Journal of Gastrointestinal Cancer (2019) 50:400–407
https://doi.org/10.1007/s12029-018-0085-4

ORIGINAL RESEARCH

Evaluating the Ability of the New Subclassification to Prognosticate Outcomes Following Hepatectomy for Patients with HBV-Related HCC

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Published online: 7 March 2018

Abstract

Background Recently, experts proposed subclassification for BCLC B patients. In this study, we aimed to evaluate the efficient of subclassification of patients with hepatitis B virus-related hepatocellular carcinoma (HCC) in Barcelona Clinic Liver Cancer (BCLC) staging system.

Methods Seven hundred twenty-nine consecutive hepatitis B virus-related HCC patients with BCLC stage B classification who underwent hepatectomy in the period 2006–2012 were retrospectively analyzed. Patients were reclassified based on the new proposed subclassification of the BCLC B stage from B1 to B4. The prognosis of subclassification was tested using Kaplan-Meier statistics analysis.

Results There were 145 (19.9%), 480 (65.8%), 62 (8.5%), and 42 (5.8%) patients in B1, B2, B3, and B4, respectively. The result suggested that overall and tumor-free survival rates among the B1, B2, and B3 subclassification in the Bolondi system had significant difference ($P < 0.05$). However, no significant difference was found between B3 and B4 subclassifications. Cox regression showed that BCLC B subclassification, largest/smallest diameter, and anatomic liver resection were independent predictors of tumor-free survival. BCLC B subclassification and anatomic liver resection were independent predictors of overall survival.

Conclusions The subclassification of BCLC stage B can be used in patients with HBV-related HCC who underwent curative intent hepatectomy. Patients in BCLC B1 and B2 subgroups should be treated more aggressively than patients in B3 and B4 subgroups. B3 and B4 groups should be merged for patients with HBV-related HCC who underwent curative intent hepatectomy.

Keywords BCLC · Hepatitis B virus · Hepatocellular carcinoma · Surgery · Subclassification

Introduction

The Barcelona Clinic Liver Cancer (BCLC) classification is widely adopted in the management of hepatocellular carcinoma (HCC). Patients were stratified into five stages which include very early stage (0), early stage (A), intermediate stage (B), advanced stage (C), and terminal stage (D) [1, 2]. BCLC B consists of patients with large or multinodular HCC, Child-Pugh score of A or B, and performance status 0 in the absence of vascular invasion and extrahepatic metastasis [3]. The European Association for the Study of Liver (EASL) and American Association for the Study of Liver Disease (AASLD) recommend transarterial chemoembolization (TACE) should be the standard of care for BCLC B HCC [3–5]. However, recent studies found that wide variation existed in BCLC B. Some patients obtained good outcome after curative hepatectomy even if the tumor is beyond BCLC stage B classification. BCLC B account for about 30% in patients with HCC; a single treatment option may be too rigorous to all patients in this group.

Recently, a panel of experts divided the BCLC B stage into four subgroups for providing more options to patients [6]. In the new subclassification of BCLC stage B, patients were reclassified from B1 to B4, which was based on Child-Pugh score, beyond Milan and within up-to-seven, Eastern

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Cooperative Oncology Group (ECOG) performance status, and portal vein thrombosis. The new subclassification was assessed by few studies, which results in controversial opinion [7, 8]. Furthermore, it has not been verified in patients with HBV-related HCC now, especially for patients after curative intent surgery. In this study, we aim to evaluate the ability of the new subclassification to prognosticate outcomes following hepatectomy for patients with HBV-related HCC. To the best of our knowledge, this is the first study which applied the subclassification to patients with HBV-related HCC who underwent curative hepatectomy.

Methods

Patients

This study was approved by the Ethics Committee of Nanchong Central Hospital. The data of HBV-related HCC patients who underwent curative intent hepatectomy at the Nanchong Central Hospital in Sichuan were obtained between January 2006 and December 2012. The HCC was confirmed by pathology. Of the total 787 patients who underwent curative intent hepatectomy, 58 patients were excluded because of preoperative TACE, incomplete clinical data, or lost to follow-up ($n = 25$). Finally, 729 consecutive patients were recruited. Only patients who met the following inclusion criteria were enrolled into this study: (1) patients with BCLC stage B and HBV-related HCC who underwent hepatectomy; (2) patients age > 18 years and ≤ 70 years; (3) 0 score of performance status [9]; (4) no evidence of extrahepatic metastasis; (5) no history of other malignancies; (6) adequate liver remnant size after liver resection; (7) complete resection of macroscopic tumor nodules according to the criteria in our previous study; (8) Child-Pugh A-B of liver function with serum total bilirubin ≤ 1.5 times the upper limit of normal, ALT and AST ≤ 2 times the upper limit of normal. Exclusion criteria included patients who had incomplete clinical data and lost to follow-up within 60 days after discharge. We excluded patients with macroscopic tumor invasion into major portal/hepatic veins because of the dismal prognosis of patients with those characteristics. Considering the consistency of inclusion criteria, we also excluded patients who underwent palliative tumor resection.

Subclassification

We divided the BCLC B stage into four substages (Table 1) according to the subclassification proposed by Bolondi et al. [6].

In the subclassification, we used up-to-seven criteria and Milan criteria. Up-to-seven criteria include tumor diameter of the largest nodule (cm) + number of nodules ≤ 7 [10]. Milan criteria were as follows: the presence of a single nodule tumor diameter ≤ 5 cm and multi-tumor nodule no more than three, each nodule ≤ 3 cm [11].

Table 1 Subclassification for patients at first observation with BCLC stage B HCC

BCLC substage	B1	B2	B3	B4
Child-Pugh score	5–7	5–6	7	8–9
Beyond Milan and within up-to-seven	In	Out	Out	Any
ECOG (tumor related) (performance status)	0	0	0	0–1
Portal vein thrombosis	No	No	No	No

BCLC Barcelona Cancer Liver Clinic, *ECOG* Eastern Cooperative Oncology Group

Hepatectomy

Hepatectomy was carried out through subcostal incision. During surgery, intraoperative ultrasonography (IOUS) was performed to assess the tumor and help to remove all tumors for multiple tumor nodulars. Pringle maneuver was performed for less intraoperative bleeding. Liver parenchyma dissection was performed by clamp crushing method. Major hepatectomy was defined as the removal of three or more Couinaud segments. Anatomic liver resection was performed if the tumor is within a Couinaud segment/sector/hemiliver with sufficient future liver remnant; otherwise, nonanatomic liver resection was performed. Pringle maneuver was performed to reduce intraoperative blood loss.

Follow-up

The follow-up program was designed as previously described. In short, patients were followed up at a 2-month interval in the first 2 years after discharge from hospital and at a 3-month interval thereafter. At each follow-up visit, all the patients received a detailed history interview and physical examination and underwent serological examination including alpha fetoprotein (AFP) level, liver function and hepatitis virus serum immunology, and an abdominal ultrasonography. A contrast-enhanced CT or MRI was performed once every 6 months or earlier if tumor recurrence was clinically suspected. The diagnostic criteria for tumor recurrence were the same as for the initial diagnosis. Patients with tumor recurrence underwent multimodal treatments including re-resection, TACE, percutaneous radiofrequency ablation, percutaneous ethanol injection, and conservative therapy [12].

Statistical Analysis

Continuous data are shown as mean ± standard deviation, and discrete variables as absolute and relative frequencies. Comparison of continuous data was carried out using

Student's t test or Mann-Whitney U test. Comparison of discrete variable was carried out using the Fisher's exact test or the χ^2 test with Yates correction, as appropriate. Cumulative overall survival was estimated by the Kaplan-Meier method, and statistical comparison of survival distribution was analyzed by the log-rank test. Associations with a P value ≤ 0.1 at univariate analysis were entered into a Cox's stepwise multivariate regression analysis. A P value < 0.05 in two-tailed test was considered statistically significant. Statistical analysis was performed using SPSS software (IBM version 22.0, NY).

Results

Baseline Characteristics

A total of 729 patients with HBV-related HCC were included into this study. The characteristics of patients are described in Table 2. Median follow-up time was 40.2 months. Four hundred forty-eight patients have single tumor, while 281 patients have multiple tumors. Two hundred sixty-nine patients have tumor located in the left hemiliver, 383 patients have tumor located in the right hemiliver, and 77 patients have tumor located in both right and left hemilivers.

Stratification According to the New Proposed BCLC B Subclassification

One hundred forty-five (19.9%) patients were in B1 subgroup, 480 (65.8%) patients in B2 subgroup, 62 (8.5%) patients in B3 subgroup, and 42 (5.8%) patients in B4 subgroup. The median tumor-free survival time of B1, B2, B3, and B4 was 51.9, 22.3, 13.0, and 10.3 months respectively. The median overall survival time of B1, B2, B3, and B4 was 59.8, 35.4, 20.9, and 15.9 months respectively.

Survival Analysis

The 1-, 3-, and 5-year tumor-free survival was 69.1, 40.7, and 25.2. The 1-, 3-, and 5-year overall survival was 77.6, 50.7, and 33.8% for all included patients in this study. The Kaplan-Meier overall survival curves of the B1, B2, and B3 substages in the Bolondi system had significant difference ($P < 0.05$). However, no significant difference was found between B3 and B4 subgroups. (Fig. 1).

Univariate analysis for tumor-free survival and overall survival in the whole cohort indicated that the BCLC B subclassification, largest/smallest diameter, tumor number, Child-Pugh score, platelet counts, anatomic liver resection, major hepatectomy, and Model for End-Stage Liver Disease (MELD) score were associated with worse survival (Tables 3 and 4). In Cox's regression multivariate analysis, BCLC B subclassification, largest/smallest diameter, and anatomic liver resection were independent predictors of tumor-free survival. BCLC B subclassification and anatomic liver resection were independent predictors of overall survival. (Tables 3 and 4).

Using Modified BCLC B Subclassification

We used the modified BCLC B subclassification which was proposed by Yeonjung Ha et al. [8]. The modified subclassification merged B3 and B4 with BIII, and B1 and B2 are the same as BI and BII. The tumor-free survival and overall survival have significant difference among the modified subclassifications ($P < 0.01$) (Fig. 2).

Complications After Surgery

Complications were measured with Clavien-Dindo classification. The most frequent postoperative complications include ascites, pulmonary infection, and liver failure. Patients in B3 and B4 have more severe complications than patients in B1 and B2 subgroups (Table 5).

Discussion

The BCLC staging system provides guidance for clinical decisions. About 30% patients with HCC were classified into BCLC stage B, who are recommended to be treated with TACE. The 2-year survival rate varies from 20 to 60% after TACE [13]. Several studies found the survival can be improved using other optional treatment methods, such as curative intent hepatectomy [14–16]. Considering the heterogeneous in BCLC stage B, a group of expertise proposed a new subclassification for providing better treatment decisions and improving prognosis of HCC in 2012.

In this study, we assessed the validity of the subclassification to patients with HBV-related HCC who underwent curative intent hepatectomy. Significant difference has been found between B1, B2, and B3 subgroups. Patients in B1 group have better survival rate than the other groups; patients in B3 and B4 subgroups who underwent hepatectomy have worst survival rate. However, no significant difference of survival has been found between B3 and B4 groups. Patients in BCLC B4 subgroup have deteriorated liver function; most of these patients were treated with TACE. In this study, there are only 42 patients in B4 group which may cause bias.

Giannin et al. [11] applied the new subclassification to patients with untreated HCC, which results in suggesting that the new subclassification is an independent prognosis factors and performs good efficiency to stratify HCC patients in BCLC stage B. Ciria et al. [17] found that better survival has been obtained in B1 subgroup patients who have well/

Table 2 Baseline characteristics of all patients in the cohort

Characteristics	All patients	BCLC B substage				*P* value
	(*n* = 729)	B1 (*n* = 145)	B2 (*n* = 480)	B3 (*n* = 62)	B4 (*n* = 42)	
Age (years), mean ± SD	50.55 ± 10.92	52.11 ± 9.77	50.22 ± 11.23	50.03 ± 11.51	49.67 ± 9.89	0.28
Male, no. (%)	612 (83.95)	128 (88.28)	393 (81.88)	55 (93.55)	36 (92.86)	0.20
Presence of cirrhosis, no. (%)	569 (78.05)	125 (86.21)	376 (78.33)	37 (59.68)	31 (73.81)	< 0.01
Total tumor diameter, cm, mean ± SD	8.77 ± 4.14	4.47 ± 0.86	10.05 ± 3.98	9.28 ± 2.96	8.15 ± 4.30	< 0.01
Largest/smallest diameter, median (range)	2.83 (1.0–16.87)	2.54 (1.0–9.66)	3.15 (1.0–18.29)	2.88 (1.0–20.2)	2.74 (1.0–17.92)	0.07
Largest tumor diameter, cm, mean ± SD	5.26 ± 3.71	4.02 ± 0.79	6.36 ± 3.22	5.42 ± 2.59	5.18 ± 3.72	< 0.01
Tumor number, no. (%)						< 0.01
1	448 (61.45)	46 (31.72)	316 (65.83)	51 (82.26)	35 (83.33)	
2	226 (31.00)	89 (61.38)	123 (25.63)	7 (11.29)	7 (16.67)	
≥ 3	55 (7.54)	10 (6.90)	41 (8.54)	4 (6.45)	0 (0)	
Child-Pugh score, no. (%)						< 0.01
A5	545 (78.33)	127 (87.98)	418 (88.76)	0	0	
A6	73 (9.22)	12 (8.74)	61 (11.00)	0	0	
B7	69 (9.96)	6 (3.28)	1 (0.24)	62 (96.77)	0	
B8	40 (2.19)	0	0	0	40 (75.0)	
B9	2 (0.29)	0	0	0	2 (12.5)	
Alpha fetoprotein ≥ 200 ng/mL, no. (%)	474 (65.02)	89 (61.38)	318 (66.25)	43 (69.35)	24 (57.14)	0.42
Platelet counts, $\times 10^9$	182.57 ± 75.78	166.46 ± 55.89	191.21 ± 78.72	196.77 ± 81.09	119.07 ± 51.07	< 0.01
Antivirus, yes/no	119/610	21/124	74/406	15/47	9/33	0.24
HBV-DNA load, IU/mL, $\leq 10^4/10^4$–$10^6/> 10^6$	252/274/203	54/40/51	154/201/125	28/19/15	16/14/12	0.03
Hepatectomy, anatomical/nonanatomical	331/398	89/56	223/257	9/53	20/32	< 0.01
Major hepatectomy, yes/no	66/663	3/142	58/422	3/59	2/40	< 0.01
Intraoperative blood transfusion, yes/no	131/598	3/142	100/380	11/51	17/25	< 0.01
Tumor capsule, complete/incomplete	440/289	113/32	262/218	33/29	32/10	0.71
Microvascular invasion, presence/absence	382/347	89/56	229/251	35/27	29/13	< 0.01
MELD score, ≤ 8/8–10/≥ 10	578/123/28	123/19/3	412/57/11	32/21/9	11/26/5	< 0.01

BCLC Barcelona Clinic Liver Cancer, *ECOG* Eastern Cooperative Oncology Group, *SD* standard deviation, *MELD* Model for End-Stage Liver Disease

moderate differentiation combined with no microvascular invasion. However, Weinmann et al. [7] could not confirm the efficiency of the new subclassification. So, the new subclassification system needs to be verified in further studies. Ha et al. [8] found that there was no significant difference in median survival time between B3 and B4 for BCLC stage B patients who were initially treated with TACE. The study suggested that B3 and B4 should be merged into the new subclassification of BCLC stage B, which is consistent with our results.

In this study, the 1-, 3-, and 5-year overall survival rate was 77.6, 50.7, and 33.8%, which is comparable with previous studies. Jian-hong Zhong reported 908 patients who underwent hepatic resection with 1-, 3-, and 5-year overall survival rate of 88, 62, and 39% respectively [16]. A randomized controlled trial reported patients who underwent hepatic resection with 1- and 3-year overall survival rate of 76.1 and 51.5% respectively [15]. The patients in the B1 group did extremely well maybe because of tumor size. So we used total tumor diameter, largest/smallest diameter, and largest tumor diameter to stratify patients based on tumor size. The results suggested that largest/smallest diameter was independent factor for tumor-free survival.

Patients with BCLC stage B HCC who underwent TACE have a lower survival rate in previous studies when compared with hepatectomy [15, 16]. However, the median survival time was 16.0 and 13.53 months in B3 and B4 subgroups respectively in our study, which is comparable with previous reported median survival time of TACE. The median survival time of TACE was 14 months in a randomized controlled study and 23.7 months in the study which contained 351 patients who underwent TACE [15, 16]. The results of this study suggested BCLC B subclassification could stratify the patients who underwent curative intent resection with poor prognosis. Patients in B1 and B2 groups should be treated more aggressively, such as hepatic resection or liver transplantation (in up-to-seven criteria). Patients in B3 and B4 subgroups should be treated with TACE rather than hepatectomy. Further

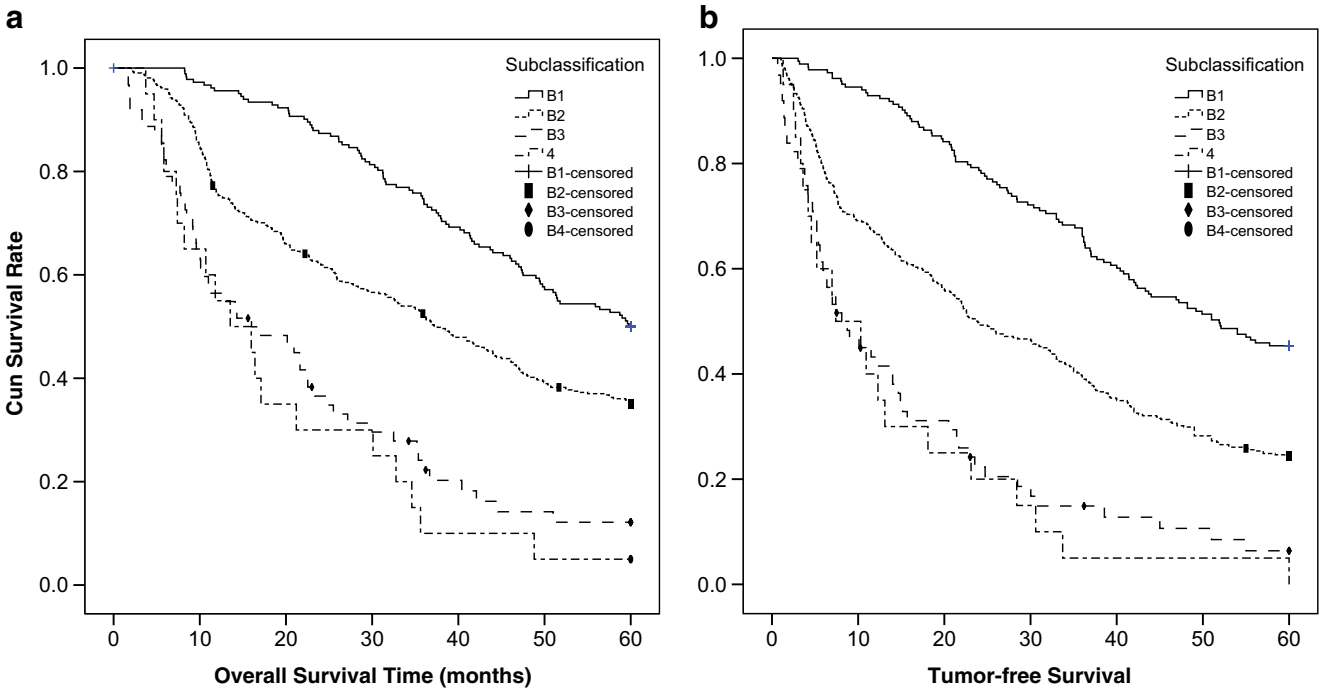

Fig. 1 Kaplan-Meier curves for overall survival (**a**) and tumor-free survival (**b**) according to the subclassification for BCLC B HCC treated with hepatic resection. Median overall survival time after surgery differed significantly among the B1, B2, and B3 patients ($P < 0.01$ for B1 vs. B2; $P < 0.01$ for B2 vs. B3; $P = 0.14$ for B3 vs. B4). Median disease-free survival time after surgery differed significantly among the B1, B2, and B3 patients ($P < 0.01$ for B1 vs. B2; $P < 0.01$ for B2 vs. B3; $P = 0.24$ for B3 vs. B4)

comparative studies are needed to identify the optimal treatment for BCLC B3 and B4 subgroups.

In this study, Cox's regression found that BCLC subclassification and anatomic liver resection were independent predictors for tumor-free survival and overall survival, which suggested that the BCLC subclassification has a good stratification for HBV-related BCLC stage B HCC. Early studies have suggested that anatomic liver resection has oncologically

Table 3 Univariate (Kaplan-Meier) and multivariate (Cox proportional hazard regression) analysis of tumor-free survival in 683 patients with BCLC B HCC

Variables	Univariate	Multivariate	
	P value	HR (95% CI)	*P* value
BCLC B subclassification	< 0.001	3.381 (2.793–4.092)	< 0.001
Age, < 65 vs. ≥ 65	0.082	–	–
Male/female	0.369	–	–
Liver cirrhosis	0.754	–	–
Total tumor diameter classification	0.368	–	–
Largest/smallest diameter	< 0.001	1.682 (1.395–2.209)	0.022
Tumor number	0.018	1.037 (0.902–1.191)	0.611
Child-Pugh score	0.022	0.971 (0.819–1.152)	0.738
Alpha fetoprotein ≥ 200 ng/mL	0.421	–	–
Platelet counts < 127 vs. ≥ 127×10^9	0.036	1.019 (0.828–1.255)	0.589
Antivirus, yes/no	0.987	–	–
HBV-DNA load, IU/mL, ≤ 10^4/10^4–10^6/> 10^6	0.856	–	–
Hepatectomy, anatomical/nonanatomical	< 0.001	1.869 (1.498–2.331)	< 0.001
Major hepatectomy, yes/no	< 0.001	1.247 (0.943–1.649)	0.122
Intraoperative blood transfusion yes/no	0.079	–	–
Tumor capsule, complete/incomplete	0.785	–	–
Microvascular invasion, presence/absence	0.149	–	–
MELD score, ≤ 8/8–10/≥ 10	0.004	1.138 (0.906–1.429)	0.268

Table 4 Univariate (Kaplan-Meier) and multivariate (Cox proportional hazard regression) analysis of overall survival in 683 patients with BCLC B HCC

Variables	Univariate	Multivariate	
	P value	HR (95% CI)	*P* value
BCLC B subclassification	< 0.001	4.266 (3.494–5.210)	< 0.001
Age, < 65 vs. ≥ 65	0.094		
Male/female	0.396		
Liver cirrhosis	0.673		
Total tumor diameter classification	0.455		
Largest/smallest diameter	0.003		
Tumor number	0.007	1.210 (1.031–1.552)	0.179
Child-Pugh score	0.013	0.589 (0.301–0.985)	0.634
Alpha fetoprotein ≥ 200 ng/mL	0.948		
Platelet counts < 127 vs. 127 × 109	< 0.001	0.543 (0.839–1.323)	0.652
Antivirus, yes/no	0.519		
HBV-DNA load, IU/mL, $\leq 10^4/10^4$–$10^6/> 10^6$	0.806		
Hepatectomy, anatomical/nonanatomical	< 0.001	2.011 (1.569–2.511)	< 0.001
Major hepatectomy, yes/no	0.027	1.205 (0.903–1.608)	0.205
Intraoperative blood transfusion, yes/no	0.144	–	–
Tumor capsule, complete/incomplete	0.852	–	–
Microvascular invasion, presence/absence	0.164	–	
MELD score, ≤ 8/8–10/≥ 10	0.015	1.114 (0.876–1.416)	0.380

advantage to nonanatomic resection [18–20]. We recommend anatomic resection to patients with HBV-related BCLC stage B HCC if they have compensated liver remnant.

Our studies have some limitations. This is a retrospective study. The numbers of patients in each subgroup varied significantly; especially, there were only 42 patients in B4

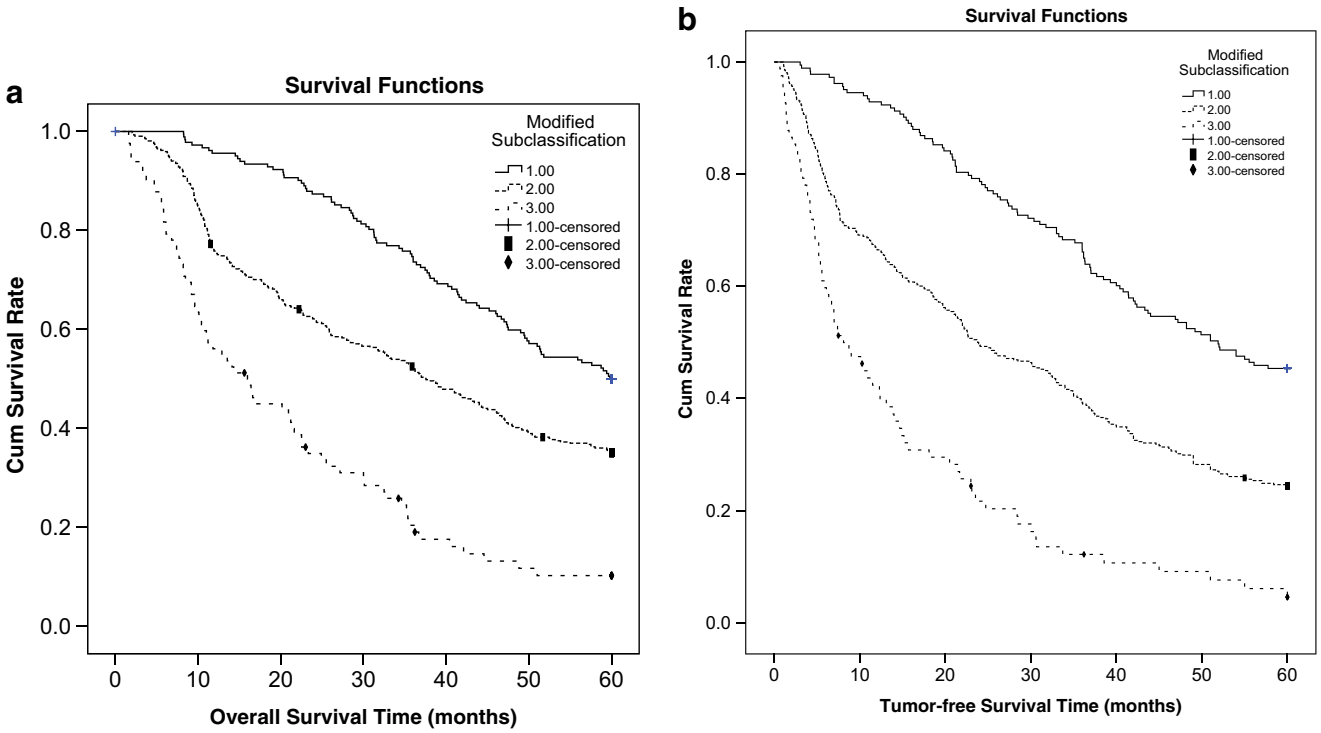

Fig. 2 Kaplan-Meier curves for overall survival (**a**) and tumor-free survival (**b**) according to the revised subclassification. The tumor-free survival and overall survival have significant difference among the modified subclassifications ($P < 0.01$)

Table 5 Postoperative complication measured by Clavien-Dindo Classification

Grade	All patients, no. (%)	BCLC B substage				*P* value
	(*n* = 729)	B1 (*n* = 145)	B2 (*n* = 480)	B3 (*n* = 62)	B4 (*n* = 42)	
Grade I	41 (5.6)	3	25	8	5	< 0.05
Grade II	87 (11.9)	11	54	15	7	
Grade III-a	22 (3.0)	1	9	7	5	
Grade III-b	18 (2.5)	0	5	9	4	
Grade IV-a	32 (4.4)	0	9	17	6	
Grade IV-b	4 (0.5)	0	2	1	1	
Grade V	7 (0.9)	0	3	2	2	

subgroup. There was no significant difference on survival between B3 and B4 patients due to the small sample size in each subgroup. As our study included only patients with HBV-related BCLC stage B HCC who received curative intent hepatectomy, the prognoses of patients who underwent TACE could not be compared. Further studies are needed to compare the prognosis of patients who were treated with hepatectomy or TACE in each subgroup of BCLC stage B subclassification.

Conclusion

The subclassification of intermediate-stage HCC can be used in patients with HBV-related hepatocellular carcinoma who underwent curative intent hepatectomy. Patients in BCLC B1 and B2 subgroups should be treated more aggressively than patients in B3 and B4 subgroups. B3 and B4 groups should be merged for patients with HBV-related HCC who underwent curative intent hepatectomy.

Funding This study was funded by the foundation of innovation seeding project of Science & Technology Department of Sichuan Province [2017-64] and the cooperative project of Nanchong City with North Sichuan Medical College [NSMC20170461].

Compliance with Ethical Standards

This study was approved by the Ethics Committee of Nanchong Central Hospital

Conflict of Interest The authors declare that they have no conflicts of interest.

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