Table 1: Summary of staging systems for Child-Pugh-based and ALBI-based BCLC systems

BCLC stage	**0**	**A**	**B**	**C**	**D**
Performance status	0	0	0	1-2	3-4
Tumour stage	Single <2 cm	Single or 3 nodules <3 cm	Multinodular	Vascular invasion or Extrahepatic spread	Any
Child-Pugh grade	A	A-B	A-B	A-B	C
†ALBI grade	1	1-2	1-2	1-2	3

ALBI, Albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer

†Modification of BCLC system by direct substitution of Child-Pugh grade by ALBI grade

Table 2: Characteristics of patients

	Hong Kong	Japan	United Kingdom
	n = 1532	n = 1502	n = 662
Male gender	1316 (85.9%)	1067 (71.0%)	539 (81.4%)
Age (years, mean ± SD)	58.9 ± 11.9	67.8 ± 9.4	63.8 ± 11.0
Hepatitis B	1252 (81.7%)	247 (16.4%)	92 (13.9%)
Hepatitis C	92 (6.0%)	1050 (69.9%)	162 (24.5%)
Non-B/Non-C	196 (12.8%)	222 (14.8%)	330 (49.8%)
Child-Pugh grade			
A	1125 (73.4%)	1028 (68.4%)	472 (71.3%)
B	349 (22.8%)	360 (24.0%)	164 (24.8%)
C	58 (3.8%)	114 (7.6%)	26 (3.9%)
ALBI grade			
1	609 (39.8%)	469 (31.2%)	310 (46.8%)
2	774 (50.5%)	873 (58.1%)	305 (46.1%)
3	149 (9.7%)	160 (10.7%)	47 (7.1%)
Follow-up [months, median (range)]			
Entire cohort	13.7 (0.1-167.1)	44.9 (0.1-275.1)	20.1 (0.1-138.5)
Curative treatment	136.6 (0.1-167.1)	75.5 (0.1-275.1)	55.4 (0.6-138.5)
Palliative treatment	5.3 (0.1-106.6)	17.3 (0.1-167.5)	12.0 (0.1-63.5)
Treatment modality			
Liver transplantation	8 (0.5%)	0 (0.0%)	115 (17.4%)
Surgical resection	517 (33.7%)	496 (33.0%)	70 (10.6%)
Local ablative therapy	71 (4.6%)	416 (27.7%)	73 (11.0%)
Transarterial therapy	242 (15.8%)	367 (24.4%)	180 (27.2%)
Systemic agent	188 (12.3%)	16 (1.1%)	95 (14.4%)
Best supportive treatment	506 (33.0%)	207 (13.8%)	129 (19.5%)
Tumour size (mm, mean ± SD)	74 ± 48	38 ± 31	57 ± 42
Multiple tumours	744 (48.6%)	674 (44.9%)	296 (44.7%)
Vascular invasion	412 (26.9%)	234 (15.6%)	134 (20.2%)
Extrahepatic spread	129 (8.4%)	42 (2.8%)	47 (7.1%)
Child-Pugh-based BCLC			
0	45 (2.9%)	245 (16.3%)	34 (5.1%)
A	391 (25.5%)	691 (46.0%)	201 (30.4%)
B	170 (11.1%)	181 (12.1%)	166 (25.1%)
C	805 (52.5%)	260 (17.3%)	214 (32.3%)
D	121 (7.9%)	125 (8.3%)	47 (7.1%)

ALBI-based BCLC			
0	40 (2.6%)	110 (7.3%)	22 (3.3%)
A	390 (25.5%)	799 (53.2%)	209 (31.6%)
B	166 (10.8%)	172 (11.5%)	162 (24.5%)
C	734 (47.9%)	247 (16.4%)	201 (30.4%)
D	202 (13.2%)	174 (11.6%)	68 (10.3%)

ALBI, Albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; SD, standard derivation

Table 3: The comparison of prognostic performance between Child-Pugh-based and ALBI-based BCLC systems in terms of homogeneity, discriminatory ability, and monotonicity.

	Homogeneity LR chi-square test		**Linear trend chi-square test**		**c-index (95% CI)**	
	CP-based BCLC	ALBI-based BCLC	CP-based BCLC	ALBI-based BCLC	CP-based BCLC	ALBI-based BCLC
Entire cohort	1489.866	1499.605	606.376	639.472	0.750 (0.738-0.762)	0.750 (0.739-0.761)
Region						
Hong Kong	780.516	781.067	532.700	534.211	0.734 (0.716-0.751)	0.737 (0.719-0.755)
Japan	497.786	513.848	98.679	118.793	0.740 (0.720-0.760)	0.737 (0.718-0.756)
United Kingdom	119.803	119.355	69.065	66.805	0.670 (0.641-0.698)	0.673 (0.644-0.701)
Aetiology						
Hepatitis B	787.267	775.677	486.029	486.315	0.748 (0.730-0.766)	0.749 (0.731-0.767)
Hepatitis C	414.440	422.341	79.730	88.212	0.730 (0.709-0.751)	0.724 (0.704-0.744)
Non-B/Non-C	240.273	254.512	120.927	130.910	0.720 (0.693-0.747)	0.728 (0.701-0.754)
Treatment intent						
Curative	152.313	174.928	77.123	99.632	0.650 (0.630-0.670)	0.654 (0.634-0.673)
Palliative	423.362	437.921	81.602	91.374	0.665 (0.650-0.680)	0.668 (0.653-0.683)

ALBI, Albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CP, Child-Pugh

Supplementary figure 1: Kaplan-Meier survival plots comparing overall survivals for Hong Kong, Japanese and United Kingdom patients stratified by (a-c) Child-Pugh-based BCLC and (d-f) ALBI-based BCLC staging systems, respectively.

Supplementary figure 2: Kaplan-Meier survival plots comparing overall survivals for hepatitis B, hepatitis C and non-B/non-C patients stratified by (a-c) Child-Pugh-based BCLC and (d-f) ALBI-based BCLC staging systems, respectively.

Supplementary figure 3: Kaplan-Meier survival plots comparing overall survivals for patients receiving curative and palliative therapies stratified by (a,b) Child-Pugh-based BCLC and (c,d) ALBI-based BCLC staging systems, respectively.

Usefulness of albumin-bilirubin (ALBI) grade for evaluation of prognosis of 2584 Japanese patients with hepatocellular carcinoma

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Running title: ALBI grade for prognosis of HCC

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Abstract

Background/Aim: The Child-Pugh classification has some non-objective factors, with chronic hepatitis indistinguishable from early liver cirrhosis in Child-Pugh A. We retrospectively evaluated the efficacy of albumin-bilirubin (ALBI) grade, which has been proposed as a new classification for hepatic function, for grading HCC patients based on hepatic function and predicting their prognosis.

Method: From 2000 to 2014, 2584 naïve HCC (69.0±9.8 years old, 1850 males, 734 females, Child-Pugh class A:B:C=1871:558:155) were enrolled. TNM staging was determined using the classification of the Liver Cancer Study Group of Japan and ALBI grade, instead of Child-Pugh classification (ALBI-T score) (Table 1), and is similar to the Japan Integrated Staging (JIS) score. We retrospectively compared ALBI-T and JIS scores in these patients.

Results: Of patients classified as Child-Pugh A (n=1871), 1285 with 5 points were divided into 858 with ALBI grade 1 and 427 with grade 2, while 586 with 6 points were divided into 53 with grade 1 and 533 with grade 2. The ratio of ALBI grade 2 patients with a Child-Pugh score of 6 points (91.0%) was similar to that of those with 7 points (91.8%). Patients with a lower ALBI-T score (0-5 points) showed a better median survival time (MST) than those with a corresponding lower JIS score (137.7:83.2:53.4:27.4:5.0:1.4 vs. 97.6:74.9:39.7:15.0:4.0:1.0 months).

Conclusion: ALBI grade was found to be superior for distinguishing patients with better hepatic function. ALBI-T scoring may be a better total prognostic scoring system for predicting survival of Japanese patients with HCC.

Key words: ALBI grade, hepatocellular carcinoma, prognosis, scoring system, JIS score

Introduction

Various systems for predicting the survival of patients with hepatocellular carcinoma (HCC) have been proposed, such as Japan Intergrade Staging (JIS) ***[1]***, Cancer of the Liver Italian Program (CLIP) score ***[2]***, Barcelona Clinic Liver Cancer (BCLC) stage ***[3]***, and bilirubin, albumin, lens culinaris agglutinin A-reactive fraction of α-fetoprotein (AFP), AFP and des-γ-carboxy prothrombin (BALAD) ***[4]*** scoring systems. JIS score has been reported to be superior for Japanese patients in consideration of the clinical situation in regard to diagnosis and therapies for HCC. The JIS scoring system is comprised of both Child-Pugh classification ***[5]*** and tumor node metastasis (TNM) stage of the Liver Cancer Study Group of Japan (LCSGJ), 5th edition ***[6]*** (Table 1). Although Child-Pugh classification is widely used for evaluation of hepatic reserve function, related problems include use of non-objective factors (ascites, hepatic encephalopathy), while Child-Pugh A includes chronic hepatitis (CH) with normal hepatic function and early liver cirrhosis (LC) accompanied by slightly derogated hepatic function. Recently, a simple and objective method for evaluation of hepatic reserve function using only albumin and total-bilirubin measurements was proposed as albumin-bilirubin (ALBI) grade [(log10 bilirubin (μmol/L) x 0.66) + (Albumin (g/L) x -0.0852): Grade 1:2:3 = ≤-2.60:<-2.60 to ≤-1.39:>-1.39] ***[7]***. In the present study, we evaluated the efficacy of ALBI grade for predicting the prognosis of HCC patients.

Materials and Methods

From 2000 to 2014, 2584 patients with naïve HCC admitted to Ehime Prefectural Central Hospital (n=1325) and Ogaki Municipal Hospital (n=1259) were enrolled [average age: 69.0±9.8 years old, 1850 males, 734 females, hepatitis C virus (HCV) : hepatitis B virus (HBV) : HBV&HCV : alcohol : others=1723 : 308 : 26 : 149 : 378, Child-Pugh class A : B : C=1871 : 558 : 155] (Table 2). Scoring was determined based on TNM stage shown in the LCSGJ 5th edition and ALBI grade (ALBI-T score), instead of Child-Pugh classification (Table 1), such as with JIS scoring. ALBI-T score is obtained by adding the TNM stage from the LCSGJ 5th edition to the ALBI grade and then subtracting 2 (e.g., HCC with TNM stage II and ALBI grade 1 = ALBI-T score 1). We retrospectively evaluated the ability of both ALBI-T and JIS score for evaluation of hepatic reserve function shown by ALBI grade and Child-Pugh classification in HCC patients and for predicting prognosis. In addition, we compared ALBI-T scoring with other reported prognostic scoring systems (CLIP score, BCLC stage, BALAD score) in regard to prognosis prediction.

Prior to 2005, HCC patients fulfilling the Milan criteria ***[8]*** and classified as Child-Pugh A or B were treated with surgical resection ***[9,10]*** or radiofrequency ablation (RFA) ***[11,12]***, if possible, at our institution. For those with advanced HCC, surgical resection was selected in cases with a single nodule and good hepatic reserve

function, and transcatheter arterial chemoembolization (TACE) ***[13]***, or hepatic arterial chemotherapy (HAIC) ***[14]*** were selected in unresectable HCC cases. After 2005, all treatments were performed following the Japanese practical guidelines for HCC ***[15,16]*** as possible.

Surveillance was mainly performed using ultrasonography (US). HCC was diagnosed based on an increasing course of AFP, as well as dynamic CT ***[17]***, magnetic resonance imaging (MRI), and/or contrast enhanced US (CEUS) with perflubutane (Sonazoid®, Daiichi Sankyo Co., Ltd. Tokyo, Japan) ***[18]*** findings. TNM stage was determined as reported in studies for staging of HCC according to the LCSGJ 5th edition (Table 1). Patients positive for hepatitis B virus surface antigen (HBsAg) were judged to have HCC due to the presence of HBV, while those positive for anti-HCV were judged to have HCC due to HCV.

The study protocol was approved by the Institutional Ethics Committee of Ehime Prefectural Central Hospital (No. 26-11).

Statistical analysis

Data are expressed as the mean ± standard deviation (SD). Statistical analyses were performed using a log-rank test and Kaplan-Meyer methods, or a χ square test, Fischer's exact test, or Mann-Whitney's U test, as appropriate. All statistical analyses were performed using SPSS version 21 (IBM SPSS Japan Inc., Tokyo, Japan). A p value

of less than 0.05 was considered to indicate statistical significance.

Results

In the present study, we re-evaluated hepatic reserve function based on ALBI grade. In Child-Pugh A cases (n=1871), 1285 patients with 5 points were divided into 858 (66.8%) with ALBI grade 1 and 427 (33.2%) with grade 2. The ratio of ALBI grade 2 among patients with a Child-Pugh score of 6 points (class A) was 91.0%, which was similar to that of those with 7 points (class B) (91.8%). Furthermore, the ratio of ALBI grade 3 among patients with a Child-Pugh score of 9 points (class B) was 50.0%, which was similar to that of those with 10 points (class C) (52.8%). As for those with a Child-Pugh score of 11 or more, the percentage of patients with ALBI grade 3 was 83.9% and none were classified as ALBI grade 1 (Figure 1). The correlations of JIS and ALBI-T scores are shown in Figure 2a. There was a tendency for JIS score to include not only a corresponding score but also a larger ALBI-T score.

Patients with lower ALBI-T scores 0, 1, 2, 3, 4, and 5 (n=237 : 776 : 733 : 474 : 287 : 77) showed better prognosis than those with a corresponding lower JIS score 0, 1, 2, 3, 4, and 5 (n=479 : 913 : 609 : 357 : 155 : 71) [median survival time (MST) for ALBI-T score = 137.7, 83.2, 53.4, 27.4, 5.0, 1.4 months, respectively; MST for JIS score = 97.6, 74.9, 39.7, 15.0, 4.0, 1.0 months, respectively) (Figure 2b and 2c). ALBI-T score 0, 1, 2, 3 show better prognosis than those with corresponding JIS score significantly (P

values of 0, 1, 2 and 3: 0.021, 0.006, 0.002 and <0.001) (Figure 3). Similar findings were obtained in comparisons between ALBI-T score and CLIP score, BCLC stage, and BALAD scores after exclusion of cases lacking data for each score. The MST of 2573 patients with a CLIP score of 0, 1, 2, 3, 4, 5, and 6 (n=1620, 591, 144, 91, 76, 37, 14, respectively) was 85.0, 55.0, 23.5, 9.0, 2.7, 1.4, and 0.9 months, respectively. In addition, that of 2584 with BCLC stage 0, A, B, C, and D (n=178, 1229, 325, 606, 246, respectively) was 85.0, 77.0, 40.7, 23.5, and 8.2 months, respectively, and that of 2390 with a BALAD score of 0, 1, 2, 3, 4, and 5 (n=817, 753, 435, 261, 104, 20, respectively) was 90.4, 50.6, 32.7, 12.8, 2.7, and 1.5 months, respectively. BCLC stage B and C could not be separated (Figure 4). These results indicated that ALBI-T was superior to the others for the present cohort (Table 3).

Figure 5 shows the frequency of each therapy for each grade of ALBI-T score and its corresponding JIS score. The ratio of patients who underwent surgical resection or RFA was higher among those with an ALBI-T score of 0, 1, 2, 3, 4 and 5 as compared to the corresponding JIS score (94.5% vs. 92.9%, P=0.159; 88.3% vs. 81.4%; P<0.001; 67.8% vs. 56.2%; P<0.001; 40.0% vs. 25.8%, P=0.001; and 12.5% vs. 5.8%, P=0.165, and 7.1 vs. 0.0%, P=0.439 respectively).

Discussion

With progression of the aging society in Japan, the frequency of non-B non-C HCC

cases has become greater ***[19]***. In other report, an increase in the number of HCC patients without both HCV and HBV (non-B non-C HCC), who are earlier stage LC (Child-Pugh class) as compared to viral hepatitis patients, has been reported ***[20]***. On the other hand, it has also been noted that the risk of HCC remains even after sustained virologic response (SVR) in LC patients due to HCV ***[21]***, while we previously reported that HCC surveillance should be performed even for chronic liver disease (CLD) patients with HCV who obtained an SVR with interferon therapy and that they have good hepatic function ***[22]***. Recently, direct acting antiviral (DAA) therapy has been utilized ***[23-25]***, which is a strong standard therapeutic option that can easily obtain an SVR even for compensated LC due to HCV with good hepatic reserve function. Although there are no data for the rate of HCC after an SVR is obtained with DAA therapy or if the number of CLD patients with HCV who develop future decompensated LC is decreased, an increase in the frequency of non-B non-C HCC including HCC among LC patients due to HCV after obtaining SVR is expected in Japan and a more effective evaluation method to sort patients with better hepatic reserve function for predicting prognosis will be needed. The present results concerning the distribution of ALBI grade in each Child-Pugh score suggest that ALBI grade is better for more detailed evaluation of patients with good hepatic function as compared to the Child-Pugh classification.

In the present study, patients with a Child-Pugh score of 5 points (class A) could be

divided into ALBI grade 1 (66.8%) and grade 2 (33.2%), while the percentage of grade 2 cases among those with a Child-Pugh score of 6 points (class A) was 91.0%, which was similar to those with a score of 7 points (class B) (91.8%), and the ratio of ALBI grade 3 among patients with a Child-Pugh score of 9 points (class B) was 50.0%, which was similar to that of those with 10 points (class C) (52.8%). These results indicate that the classification based on Child-Pugh score is not able to clarify the border between Child-Pugh class A with a score of 6 and class B with a score of 7, or between class B with a score of 9 and class C with a score of 10. Some patients with Child-Pugh score 7 and lower ALBI grade can be treated in the same manner as those with Child-Pugh A, while some with a Child-Pugh score of 9 and a higher grade of ALBI should be treated the same as Child-Pugh C.

It is well known that survival of HCC patients depends on not only tumor progression but also hepatic reserve function. JIS score, CLIP score, BCLC stage, and BALAD score, which consider both tumor and hepatic reserve function factors, have been proposed as effective for predicting survival in these patients. JIS score has been considered to be more effective than other scores for predicting prognosis of Japanese HCC patients. Kudo reported that the cumulative 10-year survival rates for patients with the best prognosis in the CLIP score (score 0) and JIS score (score 0) staging systems were 23% and 65%, respectively ($P<0.01$). ***[1,26]***. The reason why HCC is often diagnosed

in an earlier stage in Japan as compared to other countries is because of developments in the surveillance program for screening of HCC. Thus, ALBI-T score, which is consistent with TNM stage according to the LCSGJ 5th edition and ALBI-grade, is thought to be a more suitable staging system than CLIP score for predicting survival Japanese HCC patients, too.

Moreover, the ability of BCLC stage for predicting prognosis was shown to be inferior to that of ALBI-T score, possibly because the combinations of TNM stage according to the LCSGJ 5th edition (I, II, III) and Child-Pugh classification (A, B) can not be clearly distinguished in patients classified as BCLC stage A. On the other hand, BALAD score, which consists of bilirubin, albumin, and tumor markers (AFP, lens culinaris agglutinin A-reactive fraction of AFP, des-γ-carboxy) and is similar to ALBI-T score, and its ability to predict prognosis of HCC patients is considered to be inferior to ALBI-T. It is thought that TNM stage according to the LCSGJ 5th edition, which can categorize small HCC tumors into each grade, is better for estimating prognosis than tumor markers especially in early HCC. In our analysis, ALBI grade could distinguish the patients with better hepatic function from those with Child-Pugh A. Patients with ALBI-T score 0 showed better liver function than those with JIS score 0, and patients with ALBI-T score 1, 2 and 3 showed higher ratio of curative treatments (e.g. resection or RFA) than those with JIS score 1, 2 and 3. Those are thought to be reasons that ALBI-T score showed

better predictive value for prognosis of Japanese HCC patients especially in lower scores than JIS score. The reason why ALBI-T score showed a better ability to predict prognosis as compared to other scoring systems may be because it is consistent with TNM stage of the LCSGJ 5th edition, which is suitable for categorizing small HCC tumors, and ALBI grade, which is better for evaluating hepatic reserve function.

HCC patients can be divided into some subgroups with indications for different therapeutic options due to tumor stage and/or hepatic reserve function. In addition to a total prognostic scoring system, a prognostic scoring system for each therapeutic modality ***[27,28]*** or tumor status ***[29,30]*** is needed. Each should be used for different purposes in accordance with the individual situation.

In summary, ALBI grade was thought to be useful for distinguishing patients with better hepatic function and ALBI-T score using both ALBI grade and TNM stage according to the LCSGJ 5th edition was shown to be superior as a total prognostic scoring system for predicting survival of Japanese patients with HCC.

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