Development of a clinical scoring model to predict the overall and relapse-free survival of patients with hepatocellular carcinoma following a hepatectomy

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Abstract. Hepatocellular carcinoma (HCC) is a highly lethal disease, and surgical resection is one of the major treatment methods used. However, to date, at least to the best of our knowledge, there is no effective prognostic scoring system for the overall survival (OS) and relapse-free survival (RFS) of patients following hepatectomy. The present study developed a low-cost and easy-to-use model based on the clinicopathological characteristics of patients with HCC for assessment of outcome prediction and risk stratification. A total of 690 patients with HCC undergoing surgery were included and randomly divided into two cohorts (n=345). Cox regression analysis was conducted to investigate the association between the clinicopathological and treatment features, and patient survival. Multivariate analysis revealed that ascites, vascular tumor thrombus, low tumor differentiation and extrahepatic metastasis were independent risk factors for OS. Extrahepatic metastasis and multiple tumors were independent risk factors to predict tumor recurrence. These variables were weighted to construct the ascites, vascular tumor thrombus, low tumor differentiation, extrahepatic metastasis and multiple tumors (AVLEM) score based on the cumulative incidence (CuI) of the aforementioned variables, and the patients were classified into grade 0 (CuI=0), grade 1 (CuI=1 for OS and CuI ≥1 for RFS), and grade 2 (CuI ≥2) subgroups, respectively. Kaplan-Meier analysis revealed that the OS and RFS differed significantly among the subgroups; however, the survival rate between the two cohorts did not exhibit any marked differences. On the whole, the present study demonstrates that with this AVLEM scoring system, patients with HCC with a high score had a poor OS and RFS; thus, it is suggested that such patients undergo imaging examinations following a hepatectomy more frequently.

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Abbreviations: HCC, hepatocellular carcinoma; CuI, cumulative incidence; RFS, relapse-free survival; OS, overall survival; AVLEM, ascites, vascular tumor thrombus, low tumor differentiation, extrahepatic metastasis and multiple tumors; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; CT, computed tomography; MRI, magnetic resonance imaging; AFP, alpha-fetoprotein; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactic dehydrogenase; TBIL, total bilirubin; TC, total cholesterol; BDG, biliary duct and gallbladder invasion; BDTO, blood transfusion during operation; PLT, platelet

Key words: hepatocellular carcinoma, overall survival, relapse-free survival, score model

Introduction

Primary liver cancer is the third leading cause of cancer-related mortality worldwide, and hepatocellular carcinoma (HCC) is the most common type of liver cancer, comprising 75-85% of cases (1). In Asia, liver cancer is the fifth most commonly diagnosed type of cancer with a steady annual increase in incidence and is the second leading cause of cancer-related mortality (2). Although resection constitutes one of the optimal methods for the treatment of patients with HCC, in the majority of Asian centers, due to a higher volume of cases and limited expertise, the overall survival (OS) rate of patients remains unsatisfactory and tumor recurrence is frequent. Therefore, identifying the risk factors for the OS and relapse-free survival (RFS) of patients with HCC following a hepatectomy will help to determine other therapeutic and management strategies. At present, there are prognostic prediction strategies based on gene expression differences (3-5) and mutations (6,7); however, these prediction models require additional detection methods which are associated with high costs, and are not suitable for all patients with HCC undergoing hepatectomy. Thus, an accurate model based on clinicopathological data is warranted in order to be able to predict the OS and the probability of tumor recurrence following curative resection.

The present study collected the clinicopathological and treatment data of 690 patients with HCC and randomly divided the patients into two cohorts, namely the training and

validation sets (6). Univariate and multivariate analyses were performed to identify the prognostic risk events for OS and RFS. In addition, a scoring system was constructed by counting the cumulative occurrences of survival-associated risk events. The prognosis prediction scoring system based on the pathological factors is a low-cost and easy-to-use tool specifically developed for the prediction of OS and RFS, and may aid in the risk stratification of patients with HCC in clinical practice, as well as in clinical trials.

Patients and methods

Patients. The present study included 690 patients with HCC who underwent surgery at the Sun Yat-Sen Memorial Hospital (Guangzhou, China) between January, 2013 and December, 2019 (ethics approval no. SYSEC-KY-KS-2019-039). Curative resection was defined as the complete removal of the liver tumor tissues with no evidence of residual microscopic tumors. Serum hepatitis B surface antigen (HBsAg), hepatitis e antigen (HBeAg) and hepatitis B virus (HBV) DNA levels were determined using an ELISA kit (Abbott) and real-time polymerase chain reaction using respective kits (Sansure Biotech), respectively. Cirrhosis was clinically defined based on the findings on the ultrasound, computed tomography (CT), upper gastrointestinal endoscopy and laboratory tests. Patients with a history of anticancer therapy prior to surgery, those with other types of malignant tumors, or those who received previous locoregional therapies such as hepatectomy, radiotherapy, transarterial chemoembolization, radiofrequency ablation, percutaneous ethanol injection and patients who were lost to follow-up following the hepatectomy were excluded from the study.

Surgery. Overall, the evaluation of the general condition and liver function reserve of the patients was performed before surgery. Standard operative techniques for hepatectomy were used. The tumor was completely removed to ensure that the surgical margin was free of any residual tumor, while sufficient functional liver tissue was retained to compensate for liver function, and reduce operative mortality and post-operative complications. Selective clamping of the portal vein and hepatic artery was performed when feasible (8).

Clinicopathological information. The relevant clinicopathological data were extracted retrospectively from the electronic medical records of the patients with HCC. HCC was diagnosed according to the Guidelines for Diagnosis and Treatment of Primary Liver Cancer in China, including ultrasonography, CT, magnetic resonance imaging (MRI), digital subtraction angiography, nuclear medical imaging, liver puncture biopsy, serological molecular markers and pathological diagnosis. The TNM stage was judged according to the eighth Edition of the American Joint Committee on Cancer (AJCC) TNM Staging for Liver Tumors. The cut-off points for age, pre-operative serum alpha-fetoprotein (AFP), post-operative AFP, albumin (ALB), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactic dehydrogenase (LDH), total bilirubin (TBIL), total cholesterol (TC) and platelet (PLT) levels before surgery were 50 years, 200 ng/ml, 25 ng/ml, 50 g/l, 100 μ/l, 40 μ/l, 35 μ/l, 252 μ/l, 22.2 μmol/l, 6 mmol/l and $125x10^9$/l, respectively, according to clinical thresholds.

Follow-up. Post-operative follow-up was scheduled every 3 months with a chest CT scan or an abdominal MRI for the first 2 years and every 6 months thereafter. The primary endpoints of the study were RFS, which was defined as the time from randomization to the first documented tumor recurrence, and OS, which was defined as the time from randomization to death by any causes. Tumor recurrence was suspected on the detection of new hepatic lesions on an ultrasound, dynamic CT scan, or MRI. Further investigations (such as a chest CT scan, full-body bone scan and positron emission tomography-CT) were performed when there was a clinical suspicion of extrahepatic metastases.

Statistical analysis. Continuous variables that conformed to the Gaussian distribution are expressed as the mean ± standard deviation and compared using the Student's t-test. Otherwise, they are expressed as the median and interquartile range, and analyzed using the non-parametric Wilcoxon rank-sum test. Categorical variables are expressed as percentages and were compared using the χ^2 test. The Kaplan-Meier method followed by comparisons with the log-rank tests was used to calculate the OS and RFS rates. Clinicopathological and treatment variables found to bear prognostic significance ($P<0.1$) in the univariate analysis were entered into a Cox multivariate proportional hazards model (95% confidence interval) to determine the independent association with survival and recurrence ($P<0.2$ in both cohorts were considered to be statistically significant) (9,10). $P<0.05$ was considered to indicate a statistically significant difference. Statistical analysis was carried out using SPSS version 21.0 software (IBM Corp.).

Results

Clinicopathological and treatment characteristics. In order to illustrate the subsequent statistical results are repeatable, a total of 690 patients with HCC underwent curative resection were randomly assigned to the training and validation groups, each group containing 345 patients (groups A and B). To validate the randomness of the grouping, the clinicopathological characteristics and treatments of the two groups were compared and the significant differences were not found ($P>0.1$), which declared the random allocation valid (Table I).

Univariate and multivariate analysis for overall survival. COX regression was conducted to analyze the associations between the patient variables and OS in groups A and B (Tables II and III). Univariate regression analysis revealed that abnormal ALB, AST and ALP levels before surgery, abnormal AFP levels before and after surgery, ascites, tumor size, tumor multiplicity, TNM stage, tumor differentiation level, capsule invasion, vascular tumor thrombus, gross tumor thrombus, vascular invasion, biliary duct and gallbladder invasion (BDG), extrahepatic metastasis and blood transfusion during operation (BDTO) were prognostic factors for OS in the two groups. When factors associated with outcome in the univariate analyses ($P<0.1$) were incorporated into a multivariate model analysis, with $P<0.2$ set as the marker for significant differences in both groups, only

Table I. Clinicopathological characteristics and treatments of the patients.

Variable	Group A	Group B	P-value
Clinical characteristics			
Patients (n)	345	345	-
Male (n)	300 (87.0 %)	296 (85.8 %)	0.657
Age (years)	53.0 (42.5-62.0)	52.0 (44.0-60.0)	0.638
Alcohol consumption (n)	58 (16.9%)	65 (19.0%)	0.475
HBsAg (n)	291 (84.3%)	294 (85.2%)	0.751
HBeAg (n)	47 (17.6%)	35 (13.0%)	0.140
HBV DNA (lg, copies/ml)	4.4 (3.0-5.6)	4.1 (3.0-5.5)	0.277
ALB (g/l)	41.3 (38.2-44.2)	41.7 (38.2-44.5)	0.355
ALT (U/l)	39.0 (27.0-64.0)	37.0 (25.3-55.0)	0.121
AST (U/l)	45.0 (32.0-70.0)	43.0 (31.0-65.0)	0.245
TBIL (μmol/l)	14.7 (11.4-19.9)	14.6 (11.1-20.4)	0.980
ALP (U/l)	94.0 (74.0-127.0)	96.5 (75.0-125.0)	0.788
LDH (U/l)	224.5 (189-269.8)	225.0 (185.0-279.5)	0.959
TC (mmol/l)	4.8 (4.2-5.6)	5.0 (4.3-5.8)	0.479
PLT ($x10^9$/l)	178.0 (139.0-243.0)	183.5 (135.0-250.5)	0.967
AFP (ng/ml, BS)	187.6 (10.2-3493.5)	177.0 (9.3-3310.0)	0.933
AFP (ng/ml, AS)	12.2 (4.4-157.5)	14.3 (4.3-174.7)	0.470
Pathological characteristics			
Cirrhosis (n)	258 (74.8%)	259 (75.1%)	0.929
Ascites (n)	57 (16.7%)	55 (16.1%)	0.836
Tumor number (n)			
1	259 (75.1%)	262 (75.9%)	0.690
2	39 (11.3%)	45 (13.0%)	
3	10 (2.9%)	9 (2.6%)	
≥4	37 (10.7%)	29 (8.4%)	
Tumor size (cm)	5.5 (3.5-10.0)	6.0 (3.2-10.0)	0.982
TNM stage (n)			
I	130 (37.7%)	115 (33.3%)	0.280
II	91 (26.4%)	113 (32.8%)	
III	106 (30.7%)	103 (29.9%)	
IV	18 (5.2%)	14 (4.1%)	
Differentiation (n)			
Low	131 (38.3%)	140 (41.2%)	0.526
Median	149 (43.6%)	134 (39.3%)	
High	62 (18.1%)	67 (19.6%)	
Capsule invasion (n)	234 (67.8%)	226 (65.9%)	0.590
Vascular tumor thrombus (n)	189 (54.8%)	189 (55.1%)	0.933
Gross tumor thrombus (n)	67 (19.4%)	62 (18.0%)	0.626
Vascular invasion (n)	205 (59.4%)	213 (61.7%)	0.533
BDG (n)	14 (4.1%)	13 (3.8%)	0.843
Extrahepatic metastasis (n)	29 (8.4%)	24 (7.0%)	0.475
Treatment			
Pre-operative antiviral (n)	121 (41.6%)	129 (44.0%)	0.575
Post-operative antiviral (n)	234 (80.4%)	225 (76.5%)	0.253
BTDO (ml)	300.0 (150.0-800.0)	400.0 (150.0-700.0)	0.696
TACE (n)	170 (53.8%)	157 (48.6%)	0.189
Overall chemotherapy (n)	51 (17.0%)	41 (13.3%)	0.204
Portal vein chemotherapy (n)	58 (19.5%)	50 (16.2%)	0.291

HBV, hepatitis B virus; HBsAg, HBV surface antigen; HBeAg, HBV e antigen; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALP, alkaline phosphatase; LDH, lactic dehydrogenase; TC, total cholesterol; PLT, platelet; AFP, α-fetoprotein; BS, before surgery; AS, after surgery; BDG, Biliary duct and gallbladder invasion; BTDO, blood transfusion during operation; TACE, transarterial chemoembolization.

Table II. COX regression analysis of prognostic variables for overall survival in group A.

	Univariate		Multivariate	
Variables	HR (95% CI)	P-value	HR (95% CI)	P-value
Clinical characteristics				
Sex (male/female)	0.851 (0.485-1.491)	0.572		
Age, years (>50/≤50)	0.837 (0.574-1.221)	0.355		
Alcohol consumption (yes/no)	1.951 (1.233-3.087)	0.004	2.145 (1.039-4.429)	0.039
HBsAg (+/-)	1.016 (0.597-1.729)	0.954		
HBeAg (+/-)	1.274 (0.765-2.121)	0.352		
HBV DNA (+/-)	1.192 (0.717-1.979)	0.498		
ALB, g/l (≥40/<40)	0.639 (0.433-0.945)	0.025	0.630 (0.350-1.134)	0.123
ALT U/l (≥40/<40)	1.357 (0.922-1.999)	0.122		
AST, U/l (≥35/<35)	1.865 (1.164-2.986)	0.009	1.405 (0.652-3.029)	0.385
TBIL, μmol/l (≥22.2/<22.2)	1.353 (0.850-2.154)	0.202		
ALP, U/l (≥100/<100)	1.877 (1.274-2.764)	0.001	1.307 (0.685-2.494)	0.416
LDH, U/l (≥252/<252)	1.011 (0.620-1.647)	0.966		
TC, mmol/l (≥6/<6)	1.667 (0.993-2.800)	0.053	1.519 (0.770-2.994)	0.227
PLT, (≥125x10^9/<125x10^9/l)	1.220 (0.725-2.053)	0.453		
AFP, ng/ml (≥200/<200, BS)	1.677 (1.132-2.484)	0.010	1.167 (0.557-2.445)	0.683
AFP, ng/ml (≥25/<25, AS)	2.314 (1.542-3.473)	0.001	1.277 (0.589-2.768)	0.536
Pathological characteristics				
Cirrhosis (yes/no)	1.578 (0.995-2.502)	0.052	2.128 (1.015-4.461)	0.046
Ascites (yes/no)	1.757 (1.115-2.769)	0.015	1.913 (0.864-4.233)	0.110
Tumor size, cm (>5/≤5)	2.019 (1.369-2.976)	0.001	0.972 (0.409-2.310)	0.950
Tumor number (multiple/single)	2.185 (1.476-3.236)	0.001	1.131 (0.558-2.292)	0.732
TNM stage (III + IV/I + II)	2.326 (1.595-3.391)	0.001	0.437 (0.119-1.600)	0.211
Differentiation (III + IV/I + II)	1.908 (1.310-2.778)	0.001	1.972 (1.047-3.714)	0.036
Capsule invasion (yes/no)	2.525 (1.580-4.037)	0.001	2.098 (0.939-4.686)	0.071
Vascular tumor thrombus (yes/no)	2.922 (1.947-4.450)	0.001	2.389 (1.126-5.068)	0.023
Gross tumor thrombus (yes/no)	2.774 (1.828-4.210)	0.001	1.325 (0.470-3.739)	0.595
Vascular invasion (yes/no)	2.334 (1.586-3.436)	0.001	2.099 (0.546-8.073)	0.281
BDG (yes/no)	4.324 (2.247-8.320)	0.001	2.332 (0.709-7.667)	0.163
Extrahepatic metastasis (yes/no)	2.677 (1.496-4.791)	0.001	2.979 (1.139-7.791)	0.026
Treatment				
Pre-operative antiviral (yes/no)	0.996 (0.678-1.464)	0.985		
Post-operative antiviral (yes/no)	1.160 (0.765-1.759)	0.486		
BTDO, ml (≥400/<400)	1.544 (1.051-2.269)	0.027	0.437 (0.216-0.886)	0.022
TACE (yes/no)	0.874 (0.592-1.290)	0.497		
Overall chemotherapy (yes/no)	0.530 (0.283-0.993)	0.048	0.340 (0.132-0.875)	0.025
Portal vein chemotherapy (yes/no)	0.885 (0.546-1.435)	0.621		

HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; HBsAg, HBV surface antigen; HBeAg, HBV e antigen; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALP, alkaline phosphatase; LDH, lactic dehydrogenase; TC, total cholesterol; PLT, platelet; AFP, α-fetoprotein; BS, before surgery; AS, after surgery; BDG, Biliary duct and gallbladder invasion; BTDO, blood transfusion during operation; TACE, transarterial chemoembolization.

ascites, vascular tumor thrombus, extrahepatic metastasis and the tumor differentiation level were independent risk factors for OS (Tables II and III).

Univariate and multivariate analysis for relapse-free survival. COX regression analysis was also conducted to determine the associations between variables and RFS in groups A and B (Tables IV and V). Univariate regression analysis revealed that the patients' age, abnormal ALB, AST and LDH levels before surgery, abnormal AFP levels before and after surgery, ascites, tumor size, tumor number, TNM stage, tumor differentiation level, capsule invasion, vascular tumor thrombus, gross tumor thrombus, vascular invasion, BDG, extrahepatic metastasis, antiviral therapy, BDTO and

Table III. COX regression of prognostic variables for overall survival in group B.

	Univariate		Multivariate	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
Clinical characteristics				
Sex (male/female)	1.046 (0.607-1.803)	0.870		
Age, years (>50/≤50)	1.032 (0.708-1.502)	0.871		
Alcohol consumption (yes/no)	1.013 (0.649-1.580)	0.956		
HBsAg (+/-)	1.254 (0.716-2.197)	0.428		
HBeAg (+/-)	1.713 (0.928-3.163)	0.085	1.122 (0.424-2.969)	0.816
HBV DNA (+/-)	1.602 (0.959-2.676)	0.072	1.726 (0.680-4.383)	0.251
ALB, g/l (≥40/<40)	0.560 (0.382-0.820)	0.003	0.800 (0.374-1.713)	0.566
ALT U/l (≥40/<40)	1.247 (0.856-1.816)	0.250		
AST, U/l (≥35/<35)	2.708 (1.666-4.399)	0.001	2.324 (0.676-7.992)	0.181
TBIL, μmol/l (≥22.2/<22.2)	0.910 (0.549-1.509)	0.715		
ALP, U/l (≥100/<100)	2.335 (1.589-3.432)	0.001	1.717 (0.836-3.526)	0.141
LDH, U/l (≥252/<252)	2.373 (1.529-3.683)	0.001	1.042 (0.417-2.607)	0.929
TC, mmol/l (≥6/<6)	1.210 (0.698-2.096)	0.497		
PLT, (≥125x10^9/<125x10^9/l)	0.981 (0.634-1.519)	0.933		
AFP, ng/ml (≥200/<200, BS)	1.698 (1.140-2.527)	0.009	1.001 (0.392-2.557)	0.998
AFP, ng/ml (≥25/<25, AS)	2.000 (1.348-2.969)	0.001	1.054 (0.419-2.652)	0.912
Pathological characteristics				
Cirrhosis (yes/no)	1.109 (0.716-1.718)	0.643		
Ascites (yes/no)	2.418 (1.542-3.792)	0.001	3.464 (1.310-9.164)	0.012
Tumor size, cm (>5/≤5)	2.684 (1.795-4.011)	0.001	0.738 (0.249-2.184)	0.583
Tumor number (multiple/single)	1.438 (0.959-2.156)	0.079	0.579 (0.212-1.581)	0.287
TNM stage (III+IV/I+II)	2.638 (1.826-3.813)	0.001	1.502 (0.291-7.744)	0.627
Differentiation (III+IV/I+II)	2.026 (1.397-2.940)	0.001	2.527 (1.179-5.419)	0.017
Capsule invasion (yes/no)	1.552 (1.038-2.321)	0.032	0.918 (0.410-2.056)	0.835
Vascular tumor thrombus (yes/no)	2.423 (1.625-3.611)	0.001	1.904 (0.741-4.892)	0.181
Gross tumor thrombus (yes/no)	3.126 (2.085-4.687)	0.001	2.701 (0.899-8.119)	0.077
Vascular invasion (yes/no)	2.410 (1.650-3.520)	0.001	0.521 (0.101-2.682)	0.436
BDG (yes/no)	3.709 (1.868-7.365)	0.001	1.987 (0.540-7.318)	0.302
Extrahepatic metastasis (yes/no)	1.923 (0.973-3.801)	0.060	3.706 (1.144-12.002)	0.029
Treatment				
Pre-operative antiviral (yes/no)	1.258 (0.868-1.823)	0.225		
Post-operative antiviral (yes/no)	1.544 (1.021-2.335)	0.039	0.860 (0.331-2.233)	0.757
BTDO, ml (≥400/<400)	2.307 (1.588-3.351)	0.001	1.542 (0.706-3.369)	0.278
TACE (yes/no)	1.219 (0.830-1.791)	0.311		
Overall chemotherapy (yes/no)	1.126 (0.650-1.950)	0.672		
Portal vein chemotherapy (yes/no)	0.568 (0.310-1.038)	0.066	0.362 (0.138-0.949)	0.039

HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; HBsAg, HBV surface antigen; HBeAg, HBV e antigen; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALP, alkaline phosphatase; LDH, lactic dehydrogenase; TC, total cholesterol; PLT, platelet; AFP, α-fetoprotein; BS, before surgery; AS, after surgery; BDG, Biliary duct and gallbladder invasion; BTDO, blood transfusion during operation; TACE, transarterial chemoembolization.

overall chemotherapy were prognostic factors for RFS in both groups. When the factors associated with outcome in univariate analyses (P<0.1) were incorporated into a multivariate model analysis, with P<0.2 set as the marker for significant differences in both groups, only the tumor number and extrahepatic metastasis were independent risk factors for RFS (Tables IV and V).

Construction of the prognostic scoring system. Ascites, vascular tumor thrombus, low tumor differentiation and extrahepatic metastasis at the time of hepatectomy were four parameters for the prediction of a poor OS. Multiple tumors and extrahepatic metastasis were predictive of tumor recurrence; thus, these variables were weighted to construct the ascites, vascular tumor thrombus, low tumor differentiation,

Table IV. COX regression of prognostic variables for relapse-free survival in group A.

	Univariate		Multivariate	
Variables	HR (95% CI	P-value	HR (95% CI)	P-value
Clinical characteristics				
Sex (male/female)	0.978 (0.657-1.457)	0.913		
Age, years (>50/≤50)	0.700 (0.534-0.918)	0.010	1.857 (1.126-3.064)	0.015
Alcohol consumption (yes/no)	1.297 (0.908-1.852)	0.153		
HBsAg (+/-)	1.440 (0.955-2.172)	0.082	-	-
HBeAg (+/-)	0.984 (0.663-1.461)	0.936		
HBV DNA (+/-)	1.373 (0.948-1.987)	0.093	0.978(0.555-1.723)	0.939
ALB, g/l (≥40/<40)	0.767 (0.580-1.013)	0.062	0.647 (0.378-1.108)	0.113
ALT U/l (≥40/<40)	1.206 (0.915-1.589)	0.183		
AST, U/l (≥35/<35)	1.727 (1.248-2.389)	0.001	0.899 (0.478-1.693)	0.742
TBIL, μmol/l (≥22.2/<22.2)	1.366 (0.972-1.920)	0.072	1.198 (0.646-2.223)	0.567
ALP, U/l (≥100/<100)	1.724 (1.308-2.272)	0.001	1.027 (0.617-1.710)	0.918
LDH, U/l (≥252/<252)	1.425 (1.016-2.000)	0.040	1.409 (0.787-2.522)	0.248
TC, mmol/l (≥6/<6)	1.521 (1.018-2.273)	0.041	2.041 (1.163-3.582)	0.013
PLT, (≥125x10^9/<125x10^9/l)	1.476 (0.995-2.190)	0.053	0.563 (0.286-1.107)	0.096
AFP, ng/ml (≥200/<200, BS)	1.859 (1.403-2.465)	0.001	1.560 (0.868-2.804)	0.137
AFP, ng/ml (≥25/<25, AS)	2.076 (1.558-2.767)	0.001	1.166 (0.622-2.186)	0.631
Pathological characteristics				
Cirrhosis (yes/no)	1.687 (1.199-2.373)	0.003	2.053 (1.092-3.863)	0.026
Ascites (yes/no)	1.384 (0.973-1.968)	0.071	0.842 (0.392-1.811)	0.661
Tumor size, cm (>5/≤5)	2.050 (1.551-2.708)	0.001	1.860 (0.906-3.819)	0.091
Tumor number (multiple/single)	2.088 (1.553-2.808)	0.001	2.815 (1.569-5.049)	0.001
TNM stage (III + IV/I + II)	2.869 (2.181-3.774)	0.001	0.349 (0.116-0.048)	0.061
Differentiation (III + IV/I + II)	1.597 (1.214-2.100)	0.001	0.883 (0.522-1.495)	0.644
Capsule invasion (yes/no)	1.891 (1.388-2.575)	0.001	1.168 (0.654-2.086)	0.600
Vascular tumor thrombus (yes/no)	2.424 (1.820-3.228)	0.001	1.611 (0.919-2.823)	0.096
Gross tumor thrombus (yes/no)	3.579 (2.625-4.880)	0.001	4.355 (1.71-10.898)	0.002
Vascular invasion (yes/no)	2.756 (2.087-3.663)	0.001	1.905 (0.635-5.715)	0.250
BDG (yes/no)	3.026 (1.685-5.435)	0.001	1.179 (0.409-3.400)	0.761
Extrahepatic metastasis (yes/no)	2.634 (1.727-4.015)	0.001	2.470 (0.973-6.266)	0.057
Treatment				
Pre-operative antiviral (yes/no)	1.163 (0.883-1.533)	0.283		
Post-operative antiviral (yes/no)	1.396 (1.022-1.906)	0.036	0.824 (0.450-1.510)	0.532
BTDO, ml (≥400/<400)	1.864 (1.416(2.453)	0.001	1.005 (0.587-1.721)	0.985
TACE (yes/no)	0.877 (0.663-1.159)	0.356		
Overall chemotherapy (yes/no)	0.690 (0.470-1.104)	0.059	0.684 (0.374-1.250)	0.217
Portal vein chemotherapy (yes/no)	0.905 (0.642-1.277)	0.571		

HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; HBsAg, HBV surface antigen; HBeAg, HBV e antigen; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALP, alkaline phosphatase; LDH, lactic dehydrogenase; TC, total cholesterol; PLT, platelet; AFP, α-fetoprotein; BS, before surgery; AS, after surgery; BDG, Biliary duct and gallbladder invasion; BTDO, blood transfusion during operation; TACE, transarterial chemoembolization.

extrahepatic metastasis and multiple tumors (AVLEM) score to predict patient OS or RFS. The OS predictive model was constructed based on the four aforementioned independent risk factors. The patients were divided into three subgroups as follows: Grade 0 (G0), no ascites, with highly differentiated tumors, no vascular tumor thrombus and no extrahepatic metastasis; grade 1 (G1), only one risk factor was positive; and grade 2 (G2), more than one risk factor was positive. Similarly, the RFS predictive model was constructed based on the two of the aforementioned risk factors. The patients were divided into two subgroups as follows: Grade 0 (G0), single tumor and no extrahepatic metastasis; grade 1 (G1), multiple tumors

Table V. COX regression of prognostic variables for relapse-free survival in group B.

	Univariate		Multivariate	
Variables	HR (95% CI)	P-value	HR (95% CI)	P-value
Clinical characteristics				
Sex (male/female)	1.016 (0.681-1.514)	0.939		
Age, years (>50/≤50)	0.755 (0.574-0.994)	0.046	0.789 (0.481-1.293)	0.347
Alcohol consumption (yes/no)	0.830 (0.578-1.190)	0.310		
HBsAg (+/-)	1.474 (0.963-2.258)	0.074	-	-
HBeAg (+/-)	2.037 (1.351-3.071)	0.001	2.038 (1.083-3.838)	0.027
HBV DNA (+/-)	1.135 (0.800-1.609)	0.478		
ALB, g/l (≥40/<40)	0.702 (0.527-0.933)	0.015	0.766 (0.473-1.239)	0.276
ALT U/l (≥40/<40)	1.237 (0.936-1.635)	0.135		
AST, U/l (≥35/<35)	1.949 (1.413-2.687)	0.001	1.718 (0.931-3.173)	0.084
TBIL, μmol/l (≥22.2/<22.2)	1.043 (0.729-1.492)	0.817		
ALP, U/l (≥100/<100)	1.210 (0.915-1.600)	0.181		
LDH, U/l (≥252/<252)	1.585 (1.136-2.212)	0.007	0.867 (0.477-1.575)	0.639
TC, mmol/l (≥6/<6)	1.001 (0.667-1.502)	0.995		
PLT, (≥125x10^9/<125x10^9/l)	1.121 (0.792-1.588)	0.519		
AFP, ng/ml (≥200/<200, BS)	1.706 (1.275-2.282)	0.001	1.300 (0.702-2.405)	0.404
AFP, ng/ml (≥25/<25, AS)	1.800 (1.339-2.421)	0.001	0.988 (0.543-1.795)	0.967
Pathological characteristics				
Cirrhosis (yes/no)	1.166 (0.847-1.604)	0.346		
Ascites (yes/no)	1.995 (1.412-2.819)	0.001	2.003 (1.028-3.902)	0.041
Tumor size, cm (>5/≤5)	1.881 (1.413-2.503)	0.001	1.426 (0.755-2.694)	0.274
Tumor number (multiple/single)	1.524 (1.126-2.063)	0.006	1.482 (0.837-2.624)	0.177
TNM stage (III + IV/I + II)	1.827 (1.379-2.419)	0.001	0.817 (0.288-2.313)	0.703
Differentiation (III + IV/I + II)	1.678 (1.271-2.216)	0.001	1.464 (0.896-2.392)	0.128
Capsule invasion (yes/no)	1.462 (1.084-1.973)	0.013	0.943 (0.565-1.573)	0.821
Vascular tumor thrombus (yes/no)	1.886 (1.417-2.511)	0.001	0.830 (0.486-1.416)	0.494
Gross tumor thrombus (yes/no)	2.279 (1.642-3.161)	0.001	1.361 (0.638-2.906)	0.425
Vascular invasion (yes/no)	1.753 (1.304-2.356)	0.001	0.924 (0.344-2.487)	0.876
BDG (yes/no)	2.671 (1.445-4.940)	0.002	2.199 (0.710-6.809)	0.172
Extrahepatic metastasis (yes/no)	2.256 (1.387-3.669)	0.001	2.070 (0.748-5.726)	0.161
Treatment				
Pre-operative antiviral (yes/no)	1.095 (0.825-1.454)	0.530		
Post-operative antiviral (yes/no)	1.346 (0.996-1.820)	0.053	0.788 (0.433-1.434)	0.435
BTDO, ml (≥400/<400)	1.626 (1.233-2.143)	0.001	1.141 (0.687-1.895)	0.612
TACE (yes/no)	1.249 (0.944-1.652)	0.119		
Overall chemotherapy (yes/no)	0.949 (0.632-1.426)	0.802		
Portal vein chemotherapy (yes/no)	0.580 (0.378-0.891)	0.013	0.397 (0.214-0.737)	0.003

HR, hazard ratio; CI, confidence interval; HBV, hepatitis B virus; HBsAg, HBV surface antigen; HBeAg, HBV e antigen; ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; ALP, alkaline phosphatase; LDH, lactic dehydrogenase; TC, total cholesterol; PLT, platelet; AFP, α-fetoprotein; BS, before surgery; AS, after surgery; BDG, Biliary duct and gallbladder invasion; BTDO, blood transfusion during operation; TACE, transarterial chemoembolization.

or extrahepatic metastasis, multiple tumors combined with extrahepatic metastasis (Table SI).

Application of the AVLEM score to predict OS. The Kaplan-Meier curves of OS for the patients in groups A and B are presented in Fig. 1. The average 1-, 3- and 5-year OS rates in the G0 subgroup were 97.9% (98.0% in group A and 97.8% in group B), 90.4% (89.3% in group A and 91.4% in group B) and 79.5% (78.3% in group A and 80.7% in group B), respectively. The average 1-, 3- and 5-year OS rates in the G1 subgroup were 89.0% (87.5% in group A and 90.5% in group B), 67.6% (63.3% in group A and 71.8% in group B) and 53.9% (50.9%

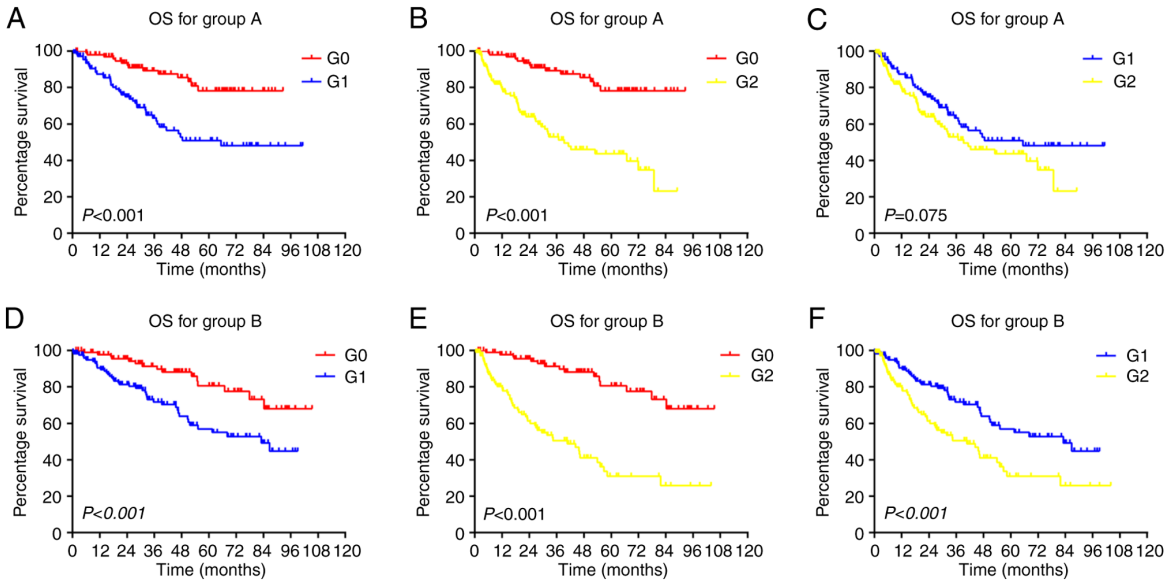

Figure 1. Kaplan-Meier curves of the OS of the patients in the subgroups in the two cohorts. The OS of the G0, G1 and G2 subgroups was compared between patients in (A-C) cohort A and (D-F) cohort B. Significant differences were observed between the G0 and G1, and G0 and G2 subgroups in both cohorts (P<0.001); the difference between the G1 and G2 subgroups in cohort B was also significant (P<0.001); however, cohort A, the difference was not significant (P=0.075). OS, overall survival.

in group A and 57.0% in group B), respectively. The average 1-, 3- and 5-year OS rates in the G2 subgroup were 80.2% (79.89% in group A and 80.5% in group B), 52.0% (52.9% in group A and 51.1% in group B) and 38.0% (43.7% in group A and 32.3% in group B), respectively. Overall, the G0 subgroup had a better OS than the G1 and G2 subgroups (P<0.001). The G1 subgroup also had a better OS than the G2 subgroup (P<0.001) in the group B cohort; however, the difference was not significant (P=0.075) in the group A cohort. Comparisons were also made for each subgroup between groups A and B (Fig. S1), and it was found that the OS of the patients did not differ significantly between these two groups (P>0.05).

Application of the AVLEM score to predict RFS. The Kaplan-Meier curves of the RFS of patients in groups A and B are presented in Fig. 2. The average 1-, 2- and 3-year RFS rates in the G0 subgroup were 65.7% (65.7% in group A and 65.8% in group B), 55.6% (55.2% in group A and 56.0% in group B) and 48.2% (46.7% in group A and 49.6% in group B), respectively. The average 1-, 2- and 3-year RFS rates in the G1 subgroup were 45.9% (42.0% in group A and 49.7% in group B), 32.3% (28.0% in group A and 36.5% in group B) and 25.7% (20.3% in group A and 31.0% in group B), respectively. The G0 subgroup had a better RFS than the G1 subgroup in both cohorts (P<0.001). Comparisons were also made for each subgroup between groups A and B (Fig. S2), and RFS of the patients was not found to differ significantly between these two groups (P>0.05).

Discussion

Currently, surgery is considered the best candidate therapy for patients with solitary HCC, while the prognostic staging of HCC following curative hepatectomy remains a challenge; although several staging systems have been proposed, none have been universally adopted, since HCC is heterogeneous and is influenced by tumor burden (11), viral infections (12), liver function (13), immune response (14) and metabolic abnormalities (15). An ideal prognostic model for risk stratification needs to be developed with appropriate methods. The present study collected the information of 690 patients from a hospital in South China and randomly divided the patients into two cohorts. First, all the indicators were compared to validate the randomness of the grouping, and no significant differences were found for each indicator between the two cohorts. The variables were then subjected to univariate and multivariate regression analysis for each cohort. The variables with significant differences (P<0.1) in the univariate regression analysis were considered as possible risk factors for further multivariate regression analysis (9,10). Finally, the risk factors (P<0.2 in multivariate regression analysis in both cohorts) were used to develop a prognostic scoring system based on the risk factor cumulative incidence (CuI). These analytical methods illustrate that the statistical results are repeatable in this population.

Previous studies have focused on the identification of prognosis-associated biomarkers (16-18), which normally require additional detections. The AVLEM score used herein is free of any specific laboratory test and is regarded as an advantage, since it relies on baseline information, which is readily available in retrospective analyses. In the patients, ascites, low tumor differentiation, vascular tumor thrombus and extrahepatic metastasis were independent predictors for a poor OS. Based on the CuI for the four aforementioned risk factors, the patients were divided into the G0 (CuI=0), G1 (CuI=1) and G2 (CuI ≥2) subgroups. The average 1-, 3-, 5-year OS rates were 97.9, 90.4 and 79.5% in the G0 subgroup; 89.0, 67.6 and 53.9% in the G1 subgroup; and 80.2, 52.0 and 38.0% in the G2 subgroup, respectively. The median OS rate in the G2 subgroup was ~3 years, the median OS in the other two subgroups, especially G0, was more than five years. The prognostic strata

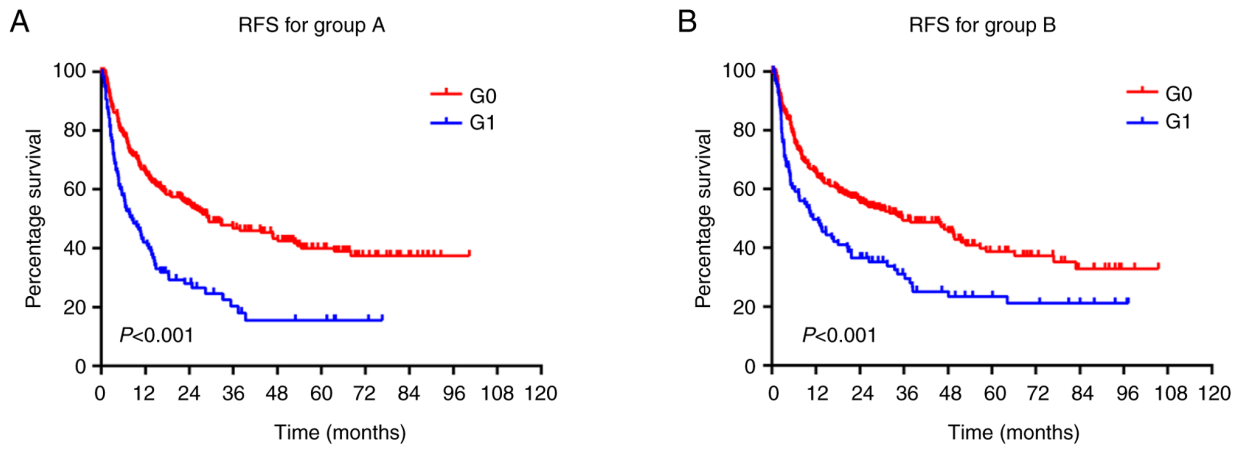

Figure 2. Kaplan-Meier curves of the RFS of patients in the subgroups in the two cohorts. The RFS of the G0 and G1 subgroups was compared in (A) group A, and (B) group B. Significant differences were observed between the G0 and G1 subgroups in both cohorts (P<0.001). RFS, relapse-free survival.

based on the four pathological factors can be used for the estimation of patient OS following hepatectomy. Moreover, the patients' pre-operative nutritional and immunological status also affects surgical prognosis. A controlling nutritional status (CONUT), calculated based on serum ALB, total lymphocyte count, TC, BTDO and other variables has been reported as an independent predictor of OS. A higher CONUT score (low ALB, low lymphocyte count and low TC) has been shown to be significantly associated with a poor OS (19,20). In the present study, apart from ALB and BTDO, AFP, AST, ALP, tumor size and capsule invasion were also probable factors for the prediction of OS when going univariate analysis.

The main reason for HCC being difficult to treat is its high recurrence rate. The early detection of HCC recurrence and early intervention can improve patient prognosis following hepatectomy. However, high-frequency screening for all patients with HCC is not a cost-effective strategy. Tumor multiplicity and a large tumor size are two accepted poor prognostic indicators of HCC recurrence, even though there are other clinicopathological variables considered to be associated with RFS (21,22). In the present study, apart from tumor multiplicity, extrahepatic metastasis was an independent predictor for tumor recurrence; this is in accordance with published data demonstrating that the intrahepatic recurrence of HCC is attributable to metastasis (23). Moreover, patient age, pre-operative ALB, AST, LDH and AFP levels before and after surgery, ascites, tumor size and differentiation level, vascular invasion, treatment and TNM stage were all possible risk factors related to tumor recurrence in the present study, even though they were not independent risk factors, these are partially consistent with published data (24-26); however, since the variables and the patients included in each research group varied, the independent prognostic risk factors also differed. The present study included comprehensive clinicopathological variables and antitumor and antiviral treatments, which made the statistical analysis and scoring model more stringent. The G0 and G1 subgroups were classified according to risk factor CuI for the further analysis of RFS. Kaplan-Meier analysis revealed that patients in the G1 subgroup were more likely to have tumor recurrence compared with those the G0 subgroup. According to the AVLEM scoring system, high-frequency follow-up and screening for patients in the G1 subgroup with extrahepatic metastasis or multiple tumors are more necessary than for patients in the G0 subgroup without extrahepatic metastasis or with solitary tumors.

HBV infection remains the leading risk factor for HCC, with a slight decline in the majority of Asian countries (2). Patients with HBV infection suffer from malignancy, as well as chronic hepatitis B infection. A high HBV-DNA load, intrahepatic metastasis and multicenter recurrence are independent risk factors for a poor OS (27,28). HBV reactivation affects the post-operative survival of patients with HCC with a low pre-operative HBV-DNA level (29), and the loss of HBsAg is associated with a reduced risk of late recurrence following liver resection in patients with HBV-related HCC (30); thus, antiviral treatment leads to an improved OS and a lower HCC recurrence rate following curative resection in patients with HBV-associated HCC (31,32). Other researchers have found that including data on the serum levels of HBsAg or removing data on the level of HBV DNA do not alter the accuracy of the risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B) scoring system in determining the risk of developing HCC in patients with chronic HBV infection (33). The surgical outcome of patients with HBsAg-negative HCC has been found to not differ significantly compared with those with HBsAg-positive HCC (34). These results suggest that HBV infection in different HCC patients has diverse effects on surgical outcomes. In the present study, HBV-associated viral factors (HBsAg, HBeAg and HBV DNA) and antiviral treatments before or after hepatectomy were not independent risk factors for survival. This may be the reason that the viral loads in the patients in the present study differed, and a high pre-operative viral load led to a poorer OS and RFS than a low viral load (28). In addition, the HBV genotype is associated with tumor recurrence and genotype C results in greater tumor recurrence rate compared with genotype B (35). Furthermore, different antiviral drugs also result in significantly different prognoses in patients with HBV-associated HCC following hepatectomy (36-38); however, in the present study, patients were not divided into subgroups for further analysis according to HBV load, viral genotype and antiviral drugs.

The present study established the AVLEM scoring system requiring only simple clinicopathological information (including ascites, vascular tumor thrombus, tumor differentiation level, extrahepatic metastasis and multiple lesions), which is a low-cost scoring model to predict recurrence and the OS of patients with HCC undergoing curative resection; however, this system has certain limitations. First, the patients used to construct this scoring system were from a single center, and larger samples from other centers are required to validate this system. Second, the present study was a retrospective cross-sectional study, which limits the amount of data used. Thus, further larger multi-institutional cohort studies are warranted to validate the prognostic value of the scoring system used herein, mirroring the management of HCC in real-life clinical situations. Third, the effectiveness of the scoring model was only evaluated by analyzing the OS and RFS of patients in each subgroup. It would be beneficial to evaluate the receiver operating characteristic curve of this scoring model by using more HCC cohorts in the future.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

WD analyzed the data and wrote the manuscript. FC and YL collected the patient electronic medical records and scheduled follow-up visits. LX designed the study and revised the manuscript. WD and FC confirmed the authenticity of all the raw data. All authors reviewed the results, and have read and approved the final version of the manuscript.

Ethical approval and consent to participate

The present study was reviewed and approved by the Ethics Committee of the Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China. Written informed consent for this study provided by all the patients included in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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