Original Article

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The APP Score: A simple serum biomarker model to enhance prognostic prediction in hepatocellular carcinoma

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SUMMARY The prognosis for patients with hepatocellular carcinoma (HCC) depends on tumor stage and remnant liver function. However, it often includes tumor morphology, which is usually assessed with imaging studies or pathologic analysis, leading to limited predictive performance. Therefore, the aim of this study was to develop a simple and low-cost prognostic score for HCC based on serum biomarkers in routine clinical practice. A total of 3,100 patients were recruited. The least absolute shrinkage and selector operation (LASSO) algorithm was used to select the significant factors for overall survival. The prognostic score was devised based on multivariate Cox regression of the training cohort. Model performance was assessed by discrimination and calibration. Albumin (ALB), alkaline phosphatase (ALP), and alpha-fetoprotein (AFP) were selected by the LASSO algorithm. The three variables were incorporated into multivariate Cox regression to create the risk score (APP score = 0.390* ln (AL**P**) + 0.063* ln(AF**P**) - 0.033*A**L**B). The C-index, K-index, and time-dependent AUC of the score displayed significantly better predictive performance than 5 other models and 5 other staging systems. The model was able to stratify patients into three different risk groups. In conclusion, the APP score was developed to estimate survival probability and was used to stratify three strata with significantly different outcomes, outperforming other models in training and validation cohorts as well as different subgroups. This simple and low-cost model could help guide individualized follow-up.

Keywords hepatocellular carcinoma, serum biomarker, overall survival, prognostic score, individualized prediction

1. Introduction

Hepatocellular carcinoma (HCC) is the fourth leading cause of cancer-related mortality worldwide (*1*). Most patients with HCC have associated chronic liver disease and are usually in the stage of cirrhosis in which development of HCC is one of the main causes of liver-related mortality (*2*). Thus, the prognosis for patients with HCC depends on tumor stage and remnant liver function.

At present, several conventional staging systems such as the American Joint Committee on Cancer (AJCC), China Liver Cancer Staging (CNLC), and Barcelona Clinic Liver Cancer (BCLC) have been proposed for prognostic prediction (*3-5*). However, these systems often include tumor morphology such as tumor size, the number of tumors, and vascular invasion, which are usually assessed with imaging studies or pathologic analysis, leading to limited predictive performance (*6-8*).

Recently, an objective serology-based model known as the BALAD score, which combines bilirubin and albumin with three serum biomarkers (alpha-fetoprotein [AFP], Lens culinaris agglutinin-reactive alpha-fetoprotein [AFP-L3%], and des- gamma-carboxy prothrombin [DCP]), was reported for survival prediction in HCC (*9*). However, it has not been widely used to measure AFP-L3 and DCP, limiting its use in routine clinical practice. The albumin-bilirubin (ALBI) grade also has been used to evaluate liver function in cirrhotic patients and it has a relatively good correlation with prognosis (*10*), but it cannot be used to predict survival in patients with HCC.

Robust molecular subclasses of HCC have also been reported as a result of gene sequencing and/or gene expression profiling over the last decade (*11,12*). However, reliable biomarkers are still needed, and the implementation of tumor subgroups in clinical practice remains challenging due to technical challenges and

cost.

Therefore, the aim of this study was to develop a simple and low-cost prognostic score for HCC that is based on serum biomarkers in routine clinical practice.

2. Patients and Methods

2.1. Patients

Patients with HCC who were seen between January 2012 and December 2018 were identified from a multicenter database. This study was approved by the institutional ethics committee of Mengchao Hepatobiliary Hospital of Fujian Medical University (NO.:2023_045_01) and followed the principles of the Declaration of Helsinki. Informed consent was obtained from each patient for their data to be used for research purposes.

The inclusion criteria included: *i*) HCC diagnosis confirmed by pathology, *ii*) curative resection, *iii*) no macrovascular invasion, *iv*) no distant metastasis, and *v*) Child-Pugh class A or selected B liver function (score ≤ 7). Exclusion criteria were preoperative anticancer therapy, palliative treatment, incomplete data, and loss to follow-up within 2 months of surgery.

2.2. Clinicopathologic variables and follow-up

Blood samples were obtained up to 14 days before surgery for routine laboratory tests for blood cell counts, hepatic and renal function, alpha-fetoprotein (AFP), hepatitis B virus (HBV) and hepatitis C virus (HCV) immunology, and hepatitis B virus deoxyribonucleic acid (HBV-DNA) load. Preoperative imaging studies included chest radiography, abdominal ultrasonography, and contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen.

Patients were followed up with once every 3 months for the first two years after discharge from the hospital and every 3-6 months in subsequent years. The follow-up program included liver function, AFP level, and abdominal ultrasound. Contrast-enhanced CT or MRI was performed when tumor recurrence was clinically suspected. The end-point of the study was overall survival (OS). OS was defined as the interval between the date of surgery and the date of patient death or last follow-up. The follow-up on October 31, 2023 was censored.

2.3. Statistical analysis

Continuous variables were expressed as the mean (standard deviation, SD) and were compared using the Student *t*-test or as the median (interquartile range, IQR) and compared using the Mann-Whitney *U* test. Categorical variables were expressed as *n* (%) and compared using the chi-square test or Fisher's exact test. Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test.

The least absolute shrinkage and selector operation (LASSO) algorithm, with penalty parameter tuning conducted by 10-fold cross-validation, was used to select the significant factors for OS. The prognostic score was created based on multivariate Cox regression of the training cohort.

Model performance was assessed by discrimination and calibration. Model discrimination was measured with Harrell's C-index, Gönen& Heller's K-index, and time-dependent areas under the receiver operating characteristic curve (tdAUC) (*13*). Model calibration was assessed using a calibration curve.

The model was compared to staging systems including Italian Liver Cancer (ITA.LI.CA) (*14*), the 8th American Joint Committee on Cancer Tumor-Node-Metastasis (the 8th AJCC TNM) (*3*), Barcelona Clinic Liver Cancer (BCLC) (*5*), China Liver Cancer Staging (CNLC) (*4*), and Japan Integrated Staging (JIS) (*15*). It was also compared to other models including the albumin-bilirubin (ALBI) grade (*10*), systemic immune-inflammation index (SII) (*16*), neutrophil times the γ-glutamyl transpeptidase to lymphocyte ratio (NrLR) (*17*), prognostic nutritional index (PNI) (*18*), and platelet-to-lymphocyte ratio (PLR) (*19*) in each cohort as well as in different subgroups (Supplemental Table S1, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=225*).

All statistical tests were 2-tailed and a $p < 0.05$ was considered statistically significant. Statistical analysis was performed with R version 3.5.2 (*http://www.r-project.org/*). The R packages "table1", "rms", "CPE", "timeROC", "stdca", "survminer", and "survival" were used in this study.

3. Results

3.1. Baseline characteristics

A total of 3,100 HCC patients were enrolled and randomly divided into the training (n = 2,100) and validation (n = 1,000) cohorts (Figure 1) in a 2:1 ratio.

The baseline characteristics of patients are shown in Table 1. Of the total, 2,716 (87.6%) patients were positive for viral hepatitis. 2,172 (70.1%) patients were positive for liver cirrhosis. The average size of intrahepatic tumors was 5.64 cm (SD, 3.51 cm). Pathological examinations revealed microvascular invasion in 872 patients (28.2%). There were no significant differences in clinicopathologic features between the training and validation cohorts.

3.2. OS

In this study, the median survival of the entire cohort was 5.31 years (95% CI: 5.23-5.48), with 1-year, 3-year, and 5-year OS rates of 92.1%, 75.7%, and 57.6%,

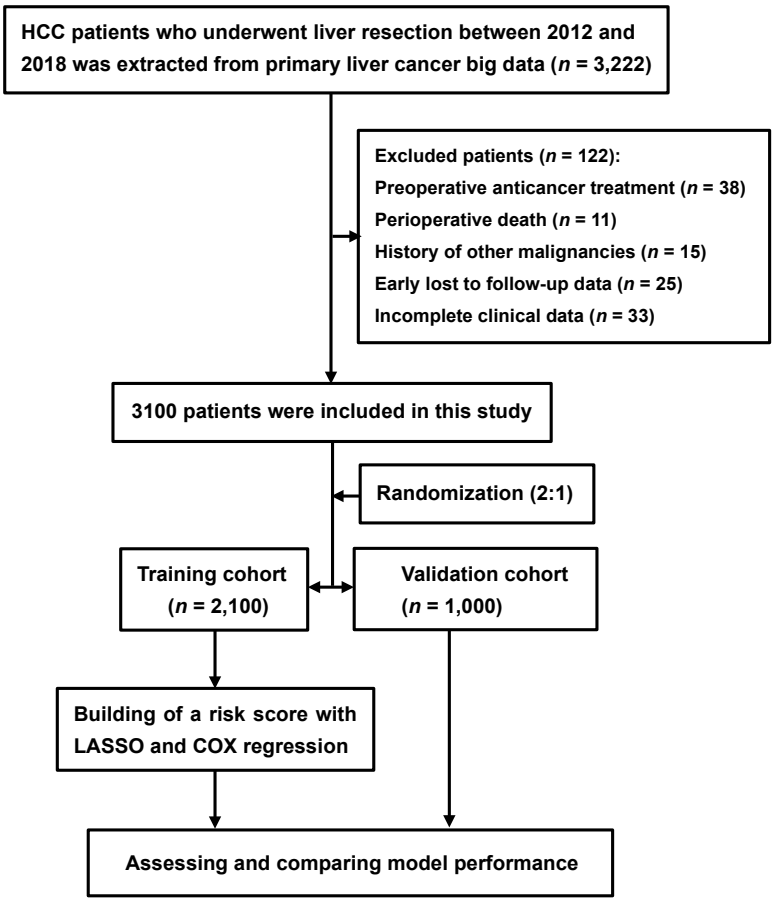

Figure 1. Flow chart for the study design. HCC, hepatocellular carcinoma; LASSO, least absolute shrinkage and selector operation.

Table 1. Baseline characteristics of patients

Variables	Entire cohort (n = 3,100)	Training cohort (n = 2,100)	Validation cohort (n = 1,000)	p-value
Patient factors				
Age [year, Mean (SD)]	51.9 (10.7)	51.8 (10.9)	52.2 (10.5)	0.281
Sex, male/female	2,653/447 (85.6%/14.4%)	1,808/292 (86.1%/13.9%)	845/155 (84.5%/15.5%)	0.260
Etiology				0.750
Hepatitis B	2,716 (87.6%)	1,834 (87.3%)	882 (88.2%)	
Hepatitis C	52 (1.7%)	35 (1.7%)	17 (1.7%)	
Other	332 (10.7%)	231 (11.0%)	101 (10.1%)	
Liver cirrhosis, Absence/Presence	928/2,172 (29.9%/70.1%)	654/1,446 (31.1%/68.9%)	274/726 (27.4%/72.6%)	0.037
Laboratory parameters				
WBC [10^9/L, Mean (SD)]	5.35 (1.71)	5.33 (1.64)	5.40 (1.83)	0.283
Neutrophil [10^9/L, Mean (SD)]	3.18 (1.36)	3.15 (1.28)	3.24 (1.52)	0.724
Lymphocyte [10^9/L, Mean (SD)]	1.63 (0.60)	1.64 (0.59)	1.63 (0.61)	0.283
Monocyte [10^9/L, Mean (SD)]	0.31 (0.13)	0.31 (0.12)	0.31 (0.13)	0.928
Hemoglobin [g/L, Mean (SD)]	143 (15.1)	143 (15.1)	143 (15.1)	0.306
RBC [10^9/L, Mean (SD)]	4.67 (0.52)	4.66 (0.52)	4.67 (0.52)	0.801
PLT [10^9/L, Mean (SD)]	164 (67.2)	164 (66.1)	163 (69.7)	0.557
ALB [g/L, Mean (SD)]	42.4 (3.70)	42.4 (3.73)	42.2 (3.62)	0.261
TBIL [μmol/L, Median (IQR)]	13.2 [10.5, 16.9]	13.3 [10.6, 16.8]	13.2 [10.5, 17.0]	0.904
GGT [IU/L, Median (IQR)]	54.0 [33.0, 96.0]	53.0 [33.0, 94.0]	56.0 [32.8, 100]	0.420
ALP [IU/L, Median (IQR)]	79.0 [65.0, 101]	79.0 [65.0, 100]	79.0 [65.0, 101]	0.329
AFP [ng/mL, Median (IQR)]	48.0 [5.40, 961]	50.0 [5.40, 920]	43.2 [5.30, 1080]	0.753
Tumor factors				
Tumor size [cm, Mean (SD)]	5.64 (3.51)	5.60 (3.53)	5.73 (3.45)	0.326
Tumor number, Solitary/Multiple	3,011/89 (97.1%/2.9%)	2,029/71 (96.6%/3.4%)	982/18 (98.2%/1.8%)	0.019
MVI, Absence/Presence	2,227/873 (71.8%/28.2%)	1,510/590 (71.9%/28.1%)	717/283 (71.7%/28.3%)	0.940

Abbreviations: WBC, white blood cell count; RBC, red blood cell count; PLT, platelet count; ALB, albumin; TBIL, total bilirubin; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; AFP, alpha-fetoprotein; MVI, microvascular invasion; SD, standard deviation; IQR, interquartile range.

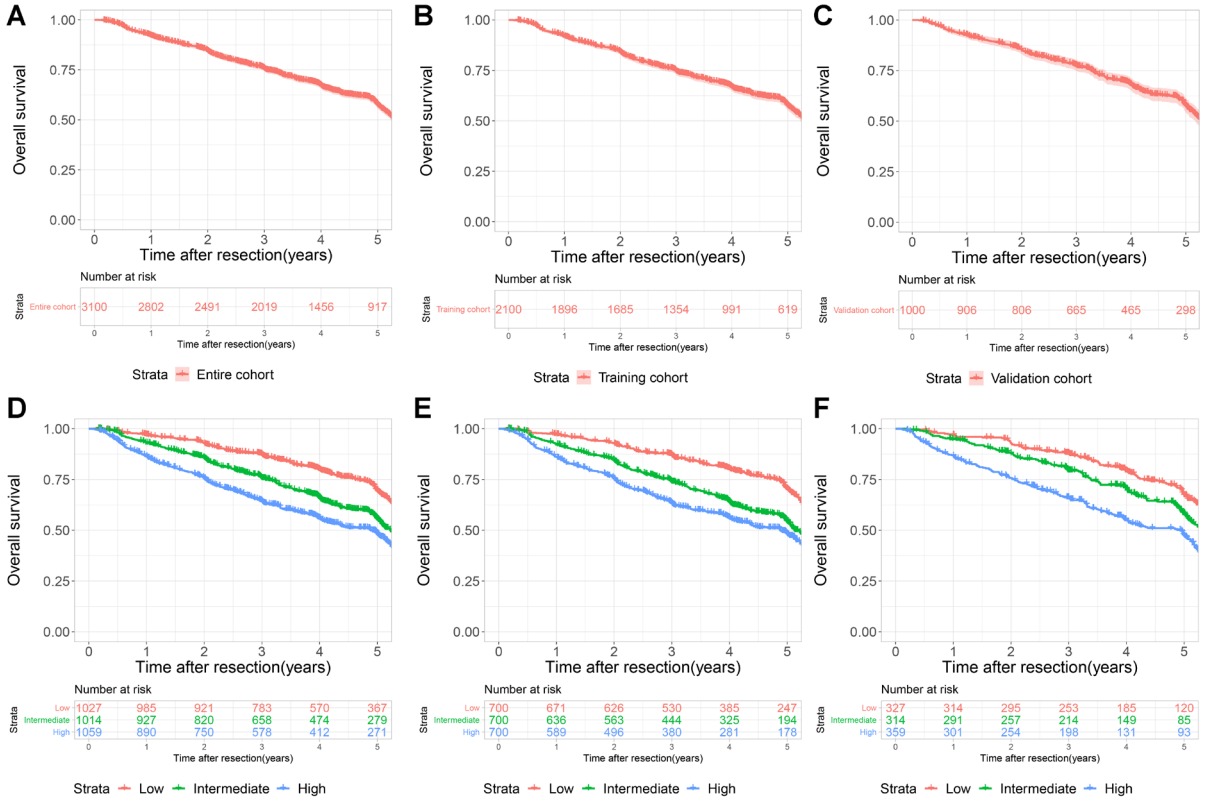

Figure 2. Overall survival. (A) Entire cohort, **(B)** Training cohort, **(C)** Validation cohort, **(D)** Entire cohort stratified by APP score, **(E)** Training cohort stratified by APP score, **(F)** Validation cohort stratified by APP score.

Table 2. Multivariable Cox regression analysis of factors associated with OS in the training cohort

Variables	Multivariable		
	HR (95% CI)	β	*p*-value
ALB, g/L	0.967 (0.950-0.984)	-0.033	< 0.001
ln(ALP)	1.478 (1.311-1.665)	0.390	< 0.001
ln(AFP)	1.065 (1.045-1.086)	0.063	< 0.001
APP score = 0.390* ln(AL**P**) + 0.063* ln(AF**P**) - 0.033*A**L**B			

Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval; ALB, albumin; ALP, alkaline phosphatase; AFP, alpha-fetoprotein.

respectively (Figure 2A). There were no significant differences in survival between the training and validation cohorts (median OS: 5.31 years [95% CI: 5.23-5.56] *vs*. 5.32 years [95% CI: 5.17-5.58]), (Figure 2B, 2C).

3.3. Devising the APP score

The LASSO algorithm was used to select the significant factors for OS in the training cohort (Supplemental Figure S1, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=225*). Albumin (ALB), alkaline phosphatase (ALP), and alpha-fetoprotein (AFP) were finally selected. The three variables were incorporated into multivariate Cox regression to create the risk score (**APP score** = 0.390* ln(AL**P**) + 0.063* ln(AF**P**) - 0.033*A**L**B) (Table 2).

3.4. Risk stratification

Based on the score calculated using the APP score, with 1.26 and 1.57 as the cutoff values (which correspond to the 33rd and 66th centiles), the patients were classified into low-risk, intermediate-risk, and high-risk groups. In the training cohort, the median OS of the low-risk, intermediate-risk, and high-risk groups was 7.55 years (95% CI: 6.24-NA), 5.13 years (95% CI: 5.01-5.44), and 4.88 years (95% CI: 4.33-5.15), respectively. With the low-risk group as a reference, the hazard ratios (HRs) for intermediate-risk and high-risk groups were 1.78 (95% CI: 1.46-2.07; $p < 0.001$) and 2.21 (95% CI: 1.87-2.62; $p < 0.001$), respectively (Table 3). The median OS of the three risk groups in the validation cohort was 8.01 years (95% CI: 5.51-8.72), 5.32 years (95% CI: 5.06-6.00), and 4.96 years (95% CI: 4.01-5.17), respectively. With stratum 1 as a reference, the HRs for strata 2 and 3 were 1.41 (95% CI: 1.10-1.82; $p < 0.001$) and 2.01 (95% CI: 1.59-2.54; $p < 0.001$), respectively (Table 3). Kaplan-Meier analysis showed that the OS rates stratified prognosis among the three risk groups in the training, validation, and entire cohorts ($p < 0.001$) (Figure 2D, 2F).

3.5. Assessment and comparison of model performance

Table 3. Median OS, hazard ratio, and p-value according to each risk group as defined by the APP score

Cohort	Risk group	*n*	Median OS (95% CI), years	Hazard ratio (95% CI)	*p*-value
Training	Low	700	7.55 (6.24, NA)	1	
	Intermediate	700	5.13 (5.01, 5.44)	1.78 (1.46, 2.07)	< 0.001
	High	700	4.88 (4.33, 5.15)	2.21 (1.87, 2.62)	< 0.001
Validation	Low	327	8.01 (5.51, 8.72)	1	
	Intermediate	314	5.32 (5.06, 6.00)	1.41 (1.10, 1.82)	< 0.001
	High	359	4.96 (4.01, 5.17)	2.01 (1.59, 2.54)	< 0.001
Entire	Low	1,027	7.55 (6.24, 8.72)	1	
	Intermediate	1,014	5.23 (5.07, 5.45)	1.62 (1.41, 1.87)	< 0.001
	High	1,059	4.88 (4.33, 5.10)	2.13 (1.86, 2.44)	< 0.001

Abbreviations: OS, overall survival; CI, confidence interval.

Table 4. Comparison of model performance between the APP score and other models in predicting overall survival

Models	Cohort	C-index	K-index	1-yr AUC	3-yr AUC	5-yr AUC
Current model						
APP score	Training	0.619 (0.010)	0.595 (0.009)	0.685 (0.021)	0.660 (0.014)	0.610 (0.016)
	Validation	0.613 (0.015)	0.574 (0.013)	0.670(0.033)	0.659(0.021)	0.581(0.023)
Previous model						
ALBI grade	Training	0.554 (0.011)	0.550 (0.009)	0.541 (0.025)	0.571 (0.015)	0.572 (0.016)
	Validation	0.543 (0.015)	0.531 (0.013)	0.543 (0.032)	0.562 (0.023)	0.544 (0.023)
SII	Training	0.542 (0.011)	0.528 (0.007)	0.599 (0.024)	0.559 (0.015)	0.523 (0.016)
	Validation	0.549 (0.015)	0.526 (0.007)	0.551 (0.037)	0.538 (0.023)	0.552 (0.023)
NrLR	Training	0.584 (0.011)	0.525 (0.003)	0.653 (0.023)	0.611 (0.015)	0.570 (0.018)
	Validation	0.576 (0.015)	0.528 (0.008)	0.619 (0.035)	0.584 (0.023)	0.559 (0.023)
PNI	Training	0.559 (0.011)	0.552 (0.009)	0.554 (0.024)	0.584 (0.015)	0.571 (0.016)
	Validation	0.551 (0.015)	0.535 (0.013)	0.566 (0.032)	0.563 (0.023)	0.552 (0.023)
PLR	Training	0.541 (0.011)	0.527 (0.008)	0.582 (0.024)	0.562 (0.015)	0.539 (0.016)
	Validation	0.544 (0.015)	0.539 (0.010)	0.561 (0.036)	0.546 (0.023)	0.546 (0.023)
Staging system						
ITA.LI.CA	Training	0.606 (0.010)	0.580 (0.008)	0.687 (0.021)	0.636 (0.014)	0.599 (0.015)
	Validation	0.604 (0.015)	0.584 (0.012)	0.667 (0.033)	0.641 (0.021)	0.583 (0.022)
AJCC TNM^{8th}	Training	0.576 (0.009)	0.565 (0.008)	0.600 (0.020)	0.607 (0.013)	0.597 (0.013)
	Validation	0.589 (0.013)	0.575 (0.011)	0.642 (0.031)	0.608 (0.019)	0.592 (0.019)
BCLC	Training	0.512 (0.004)	0.512 (0.004)	0.510 (0.008)	0.517 (0.005)	0.511 (0.006)
	Validation	0.515 (0.005)	0.517 (0.006)	0.520 (0.008)	0.521 (0.007)	0.511 (0.009)
CNLC	Training	0.592 (0.009)	0.579 (0.008)	0.648 (0.018)	0.609 (0.013)	0.602 (0.014)
	Validation	0.578 (0.013)	0.573 (0.011)	0.590 (0.030)	0.606 (0.019)	0.575 (0.020)
JIS	Training	0.572 (0.008)	0.554 (0.007)	0.599 (0.020)	0.602 (0.013)	0.591 (0.012)
	Validation	0.588 (0.013)	0.571 (0.010)	0.639 (0.030)	0.607 (0.019)	0.580 (0.019)

Figures in parentheses are the standard error. *Abbreviations*: AUC, area under the receiver operating characteristic curve; ALBI grade, albumin-bilirubin grade; SII, systemic immune-inflammation index; NrLR, neutrophil times the γ-glutamyl transpeptidase-to-lymphocyte ratio; PNI, prognostic nutritional index; PLR, platelet-to-lymphocyte ratio; ITA.LI.CA, Italian Liver Cancer; AJCC TNM, American Joint Committee on Cancer Tumor-Node-Metastasis, BCLC, Barcelona Clinic Liver Cancer; CNLC, China liver cancer staging; JIS, Japan integrated staging.

In the training cohort, the C-index of the APP score, ALB, ln(ALP), and ln(AFP) were as follows: 0.619, 0.554, 0.581, and 0.584, respectively. In the validation cohort, the C-index of the APP score, ALB, ln(ALP), and ln(AFP) were as follows: 0.613, 0.539, 0.568, and 0.588, respectively. The C-index, K-index, and time-dependent AUC (1, 3, and 5 years) showed that the APP score was greater than the other 5 staging systems and 5 previous models in training and validation cohorts (Table 4, Figure 3).

Overall, the calibration curves fit well between the predicted and actual outcome in terms of the probability of 1-, 3- and 5-year OS in the training and validation cohorts (Figure 4).

3.6. Subgroup analysis

The APP score was validated in different subgroups of patients according to etiology (non-viral hepatitis and viral hepatitis), liver background (non-liver cirrhosis and liver cirrhosis), tumor size (< 5 cm and ≥ 5 cm), and microvascular invasion (no microvascular invasion and microvascular invasion). The time-dependent AUC for the APP score was still superior to those models, suggesting a consistent performance in these subgroups (Supplemental Figure S2-S5, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=225*). The APP score was able to stratify patients into the three aforementioned strata across 4 different subgroups, indicating a favorable

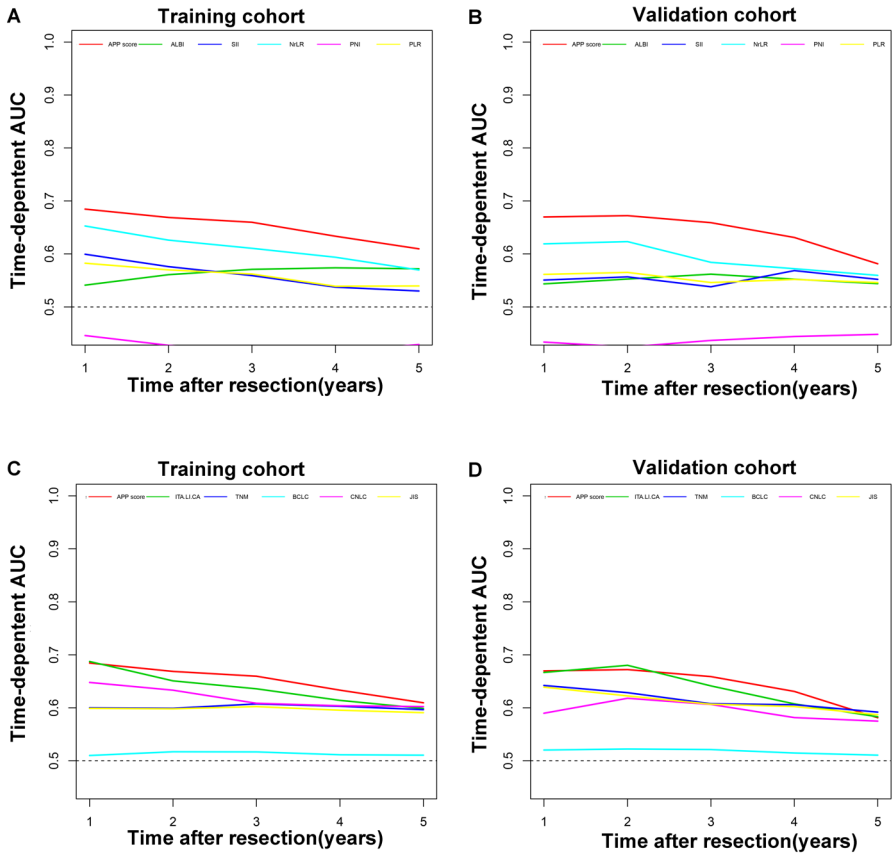

Figure 3. Comparison of the time-dependent AUC between the APP score and other models and staging systems. (A) Between the APP score and previous models in the training cohort, **(B)** Between the APP score and previous models in the validation cohort, **(C)** Between the APP score and staging systems in the training cohort, **(D)** Between the APP score and staging systems in the validation cohort. *Abbreviations*: AUC, area under the receiver operating characteristic curve; ALBI grade, albumin-bilirubin grade; SII, systemic immune-inflammation index; NrLR, neutrophil times the γ-glutamyl transpeptidase-to-lymphocyte ratio; PNI, prognostic nutritional index; PLR, platelet-to-lymphocyte ratio; ITA.LI.CA, Italian Liver Cancer; AJCC TNM, American Joint Committee on Cancer Tumor-Node-Metastasis; BCLC, Barcelona Clinic Liver Cancer; CNLC, China liver cancer staging; JIS, Japan integrated staging.

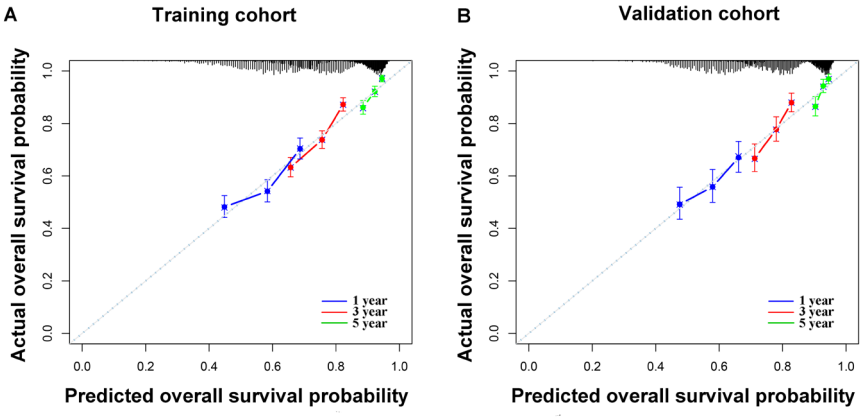

Figure 4. Calibration curves for the APP score. (A) Training cohort, **(B)** Validation cohort.

risk stratification in different populations (Supplemental Figure S6, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=225*).

3.7. Risk stratification for recurrence by APP score

In the entire cohort, the 1-, 3-, and 5-year recurrence-free survival (RFS) rates were 74.2%, 53.1%, and 37.6%, respectively (Supplemental Figure S7A, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=225*). Kaplan-Meier analysis revealed no differences in RFS between the training and validation cohorts (Supplemental Figure S7B-C, *https://www.biosciencetrends.com/action/getSupplementalData.*

php?ID=225). Using the cutoff values above, the patients were stratified into low-risk, intermediate-risk, and high-risk groups. Kaplan-Meier analysis showed that the RFS rates stratified prognosis among the three risk groups in the training, validation, and entire cohorts ($p < 0.001$) (Supplemental Figure Figure S7D-F, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=225*).

4. Discussion

Based on this large retrospective cohort study, a risk score (APP score) has been developed and verified to predict long-term survival and stratify patients into three risk groups. This model can be calculated from simple, low-cost, and easily obtained blood tests, providing individualized and stratified survival estimates with a favorable level of performance.

The diagnosis of and prognosis for HCC mainly rely on tumor burdens and hepatic function reserve (*20*). Tumor burdens (such as tumor size, tumor number, and vascular invasion) were assessed radiologically or pathologically. However, there might be some variations depending on the method of assessment. Discrepancies exist, and especially with regard to vascular invasion or the number of tumors, so many clinicians suggest using other methods, such as serum biomarkers, as the ideal choice (*21*). The current study used three serum biomarkers (**A**LB, AL**P**, and AF**P**) to create the risk score (APP score). The score is more powerful than other staging systems and models. This simple and low-cost model can help physicians with clinical monitoring.

Liver function is a basic routine blood test to evaluate hepatic function reserve. The APP score is applicable on the basis of two liver function markers (albumin and ALP). Albumin is an important component of the liver. Hypoalbuminemia in HCC is not only induced by impaired liver function due to underlying chronic liver disease but is also associated with a sustained systemic inflammatory reaction (*22*). Albumin has been integrated into several staging systems, including the BCLC and JIS systems (*5,15*).

ALP is widely distributed in human tissues as an enzyme and is metabolized by the liver and finally excreted in the bile (*23*). It is an independent prognostic factor for patients with HCC and is included as one of the parameters in some staging systems such as the CUPI system (*24,25*).

AFP is the most important biomarker used as a screening, diagnostic, and prognostic indicator for HCC (*4*). A higher level of AFP is related to more aggressive tumor features, poorer survival, and poorer treatment responses (*26-29*). A study has shown that patients with AFP-negative HCC have better long-term outcomes than those with AFP-positive HCC (*30*).

There are several limitations to this study. First, selection bias was hard to avoid in a retrospective study. However, this bias has been minimized through use of a large cohort. Second, our model was mainly based on patients with HBV-related HCC who might present with different tumor characteristics than other etiologies such as HCV or alcohol use. However, a subgroup analysis by etiology suggested that our model could be used effectively in patients with etiologies other than HBV. Nonetheless, further external validation is required in different regions.

In summary, the APP score is a novel model based on a simple, low-cost routine blood test and it outperforms other staging systems and previous models. The model stratifies patients into three strata with significantly different outcomes. It provides prognostic information to supplement the tumor staging systems in wide use.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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