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**Preoperative ALBI grade predicts the outcomes in non-B non-C HCC patients
undergoing primary curative resection**

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Abbreviations:

NBNC, non-B non-C; HCC, hepatocellular carcinoma; BCLC: Barcelona Clinic Liver

Cancer; OS: Overall survival; DFS: Disease-free survival; HR: Hazard ratio; HBV: Hepatitis B virus; AFP: alpha-fetoprotein; HBsAg: hepatitis B surface antigen; anti-HBc, hepatitis B core antibodies; ALBI, albumin-bilirubin; OBI, occult hepatitis B infection.

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ABSTRACT

Background

The albumin-bilirubin (ALBI) grade has been validated as a significant predictor for hepatocellular carcinoma (HCC). However, there is little information about the ALBI grade in patients with non-B non-C HCC (NBNC-HCC) receiving surgery.

Aim

This study aimed to evaluate ALBI grade as a prognostic factor in patients with NBNC-HCC after primary curative resection.

Method

This retrospective study enrolled 2137 HCC patients, who received HCC resection between January 2001 and April 2016 at Kaohsiung Chang Gung Memorial Hospital. With exclusion criteria of patients who had chronic hepatitis B or chronic hepatitis C, and prior HCC treatment before resection and received liver transplantation and BCLC stage B or C, finally we enrolled 168 NBNC-HCC patients who received primary curative resection. ALBI score used for grading as well as clinicopathologic features was analyzed, the formula of ALBI score was $\log_{10} [\text{albumin (mg/dL)} \times 17.1] \times 0.66 - \text{albumin (g/dL)} \times 0.85$.

Result

There were 66 (39.3%), 98 (58.3%), and 4 (2.4%) patients who were stratified into ALBI grade I, II, and III, respectively. Patients with ALBI grade II/III had older age ($p = 0.002$), hypoalbuminemia ($p < 0.001$), and Child Pugh B ($p = 0.009$), they also had poor overall survival compared with those with ALBI grade I ($p = 0.003$). The patients without liver cirrhosis had better survival rate in ALBI grade 1 group ($P =$

0.012). In multivariate analysis, tumor number ($p = 0.001$) and tumor stages (pTNM stages) ($p = 0.007$) were independent prognostic factors for recurrence. In predictors for mortality, AFP ($p = 0.004$), ALBI grade ($p = 0.004$), tumor number ($P=0.003$) and tumor stages (pTNM stages) ($p < 0.001$) were independent prognostic factors.

Conclusion

Preoperative ALBI grade can be used to predict the mortality in patients with NBNC-HCC after primary curative resection.

Keywords: ALBI, NBNC, hepatocellular carcinoma, resection, recurrence

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide, and is ranked the second most frequent cause of cancer-related death^{1, 2}. Hepatitis B virus (HBV) and hepatitis C virus (HCV) infection are the main causes of HCC³. In Taiwan, the major cause of HCC is HBV infection, followed by HCV, similar to many other Asian countries⁴⁻⁶. With a universal HBV vaccination program for newborn/infants, the change of lifestyle, and antiviral therapy for HBV and HCV, the incidence of virus-related HCC was decreasing over the last decade. However, the number of HCC patients with neither HBV nor HCV infection, also known as non-B, non-C HCC (NBNC-HCC), has been increasing annually, currently accounting for 11% of all cases in Taiwan⁷, it is similar with Korea and Japan^{8, 9}, an HCV-endemic country. These results suggest(showed) that NBNC-HCC is becoming a significant subgroup of HCC in areas of East Asia, and this area was previously endemic for CHB and CHC and had a high incidence of viral-related HCC.

Curative resection is a potential and the most effective treatment for HCC; it can contribute to survival benefit for patients with early-stage disease when liver transplantation is not immediately accessible¹⁰, while Hepatic functional reserve has

always been considered to be critical for outcomes of HCC patients due to cirrhosis progression¹¹. Child-Pugh grade is the most widely used assessment method for hepatic functional reserve, it includes albumin, PT/INR, ascites and hepatic encephalopathy, but its highly subjective factors, such as severity of ascites and degree of hepatic encephalopathy, may affect assessment ability^{12, 13}. Recently, there are many studies demonstrated the albumin-bilirubin (ALBI) grade, which was described in 2015 by Johnson et al¹⁴, for evaluating hepatic function and predicting the prognosis of patients with HCC following liver resection¹⁵⁻¹⁸. However, most studies enrolled viral-related HCC, there was little information in regard to the impact of ALBI grade in patients with NBNC-HCC after curative resection. Because the prevalence of nonviral HCC is increasing in Taiwan, it is a good time to evaluate the effect of the pre-operative ALBI grades in predicting the outcomes of patients with NBNC-HCC after primary curative hepatectomy.

Patients and methods

Ethics Statement

This study complies with the standards of the Declaration of Helsinki and current ethical guidelines, and approval was obtained from the Ethics Committee of Chang Gung Memorial Hospital (IRB approval number: 201901103B0). The requirement for informed consent for this study was waived by the Institutional Review Board, and all

the data were analyzed anonymously.

Patients

We retrospectively reviewed the Kaohsiung Chang Gung Memorial Hospital HCC registry data, and consisted of data for 2137 HCC patients received HCC resection from January 2001 to April 2016. The HCC diagnosis was based on the criteria of the international guidelines^{19, 20} or confirmed by the histology results if those were available. The flow chart of the patients' enrollment is shown in Figure 1. Those who were excluded due to the following reasons: 1134 patients with hepatitis B, 543 patients with hepatitis C, and 97 patients had both hepatitis B and C; 76 patients had been received HCC treatment before resection, 20 patients had received liver transplantation, and 99 patients met BCLC stage C or BCLC stage B with multiple unresectable HCCs tumors; finally, we enrolled 168 NBNC-HCC patients for analysis.

Methods

Patient's demographics, serum biochemistry, and tumor burden were obtained through medical records review, and diagnosis of cirrhosis was documented by resected non-tumor pathologic report. Blood tests were taken within 1 week before resection. ALBI score was calculated from the formula: $ALBI\ score = (\log_{10}\ bilirubin \times 0.66) + (albumin \times -0.085)$, where the units of bilirubin and albumin were in units of $\mu\text{mol/l}$ and g/l , respectively. The ALBI grades were stratified into three grades: grade I, ≤ -2.60 ; grade II, -2.60 to ≤ -1.39 ; and grade III, > -1.39 , as reported previously¹⁴. Disease-free survival (DFS) was defined as the period from tumor

removal by resection until the detection of recurrence. Overall survival (OS) was defined as the interval between the dates of resection and death, last contact, or 31 December, 2018.

Statistical analysis

Statistical analyses were performed using SPSS 23.0 statistical package (SPSS, Inc., Chicago, IL, USA). We used chi-square test and Fisher's exact test for categorical variables. The t-test or Mann-Whitney U test were used for continuous variables. The relationship between DFS, OS, and the ALBI grades were analyzed using Kaplan–Meier survival curves and the log-rank test, and $p < 0.05$ was considered statistically significant. Factors those were significant in the univariate analysis ($p < 0.05$) were included in a multivariate analysis by using a Cox forward stepwise variable selection process of the estimated OS and DFS.

Results

Characteristics of the study population

Patient characteristics are shown in Table 1. There were 131 (78%) men and 37 (22%) women with the mean age of 66 years at enrollment, 58 patients (34.5%) had diabetes mellitus. Liver cirrhosis was observed in 38 patients (22.6%) and high preoperative AFP levels (>200 ng/mL) were observed in 25 (15.3%) patients. The mean tumor size was 5.3 ± 3.7 cm, and 4 patients had multiple tumors. As table 1 showed, 66, 98, and 4 patients were designated as ALBI grade I, II, and III, respectively; compared to patients with ALBI grade I, patients with ALBI grade II and III were significantly older ($p = 0.002$), lower level of serum albumin ($p < 0.001$), and

higher percentage of Child-Pugh grade B ($p = 0.009$), but it was no differences in serum bilirubin level and tumor characteristics between these two groups.

Survival analysis

After a median follow-up of 59 months, 74 patients (44%) had recurrent HCCs, and 14 (8.3%) died. The one-, three-, and five-year DFS were 80.4%, 66.3%, and 56.8%, respectively (Figure 2A). We further investigated the predictive value of the ALBI grade of all subjects, it was no significances between patients with ALBI grades I and II/III (Figure 2B). In the OS analysis, the one-, three-, and five-year OS were 95.8%, 86.7%, and 81.9%, respectively (Figure 2C) and the groups with ALBI grade I had better OS than patients with ALBI grades II/III ($p = 0.003$) (Figure 2D). We further stratified by cirrhotic status (Figure 3), NBNC-HCC patients with ALBI grade I had better OS than those with ALBI grades II/III in cirrhotic status ($p = 0.012$) (Figure 3A), however, there was no significant difference in cirrhotic status (Figure 3B).

Independent factors for DFS and OS of NBNC-HCC patients after curative resection

Based on multivariate Cox proportion hazards model, AFP >200 ng/mL (hazard ration [HR], 2.070, 95% CI= 1.114 – 3.848, $P=0.021$), tumor number (HR, 10.770, 95% CI= 2.513 – 46.153, $P=0.001$) and pTNM stages (HR, 1.962, 95% CI= 1.199 – 3.210, $P=0.007$) were independent risk factors for HCC recurrence (Table 2). In OS analysis, the multivariate Cox proportional hazards model revealed that age >60 years (HR, 2.939, 95% CI= 1.995 – 8.850, $P=0.005$), AFP >200 ng/mL (HR, 4.785, 95% CI= 1.943 – 11.783, $P=0.001$), ALBI grade II/III (HR, 3.689, 95% CI= 1.512 – 8.997,

$P=0.004$), multiple tumor number (HR, 9.993, 95% CI= 2.177 – 45.866, $P=0.003$) and pTNM staging (HR, 8.853, 95% CI= 2.795 – 28.043, $P<0.001$) were independent risk factors for survival (Table 3), in contrast with those, Child-Pugh grade was not an independent risk factor for survival after adjusting other factors in the multivariate analysis.

Discussion

To the best of our knowledge, this is the first study to identify pre-operative ALBI grade as a useful biomarker for the assessment of NBNC-HCC after curative resection. OS rates at 5 year post curative resection were 91.8% in ALBI grade I NBNC-HCC patients, but only 74.8% in grade II/III NBNC-HCC patients. In the era of preventable strategies for HBV infections and curative intent for HCV infection, the outcomes of NBNC-HCC deserved more attention. Currently, many literatures have been proven that the use of the ALBI score relating to prognosis of post hepatectomy, radiofrequency ablation, transarterial chemoembolization, radiotherapy and systemic therapy²¹. This study was a large-scale cohort study and demonstrated that a higher grade of preoperative ALBI grade correlated with poor OS, but not with HCC recurrence, among NBNC-HCC patients after resection.

The Child-Pugh grading system is traditionally used for liver function

assessment in patients with liver disease, it was created in the early 1970s as a method for prognostication of chronic liver disease²². In addition, many HCC staging systems, such as BCLC, Cancer of the Liver Italian Program (CLIP), and Japan integrated staging (JIS), are also integrated Child-Pugh grading. However, ascites and hepatic encephalopathy, two of five parameters for Child-Pugh scoring evaluation, are dependent on physical examination and can be modified by the medication. Recently, the ALBI score has been established for evaluating hepatic functional reserve; in contrast to Child-Pugh scoring, ALBI score only used two objective serological values, albumin and bilirubin, whereas subjective factors as ascites and encephalopathy are not included. A growing number of clinical investigations suggested that ALBI grade can more accurately predict the incidence of postoperative liver failure and OS compared with Child-Pugh system. In the present study, we also compared the areas under the curve (AUC) for the Child-Pugh score and ALBI grade in predicting postoperative survival, and the result showed that ALBI grade had higher AUC compared with Child-Pugh score (0.618 vs. 0.515) (data not shown). This result might be explained that ALBI score classified Child-Pugh grade A into ALBI grade I and grade II with different prognosis at each grade.

Although HBV and HCV are still the leading causes of HCC, the incidence of NBNC HCC has been increasing in Taiwan¹⁹; consequently, the rates of resected NBNC HCC in our cohort has also been increasing. The percentage of cases in the present study was increasing, from 13% in 2001-2005 to 29% in 2006-2010, and finally to 58% in 2011-2016. The magnificent data implied that NBNC-HCC issue should not be overlooked, although the present study did not have a control arm for patients with viral hepatitis. Comparing to our prior studies^{17, 23}, patients with NBNC-HCC had a higher proportion of diabetes, this result was compatible with a large cohort study in Taiwan, which enrolled 3,843 patients with HCC from The Taiwan Liver Cancer Network (TLCN)⁷. Huang *et al* has investigated 411 patients with NBNC-HCC, 420 matched patients with HBV-HCC, and 420 matched patients with HCV-HCC, in which the high prevalence (33%) of DM in the NBNC-HCC cohort. In addition, the degrees of fatty change of liver tissue in our cohort were similar with the above study done by Huang, it was significantly more associated with patients with NBNC-HCC than patients with HBV-HCC or HCV-HCC. Our results confirmed that metabolic risk factors were associated with patients with NBNC-HCC.

In the present study, aside from the ALBI grade, we also found that serum AFP, multiple tumor number, and pTNM stage were independent risk factors for HCC recurrence. Furthermore, age, AFP, tumor number and pTNM stage were risk factors for OS. These results were similar with the previous studies^{17, 24, 25}, but not all the same, the difference from the previous studies may be due to the HCC population. In the present study, we focused on the NBNC-HCC patients after curative resection, while the previous studies focusing on the HBV or HCV or both related HCC. The underlying mechanism of HCC from non-viral hepatitis must (may) be different from viral hepatitis. However, we believed that preoperative ALBI grade is a useful marker for predicting the outcomes of HCC patients after curative resection regardless of patients with HBV-, HCV-, or NBNC-related HCC.

In the present study, we did not have data regarding the occult hepatitis B infection (OBI), and it was reported that OBI played an important role in the progression of cirrhosis and the development of HCC in several epidemiological and molecular studies. OBI is defined as the presence of replication-competent HBV DNA in the liver and/or HBV DNA in the blood in person with serum HBsAg negativity assessed by currently available assays²⁶. OBI is the combined result of host immune

control and different genomic expressions of the virus, it leads to a virological quiescent state, hence, the vast majority of OBI cases have low levels of HBV DNA²⁷. The prevalence of OBI varied from region to region worldwide and patient populations, a higher rates reported in Asia²⁸. In Taiwan, the prevalence was 0.11% in blood donors²⁹ and 10.9% in HBV vaccinated children³⁰, and in patients with HBsAg-negative HCC, the prevalence of OBI may be higher. A meta-analysis showed an increased risk of HCC in both retrospective (OR: 6.06) and prospective studies (OR: 2.86)³¹, although most patients did not have the data of serum HBV DNA for evaluation whether OBI might be involved, the result of ALBI grade predicting the outcomes of NBNC-HCC after resection was unchanged.

We acknowledge the following limitations. First, this study was a single-center retrospective study, in this study, we didn't collect the data by the intraoperative blood loss, amount of fluid received, blood transfusion, and the size of the remnant liver volume, but previous study showed that the above data were not statistically significant³². Second, this was a retrospective data from medical record and some patient were lost follow up; therefore, for prognosis evaluation, a prospective study is needed for further assessment on the precise time of ALBI grade. Moreover, in the

present study, due to the missing data, we could not collect the data of hepatitis core antibodies (anti-HBc) to exclude possible occult or past HBV infections among patients with NBNC-HCC despite HBsAg-negative, especially in an HBV-endemic country. The complete analysis including the status of anti-HBc, hepatitis B surface antibody, and HBV DNA, was our noteworthy strengths in this study to clarify the role of occult HBV infection in these patients. In the present study, we excluded the data of hepatitis B core antibodies (anti-HBc) for no related data in the medical records of the patients with HCC. Occult hepatitis viral infection may also require to considerate that Taiwan is an endemic area for HBV infection, and the prevalence of anti-HBc may be high for those born before universal vaccination was instituted.

Conclusions

In conclusion, we concluded that ALBI grade may predict the OS in NBNC-HCC patients after curative resection. On the other hand, although there was no significant difference in HCC recurrence stratified by ALBI grade, we still observed that patients with ALBI grade II/III had poorer DFS than those with ALBI grade I. Hence, we believed that the ALBI grade is a promising noninvasive marker for prediction the outcomes of NBNC-related HCC patients after curative resection.

Declarations

Ethics approval and consent to participate

The clinical data was acquired with the approval and permission of the Institutional Review Board of the Kaohsiung Chang Gung Memorial Hospital. The study protocol was approved by the Institutional Review Board of the Kaohsiung Chang Gung Memorial Hospital. The written informed consent was waived according to Institutional Review Board due to the retrospective design of the study with no relevant to human biological ethic problems.

Consent for publication

Not applicable.

Availability of data and material

All analyzed data are included in this published article. The original data are available upon reasonable request to the corresponding author.

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Author Contributions

Conception and design: Ming-Chao Tsai; Manuscript writing: Yu-Chieh Tsai; Collection and assembly of data: Fai-Meng Sou, Yueh-Wei Liu, Yi-Ju Wu, Chee-Chien Yong, Kuang-Den Chen, Pao-Yuan Huang, Wei-Ru Cho, Ching-Hui Chuang, Chang-Chun Hsiao, Tsung-Hui Hu; Data analysis and interpretation: Ching-Hui

Chuang, Chang-Chun Hsiao. All authors approved the final version of the manuscript.

Competing Interests: The authors declare no competing interests.

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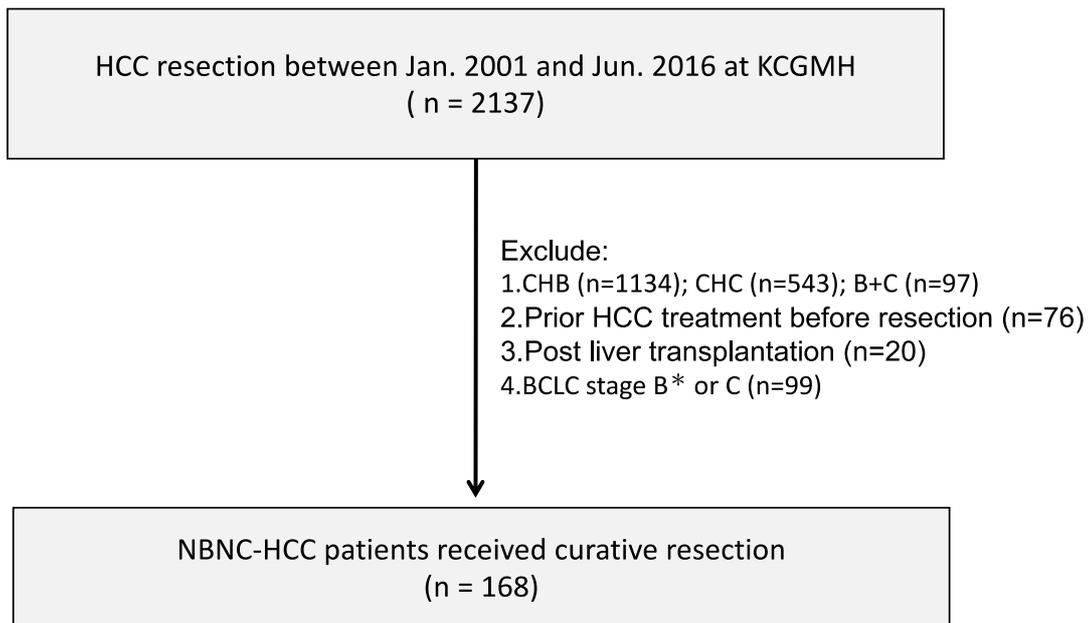
Figure legends:

Figure 1. Schematic flowchart of the enrolment process

Figure 2. The disease-free survival (DFS) rate and overall survival (OS) rate in NBNC-HCC after resection. (A) DFS in the study population (B) DFS between ALBI Gr I vs. Gr II/III (C) OS in the study population (D) DFS between ALBI Gr I vs. Gr II/III.

Figure 3. The cumulative overall survival in patients with NBNC-related HCC after curative resection among (A) non cirrhotic patients and (B) cirrhotic patients.

Figure 1. Schematic flowchart of the enrolment process

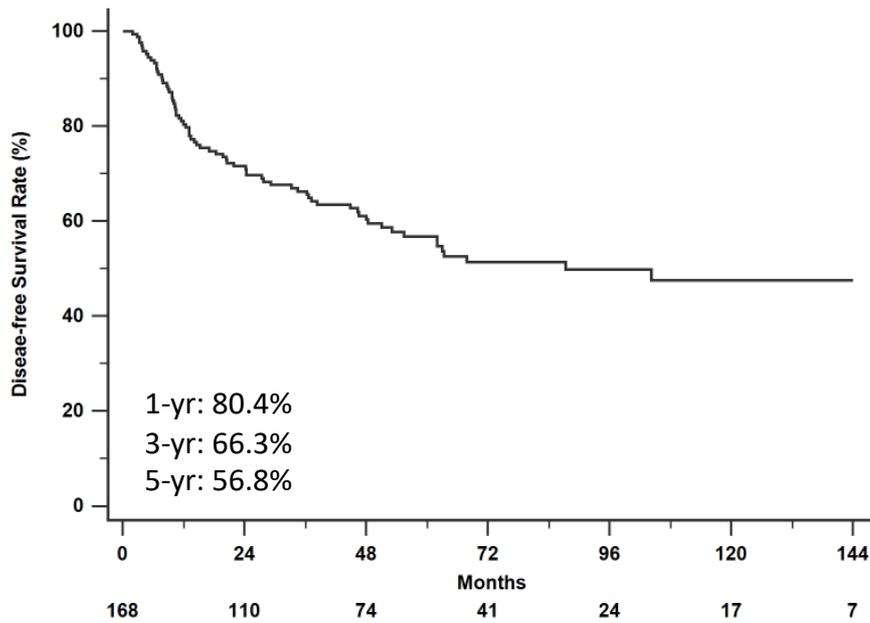


* Exclude multiple HCCs in BCLC stage B

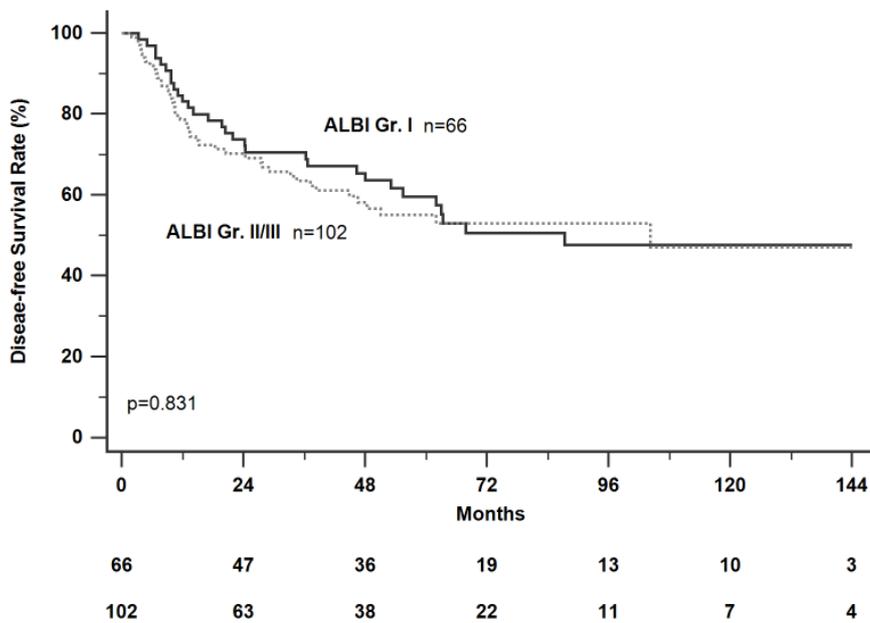
KCGMH, Kaohsiung Chang Gung Memorial Hospital; CHB, chronic hepatitis B; CHC, chronic hepatitis C; B+C, chronic hepatitis B and C; NBNC, non-B non-C

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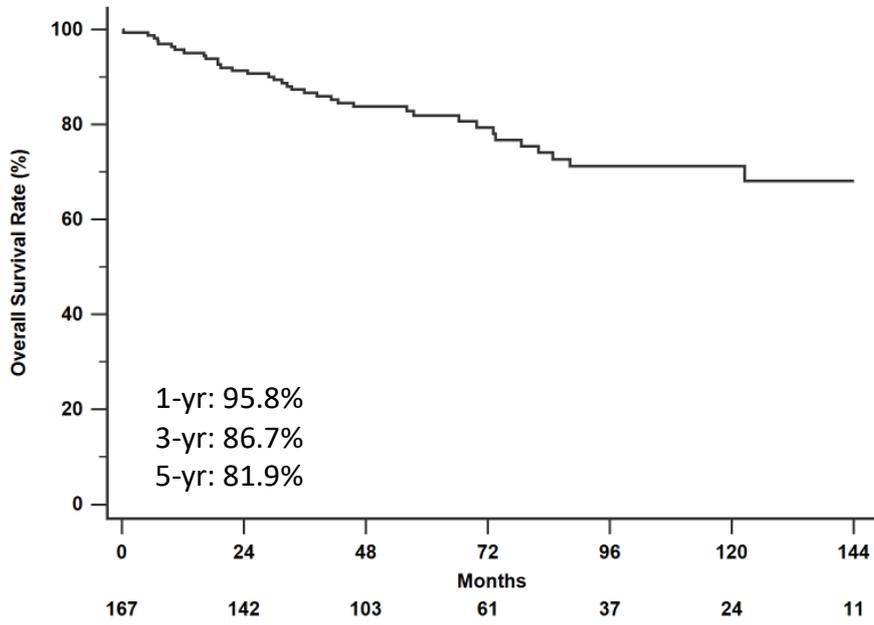
(A)



(B)



(C)



(D)

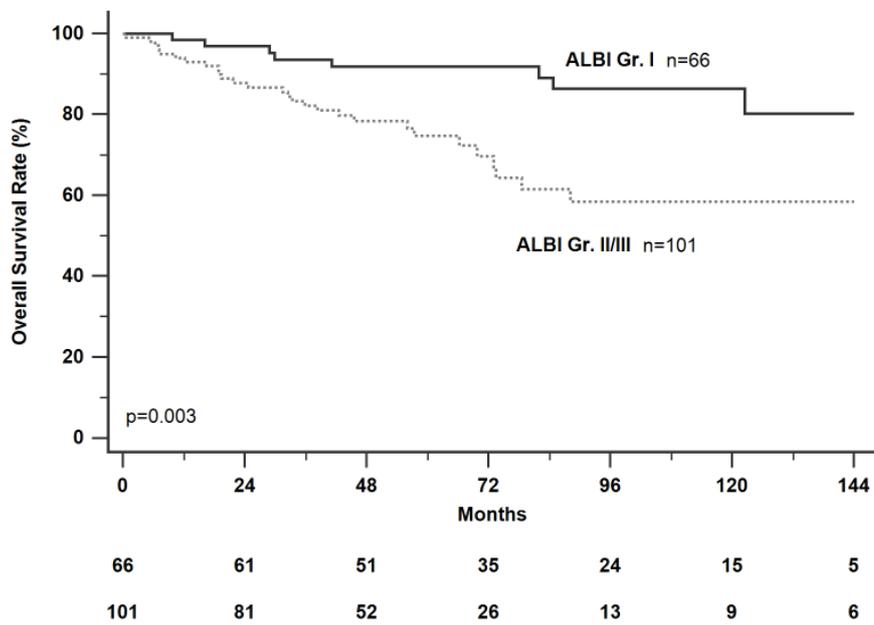
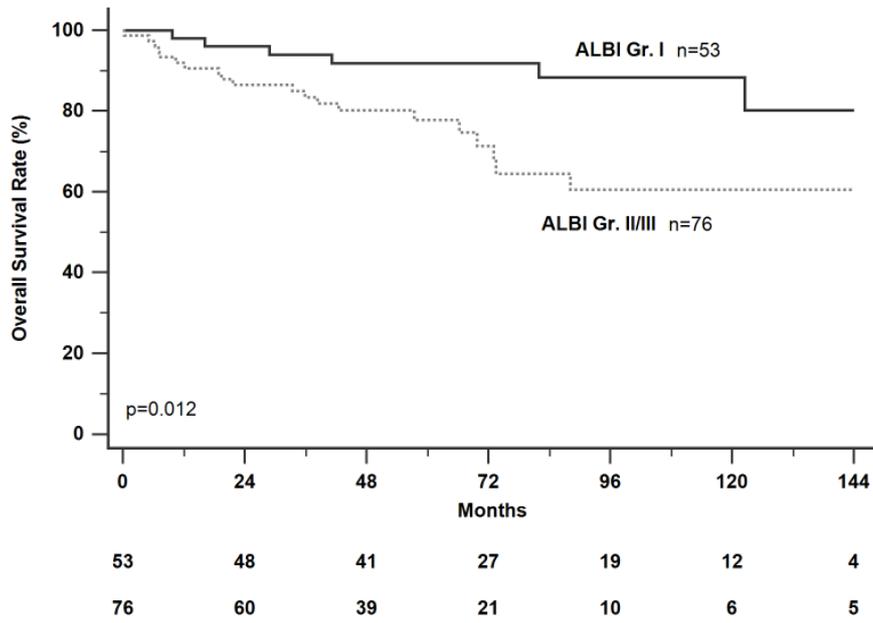


Figure 3. The cumulative overall survival in patients with NBNC-related HCC after curative resection among (A) non cirrhotic patients and (B) cirrhotic patients.

(A)



(B)

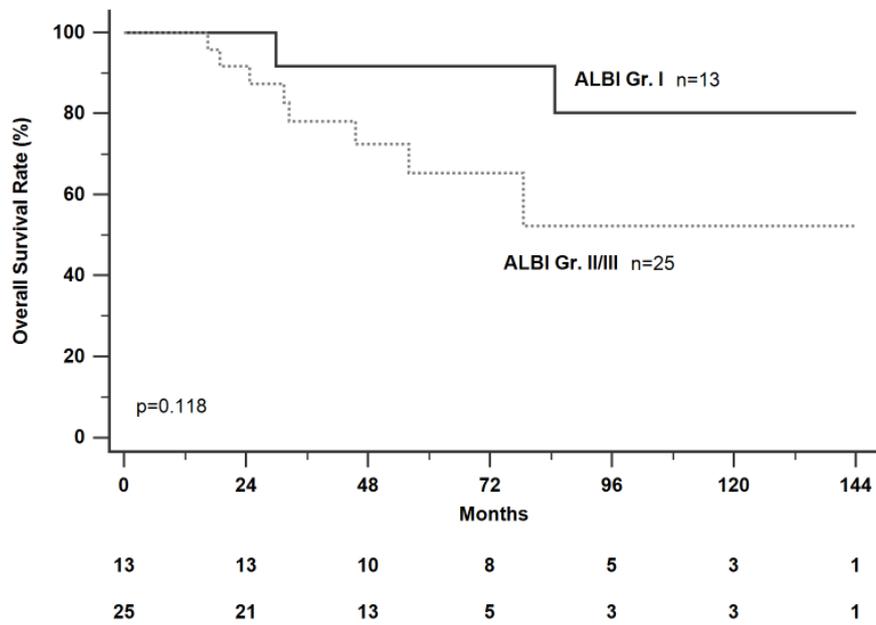


Table 1. Comparison of clinical and pathological characteristics between patients with pre-operative ALBI grades I and II

	Total (n=168)	ALBI grade I (n=66)	ALBI grade II/III (n = 102)*	P value
Age (years; mean \pm SD)	65.2 \pm 12.2	58.9 \pm 11.8	64.8 \pm 12	0.002
Male, n (%)	131 (78%)	56 (84.8%)	75 (73.5%)	0.084
Diabetes mellitus, n (%)	58 (34.5%)	22 (33.3%)	36 (35.3%)	0.794
Hypertension, n (%)	90 (58.1%)	37 (60.7%)	53 (56.4%)	0.598
Current alcohol intake ^S , n (%)	32 (24.2%)	16 (32.7%)	16 (19.3%)	0.083
AST (U/L; mean \pm SD)	41.6 \pm 74.4	34.7 \pm 19.3	46.1 \pm 94.1	0.333
ALT (U/L; mean \pm SD)	44.1 \pm 109.4	39.5 \pm 23.3	47.2 \pm 139.3	0.658
Total bilirubin (mg/dL; mean \pm SD)	0.8 \pm 0.3	0.8 \pm 0.3	0.8 \pm 0.4	0.132
Albumin (g/dL; mean \pm SD)	3.7 \pm 0.6	4.2 \pm 0.3	3.4 \pm 0.4	<0.001
Platelet (<150000 u/l), n (%)	38 (22.9%)	14 (21.5%)	24 (23.8%)	0.739
AFP (> 200ng/ml), n (%)	25 (15.3%)	11 (16.9%)	14 (14.3%)	0.647
Liver cirrhosis, n (%)	38 (22.6%)	13 (19.7%)	25 (24.5%)	0.466
Tumor size (cm; mean \pm SD)	5.3 \pm 3.7	4.5 \pm 2.9	5.9 \pm 4.1	0.09
Tumor number (single: multiple)	164 : 4	65 : 1	99 : 3	0.554
Child-Pugh grade (A : B)	158 : 10	66:0	92 : 10	0.009
BCLC stage (0 : A : B)	17 : 87 : 64	10 : 35 : 21	7 : 52 : 43	0.144
Pathological features				
Fat content (%) in nontumor tissue, n (%) **				0.064

>30%	24 (17.5%)	15 (26.3%)	9 (11.3%)	
5%-30%	37 (27.0%)	15 (26.3%)	22 (27.5%)	
<5%	76 (55.5%)	27 (47.4%)	49 (61.3%)	
Vascular invasion, n (%)	55 (35%)	19 (29.7%)	36 (38.7%)	0.224
pTNM stage (I : II : III)	101 : 58 : 8	41 : 23 : 1	60 : 35 : 7	0.289
Histological grade (well : moderate: poor)	31 : 125 : 11	14 : 50 : 2	17 : 75 : 9	0.365

AST=Aspartate aminotransferase; ALT=Alanine aminotransferase; AFP = α -fetoprotein; BCLC=Barcelona Clinic Liver Cancer; ALBI = albumin-bilirubin

*4 cases are ALBI grade III

[§]>80g ethanol per day

**137 cases had available data

Table 2. Univariate and multivariate analysis of prognostics factors for recurrence in NBNC-HCC patients after curative resection

Variable	Comparison	Univariate		Multivariate	
		HR (95%CI)	P value	HR (95%CI)	P value
Age(years)	>60 vs ≤60	1.316 (0.815-2.125)	0.216		
Sex	Male vs. Female	1.220 (0.698-2.131)	0.485		
DM history	Yes vs. No	1.286 (0.800-2.068)	0.299		
Hypertension	Yes vs. No	1.184 (0.694-2.020)	0.536		
Alcoholic history	Yes vs. No	1.353 (0.748-2.446)	0.318		
AFP (ng/ml)	>200 vs. ≤200	2.065 (1.149-3.710)	0.015	2.070 (1.114-3.848)	0.021
Platelet($10^9/L$)	≤150 vs. > 150	1.264 (0.754-2.119)	0.375		
Albumin(g/dL)	≤3 vs. > 3	1.358 (0.833-2.215)	0.220		
Liver cirrhosis	Yes vs. No	0.950 (0.552-1.635)	0.853		
Child-Pugh grade	B vs. A	1.216 (0.682-2.168)	0.508		
ALBI grade	II/III vs. I	1.052 (0.662-1.671)	0.831		
Tumor size (cm)	>5 vs. ≤5	1.024 (0.634-1.653)	0.923		
Tumor no.	Multiple vs. Single	2.847 (0.892-9.084)	0.077	10.770 (2.513-46.153)	0.001
BCLC stage	B vs. 0/A	1.004 (0.625-1.615)	0.985		
Liver fat content (%)	>30 vs. ≤30	1.472 (0.811-2.673)	0.204		

Vascular invasion	Yes vs. No	0.798 (0.479-1.329)	0.386		
pTNM stages	II+III vs. I	2.084 (1.302-3.336)	0.002	1.962 (1.199-3.210)	0.007
Histology stages	Poor vs. well/moderate	1.699 (0.682-4.232)	0.255		

DM=Diabetes mellitus; AST=Aspartate aminotransferase; ALBI = albumin-bilirubin
; BCLC=Barcelona Clinic Liver Cancer;

Table 3. Univariate and multivariate analysis of prognostics factors for overall survival in NBNC-HCC patients after curative resection

Variable	Comparison	Univariate		Multivariate	
		HR (95%CI)	P value	HR (95%CI)	P value
Age(years)	>60 vs ≤60	2.117 (0.995-4.507)	0.052	2.939 (1.995-8.850)	0.005
Sex	Male vs. Female	0.983 (0.462-2.093)	0.965		
DM	Yes vs. No	1.324 (0.670-2.617)	0.420		
Hypertension	Yes vs. No	0.885 (0.364-2.152)	0.787		
Alcoholic history	Yes vs. No	1.601 (0.630-4.064)	0.322		
AFP (ng/ml)	>200 vs. ≤200	3.475 (1.648-7.329)	0.001	4.785 (1.943-11.783)	0.001
Platelet($10^9/L$)	≤150 vs. > 150	0.666 (0.276-1.605)	0.365		
Albumin(g/dL)	≤3 vs. > 3	2.028 (0.872-4.716)	0.101		
Liver cirrhosis	Yes vs. No	1.305 (0.629-2.706)	0.475		
Child-Pugh grade	B vs. A	1.735 (0.526-5.723)	0.365		
ALBI grade	II/III vs. I	3.126 (1.415-6.916)	0.005	3.689 (1.512-8.997)	0.004
Tumor size (cm)	>5 vs. ≤5	2.242 (1.163-4.321)	0.016		
Tumor no.	Multiple vs. Single	3.705 (1.133-12.113)	0.03	9.993 (2.177-45.866)	0.003
BCLC stage	B vs. 0/A	2.323 (1.202-4.492)	0.012		
Liver fat content (%)	>30 vs. ≤30	0.454 (0.105-1.965)	0.291		

Vascular invasion	Yes vs. No	0.618 (0.290-1.317)	0.213		
pTNM stages	III vs. I+II	6.395 (2.171-18.834)	0.001	8.853 (2.795-28.043)	<0.001
Histology stages	Poor vs. well/moderate	2.421 (0.732-8.001)	0.147		

DM=Diabetes mellitus; AST=Aspartate aminotransferase; ALBI = albumin-bilirubin; BCLC=Barcelona Clinic Liver Cancer;

Figures

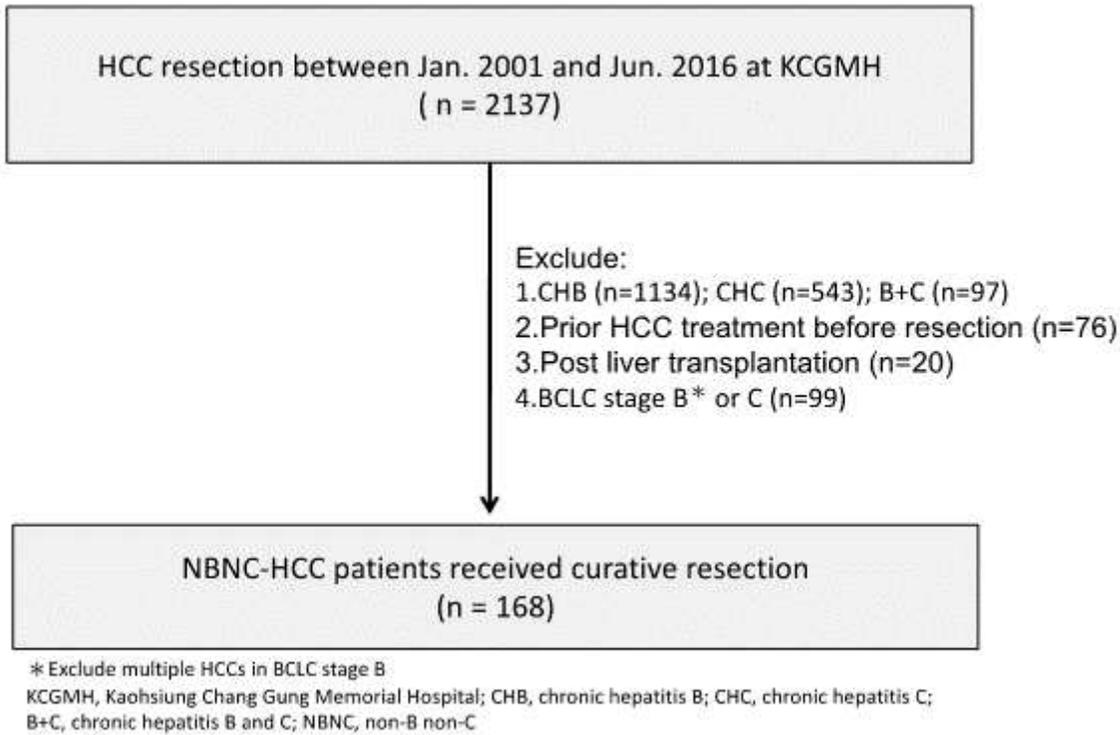


Figure 1

Schematic flowchart of the enrolment process

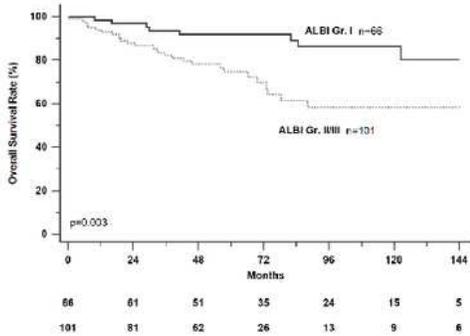
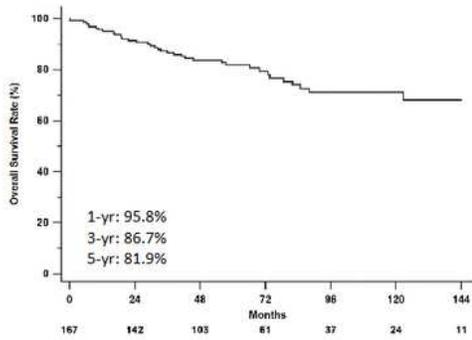
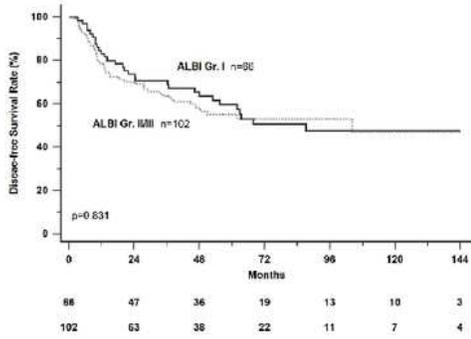
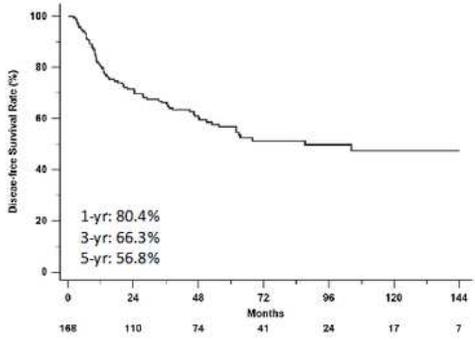


Figure 2

The disease-free survival (DFS) rate and overall survival (OS) rate in NBNC-HCC after resection. (A) DFS in the study population (B) DFS between ALBI Gr I vs. Gr II/III (C) OS in the study population (D) DFS between ALBI Gr I vs. Gr II/III.

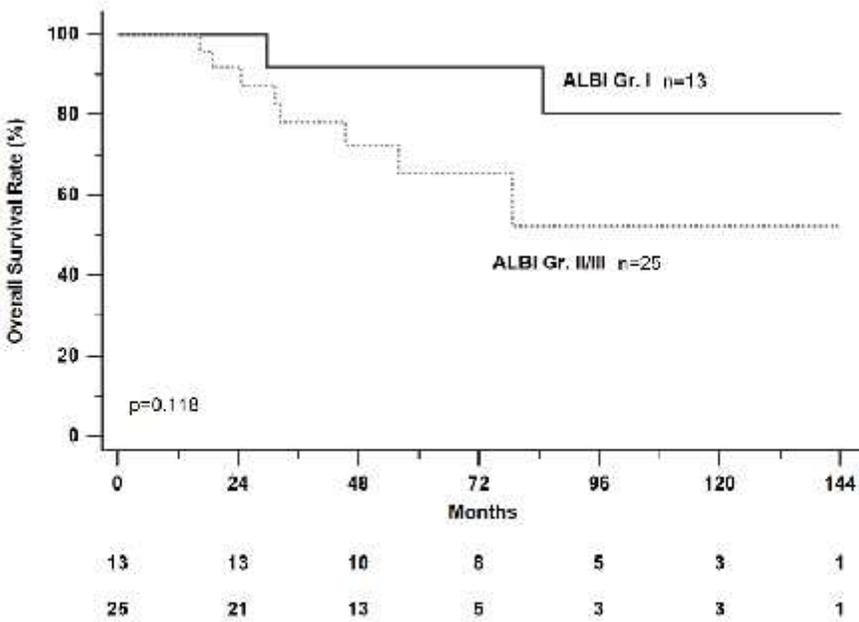
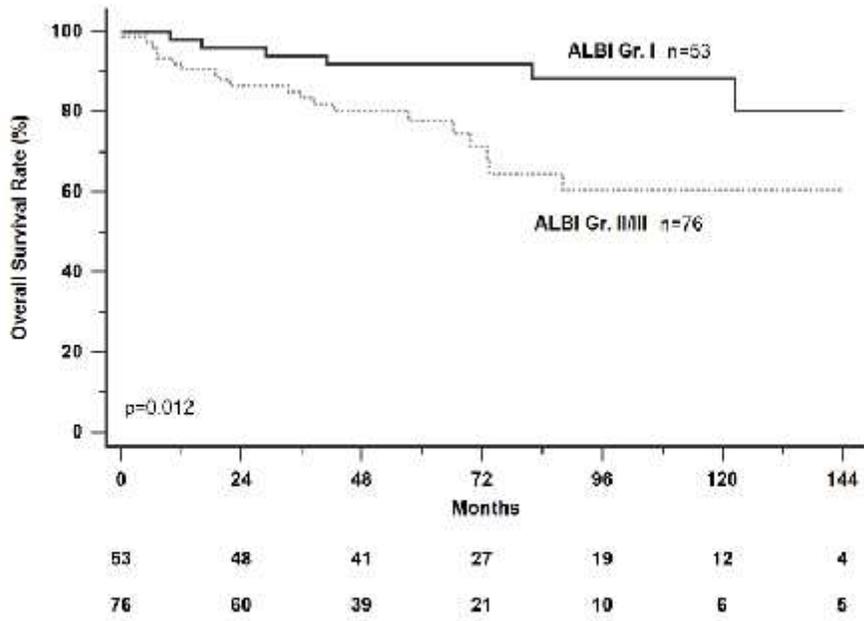


Figure 3

The cumulative overall survival in patients with NBNC-related HCC after curative resection among (A) non cirrhotic patients and (B) cirrhotic patients.