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ORIGINAL RESEARCH

A New Risk Score Based on Lipid Indicators for Patients with Advanced Hepatocellular Carcinoma

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Background: The prognosis is extremely troubling in advanced hepatocellular carcinoma (HCC). Prognostic scores have been developed. Yet, the positive predictive values might appear inadequate. This retrospective study aimed to develop a quick and efficient risk score to assess prognosis and clinical response.

Methods: A total of 391 hCC patients were enrolled and were divided into training and validation groups between 2015 and 2024. Patients were separated into high-risk and low-risk groups using X-tile software. Using the COX proportional risk model analysis method, we then created a risk score and examined them using Kaplan-Meier, time-dependent receiver operating characteristics (ROC) curve, and nomogram analysis.

Results: In predicting overall survival (OS), free fatty acid/high-density lipoprotein cholesterol (FFHL), tumor size, and BCLC stage were independent prognostic variables. A new risk score was developed just above and used as a prognostic factor ($p < 0.001$ in the training and validation groups) and had a high time-dependent ROC for progress-free survival (PFS) (area under the curve [AUC] 0.688–0.789 in the training group; AUC 0.592–0.741 in the validation group) and OS (AUC 0.812–0.918 in the training group; AUC 0.692–0.981 in the validation group). In comparison to the best overall response (BOR), the score offered a more accurate evaluation of durable clinical benefit (DCB) ($p < 0.001$ in the training and validation group; $p = 0.061$ vs 0.001 in the training and validation group).

Conclusion: A new score based on lipid markers is a useful tool for evaluating prognosis and distinguishing patients with DCB.

Keywords: hepatocellular carcinoma, survival, prognosis, clinical response, risk score

Introduction

Hepatocellular carcinoma (HCC) accounts for 85–90% of liver cancer cases worldwide and ranks third in terms of mortality.[1,2] One of the main nations with liver cancerous growth is China. About 70% of patients are advanced when they are first diagnosed and cannot benefit from radical treatment. Patients have an extremely disappointing prognosis with less than 20% of them alive until five years.[3] To predict HCC, the scientific community has developed several composite biomarkers and scores, including alpha-fetoprotein (AFP) subtype L3,[4] an HCC risk score (called aMAP score),[5] and Galad score.[6] Nevertheless, due to their complexity, these outstanding clinical risk models might have low positive predictive values. Further research to identify useful biomarkers to direct treatment and forecast prognosis for HCC may have some clinical utility.

In addition to aberrant prothrombinogen and AFP, clinical test signs such as albumin-bilirubin grading, ascites, and tumor size and number are correlated with the prognoses of HCC patients.[7–9] Serum lipid markers' high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), lipoprotein A-I, and lipoprotein B levels can partially reflect the level of abnormal lipid metabolism.[10] However, the predictive value of these markers is limited, and the assessment models are somewhat disturbed.[11] Low HDL-C levels increase the invasiveness of cancer cells, which in turn promotes tumor progression.[12,13] Combining abnormally increased free fatty acid (FFA) with tumor markers such as carcinoembryonic antigen (CEA) and cancer antigen 19–9 (CA199) can improve prognosis.[14] Nevertheless, it has been discovered that individual lipid markers have limited clinical value in reflecting the degree of abnormalities in lipid metabolism and visualizing the future.[15]

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Further research in cholangiocellular carcinoma, colon cancer, and other malignancies has confirmed the predictive significance of serum composite lipid metabolism indicators on tumor aggressive phenotypes and prognosis.[16,17] However, there are fewer studies in HCC. Prior research[18,19] demonstrated that high levels of FFA/HDL-C (FFHL) had shorter overall survival (OS) and progression-free survival (PFS). FFHL was an independent OS prognostic factor in multivariate analysis. These studies, however, failed to validate the recently developed compound markers.

A significant area of research is the application of lipid metabolism-related prognostic risk scores to the construction of prognostic risk models. Researchers have previously developed predictive models of lipid metabolism-related risk scores through statistical methods such as single-cell sequencing and machine learning.[20,21] Nevertheless, the most commonly used tests only apply to Western populations, so it is important to ascertain whether these tests also apply to Chinese HCC patients. We proposed constructing a quick, affordable, and efficient risk score based on lipid metabolism-related risk scores for assessing prognosis and medication therapy response, and then building a nomogram model for prognosis.

In this study, we used and integrated previous studies[18,19] to establish and validate the predictive prognostic value of risk scores using training and validation data. Considering the expanding proof of the basic research of abnormal lipid metabolism in the improvement of HCC, further investigation of serum lipid composite metabolism-based risk scores in the turn of events of HCC might give a viable device for upgrading the administration of HCC.

Materials and Methods

Ethical approval was provided by the Peking University International Hospital and informed consent was obtained from all patients (grant no. Y-NESTLE2002QN-0296). This study was conducted in accordance with the Declaration of Helsinki.

Patient and Data Collection

Based on previous studies,[18,19] we conducted data verification and further analysis of the results. Inclusion criteria:[19] 1. Pathologically definite diagnosis of HCC; 2. Blood routine, biochemistry, coagulation, hepatitis B Virus (HBV)-DNA, and AFP tests before diagnosis or 1–2 weeks before initial treatment. Exclusion criteria:[19] 1 Unclear pathological diagnosis; 2. Patients on antiviral therapy; 3. Patients with previous liver transplantation, type 2 diabetes, hypertension, hyperlipidemia, family history of obesity, fatty liver or atherosclerosis, body mass index (BMI)>27, or other malignancies; 4. Lack of one or more blood hematological tests. As the training group for this study, we utilized the 300 hCC patients listed in the prior research.[19] Additionally, as the validation group, we gathered clinical data from 91 hCC patients. A total of 91 patients with newly diagnosed or follow-up surveillance HCCs who matched the eligibility criteria were recruited from December 2021 to January 2024 in the cohort study. A detailed flow chart is shown in Figure 1. The inclusion and exclusion criteria are available

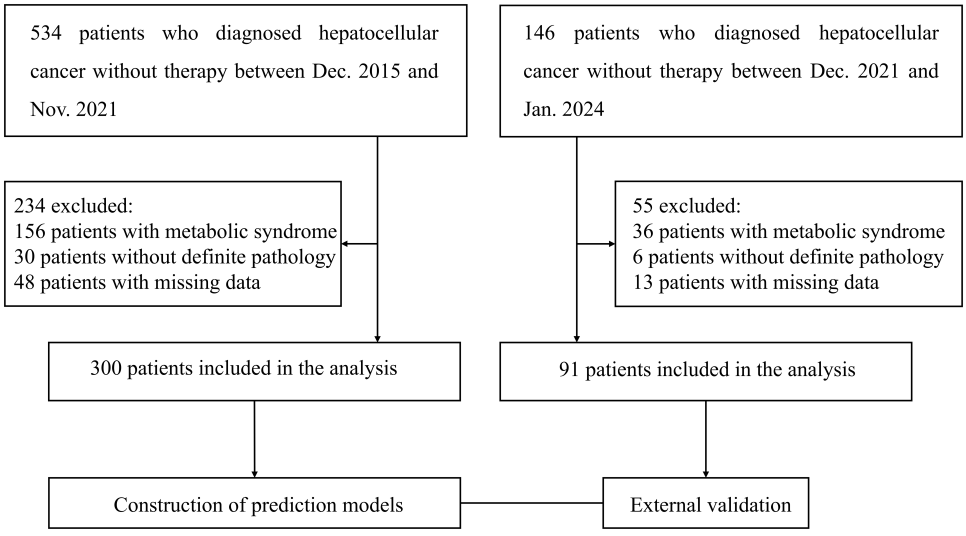

Figure 1 Flow chart for screening eligible patients.

in earlier research.[19] Tumor assessment examinations can also be discovered in the prior study.[19] Patients were put on a somewhat standardized diet with a reference daily sugar, protein, and cholesterol ratio of 3:2:1 as a result of blood tests that were performed on them after their diagnosis. Tumor parameters (Barcelona Clinic Liver Cancer [BCLC] stage, Child-Pugh score, metastatic sites, baseline tumor size, vascular invasion, Ki-67, and therapeutic approach) and patient characteristics (age, gender, HBV status, blood tests, biochemical testing, coagulation tests) were all included in the enrollment data.

Scoring Model Development and Validation

The risk score was developed in the training group. The best cutoff values were screened and validated of each factor in the baseline clinical variables (age, gender, Eastern Cooperative Oncology Group [ECOG] status, index of blood tests, baseline tumor size, Child-Pugh score, BCLC stage, vascular invasion, Ki-67, therapeutic approach, and metastatic sites). The final score took into account three important elements. Each of these three variables was given a point, and the scoring model was the sum of all the points. The model's ability to discriminate was evaluated using the Area Under the Curve (AUC). Harrell's Discriminant Consistency Index (C-index) was used to assess the model's correctness.

Indicators on Hematology

Apolipoprotein B (Apo B), fibrinogen (FIB), HDL-C, FFA, neutrophil (NEU), lymphocyte (LYM), platelet (PLT), and albumin (ALB) levels were all measured in the serum within a week of the diagnosis. These parameters were collected and recorded based on patients and data. We defined the following markers based on the findings of earlier research:[19,22,23]

AHLR stands for albumin: HDL-C ratio (ALB/HDL-C);
FFHL stands for FFA: HDL-C ratio (FFA/HDL-C);
FARI stands for fibrinogen: albumin ratio (FIB/ALB);
NLR stands for neutrophil: lymphocyte ratio (NEU/LYM);
PLR stands for platelet: lymphocyte ratio (PLT/LYM).

Follow-Up

The main method of patient follow-up was through outpatient visits or phone calls every 10 ± 2 week. Complete response (CR), partial response (PR), or stable disease (SD) lasting more than six months was classified as a durable clinical benefit (DCB);[24] progressed disease (PD) or SD lasting less than six months was classified as no durable benefit (NDB). The best response noted from the beginning of treatment until the disease progression or recurrence is known as the best overall response (BOR). In terms of BOR, CR/SD/PR groups were used. Patients who had no incidents during the previous follow-up were excluded. 13.5% of the data were missing. From the time of diagnosis till the date of death from any cause, OS was computed. PFS was defined as the period between the date of diagnosis and the date of last follow-up or new metastasis, whichever came first.

Statistical Analysis

Statistical analysis was performed using R software (http://www.rproject.org/) version 3.6.1, IBM SPSS (version 26.0; SPSS Inc, Chicago, IL, USA), and X-tile[25] software version 3.6.1 (Yale University). The continuous variables were tested using the median (interquartile range [IQR]) two-sided Mann–Whitney *U*-test; the categorical variables were tested using the χ^2 test or Fisher's exact test. The Kaplan–Meier approach and the Log rank test were employed to determine the OS and PFS for each group. Cox regression models, both univariate and multivariate, were used to find independent predictors of OS. Time-dependent receiver operating characteristics (ROC) curve analysis was carried out using the "timeROC" package of version R 3.6.1 (http://www.r-project.org/). Age, sex, BCLC stage, FFHL, AHLR, PLR, NLR, and risk score were combined to create the nomograms using the survivals and rms R packages. Calibration curves were used to assess the accuracy of nomograms in predicting 1-, 3-, and 5-year survival using the "rmda" package. P-values less than 0.05 were regarded as statistically significant.

Results

Patients Baseline

Clinicopathological features were performed on 191 patients receiving standard treatment according to patient willingness or ECOG status. The 91 recently acquired patients served as the validation group, while the group from the earlier study[16] served as the training group (Table 1). In the training group, the mOS and mPFS were 60.1 months and

Table 1 Characteristics of the Two Groups of HCC Patients

Variable	Training Group (n=300)	Validation Group (n=91)	*p*
Baseline data [IQR]			
AHLR	42.4 [34.7–53.3]	37.9 [31.7–45.4]	0.513
FFHL	429.6 [267.9–706.5]	475.0 [340.5–700.0]	0.829
AFP	25.9 [4.1–995.6]	31.5 [16.8–260.1]	0.812
FARI	6.9 [6.0–8.8]	10.7 [8.3–14.2]	0.127
NLR	3.1 [1.8–5.7]	3.2 [2.2–5.2]	0.275
PLR	116.4 [83.9–179.7]	171.3 [127.4–232.5]	0.827
Tumor size	4.7 [2.8–7.5]	6.4 [4.3–8.8]	0.513
Covariate			
Age [IQR]	60 [53–66]	65 [61–70]	0.275
Male, n (%)	243 (81)	66 (72.5)	0.058
HBV-DNA, n (%)			0.282
Yes	85 (28.3)	30 (33.0)	
No	207 (71.7)	61 (67.0)	
Therapeutic approach, n (%)			0.791
Radical operation	93 (31.0)	30 (33.0)	
Anti-PD-1/PD-L1 alone	52 (17.3)	20 (22.0)	
TKI alone	65 (21.6)	17 (18.7)	
TKI+ anti-PD-1/PD-L1	74 (24.7)	21 (23.0)	
Unknown	16 (5.4)	3 (3.3)	
Child-Pugh score, n (%)			0.972
A	101 (33.7)	32 (35.2)	
B	156 (52.0)	46 (50.5)	
C	43 (14.3)	13 (14.3)	
BCLC stage, n (%)			0.181
A	51 (17.0)	12 (13.2)	
B	118 (38.4)	48 (52.8)	
C	112 (37.3)	27 (29.7)	
D	19 (6.3)	4 (4.3)	
Vascular invasion, n (%)			0.435
None	170 (56.7)	47 (51.6)	
Micro	80 (26.7)	31 (34.1)	
Macro	45 (15.0)	13 (14.3)	
Ki-67, n (%)			0.215
0–29%	142 (47.3)	43 (47.2)	
30–59%	89 (29.3)	40 (43.9)	
60–100%	32 (10.7)	8 (12.8)	
Metastases site, n (%)			0.507
≤2	216 (72.0)	65 (71.4)	
>2	84 (28.0)	26 (28.6)	

Abbreviations: IQR, interquartile range; n, number; AHLR, albumin/high density - lipoprotein cholesterol radio; FFHL, free fatty acid/high-density lipoprotein cholesterol; AFP, alpha-fetoprotein; BCLC, Barcelona clinical liver cancer stage; FARI, Fibrinogen-Albumin Ratio Index; PLR, Platelet-to-lymphocyte; NLR, Neutrophil-to-lymphocyte.

10.9 months. A median follow-up of 44.7 months (IQR 13.3–61.6). In the validation group, the mOS and mPFS were 40.3 months and 11.4 months. A median follow-up of 43.2 months (IQR 29.7–46.7) (In the validation group, the median OS was longer than the period to gather patients because a subset of patients did not receive therapy after diagnosis, and the OS length for such individuals began with disease diagnosis). In the training group, the median values for AHLR, FFHL, FARI, NLR, PLR and tumor size were 42.4 (IQR 34.7–53.3), 429.6 (IQR 267.9–706.5), 6.9 (IQR 6.0–8.8), 3.1 (IQR 1.8–5.7), 116.4 (IQR 83.9–179.7) and 4.7 cm (IQR 2.8–7.5), respectively. In the validation group, the median values of the six factors were 37.9 (IQR 31.9–45.4), 475 (IQR 340.5–700), 10.7 (IQR 8.3–14.2), 3.2 (IQR 2.2–5.2), 171.3 (IQR 127.4–232.5) and 6.4cm (IQR 4.3–8.8), respectively. There was no difference in the patient covariates between the training and validation groups before the treatment. Table 1 provides an overview of the patients' other features.

OS and PFS in the Training and Validation Group of AHLR and FFHL

X-tile analysis illustrated the optimal cut-off value of the AHLR and FFHL.[19] Based on the cut-off value, the cases were identified into low and high groups. The best cutoff values for AHLR and FFHL were 77.0 and 840.3.[19] In the training group, the differences in PFS and OS among HCC patients were analyzed using AHLR and FFHL in the two groups with high and low levels. High and low AHLR levels with median PFS were 3.2 and 7.3 months ($p < 0.001$), and high and low FFHL levels with median PFS were 3.5 and 7.6 months ($p = 0.001$).[19] High levels of AHLR and FF-HL (AHLR: 72.4%, 54.1%, and 45.2%, $p < 0.001$; FF-HL: 67.8%, 53.8%, and 46.2%, $p < 0.001$) compared with low levels of AHLR and FFHL (AHLR: 89.3%, 57.9%, and 51.7%; FF-HL: 91.2%, 59.3%, and 55.2%) with lower 1-year, 2-year, and 3-year OS.[19]

Overall, 91 hCC patients diagnosed and treated between 2021–12 and 2024–01 were chosen using a validation group. When comparing the differences in PFS between patients with AHLR and FFHL, the median PFS in the two groups with high and low AHLR levels was 5.3 months and 8.1 months (p=0.048) (Figure S1a, the median PFS in the two groups with high and low FFHL levels was 7.5 months and 8.2 months (p=0.661) (Figure S1b). In summary, PFS was substantially shorter in patients with high AHLR levels than in those with low AHLR levels.

In the group with high AHLR level, the 1-year, 2-year, and 3-year OS rates were 63.8%, 41.1%, and 17.3%, respectively; in the group with low AHLR level, the 1-year, 2-year, and 3-year OS rates were 82.3%, 54.9%, and 40.7%, respectively (Figure S1c). The difference in survival between the two groups was statistically significant (p=0.037). The 1-year, 2-year, and 3-year OS rates of patients with high FFHL levels were 52.7%, 38.9%, and 13.4%, respectively, and the 1-year, 2-year and 3-year OS rates of patients with low FFHL level were 81.2%, 58.0%, and 38.2%, respectively (Figure S1d). The survival difference between the two groups was statistically significant (p=0.003). In conclusion, compared to the low-level group, patients with high AHLR and high FFHL levels had much shorter 1-, 2-, and 3-year OS rates.

Establishment of the Risk Score

The optimum cut-off values for 5-year OS were determined by analyzing the following parameters: FARI, tumor size, PLR, NLR, and AFP. This permitted the X-tile software to differentiate between high-risk and low-risk groups (Figure 2 and S2). The results suggested that in the training group, the optimal cut of values for FARI and tumor size were 7.3 and 8.3 cm (Figure 2a and b) ($p<0.001$). No statistical difference was found for the other three factors (Figure S2). Other factors, including FFHL, AHLR, and AABR, results have been described in previous work.[19]

Univariate and multivariable COX regression analyses were conducted in the training and validation groups to identify independent prognostic factors for OS (Table 2). In the univariate analysis of the training and validation groups, FFHL levels, tumor size, FARI, and BCLC stage were associated with OS. Factors of significance in univariate analysis ($p<0.05$) were integrated into multivariate analysis. Hazard ratios with a 95% confidence interval (CI) were analyzed. The multivariable analysis's training and validation groups found that FFHL levels, tumor size, and BCLC stage had a strong correlation with OS. These three factors are independent prognostic factors of OS. In this study, the three independent prognostic factors just mentioned were used as a single indicator of risk score, and if each indicator was greater than the optimal cutoff value, it was counted as 1 point, a total of 3 points.

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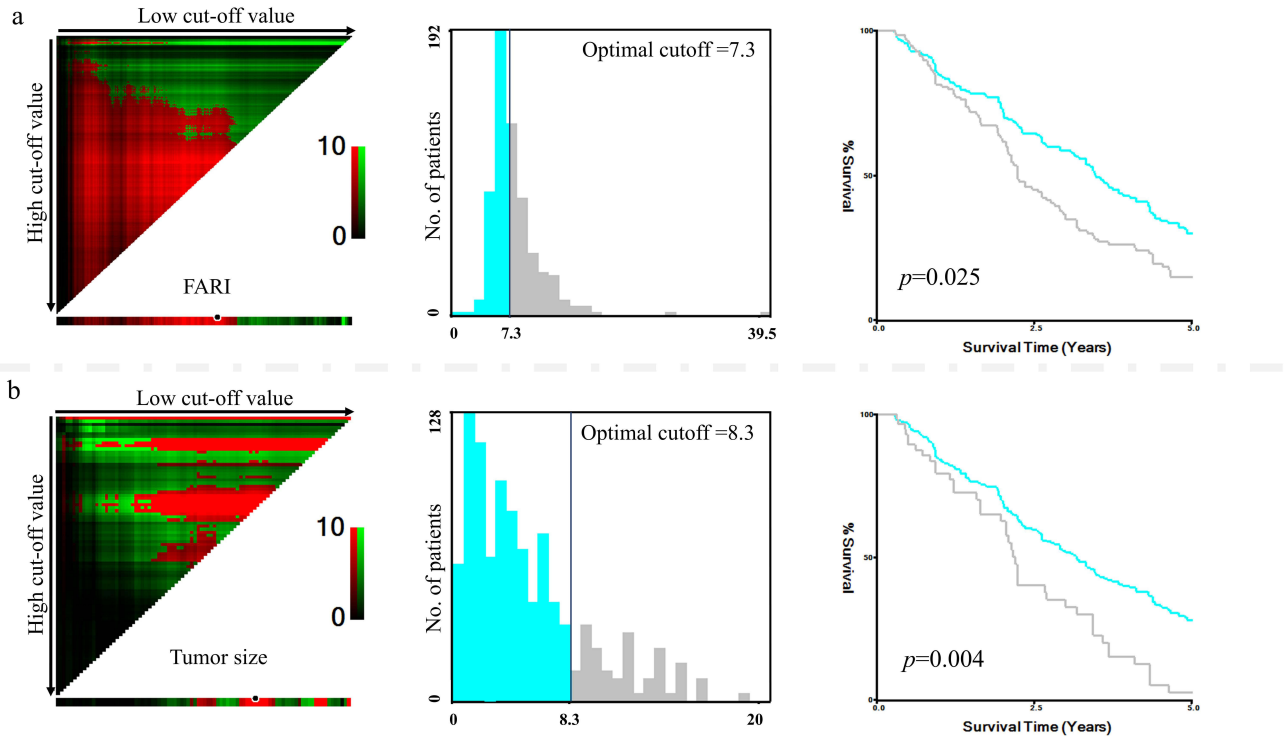

Figure 2 X-tile plots of prognostic markers FARI and tumor size on HCC patients. The X-tile plot of the 5-year disease-related survival of the training group is represented (**a** and **b**, left). (**a**) shows the X-tile analysis of FARI on a cohort of 192 hCC (**a**, left). Note the cloud of high value for a subpopulation of higher level's people. Using this X-tile plot, the maximum value for a single cut-point occurs of 7.3 (**a**, middle). The red color of the cloud illustrates the fact that higher FARI level tumors do worse. This optimal cut-point was validated by dividing a separate cohort and was found to be statistically significant (p = 0.025, **a**, right). (**b**) shows the X-tile analysis of tumor size on a cohort of 128 hCC (**b**, left). Note the cloud of high value for a subpopulation of larger tumors. Using this X-tile plot, the maximum value for a single cut-point occurs at 8.3 (**b**, middle). The red color of the cloud illustrates the fact that larger tumor-size tumors do worse. This optimal cut-point was validated by dividing a separate cohort and was found to be statistically significant (p = 0.004, **b**, right).

Comparison of the Risk Score in Prognosis Ability

In the training and validation groups, time-dependent ROC analysis showed that the prognostic value of the risk score for OS was significantly better than other variables, but there was no statistical difference between risk score and BCLC (Figure 3a and c). The AUC of risk score was significantly greater than other variables at the 1, 2, 3, 4, and 5-year time points. For example, in the

Table 2 Univariate and Multivariable Analyses of Overall Survival

Variables	Training Group						Validation Group					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Sex	1.433	0.787–2.610	0.24				1.255	0.654–2.406	0.496			
Females												
Males												
Age	0.838	0.503–1.397	0.49				1.145	0.555–2.363	0.71			
≤60												
>60												
AHLR	0.343	0.196–0.599	<0.001	0.666	0.316–1.403	0.285	0.8	0.388–1.649	0.55			
>77												
≤77												
FFHL	0.284	0.170–0.474	<0.001	0.379	0.193–0.745	0.005	0.506	0.403–0.614	0.003	0.74	0.364–1.503	0.041
>840.3												
≤840.3												

(*Continued*)

Table 2 (Continued).

Variables	Training Group						Validation Group					
	Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Size	0.296	0.164–0.532	<0.001	0.342	0.181–0.646	0.009	0.618	0.344–0.807	0.016	0.391	0.187–0.818	0.013
>8.3cm												
≤8.3cm												
FARI	0.438	0.262–0.733	0.002	0.577	0.335–0.995	0.027	0.663	0.237–0.86	0.035	0.823	0.274–2.468	0.73
>7.3												
≤7.3												
AFP	0.503	0.296–0.856	0.011	0.843	0.48–1.479	0.551	0.867	0.406–1.851	0.71			
>13.9												
≤13.9												
PLR	0.954	0.574–1.585	0.86				1.846	0.897–3.798	0.09			
≤128.9												
>128.9												
NLR	1.544	0.56–4.26	0.401				1.771	0.79–3.972	0.17			
>10.7												
≤10.7												
BCLC	15.044	8.061–28.077	<0.001	11.873	6.051–23.298	<0.001	4.08	2.48–6.71	<0.001	3.486	1.919–6.332	<0.001
A												
B												
C												
D												
Child-Pugh	0.279	0.158–0.494	<0.001	0.814	0.444–1.492	0.506	0.273	0.113–0.657	0.004	0.846	0.366–1.959	0.69
C												
B												
A												

Abbreviations: CI, confidence interval; HR, hazard ratio; AFP, alpha-fetoprotein; AHLR, albumin high-density lipoprotein cholesterol; FFHL, free acid- high-density lipoprotein cholesterol; FARI, Fibrinogen-Albumin Ratio Index; PLR, Platelet-to-lymphocyte; NLR, Neutrophil-to-lymphocyte; BCLC, Barcelona clinical liver cancer stage; CM, centimeter.

training group (Figure 3a), the C-index for 4-year OS probability prediction in risk score was 0.837 (95% CI 0.736–0.865), which was significantly higher than the BCLC stage (C-index 0.816, 95% CI 0.477–0.828); in the validation group (Figure 3c), the C-index for 4-year OS in risk score was 0.889 (95% CI 0.769–0.901), which was also greater than BCLC stage (C-index 0.805, 95% CI 0.692–0.863). However, the risk score did not show a better predictive value for PFS than other values in the training group and validation group (Figure 3b and d). In the training group, the 2-year PFS C-index was 0.691 (95% CI 0.646–0.698) for the risk score and 0.681 (95% CI 0.597–0.690) for the BCLC stage; in the validation group the risk score was 0.621 (95% CI 0.561–0.717) and BCLC stage was 0.611 (95% CI 0.524–0.658) (Figure 3b and d). These results suggested that the risk score was a better predictor of OS than other factors.

OS and PFS Assessed by the Risk Score

Subsequently, we examined the variations in PFS and OS between patients in the training and validation groups and discovered that neither PFS nor OS differed significantly between the two groups (Figure 4). According to risk scores (0–3), patients in the training and validation groups were divided into 4 groups for OS analysis, as shown in Figure 5. The findings demonstrated that the shorter the OS, the higher the risk score of the patients in the training group ($p<0.001$) (Figure 5a). Patients in the validation group were categorized into three groups based on OS analysis risk scores 0–2 ($p<0.001$) (Figure 5b). Additionally, the results showed that the OS got shorter the higher the risk score.

When analyzing the difference in PFS for each risk score between the training group and the validation group, the results showed that the PFS for each risk score in the training group was significantly different ($p<0.001$) (Figure 6a). However, the survival analysis curves of the three groups with a risk score of 0–2 were crossed in the validation group ($p=0.031$) (Figure 6b). As

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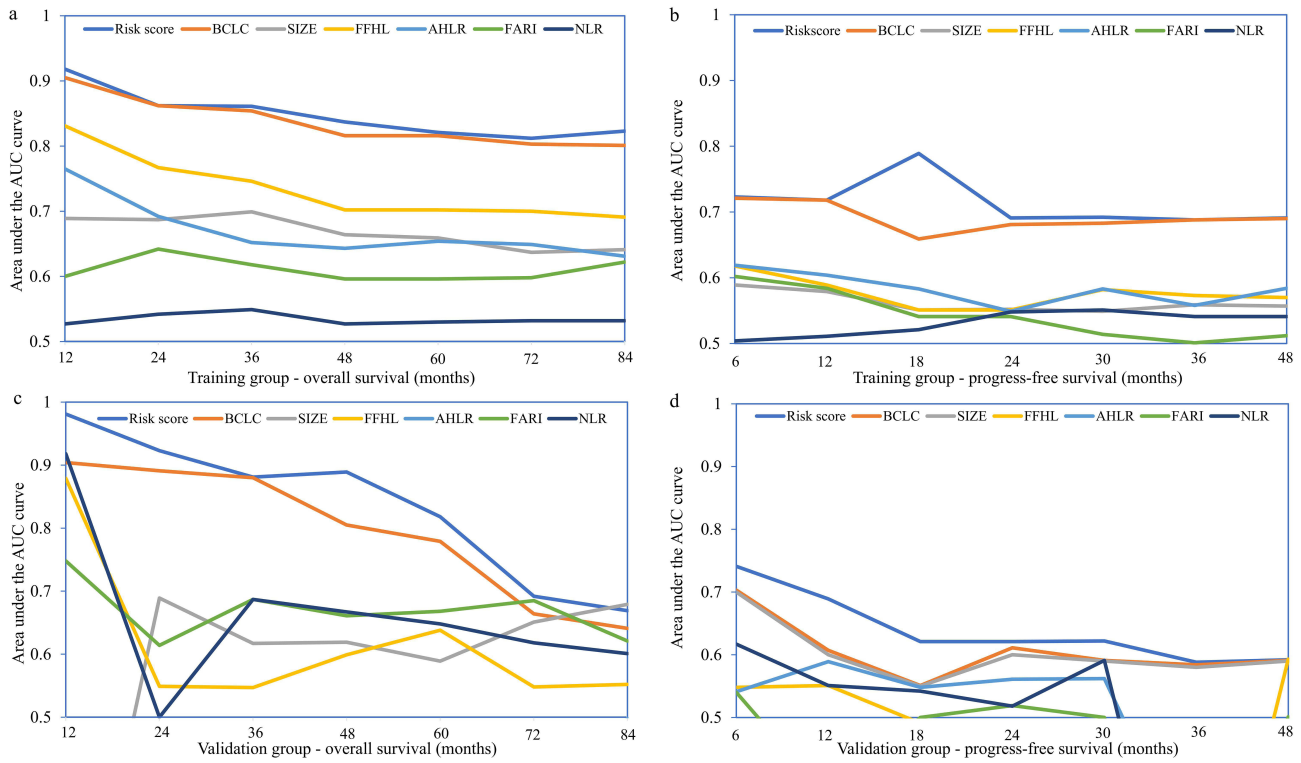

Figure 3 Time-dependent ROC curve analysis comparing the ability of risk score, BCLC, tumor size, FFHL, AHLR, FARI, and NLR in predicting (**a**) OS in the training groups, (**b**) PFS in the training groups, (**c**) validation OS, and (**d**) validation PFS. The horizontal axis represents time and the vertical axis represents the area under the corresponding ROC curves for survival at different time points.

Abbreviations: ROC, receiver operating characteristic, BCLC, Barcelona Clinic Liver Cancer, FFHL, free fatty acid/high-density lipoproteins, AHLR, albumin/high-density lipoproteins, FARI, Fibrinogen-Albumin Ratio Index, NLR, neutrophil-lymphocyte ratio, PFS, progress-free survival, OS, overall survival.

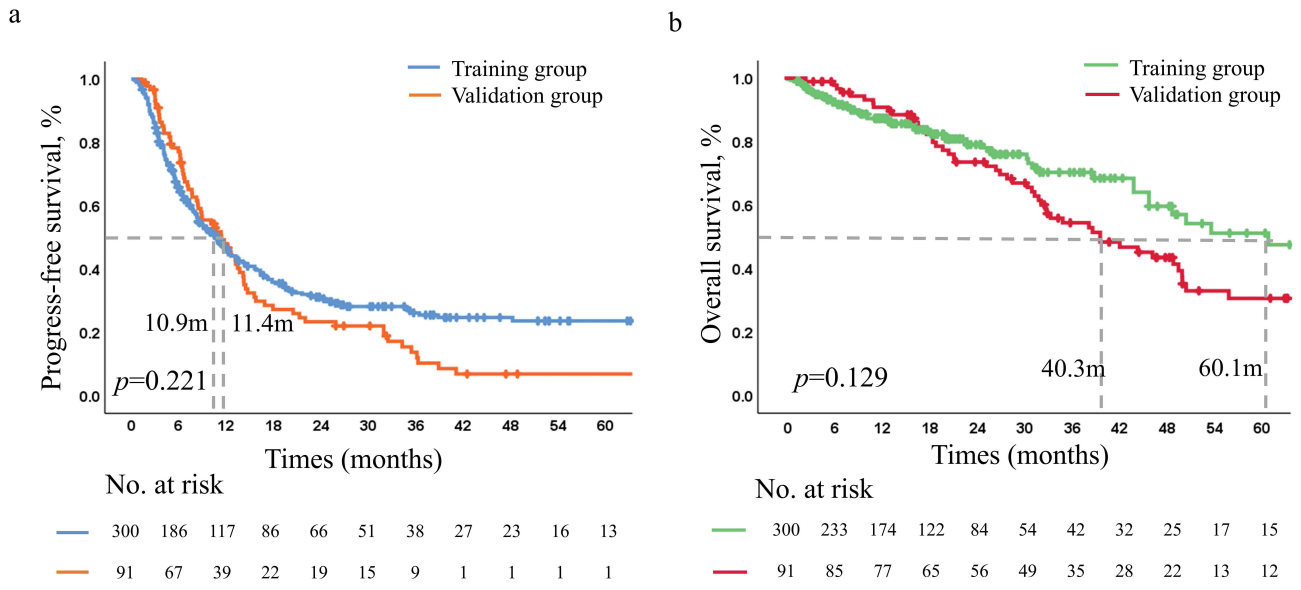

Figure 4 Kaplan-Meier analysis of progression-free survival (**a**) and overall survival (**b**) between the training and validation groups. The number, median overall survival, and progression-free survival can be seen clearly.

a result, for PFS analysis, we separated the patients into two groups: those with risk factors and those without, and we discovered that the former had a shorter PFS (p=0.016) (Figure S3a). When patients were separated into low/no risk score and high-risk score groups for PFS analysis, it was discovered that patients with high-risk scores had short PFS (p=0.049) (Figure S3b).

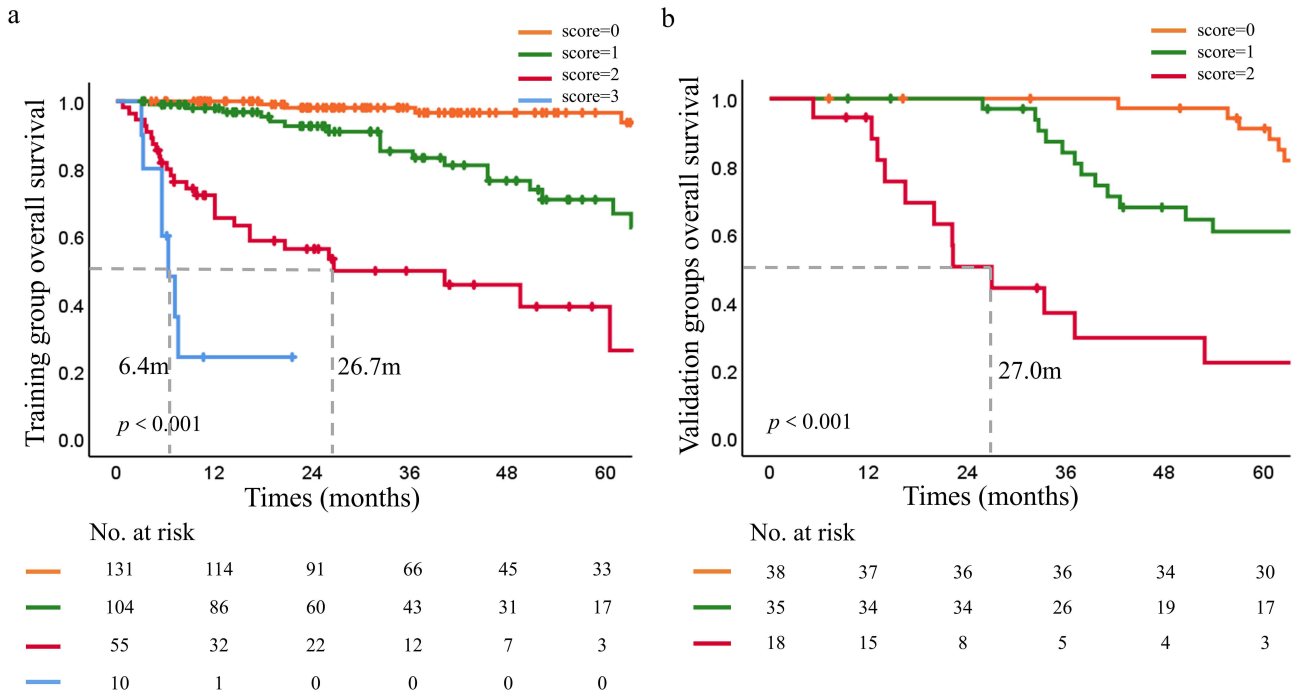

Figure 5 Kaplan-Meier analysis of OS between the training groups (**a**) and validation groups (**b**) in different risk scores (0–3). P < 0.05 was statistically significant.

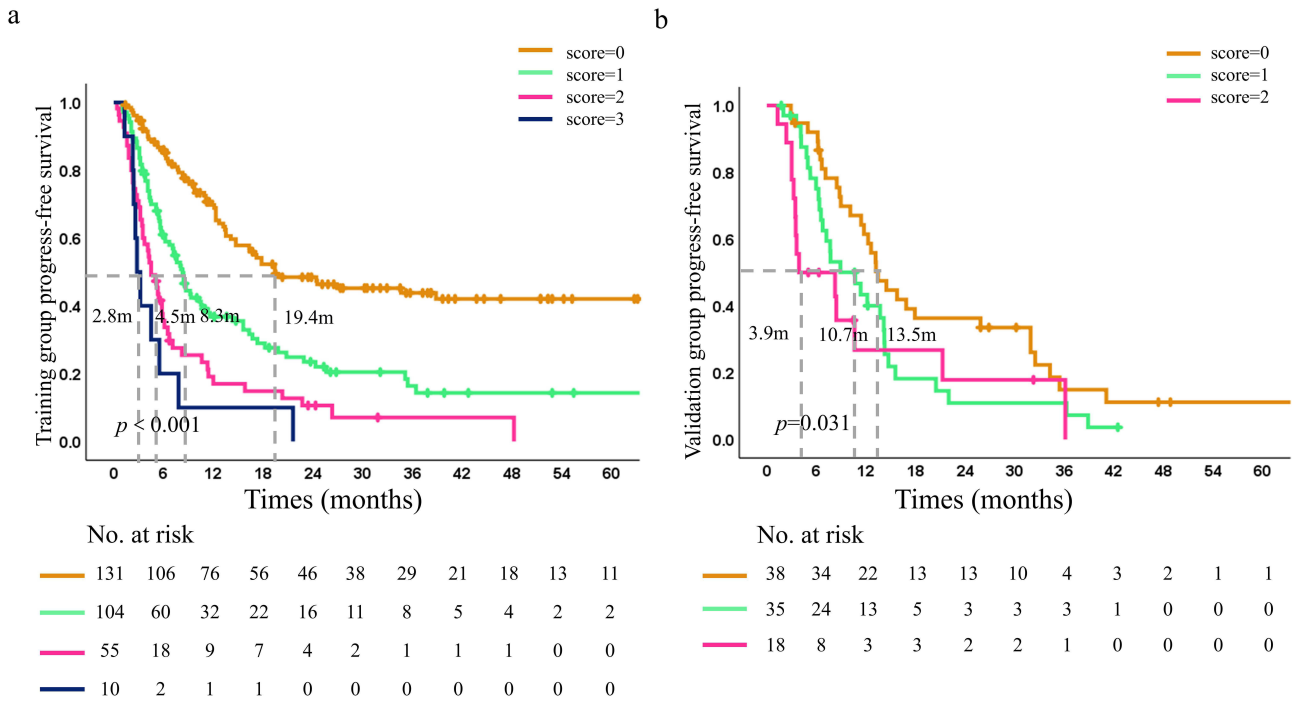

Figure 6 Kaplan-Meier analysis of PFS between the training groups (**a**) and validation groups (**b**) in different risk scores (0–3). P < 0.05 was statistically significant.

Effective Evaluation of the Risk Score in Predicting Response (DCB and NDB)

The risk score showed high efficiency in assessing patient benefits. When RECIST1.1 was used to assess efficacy, risk scores were statistically different in PR/SD/PD in the training group (p<0.001, Figure S4a). Risk scores were also statistically different between the DCB and NDB groups (p<0.001, Figure S4b). The number of patients with efficacy in

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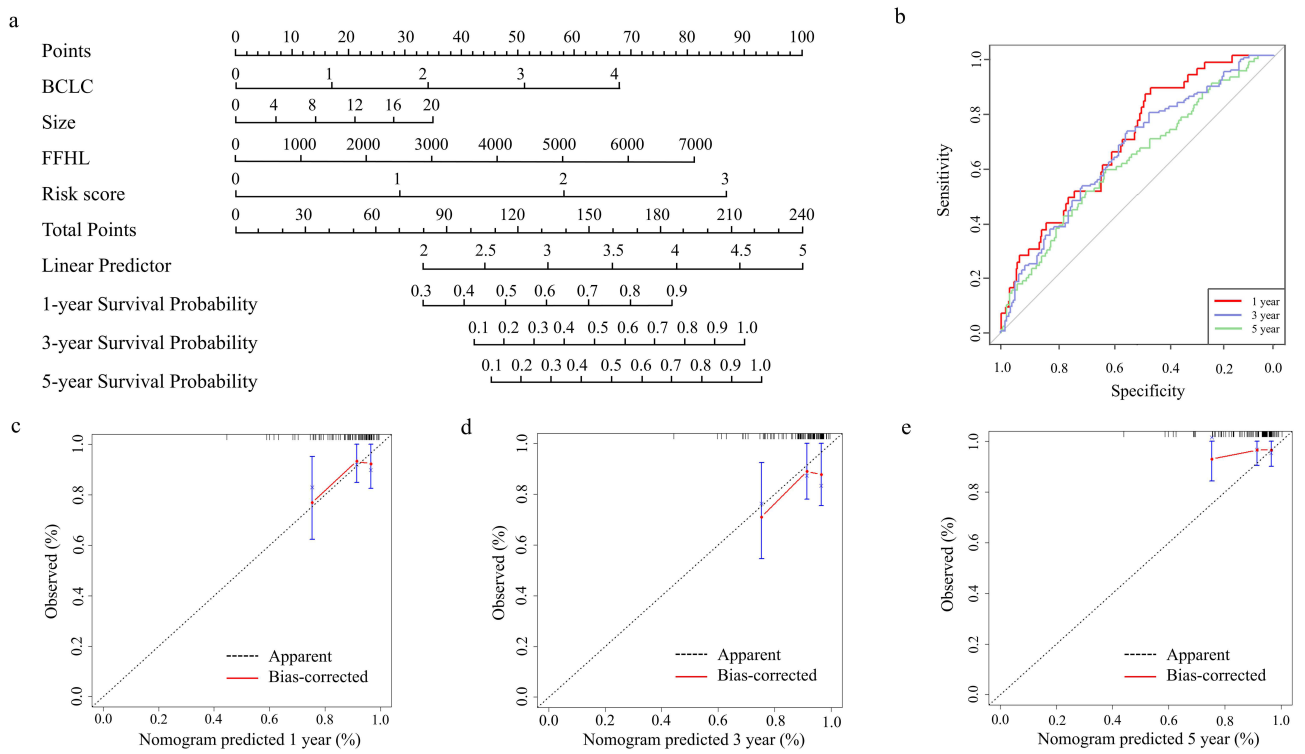

Figure 7 Survival nomogram (**a**) in validation groups. The total points of each patient can be used to predict survival outcomes. ROC curves for the prediction of death within 1, 3, and 5 years among HCC patients (**b**). Calibration curve for the prediction of death within 1, 3, 5 years (**c–e**).
Abbreviations: BCLC, Barcelona Clinic Liver Cancer, AHLR, albumin/high-density lipoproteins, FFHL, free fatty acid/high-density lipoproteins, PLR, platelet-lymphocyte ratio, NLR, neutrophil-lymphocyte ratio.

each risk score is shown in Figure S4c. There was a statistical difference in the risk score between the DCB group and the NDB group (Figure S4e), but not in PR/SD/PD among the patients in the validation group (Figure S4d). Figure S4f displayed the number of patients having treatment effects in each risk score.

Nomogram and Verification for OS

In the training and validation groups, BCLC stage, tumor size, AHLR, FFHL, PLR and NLR were selected to construct a nomogram for predicting 1-year, 3-year, and 5-year survival of patients with advanced HCC. Each variable in the score table was given a number, and the survival rate was predicted using the total score (Figure 7a and S5a). In the training group, the 1-year, 3-year and 5-year AUC values were 0.75 (95% CI: 0.67–0.84), 0.65 (95% CI: 0.59–0.72), 0.62 (95% CI: 0.55–0.69), respectively (Figure 7b). The calibrated curve indicated a notable consensus that real time to survival in the 1-year and 3-year showed good agreement with the predicted survival rate (Figure 7c and d). The five-year survival period did not match the expected survival rate very well (Figure 7e). In the validation group, the 1-year, 3-year, and 5-year AUC values were 0.81 (95% CI: 0.66–0.96), 0.77 (95% CI: 0.67–0.88), 0.73 (95% CI: 0.59–0.88), respectively (Figure S5b). The calibration curve of the nomogram for 1-year, 3-year, and 5-year survival probabilities demonstrated poor agreement between prediction and observation (Figure S5c–Se).

Discussion

Through the enhancement of the fatty acid production pathway, the recruitment and activation of signal molecules, participation in autophagy, effervescent cholesterol, and other activities, abnormal lipid metabolism can contribute to the development of cancer.[26–28] These processes also foster an environment that allows tumor cells to proliferate and evade immune response, which worsens patients' prognosis.[29] Through the lipid metabolic route, the liver primarily controls the synthesis, storage, and oxidation of lipids, particularly the synthesis of fatty acids and cholesterol, which are thought to be indicators of many malignancies.[30] A range of malignancies are thought to be independently predicted by high

HDL-C levels (Hazard Ratio [HR] = 0.63, p < 0.001),[31] high FFA levels (HR = 0.65, p < 0.001),[13] and low lipoprotein levels (HR = 0.46, p < 0.001).[32] Research has indicated that patients with low non-HDL-C /HDL-C levels had a longer survival time (59.00 months vs 52.35 months), and multivariate analysis revealed a significant correlation between non-HDL-C /HDL-C and OS in patients with colon cancer (HR = 0.388, p=0.003).[16] It is challenging to use biomarkers alone to predict prognosis due to confounding variables. The majority of biomarkers and risk model suggestions were derived from clinical trial subgroup analysis or solid tumor experiences at specific institutions.[33,34] Despite years of dedication by researchers to the study of lipid metabolism and the onset of cancer, predictive risk scores are still lacking.

This study collected more clinicopathological information on patients with HCC before treatment. Among multiple clinicopathological factors, FFHL, BCLC stage, and tumor size were identified as independent prognostic factors for OS. Based on the above three factors, a risk score (0–3) was constructed. Further analysis showed that the risk score had stronger predictive power, and the higher the risk score, the shorter the OS and PFS. Furthermore, the risk score demonstrated a high degree of efficacy in evaluating patient benefit.

First, this study was based on the results of a previous study, expanded the sample size, and confirmed the reliability of this result in a verification group. Previous study[19] has shown that the clinical significance of FFHL in predicting OS and PFS is better than that of a single lipid-related parameter, such as AFP, ECOG score, Child-Pugh grade, etc., which can be used as a non-tumor biomarker to supplement the predictive and prognostic ability of other indicators. Similar results were reported in this investigation. In addition, a risk score was created based on FFHL, tumor size, and BCLC stage. This study builds on earlier research by utilizing multiple parameters to create a comprehensive score that is used to evaluate prognosis.

Then, new research on risk models[18,35] has been presented to forecast the probability that HCC may progress. Lipid-endoplasmic reticulum stress-related gene risk scores for prognosis prediction have been developed and confirmed by prior research[18] using literature and The Cancer Genome Atlas (TCGA) and International Cancer Genome Collaboratory (ICGC) databases, which contain very significant and comprehensive genes. A nomogram, immunosuppressive events, and clinicopathology features were compared with a 10-gene risk signature in individuals with HCC. According to this risk model, M2 macrophage and T cell immunoglobulin and mucin-3 (TIM-3) expression were strongly correlated with higher risk scores, which were associated with a worse prognosis. A different study[35] thoroughly assessed several risk-scores designed to forecast HCC in individuals with HBV. In the derivation and validation cohorts of their original investigations, all scores yielded substantial predictions for the development of HCC (c-statistic: 0.76–0.95). All independent studies of patients of Caucasian/mixed origin or Asian patients have found that Pathogenetic Global Evaluation of Biochemical (PAGE-B), the only HCC risk score developed in a Caucasian cohort, and more recently, modified PAGE-B (mPAGE-B), a score developed in an Asian cohort, offer good predictability with 99–100% negative predictive value for 5-year HCC prediction. Unfortunately, these models are either predicated on bioinformatic analysis, which invariably drives up patient expenses, or they failed to fully account for the impact of serologically specific components in the particular prognostic model of virus infection. In contrast to existing models, the risk score in this study provides patients with quick access, minimal cost, and thorough clinical information. It is easy to obtain explicit markers for factor determination.

Moreover, research[36] showed that predicting DCB was preferred in several risk scores that were based on robust economic conditions and procedures. Intratumoral heterogeneity, tumor mutation burden (TMB), and several genomic biomarkers were among the criteria used to develop a DCB prediction model. The DCB multi-feature model showed a greater predictive value, with AUC = 0.77 (cohort 1) and 0.78 (cohort 2).[36] However, as alternative predictors to numerous types of malignancies, retrospective studies have demonstrated that TMB and programmed death ligand 1(PD-L1) expression in tumor cells of patients with advanced HCC similarly perform poorly in HCC and are not substantially associated with objective response rate.[37] Thus, we employed risk scores to consistently reveal DCB in both training and validation groups by tracking peripheral blood indicators and clinicopathological data of HCC patients before therapy. The risk score in this study offers straightforward, easy predictors and value ranges that could effectively distinguish DCB.

Interestingly, prior studies[38] illustrated that 1163 older adults with HCC were divided into a training set and a validation set. Important predictors, such as Child-Pugh grade, T stage, treatment style, lung metastasis, and bone metastasis, were used to develop nomograms for prediction. The AUC of the nomogram in the training group and validation group was 0.805 and 0.797, respectively. The calibration curve confirmed the acceptable consistency of the nomograms, the decision curve analysis

(DCA) confirmed their high clinical value, and the ROC curve had good discriminability within both training and validation cohorts. In this study, to exploit the full potential of the risks model, a nomogram was prepared to combine risk score, age, sex, BCLC stage, tumor size, AHLR, FFHL, PLR, and NLR. The calibration curves based on the training group demonstrated strong predictive performance. Nevertheless, the adjustment curve did not demonstrate strong predictive performance for the 1-, 3-, and 5-year survival probabilities in the validation group. This is different from previous studies. This phenomenon may have the following primary causes: 1. There was a modest patient sample size in the validation group. 2. There were gaps in the patient survival data in the validation group.

FFHL, tumor size, and BCLC stage are the three indicators that make up the risk score. Elevated FFHL is a strong adverse predictive factor for survival in advanced HCC, according to preliminary research.[19] According to recent research,[39] there may be a favorable correlation between low cholesterol and high FFA with the development and risk of cancer. This is mostly due to the fact that increased FFA provides the energy metabolism and membrane components that malignant development cells need to promote the spread and metastasis of cancer. Patients with HCC have been proven to have poor prognoses based on tumor size and BCLC stage.[40] Cox regression analysis in this study demonstrated that BCLC stage, tumor size, and FFHL were independent predictive variables. As such, the mechanisms underlying some risk score components are poor indicators that encourage tumor growth and spread.

The study's retrospective design, potential recall bias, small sample sizes, electronic case system restrictions, and inability to assess the predictive power of treatment pattern heterogeneity over an extended period of time based on a single-center experience were among its limitations. Then, diets were standardized before lab testing, although it was not possible to fully rule out patients with combination insidious metabolic syndrome. Lastly, the optimal cut-off value may be found using a different study population. In summary, further prospective study is required.

There are several strengths in this study. This is an additional confirmation of earlier research[21] and a novel risk score based on tumor size, BCLC stage, and lipid-related composite markers →FFHL for patients with advanced HCC receiving single or combined treatments. Each of these factors is an independent prognostic factor for OS. In addition, the model integrated both neoplastic and non-neoplastic components, suggesting that the greater the risk score, the shorter the OS and PFS, and the higher the frequency of NCB. Furthermore, a comprehensive verification process was carried out and a nomogram based on the identified risk scores was developed, which can accurately forecast 1-, 3-, and 5- OS probabilities.

Prognosis and treatment response can be evaluated and complemented by this model with more accuracy. This helps clinicians to quickly assess patients before treatment. Determining this risk score is fundamentally important because it allows for a thorough assessment of the prognosis and treatment responsiveness of HCC patients by incorporating pre-treatment clinicopathological data and the superior benefit/cost ratio. In the future, clinical applications using this paper's prognosis prediction could lead to a large increase in survival under unclear or incomplete situations.

Conclusion

In conclusion, a more straightforward, quick, and accessible risk score has been used to develop a prognostic and predictive model for patients with advanced HCC before treatment. The score composed of both neoplastic and non-neoplastic indications may provide a general method for biomarkers in patients with advanced HCC who have received initial treatment. This score is expected to provide useful feedback for improving the prognosis and prediction of patients with advanced HCC.

Abbreviations

HCC, Hepatocellular carcinoma; AFP, alpha-fetoprotein; HDL-C, high-density lipoprotein concentration; LDL-C, low density lipoprotein cholesterol; FFA, free fatty acid; CEA, carcinoembryonic antigen; AUC, the area under the curve; OS, overall survival; PFS, progression-free survival; BCLC, Barcelona Clinic Liver Cancer; HBV, Chronic viral hepatitis B; ECOG, Eastern Cooperative Oncology Group; CA199, cancer antigen 19-9; BMI, body mass index; ALB, albumin; Apo B, apolipoprotein B; FIB, fibrinogen; NEU, neutrophil; LYM, lymphocyte; PLT, platelet; AHLR, stands for albumin, HDL-C ratio; FFHL, FFA/HDL-C; AABR, ALB/Apo B; FARI, FIB/ALB; NLR, NEU/LYM; PLR, PLT/LYM; CR, complete response; PR, partial response; SD, stable disease; DCB, durable clinical benefit; PD, progressed disease; NDB, no durable benefit; BOR, best overall response; IQR, interquartile range; CI, confidence interval; HR, hazard ratio; TCGA, The Cancer

Genome Atlas; ICGC, International Cancer Genome Collaboratory; TIM-3, T cell immunoglobulin and mucin-3; TMB, tumor mutation burden; PD-L1, programmed death ligand 1; DCA, Decision Curve Analysis; PAGE-B, Pathogenetic Global Evaluation of Biochemical; mPAGE-B, modified PAGE-B.

Data Sharing Statement

The datasets generated during the current study are not publicly available due to the failed consent to publish about the patients' information but are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Peking University International Hospital.

Consent to Publish

No person's data in any form included any individual details, images, or videos.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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