A model combining TNM stage and tumor size shows utility in predicting recurrence among patients with hepatocellular carcinoma after resection

Objective: Hepatocellular carcinoma (HCC) recurrence is a clinical challenge. An accurate prediction system for patients with HCC is needed, since the choice of HCC treatment strategies is very important.

Patients and methods: A total of 804 patients with HCC who underwent curative resection at Sun Yat-sen University Cancer Center were included in this study. Demographics, clinical-pathological data, and follow-up information were collected.

Results: A logistic regression analysis was conducted to investigate the relationships between clinical features and HCC recurrence. Tumor size (OR=1.454, 95% CI: 1.047–2.020, P=0.026) and TNM stage (OR=1.360, 95% CI: 1.021–1.813, P=0.036) were independent predictors of HCC recurrence after curative resection. Therefore, the following equation was established to predict HCC recurrence: 0.308×TNM+0.374×tumor size−0.639. The equation score was 0.53±0.23 in patients who experienced HCC recurrence compared with 0.47±0.26 in other patients. A similar trend was observed in patients who survived after the last follow-up, compared with those who did not, with scores of 0.37±0.26 vs 0.52±0.22, respectively (P<0.001). The Kaplan–Meier analysis showed that patients with HCC with equation values >0.5 had significantly worse outcomes than those with equation values ≤0.5 (P<0.001) for overall survival (OS) and recurrence (P=0.043). Multivariate Cox analyses showed that tumor multiplicity (P=0.039), involucrum (P=0.029), vascular invasion (P<0.001), and equation value (P<0.001) were independent prognostic variables for OS, whereas tumor multiplicity (P=0.01), tumor differentiation (P=0.007), vascular invasion (P<0.001), involucrum (P=0.01), and equation value (P<0.001) were independent prognostic variables for HCC recurrence.

Conclusion: We established a novel and effective equation for predicting the probability of recurrence and OS after curative resection. Patients with a high recurrence score, based on this equation, should undergo additional high-end imaging examinations.

Keywords: hepatocellular carcinoma, recurrence, tumor size, TNM stage, equation

Introduction

Hepatocellular carcinoma (HCC) remains the third most common malignancy in the world due to the increased incidence of nonalcoholic fatty liver disease and the high infection rate of hepatitis virus. The prognosis of HCC depends on tumor expansion. One of the few opportunities for patients with HCC to achieve a cure is surgical resection. However, it is well known that HCC recurrence after hepatectomy is a major risk factor that affects survival. A proportion of patients with HCC experience HCC recurrence after hepatectomy, which is associated with a poor prognosis.
recurrence after complete HCC resection. Therefore, HCC recurrence is a main clinical challenge of HCC treatment. An accurate prediction system for patients with HCC is needed, since the choice of HCC treatment strategy is very important.

Identifying patients with high or low risks of recurrence after hepatectomy for HCC will help determine other therapy and management strategies. Recently, several prognostic after hepatectomy for HCC will help determine other therapy and management strategies.7,8 Recently, several prognostic staging systems have been reported, such as the Japanese General Stage score, the cancer of the liver Italian program (CLIP) score, and the Barcelona Clinical Liver Cancer staging system.9–12 Although these staging systems help divide patients into different groups with different outcomes, they are not suitable for use in predicting recurrence after HCC resection. Therefore, an accurate model is needed to predict the likelihood of HCC recurrence after curative resection.

Although some clinicopathological data, such as tumor multiplicity and serum α-fetoprotein (AFP) levels, have been established as poor prognostic indicators and risk factors for HCC recurrence, such clinicopathological data have limited prognostic value when used alone. Combining indicators provides an effective method for improving the prognostic value. Therefore, the objective of this study was to construct an equation for distinguishing the risk of recurrence based on routine markers in patients with HCC who had undergone an HCC curative resection.

**Patients and methods**

**Patients**

A total of 804 patients with HCC who underwent curative resection at the Sun Yat-sen University Cancer Center were included in this study. The inclusion criteria were as follows: 1) pathological diagnosis of HCC (by an experienced pathologist), 2) patients with complete clinicopathological and follow-up data, and 3) patients who did not receive any chemotherapy or radiotherapy prior to the surgery. The study protocol was approved by the Clinical Research Ethics Committee of the Sun Yat-sen University Cancer Center. All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Declaration of Helsinki (1975), as revised in 2008. Written informed consent was obtained from all patients prior to inclusion in this study.

**Demographic and clinicopathological data collection**

Demographic and clinicopathological data, including age, sex, hepatitis B surface antigen (HBsAg), serum AFP level, liver cirrhosis nodule, tumor size, tumor multiplicity, tumor encapsulation, tumor differentiation, TNM stage, and micro-vascular invasion, were collected. The TNM stage in this study was defined according to the American Joint Committee on Cancer TNM Staging for Liver Tumors as follows:17 primary tumor (T): (T0) no evidence of primary tumor; (T1) solitary tumor without vascular invasion; (T2) solitary tumor with vascular invasion or multiple tumors less than 5 cm in size; (T3a) multiple tumors more than 5 cm in size; (T3b) single tumor or multiple tumors of any size, involving a major branch of the portal vein or hepatic vein; and (T4) tumor(s) with direct invasion of adjacent organs, other than the gallbladder, or with perforation of visceral peritoneum. Regional lymph nodes (N): (N0) regional lymph nodes cannot be assessed; (N1) regional lymph node metastasis. Distant metastasis (M): (M0) no distant metastasis and (M1) distant metastasis.

**Follow-up**

After receiving curative hepectomies, patients with HCC underwent follow-ups and received serological and imaging examinations, including serum AFP level analysis, abdomen ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI), once every 1–6 months. For patients without evidence of an event, the last follow-up date was obtained from the medical record.

**Statistical analyses**

Statistical analyses were performed using SPSS (version 16.0, SPSS Inc., Chicago, IL, USA). A Student’s t-test and Pearson’s chi-squared test, or Fisher’s exact test, were chosen for examining the correlations between HCC recurrence and clinical and pathological variables. Survival curves were constructed using the Kaplan–Meier method (log-rank test). A logistic regression was performed to construct the recurrence prediction equation. A multivariate Cox proportional hazards regression model was used to evaluate the independence of the equation in predicting outcomes. Differences with P-values less than 0.05 were defined as significant.

**Results**

**Associations between clinical features and HCC recurrence**

The associations between HCC recurrence and clinical features are shown in Table 1. Significantly more patients experienced HCC recurrences among patients with larger tumor size (P=0.008), poor-undifferentiated tumor differentiation.
A model predicts HCC recurrence

**Construction and performance of the HCC recurrence equation**

A logistic regression was conducted to analyze the relationships between clinical features and HCC recurrence (Table 2). Tumor size (OR=1.544, 95% CI: 1.118–2.131, P=0.008), tumor differentiation (OR=1.667, 95% CI: 1.014–2.743, P=0.044), and TNM stage (OR=1.439, 95% CI: 1.085–1.908, P=0.012) were predictors of HCC recurrence after curative resection. However, only tumor size (OR=1.454, 95% CI: 1.047–2.020, P=0.026) and TNM stage (OR=1.360, 95% CI: 1.021–1.813, P=0.036) were independent predictors of HCC recurrence after curative resection. Therefore, the following equation was established to predict HCC recurrence: 0.308×TNM+0.374×tumor size–0.639. To validate the equation in the prediction of HCC recurrence after curative resection, we compared the equation value among patients with different prognoses, as shown in Figure 1. The equation score was 0.53±0.23 in patients who experienced an HCC recurrence, compared with 0.47±0.24 for other patients. Moreover, a similar trend was observed in patients who survived after the last follow-up, compared with those who did not (0.37±0.26 vs 0.52±0.22 [P<0.001]).

**Performance of the HCC recurrence equation in patient prognosis**

To determine the prognostic impact of the equation on patients with HCC, we conducted a Kaplan–Meier survival analysis using data from the 804 patients with HCC who were enrolled in this study. Based on the mean equation values,
we divided the 804 patients into two groups: those with equation values $>0.5$ and those with equation values $\leq 0.5$. In the equation value $>0.5$ cohort, the Kaplan–Meier analysis revealed that these patients with HCC had significantly worse recurrence outcomes than those in the other cohort ($P=0.043$). Similar trends were observed for overall survival (OS), which showed that patients with HCC with equation values $>0.5$ had significantly worse outcomes than those with equation values $\leq 0.5$ ($P<0.001$), as shown in Figure 2.

To further explore the relationship between the equation and clinical features, patients with HCC with equation values $>0.5$ were compared to those with equation values $\leq 0.5$ (Table 3). The patients with HCC with equation values $>0.5$ exhibited the majority of poor HCC clinical features.

**Univariate and multivariate Cox analyses of HCC prognostic variables**

To evaluate whether equation value was an independent risk factor for HCC outcomes, both univariate and multivariate Cox analyses were conducted. Age, serum AFP level, tumor size, tumor multiplicity, tumor differentiation, TNM stage, vascular invasion, involucrum, and equation value were all found to be prognostic variables for OS in patients with HCC. In the multivariate analysis, only tumor multiplicity ($P=0.039$), involucrum ($P=0.029$), vascular invasion ($P<0.001$), and equation value ($P<0.001$) were independent prognostic variables that were associated with OS (Table 4). Similarly, after conducting univariate and multivariate Cox analyses, tumor multiplicity ($P=0.01$), tumor differentiation
Subgroup analyses of equation values in patients with HCC

A stratified survival analysis was also conducted to further reveal the significance of equation values among patients with HCC. The equation score was significantly higher in patients with multiple tumors than in those with single tumors (0.63±0.17 vs 0.44±0.24, P<0.001). Additionally, the equation score in patients with incomplete involucrum was 0.52±0.23, compared to 0.48±0.24 in patients with complete involucrum (P=0.042). The equation score was 0.52±0.23 and 0.44±0.24, respectively, in patients with abnormal and normal serum AFP levels (P<0.001). Among patients with well-differentiated tumors, the equation score was 0.35±0.25, compared with 0.52±0.23 in patients with poorly differentiated tumors (P<0.001). For patients with and without liver cirrhosis, the equation scores were 0.49±0.24 and 0.57±0.22 (P<0.001), respectively, whereas in patients with positive and negative vascular invasion, the scores were 0.67±0.14 and 0.47±0.24, respectively (P<0.001), as shown in Figure 3.

Discussion

In this study, we explored the risk factors for recurrence in patients with HCC who underwent curative resection. Moreover, we established a novel, effective, and valid equation for predicting the probability of recurrence and OS after curative resection. TNM stage and tumor size were integrated into the equation, and the Kaplan–Meier survival analysis showed that patients with HCC with higher equation values displayed worse outcomes.

The etiology of HCC is variable and includes chronic virus infection, nonalcoholic liver disease, aflatoxin, and other complications.18 Due to the increased incidence of

Table 3 Association between clinical features and equation scores in hepatocellular carcinoma

| Variables                  | Equation score | P-value |
|---------------------------|----------------|---------|
|                           | >0.5           | ≤0.5    |
| Sample size               | 382            | 422     |
| Age (years)               | 47.95±12.12    | 49.71±11.72 | 0.036 |
| Sex, n (%)                | Male 342 (89.5) | 369 (87.4) | 0.355 |
|                           | Female 40 (10.5) | 53 (12.6) |
| HBsAg, n (%)              | Positive 331 (86.6) | 339 (80.3) | 0.016 |
|                           | Negative 51 (13.4) | 83 (19.7) |
| AFP (ng/mL), n (%)        | <20 60 (15.7) | 119 (28.2) | <0.001 |
|                           | ≥20 322 (84.3) | 303 (71.8) |
| Cirrhosis, n (%)          | Yes 289 (75.7) | 364 (86.5) | <0.001 |
|                           | No 93 (24.3) | 57 (13.5) |
| Tumor multiplicity, n (%) | Single 175 (45.8) | 357 (84.6) | <0.001 |
|                           | Multiple 207 (54.2) | 65 (15.4) |
| Differentiation, n (%)    | Well-moderate 14 (3.7) | 55 (13.0) | <0.001 |
|                           | Poor-undifferentiated 368 (96.3) | 367 (87.0) |
| Vascular invasion, n (%)  | Yes 125 (32.7) | 24 (5.7) | <0.001 |
|                           | No 257 (67.3) | 397 (94.3) |
| Involucrum, n (%)         | Complete 146 (38.3) | 190 (45.1) | 0.051 |
|                           | Incomplete 235 (61.7) | 231 (54.9) |
| Lymph node metastasis, n (%) | Positive 29 (7.6) | 16 (3.8) | 0.020 |
|                           | Negative 353 (92.4) | 405 (96.2) |

Abbreviations: AFP, α-fetoprotein; HBsAg, hepatitis B virus surface antigen.

Table 4 Univariate and multivariate analyses of prognostic variables for overall survival

| Variables                  | Univariate analysis OR 95% CI           | P       | Multivariate analysis OR 95% CI           | P       |
|---------------------------|----------------------------------------|---------|------------------------------------------|---------|
| Age (years)               | 0.991 0.984–0.997                       | 0.004   |                                          |         |
| Sex                       | 0.870 0.683–1.110                       | 0.263   |                                          |         |
| HBsAg                     | 1.166 0.949–1.433                       | 0.143   |                                          |         |
| AFP                       | 1.254 1.048–1.502                       | 0.014   |                                          |         |
| Cirrhosis                 | 0.976 0.800–1.190                       | 0.808   |                                          |         |
| Tumor size (cm)           | 1.644 1.370–1.972                       | <0.001  | 1.199 1.010–1.424                       | 0.039   |
| Tumor multiplicity        | 1.640 1.400–1.921                       | <0.001  |                                          |         |
| Differentiation           | 1.627 1.239–2.136                       | <0.001  |                                          |         |
| TNM                       | 2.078 1.774–2.433                       | <0.001  |                                          |         |
| Vascular invasion         | 2.586 2.139–3.126                       | <0.001  | 1.891 1.541–2.320                       | <0.001  |
| Involucrum                | 1.376 1.178–1.607                       | <0.001  | 1.196 1.018–1.404                       | 0.029   |
| Equation score            | 4.952 3.535–6.937                       | <0.001  | 3.242 2.231–4.711                       | <0.001  |

Abbreviations: AFP, α-fetoprotein; HBsAg, hepatitis B virus surface antigen.
obesity in the Western countries and the chronic virus infections in Asia, the incidence of HCC has remained high.19–21 Many studies have demonstrated the prognostic value of TNM stage, tumor burden, and impaired liver function (liver fibrosis, liver cirrhosis, and decompensated liver function) in HCC.22–27 Other studies have also reported that for HCC caused by chronic hepatitis B virus infection, many HBV-related indicators, including hepatitis B virus DNA load, HBsAg, and antiviral treatment, also affect the prognosis of patients with HCC.21,28–33 However, these prognostic indicators have limited value when used alone. How to combine data to improve prognostic value is a clinically practical issue. The CLIP score was the first system that took liver function and tumor characteristics into consideration for the classification of HCC treatment. However, the prognostic performance was reported to be poor because ~80% of the patients were classified with scores of 0–2.34,35 In this study, we combined TNM stage and tumor size into an equation. We have conducted a multivariable logistic regression analysis and included age, sex, HBsAg status, AFP level,
tumor multiplicity, and other variables to determine which variables are most related to HCC recurrence and constructed a prediction equation. Our results suggest that TNM stage and tumor size are most relevant to HCC recurrence. Therefore, other variables were not included in our equation, and the Kaplan–Meier survival analysis shows that the equation value could effectively predict the outcomes of the HCC population.

Combining several markers into one equation allows an analysis of patients with HCC with more comprehensive information and provides individualized risk assessments. Similar to the results from a previous study, our results indicate that tumor size is an independent risk factor for recurrence in patients with HCC. Tumor size is one of the most important tumor burden parameters. The results of this and previous studies indicate that advanced TNM stage closely associates with the development of HCC because of its positive correlation with tumor size and poor OS. Our equation exhibited superior discrimination of HCC recurrence in patients. Hence, the equation could be used to guide routine follow-up for patients. Especially, patients with HCC with high recurrence scores should undergo examinations more frequently, such as MRI or CT examinations, even if the most recent examination after curative resection indicates no cause for concern.

AFP and tumor multiplicity have been reported as prognostic markers in HCC. AFP is a serum HCC marker that has been previously used to monitor HCC recurrence. However, AFP levels can also be elevated in some diseases, such as liver cirrhosis and female reproductive system tumors. Although high preoperative AFP levels are associated with poorer HCC outcomes, there is a certain proportion of patients with HCC with AFP levels that are within the upper limit of normal. For those AFP-negative patients with HCC, AFP is not a suitable prognostic marker. In this study, patients with HCC with abnormal or normal AFP levels could be effectively stratified using this equation. Tumor multiplicity is another prognostic marker that has been reported in HCC. According to this study, equation scores significantly differ between patients with a single HCC and those with multiple HCCs. No matter whether patients with HCC have a single tumor or multiple tumors, our equation can further risk stratify these subpopulations with HCC.

Whether or not the equation can improve the prognosis of patients with HCC remains an interesting and important question. The main reason why HCC is difficult to treat is its high recurrence rate. Moreover, the clinical symptoms of HCC are not obvious. When the typical symptoms occur, HCC has typically progressed to a state that makes treatment difficult. Therefore, the method for screening patients with HCC after surgery to facilitate early recurrence detection is a clinically critical problem. The early detection of HCC recurrence and early intervention can improve patient prognosis. However, high-frequency screening of all patients is not a cost-effective strategy. According to the results of this study, high-frequency follow-up and screening for high-risk patients, early detection of HCC recurrence, and early interventions may ultimately improve the prognosis of patients. However, this requires further prospective studies to confirm.

**Conclusion**

Here we established a novel and effective equation for predicting the probability of recurrence and OS after curative resection. Patients with a high recurrence score, based on this equation, should undergo additional high-end imaging examinations. Although our equation showed good performance, several limitations need to be addressed. First, the equation was derived from data collected at a single institution. Second, the etiology of HCC in China is mostly due to chronic hepatitis B. Third, because this study was a retrospective study, the results may be biased. For future performance algorithms, prospective cohort studies are needed.

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**Disclosure**

The authors declare that they have no financial or personal relationships with other people or organizations that could inappropriately influence this work. The authors report no other conflicts of interest in this work.

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