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Prognostic factors of patients after liver cancer surgery

Based on Surveillance, Epidemiology, and End Results database

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Abstract

This study aimed to investigate the prognostic factors of patients after liver cancer surgery and evaluate the predictive power of nomogram. Liver cancer patients with the history of surgery in the Surveillance, Epidemiology, and End Results database between 2000 and 2016 were preliminary retrieved. Patients were divided into the survival group (n=2120, survival ≥5 years) and the death group (n=2615, survival < 5 years). Single-factor and multi-factor Cox regression were used for analyzing the risk factors of death in patients with liver cancer after surgery. Compared with single patients, married status was the protective factor for death in patients undergoing liver cancer surgery (HR=0.757, 95%CI: 0.685–0.837, $P < .001$); the risk of death in Afro-Americans (HR=1.300, 95% CI: 1.166–1.449, $P < .001$) was higher than that in Caucasians, while the occurrence of death in Asians (HR=0.821, 95%CI: 0.1754–0.895, $P < .0012$) was lower; female patients had a lower incidence of death (HR=0.875, 95%CI: 0.809–0.947, $P < .001$); grade II (HR=1.167, 95%CI: 1.080–1.262, $P < .001$), III (HR=1.580, 95%CI: 1.433–1.744, $P < .001$), and IV (HR=1.419, 95%CI: 1.145–1.758, $P=0.001$) were the risk factors for death in patients with liver cancer. The prognostic factors of liver cancer patients after surgery include the marital status, race, gender, age, grade of cancer and tumor size. The nomogram with good predictive ability can provide the prediction of 5-year survival for clinical development.

Abbreviations: CI = confidence interval, HR = hazard ratio, SEER = Surveillance, Epidemiology, and End Results.

Keywords: clinicopathologic characteristics, liver cancer, prognostic factors

1. Introduction

Liver cancer is the sixth commonly diagnosed cancer and the third leading cause of cancer-related death, with estimated 905,677 new cases and 830,000 cancer deaths from the GLOBOCAN 2020 database.[1] The incidence and mortality of liver cancer grow rapidly worldwide according to the estimates of the World Health Organization in 2019,[2] which ranks fifth in terms of global incidence and second in terms of mortality for men, respectively.[3] Patients with liver cancer have a poor prognosis. Although the diagnosis and treatment of liver cancer have been greatly developed in the past years, the efficacy is still unsatisfied.

The treatments for early-stage patients include hepatectomy, transplantation and radiofrequency ablation.[4–7] However, most patients are diagnosed at an advanced stage of liver cancer, thus the curative rates of the above treatments are relatively low.[8] Therapies for patients at more advanced stage contain trans-arterial chemoembolization and chemotherapy.[7] However, the chemoresistance of liver cancer is considerably high and this may lead to a low overall response rate.[9] Only one-third of patients can benefit from the chemotherapy, and the long-term use of chemotherapeutic drugs can also bring patients toxicity and/or drug inefficacy. Even though the patients accept surgical treatments, the prognosis is still poor due to the frequent relapse. Current studies show that the 5-year survival of liver cancer patients after surgery (hepatectomy, transplantation, systemic chemotherapy and trans-arterial chemoembolization) ranges from 37% to 65%, while the recurrence rate is extremely high as 75% to 100%.[10–12] Therefore, the prediction of risk factors for long-term survival of liver cancer patients is important in clinic practice.

The present study retrieving the information of liver cancer patients after surgery from the Surveillance, Epidemiology, and End Results (SEER) database aimed to investigate the prognostic factors and the power of prediction nomogram to improve the survival of patients.

2. Materials and methods

2.1. Patients

Liver cancer patients with the history of surgery in the SEER database between 2000 and 2016 were preliminary retrieved, and

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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Table 1

Characteristics of included liver cancer patients in death and survival groups.

Variables	Death group (n=2615)	Survival group (n=2120)	Statistic	P
Marital status, n (%)			χ^2=44.75	<.001
Single	400 (15.60)	313 (15.10)		
Married	1629 (63.60)	1425 (68.90)		
Separation/divorce	276 (10.80)	229 (11.10)		
Widow	256 (10.00)	100 (4.80)		
Race, n (%)			χ^2=26.55	<.001
Caucasians	1728 (66.10)	1416 (66.80)		
Afro-Americans	318 (12.20)	169 (8.00)		
Asians	533 (20.40)	506 (23.90)		
Other	36 (1.40)	29 (1.40)		
Gender, n (%)			χ^2=0.12	.728
Male	1897 (72.50)	1529 (72.10)		
Female	718 (27.50)	591 (27.90)		
Histologic type, n (%)			χ^2=16.08	<.001
Adenomas/adenocarcinomas	2574 (98.40)	2069 (97.60)		
Complex and mixed stromal neoplasms	11 (0.40)	32 (1.50)		
other	30 (1.10)	19 (0.90)		
Grade, n (%)			χ^2=90.48	<.001
I	773 (29.60)	824 (38.90)		
II	1198 (45.80)	985 (46.50)		
III	556 (21.30)	255 (12.00)		
IV	88 (3.40)	56 (2.60)		
Brain metastasis, n (%)			χ^2=3.81	.051
No	2597 (99.30)	2114 (99.70)		
Yes	18 (0.70)	6 (0.30)		
First malignant primary indicator, n (%)			χ^2=40.14	<.001
No	372 (14.20)	176 (8.30)		
Yes	2243 (85.80)	1944 (91.70)		
Age, Mean (SD)	62.23 (12.51)	57.23 (13.16)	t=13.36	<.001
Size, M (Q1, Q3)	5.00 (3.00, 8.00)	3.50 (2.10, 5.70)	Z=15.41	<.001
Survival time, M (Q1, Q3)	17.00 (7.00, 33.00)	121.00 (97.00, 144.00)	Z=59.26	<.001

n (%) represents the number of cases and the constituent ratio; M (Q1, Q3) describes median and interquartile range.

patients with missing data were deleted. Patients with missing data of grade stage, race, liver metastasis, survival outcome, survival time and tumor size were excluded.

All included data were collated and recoded. Possible influencing factors were regrouped according to Table 1 for statistical analysis. Patients who survived longer than 5 years were assigned into the survival group (n=2120), and those who survived shorter than 5 years were assigned into the death group (n=2615). The SEER database (https://seer.cancer.gov/) is a free database of the United States National Cancer Institute which collects the basic demographics and some cancer characteristics of patients from different parts. All the information of the cancer registries was strictly handled to protect the confidentiality of the participants.

2.2. Collection of baseline information

Baseline characteristics including material status, race, gender, age, histologic type, grade of cancer, brain metastasis, first malignant primary indicator, size of tumor and survival time were retrieved in the present study.

2.3. Statistical analysis

Two side-test was performed in this study. $P<.05$ was considered statistically significant. All statistical analysis was completed using *R* statistical analysis software.

Comparison of the characteristic difference between the death group and the survival group: Normally distributed measurement data were described by mean ± standard deviation ($\overline{x}\pm s$), and independent samples t test was used for comparison between groups; non-normal data were described by median and interquartile range (M (Q1, Q3)); the Mann–Whitney U rank-sum test was used for comparison between groups; enumeration data were described by the number of cases and the constituent ratio (n (%)), and the comparison between groups was performed by χ^2 test or Fisher's exact probability test. Single-factor and multi-factor Cox regression were used to analyze the risk factors of death in patients with liver cancer. The statistically significant variables in multi-factor Cox regression were utilized to recalculate the regression model, and the nomogram was drawn to predict the probability of death at 5 years.

Assessment of prediction nomogram: (1) C index was calculated to evaluate the predictive power of multi-factor COX regression nomograms: C=0.50 indicated no predictive power; $0.51\leq C\leq 0.70$ showed low accuracy of prediction; $0.71\leq C\leq 0.9$ meant moderate accuracy of prediction; $C>0.90$ exhibited high accuracy of prediction. (2) Calibration diagram: The predictive mortality rate by nomograph was formed from low to high, and divided into 3 groups according to the quartile. The Kaplan–Meier was used to calculate the mean of the predicted survival probability and the corresponding actual survival probability of each group. The predicted and actual

Table 2

Influence of prognostic factors on patients after liver cancer surgery.

	Single-factor		Multi-factor	
Variables	HR (95%CI)	P	HR (95%CI)	P
Marital status				
Single (reference)				
Married	0.930 (0.846, 1.024)	.141	0.757 (0.685, 0.837)	<.001
Separation/divorce	1.026 (0.900, 1.171)	.696	0.858 (0.750, 0.980)	.024
Widow	1.556 (1.362, 1.802)	<.001	0.949 (0.815, 1.106)	.510
Race				
Caucasians (reference)				
Afro-Americans	1.319 (1.187, 1.466)	<.001	1.300 (1.166, 1.449)	<.001
Asians	0.869 (0.799, 0.946)	.001	0.821 (0.754, 0.895)	<.001
Other	1.006 (0.756, 1.339)	.965	0.931 (0.683, 1.270)	.652
Gender				
Male (reference)				
Female	1.006 (0.934, 1.084)	.866	0.875 (0.809, 0.947)	<.001
Histologic type				
Adenomas/adenocarcinomas (reference)				
Complex and mixed stromal neoplasms	0.332 (0.201, 0.553)	<.001	0.691 (0.396, 1.206)	.194
other	1.115 (0.803, 1.549)	.515	1.015 (0.722, 1.428)	.931
Grade				
I (reference)				
II	1.14 (1.055, 1.230)	<.001	1.167 (1.080, 1.262)	<.001
III	1.586 (1.440, 1.757)	<.001	1.580 (1.433, 1.744)	<.001
IV	1.220 (0.994, 1.495)	.056	1.419 (1.145, 1.758)	.001
Brain metastasis				
No (reference)				
Yes	1.992 (1.309, 3.030)	.001	1.578 (0.964, 2.581)	.067
First malignant primary indicator				
No (reference)				
Yes	0.690 (0.626, 0.761)	<.001	0.558 (0.480, 0.650)	<.001
Age, M (Q1, Q3)	1.027 (1.024, 1.030)	<.001	1.028 (1.025, 1.032)	<.001
Size, M (Q1, Q3)	1.002 (1.001, 1.002)	<.001	1.001 (1.001, 1.002)	<.001

CI=confidence interval, HR=hazard ratio.

survival rate were combined to obtain 3 calibration points. The predicted calibration curve was attained by connection of 3 calibration points. In theory, the standard curve is a straight line passing through the origin of the coordinate axis with a slope of 1. The closer the predicted calibration curve is to the standard curve, the better the predictive ability of the nomogram is.

3. Results

3.1. Baseline information of included patients

Among 4735 included patients in this study, 2615 cases had a survival time of shorter than 5 years (death group), and 2120 had a survival time of longer than 5 years (survival group). The age of the death group was older than that of the survival group (62.23 ± 12.51 vs 57.23 ± 13.16; $P < .001$), and the tumor size was larger (5.00 ± 3.00, 8.00 vs 3.50 ± 2.10, 5.70; $P < .001$). The median survival time of the death group was shorter than that of the survival group (17.00 vs 121.0 months, $P < .01$) (Table 1).

3.2. Influence of prognostic factors on patients undergoing liver cancer surgery

Table 2 exhibited the results of single-factor and multi-factor Cox regression analysis. Single-factor analysis revealed that widows had a higher risk of death in patients undergoing liver cancer surgery (HR=1.566, 95%CI: 1.362–1.802), $P < .001$); the risk of death in the Afro-Americans was 1.319 times that of the Caucasians (HR=1.319, 95%CI: 1.187–1.466, $P < .001$); Asians had lower death ratio than Caucasians (HR=0.869, 95%CI: 0.799–0.946, $P < .001$); the incidence of death in patients with complex and mixed stromal neoplasms was lower than patients with adenomas and adenocarcinomas (HR=0.332, 95%CI: 0.201–0.553, $P < .001$); the risk of death increased with the increasing age (HR=1.027, 95%CI: 1.024–1.030, $P < .001$).

Multi-factor analysis demonstrated that compared with single patients, married status was the protective factor for death in patients undergoing liver cancer surgery (HR=0.757, 95% CI: 0.685–0.837, $P < .001$); Afro-Americans had a higher prevalence of death (HR=1.300, 95%CI: 1.166–1.449, $P < .001$) than Caucasians while the incidence of Asians was lower (HR=0.821, 95%CI: 0.1754–0.895, $P < .001$); female patients had a lower incidence of death than male (HR=0.875, 95%CI: 0.809–0.947, $P < .001$); grade II (HR=1.167, 95%CI: 1.080–1.262, $P < .001$), III (HR=1.580, 95%CI: 1.433–1.744, $P < .001$), and IV (HR=1.419, 95%CI: 1.145–1.758, $P = .001$) were the risk factors for death in patients with liver cancer. The increasing age (HR=1.028, 95%CI: 1.025–1.032, $P < .001$) and tumor size (HR=1.001, 95%CI: 1.001–1.002, $P < .001$) were risk factors for death of liver cancer patients (Table 2).

3.3. 5-Year survival probability nomograms in patients after liver cancer surgery

The multivariate Cox regression variables with statistical significance ($P < .05$) were generated to reconstruct a regression model and draw the nomogram to predict the probability of death among the patients (Fig. 1). The probability of 5-year survival could be estimated by adding the related scores projected in the Figure 1. The prediction ability of the nomogram was general (C: 0.636, 95%CI: 0.626–0.646).

The calibration chart of the 5-year survival probability prediction of patients undergoing liver cancer surgery showed that the predicted survival probability curve of the nomogram was close to the corresponding standard curve of actual survival probability (calculated by the Kaplan–Meier estimate (KM) method), indicating that the nomogram had a good predictive ability (Fig. 2).

4. Discussion

Considering the increasing incidence and mortality of liver cancer,[13] our study focused on investigating the prognostic factors of liver cancer in order to provide the references for clinical diagnosis and treatment. In the current study, a total of 4735 patients from SEER database were included, and all patients were divided into the death group (n=2615) and the survival group (n=2120) according to the survival time. Results demonstrated that the survival probability of liver cancer patients can be influenced by the marital status, race of patients, gender, age, grade of cancer and size of tumor.

He et al suggested that married patients may access the medical remedy better than others,[14] bringing early detections and treatments. In our study, we found that the marital status was related to the morbidity of liver cancer after surgery. Married patients had lower risk of death than others. Several biological, psychological and social theories have been postulated to explain survival benefits associated with marriage.[14] The likely reason may be related to the following factors: married patients have better adherence to prescribed treatments than unmarried patients; married patients can provide their spouses with adequate social support and share the emotional burden of psychological distress, anxiety and depression resulting from the diagnosis of liver cancer.[14] Interestingly, our finding showed that a separation/divorce was also a protecting factor after surgery for liver cancer ($P=.02$), which is controversial. Unfortunately, we cannot compare the effects among different single patients, as our data do not provide detailed information on the reasons for separation/divorce, whether voluntary or passive. Racially, the risk of death in Afro-Americans was higher than Caucasians, and Asians had lower risk than Caucasians. The rates of overweight and obesity were lower in Asians in comparison with other ethnic groups in the US, and this probably has an impact in the development of liver cancer. Previous studies confirmed the higher risk of Afro-Americans and pointed out the reason why Afro-Americans had longer delay to surgery than others.[15,16] Since the inferiority in finance and socioeconomic status and the longer delay between diagnosis and surgery of Afro-Americans kept them away from better medical consultation and resources financially as well as possibility of treatment in early stage. We also observed that the occurrence of death in female patients was higher than that in male, which is in line with the study conducted by Chen et al.[17] The reason may be the protective role of estrogens via suppressing liver cancer cell growth through upregulation of NLRP3 inflammasome in women.[18,19]

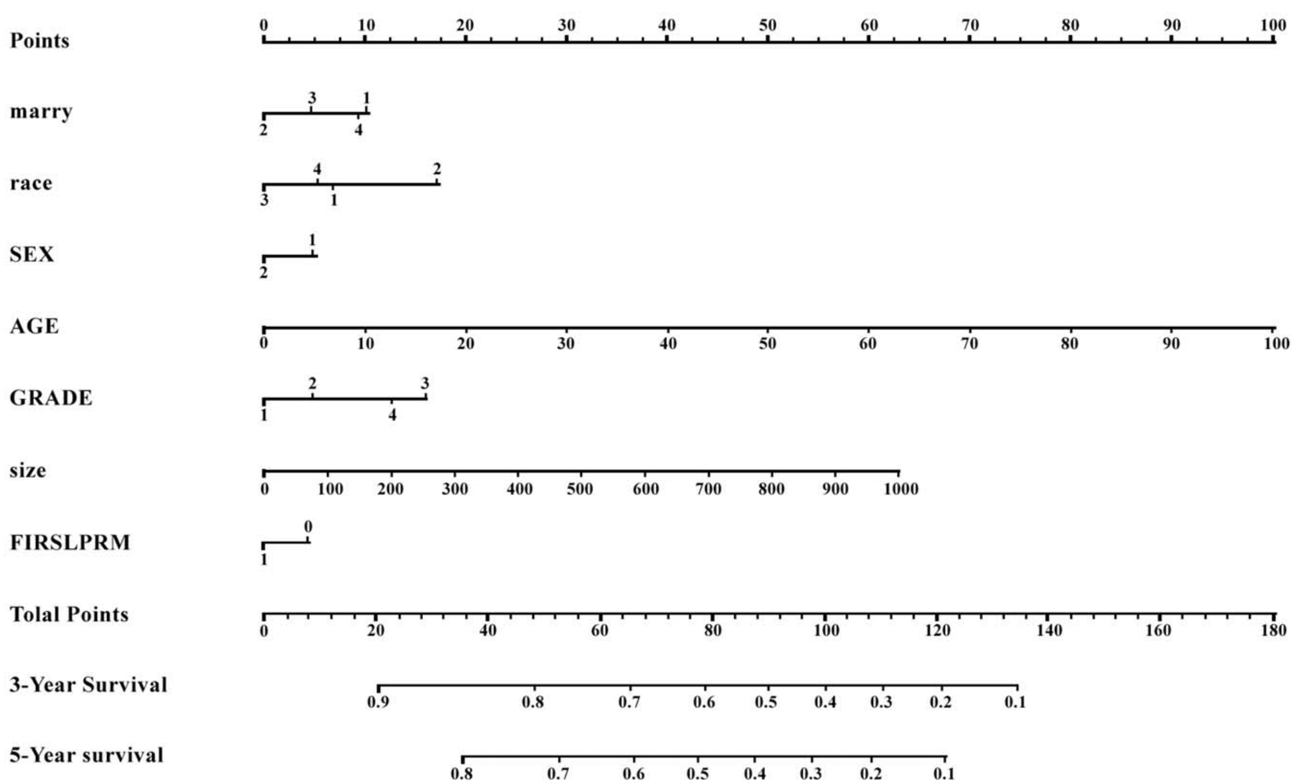

Figure 1. Survival probability prediction nomogram of patients undergoing liver cancer surgery.

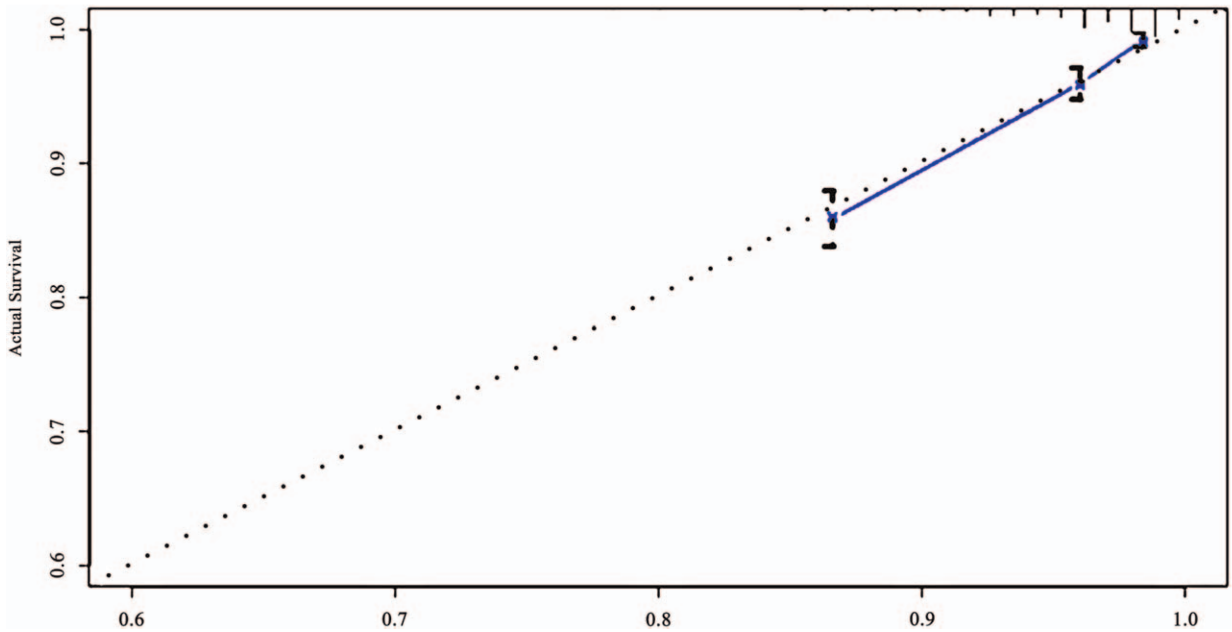

Figure 2. Calibration chart of 5-year survival probability of patients undergoing liver cancer surgery.

It is well known that patients with poorly differentiated/undifferentiated tumors have better prognosis than those with highly differentiated and moderately differentiated tumors.[20,21] Current study confirmed that compared with the differentiation degree of grade I, grade II, III, and IV were considered to be the risk factors for death in patients with liver cancer. Age has prognostic effects on many solid cancers. Our study revealed the higher risk of death in older liver cancer patients. Zhang et al exhibited the significant differences including pathologic grading, histologic type, stage, and tumor size in different age groups, and the results revealed the higher mortality of liver cancer patients in older ages.[22] Aged patients have a worse survival, which is compensated by worse liver function, less aggressive therapy, and slower recovery. Conversely, the study constructed by Cho et al illustrated the poorer prognosis in younger patients according to the advanced tumor stage at diagnosis,[23] because they are at a more advanced stage at diagnosis with more aggressive tumor.

After analyzing the influence factors of the long-time survival of liver cancer patients undergoing surgery, we constructed the nomogram to predict the 5-year survival of included patients based on the SEER database. The calibration chart of the 5-year survival probability prediction of patients undergoing liver cancer surgery showed that the predicted survival probability curve of the nomogram was close to the corresponding standard curve of actual survival probability, indicating that the nomogram had a good predictive ability.

The present study has some limitations as follows: a. the study is a retrospective study with selection bias and the sources of bias could not be controlled. This indicates that the findings of our study should be interpreted with caution and further studies are needed to be carried out to validate the conclusions of our study. b. SEER database contains basic demographics and some clinical characteristics, unable to provide us with other information, such as the association between dietary patterns, vitamin D or concurrent hepatitis B infection and liver cancer. Although studies conducted by Yang et al pointed out that several healthy dietary patterns (e.g., Alternative Healthy Eating Index) may decrease liver cancer risk[24]; Zhang et al reported a relationship between serum vitamin D levels and the risk of liver cancer[25]; Lebossé and Zoulim mentioned that hepatitis B infection is a risk factor of liver cancer development for patients with HBV chronic infection.[26] In spite of limitations above, by using liver patients from the SEER database between 2000 and 2016, the large population and multiple centers were a convincing basis for the current study. In the future, the prospective studies should be carried out and the clinical data will be collected systematically to improve the reliability of the conclusion of this study.

5. Conclusions

The survival probability of liver cancer patients can be influenced by the marital status, race of patients, gender, age, grade of cancer and size of tumor. The present nomogram with good predictive ability can provide the prediction of 5-year survival for clinical development.

Author contributions

Conceptualization: Fangfang Liang, Jincai Zhong.
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