Original Article

A scoring model combining serum alpha-fetoprotein and tumor size and number predicts prognosis in hepatitis B virus-related hepatocellular carcinoma patients after curative hepatectomy

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Background: More in-depth models, such as biomarker and anatomical information, are needed to predict individualized prognoses of hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) after curative liver resection. alpha-fetoprotein (AFP) has conflicting value in predicting prognosis. We aimed to investigate the significance of an AFP score model as a potential predictor of prognosis after radical resection in patients with HBV-related HCC.

Methods: This study retrospectively analyzed 397 patients with HBV-related HCC who underwent hepatic resection between 2001 and 2013. Serum AFP level, tumor size, and tumor number were calculated by adding individual points for the AFP score model. Patient and tumor characteristics were tested for prognostic significance using ANOVA and chi-squared test, respectively. The receiver operating characteristic (ROC) curve was used to identify the AFP score model with or without other risk factors to discriminate patients. Kaplan-Meier and Cox's analyses were performed to pinpoint risk factors for overall survival (OS) and disease-free survival (DFS) in the patients.

Results: The cutoff value for the AFP score model was set at 2 using the ROC curve, with good specificity and sensitivity for OS and DFS. According to the AFP score model, 185 patients were in the AFP score >2 group, and 212 were in the AFP score ≤2 group. The median OS in the AFP score ≤2 and AFP score >2 groups were 173.4±1.00 *vs.* 50.30±8.67 m, respectively (P=0.000). The median DFS in the AFP score ≤2 and AFP score >2 groups were 17.20±3.66 *vs.* 73.7±10.39 m (P=0.000), respectively. Analyses from Cox's multivariate proportional hazard model indicated that AFP score (HR =0.563, 95% CI: 0.398–0.798, P=0.001), MVI (HR =0.653, 95% CI: 0.441–0.967, P=0.033), and cirrhosis (HR =0.358, 95% CI: 0.185–0.696, P=0.002) were risk factors for OS. The multivariate Cox model identified MVI (HR =1.589, 95% CI: 1.496–2.854, P=0.003) and AFP score (HR =0.876, 95% CI: 0.404–0.925, P=0.040) as risk factors of DFS. According to the stratification by the AFP score with MVI, the mean OS in the AFP score >2 group combined with the MVI group was significantly shorter, compared with that in the AFP score >2 group without the MVI group (65.58±9.18 *vs.* 94.21±8.25 m, P=0.024). The mean OS in the AFP score >2 group combined with the cirrhosis group is significantly shorter than that in the AFP score ≤2 group without the cirrhosis group (64.08±7.38 *vs.* 145.31±8.38 m, P=0.000).

Conclusions: The AFP score model categorizes HCC patients with relatively good liver function after radical resection with low- and high-risk prognosis.

Keywords: Hepatocellular carcinoma (HCC); AFP score model; prognosis

Submitted Dec 01, 2018. Accepted for publication Jul 09, 2019.
doi: 10.21037/tcr.2019.07.49
View this article at: http://dx.doi.org/10.21037/tcr.2019.07.49

Introduction

Primary hepatocellular cancer (HCC) is common worldwide and is one of the most common causes of cancer mortality (1-4). Currently, surgical treatment is available to improve outcomes in some selected patients (5). However, primary lesion, tumor metastasis, and concomitant underlying diseases (such as cirrhosis) should also be taken into consideration for surgical resection.

Various cancer stage systems have been proposed to stratify HCC patients to help physicians decide on surgical treatment. Some common stage systems are tumor-node-metastasis (TNM) stage, Okuda staging, Cancer of the liver Italian Program (CLIP) score, Barcelona Clinic Liver Cancer (BCLC) stage, Chinese University Prognostic Index (CUPI), and Japanese Integrated Scoring (JIS) (6-10). The European Association for Study of Liver (EASL) in 2012 and the American Associations for Study of Liver Diseases (AASLD) in 2017 published guidelines for HCC treatment reporting well-defined hepatectomy indications for HCC: patients with a single HCC <5 cm or up to 3 tumors all less than 3 cm with completely preserved liver function and no portal hypertension (11,12). However, the above guidelines excluded some potentially resectable HCC patients to some extent.

The use of neoadjuvant therapies for successful curative interventions in down-staging HCC has seen a significant rise owing to the recent advances in oncology. Adjuvant therapies, however, were already in use to control local recurrence or distant metastasis before acceptance for use in HCC. HCC patients with portal vein hypertension have a more dismal outcome in contrast to compensated patients. The effects of cirrhosis on surgery are unclear, given the existence of different clinical stages in the histological variability of cirrhosis. So it is worth noting that some cirrhosis patients without portal vein hypertension might have curative hepatectomy beyond limitation on anatomical information (tumor size and number). Nevertheless, There is a need for a new accurate prediction system for surgical resection among HCC patients.

Serum AFP is a widely used cancerous biomarker for hepatocarcinogenesis and is a prognostic indicator for recurrence (13,14). Higher AFP levels reportedly are associated with nodular size, microvascular invasion (MVI), and other factors (15-18). A French study group subsequently combined blood AFP level with nodules number and size, considering the simplicity and feasibility, and the result showed the effect of integration on prognosis after liver transplantation (16,19,20). However, whether the AFP score model could predict the prognosis of HCC patients after liver resection needs further research.

To that effect, we proposed the AFP score model based on the preoperative AFP levels combined with nodule number and size to predict the prognosis of HCC patients after liver resection in the present study.

Methods

Patients and clinicopathological information

We recruited 397 patients with HCC from the Prince of Wales Hospital, Hong Kong, China, from November 2001 to November 2013. The criteria for patient inclusion were: (I) the presence of positive HBsAg; (II) liver function tests showing Child-Pugh grade A and clearance of indocyanine green less than 15% at 15 minutes (ICG-R15); (III) absence of distant metastasis; (IV) patients who accepted curative liver resection; (V) patients without autoimmune liver diseases or serious heart, lung, kidney, or blood diseases. The criteria for patient exclusion were: (I) the presence of other types of malignant tumors; (II) accompanied by portal vein hypertension; (III) the presence of other types of hepatic viral infections. Chart flow for patient selection is shown in *Figure 1*. All patients or their legal representatives gave written informed consent for all investigations and inquiries that were conducted during this study. The hospital ethical committee approved the design of the study.

Serum AFP concentration was measured using the electrochemiluminescence immunoassay (E170 Analytics; Roche Diagnostics Corp., Indianapolis, IN) (21). The AFP data included in this analysis are preoperative measurements obtained before the date of resection. The data on other biochemical markers, including albumin, alanine aminotransferase (ALT), and bilirubin, were retrieved from

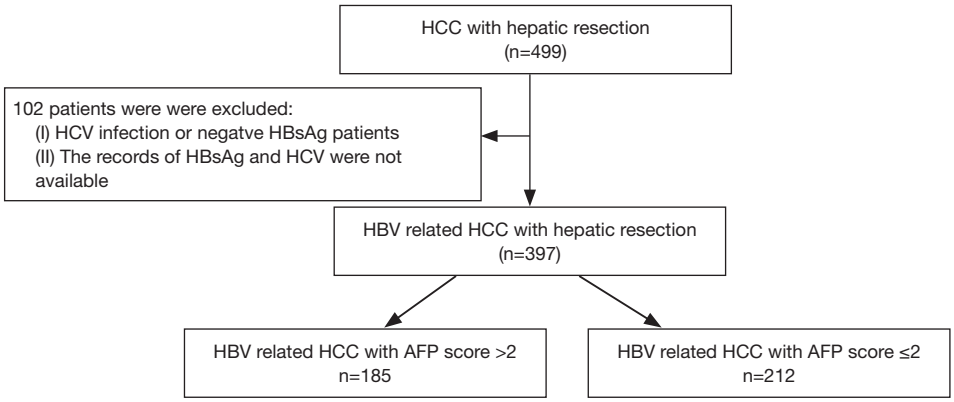

Figure 1 Chart flow. HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus; AFP, alpha-fetoprotein.

Table 1 Point of AFP score model

Variables	Point
Largest diameter (cm)	
≤3	0
3–6	1
>6	4
Number of nodules	
1–3	0
4 and more	2
AFP level (μg/L)	
≤100	0
100–1,000	2
>1,000	3

AFP, alpha-fetoprotein.

the medical records of patients. The degree of fibrosis (including cirrhosis) was diagnosed by imaging examination (ultrasonography, CT, or MRI) or pathology. Microvascular invasiveness was diagnosed in liver specimens by pathology. Following resection, all liver specimens were examined by a single, dedicated liver pathologist who was blinded to all patients' identities and clinical outcomes.

AFP score model

The AFP score is calculated by adding individual points for each obtained variable, as shown in *Table 1* and was calculated for each patient enrolled in the study (*Table 1*).

Follow-up evaluations

Follow up evaluation were performed in outpatients every three months during the first postoperative year, every four months of the second postoperative year, and every six months after that. Images with CT or MRI were obtained during postoperative follow-up examinations. Tumor recurrence was diagnosed using CT or MRI scans. OS was defined as the time from operation to death or 8 November 2018; DFS as the time from curative hepatectomy to the first occurrence of either intra- or extra-hepatocellular metastasis.

Statistical analysis

All statistical analyses were performed by SPSS 20. Continuous variables are shown as the means ± standard deviation. The One-way analysis of variance (ANOVA) was used to identify significant differences. Categorical variables by the chi-squared test were used to identify significant differences between groups. The ROC curve was generated to identify the AFP score to categorize survived patients. A Kaplan-Meier survival curve was used to estimate recurrence and survival. The univariable Cox regression was carried out to evaluate the effects of various clinicopathological variables on survival. Only results with a P value <0.05 were considered statistically significant.

Results

Patients characteristics

A total of 397 patients were eligible for the present study. All the patients received curative resection for primary

Table 2 Baseline characteristics of the investigated population

Clinical character	All patients
Age (years)	56.42±9.96 [27–81]
Gender (female/male)	53/344
Differentiation (well/moderate/poor)	46/308/43
AJCC stages (1/2/3)	248/101/48
Biology pre-operation	
ALT (U/L)	51.88±38.39 [10–283]
Albumin (g/L)	40.52±4.93 [24–81]
Bilirubin (μmol/L)	11.18±6.27 [3–83]
Vascular invasion (negative/positive)	302/95
Degree of fibrosis (normal/fibrosis/cirrhosis)	38/123/236
HCC features	
Tumor diameter (cm)	4.73±3.33 [1–24]
Tumor number	1.29±0.77 [1–7]
AFP (μg/L)	2,220.36±7,405.23 [1–69,980]
Neoadjuvant treatment (yes/no)	43/354
Adjuvant treatment (yes/no)	128/269
Anti-virology treatment (yes/no/unclear)	119/240/38
Operation modality (LH/OH)	161/236
Blood loss (mL)	223.54±48.91

ALT, alanine aminotransferase; LH, laparoscopic hepatectomy; OH, open hepatectomy.

tumors, as well as laparoscopic hepatectomy (LH) (n=161) and open hepatectomy (OH) (n=236, including patients who reverted from LH to OH). There were 302 patients with clear information about blood loss. The mean blood loss volume of the patients was 223.54±48.91 mL. The demography, antiviral treatment history, neoadjuvant or adjuvant treatment, information about the operation, and the biochemical and clinical characteristics of the included patients are presented in *Table 2*. Two hundred and forty patients had no antiviral treatment history, while 119 patients had received antiviral treatment before hepatic resection. The other 38 patients were not sure if they had had antiviral treatment or not. In the retrospective study,

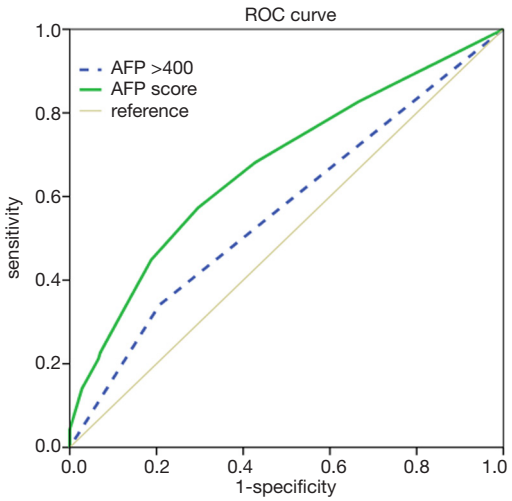

Figure 2 The receivers operating characteristics (ROC) curve showing the overall accuracy of the AFP score and AFP >400 μg/L risk factors for predicting prognoses. The optimal cut-off point of the AFP score is 2. AFP, alpha-fetoprotein.

128 patients had postoperative treatment history, and 43 patients had received neoadjuvant treatment.

During the followed-up period, the mean OS and DFS were 66.38±49.03 and 48.68±48.10 m, respectively. Furthermore, the number of patients with AFP ≤100, 100 μg/L < AFP <1,000 μg/L and ≥1,000 μg/L were 241, 83, and 73, respectively. The difference in the rate of OS between the three groups was significant (P=0.003). There were 167, 138, and 92 patients with tumor sizes ≤3, ≤6, and >3 and >6 cm, respectively. The difference in the rate of OS and DFS between the three groups was significant (P=0.000). Although the patients with tumor size >6 cm and AFP level >1,000 μg/L are fewer than the tumor sizes ≤6 cm and AFP levels ≤1,000 μg/L, the proportion of the patients cannot be ignored.

Determination of cut-off values for AFP score model

We used ROC curve analyses to test for the AFP score model's capacity as a prognostic factor. As the results in *Figure 2* show, the AUC of the AFP score model and AFP >400 μg/L were 0.673 [95% confidence interval (CI) =0.619–0.726] and 0.567 (95% CI =0.510–0.624), respectively, for predicting survival. Furthermore, we performed ROC curve analyses to identify the optimal cut-off value, and the value we obtained for AFP score model cutoff was 2.

Table 3 Clinical characteristics of the two subgroups

Clinical character	Subgroup		P value
	AFP score >2	AFP score ≤2	
Age (years)	55.20±10.74	57.32±9.24	0.035
Gender (female/male)	21/148	32/196	0.658
Differentiation (well/moderate/poor)	12/135/22	34/173/21	0.037
ALT (U/L)	54.10±38.71	50.24±38.16	0.323
Albumin (g/L)	39.48±5.68	41.29±4.14	0.000
Bilirubin (μmol/L)	11.16±8.02	11.22±4.59	0.953
RBC ($\times10^{12}$/L)	13.67±1.84	14.69±9.41	0.166
WBC ($\times10^{9}$/L)	6.60±1.86	5.83±1.80	0.013
PLT ($\times10^{12}$/L)	192.95±76.23	161.63±71.88	0.000
HBV DNA (copies/mL)	12,627,910.55±40,195,981.53	18,218,314.12±47,020,864.95	0.577
LH/OH	87/82	74/154	0.000
Blood loss (mL)	231.87±36.70	212.67±42.27	0.732
Antiviral treatment (yes/no)	36/133	83/145	0.004
Neoadjuvant treatment (yes/no)	26/143	17/211	0.012
Adjuvant treatment (yes/no)	68/101	60/168	0.003
MVI (negative/positive)	103/66	199/29	0.000
Cirrhosis (negative/positive)	79/90	82/146	0.039
Differentiation (well/moderate/poor)	12/135/22	34/173/21	0.037
Tumor diameter	7.03±3.82	3.02±1.31	0.000
Tumor number	1.43±1.007	1.20±0.558	0.005
AFP (μg/L)	5,063.23±10,737.89	125.62±455.5	0.000

ALT, alanine aminotransferase; RBC, red blood cell; WBC, white blood cell; PLT, platelets; HBV, hepatitis B virus; LH, laparoscopic hepatectomy; OH, open hepatectomy; MVI, microvascular invasion; AFP, alpha-fetoprotein.

Impact of the AFP score model on overall survival (OS) and disease-free survival (DFS)

Of the 397 patients selected for our studies, 185 patients were put in the AFP score >2 group, and 212 in the AFP score ≤2 group. As shown in *Table 3*, the patients with an AFP score >2 had significant differences in age (P=0.035), tumor differentiation (P=0.037), tumor size (P=0.000), tumor number (P=0.005), vascular invasion (P=0.000), cirrhosis (P=0.039), albumin (P=0.000), white blood cells (WBCs) (P=0.013), platelets (PLT) (P=0.000), neoadjuvant treatment (P=0.012), adjuvant treatment (P=0.003), antiviral treatment (P=0.004), and operation choice (P=0.000). However, the two groups had no significant difference in some factors (such as gender, ALT, bilirubin, RBC, HBV DNA level, and blood loss) between them.

We also estimated the cumulative OS and PFS using the Kaplan-Meier method (*Figure 3*). The results showed that the 1-, 3-, and 5-year OS incidences were 95.6%, 85.0%, and 79.6%, respectively, in the AFP score ≤2 group, while the 1-, 3-, and 5-year OS incidences were 94.1%, 79.7%, and 65.9%, respectively, in the AFP score >2 group. The OS rate in the AFP score >2 group was significantly lower than that in the AFP score ≤2 group (37.3% *vs.* 65.40%, P=0.000). Similarly, the recurrence rate in the AFP score >2 group was significantly higher than that in the AFP score ≤2 group (65.1% *vs.* 51.8%,

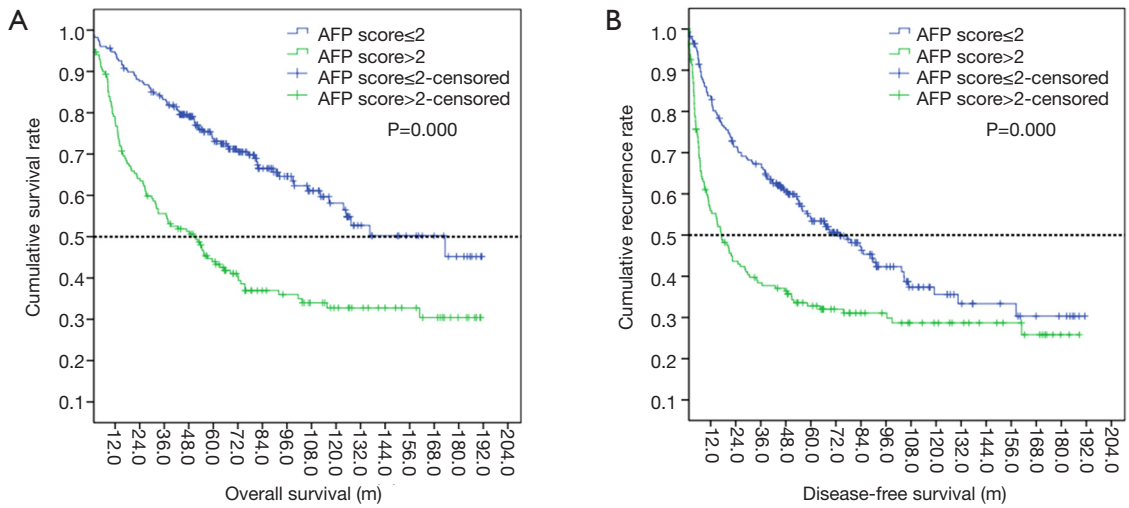

Figure 3 The Kaplan-Meier analysis of OS and DFS in 397 patients subdivided according to their AFP score. The cut-off point of 2 (green line denoted an AFP score >2; blue line denotes an AFP score ≤2). OS, overall survival; DFS, disease-free survival; AFP, alpha-fetoprotein; m, months.

P=0.010). Furthermore, the results showed that there were significant differences in the median OS and DFS between the two groups. The median OS in the AFP score ≤2 and AFP score >2 groups were 173.4±1.00 and 50.30±8.67 m, respectively, with a significant difference (P=0.000). In the same way, the median PFS in the AFP score >2 group was shorter than that in the AFP score ≤2 group (17.20±3.66 *vs.* 73.7±10.39 m, P=0.000).

Prognostic risk factors for OS and DFS

Some factors without differences in the two groups did not undergo univariate and multivariate analyses. The important clinical factors and prognostic factors that were compared by univariate and multivariate analyses to identify potential risk factors are shown in *Table 4*. The univariate analysis revealed that AFP score (HR =3.173, 95% CI: 2.097–4.802, P=0.000), MVI (HR =2.427, 95% CI: 1.509–3.906, P=0.000), and cirrhosis (HR =1.980, 95% CI: 1.314–2.984, P=0.001) were risk factors for OS. Ultimately, the multivariate Cox proportional hazards model confirmed that AFP score (HR =0.563, 95% CI: 0.398–0.798, P=0.001), MVI (HR =0.653, 95% CI: 0.441–0.967, P=0.033), and cirrhosis (HR =0.358, 95% CI: 0.185–0.696, P=0.002) were indeed risk factors of OS.

Univariate analysis, likewise, showed (*Table 4*) that AFP score (HR =1.738, 95% CI: 1.154–2.617, P=0.008) and MVI (HR =2.387, 95% CI: 1.441–3.953, P=0.001) were risk factors for DFS, an outcome predictably backed by the multivariate Cox proportional hazards model with findings of MVI (HR =1.589, 95% CI: 1.496–2.854, P=0.003) and AFP score (HR =0.876, 95% CI: 0.404–0.925, P=0.040).

The prognostic significance of MVI or cirrhosis as stratified by the AFP score model on OS

We explored the prospect of prognostic significance on OS when stratified by the AFP score model combined with MVI or cirrhosis. According to stratification by the AFP score with MVI (*Figure 4A*), the mean OS in the AFP score >2 combined with the MVI group compared with no MVI group were 65.58±9.18 and 94.21±8.25 m, respectively, with significant difference (P=0.024). Equally, the mean OS in the AFP score ≤2 group combined with the MVI group compared with no MVI group were 87.76±13.14 and 129.66±5.89 m, respectively, (P=0.064). Also shown in *Figure 4A* are the 1-, 3-, and 5-year OS rates in the AFP score >2 group combined with the MVI group compared with the score >2 without the MVI group at 74.2%, 43.9%, and 31% and 80.3%, 63.3%, and 52.6%, respectively. The 1-, 3-, and 5-year OS rates in the AFP score ≤2 group combined with MVI group compared with AFP score ≤2 without the MVI group were 91.3%, 73.9%, and 64.1% and 95.1%, 84.3%, and 74.7%, respectively. From these data, the performance of the AFP score >2 model combined with MVI in predicting OS was the most remarkable one. ROC

Table 4 Univariate and multivariate analyses of the clinical characteristics for OS and DFS

Variable	OS						DFS					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Gender (female/male)	1.521	0.839–2.756	0.165	–	–	–	1.354	0.758–2.417	0.305	–	–	–
Differentiation (well/moderate-poor)	1.153	0.621–2.143	0.652	–	–	–	1.043	0.561–1.939	0.895	–	–	–
Antiviral treatment (no/yes)	0.731	0.473–1.128	0.156	–	–	–	1.215	0.809–1.825	0.348	–	–	–
Neoadjuvant treatment (no/yes)	0.724	0.379–1.381	0.325	–	–	–	1.437	0.742–2.785	0.280	–	–	–
Adjuvant treatment (no/yes)	1.281	0.840–1.953	0.249	–	–	–	1.125	0.734–1.725	0.589	–	–	–
LH/OH	1.086	0.727–1.623	0.686	–	–	–	–	–	–	–	–	–
MVI (negative/positive)	2.427	1.509–3.906	0.000	0.653	0.441–0.967	0.033	2.387	1.441–3.953	0.001	1.589	1.496–2.854	0.003
Cirrhosis (negative/positive)	1.980	1.314–2.984	0.001	0.358	0.185–0.696	0.002	1.435	0.957–2.151	0.080	–	–	–
AFP score model (AFP score ≤2/ AFP score >2)	3.173	2.097–4.802	0.000	0.563	0.398–0.798	0.001	1.738	1.154–2.617	0.008	0.876	0.404–0.925	0.040

OS, overall survival; DFS, disease-free survival; LH, laparoscopic hepatectomy; OH, open hepatectomy; MVI, microvascular invasion; AFP, alpha-fetoprotein.

curve analyses (*Figure 4B*) also showed that the AUC of the AFP score combined with MVI, AFP score alone, and MVI alone were 0.658 (P=0.000, 95% CI: 0.604–0.712), 0.638 (P=0.000, 95% CI: 0.583–0.693), and 0.580 (P=0.006, 95% CI: 0.523–0.636), respectively. The findings suggest that the predictability of the AFP score alone or with MVI is more sensitive to survival, and both were superior to that of MVI alone.

We next analyzed the impact of combining the AFP score with cirrhosis on OS. As shown in *Figure 4C*, compared with the mean OS (145.31±8.38 m) in the AFP score ≤2 group without cirrhosis, the mean OS in the AFP score ≤2 group combined with the cirrhosis group, AFP score >2 group without the cirrhosis group, and the AFP score >2 group combined with the cirrhosis group were 114.71±7.30, 106.41±9.61, and 64.08±7.38 m, respectively, with significance differences (P1=0.024, P2=0.000, and P3=0.000). *Figure 4C* also shows that the 1-, 3-, and 5-year OS rates in the AFP score >2 group combined with the cirrhosis group compared to AFP score >2 without cirrhosis were 76.5%, 50.4%, and 37.6% and 79.8%, 62.0%, and 52.0%, respectively. The 1-, 3-, and 5-year OS rates in the AFP score ≤2 group combined with the cirrhosis group and in the AFP score ≤2 without cirrhosis were 92.4%, 79.9%, and 69.6% and 97.6%, 88.9%, and 80.5%, respectively. From the data above, the performance of AFP score >2 combined with cirrhosis in predicting OS was the most remarkable one. ROC curve (*Figure 4D*) also showed that the AUC of the AFP score combined with cirrhosis, AFP score alone, and cirrhosis alone were 0.683 (P=0.000, 95% CI: 0.631–0.736), 0.638 (P=0.000, 95% CI: 0.583–0.693), and 0.581 (P=0.005, 95% CI: 0.525–0.637), respectively.

Discussion

This study explores the value of the AFP score model in the prognosis of HBV-related HCC patients after liver resection. Based on the Kaplan-Meier analysis, patients with an AFP score >2 displayed worse outcomes. Also, we

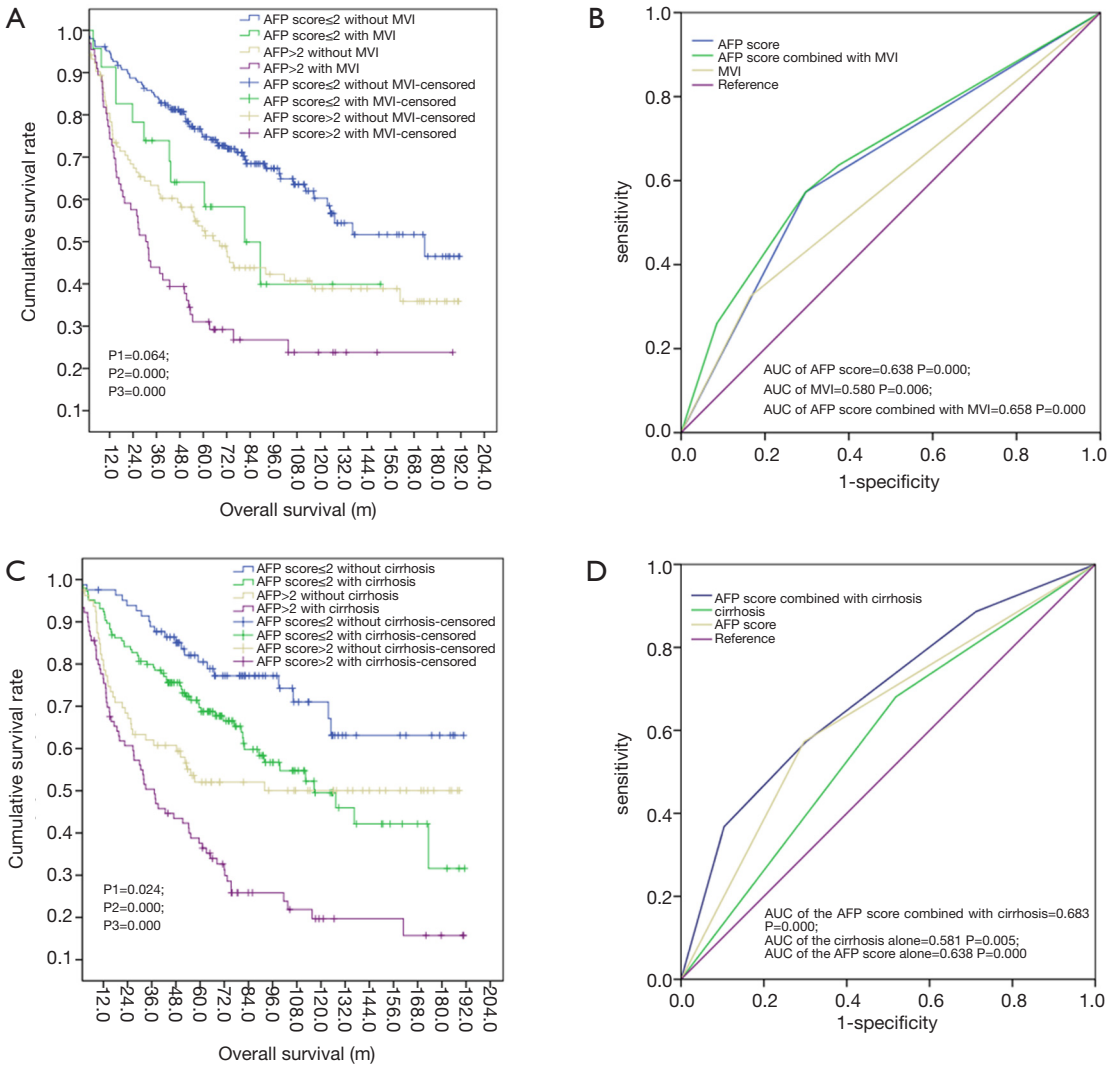

Figure 4 The Kaplan-Meier analysis and ROC curve in 397 patients stratified by the AFP score combined with MVI or cirrhosis (P1, P2, and P3 indicate the data compared to AFP score ≤2 without MVI or cirrhosis). In *Figure 4A*, 66 patients with an AFP score >2 with MVI, 103 patients with an AFP score >2 without MVI, 23 patients with an AFP score ≤2 with MVI, and 205 patients with an AFP score ≤2 without MVI had their OS compared using the Kaplan-Meier analysis (blue line denotes an AFP score ≤2 without MVI; green line denoted an AFP score ≤2 with MVI; yellow line denotes an AFP score >2 without MVI; red line denotes an AFP score >2 with MVI). Similarly, in *Figure 4C*, 90 patients with an AFP score >2 with cirrhosis, 80 patients with an AFP score >2 without cirrhosis, 145 patients with an AFP score ≤2 with cirrhosis, and 82 patients with an AFP score ≤2 without cirrhosis had their OS compared using the Kaplan-Meier analysis (blue line denotes an AFP score ≤2 without MVI; green line denotes an AFP score ≤2 with MVI; yellow line denotes an AFP score >2 without MVI; red line denotes an AFP score >2 with MVI). In *Figures 4B* and *D*, the ROC curve analysis shows the accuracy of the AFP score combined with MVI or cirrhosis in discriminating between subgroups. ROC, receiver operating characteristic; MVI, microvascular invasion; AFP, alpha-fetoprotein; m, months.

demonstrated that an AFP score >2 with MVI and cirrhosis could further highlight patients with very poor prognosis.

Previous studies have highlighted the interaction between AFP levels and other biological and pathophysiological roles in cancer (17,18). Our group reported previously that preoperative serum AFP levels >400 μg/L predict poor overall and recurrence-free survival after hepatectomy (22). In the present study ROC curves showed further that the

AFP score model could predict outcomes effectively after HCC resection when the AFP score value is 2. Notably, applying the ROC curve method, the present study showed that an AFP score >2 has a better sensitivity or specificity in predicting survival than AFP >400 μg/L alone. The AFP score >2 exhibited superior categorization of HCC prognoses after resection, which could be used to stratify patients and guide follow-up. The result is similar to previous reports that the AFP score model has a prognostic value in HCC recurrence after liver transplantation (20). The above data suggest that the AFP score model might be a powerful prognostic marker for HBV-related HCC patients after radical resection.

Combining several other factors with the AFP score model would provide comprehensive and individualized risk assessments. It is accepted generally that MVI and cirrhosis are strong prognostic factors for poor outcome after liver resection (23,24). Our past data had also confirmed the effects of cirrhosis alone on prognosis in HCC patients after resection (25). In the present study, we combined the AFP score with MVI or cirrhosis to stratify patients according to responses to therapy. Data obtained from these inquisitions showed that an AFP score >2 with or without MVI decreased the risk of survival significantly. The ROC curve results indicate that the new combination of higher AFP scores with MVI at an initial visit predicted more poor survivals, which may help guide clinicians to predict disease prognosis. On the other hand, AFP ≤2 with MVI induced no significant difference in OS.

A previous study reported that MVI is common in HCC patients with large size and multiple nodules (10). Nevertheless, the effect of AFP on angiogenesis in HCC remains unclear to date. So whether an AFP score ≤2 is related to MVI or not needs further research. We added more confidence in the ability to predict clinical prognosis by combining the AFP score and cirrhosis rather than go with cirrhosis alone. A chronic viral infection reportedly induces inflammation, which progresses eventually to cirrhosis. Chronic viral inflammation and the degree of fibrosis play very important roles in determining postoperative survival and DFS in patients with HCC (26-28). However, we did not, at this time, compare the degree of cirrhosis in predicting the prognosis of HCC. We expect to investigate these claims in subsequent studies.

It is accepted widely that proper treatment affects the progression and prognosis of HCC, with the outcome of antiviral therapy on HBV-related HCC recurrence after hepatic resection an example of positivity (29). However, we did not observe a similar significant improvement in survival among the 119 patients with clear antiviral treatment before hepatic resection. More research should stratify patients according to the type of antiviral treatment, HBV DNA level, and immune status before surgical resection.

It is worth noting that surgical resection offers a curative option and a better OS. Some meta-analyses have revealed significantly improved outcomes following LH in patients with HCC and underlying cirrhosis (30,31). In the real world, patients receive surgery and perioperative anti-treatment to improve OS and DFS. Adjuvant and neoadjuvant treatments have gained popularity according to the therapeutic algorithms for CC. Previous research has shown that local ablation, TACE, and sorafenib provide significant survival benefits (32-35). Yet, in the present study, LH and OH provided a similar impact on survival or recurrence. Although neoadjuvant/adjuvant therapy was used to downstage and control distant metastasis, no improvements were observed in survival and recurrence in our patients. As a matter of fact, in this present research, the relatively relaxed included criteria and insufficient data might have led to negative results. New clinical trials to determine the effects of anticancer therapy in HCC patients are needed.

Some limitations to the present study should be noted. First, this is a retrospective study from a single center. Second, the selection criteria for HCC patients were very restrictive, with patients who did not have blood AFP data, patients who presented incomplete medical records, those with relatively worse liver function, or those who failed to be followed up excluded. So, the study sample size was relatively small, especially for the subgroup analysis. Therefore, comprehensive, randomized multicenter studies are required to recruit high homogeneous patients and analyze patients with complete data.

In conclusion, our data suggest that the AFP model categorizes HCC patients with relatively good liver functions after radical resection into low and high-risk prognoses. This important finding suggests that the adoption of the AFP score model combined with MVI or cirrhosis is a powerful prognostic predictor for HBV-related HCC. Comparisons of pathological features and liver disease etiology between the high and low AFP score groups warrants further research.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.07.49). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The hospital ethical committee approved the design of the study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was taken from all patients.

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Cite this article as: Wei B, Chen JS, Yang SL, Chen GG, He H. A scoring model combining serum alpha-fetoprotein and tumor size and number predicts prognosis in hepatitis B virus-related hepatocellular carcinoma patients after curative hepatectomy. Transl Cancer Res 2019;8(4):1438-1448. doi: 10.21037/tcr.2019.07.49

