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Application of the albumin-bilirubin grade for predicting prognosis after curative resection of patients with early-stage hepatocellular carcinoma

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ABSTRACT

Background: Patients with Barcelona Clinic Liver Cancer (BCLC) 0 + A are considered to have early-stage hepatocellular carcinoma (HCC). The albumin-bilirubin (ALBI) grade is a significant predictor of overall survival (OS) for HCC. However, data are lacking to support its significance for patients with early-HCC.
Methods: We recruited 318 patients with early-HCC who underwent curative resection between January 2012 and August 2013. The Kaplan–Meier method and log-rank tests were used to compare OS of patients with different ALBI grades. Cox regression analysis was applied to evaluate ALBI grade as an independent predictor of OS.
Results: Early-HCC patients with ALBI grade II experienced significantly shorter OS ($p < 0.001$) and higher death rates. In the Child-Pugh (C-P) grade-A group, patients with ALBI grade I had a more favorable prognosis than those with grade II ($p < 0.001$), while the C-P grade did not distinguish patients with poor prognosis from the entire group. Cox regression analysis demonstrated that ALBI grade was the most significant independent predictor of OS, and the ALBI grade retained its clinical significance in low α-fetoprotein subgroup.
Conclusion: ALBI grade predicted OS in patients with early-HCC. Reclassification of C-P grade according to ALBI grade might improve the management of HCC.

1. Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and is a major cancer in China with a recently escalating incidence and an increasing death rate [1,2]. Surgery with curative potential remains the most effective treatment [3]; however, overall survival (OS) after curative resection remains unsatisfactory [4]. Because the majority of patients with HCC who undergo curative resection have associated chronic liver cirrhosis [5], it is widely recognized that the survival of patients with HCC relies on underlying liver function as well as tumor stage [3,6–10].

Evaluation of preoperative liver function can provide information vital for predicting the risk of death after curative resection. The Child-Pugh (C-P) score, which was designed to assess the prognosis of patients with cirrhosis [11,12], is the most widely used tool to evaluate liver function of patients with HCC to facilitate the systematic management of HCC [4]. However, it remains to be determined whether the C-P score is appropriate for evaluating liver function of patients with HCC [13,14]. Further, the correlation between ascites and serum albumin levels, which are 2 basic variables considered in determining the C-P score, and the highly subjective evaluation of ascites and encephalopathy may greatly diminish the accuracy of assessment [9].

Recently, a novel evaluation model called the albumin-bilirubin (ALBI) grade exhibits impressive performance for predicting the prognosis of patients with HCC [9]. The model employs the results of 2 routine clinical tests (albumin and bilirubin) and can stratify patients with HCC into three risk categories. Patients with different ALBI grades experience significantly different OS during follow-up. Moreover, patients with the same C-P score experience significantly different OS when stratified according to ALBI grade, which indicates that the performance of ALBI might compare favorably with that of the C-P score for predicting the OS of patients with HCC.

Currently, the Barcelona Clinic Liver Cancer (BCLC) stage is the most commonly used HCC staging system [4] and offers the advantage of integrating prediction of survival outcomes and treatment options [15]. In clinical practice, patients with BCLC stage 0 and A are usually stratified as early-stage patients with relatively low tumor burden and better prognosis [16,17]. However, 30%–50% of patients with early-stage disease and those who receive recommended therapy according to BCLC stage, die within 5 years after treatment [4,15]. Therefore, the

Abbreviations: HCC, hepatocellular carcinoma; OS, overall survival; C-P, Child-Pugh; ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; AFP, α-fetoprotein.

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identification of patients with high risk in early-stage HCC group is an urgent matter.

Early-stage patients with HCC (C-P A and B) comprise 2 distinct liver-function subgroups, suggesting that preoperative liver function plays an important role in OS. Unfortunately, little evidence is available to support the application of the ALBI grade to patients with early-stage HCC, particularly for those who undergo curative resection. Although a pilot study demonstrates the predictive value of ALBI in patients undergoing resection [8], its value for patients with early-stage HCC was not investigated.

2. Materials and methods

2.1. Study design

Two independent cohorts of patients were included in the present retrospective study. From January to July 2012, we recruited 160 patients with early-stage HCC (BCLC 0 + A stage) undergoing curative resection (cohort 1) at Zhongshan Hospital (Fudan University, Shanghai, China). The second independent group (cohort 2) included 158 patients with early-stage HCC who were recruited from August 2012 to August 2013. HCC was defined according to the results of imaging studies and biochemical assays, and diagnosis was confirmed using histopathology according to the criteria of the American Association for the Study of Liver Diseases guidelines [6]. HCC stage was defined according to the BCLC guidelines [4]. Tumor differentiation was determined using the Edmondson grading system [18]. A serum sample (6 ml) for routine liver function tests was collected 2 days before resection. The Research Ethics Committee of Zhongshan Hospital granted approval for the use of human subjects, and informed consent was obtained from each patient.

Post-treatment surveillance was performed as described previously [16]. Briefly, patients were monitored every 3 to 4 months after resection for serum α-fetoprotein (AFP) levels and were further assessed using abdomen ultrasonography and chest X-rays. The follow-up ended in February 2016. OS was defined as the interval between the dates of surgery and death or the interval between surgery and the last observation [16].

2.2. Determination of serum albumin and total bilirubin

Serum albumin was determined by Bromocresol green (BCG) method (Roche Diagnostic) and serum total bilirubin was determined by vanadium oxidation method (Wako). Hitachi 7600 chemistry analyzer was used to measure serum albumin and total bilirubin.

2.3. Calculation of C-P and ALBI scores

The C-P score was calculated according to albumin, total bilirubin, prothrombin time, ascites, and encephalopathy. The C-P grades were stratified as follows: grade A, 5–6 points; grade B, 7–9 points; and grade C, 10–15 points [8]. The ALBI score was calculated as follows: linear predictor = $(\log_{10}\text{bilirubin} \times 0.66) + (\text{albumin} \times -0.085)$, where the units of bilirubin and were μmol/l and g/l, respectively. The ALBI grades were stratified as follows: grade I, ≤−2.60; grade II, −2.60 to ≤−1.39; and grade III, >−1.39 [9].

2.4. Statistical analysis

Statistical analyses were performed using SPSS 17.0 software (IBM). Experimental values of continuous variables are expressed as the mean ± standard error of the mean. The chi-squared test, Fisher's exact probability tests, and the Student *t*-test were used as appropriate to evaluate the significance of differences in data between groups. If the differences within groups were not homogeneous, the nonparametric Mann–Whitney test or the Wilcoxon signed-rank test was used. A receiver operating characteristics (ROC) curve was used to evaluate the predictive value of ALBI and the C-P score. The relationship between OS and ALBI/C-P score was analyzed using Kaplan–Meier survival curves and the log-rank test, and $p < 0.050$ was considered statistically significant.

3. Results

3.1. Patient characteristics

We recruited 318 patients who were pathologically diagnosed with early-stage HCC from January 2012 to August 2013. The study population included 2 independent cohorts (cohort 1, 160 patients; cohort 2, 158 patients). In cohort 1, 54 of 160 patients died before the last follow-up (median follow-up, 44.00 months; range, 5.70–48.00 months). Of the patients included in cohort 2, 130 were alive at a median follow-up time of 33.60 months (range, 3.60–42.00 months). According to the C-P grade, the majority of patients had grade A (total, 304/318, 95.60%; cohort 1, 153/160, 95.63%; and cohort 2, 151/158, 95.57%). According to ALBI grade, 71.07% (226/318) of patients were stratified into grade I (cohort 1, 111/160, 69.38%; cohort 2, 115/158, 72.78%), and the other patients were stratified into grade II. All clinicopathologic characteristics of the patients are summarized in Table 1. Cohort 2 patients were prone to have multiple tumors ($p = 0.039$) (Table 1), and there were no significant differences between the other characteristics of the 2 cohorts.

3.2. ALBI grades correlate with the OS of patients with early-stage HCC

We first investigated the predictive value of the ALBI grade for all subjects. During follow-up, 82 patients died (25.79%). The OS and death rates of patients with ALBI grade II were significantly (Fig. 1A) shorter and higher, respectively, compared with those of patients with ALBI grade I (42/92 [45.65%] vs 40/226 [17.70%], $p < 0.001$) (Fig. 1B).

Table 1
The clinicopathologic characteristics of patients in the training and validation cohorts.

Characteristics		No. of patients	Cohort 1		Cohort 2		*p*
			N = 160	%	N = 158	%	
Age (y)	≤50	133	68	42.77	65	41.71	NS
	>50	185	92	57.23	93	58.29	
Sex	Women	57	26	17.47	31	19.63	NS
	Men	261	134	82.53	127	80.37	
AFP, ng/ml	≤400	236	113	70.48	123	76.07	NS
	>400	82	47	29.52	35	23.93	
ALT, U/l	≤75	301	154	96.38	146	92.02	NS
	>75	18	6	3.62	12	7.98	
HBsAg	Negative	44	20	12.05	24	14.72	NS
	Positive	274	140	87.95	134	85.28	
Liver cirrhosis	No	84	39	24.70	45	28.22	NS
	Yes	234	121	75.30	113	71.78	
No. of tumors	Single	297	154	95.78	143	90.18	*0.039**
	Multiple	21	6	4.22	15	9.82	
Tumor size, cm	≤5	227	110	68.67	117	71.78	NS
	>5	91	50	31.33	41	28.22	
Tumor encapsulation	Complete	205	105	65.66	100	63.80	NS
	None	113	55	34.34	58	36.20	
Satellite lesion	No	301	152	95.18	149	92.64	NS
	Yes	17	8	4.82	9	7.36	
Vascular invasion	No	214	106	66.27	108	66.26	NS
	Yes	104	54	33.73	50	33.74	
Tumor differentiation	I–II	217	105	65.06	112	70.55	NS
	III–IV	101	55	34.94	46	29.45	
Child-Pugh score	A	304	153	92.17	151	88.34	NS
	B	14	7	7.83	7	11.66	
AlBI	≤−2.6	226	111	70.48	115	73.01	NS
	>−2.6	92	49	29.52	43	26.99	

Abbreviation: ALBI, albumin-bilirubin grade. * indicated significant difference between two cohorts.