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Original Article

Prospective analysis of risk factors for hepatocellular carcinoma in patients with HBV-related liver cirrhosis

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Abstract: Background: Hepatocellular carcinoma (HCC) is associated with liver cirrhosis, especially HBV-related cirrhosis. Early detection offers the best odds of improving HCC outcomes. The current study aimed to discover predictive factors for development of HCC in Chinese Han patients with HBV-related liver cirrhosis. Methods: A total of 177 patients, aged 40 to 60 years, with HBV-related liver cirrhosis in Child-Pugh class A or B, were enrolled. The predictive value of different risk factors was evaluated using Kaplan-Meier and Cox regression methods. Results: At the end of follow-up, 38 patients developed HCC. According to Cox regression analysis, five variables showed an independent predictive value for development of HCC, including age more than 55 years, history of esophageal variceal bleeding, prothrombin activity less than 75%, platelet count less than 75 × 10^3/mm^3, and AFP levels more than 38 ng/mL. Serum AFP levels were significantly increased in poorly-differentiated patients, compared to the moderately differentiated group and well differentiated group. Conclusion: The present study found that five risk factors (age, esophageal variceal bleeding history, prothrombin activity, platelet count, and AFP) may be predictive values for patients with HBV-related cirrhosis. A simplified score, made up of these risk factors, enabled present researchers to identify patients with cirrhosis that were at high risk or low risk for development of HCC. Higher AFP levels were significantly related to poorly-differentiated patients.

Keywords: Hepatitis B virus, hepatocellular carcinoma, prognostic factors, univariate and multivariate analysis

Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide [1]. Occurrence and development of HCC is a complicated process involving external environmental carcinogenesis factors, virus factors, autoimmune deficiency, and gene expression levels [2-4]. HCC patients usually have a poor prognosis in the symptomatic phase, leading to high mortality. Therefore, early detection of HCC offers the best chance to improve HCC outcomes. China is a high-prevalence areas for hepatitis B virus (HBV) infections [5]. Previous reports have indicated that cumulative 5-year liver cirrhosis incidence is 12%-15% in chronic hepatitis B patients, while cumulative 5-year liver cancer incidence is 6%-15% in patients with chronic liver cirrhosis [6, 7]. Therefore, screening and surveillance for HCC in patients with cirrhosis is important. It can be an efficient way to reduce HCC mortality. Current diagnostic tools for screening and early detection of HCC include abdominal ultra-sonographies, computed tomography, magnetic resonance imaging, and serum α-fetoprotein (AFP) levels [8-10]. However, the efficacy of these detection items in reducing incidence of HCC in Chinese Han patients has been rarely reported. A better understanding of these risk factors could lead to more useful and efficient surveillance programs.

The aim of the current research was to discover predictive factors for development of HCC in Chinese Han patients with HBV-related liver cirrhosis. Furthermore, this study conducted the predictive index to classify different risks levels in cirrhosis patients progressing to HCC during a 5-year follow-up period. Remarkably, the current study also examined the association between pathologic differentiation degrees and characteristics of patients with HCC.

Patients and methods

Patients

From July 2011 to July 2016, 177 hospitalized Fujian Han patients, with HBV-related liver cirrhosis but no detectable HCC, were enrolled. Cirrhosis was histologically verified by liver biopsies in 104 patients (58.8%). All patients included in this study met the following criteria: 1) HBV-related hepatic cirrhosis; 2) Age ranged from 40 to 60 years; 3) Child- Pugh class A or class B; 4) Availability to attend regular visits; and 5) Absence of severe extrahepatic diseases. Patients with alcoholic cirrhosis, primary biliary cirrhosis, drug-induced cirrhosis, autoimmune cirrhosis, and other non-HBV related liver cirrhosis were excluded. All patients were required to perform the abdominal ultrasonography test to monitor levels of serum AFP every 3 or 6 months [11]. The study was terminated at the time of HCC diagnosis, patient death, or when patients were lost to follow-up. The current study was approved by the Ethics Committee of First Affiliated Hospital, Fujian Medical University. Written informed consent was obtained from all subjects.

Follow up

The following data were collected: age, gender, HBeAg and HBV DNA, serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and AFP, prothrombin activity (PTA), platelet count, esophagogastric varices with a bleeding history, family history of HBV infections, and use of alcohol and cigarettes. This study included 133 men (75.14%) and 44 women (24.85%). A total of 102 patients (57.63%) were Child-Pugh class A, while 75 (42.37%) were class B.

The average follow-up time was 55.3 ± 10.6 months. During the follow-up period, all patients were examined via abdominal ultrasonography. Concentrations of serum AFP were measured and routine biochemical and immunological tests were conducted every 3 to 6 months. Criteria for diagnosis of HCC included rising serum AFP concentrations and imaging evidence of intrahepatic or extrahepatic. Radiological criteria for diagnosis of HCC were: (a) One or more hypoechoic, hyperechoic, or mixed nodules on ultrasonography in association with one or more hyper-vascular nodules with enhancement in the arterial phase on computed tomography (CT); and/or (b) One or more hyper-vascular nodules on magnetic resonance imaging (MRI) with gadolinium infusion. When findings on CT scans or MRIs were inconclusive or discordant, hepatic angiographies with an infusion of iodized oil (Lipiodol, UltraFluide, Laboratoires Guerbet, Aulnay-sous-Bois, France) were performed. Serum AFP levels were measured by IMx Microparticle Enzyme Immunoassay (MEIA) system (Abbott Laboratories, Abbott Park, Illinois, USA). ELISA method (Beijing Wantai Biological Pharmacy, Beijing, China) was used to detect HBsAg and HBeAg levels. Positive results were interpreted as Optical Density ≥ 2.1 × NC (average of negative control, calculated as 0.05 if less than 0.05). HBV DNA kit used a nucleic acid lysis buffer to allow rapid lysis and release of HBV DNA from 5 μl serum. All kits were provided by Sansure Biotech Inc. (Hunan, China) and used according to manufacturer instructions. Extracted HBV DNA was subsequently amplified by Genome Diagnostic HBV quantification kit (Sansure Biotech Inc., China) for RT-qPCR using a Roche Lightcycler 480 analyzer (Roche Corporation, Basel, Switzerland). AST and ALT were determined using an automatic biochemistry analyzer cobas8000 (Roche Diagnostics, Switzerland), according to manufacturer instructions, on the principle of Enzyme Kinetics with standard substance and quality control substance from American Bio-Rad Laboratories (Hercules). The upper limit of normal (ULN) for ALT and AST was 40 U/L and 35 U/L, respectively.

Patients with both focal lesions under ultrasound examinations and elevated AFP concentrations (> 250 ng/ml) were further examined by computed tomography, even fine-needle aspiration biopsies. Liver biopsies were fixed by immersion in alcoholic Bouin's liquid for 6 to 10 hours, then embedded in paraffin. They were finally stained with hematoxylin-eosin-safran, Masson's trichrome, and picrosirius red. The following histological features were studied: 1) Large-cell dysplasia; 2) Small cell changes; and 3) Cellular inflammatory infiltrate. A final diagnosis of HCC was according to the criteria of NCCN clinical practice guidelines of oncology [12]. At the end of the follow-up period, 38 (21.47%) of 177 patients had developed HCC. HCC diagnosis was confirmed by positive histologic examinations in 28 of 38 patients (73.68%) and hepatic focal lesions under image examinations with serum AFP levels more than 250 ng/mL (n = 10, 26.32%).

Statistical analysis

The end-point was an appearance of HCC. The end of the follow-up period was the time when patients were lost to follow-up (17/177, 9.6%). Data was analyzed by SPSS version 22.0 software (SPSS Inc, USA) and GraphPad Prism software version 5.0 (GraphPad Software, USA). Kaplan-Meier analysis was utilized to determine the probability of the appearance of HCC during the 5-year follow-up period. Meaningful variables in the univariate analysis were selected for the Cox proportional hazards model. Continuous variables were compared using Student's t-test and are expressed as mean ± SD. Chi-squared test was used to compare frequencies. All data were analyzed using SPSS 22.0 statistical package (SPSS, Inc.). All tests were two-sided, with *P* values less than 0.05 indicating statistical significance.

Results

Baseline characteristics of patients enrolled in the study (n = 177)

A total of 177 patients with HBV-related liver cirrhosis were enrolled in the current study. At the end of the follow-up period, 38 (21.47%) of the 177 patients had developed HCC. HCC diagnosis was confirmed by positive histologic examinations in 28 of 38 patients (73.68%) and hepatic focal lesions under an image examination with serum AFP levels more than 250 ng/mL (n = 10, 26.32%). Baseline demographics, laboratory tests, and clinical data are listed in **Table 1**. A total of 38 of the 177 (21.5%) patients developed HCC. Thirty-three patients (86.8%) were male. Compared to female patients, males had a higher risk of developing HCC (5 vs 33, $P < 0.05$). The mean age of patients developing HCC was 56.61 years. Patients with HCC were significantly older than those without HCC (56.61 ± 10.35. vs 52.24 ± 11.41, respectively, $P = 0.035$). Moreover, 18 patients (47.4%) were in Child-Pugh class B, while 20 patients had a family story of HBV infection. Additionally, 15 patients (39.5%) had a history of smoking, while 16 patients (42.1%) had a history of alcoholism (**Table 1**).

Five years of follow-up and detection of HCC

During the first year of the follow-up period, no HCC cases were reported. In the second year, incidence of HCC was 3.9%. It was 5.6% in the third, 5.6% in the fourth, and 6.2% in the fifth year. The average annual incidence rate was 4.28%. The cumulative incidence was 3.3% for the second year. It was 11.7% for the third year, 16.0% for the fourth year, and 23.5% for the fifth year.

Establishing predictive models and validating the predictive scale

Variables with *P* values less than 0.05 were shown to be significantly associated with HCC, according to univariate analysis (**Table 1**). For continuous variables, receiver operating characteristics (ROC) curves were utilized to estimate optimal cutoff values, including age > 55 years old ($P = 0.002$), history of smoking ($P = 0.034$), presence regular alcohol drinking ($P = 0.004$), history of esophageal variceal bleeding ($P < 0.001$), platelet count less than $75 \times 10^3/mm^3$ ($P = 0.011$), concentration of AST three times higher than normal ($P = 0.025$), levels of AFP greater than 38 ng/mL ($P < 0.001$), and prothrombin activity under 75% ($P = 0.001$).

Cox regression analysis was carried out to calculate the prognostic index of those variables. Multivariate analysis demonstrated that age, esophageal variceal bleeding history, platelet count, AFP levels, and prothrombin activity were significantly related to occurrence of HCC (all *P* values < 0.05) (**Table 2**). Prognostic index = 0.05 (if the age ≥ 55 years) + 1.036 (if there was a history of esophageal variceal bleeding) + 0.074 (if the prothrombin activity < 75%) + 0.009 (if the platelet count $< 75 \times 10^3/mm^3$) + 0.002 (if the AFP level > 38 ng/mL). Scores ranged from 0 to 1.171. The cut-off point of the low risk group was under 0.125, according to ROC curve analyses (**Figure 1**). All patients were classified into 2 groups: low risk scores below 0.125 (n = 117, 9 with HCC) and high risk when scores were above 0.125 (n = 60, 29 with HCC). The cumulative risk for occurrence of HCC during the 5 years was 7.70% in the low risk group, compared with 48.33% in the high-risk group ($P = 0.0001$) (**Figure 2**).

Serum AFP was associated with pathologic differentiation degree in patients with HCC

Hepatocellular carcinoma was verified by positive histologic examinations in 28 of 38 patients (73.68%). In the 28 cases of HCC patients, there were 12 cases in the AFP ≤ 20 ng/mL group, 13 cases in AFP 20-400 ng/mL group,

Table 1. Baseline clinical and biological data of patients with LC enrolled in the study

Factor	n	With HCC	% HCC	Survival time	95% CI	Log Rank test *P* value
Gender						
Male	133	33	24.8%	54.714 ± 0.976	52.801-56.627	
Female	44	5	11.4%	57.20 ± 1.181	54.889-59.520	0.071
Age (year)						
> 55	81	27	33.3%	57.396 ± 0.891	50.289-55.489	
≤ 55	96	11	11.5%	52.889 ± 1.327	55.650-59.142	0.002
Child-Pugh class						
A	102	20	19.6%	55.294 ± 1.094	53.149-57.439	
B	75	18	24.0%	55.387 ± 1.139	53.155-57.618	0.542
Family history						
Yes	42	20	47.6%	54.833 ± 1.725	51.453-58.214	
No	135	18	13.3%	55.489 ± 0.892	53.741-57.237	0.677
Smoking						
Yes	46	15	32.6%	53.326 ± 1.751	49.895-56.758	
No	131	23	17.6%	56.038 ± 0.871	54.331-57.745	0.034
Alcohol						
Yes	43	16	37.2%	52.209 ± 1.938	48.806-56.404	
No	134	22	16.4%	56.209 ± 0.830	54.581-57.837	0.004
Bleeding						
Yes	39	19	48.7%	54.794 ± 0.894	53.040-56.547	
No	138	19	13.8%	59.136 ± 0.590	57.980-60.293	< 0.001
HBeAg (PEIU/mL)						
Positive	58	12	18.9%	58.800 ± 1.038	56.765-60.835	
Negative	119	26	22.7%	58.792 ± 0.533	57.747-59.838	0.768
HBV DNA (IU/mL)						
> 500	61	18	29.5%	58.344 ± 0.694	56.985-59.704	
≤ 500	116	20	17.2%	59.654 ± 0.361	58.946-60.362	0.236
Platelet count (10^3/mm^3)						
< 75	79	24	30.4%	56.694 ± 0.968	54.797-58.590	
≥ 75	98	14	14.3%	53.646 ± 1.288	51.121-56.170	0.011
AFP (ng/ml)						
> 38	37	23	62.2%	56.419 ± 1.801	52.889-59.949	
38	140	15	10.7%	59.427 ± 0.348	58.746-60.108	< 0.001
ALT (U/L)						
> 40	57	14	24.6%	55.175 ± 1.439	52.356-57.995	
≤ 40	120	24	20.0%	55.408 ± 0.951	53.544-57.273	0.531
AST (U/L)						
> 3N	7	4	57.1%	52.857 ± 2.699	47.568-58.147	
≤ 3N	170	34	20.0%	55.435 ± 0.818	53.831-57.039	0.025
PTA (%)						
> 75	79	3	3.8%	55.738 ± 1.286	53.216-58.259	
< 75	98	35	35.7%	55.701 ± 1.053	53.638-57.764	0.001

and 3 cases in the AFP > 400 ng/mL group. Pathologic differentiation degrees were significantly different among the three groups (*P* = 0.012).

Next, according to pathologic differentiation degrees, the 28 HCC patients were divided into three groups: poorly-differentiated (N = 4), moderately differentiated (N = 10), and well differ-

Table 2. Relationship of baseline characteristics data and occurrence of HCC according to the Cox regression model

Factor	n	Patients with HCC	% HCC	Cox regression					
				RC	SE	Wald	*P* value	HR	95% CI
Gender									
Male	133	33	24.8%	0.022	0.377	0.003	0.953	1.022	0.488-2.140
Female	44	5	11.4%						
Age (year)									
> 55	81	27	33.3%	0.050	0.016	9.510	0.002	1.051	1.018-1.085
≤ 55	96	11	11.5%						
Child-Pugh class									
A	102	20	19.6%	0.129	0.340	0.143	0.705	0.879	0.452-1.711
B	75	18	24.0%						
Family history									
Yes	42	20	47.6%	0.287	0.433	0.440	0.507	0.750	0.321-1.753
No	135	18	13.3%						
Smoking									
Yes	46	15	32.6%	0.150	0.489	0.094	0.759	0.861	0.330-2.244
No	131	23	17.6%						
Alcohol									
Yes	43	16	37.2%	0.318	0.497	0.409	0.522	1.374	0.519-3.640
No	134	22	16.4%						
Bleeding									
Yes	22	2	9.1%	1.036	0.367	7.967	0.005	2.817	1.372-5.781
No	155	36	23.2%						
HBeAg (PEIU/mL)									
Positive	58	12	18.9%	0.221	0.344	0.414	0.520	1.247	0.636-2.446
Negative	119	26	22.7%						
HBV DNA (IU/mL)									
> 500	61	18	29.5%	< 0.001	< 0.001	0.051	0.822	0.099	1.000-1.000
≤ 500	116	20	17.2%						
Platelet count (10^3/mm^3)									
< 75	79	24	30.4%	0.009	0.003	7.051	0.008	1.009	1.002-1.016
≥ 75	98	14	14.3%						
AFP (ng/mL)									
> 38	34	13	38.2%	0.002	0.001	7.992	0.005	1.002	1.001-1.003
≤ 38	143	25	17.5%						
ALT (U/L)									
> 40	57	14	24.6%	0.002	0.004	0.266	0.606	0.998	0.990-1.006
≤ 40	120	24	20.0%						
AST (U/L)									
> 3N	7	4	57.1%	0.005	0.006	0.657	0.418	0.995	0.982-1.007
≤ 3N	170	34	20.0%						
PTA (%)									
> 75	79	3	3.8%	0.074	0.014	27.217	< 0.001	0.928	0.903-0.955
< 75	98	35	35.7%						

Note: RC (regression coefficient), HR (Hazard ratio).

entiated group (N = 14). Serum AFP levels among the groups were statistically different (*P* = 0.018). They were significantly increased in poorly-differentiated patients, compared to the

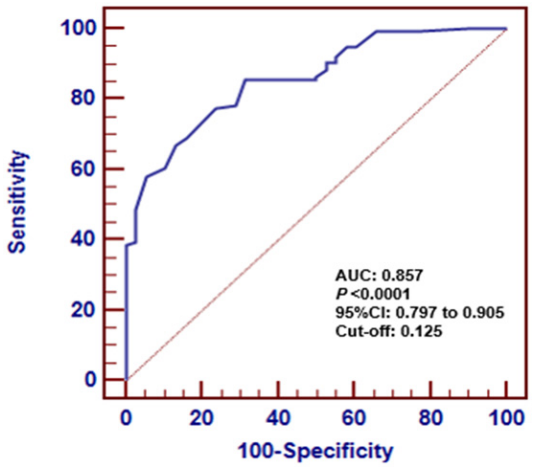

Figure 1. Receiver operating characteristic (ROC) curve analysis was used to determine the cut-off value of the prognostic index score (cut-off: 0.125). In addition, area under the ROC curve (AUC) was measured too (AUC: 0.857), which indicates the prognostic index score was in a certain accuracy to distinguish the HCC high-risk group and HCC low-risk group.

moderately differentiated group (P = 0.022) and well differentiated group (P = 0.005). However, age, platelet counts, prothrombin activity, and esophageal variceal bleeding history showed no significant differences among the three groups. (P = 0.579, P = 0.589, P = 0.166, and P = 0.387, respectively) (**Figure 3**).

Discussion

Previous studies have shown that patients with cirrhosis are at a high risk of developing HCC [2]. In the current study, HBV-related liver cirrhosis patients were enrolled. This study focused on the independent population-Chinese Fujian Han population, which have similar characteristics and genetic backgrounds. Univariate and multivariate models were used to analyze risk factors of appearance of HCC in a large series of chronic liver cirrhosis patients. Clinical and biological indexes, as risk indicators of developing to HCC, were prospectively investigated in HBV-related liver cirrhosis patients. In addition, correlation of pathologic differentiation degrees and features of patients with HCC was examined. AFP levels were increased remarkably in poorly-differentiated hepatocellular carcinoma patients, compared to moderately differentiated patients and well differentiated patients.

Univariate analysis indicated that age older than 55 years, a history of smoking and excessive drinking, history of esophageal variceal bleeding, platelet counts less than 75 × 10^3/mm^3, concentrations of AST three times higher than normal, AFP levels greater than 38 ng/mL, and prothrombin activity under 75% were major risk factors for HCC among liver cirrhosis patients. This study also observed that age > 55 years old, history of esophageal variceal bleeding, platelet counts < 75 × 10^3/mm^3, AFP > 38 ng/mL, and prothrombin activity < 75% were independently associated with development of HCC, according to multivariate analysis. In addition, a prognostic index based on these factors was carried out to estimate the occurrence of HCC. According to this index, patients were divided into 2 groups: high risk group and low risk group. Incidence of HCC in the low risk group was 7.70% and 48.33% in the high-risk group.

Previous studies have demonstrated the relationship between age and development of HCC. Patients older than 65 years were thought to be more likely to develop HCC [13-15]. Consistent with previous finings, the current study showed liver cirrhosis patients older than 55 years have a three-fold greater risk of development of HCC. The importance of increasing age as a risk factor may due to the long-term duration of basic liver diseases and exposure to risk factors associated with HCC.

The current study found that patients with HCC were more likely to have a bleeding history, which has been suggested as a risk factor for development of HCC. Generally, alimentary tract hemorrhages are the most common complication of liver cirrhosis. Esophageal variceal bleeding is a well-known risk factor, predicting the severity of liver disease for cirrhosis patients. Previous studies have demonstrated HCC could increase the risk of bleeding [16], consisted with present results. Hemorrhages indicate severe liver disease, inducing low platelet counts and accelerating hepatic functional decline. These findings should be confirmed in the future research, however.

The present study also confirmed that both a low platelet count and a decrease in prothrombin activity were significant risk factors for development of HCC, in accord with previous investigations [17-19]. It was found that liver cir-

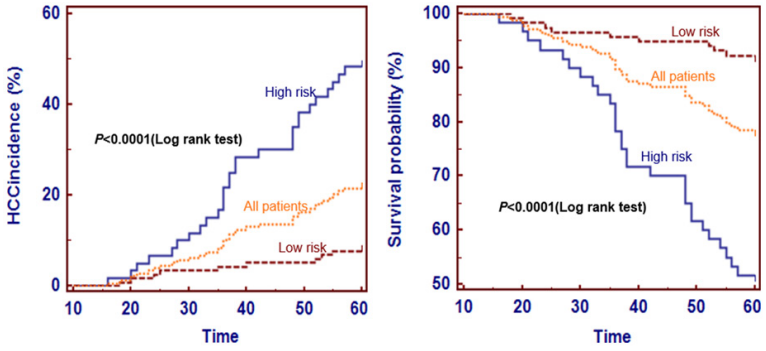

Figure 2. Cumulative risk models and survival rate models were carried out in this study: incidence of HCC obtained from the prognostic index of the 177 patients: low-risk group (5 years cumulative incidence of HCC, 7.70%), high-risk group (5 years cumulative incidence of HCC, 48.33%), as well as in the cumulative survival rate model (P = 0.0001).

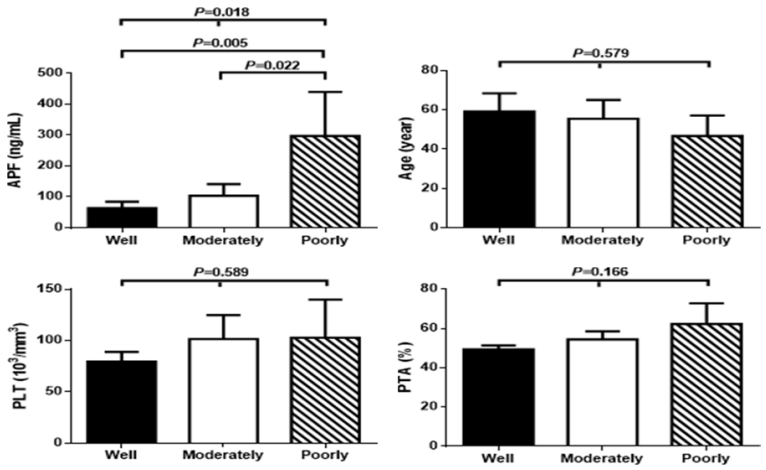

Figure 3. Serum AFP, age, platelet counts, and prothrombin activity were compared among the different pathologic differentiation groups. AFP levels were significantly increased in poorly-differentiated group, compared to moderately differentiated group (P = 0.022) and well differentiated group (P = 0.005). However, age, platelet counts, and prothrombin activity showed no significant differences among the three groups (P = 0.579, P = 0.589, and P = 0.166, respectively).

rhosis patients with a low platelet count (< 75 × 10^3/mm^3) had a three times greater risk of HCC than those with relatively high platelet counts. Similarly, patients with decreased prothrombin activity showed a ten-fold greater risk of developing HCC. In patients with liver cirrhosis, low platelet counts may result from increased platelet destruction caused by hypersplenism. In addition, increased platelet-associated immunoglobulins (PAIgG) and thrombopoietin (TPO) in patients suffering chronic liver diseases may diminish platelet production [20, 21]. In brief, the significance of these as risk factors may reflect great liver dysfunction and a prolonged duration of chronic liver diseases.

The roles of AFP in detecting and screening HCC are controversial because of falsely raised AFP levels in patients with active hepatitis [22, 23]. It was found that AFP levels greater than 38 ng/mL were associated with development of HCC, according to univariate analysis and multivariate analysis. Present results were consisted with previous studies [2, 18, 24]. It was reported that serum AFP levels could be a considerable predictive factor for malignant features [25]. In the current study, higher serum AFP levels were found in patients with poorly-differentiated HCC, which might explain the better prognosis in patients with lower AFP levels. One study mentioned that AFP negative HCC cells included simple organelles and rich free ribosomes under the electron microscope. On the contrary, an increased number of mitochondria were found in AFP positive HCC cells. The correlation of mitochondrial DNA mutations and degree of HCC malignancy has been found in many studies [26]. Whether any association exists among AFP levels, mitochondrial DNA mutations, and tumor differentiation degrees requires further research.

Smoking was not considered to be a significant risk factor for HCC in the current study. However, a significant association between smoking and risk of HCC has been observed in previous univariate analysis [27]. However, the mechanisms between smoking and hepatocarcinogenesis require further investigation.

Alcohol consumption has been proven to be an important additional risk factor for HCC in the United States. Many studies have shown that

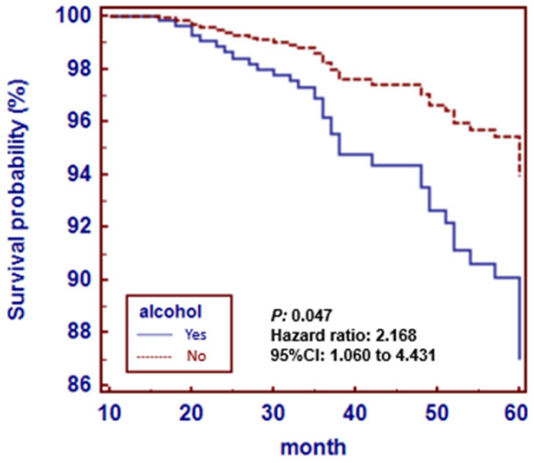

Figure 4. History of alcohol consumption (n = 16) was found in 38 HCC patients but only 19.42% of patients with cirrhosis (n = 139), showing statistical significance.

the correlation between alcohol and liver disease depends on the amount of alcohol consumed over a lifetime, a main risk factor of HCC [28]. The current study showed significant differences according to univariate analysis. However, no differences between drinking history and incidence of HCC were found in the final Cox regression model. Drinking history (n = 16) was found in 42.11% of patients developing HCC (n = 38), while only 19.42% in liver cirrhosis patients (n = 139), showing statistical significance (Hazard ratio, 2.168; 95% confidence interval, 1.060 to 4.431; *P*, 0.047) (**Figure 4**). Although it has not been stated clearly in this study yet, it seems that alcohol consumption could have more value as a predictive factor for HCC in patients with cirrhosis.

One of the limitations of the current study was the limited sample size. Further studies are necessary. Recently, genetic factors were found to play an important role in development of HCC [29]. However, the current study did not have the relevant data to examine this question. In addition, the present model was developed in patients with HBV-related cirrhosis, thus it may not be applicable to alcohol cirrhosis or other patterns of liver cirrhosis.

Conclusion

Fujian is a high-incidence district of HBV infections in China. This study designed a predictive score for Fujian Han liver cirrhosis patients. Remarkably, increasing age, platelet counts, prothrombin activity, esophageal variceal bleeding history, and AFP levels appear to correlate with HCC. This prospective model could be used to predict the possibility of development of HCC among patients with cirrhosis, playing an important role in early prevention. In the future, larger samples should be gathered and more attention should be paid to typical genetic effects, fully completing the predictive model.

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Disclosure of conflict of interest

None.

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