Prediction of long-term survival rates in patients undergoing curative resection for solitary hepatocellular carcinoma

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Abstract. The present study developed a novel laboratory-based algorithm to predict long-term survival rates in patients undergoing curative resection for solitary hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC). The present study included 426 patients with solitary HBV-related HCC who underwent surgery for primary tumors at a single center between 2003 and 2012. Demographic characteristics, laboratory analysis, clinical pathology and immunohistochemistry of topoisomerase II-a and Ki67 were analyzed. A simple prognostic risk calculator was developed using regression coefficients from multivariate models. A prognostic risk calculator incorporating tumor encapsulation, neutrophil-to-lymphocyte ratio, vascular invasion, α-fetoprotein level, Edmondson-Steiner classification, Topo II-α, prognostic nutritional index and Child-Pugh grade was constructed. The prognostic model demonstrated good discrimination with a C-index prior to adjustment of 0.81 (95% confidence interval: 0.78-0.84) and a bootstrap-corrected C-index of 0.81. Kaplan-Meier curves demonstrated that the probabilities of overall survival rates in the low-risk group were increased compared with those in the high-risk group. The areas under the receiver operating characteristic curve using the method were greater compared with those under the 7th Tumor-Node-Metastasis system and Cancer of the Liver Italian Program scoring system [0.83 vs. 0.62 and 0.77 (P<0.001), respectively]. The simple prognostic model of the present study accurately predicted survival rates in patients. Such a prognostic risk calculator for staging patients undergoing curative resection for solitary HBV-related HCC facilitates clinical surveillance and therapy.

Introduction

In 2014, hepatocellular carcinoma (HCC) was the second leading cause of cancer and the fifth most common cancer-associated mortality worldwide (1). Approximately 70-90% of patients with HCC are associated with hepatitis B virus infection in the highly endemic Asia-Pacific areas, particularly in China (2). Liver resection and transplantation are potentially curative treatments in selected patients (3). However, the clinical behavior of HCC may vary (4). In numerous patients, the disease manifests an aggressive course with a survival rate of only months. Other patients may exhibit a comparatively slow clinical development and survive for >5-10 years following diagnosis. It is imperative to develop an HCC staging classification to stratify patients and determine the probability of overall survival (OS) rate prior to therapy.

Factors, including inflammation-based indices including neutrophil-to-lymphocyte ratio (NLR) (5), platelet-to-lymphocyte ratio (PLR) (6), prognostic nutritional index (PNI) (7) and body mass index (BMI) (8) and tumor biomarkers including topoisomerase (Topo) II-α (9) and Ki67 (10) represent independent predictors of poor OS rates in patients with HCC and enabled the refinement of current prognostic models. These novel factors may be used to determine the OS and development of preventative measures in those with high risk. The traditional systems, including 7th Tumor-Node-Metastasis (TNM).system (11) and Cancer of the Liver Italian Program (CLIP) scoring system (12), may not be modified based on our understanding of cancer biology and novel prognostic variables (13).

Various prognostic models incorporating traditional and newly developed factors have been developed to focus on early-stage HCC (14), large (diameter >10 cm) HCC (15) and multiple HCC (16). Compared with conventional staging, these systems are limited in terms of prognostic accuracy in patients treated with curative resection for solitary HBV-related HCC.

Based on prognostic factors identified previously (5-10), prognostic risk calculators were developed to predict

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prognosis in patients undergoing curative resection for solitary HBV-related HCC. The accuracy of the prognostic risk calculator was compared with that of the TNM and CLIP scoring systems.

Materials and methods

Patients and tumor samples. HCC tumor samples were acquired from the Department of Patholofy, Fuzhou General Hospital (Fujian, China) between February 2003 and October 2012. The inclusion criteria were: i) Single tumor lesion; ii) without any distant metastasis, ascites or hepatic encephalopathy; iii) 0-1 Eastern Cooperative Oncology Group score (17) prior to surgery; iv) pathologically confirmed primary HCC following surgery; v) complete clinical records and follow-up data; vi) radical resection between 2003 and 2012; and vii) HBV DNA load (IU/ml) $\leq 10^4$. The exclusion criteria were: i) Preoperative anticancer treatments; ii) concomitant positive hepatitis C virus antibody; iii) incomplete clinical data or tissue biopsy specimens for extra analysis; and iv) history of inflammatory disease or active concomitant infection.

The program was approved by the Institutional Ethics Committee of Fuzhou General Hospital and informed consent was signed by all the patients.

Clinicopathological and laboratory examination. The diagnoses of Edmonson grade (18), tumor encapsulation, vascular invasion and maximal tumor diameter were based on histological examination of the surgical specimens obtained following liver resection. Blood samples were measured prior to treatment for platelet count, α-fetoprotein (AFP), albumin, neutrophil, lymphocyte, white blood cell count and prothrombin time. The cut-off point was the highest Youden Index, which was selected as the optimal threshold value (6).

Immunohistochemical (IHC) analysis. Formalin-fixed paraffin-embedded sections (4-mm thick) were heated to 60°C for 2 h, prior to being deparaffinized with xylene and rehydrated in ethanol through a descending series of concentrations (100, 100, 85 and 75%). The immunohistochemical methods described by Hemda Schmilovitz-Weiss *et al* (19) were used to analyze the expression of Ki67, using an anti-Ki67 antibody obtained from Fuzhou Maixin Biotech Co., Ltd. (Fuzhou, China). Antigenic retrieval was performed by submerging the sections into EDTA antigenic retrieval buffer and microwaving (100°C, 10 min.). The sections were incubated with an anti-Ki67 antibody (dilution, 1:200; cat. no. MAB-0672; Fuzhou Maixin Biotech Co., Ltd.) for 1 h at room temperature. Following washing, the tissue sections were treated with a ready-to-use anti-rabbit/mouse secondary antibody (1:50; cat. no. KIT-9903; Fuzhou Maixin Biotech Co., Ltd.) for 0.5 h at room temperature. 3,3'-diaminobenzidine was used as the chromogen (5 min at room temperature). The tissue sections were immersed in 3-amino-9-ethyl carbazole, counterstained with 10% Mayer's hematoxylin for 5 min at room temperature prior to being dehydrated and mounted in Crystal Mount. A light microscope (magnifications, x100 or x200) was used. The same method was used to analyze the expression of DNA Topo II-α using an anti-DNA Topo II-α antibody (dilution, 1:200; cat. no. MAB-0588; Maixin Company, Fuzhou,

China). Semi-quantitative IHC detection was used to calculate Topo II-α protein level with a 4-point scale (positive tumor cell counts, graded from 0 to 3: 0=none, 1= ≤25%, 2=25-50 and 3= ≥50%). HCC tissue samples graded 0 or 1 represented low Topo II-α expression, whereas those graded 2 or 3 were regarded as a high Topo II-α expression. Ki67 was scored as a percentage of positively stained cells: <10%='-'; 10-25%='+'; 26-50%='++'; 51-75%='+++'; and >75%='++++'. HCC tissue samples with '-' or '+' Ki67 expression suggested low Ki67 expression; and samples with '++', '+++', or '++++' Ki67 expression represented high Ki67 expression.

Follow-up. Patients who underwent hepatectomy between February 2003 and October 2012 were subjected to close clinical observation (abdominal ultrasound, AFP and liver function test) at 2-to 4-month intervals. The patients were followed up until January 1, 2015.

Statistical analysis. All statistical analyses were two-sided and P<0.05 was considered to indicate a statistically significant difference. Univariate risk ratios and their 95% confidence intervals (95% CI) were calculated using Cox proportional hazards regression (HR) models with stepwise selection. Cox multivariate proportional HR analysis was performed using forward selection method with all the variables included for their prognostic significance by univariate analysis with stepwise selection (P<0.05). Based on the outcomes of the multivariate Cox proportional hazard model, the prognostic risk calculator was formulated using R (version 3.2.1; https://www.r-project.org). The effect of the variables with the highest coefficient (absolute value) was assigned 100 points. The points were added across independent variables to obtain the total score, which was converted to predicted probabilities. The predictive performance of the prognostic risk calculator was evaluated by concordance index (C-index) and its calibration using 1,000 bootstrap samples to decrease the overfit bias. For clinical use of the model, the total scores of each patient were calculated based on multivariate analyses. The receiver operating characteristic (ROC) analysis was used to calculate the optimal cutoff values determined by maximizing the Youden index (sensitivity + specificity-1). A Kaplan-Meier curve comparing patients with high risk (score ≥ cut off point) and low risk (score < cutoff point) was obtained to show the differences (20). Analyses were performed using R version 3.2.1 and SPSS version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Demographic features and clinicopathological data. The clinical demographics, laboratory and pathological data and immunohistochemistry of Topo II-α and Ki67 are summarized in Table I. Topo II-α and Ki67 were detected in the nuclei of tumor cells (Fig. 1). The last follow-up of patients in the present study was on May 31, 2015. The median survival rate of patients was 69 months (95% CI 53.8-84.2 months). The 1-, 3- and 5-year cumulative survival rates were 86.2, 66.2 and 53.8%, respectively.

Univariate and multivariate analyses of overall survival rates. As illustrated in Table II, the COX regression univariate

Table I. Clinicopathological characteristics of 426 cases of hepatocellular carcinoma.

Characteristic	Cases (n=426)		(IQR) median	Mean ± standard deviation
	n	%		
Sex				
Male	378	88.7		
Female	48	11.3		
TNM stage				
I/II	292	68.5		
IIIa	134	31.5		
Site				
Left	101	23.7		
Right	325	76.3		
Edmondson-Steiner classification				
I-II	83	19.5		
III-IV	343	80.5		
Tumor encapsulation				
Absent	172	40.4		
Present	254	59.6		
Vascular invasion				
Absent	139	32.6		
Present	287	67.4		
Child-Pugh grade				
A	259	60.8		
B	167	39.2		
Ki67 expression				
Low	185	43.4		
High	241	56.6		
Topo II-α expression				
Low	236	55.4		
High	190	44.6		
Age (years)			53 (45-61)	52±12
≤55	205	58.1		
>55	148	41.9		
Maximal tumor diameter (cm)			5 (2.5-8.0)	5.75±4.201
≤5	219	51.4		
>5	207	48.6		
Serum AFP level (ng/ml)			149.0 (8.0-1,000)	4428.34±16919.153
≤400	215	60.9		
>400	138	39.1		
NLR			2.0 (1.0-3.0)	3.24±3.810
≤1.62	125	29.3		
>1.62	301	70.7		
PLR			94 (68-133.25)	110.98±71.996
≤114.4	281	66		
>114.4	145	34		
PNI			50 (46-54)	50.34±11.441
≤49.42	207	48.6		
>49.42	219	51.4		
BMI			22 (20-25)	22.65±3.157
≤23.296	256	60.1		
>23.296	170	39.9		

Table I. Continued.

| | Cases (n=426) | | | |
Characteristic	n	%	(IQR) median	Mean ± standard deviation
Neutrophil count (x10^9/l)			4.0 (3.0-6.0)	5.08±3.941
Lymphocyte count (x10^9/l)			2.00 (1.0-2.0)	2.05±2.046
Serum albumin (g/l)			40 (37-44)	40.23±5.560
Height (m)			1.68 (1.64-1.72)	1.675±0.06
Weight (kg)			63 (56-70)	63.66±10.088
Platelet count (x10^9/l)			183.5 (135.0-223.0)	186.31±76.164

IQR, interquartile range; TNM, tumor-node-metastasis; Topo II-α, topoisomerase II-α; AFP, α-fetoprotein; NLR, neutrophil to lymphocyte ratio [=neutrophil count (10^9/l)/lymphocyte count (10^9/l)]; PLR, platelet to lymphocyte ratio [=platelet count (10^9/l)/lymphocyte count (10^9/l)]; PNI, prognostic nutritional index [=serum albumin (g/l) + 5x lymphocyte count (10^9/l)]; BMI, body mass index [=weight (kg)/height (m)^2]. Continuous variables were expressed as mean with standard deviation or median with interquartile range.
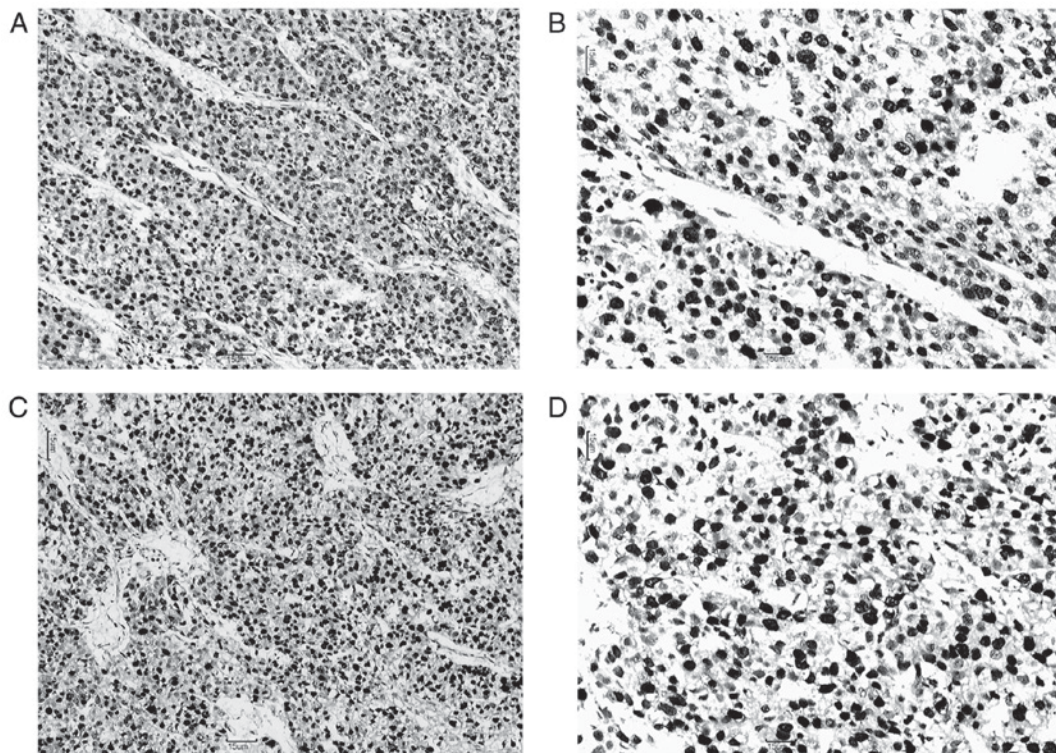

Figure 1. Nuclear Ki67 staining in a case of HCC. Increased expression of Ki67 in HCC (A) magnification, x100 and (B) x200. Nuclear Topo II-α staining in a case of HCC. Increased expression of Topo II-α in HCC (C) magnification, x100 and (D) x200. HCC, hepatocellular carcinoma; Topo II-α, topoisomerase II-α.

analysis indicated that 13 factors were associated with OS. The result demonstrated that the risk of mortality increased with vascular invasion, TNM stage IIIa, maximal tumor diameter >5.0 cm, AFP >400 ng/ml, high levels of Topo II-α and Ki67, NLR >1.62, PLR >114.4 and Child-Pugh grade B. The risk of mortality decreased with age >55 years, tumor encapsulation, Edmonson grade I-II, PNI >49.42 and BMI >23.296. Multivariate analysis was performed to develop a reduced model using the stopping rule of Akaike's information criterion with these significant factors.

The results demonstrated that patients with present vascular invasion (HR: 3.70; 95% CI: 2.18-6.28), AFP >400 ng/ml (HR: 1.47; 95% CI: 1.09-1.98), increased levels of Topo II-α (HR: 1.38; 95% CI: 1.02-1.87), NLR >1.62 (HR: 1.69; 95% CI: 1.13-2.53) and Child-Pugh grade B (HR: 3.26; 95% CI: 2.31-4.60) tended to exhibit decreased survival rates compared with patients without vascular invasion, AFP ≤400 ng/ml, decreased levels of Topo II-α, NLR ≤1.62 and Child-Pugh grade A, respectively. Patients with tumor encapsulation (HR: 0.71; 95% CI: 0.52-0.96), Edmonson grade I-II (HR: 0.54; 95% CI: 0.32-0.93), PNI >49.42 (HR: 0.71; 95% CI: 0.52-0.97) tended to live longer compared with the patients without tumor encapsulation, with Edmonson grades III-IV, or with PNI ≤49.42, respectively.

Table II. Univariate/multivariate analyses of factors associated with survival.

Characteristic	Univariate analyses			Multivariate analyses		
	HR	95% CI	P-value	HR	95% CI	P-value
Sex						
Male	Reference	0.41-1.13	0.138			
Female	0.68					
Age						
≤55	Reference	0.69-1.24	0.615			
>55	0.93					
Tumor encapsulation						
Absent	Reference	0.31-0.55	<0.001	Reference	0.52-0.96	0.025
Present	0.41			0.71		
Vascular invasion						
Absent	Reference	4.81-12	<0.001	Reference	2.18-6.28	<0.001
Present	7.6			3.7		
TNM stage						
I-II	Reference	1.78-3.16	<0.001			
IIIa	2.37					
Maximal tumor diameter (cm)						
≤5.0	Reference	1.70-3.06	<0.001			
>5.0	2.28					
Edmondson-Steiner classification						
III-IV	Reference	0.18-0.48	<0.001	Reference	0.32-0.93	0.025
I-II	0.3			0.54		
Site						
Left	Reference	0.99-2.09	0.055			
Right	1.44					
AFP (ng/ml)						
≤400	Reference	1.60-2.84	<0.001	Reference	1.09-1.98	0.012
>400	2.13			1.47		
Topo II-α						
Low	Reference	1.60-2.86	<0.001	Reference	1.02-1.87	0.035
High	2.14			1.38		
Ki67						
Low	Reference	1.56-2.90	<0.001			
High	2.13					
NLR						
≤1.62	Reference	1.78-3.85	<0.001	Reference	1.13-2.53	0.011
>1.62	2.62			1.69		
PLR						
≤114.4	Reference	1.67-2.96	<0.001			
>114.4	2.22					
PNI						
≤49.42	Reference	0.37-0.66	<0.001	Reference	0.52-0.97	0.029
>49.42	0.49			0.71		
BMI						
≤23.296	Reference	0.53-0.98	0.034			
>23.296	0.72					

Table II. Continued.

Characteristic	Univariate analyses			Multivariate analyses		
	HR	95% CI	P-value	HR	95% CI	P-value
Child-Pugh grade						
A	Reference	4.57-8.63	<0.001	Reference	2.31-4.60	<0.001
B	6.28			3.26		

Multivariate analysis, Cox proportional hazards regression model. Variables were adopted for their prognostic significance by univariate analysis with enter-stepwise selection (P<0.05). HR, hazards regression; CI, confidence interval; TNM, tumor-node-metastasis; AFP, α-fetoprotein; Topo II-α, topoisomerase II-α; NLR, neutrophil to lymphocyte ratio [=neutrophil count (10^9/l)/lymphocyte count (10^9/l)]; PLR, platelet to lymphocyte ratio [=platelet count (10^9/l)/lymphocyte count (10^9/l)]; PNI, prognostic nutritional index [=serum albumin (g/l) + 5x lymphocyte count (10^9/l)]; BMI, body mass index [=weight (kg)/height (m)^2].

Prognostic risk based on multivariate analyses. Based on multivariate analyses, the following equation was constructed: Prognostic OS score=26.49 x tumor encapsulation (present=0; absent=1) + 100.00 x vascular invasion (absent=0; present=1) + 46.40 x Edmonson grade (I-II=0; III-IV=1) + 29.32 x AFP (≤400=0; >400=1) + 24.72 x Topo II-α (low=0; high=1) + 40.18 x NLR (≤1.62=0; >1.62=1) + 25.99 x PNI (>49.42=0; ≤49.42=1) + 90.32 x Child-Pugh grade (A=0; B=1).

The optimum cutoff value of the total score was set to 234.47 by maximizing the Youden index [sensitivity=0.78; specificity=0.77; area under the curve (AUC)=0.83] and the sample was divided into high-risk (>234.47) and low-risk groups (≤234.47). Kaplan-Meier curves demonstrated that the OS rate of the low-risk group was increased compared with that of the high-risk group (Fig. 2).

Validation of prognostic accuracy. The prognostic risk calculator of OS rate was built on the basis of tumor encapsulation, vascular invasion, Edmondson-Steiner classification, AFP, Topo II-α, NLR, PNI and Child-Pugh grade with a C-index (prior to adjustment) of 0.81 (95% CI: 0.78-0.84) and a bootstrap-corrected C-index of 0.81. The calibration curve giving the survival rate probability in 5 years following the surgery indicated an optimum consistency between prediction and actual observation in our model. The curve showing the prognostic risk calculator of OS rates in 3 years demonstrated that the predictive effect of our model was relatively weak during this period (Fig. 3A and B).

Comparison of discriminatory powers. The predictive power of the model from the present study, the 7th TNM staging system and CLIP were compared by ROC curve analysis. The model was a significant improvement compared with the competing models: The AUC was increased compared with that of the 7th TNM staging system or CLIP (0.83 vs. 0.62-0.77. P<0.001; Fig. 4).

Discussion

In the present study, a prognostic risk calculator based on multivariate analysis of patients undergoing curative resection for solitary HCC was developed. The prognostic model was built on the basis of tumor encapsulation, vascular
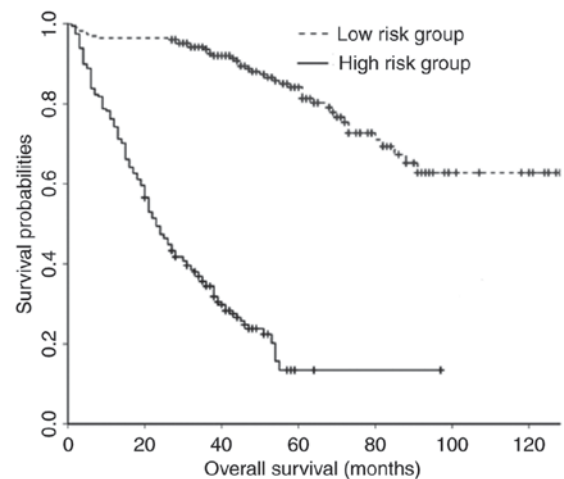

Figure 2. Survival rate curves comparing patients in the high-risk (total score >234.47) and low-risk groups (total score ≤234.47).

invasion, Edmondson-Steiner classification, AFP, Topo II-α, NLR, PNI and Child-Pugh grade with a C-index (prior to adjustment) of 0.81 (95% CI: 0.78-0.84) and a bootstrap-corrected C-index of 0.81. The calibration plots of the cohorts revealed association between the predicted and the actual survival rates.

The American Joint Committee on Cancer (AJCC) TNM system and CLIP are widely used staging systems for HCC. The traditional TNM staging system concentrates on the presentation of the neoplasm mostly, without adequately reflecting the biological characteristics of HCC (11). In a prospective study of 195 patients reported by Cillo *et al* (21), CLIP was associated with improved prognostic ability compared with the AJCC/TNM 2002 system in operative patients. The multi-dimensional model presented in the present study incorporates not only each individual pre-treatment data including liver function (Child-Pugh grade) and laboratory parameters (AFP, NLR and PNI), but also data from pathological reports confirmed following surgery, including tumor encapsulation, tumor staging (vascular invasion and TNM stage), Edmonson-Steiner grade and tumor biomarkers (Topo II-α). A comparison of this prognostic risk calculator with the CLIP or 7th TNM staging system demonstrated that the new ROC
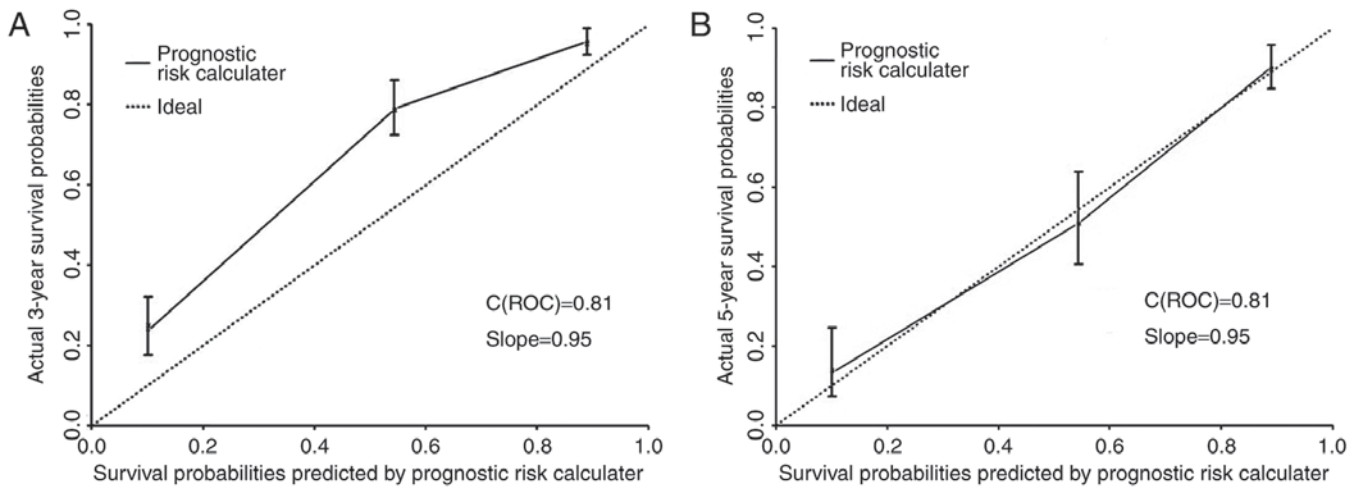
Figure 3. Calibration curves for (A) 3- and (B) 5-year prediction of overall survival rates. C(ROC), concentrated receiver operating characteristic.
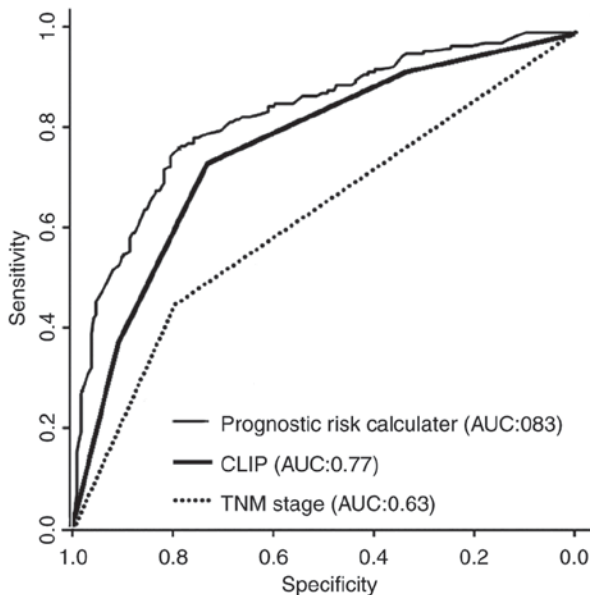

Figure 4. ROC analysis of survival rates at 5 years in the cohort using our model vs. AJCC/UICC staging and CLIP scoring systems. The model proposed in the present study improved on competing models: The AUC was increased compared with that of the 7th TNM staging system or CLIP [0.83 vs. 0.62 (P<0.001) and 0.83 vs. 0.77 (P<0.001), respectively]. ROC, receiver operating characteristic; AJCC, American Joint Committee on Cancer; UICC, Union for International Cancer Control; CLIP, Cancer of the Liver Italian Program; AUC, area under the curve; TNM, Tumor-Node-Metastasis.

curve was associated with increased sensitivity and specificity for predicting OS.

Previous studies have demonstrated that tumor vascular invasion is correlated with poor prognosis (22). Portal vein tumor thrombus and microvascular invasion are important risk factors for long-term survival rates of HCC (23,24). The multivariate analysis performed in the present study indicated that the HR of vascular invasion for OS was 3.70 and was the highest of all independent risk factors.

A clear margin is difficult when a solitary HCC lacks a capsule surrounding the tumor. Advanced surgical risks and poorer prognosis following liver resection were observed

in such patients. Therefore, it was important to consider the complete tumor capsule for a solitary HCC for surgical safety and long-term survival rate. As expected, tumor capsule was an independent prognostic factor in the present study.

Oishi *et al* (25) revealed that differentiation and angiogenic activity, proliferation, tumor size, vascular invasion and AFP ratio were negatively associated. However, Edmonson-Steiner grade was not included in any previous staging system and represents a key variable in the model in the present study.

Liver function is affected by comorbidities, including cirrhosis, HBV and HCV, and is therefore considered to predict patient outcomes [CLIP, BCLC (Barcelona Clinic Liver Cancer) and JIS (Japan Integrated Staging Score)]. In the present study, Child-Pugh grade B (HR: 3.26; 95% CI: 2.31-4.60) represented a negative prognostic factor for survival rate following radical hepatectomy and was associated with a poorer survival rate.

Cumulative evidence suggests that host inflammatory reaction serves a significant function in carcinogenesis via sustained proliferative signaling, angiogenesis and by promoting invasion and metastasis (26). The prognostic risk calculator proposed in the present study comprises comprehensive laboratory indices including inflammation-based indices (NLR and PNI), which were previously demonstrated to be independent risk factors for HCC prognosis. Emerging evidence suggests that NLR has prognostic value for patients with HCC (5). Pinato *et al* (7) demonstrated that PNI is an independent predictor of poor overall survival rate in patients with HCC at different stages and liver functional status. Recently, Fu *et al* (27) built a nomogram based on inflammatory biomarkers for resectable HCC. However, the nomogram only contained NLR not PNI. The present study demonstrated that PNI and NLR were independent predictors of OS. Multiple clinical trials have demonstrated the prognostic value of other laboratory markers of systemic inflammation including C-reactive protein and modified Glasgow prognostic score in cancer populations (16,28,29). However, in numerous hospitals, particularly those with limited medical resources, the level of serum C-reactive protein is not regularly evaluated due to the need for advanced equipment. NLR and PNI are easily determined from comprehensive blood testing and

represent appropriate laboratory markers to predict survival rates.

With advances in understanding of cancer biology, the function of biomarkers in predicting survival rates has garnered increased attention. The present study provided additional data confirming the reliability of the results. Tumor cell proliferation status is an important parameter that reflects tumor biology and directly affects the prognosis and efficiency of treatment (9,10). Topo II-α (9) is a commonly used proliferation marker that serves a function in DNA replication and chromosomal segregation by unwinding the DNA double helix. It is crucial for the active survival of cells and represents a common biomarker and target for multiple anti-cancer agents (30,31). Determination of Topo II-α expression facilitates the prognosis of overall survival rates of patients and their reaction to therapy (32). The prognostic value of Topo II-α has been discussed in different studies (33,34). In our survival rate models, Topo II-α was a key variable with an HR of 1.38 for OS. Ki67 is a traditional proliferation marker found within the cell nucleus (35) and is associated with poor prognosis in HCC (10). Univariate but not multivariate analysis indicated that Ki67 was associated with OS in the cohort of the present study.

The use of laboratory indices and tumor biomarkers as adjuncts to the tumor staging system enables the formulation of a personalized therapeutic strategy. Nevertheless, multiple limitations to our prognostic risk calculation exist. IHC analysis is not routinely used globally. Furthermore, since the patients comprised predominantly an HBV-prevalent Chinese population at a single institution and represented single-tumor patients, the outcomes are unreliable. External validation in a larger patient population is required. Additional studies with data derived from multiple centers will be necessary to investigate differences in outcomes.

To conclude, the prognostic models in the present study are widely available, user-friendly, low-cost and accurate for patients undergoing curative resection for solitary HCC. This is the first clinical evaluation of multiple parameters incorporating individual liver function, tumor stage, inflammatory indices and biomarkers, to the best of the authors' knowledge. These risk equations can be used for patient counseling and management, in addition to prognostic evaluation.

Acknowledgements

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