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Original Article

Adding nutritional status to the original BCLC stage improves mortality prediction for hepatocellular carcinoma patients in HBV-endemic regions

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Abstract: Hepatocellular carcinoma (HCC) is associated with high mortality, especially in Asian populations where chronic HBV infection is a major cause. Accurate prediction of mortality can assist clinical decision-making. We aim to (i) compare the predicting ability of Barcelona Clinic Liver Cancer classification (BCLC) stage, neutrophil-to-lymphocyte ratio (NLR), and Albumin-Bilirubin (ALBI) score in predicting short-term mortality (one- and two-year) and (ii) develop a novel model with improved accuracy compared to the conventional models. This study enrolled 298 consecutive HCC patients from our hepatology department. The prognostic values for mortality were assessed by area under the receiver operating characteristic curve (AUROC) analysis. A novel model was established and internally validated using 5-fold cross-validation, followed by external validation in a cohort of 100 patients. The primary etiology of cirrhosis was hepatitis B virus (HBV), with 81.2% of HCC patients having preserved liver function. Significant differences were observed in hemoglobin (Hb) and serum albumin levels, which reflect patients' nutrition status, between patients who survived for one year and those who died. BCLC exhibited superior predictive accuracy compared to NLR but had borderline superiority to the ALBI score. Therefore, a novel model incorporating BCLC, Hb, and serum albumin was developed, internally and externally validated, as well as subgroup sensitivity analysis. The model exhibited significantly higher predictive accuracy for one- and two-year mortality than conventional prognostic predictors, with AUROC values of 0.841 and 0.805, respectively. The novel "BCLC-Nutrition Model", which incorporates BCLC, Hb, and serum albumin, may provide improved predictive accuracy for short-term mortality in HCC patients compared to commonly used prognostic scores. This emphasizes the importance of nutrition in the management of HCC patients.

Keywords: Hepatocellular carcinoma (HCC), Barcelona Clinic Liver Cancer (BCLC) stage, neutrophil-lymphocyte ratio (NLR), albumin-bilirubin (ALBI) score, model building, nutritional status, area under receiver operating characteristic curve (AUROC), 5-fold cross-validation, internal and external validation, subgroup sensitivity analysis, short-term mortality

Introduction

Hepatocellular carcinoma (HCC), the most prevalent primary liver cancer, arises from chronic liver diseases/liver cirrhosis of different etiologies, such as chronic viral hepatitis (hepatitis B and C), alcoholic liver disease, and non-alcoholic-associated steatohepatitis (NASH) [1, 2]. HCC is ranked as the world's 3rd leading cause of cancer-related death, with increasing incidence over the years [3]. Curative HCC treatments such as surgical resection, liver transplantation, and radiofrequency ablation (RFA), are feasible for less than 30% of patients due to poor liver function or metastasis [4, 5]. Therefore, a comprehensive understanding of the risk factors and predictors of mortality in HCC patients is essential for personalized treatment and improved clinical outcomes. In addition, early recognition of high-risk mortality

patients can facilitate proactive management strategies, including surveillance, risk factor modification, and appropriate therapeutic interventions, to optimize the management of HCC and improve patient survival [6].

While the Child-Turcotte-Pugh (CTP) score is commonly used to assess the severity of cirrhosis, additional parameters such as albumin-bilirubin (ALBI) grade [7, 8], neutrophil-to-lymphocyte ratio (NLR) [9, 10], and Barcelona Clinic Liver Cancer (BCLC) classification [11, 12] have been used to predict the prognosis of patients with HCC. A systemic review of 72 studies has demonstrated that the most robust predictors of HCC-related mortality are CTP class, tumor size, α-fetoprotein (AFP) level, and presence of portal vein thrombosis, which could be categorized into liver function-related and tumor-related [13]. However, the inclusion of many decompensated patients in this study [13] may hinder these patients from receiving effective HCC treatment according to the HCC management guideline [12, 14]. In addition, the prognosis for HCC could be influenced by additional unconsidered factors such as TNM stage, the etiology of chronic liver disease, and the chosen treatment modality for HCC. It is important and convenient for physicians to have the most accurate prognostic prediction at the time of diagnosis when considering all these variables.

However, few studies have compared these common prognostic scores like ALBI score, NLR, and BCLC stage in HCC patients. In clinical practice, which score is superior to others in predicting one- and two-year mortality in HCC patients who have preserved liver function remains inconclusive. Therefore, the present study first aimed to compare the predicting ability of the current commonly used ALBI score, NLR, and BCLC stage in predicting short-term mortality (one- and two-year) of HCC patients with mostly preserved liver function. Second, a novel predicting scoring system was developed and tested to determine whether it is superior to the original three prognostic scoring systems in predicting short-term mortality (one- and two-year) of HCC patients with mostly preserved liver function.

Materials and methods

Patient recruitment

Patients diagnosed with HCC and admitted to the ward at Chang-Gung Memorial Hospital, Linkou Medical Center between July 2015 to May 2019, and who received HCC treatment/management and serial follow-up at least every three to six months were included. Patients with other primary malignancies or who lost follow-up (<2 years) were excluded. Finally, the study enrolled 298 patients (**Figure 1**).

Data collections

Personal information including age, gender, and substance consumption habits was documented upon admission. A baseline blood sample was collected for routine hemogram, liver biochemistry, international normalized ratio (INR), and alpha-fetoprotein (AFP) at the time of initial HCC diagnosis. Disease staging was determined based on Albumin-Bilirubin (ALBI) score, TNM stage (American Joint Committee on Cancer 8th edition), and Barcelona Clinic Liver Cancer (BCLC) stage, which were obtained from the electronic medical record, as they are known to accurately predict HCC survival.

Primary outcomes and scheduled follow-up periods

Patients with HCC were treated and managed according to the AASLD/EASL guidelines and the local HCC team conference's combined discussion. The primary outcomes were mortalities at one- and two-year. Survival of patients after discharge was confirmed through telephone interviews and/or analysis of medical records. Each patient was followed at least every three to six months until the date of death or May 31st, 2021, whichever occurred first.

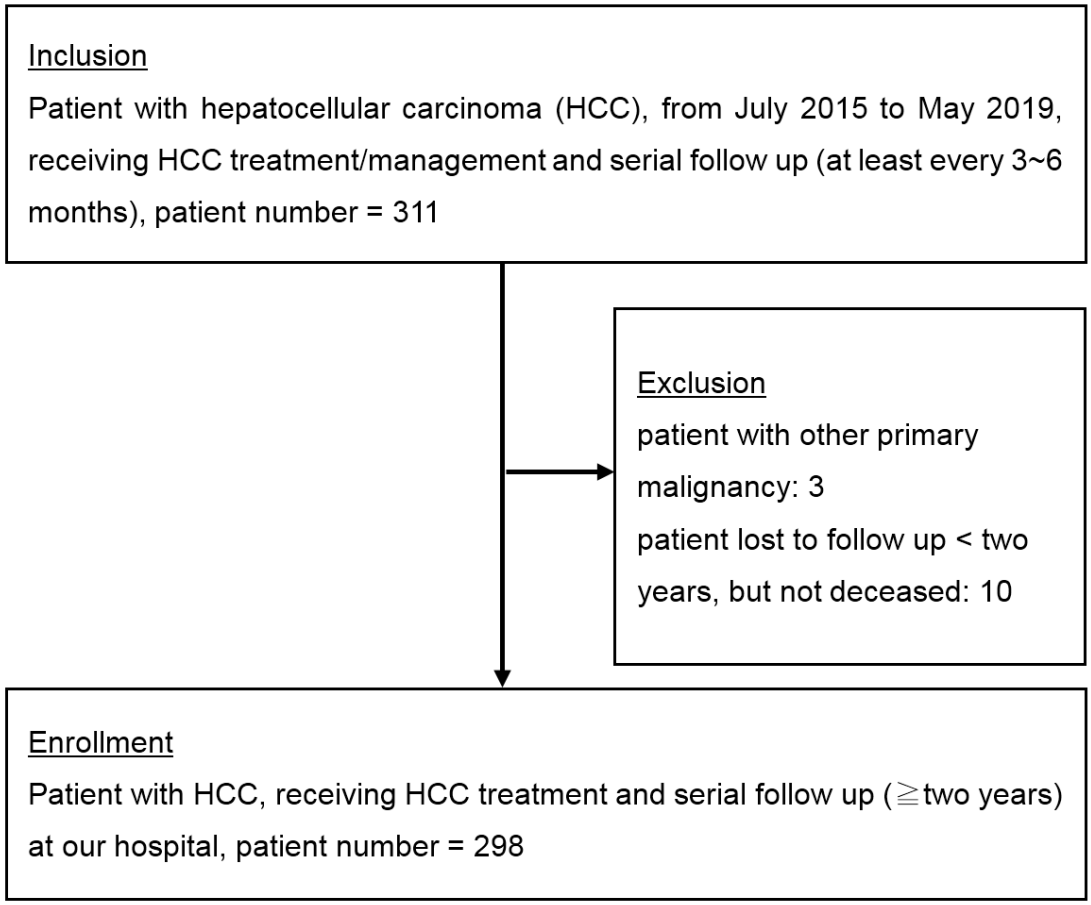
Definitions of HCC recurrence and preserved liver function

HCC recurrence was defined based on radiographic confirmation of HCC recurrence within one year of complete remission from HCC treatment, mainly through surgery and RFA. Preserved liver function was defined as Child-Turcotte-Pugh (CTP) class A in addition to compensated liver disease [15].

Statistical analysis

Normally distributed continuous data were expressed as mean ± standard deviation (SD) and compared using independent Student's t-test, while non-normal distributed continuous data were presented as the median and interquartile range (IQR) and compared using the

A



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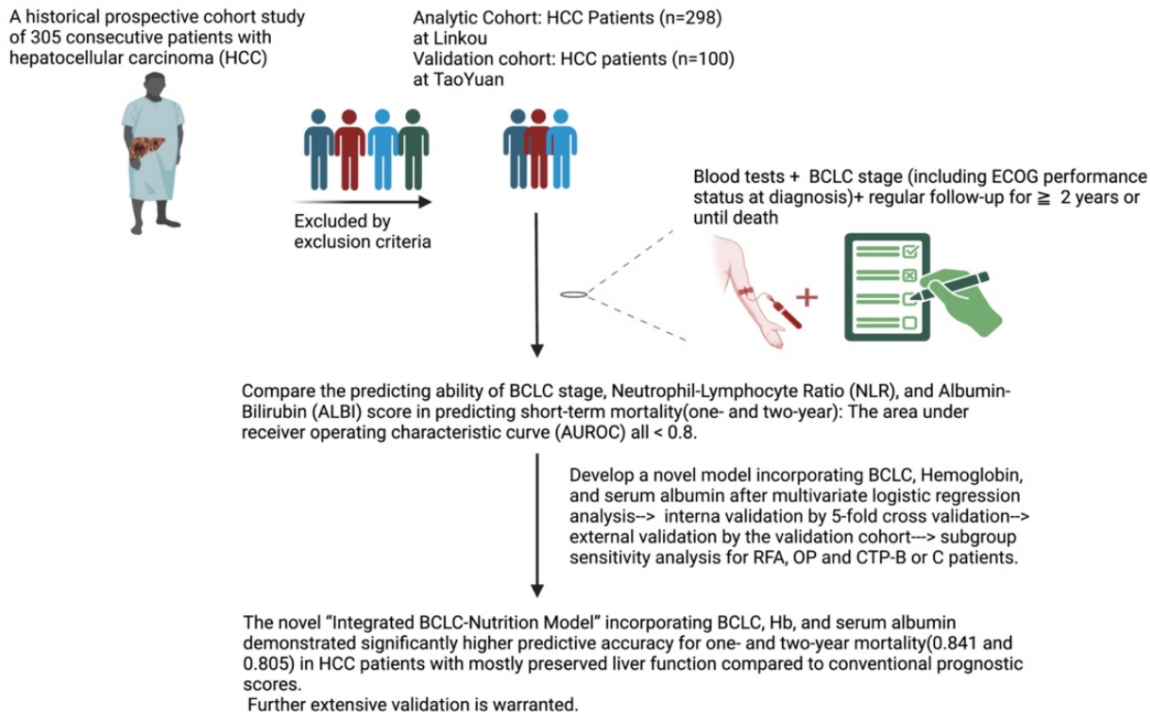

Figure 1. A. Flow chart demonstrating the process for patient recruitment, inclusion, and exclusion of HCC patients. B. The scheme diagram of the entire study.

Mann-Whitney U test. Categorical variables were presented as frequencies and percentages and compared using the χ^2 test or Fisher's exact test. The predictive ability of the novel model was evaluated by calculating the area under the receiver operating characteristic curve (AUROC) and comparing it to the ALBI grade, NLR, and BCLC stage. The predictive performance of each scoring system in predicting mortality was compared using the Delong test. The best cut-off values for ALBI grade, NLR, BCLC stage, and the new model were determined using the Youden Index. All analyses were conducted using IBM SPSS Statistics version 25 (SPSS Inc., Chicago, IL, USA), and R v4.2.2. (R Core Team, 2021; Vienna, Austria). A *P*-value less than 0.05 was considered statistically significant.

Construction of a novel prognostic model

Using the current dataset, the primary outcome was the dependent variable. The initial model included several independent variables, such as patient demographics, etiology of cirrhosis, BCLC stage, hemograms, serum biochemistry tests, AFP, and ascites status (Supplementary Tables 2 and 3). Variables with a P<0.20 in the univariate analysis were then included in a multivariate logistic regression analysis [16] to identify independent predictors that could predict primary outcomes with an AUROC >0.8, which is considered to be a good discriminatory ability [17].

Model internal and external validation

For model validation, internal validation was performed using 5-fold cross-validation. In this method, the dataset was divided into 5 equal subsets and was trained five times, with each training iteration using 4 out of the 5 subsets as the training data, while the remaining one subset is kept as the test (validation) set. Summary statistics for this procedure include the AUROC, Brier scores, and accuracy at intervals. The performance of the new model was evaluated using AUROC, Brier scores, and accuracy, as shown in Supplementary Table 4 and Supplementary Figure 2. Subsequently, an independent external validation set consisting of 100 HCC patients from our Taoyuan department was utilized for external validation.

Results

Patients' baseline characteristics

From July 2015 to May 2019, a total of 298 patients with HCC who met our inclusion and exclusion criteria were enrolled in this historical prospective study (**Figure 1**). The baseline demography is shown in **Table 1**. The mean age was 63.58 years old and 218 patients (73.2%) were male. The most common etiology of cirrhosis was chronic viral hepatitis infection, with 51.0% attributed to hepatitis B virus (HBV) and 31.9% to hepatitis C virus (HCV). Among them, 37% had received antiviral therapy. 242 (81.2%) had CTP class A liver function, 45 (15.1%) had CTP class B, and 11 (3.7%) had CTP class C. Regarding tumor stage, 62 patients (20.8%) were classified as BCLC stage 0, 99 patients (33.2%) as BCLC stage A, 44 patients (14.8%) as BCLC stage B, 88 patients (29.5%) as stage C, and 5 patients (1.7%) as stage D. ALBI grade I was observed in 138 (46.3%), grade II in 143 (48%), and grade III in 17 (5.7%). In terms of TNM stage, 153 patients (51.3%) were classified as stage I, 76 patients (25.5) as stage II, 45 patients (15.1%) as stage III, and 24 patients (8.1%) as stage IV. The treatment modalities for HCC included RFA in 92 patients (30.9%), surgery in 90 patients (30.5%), transarterial chemoembolization (TACE) in 38 patients (12.8%), immunotherapy in 5 patients (1.7), and combination therapy in 72 patients (24.1).

Table 1 presents laboratory data, including hemograms, NLR, and biochemistry results, as well as cirrhotic complications such as ascites and hepatic encephalopathy (HE) grade.

Differences in the baseline characteristic between patients who survived one year and those who died within one year

Table 1 also displays several variables that were found to be statistically different between the one-year survival and mortality groups. In the hemogram, the mortality group exhibited a significant increase in the percentage of segmented and band-form neutrophils, NLR, and INR, as well as a significant decrease in the percentage of lymphocytes and hemoglobin (Hb) compared to the survival group. In the biochemistry, the mortality group exhibited significantly higher levels of aspartate transaminase (AST),

Table 1. Baseline clinical characteristics of 298 patients with HCC

Variables	Overall (N = 298)	Survival (N = 222)*	Mortality (N = 76)#	*P*-value
*Age (years)	63.58 ± 11.17	63.32 ± 11.07	64.64 ± 11.5	0.493
*Gender (male, %)	218 (73.2)	162 (72.97)	56 (73.68)	0.948
Etiology n (%)				
Alcohol	18 (6.0)	10 (4.5)	8 (10.5)	0.057
HBV	152 (51.0)	115 (51.8)	37 (48.7)	0.688
HCV	95 (31.9)	76 (34.2)	19 (25.0)	0.136
Other	33 (11.1)	21 (9.5)	12 (15.8)	0.129
CTP n (%)				
A	242 (81.2)	196 (88.2)	46 (60.5)	<0.001
B	45 (15.1)	26 (11.8)	19 (25.0)	0.005
C	11 (3.7)	0 (0)	11 (14.5)	<0.001
BCLC n (%)				
0	62 (20.8)	57 (25.7)	5 (6.6)	<0.001
A	99 (33.2)	88 (39.6)	11 (14.5)	<0.001
B	44 (14.8)	34 (15.3)	10 (13.1)	0.786
C	88 (29.5)	43 (19.4)	45 (59.2)	<0.001
D	5 (1.7)	0 (0)	5 (6.6)	0.001
ALBI score	-2.44 ± 0.57	-2.56 ± 0.75	-2.11 ± 0.08	<0.001
ALBI grade n (%)				
1	138 (46.3)	122 (55.0)	16 (21.1)	<0.001
2	143 (48.0)	96 (43.2)	47 (61.8)	0.005
3	17 (5.7)	4 (1.8)	13 (17.1)	<0.001
TNM n (%)				
1	153 (51.3)	139 (62.6)	14 (18.4)	<0.001
2	76 (25.5)	59 (26.6)	17 (22.4)	0.468
3	45 (15.1)	18 (8.1)	27 (35.5)	<0.001
4	24 (8.1)	6 (2.7)	18 (23.7)	<0.001
Treatment modalities n (%)				
RFA	92 (30.9)	78 (34.7)	15 (19.7)	0.015
Surgery	91 (30.5)	86 (38.7)	5 (6.6)	<0.001
TACE	38 (12.8)	24 (10.8)	14 (18.4)	0.086
Immunotherapy	5 (1.7)	0 (0)	5 (6.6)	<0.001
Combination therapy	72 (24.1)	35 (15.8)	37 (48.7)	<0.001
Laboratory				
Hemogram				
*WBC (10^3/uL)	5552.36 ± 3374.21	5425.46 ± 3531.62	5919.74 ± 2859.88	0.272
*Seg + band (%)	61.4027 ± 11.91	59.87 ± 11.21	65.83 ± 12.79	<0.001
*Lymph (%)	27.39 ± 11.03	29.19 ± 10.41	22.23 ± 11.23	<0.001
*NLR	3.40 ± 4.09	2.89 ± 3.55	4.86 ± 5.11	0.002
*Hb (g/dL)	12.63 ± 2.22	13.07 ± 2.05	11.36 ± 2.2	<0.001
*PLT (10^3/uL)	149.49 ± 81.07	147.7 ± 79.67	154.68 ± 85.34	0.518
*INR	1.16 ± 0.18	1.13 ± 0.15	1.27 ± 0.22	<0.001
Biochemistry				
*Cr (mg/dL)	1.31 ± 5.64	1.42 ± 6.52	0.96 ± 0.8	0.539
*Albumin (g/dL)	3.76 ± 0.58	3.87 ± 0.52	3.42 ± 0.63	<0.001
*AST (U/L)	64.24 ± 70.46	55.4 ± 62.85	89.95 ± 84.3	0.001
*ALT (U/L)	49.09 ± 54.63	48.37 ± 58.12	51.21 ± 43.14	0.696
*AFP (ng/mL)	6781.06 ± 45238.17	717.03 ± 2920.78	25314.79 ± 88892.58	0.023
*BILT (mg/dL)	1.04 ± 1.36	0.87 ± 0.47	1.55 ± 2.51	0.02

Ascites n (%)				
0	252 (84.7)	200 (90.0)	53 (69.7)	<0.001
Slight	21 (7.0)	16 (7.2)	5 (6.6)	0.853
Moderate	3 (1.0)	1 (0.5)	2 (2.6)	0.1
Massive	21 (7.0)	5 (2.3)	16 (21.1)	<0.001
HE n (%)				
0	292 (98.0)	220 (99.1)	72 (94.7)	0.052
Grade 1	4 (1.3)	2 (0.9)	2 (2.6)	0.258
Grade 2	1 (0.3)	0 (0)	1 (1.3)	0.087
Grade 3	0 (0)	0 (0)	0 (0)	
Grade 4	1 (0.3)	0 (0)	1 (1.3)	0.087

*: one-year survival; #: one-year mortality. WBC: White blood cell; Seg + band: the sum of the percentage of segment and band form neutrophils; NLR: Neutrophil-Lymphocyte Ratio; Hb: Hemoglobin; PLT: Platelet; INR: international normalized ratio; Cr: Creatinine; BILT: total bilirubin; AST: aspartate transaminase; ALT: Alanine transaminase; AFP: Alpha Fetoprotein; BIL T: total bilirubin; RFA: radiofrequency ablation; TACE: transarterial chemoembolisation; Combination therapy: RFA ± surgery ± TACE ± immunotherapy.

Table 2. Comparison of the primary and secondary outcomes between the one-year survival and mortality groups in the Enrolled patients with HCC

Variables	Overall (N = 298)	Survival (N = 222)*	Mortality (N = 76)#	*P*-value
Primary outcome: Cumulative mortality n (%)				
1 year	76 (25.5)	0	76 (100)	
2 years	114 (38.3)	38 (17.1)	76 (100)	<0.001
Overall Survival (days)	456.48 ± 302.04	544.30 ± 281.77	153.98 ± 118.16	<0.001
Secondary outcome: HCC recurrence at 1 year/complete response n/N (%)	95 (31.9)	28/157 (17.8)	10/22 (45.5)	0.009

*: one-year survival; #: one-year mortality.

alpha-fetoprotein (AFP), and serum total bilirubin (BIL T), as well as a significant decrease in the serum albumin level compared to the survival group.

In terms of CTP class, the mortality group had a significantly higher number of patients in CTP-B and CTP-C classes. Similarly, the mortality group had significantly more patients with advanced ascites. Additionally, the mortality group had significantly more patients in BCLC-C and D, ALBI grade II and III, and TNM stage III and IV. On the other hand, the main treatment modalities in the survival group were either RFA or surgery alone.

Comparison of the primary and secondary outcomes between the one-year survival and mortality groups

As presented in **Table 2**, the cumulative mortality rate at two-year, which was also the primary outcome, remained significantly higher in the one-year mortality group compared to the one-year survival group (100% vs. 17.1%, P<0.001). Moreover, the average overall survival was 544.30 ± 281.77 days in the survival group and 153.98 ± 118.16 days in the mortality group (P<0.001).

Regarding the secondary outcome, the HCC recurrence rate at one-year after complete response was significantly higher in the mortality group compared to the survival group (45.5% vs. 17.8%, P = 0.009).

Comparisons of the ALBI score, NLR, and BCLC stage in predicting 1- and 2-year mortality by the area under the receiver operating characteristic (AUROC)

As shown in **Figure 2** and **Table 3**, the AUROC comparisons of the ALBI score, NLR, and BCLC stage in predicting the 1-year mortality showed that BCLC had the highest predictive ability, followed by ALBI score, and the NLR (BCLC: ALBI score: NLR = 0.769: 0.701: 0.679). The predictive ability of BCLC was significantly superior to that of the NLR and was borderline significantly superior to that of the ALBI grade.

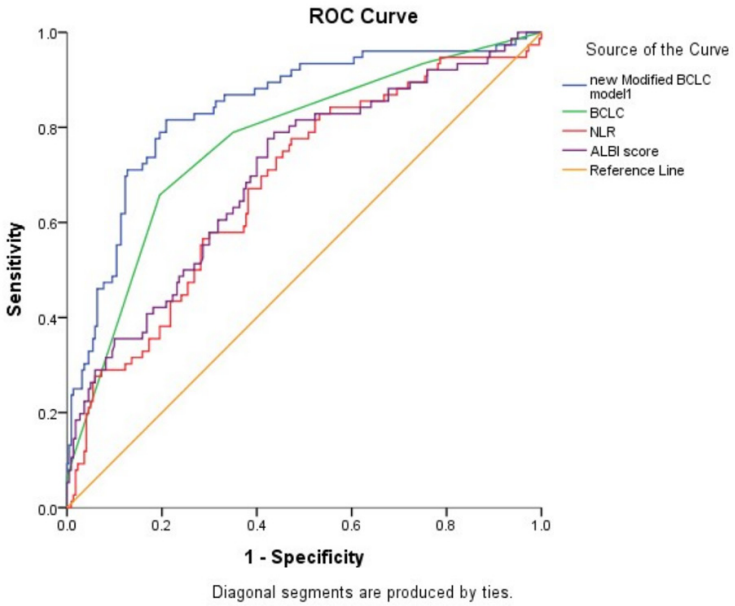

Figure 2. Comparisons of the prediction ability of the new modified BCLC model, ALBI score, NLR, and BCLC stage in predicting 1-year mortality by AUROC.

As shown in Supplementary Figure 1 and Supplementary Table 1, the AUROC comparisons of the ALBI score, NLR, and BCLC stage in predicting the 2-year mortality also showed similar findings as the 1-year did.

Predictors of one-year and two-year mortalities by univariate and multivariate analysis

Because the AUROC of the BCLC stage in predicting one-year mortality was only 0.769, indicating fair prediction ability, we planned to develop a new model that incorporates BCLC and other relevant factors to more accurately predict patients' survival. Firstly, as shown in Supplementary Tables 2 and 3, univariate analyses were conducted, and the following variables were identified as predictors of both one-year and two-year mortalities, in addition to BCLC: the sum of the percentage of segment and band form neutrophils (Seg + band), percentage of lymphocyte, serum hemoglobin, INR, as well as serum albumin, AFP, total bilirubin levels and ascites status. Secondly, multivariate logistic regression analysis in Supplementary Tables 2 and 3 demonstrated that serum hemoglobin, and serum albumin level as well as the BCLC stage could independently predict both one-year and two-year mortalities in these patients with HCC. In addition, there is no correlation between BCLC and serum albumin level (Pearson Correlation -0.1, P = 0.085).

Development of the new "Modified BCLC" model

Subsequently, a new model termed the "*Modified BCLC*" model was built from these three variables to predict one and two-year mortalities. The methods for the development of a novel model and its internal and external validation are presented in the material and method section.

The formula of the new *Modified BCLC* model is:

Score for one-year mortality = 3.154 + 0.871 (BCLC) - 0.230 (Hb) - 0.873 (Albumin)

Score for two-year mortality = 4.872 + 0.618 (BCLC) - 0.714 (Hb) - 1.149 (Albumin)

Comparisons of the prediction ability of the new Modified BCLC model with the traditional ALBI score, NLR, and BCLC stage in predicting 1-year mortality by AUROC

As shown in **Figure 2** and **Table 3**, the new "Modified BCLC" model exhibited significantly higher predicting ability than the traditional ALBI score, NLR, or BCLC stage (P<0.01). The prediction ability of the new Modified BCLC model in predicting one- and two-year mortality is 0.841 and 0.805 respectively (**Table 3** and Supplementary Table 1).

Model internal and validation

5-fold cross internal validation also showed good AUROC and Brier scores, and accuracy on the train and test sets for various primary outcome time points (Supplementary Figure 2 and Supplementary Table 4). Subsequently, an external validation set consisting of 100 HCC patients from our Taoyuan department was used for external validation. The AUROC of the new Modified BCLC model in predicting their one- and two-year mortality is 0.755 and 0.771 respectively and is much better than the BCLC

Table 3. Predicting ability of the new "Modified BCLC" model vs. other traditional HCC models at one-year

	Predicting one-year mortality			
	ALBI score	NLR	BCLC	Modified BCLC model
AUC	0.701	0.679	0.769	0.841
(95% CI)	(0.670, 0.770)	(0.609, 0.749)	(0.706, 0.832)	(0.787, 0.896)
P-value	<0.001	<0.001	<0.001	<0.001
ALBI score				
NLR	0.6151			
BCLC	0.1362	0.01803		
Modified BCLC model	<0.001	<0.001	<0.001	

ALBI: Albumin-Bilirubin (ALBI) score; NLR: Neutrophil-Lymphocyte Ratio; BCLC: Barcelona Clinic Liver Cancer.

stage alone (0.642) (Supplementary Figure 3 and Supplementary Table 5A, 5B).

Subgroup sensitivity analysis

To further confirm the feasibility of the new "Modified BCLC" model, a subgroup sensitivity analysis was conducted. The analysis included 92 patients who received RFA treatment and 91 patients who received surgery, as shown in Supplementary Figure 4 and Supplementary Table 6A. The AUROC of the one-year mortality prediction was 0.803 in the RFA subgroup and 0.840 in the surgery subgroup. There was no significant difference between these two groups (Supplementary Table 6A, P = 0.742). The AUROC for predicting one-year mortality in patients with CTP class B and C was also 0.8 (figures not shown for simplicity).

The cut-off values for the new "Modified BCLC" model

The new model's cut-off value for predicting one-year mortality was 0.2714027, with mortality rates of 19.7% and 70.6% below and above this value, respectively. Similarly, the cut-off value for predicting two-year mortality was 0.3951457, with corresponding mortality rates of 33.0% and 79.4% below and above this threshold, respectively (Supplementary Figure 5 and Supplementary Table 6B).

Discussion

HCC is associated with high cancer-related death, with increasing incidence over the years. Accurate prediction of mortality at diagnosis can provide valuable information for both doctors and patients. However, limited studies have compared the predictive abilities of commonly used prognostic scores in HCC patients with mostly preserved liver function. In this study, three commonly used prognostic systems, namely BCLC stage, NLR, and ALBI score were compared in a cohort of 298 HCC patients with mostly preserved liver function and predominantly viral etiology (82.9%). BCLC stage exhibited superior predictive accuracy compared to NLR, but it had borderline superiority to the ALBI score, with all AUROC <0.8, indicating fair prediction ability. Therefore, a new model that incorporates BCLC, Hb, and serum albumin (which may reflect patients' nutritional status) was developed. The new "BCLC-Nutrition Model" exhibited significantly higher predictive accuracy than the conventional prognostic predictors, with AUROC values of 0.841 and 0.805 for one- and two-year mortality prediction, respectively. In addition, this new model was internally and externally validated, with accuracy near or above 80%. Subgroup sensitivity analysis of patients receiving either RFA or surgery also showed that the AUROC of the new model for predicting one-year mortality was 0.803 for the RFA subgroup and 0.840 for the surgery subgroup. The AUROC of the new model was also found to be effective for patients in CTP classes B and C. Therefore, the novel BCLC-Nutrition Model demonstrated significantly higher predictive accuracy for one- and two-year mortality in HCC patients, especially those with preserved liver function compared to conventional prognostic scores. Further validation in larger cohorts is needed to establish its clinical utility and generalizability.

The BCLC classification is a well-established staging system for HCC that takes into account several factors, including tumor size, number of

tumors, extent of cancer, severity of cirrhosis, and overall health status, to guide treatment decisions. Widely adopted by healthcare providers and researchers, it provides a useful tool for clinicians in determining the best course of action for each patient [12]. In addition to the BCLC classifications, various biomarkers have been used to predict the prognosis and recurrence of HCC. The NLR, a relatively simple and inexpensive test, has been shown to predict poor clinical outcomes in patients with HCC whose NLR is greater than 2.7 [18]. A large-scale cohort study of patients with HCC also identified high baseline NLR and delta NLR as independent predictors of mortality [19]. Moreover, a systematic review demonstrated that the ALBI score was superior to the Child-Pugh score in predicting outcomes for patients with HCC [20]. Herein, a novel model incorporating BCLC, serum albumin, and Hb was developed and compared with the original BCLC, NLR, and ALBI scores, revealing its significant superiority over these existing prognostic scores. In addition, there is no correlation between BCLC and serum albumin level (Pearson Correlation -0.1, P = 0.085).

Serum albumin and Hb levels are important biomarkers for predicting the prognosis of cancer and assessing a patient's general condition. The serum albumin level can be influenced by various factors, such as liver function, nutritional status, protein-losing disease, inflammation, and systemic infection [21]. While albumin may not be directly associated with HCC, it can reflect the overall condition of HCC patients [22]. A previous study has shown albumin plays a role in inhibiting HCC tumor growth [23]. Similarly, the level of Hb is also indicative of the general condition of HCC patients [24]. A previous study has proposed the Hb level as a predictor for the early-phase outcome of liver transplantation in patients who have undergone the procedure [25]. Moreover, the level of Hb has been identified as an independent prognostic factor in HCC patients who have undergone HCC treatments [26, 27], as well as in HCC patients with possible nephropathy [28]. The Euronut SENECA study of nutrition and the elderly, conducted in 19 towns located in 12 European countries, utilized Hb and albumin as markers for assessing nutritional status [29]. Therefore, the newly developed model that incorporates BCLC, Hb, and serum albumin is referred to as the "BCLC-Nutrition Model".

This novel "BCLC-Nutrition Model" has demonstrated satisfactory predictive ability for one-year and two-year mortalities in HCC patients. The cut-off value for predicting one-year mortality was determined with mortality rates of 19.7% and 70.6% below and above this value, respectively. This model was confirmed through internal and external validations, as well as subgroup analysis. While the original BCLC classification primarily focuses on clinical and radiological parameters [30], patient-reported outcomes, such as quality of life and symptom burden (measured by the Eastern Cooperative Oncology Group performance status-ECOG) [31], are also important factors to consider in treatment decisions for HCC patients. The integration of ECOG status into the BCLC model has improved patient-centered care and optimized treatment selection [32]. Furthermore, considering cancer patients' general condition, including their nutritional status, may provide additional insights into overall survival, highlighting the importance of nutritional status in patients with HCC.

Conclusion

The newly developed "BCLC-Nutrition Model", which incorporates BCLC classification, hemoglobin (Hb), and serum albumin levels, has shown significantly improved predictive accuracy for one- and two-year mortality in HCC patients, especially those with preserved liver function compared to the conventional prognostic scores. This emphasizes the importance of nutrition in the management of patients with HCC. However, further rigorous validation in larger cohorts is needed to establish its clinical utility and generalizability.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Predicting ability of the new "Modified BCLC" model vs. other traditional HCC models at two-year

	Predicting two-year mortality			
	ALBI score	NLR	BCLC	Modified BCLC model
AUC	0.711	0.641	0.702	0.805
(95% CI)	(0.651, 0.772)	(0.577, 0.706)	(0.638, 0.765)	(0.752, 0.858)
P-value	<0.001	<0.001	<0.001	<0.001
ALBI score				
NLR	0.0931			
BCLC	0.8377	0.1151		
Modified BCLC model	<0.001	<0.001	<0.001	

ALBI: Albumin-Bilirubin (ALBI) score; NLR: Neutrophil-Lymphocyte Ratio; BCLC: Barcelona Clinic Liver Cancer.

Supplementary Table 2. Predictors of one-year mortality by univariate and multivariate analysis

Predictor variables	Univariate			Multivariate		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age	1.009	0.985-1.033	0.468			
Gender	1.013	0.561-1.830	0.965			
Etiology	0.957	0.681-1.344	0.800			
BCLC	2.722	2.045-3.624	<0.001	2.388	1.743-3.272	<0.001
Laboratory						
WBC	1.000	1.000-1.000	0.337			
Seg + band (%)	1.045	1.021-1.069	<0.001			
Lymph	0.938	0.913-0.964	<0.001			
Hb	0.689	0.603-0.787	<0.001	0.795	0.667-0.947	0.010
PLT	1.001	0.998-1.004	0.544			
INR	136.6	22.9-815.1	<0.001			
Cr	0.964	0.824-1.127	0.643			
Albumin	0.261	0.161-0.424	<0.001	0.418	0.215-0.812	0.010
AST	1.006	1.002-1.010	0.001			
ALT	1.001	0.996-1.005	0.718			
AFP	1.000	1.000-1.000	<0.001			
BILT	1.858	1.270-2.716	0.001			
Ascites	2.205	1.60-3.030	<0.001			

OR: Odds Ratio; Seg + band %: the combined percentage of segmented and band neutrophils in the white blood cell.

Supplementary Table 3. Predictors of two-year mortality by univariate and multivariate analysis

Predictor variables	Univariate			Multivariate		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age	1.028	1.006-1.051	0.012			
Gender	1.178	0.690-2.011	0.549			
Etiology	1.108	0.818-1.501	0.506			
BCLC	1.991	1.589-2.496	<0.001	1.984	1.548-2.545	<0.001
Laboratory						
WBC	1.000	1.000-1.000	0.677			
Seg + band (%)	1.031	1.010-1.052	0.004			
Lymph	0.955	0.933-0.977	<0.001			
Hb	0.708	0.627-0.799	<0.001	0.861	0.742-0.998	0.047
PLT	0.999	0.996-1.002	0.609			
INR	78.97	14.05-443.85	<0.001			
Cr	0.985	0.929-1.045	0.616			
Albumin	0.233	0.145-0.373	<0.001	0.292	0.1625-0.526	0.010
AST	1.004	1.001-1.008	0.022			
ALT	1.000	0.996-1.004	0.961			
AFP	1.000	1.000-1.000	0.004			
BILT	1.647	1.144-2.370	0.007			
Ascites	2.062	1.462-2.907	<0.001			

OR: Odds Ratio; Seg + band %: the combined percentage of segmented and band neutrophils in the white blood cell.

Supplementary Table 4. Model internal validation by 5-fold cross-validation

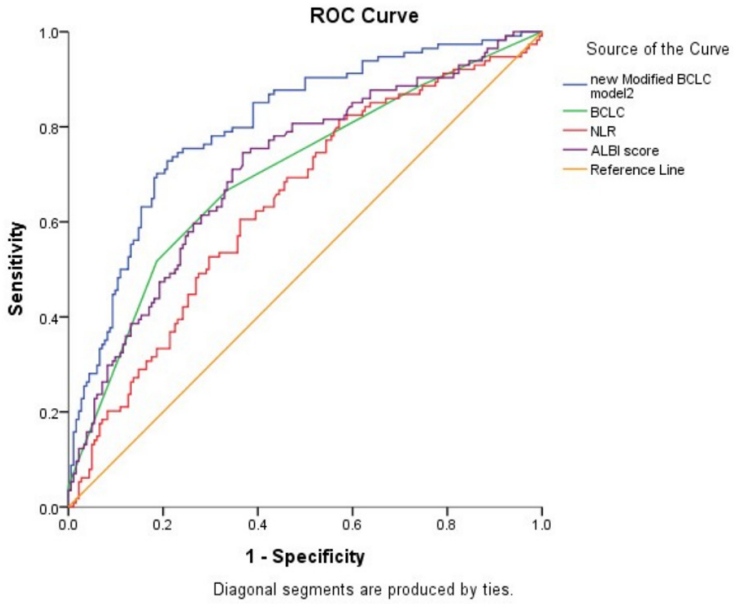
A. Cross-validation of the new prediction model in one-year mortality

		Predicting one-year mortality				
Dataset	Total N	AIC	R-Square	RMSE	AUC	Brier Score
Train	230	205.5	0.2799703	0.3732343	0.8279314	0.13668
Test	58	34.9	0.5695391	0.3134124	0.8896104	0.09133038
accuracy = 0.7931034						

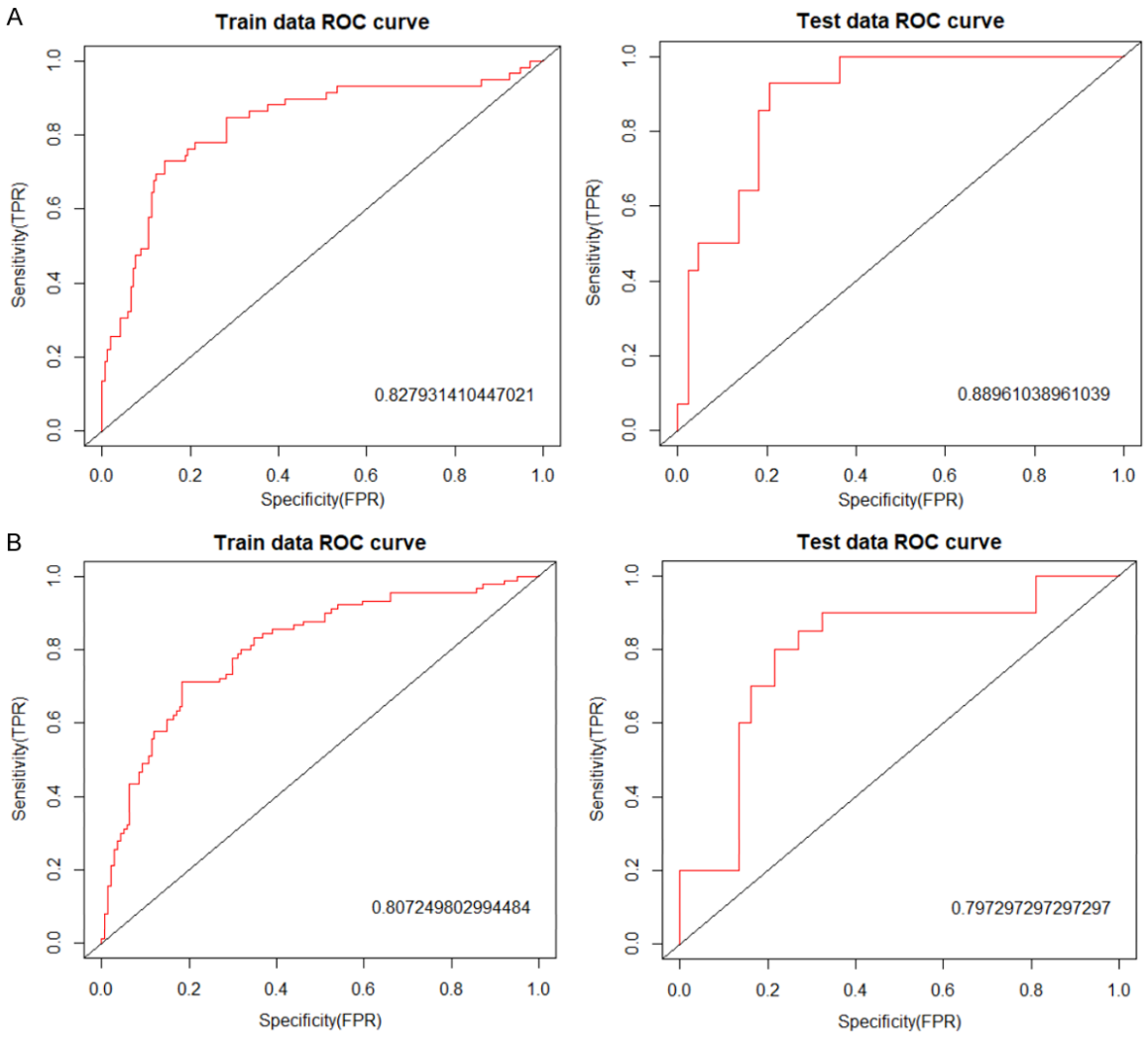
B. Cross-validation of the new prediction model in two-year mortality

		Predicting two-year mortality				
Dataset	Total N	AIC	R-Square	RMSE	AUC	Brier Score
Train	231	249.9	0.2655493	0.4238586	0.8072498	0.1743058
Test	57	65.52	0.2369408	0.4381543	0.7972973	0.1690046
accuracy = 0.7719298						

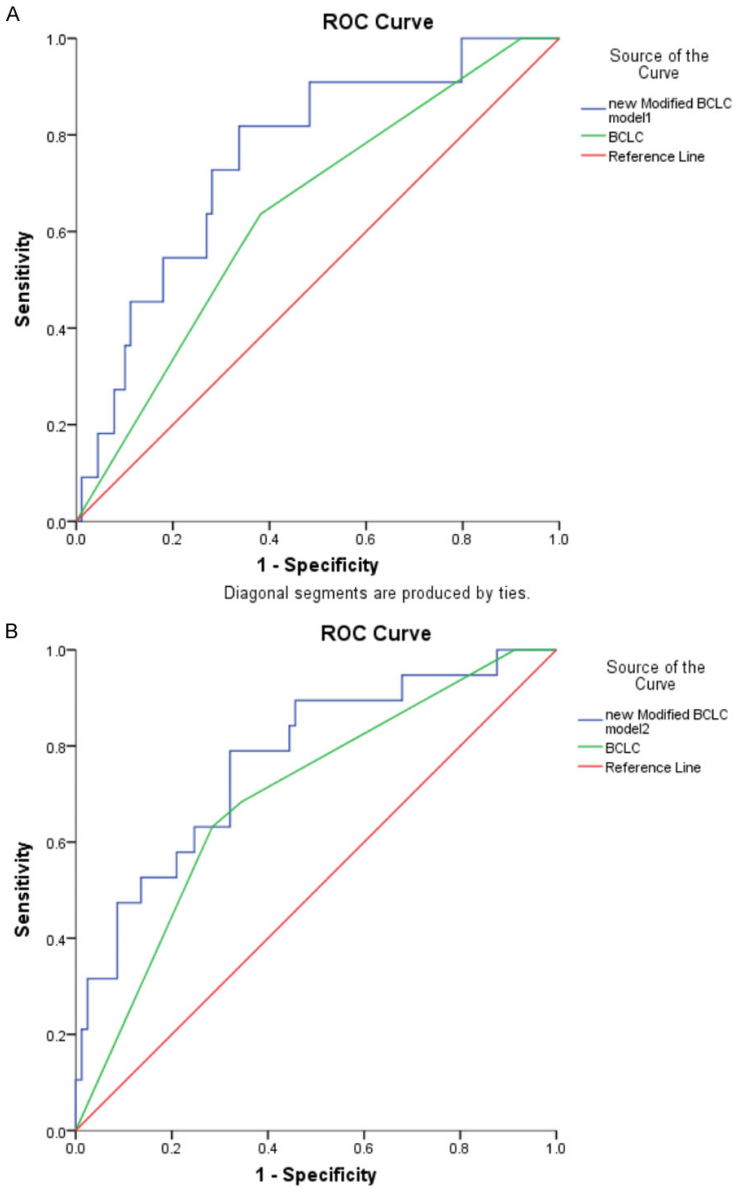
N: number; AIC: Akaike information criterion; RMSE: Root-mean-square deviation.



Supplementary Figure 1. Comparisons of the prediction ability of the new modified BCLC model, ALBI score, NLR, and BCLC stage in predicting 2-year mortality by AUROC.



Supplementary Figure 2. A. The ROC curve of the training set and the test (validation) set for predicting one-year mortality. B. The ROC curve of the training set and the test (validation) set for predicting two-year mortality.



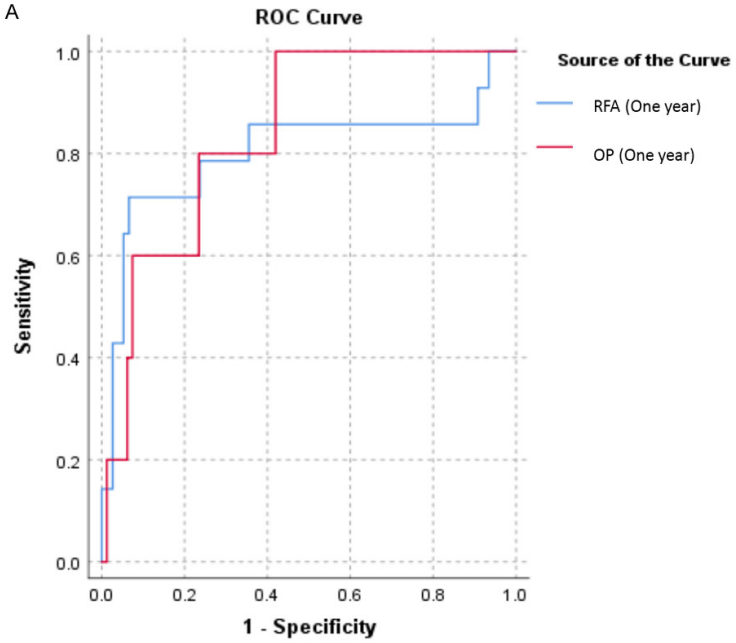
Supplementary Figure 3. An external validation cohort consisting of 100 HCC patients from our Taoyuan department demonstrated that the AUROC of the new Modified BCLC model for predicting (A) one-year mortality was 0.755 and (B) two-year mortality was 0.771.

Supplementary Table 5. Model external validation by an external validation set consisting of 100 HCC patients from our Taoyuan department

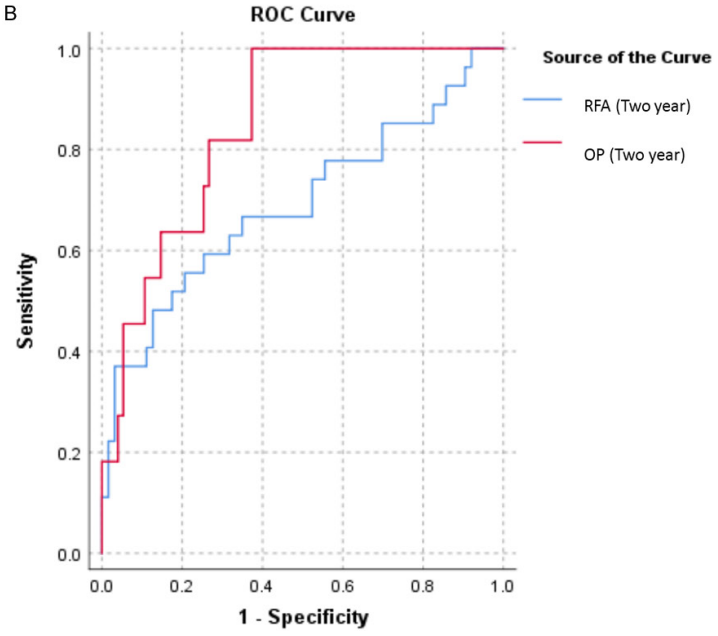
A. External validation of the new prediction model in one-year mortality						
		Predicting one-year mortality				
Dataset	Total N	AIC	R-Square	RMSE	AUC	Brier Score
External validation accuracy = 0.86	100	67.06	0.08116241	0.3014301	0.755803	0.08633723
B. External validation of the new prediction model in two-year mortality						
		Predicting one-year mortality				
Dataset	Total N	AIC	R-Square	RMSE	AUC	Brier Score
External validation accuracy = 0.86	100	87.25	0.1188932	0.3680254	0.771271	0.1247675

N: number; AIC: Akaike information criterion; RMSE: Root-mean-square deviation.

A



B



Supplementary Figure 4. Subgroup sensitivity analysis showed that the AUROC of the new Modified BCLC model for predicting (A) one-year mortality was 0.803 for the RFA subgroup and 0.840 for the surgery subgroup, and (B) two-year mortality was 0.691 for the RFA subgroup and 0.848 for the surgery subgroup.

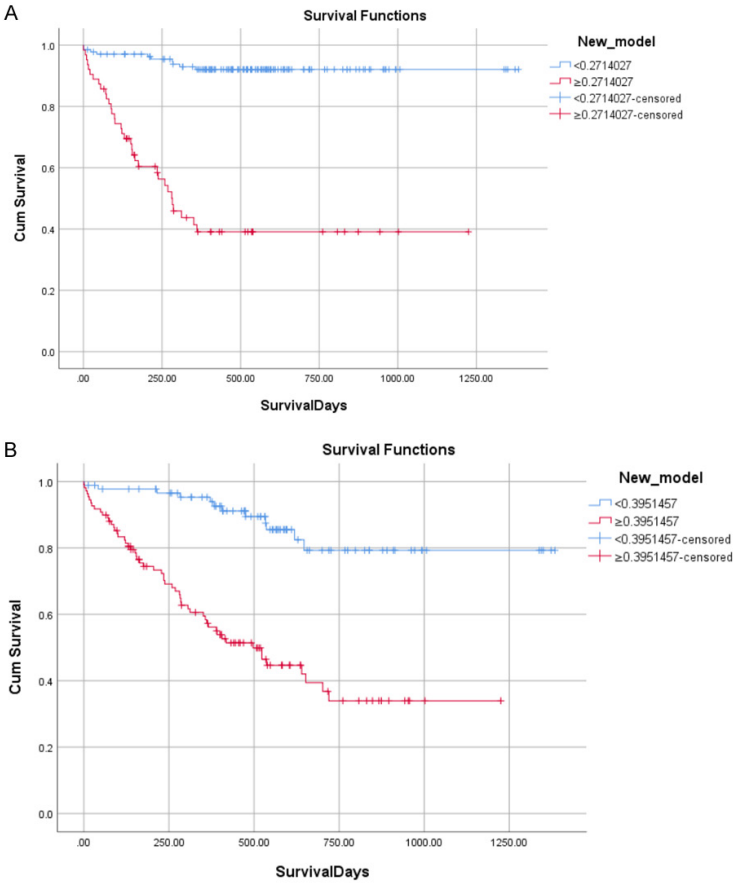
Supplementary Table 6A. Subgroup sensitivity analysis of patients receiving either RFA or surgery

	RFA	Surgery	AUROC Difference	*P*-value
New_model (one-year)	0.803	0.840	-0.037	0.742
New_model (two-year)	0.691	0.848	-0.158	0.057

RFA: Radiofrequency ablation.

Supplementary Table 6B. Cut-off values of the new modified BCLC model in predicting one- and two-year mortalities

Mortality above or below the cut-off values	
One-year, n = 76/298 (25.5%)	
modified BCLC Model	Mortality
≥0.2714027	24/34 (70.6%)
<0.2714027	52/264 (19.7%)
Two-year, n = 114/298 (38.26%)	
≥0.3951457	27/34 (79.4%)
<0.3951457	87/264 (33.0%)



Supplementary Figure 5. Survival curve of patients with the new modified BCLC model score, stratified by scores above or below the cut-off values: A. The one-year score above or below the cut-off value of 0.2714027; B. The two-year score above or below the cut-off value of 0.3951457.