)	31 (24–45.5)	.68
Alanine aminotransferase (IU/L)	40 (27–64)	38 (27–61)	.46
Serum albumin (g/L)	43.8 (41.0–45.9)	44 (41.6–46.1)	.27
Total bilirubin (μmol/L)	13.8 (10.6–18.0)	13.3 (10.8–17.7)	.51
Prothrombin time (sec)	13.4 (12.9–14.0)	13.5 (13.0–14.1)	.005
Platelet count (×10⁹/L)	186 (151–226)	188 (155–230)	.46
HBeAg positivity†	307 (47)	144 (48)	.80
Hepatitis B virus DNA (log IU/mL)	5.00 (2.88–6.78)	5.12 (2.95–6.86)	.67
Histologic analysis			
Fibrosis stage†			.83
F0	103 (16)	56 (19)	
F1	184 (28)	85 (28)	
F2	143 (22)	61 (20)	
F3	124 (19)	57 (19)	
F4‡	100 (15)	42 (14)	
Inflammation stage†§			.17
A0–A1	286 (44)	146 (49)	
A2–A3	368 (56)	155 (51)	
Steatosis†	83 (13)	51 (17)	.008

Note.—Unless otherwise specified, data are medians, with interquartile ranges in parentheses. HBeAg = hepatitis B e antigen, SWE = shear-wave elastography, TE = transient elastography, 2D = two dimensional.

* P value for comparisons between total cohort and cohort with TE examination.

† Data are numbers of patients, with percentages in parentheses.

‡ Cirrhosis.

§ A0, none; A1, mild; A2, moderate; A3, severe.

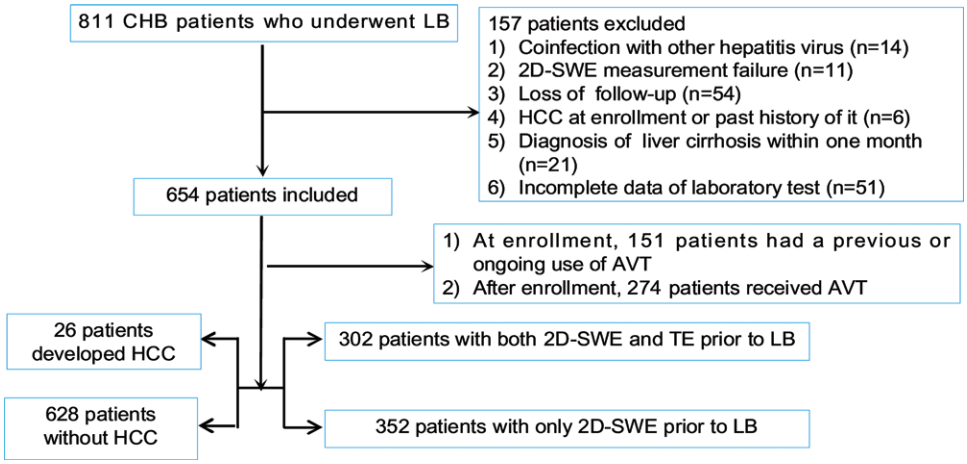

Figure 1: Diagram of patient selection. AVT = antiviral treatment, CHB = chronic hepatitis B, HCC = hepatocellular carcinoma, LB = liver biopsy, SWE = shear wave elastography, TE = transient elastography, 2D = two-dimensional.

Table 2: Univariable and Multivariable Cox Regression Analyses for the Risk of HCC Development

Variable	Univariable Analysis			Multivariable Analysis		
	Hazard Ratio	95% CI	*P* Value	Hazard Ratio	95% CI	*P* Value
Clinical data						
Age (per year)	1.07	1.03, 1.12	<.001	1.05	1.03, 1.06	<.001
Sex						
Female	1					
Male	0.86	0.32, 2.27	.76			
Body mass index (per kg/m^2)	1.07	0.95, 1.19	.26			
Antiviral treatment						
No	1					
Yes	0.81	0.36, 1.82	.61			
Diabetes	4.78	1.92, 11.91	.001			
Biochemical parameter						
AST (IU/L)	1.01	1.00, 1.02	.01			
ALT greater than or equal to upper limit of normal (IU/L)	1.85	0.78, 4.39	.17			
Serum albumin <35 g/L	0.55	0.13, 2.34	.42			
Total bilirubin (μmol/L)	1	0.98, 1.03	.99			
Prothrombin time (sec)	1.71	1.26, 2.32	.001			
Platelet count (×10^9/L)						
≥150	1			0.63	0.52, 0.77	<.001
<150	0.20	0.09, 0.44	<.001			
HBeAg positivity (%)	0.94	0.43, 2.03	.87			
HBV DNA (IU/mL)						
≤200,000	1					
>200,000	1.15	0.54, 2.49	.72			
Liver stiffness at 2D SWE						
<7.1 kPa	1					
7.1–11.5 kPa	6.45	1.41, 29.44	.02	2.78	2.04, 3.79	<.001
>11.5 kPa	13.25	3.01, 58.32	.001	3.63	2.67, 4.93	<.001

Note.—Among the 654 patients in this study, 26 developed hepatocellular carcinoma (HCC). AST = aspartate aminotransferase, ALT = alanine aminotransferase, HBeAg = hepatitis B e antigen, HBV = hepatitis B virus, SWE = shear-wave elastography, 2D = two-dimensional.

Predictive HCC Model Establishment for Risk Stratification

A Cox proportional hazards model was built based on the aforementioned parameters with a stepwise approach. The performance of this predictive HCC model was evaluated on the testing set. Overall, the AUC of this model based on the training set was 0.82 (95% CI: 0.71, 0.90), while the AUC of the testing set was 0.83 (95% CI: 0.67, 0.94) (Fig 2A). From the 5-year survival aspect, the time-dependent AUC of the training set was 0.87 (95% CI: 0.84, 0.96), while the AUC of the testing set was 0.78 (95% CI: 0.72, 0.92) (Fig 2B). The scoring system is based on each parameter in this Cox proportional hazards model (ie, age, PLT, and LSM at 2D SWE) and is abbreviated as the APS score. The APS score was calculated using the equation [age (years)] + [PLT (×10^9/L) (PLT <150 = 1; PLT ≥150 = 0) × 10] + [LSM measured with 2D SWE (<7.1 kPa = 0, ≥7.1 but <11.5 kPa = 23, ≥11.5 kPa = 29)] (Table 3).

Using 60 as the cutoff value, 508 (78%) and 146 patients (22%) in the validation cohort were classified into low-risk and high-risk groups, respectively, and the numbers of patients who developed HCC were six and 20 ($P < .001$) (Fig 3). With 60 as a cutoff to identify HCC, the sensitivity and negative predictive value were 54% (95% CI: 0.25, 0.84) and 99% (95% CI: 0.98, 1.00), respectively, at 3 years and 73% (95% CI: 0.56, 0.90) and 98% (95% CI: 0.97, 1.00) at 5 years.

Comparison of the Predictive Performance of the APS Score with Five Other Models for HCC Development

The AUCs of the several risk prediction models for HCC development at 3 and 5 years are shown in Table 4, Table E1 (online), and Figure 4. In terms of HCC development at 3 years, the APS score was comparable to the other three conventional risk prediction models, including the CU-HCC, GAG-HCC, and CAMD scores. In terms of HCC development at 5 years, the APS score had a better predictive performance than the CU-HCC score but was comparable to the GAG-HCC and CAMD scores (Table 4; Fig 4A, 4B). LSM-HCC and mREACH-B scores use LSM measured with TE as a component. In our subset cohort with available TE measurements (n = 302), the AUCs of

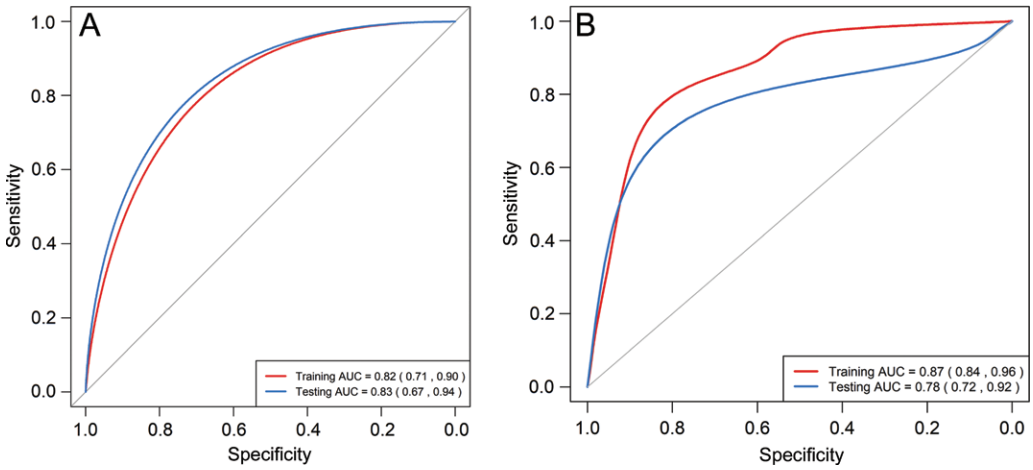

Figure 2: Graphs depict performance of the Cox proportional hazards model. **(A)** The overall area under the receiver operating characteristic curve (AUC) of the hepatocellular carcinoma prediction score constructed from age, platelet count, and liver stiffness measurement at two-dimensional shear-wave elastography, or APS score, based on the training set was 0.82 (95% CI: 0.71, 0.90), while the AUC of the testing set was 0.83 (95% CI: 0.67, 0.94). **(B)** From the 5-year survival aspect, the time-dependent AUC of the training set was 0.87 (95% CI: 0.84, 0.96), while the AUC of the testing set was 0.78 (95% CI: 0.72, 0.92).

the APS, LSM-HCC, and mREACH-B scores were 0.79 (95% CI: 0.31, 0.86), 0.79 (95% CI: 0.34, 0.94), and 0.82 (95% CI: 0.34, 0.95), respectively, at 3 years. In 5-year risk of HCC development, the AUCs of the aforementioned three scores were 0.84 (95% CI: 0.68, 0.94), 0.81 (95% CI: 0.66, 0.95), and 0.85 (95% CI: 0.72, 0.97), respectively (Table 4; Fig 4C, 4D). For patients with available TE measurements, the AUC of the APS score compared with that of the mREACH-B score in the prediction of 3-year HCC development was 0.79 versus 0.82, respectively (P = .05), with no significant difference for 5-year HCC development. Similarly, there were no significant differences between the APS score and the LSM-HCC and mREACH-B scores in terms of 5-year HCC development (Table E1 [online]).

Subgroup Analysis according to AVT, Inflammation Grade, and ALT Level

AVT improves the survival of patients with HBV infection. However, patients with CHB using AVT may still develop HCC. Previous studies demonstrated that the risk factors and the components of the predictive score may change in the era of AVT. Our score seemed to have similar good performance in patients with CHB, regardless of whether AVT was used (Table E2 [online]). In 3-year HCC development, the AUCs of the APS score were 0.82 (95% CI: 0.74, 0.91) in the AVT group and 0.79 (95% CI: 0.58, 0.99) in the non-AVT group ($P > .05$). Similarly, the AUC of the APS score for predicting 5-year HCC development was 0.86 (95% CI: 0.81, 0.92) in the AVT group and 0.83 (95% CI: 0.67, 0.99) in the non-AVT group ($P > .05$) (Fig 5A, 5B).

Inflammation status is one of the most important confounding factors in the diagnosis of fibrosis in chronic hepatitis when using 2D SWE (7). Furthermore, prior studies suggest that a higher inflammatory grade and elevated ALT levels are associated with higher LSMs at 2D SWE (13,19). Accordingly, for this study, our patients were grouped based on ALT levels and activity grade. Our results showed good performance in both the normal (n = 266) and elevated ALT level groups (n = 388) for 3- and 5-year HCC development, with AUCs of 0.82 (95% CI: 0.74, 0.91) and 0.86 (95% CI: 0.81, 0.92) and 0.79 (95% CI: 0.58, 0.99) and 0.83 (95% CI: 0.67, 0.99), respectively (Table E2 [online]; Fig 5C, 5D). Likewise, in both lower (A0, A1) and higher (A2, A3) activity grades, the APS score had good performance, with AUCs of 0.78 (95% CI: 0.48, 1.00) and 0.83 (95% CI: 0.47, 0.88), respectively, for 3-year HCC development and 0.77 (95% CI: 0.63, 0.91) and 0.84 (95% CI: 0.67, 0.88) for 5-year HCC development (Table E2 [online]; Fig 5E, 5F).

Discussion

In this study, we developed a score to predict the risk of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B without clinical cirrhosis using two-dimensional (2D) shear-wave elastography (SWE) as an important component. The score, termed the APS score, was constructed on three simple parameters (age, platelet count, and liver stiffness measured with 2D SWE) available in clinical practice. More importantly, it accurately stratified patients into distinct risk subgroups with a higher risk of HCC development if the APS score was greater than 60 ($P < .001$).

Noninvasive fibrosis staging provides prognostic information for patients with CHB (7). Liver stiffness measured with TE for stratifying the risk of HCC has been extensively studied (11,18,23–25) and has been incorporated into risk models, such as the LSM-HCC (11) and mREACH-B scores (12). An important limitation of TE is the lack of B-mode imaging guidance. In contrast, 2D SWE does provide B-mode imaging in real time and has high technical success rates and more reliable results in patients with obesity and ascites. The addition of B-mode images not only helps physicians perform liver stiffness follow-up but also allows for HCC liver surveillance (26).

Previous studies have shown potential value of 2D SWE for HCC prediction. Jeong et al (15) demonstrated that elevated liver stiffness measured with 2D SWE was associated with an

Table 3: APS Score Construction

Variable	APS Score
Age (y)	1
Platelet count	
≥150 (×10⁹/L)	0
<150 (×10⁹/L)	10
Liver stiffness at 2D SWE	
<7.1 kPa	0
7.1–11.5 kPa	23
>11.5 kPa	29

Note.—APS score = hepatocellular carcinoma prediction score constructed from age, platelet count, and liver stiffness measurement at 2D SWE; SWE = shear-wave elastography; 2D = two-dimensional.

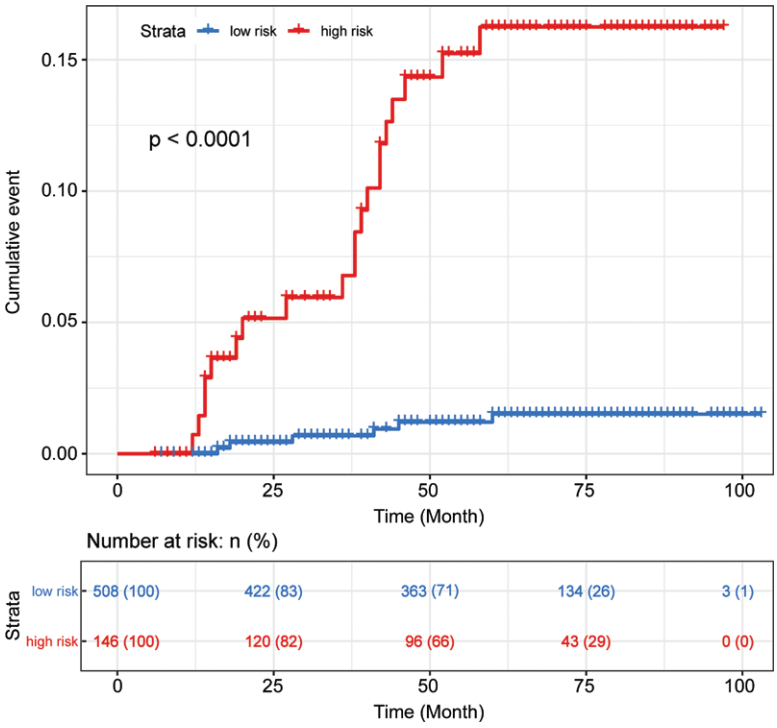

Figure 3: Graphs show comparison of cumulative hepatocellular carcinoma (HCC) development between low-risk (HCC prediction constructed from age, platelet count, and liver stiffness measurement at two-dimensional shear-wave elastography [APS score] <60) and high-risk (APS score ≥60) patients.

increased risk of HCC development. However, in that study, only one 2D SWE indicator was considered and subsequently evaluated in a smaller sample size. In our study, LSM at 2D SWE was obtained in a larger population and, when combined with other factors, proved to be an important indicator of 3- and 5-year HCC development. The APS score, which uses 2D SWE, performed better than the CU-HCC score in predicting 5-year HCC development (AUC, 0.89 vs 0.70, respectively; $P = .005$). Furthermore, for all patients, the AUC of the APS score was slightly better than that of the GAG-HCC score in the prediction of 5-year HCC development (AUC, 0.89 vs 0.82, respectively; $P = .05$). For patients with available TE measurements, the AUC of the APS score compared with that of the mREACH-B score in the prediction of 3-year HCC development was 0.79 versus 0.82, respectively ($P = .05$).

Although AVT has been considered a milestone in the prevention of HBV-related HCC, guidelines and studies have confirmed that HCC may still develop and remains a major concern (5,27). Recent research has found that the individual's risk should be assessed based on the fibrotic burden rather than a biologic gradient of serum HBV DNA levels (28). Likewise, 2D SWE–assessed fibrotic burden accounted for a large proportion of our APS score and proved to have good performance in both the AVT and non-AVT cohorts, with AUCs of 0.82 (95% CI: 0.74, 0.91) and 0.79 (95% CI: 0.58, 0.99), respectively, for 3-year HCC development and 0.86 (95% CI: 0.81, 0.92) and 0.83 (95% CI: 0.67, 0.99) for 5-year HCC development.

Some confounding factors of LSM should be considered when it is used in clinical practice. The updated guidelines on liver US elastography suggest that hepatic inflammation and ALT levels are important confounding factors in the evaluation of liver cirrhosis (29). However, given that only 74 of 654 patients (11%) had baseline ALT levels that were more than three times the upper limit of normal and none had ALT levels that were more than five times the upper limit, the effect of increased ALT levels appeared to be minimal in our cohort. In our study, the APS score performed well in both the normal and higher ALT groups, with AUCs of 0.81 (95% CI: 0.11, 1.00) and 0.80 (95% CI: 0.54, 0.89) for 3-year HCC development and 0.80 (95% CI: 0.60, 0.98) and 0.81 (95% CI: 0.66, 0.86) for 5-year HCC development. In the histologic analysis, although patients with inflammatory grades of A2 (moderate) and A3 (severe) accounted for a large proportion ($n = 368$), the APS score had similar prognostic power in the A0–A1 group and the A2–A3 group. The results revealed that our APS score established with 2D SWE and integrated with other important factors was not significantly impacted by elevated ALT levels or inflammation, while separate 2D SWE results more easily fluctuated along with ALT or inflammatory levels.

We recognized the following limitations in our study. First, the main limitation was that only 26 HCC events occurred in this relatively longer follow-up study enrolling patients with CHB without cirrhosis. Thus, extending the follow-up period and enrolling more patients are needed in the future. Furthermore, our predictive model was built from only one data set, and imbalanced distribution of the majority and minority classes could greatly affect the predictive accuracy, leading to misclassification. To solve the problem, we randomly split the data set into a training set and testing set. This approach could overcome the overfitting problem and enable our scoring system to be applied to the target population to some extent. The synthetic minority oversampling technique, which has been verified to be able to improve the performance

Table 4: Comparison the Predictive Performances of Risk Prediction Models for HCC Development with APS Score

Subgroup and Prediction Model	Three-year HCC Development		Five-year HCC Development	
	AUC	*P* Value*	AUC	*P* Value*
All patients (*n* = 654)				
APS	0.88 (0.62, 0.92)		0.89 (0.78, 0.92)	
CU-HCC	0.71 (0.51, 0.79)	.17	0.70 (0.57, 0.79)	.005
GAG-HCC	0.83 (0.59, 0.86)	.59	0.82 (0.66, 0.84)	.05
CAMD	0.72 (0.48, 0.82)	.23	0.75 (0.67, 0.86)	.11
Patients with TE examination (*n* = 302)				
APS	0.79 (0.31, 0.86)		0.84 (0.68, 0.94)	
LSM-HCC	0.79 (0.34, 0.94)	.24	0.81 (0.66,0.95)	.90
mREACH-B	0.82 (0.34,0.95)	.05	0.85 (0.72, 0.97)	.12

Note.—Data in parentheses are 95% CIs. APS score = HCC prediction score constructed from age, platelet count, and liver stiffness measurement at two-dimensional shear-wave elastography; AUC = area under the receiver operating characteristic curve; CAMD = HCC prediction score constructed from cirrhosis, age, male sex, and diabetes; CU-HCC = Chinese University HCC prediction score constructed from age, albumin level, bilirubin level, hepatitis B virus DNA level, and cirrhosis; GAG-HCC = guide with age, gender, hepatitis B virus DNA level, core promoter mutations, and cirrhosis; HCC = hepatocellular carcinoma; LSM-HCC = HCC prediction score constructed from liver stiffness measurement, age, serum albumin level, and hepatitis B virus DNA level; mREACH-B = modified risk estimation for HCC in chronic hepatitis B (constructed from liver stiffness measurement, gender, age, alanine aminotransferase level, and hepatitis B e antigen positivity); TE = transient elastography.

* *P* value indicates the comparison between the APS score and other prediction scores.

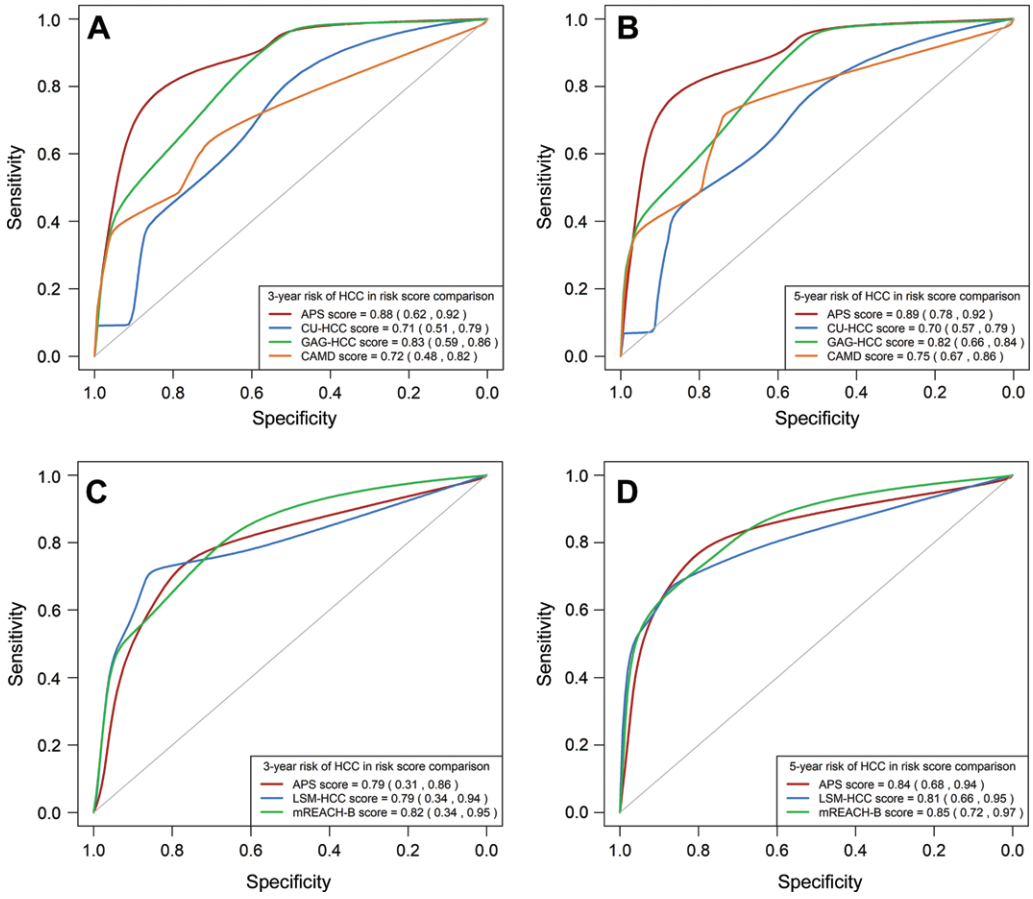

Figure 4: Receiver operating characteristic curves show the comparison of the predictive performance of the hepatocellular carcinoma (HCC) prediction score constructed from age, platelet count, and liver stiffness measurement (LSM) at two-dimensional shear-wave elastography (APS score) with five models for HCC development. **(A, B)** APS score compared with the Chinese University HCC prediction score constructed from age, albumin level, bilirubin level, hepatitis B virus [HBV] DNA level, and cirrhosis (CU-HCC score); guide with age, gender, HBV DNA level, core promoter mutations, and cirrhosis (GAG-HCC score); and HCC prediction score constructed from cirrhosis, age, male sex, and diabetes (CAMD score) for **(A)** 3-year and **(B)** 5-year HCC prediction. **(C, D)** In patients who underwent transient elastography (*n* = 302), prognostic performance of the APS score with the HCC prediction score constructed from LSM, age, serum albumin level, and HBV DNA level (LSM-HCC score) and the modified risk estimation for HCC in chronic hepatitis B (mREACH-B score) for **(C)** 3-year and **(D)** 5-year HCC prediction.

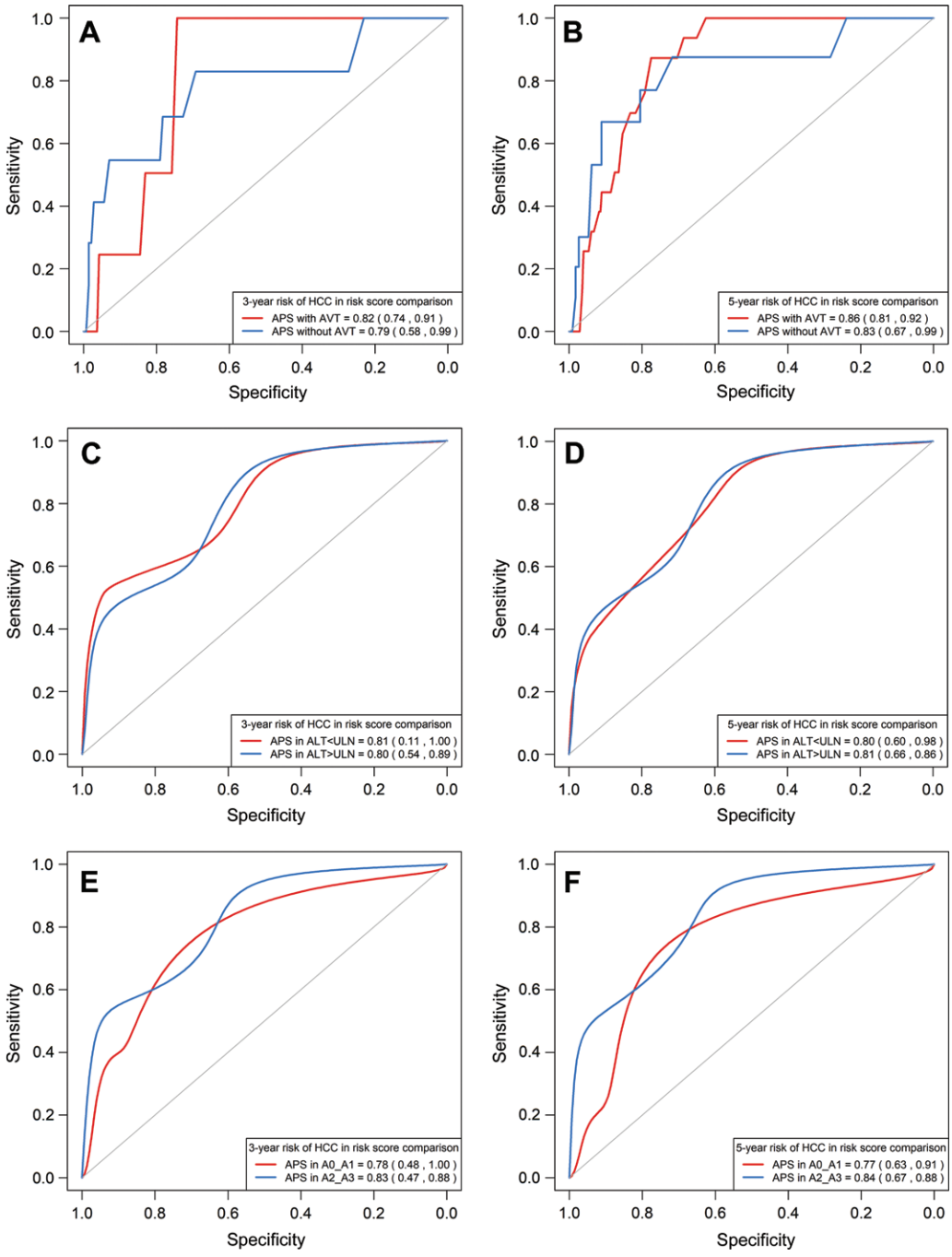

Figure 5: Receiver operating characteristic curves show the comparison of the prognostic performance of the hepatocellular carcinoma (HCC) prediction score constructed from age, platelet count, and liver stiffness measurement at two-dimensional shear-wave elastography (APS score) in patients with chronic hepatitis B. **(A, B)** Patients who underwent antiviral treatment (AVT) and did not undergo AVT for **(A)** 3-year and **(B)** 5-year HCC prediction. **(C, D)** Patients with alanine aminotransferase (ALT) levels lower than the upper limit of normal (ULN) and higher than the upper limit of normal for **(C)** 3-year and **(D)** 5-year HCC predictions. **(E, F)** Subanalysis of patients with different inflammation stages (A0 [none], A1 [mild], A2 [moderate], and A3 [severe]) using the APS score for predicting **(E)** 3-year and **(F)** 5-year HCC development.

of the predictive model in 90% of 15 cancer cases (30), was applied to address the class of imbalance. Therefore, by using the synthetic minority oversampling technique, our scoring system had better discrimination ability and better predictive performance for HCC. Second, only baseline measurements were available in our study. The association of the changes in each parameter during follow-up and the final prognosis should be further evaluated. Third, differences among US elastography manufacturers may lead to differences in measurement data. However, differences among manufacturers do not influence the diagnostic performance, as suggested by the updated liver elastography consensus statement (19). Further research is needed to validate our system across other US vendors. Finally, a few patients underwent 2D SWE after liver biopsy. This may

impact the measurements due to the risk of postbiopsy inflammation or hemorrhage.

In conclusion, the APS score, which is based on the baseline liver stiffness measurement at two-dimensional shear-wave elastography, age, and platelet count, is accurate in predicting the development of hepatocellular carcinoma (HCC) in patients with chronic hepatitis B (CHB). It is especially useful for the early detection of high-risk patients without clinical cirrhosis. Our findings appear to identify patients at elevated risk of HCC who would have otherwise been considered relatively low-risk and may not have received appropriate surveillance. The APS score may help physicians efficiently modify the management of and surveillance strategies for patients with CHB.

Author contributions: Guarantors of integrity of entire study, T.Z., G.Z., Z.H., R.Z.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, T.Z., G.Z., J.J., Z.H., M.W.; clinical studies, T.Z., G.Z., J.J., Z.H.; experimental studies, T.Z., G.Z., Z.H.; statistical analysis, T.Z., G.Z., X.D., M.W., R.Z.; and manuscript editing, T.Z., G.Z., X.D., J.Z., Z.H., R.Z.

Disclosures of Conflicts of Interest: **T.Z.** disclosed no relevant relationships. **G.Z.** disclosed no relevant relationships. **X.D.** disclosed no relevant relationships. **J.Z.** disclosed no relevant relationships. **J.J.** disclosed no relevant relationships. **Z.H.** disclosed no relevant relationships. **M.W.** disclosed no relevant relationships. **R.Z.** disclosed no relevant relationships.

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