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Original Article

Comparison of new prognostic systems for patients with resectable hepatocellular carcinoma: Albumin-Bilirubin grade and Albumin-Indocyanine Green Evaluation grade

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Aim: We aimed to compare the prognostic abilities of two novel liver function-estimating models, Albumin-Bilirubin (ALBI) and Albumin-Indocyanine Green Evaluation (ALICE) grades, in patients with hepatocellular carcinoma.

Methods: Data of 1270 patients who underwent initial hepatectomy for hepatocellular carcinoma between 1986 and 2016 were retrospectively collected from a multi-institutional database. The prognostic impact of each system was analyzed according to the results of the area under the receiver operating characteristic curve, the Cox regression model and the linear trend χ^2-test.

Results: The ALBI and ALICE scores, which were obtained before grading status, were significantly correlated (correlation coefficient 0.930; $P < 0.001$). Both ALBI and ALICE grades stratified well in terms of overall survival, and were found to be independent prognostic factors on multivariate analysis ($P < 0.05$). The area under the receiver operating characteristic curves for 5-year survival in both groups were equivalent (0.602 vs. 0.614, $P = 0.402$); however, homogeneity, discriminatory ability, and the Akaike information criterion were superior for the ALICE grade than for the ALBI grade (73.8 vs. 65.7, 43.4 vs. 34.9, and 7204.1 vs. 7212.2, respectively).

Conclusions: Both grading systems could estimate the liver function of patients with hepatocellular carcinoma. Regarding hepatectomy patients, the ALICE grade was a more suitable model than the ALBI grade.

Key words: Albumin-Bilirubin grade, Albumin-Indocyanine Green Evaluation grade, hepatocellular carcinoma, liver function, prognostic impact

INTRODUCTION

HEPATOCELLULAR CARCINOMA (HCC) mostly occurs in chronic hepatitis or liver cirrhosis; therefore, the prognosis of patients with HCC is related to tumor factors and liver function complexly. To date, the Child–Pugh (C-P) classification has been adopted worldwide as an evaluation tool of liver function. However, this classification has some limitations, including subjective factors, such as ascites and encephalopathy, and an insufficient discrimination ability; that is, most patients with HCC indicated for hepatectomy are classified as C-P grade A. Today, with the development of imaging technology and surgical techniques, a more objective and accurate method to evaluate liver function is required. Recently, two new grading systems for estimating liver function, namely, the Albumin-Bilirubin (ALBI) grade[1] and Albumin-Indocyanine green Evaluation (ALICE) grade[2] have been published in 2015 and 2016, respectively.

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The ALBI grade consists of three grades (grades 1–3), which divide the ALBI scores calculated using the following formula: $\log_{10}$ bilirubin (μmol/L) × 0.66 + albumin (g/L) × −0.085 (cut-off values of grades 1/2 and 2/3 were −2.60 and −1.39, respectively). Several studies reported its utility, as validation cohorts,[3–5] comparison with C-P grade,[6,7] and combination with HCC tumor factor.[8,9] The ALICE score is calculated, including the indocyanine green retention rate at 15 min (ICG R15) and albumin, using the following formula: $0.663 \times \log_{10}$ ICG R15 (%) – 0.0718 × albumin (g/L), and also divided into three grades by the ALICE grade (cut-off values of grades 1/2 and 2/3 were −2.20 and −1.39, respectively). To the best of our knowledge, the usefulness of the ALICE grade system has not been substantially considered, and only a few articles have compared these two grading systems.[10–12]

In the present study, we investigated the utility of the ALBI and ALICE grades as a validation cohort, and compared the prognostic impact of these systems on patients with resectable HCC using a multi-institutional database.

METHODS

THIS COHORT INCLUDED patients who underwent initial hepatectomy with curative intent for pathologically defined HCC at six institutions affiliated with the Hiroshima Surgical study group of Clinical Oncology (HiSCO) in Japan between April 1986 and June 2016. Patients' data, including clinical, laboratory, surgical, pathological, and prognostic information, were retrospectively collected from a shared multi-institutional database. A total of 1270 patients were enrolled in this cohort. Patients who underwent non-radical surgery and those who lacked clinical or prognostic information were excluded. Pathological findings of HCC within resected lesions determined the TNM stage, which is defined by the Liver Cancer Study Group of Japan. Major hepatectomy was defined as resection of at least three Couinaud segments of the liver. Survival was measured from the date of operation to the date of death or last follow up. The study conforms to the provisions of the Declaration of Helsinki, and was approved by the ethics committees of each institution (E-1206). Informed consent was obtained from the patients or patients' families.

All statistical analyses were carried out using the JMP Genomics statistical software version 13 (SAS Institute, Cary, NC, USA). Pearson's product–moment correlation coefficient was used to evaluate the correlation between the two continuous variables: ALBI score and ALICE score. Survival curves were obtained using the Kaplan–Meier method, and an analysis of prognostic factors was carried out using the log–rank test. Cut-off values of continuous variables in the present study were determined as follows: total bilirubin and cholinesterase levels deviated from their normal ranges; albumin and prothrombin time activation rates, cut-off values according to the C-P classification; platelet count, reference value according to the definition of clinically significant portal hypertension[13]; ICG R15, cut-off value according to the liver damage classification; and alpha-fetoprotein, cut-off value according to the Cancer of the Liver Italian Program scoring system.[14] Univariate and multivariate analyses were carried out to evaluate prognostic factors using a Cox proportional hazards regression model. For multivariate analysis, the ALBI and ALICE grades were entered in two different Cox regression models to avoid multicollinearity. Factors that were strongly correlated with the ALBI or ALICE scores (|correlation coefficient| >0.5) were removed from each regression model; furthermore, a stepwise procedure was carried out to regulate the confounding factors. Analyses of the short-term outcome were carried out with a similar method using logistic regression analysis. The performance of the prognostic systems was evaluated in terms of the area under the curve of the receiver operating characteristic curve (AUROC), homogeneity, discriminatory ability, and the Akaike information criterion (AIC). The AUROC was compared between the two models using DeLong's method. Homogeneity, defined as small differences in survival among patients in the same grade within each system, was determined using the likelihood ratio χ^2 calculated using the Cox regression model.[15] Discriminatory ability, defined as the large differences in survival among patients in different grades within each system, was determined using the linear trend χ^2-test.[16] The AIC, which shows the effect of the grading systems on survival, also estimated the results of the Cox regression model in each system. A model with a lower AIC is more explanatory and informative. P-values <0.05 were considered statistically significant in this study.

RESULTS

Characteristics

THE PATIENTS' BACKGROUND characteristics are presented in Table 1. The patients' median age was 67 years (range 25–91 years), and 967 (76.1%) patients were men. Among the patients, 715 (56.3%) were positive for hepatitis C virus antibody, 209 (16.5%) were positive for hepatitis B surface antigen, 20 (1.6%) were positive for both hepatitis C virus antibody

Table 1 Clinical background of patients with hepatocellular carcinoma

Patient characteristics	$n = 1270$
Age (years)†	67 (25–91)
Male/female	967 (76.1%)/303 (23.9%)
HCV/HBV/HCV + HBV/NBNC	715 (56.3%)/209 (16.5%)/20 (1.6%)/326 (25.7%)
AST (IU/L)†	38 (6–302)
ALT (IU/L)†	36 (8–253)
Total bilirubin (mg/dL)†	0.8 (0.1–3.0)
Albumin (g/dL)†	3.9 (2.4–5.4)
Cholinesterase (IU/L)†	230 (37–621)
PT (%)†	86 (13.1–175)
Platelet count ($\times 10^3$/L)†	128 (24–740)
ICG R15 (%)†	14.9 (0.9–87.4)
AFP (ng/mL)†	16.1 (0–511 205)
Child–Pugh grade A/B	1130 (89.0%)/140 (11.0%)
Liver damage A/B/C	822 (64.7%)/435 (34.3%)/13 (1.0%)
ALBI score‡	-2.55 ± 0.012
ALBI grade 1/2/3	615 (48.4%)/647 (50.9%)/8 (0.6%)
ALICE score‡	-2.01 ± 0.013
ALICE grade 1/2/3	422 (33.2%)/725 (57.1%)/123 (9.7%)
Single/multiple	894 (70.7%)/371 (29.3%)
Tumor size (mm)†	27 (5–200)
Vascular invasion	352 (27.7%)
TNM stage I/II/III/IV-A	265 (20.9%)/532 (41.9%)/363 (28.6%)/110 (8.7%)
Minor/major hepatectomy	1124 (88.5%) /146 (11.5%)
Operation time (min)†	280 (50–760)
Blood loss (ml)†	300 (10–7798)
Clavien–Dindo grade ≥IIIa	107 (8.4%)
90-day mortality	20 (1.6%)

†Median (range).
‡Mean ± SE.
AFP alpha-fetoprotein; ALBI, Albumin-Bilirubin; ALICE, Albumin-Indocyanine Green Evaluation; ALT, alanine aminotransferase; AST, aspartate transaminase; HBV, hepatitis B virus; HCV, hepatitis C virus; ICG R15, indocyanine green retention rate after 15 min; NBNC, non-B and non-C viral hepatitis; PT, prothrombin time activation rate.

and hepatitis B surface antigen, and 326 (25.7%) were negative for both. Most patients were classified as C-P grade A ($n = 1130$, 89.0%), and the remaining as C-P grade B ($n = 140$, 11.0%). None were classified as C-P grade C owing to a contraindication for hepatectomy. Patients were almost equally divided into ALBI grades 1 and 2 (615 [48.4%] and 647 [50.9%], respectively). Just eight (0.6%) patients were classified as ALBI grade 3. In contrast, the ALICE grade categorized patients into three groups: grade 1 ($n = 422$, 33.2%), grade 2 ($n = 725$, 57.1%), and grade 3 ($n = 123$, 9.7%). Patients in ALBI grade 1 were divided into ALICE grade 1 or 2. Similarly, the ALBI grade 2 patients were also divided into ALICE grade 2 or 3. All eight patients in ALBI grade 3 were classified as ALICE grade 3 (Fig. 1a). The ALBI and ALICE scores had a strong and significant correlation, with a correlation coefficient of 0.930 ($P < 0.001$; Fig. 1b).

Overall survival after hepatectomy

The overall median survival time after hepatectomy for all patients was 6.36 years, and the overall 3-, 5-, and 10-year survival rates were 78.2%, 60.0%, and 33.1%, respectively. In terms of the ALBI grade, the overall median survival time of patients in grades 1, 2, and 3 were 8.96, 4.96, and 4.33 years, respectively. The overall 5-year survival rate in all grades were 73.3%, 49.6%, and 42.9%, respectively. Prognosis was significantly better in the ALBI grade 1 patients than in the ALBI grade 2 patients ($P < 0.001$); however, a statistical difference in terms of prognosis among the ALBI grades 2 and 3 patients was not observed ($P = 0.097$; Fig. 2a). In the ALICE grades 1, 2, and 3 patients, the overall median survival times were 10.62, 5.75, and 3.98 years, respectively, and the 5-year survival rates were 76.9%, 55.5%, and 37.5%, respectively. The ALICE grade stratified patients well into three grades, and

a

		ALICE		
		grade 1	grade 2	grade 3
ALBI	grade 1	402	213	0
	grade 2	20	512	115
	grade 3	0	0	8

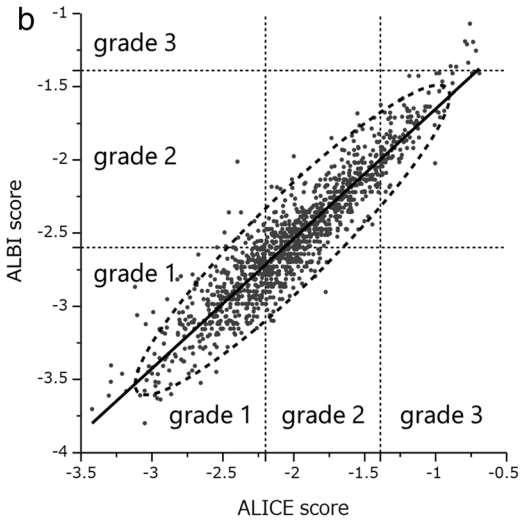


Figure 1 Relationship between the (a) Albumin-Bilirubin (ALBI) and Albumin-Indocyanine Green Evaluation (ALICE) grades and (b) ALBI and ALICE scores in 1270 patients.

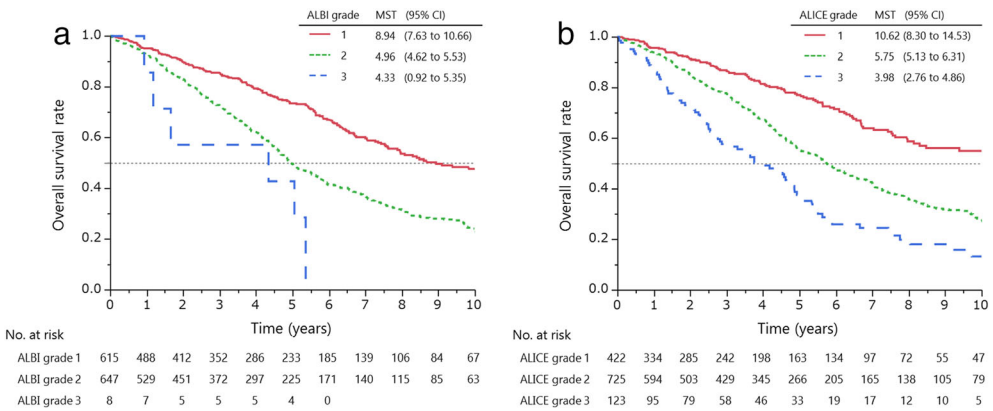


Figure 2 Kaplan–Meier curves for the overall survival according to the (a) Albumin-Bilirubin (ALBI) and (b) Albumin-Indocyanine Green Evaluation (ALICE) grades. Statistical differences were found between the ALBI (grade 1 vs. grade 2: $P < 0.001$) and ALICE (between each grade: $P < 0.001$) grades using the log–rank test. [Color figure can be viewed at wileyonlinelibrary.com]

differences in the prognosis among all grades were statistically significant ($P < 0.001$; Fig. 2b).

Independent prognostic factors

We investigated the factors related to the prognosis of patients with postoperative HCC. The following factors were extracted as prognostic factors on univariate analysis: albumin, ≤3.5 g/dL; cholinesterase, <150 IU/L; platelet count, $<100 \times 10^3/\mu L$; prothrombin time activation rate, <70%; ICG R15, ≥15%; alpha-fetoprotein, ≥400 ng/mL; C-P grade B; liver damage B or C; ALBI grade; ALICE grade; and TNM staging system (all $P < 0.05$). For multivariate analysis, variables that strongly correlated with the ALBI and ALICE grading systems, and confounding factors that were recognized by the stepwise method were excluded: total bilirubin, albumin, cholinesterase, prothrombin time activation rate, C-P grade, liver damage, and major hepatectomy in both models, and ICG R15 only in the ALICE model. Consequently, low platelet count, high alpha-fetoprotein level, ALBI grade and ALICE grades, and TNM staging system were independent factors for overall survival (Table 2).

Table 2 Cox proportional hazards regression analysis for overall survival

	Univariate analysis		Multivariate analysis			
			ALBI model		ALICE model	
Risk factors	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Male sex	1.02 (0.85–1.18)	0.836	1.16 (0.95–1.42)	0.138	1.19 (0.98–1.45)	0.086
Viral hepatitis	0.87 (0.72–1.06)	0.176	0.79 (0.65–0.97)	0.027	0.83 (0.68–1.01)	0.063
T-bil >1.2 (mg/dL)	1.29 (0.99–1.66)	0.058	—	—	—	—
Albumin ≤3.5 (g/dL)	1.71 (1.44–2.02)	<0.001				
ChE <150 (IU/L)	1.92 (1.56–2.35)	<0.001				
PLT <100 ($\times 10^3/\mu L$)	1.67 (1.41–1.97)	<0.001	1.46 (1.22–1.75)	<0.001	1.50 (1.26–1.79)	<0.001
PT <70 (%)	1.41 (1.14–1.72)	0.002	—	—	—	—
ICG R15 ≥15 (%)	1.56 (1.32–1.84)	<0.001	1.28 (1.06–1.54)	0.010		
AFP ≥400 (ng/mL)	1.38 (1.11–1.69)	0.004	1.27 (1.01–1.59)	0.043	1.26 (1.00–1.57)	0.048
Child–Pugh B	1.76 (1.40–2.19)	<0.001			—	—
Liver damage ≥B	1.78 (1.51–2.10)	<0.001	—	—		
ALBI grade						
1	Reference		Reference			
2	1.96 (1.65–2.33)	<0.001	1.74 (1.45–2.10)	<0.001		
3	3.98 (1.56–8.21)	0.006	3.29 (1.28–6.95)	0.017		
ALICE grade						
1	Reference				Reference	
2	1.98	<0.001			1.91 (1.55–2.37)	<0.001
3	3.22 (2.42–4.28)	<0.001			2.98 (2.20–4.02)	<0.001
Major hepatectomy	1.05 (0.80–1.36)	0.718	—	—	—	—
TNM stage						
I	Reference		Reference		Reference	
II	1.02 (0.81–1.29)	0.877	1.07 (0.85–1.36)	0.561	1.07 (0.85–1.35)	0.585
III	1.56 (1.24–1.98)	<0.001	1.59 (1.25–2.03)	<0.001	1.56 (1.22–1.99)	<0.001
IV-A	2.04 (1.50–2.76)	<0.001	1.92 (1.39–2.65)	<0.001	1.94 (1.40–2.68)	<0.001

AFP, alpha-fetoprotein; ALBI, Albumin-Bilirubin; ALICE, Albumin-Indocyanine Green Evaluation; ChE, cholinesterase; CI, confidence interval; HR, hazard ratio; PLT, platelet count; ICG R15, indocyanine green retention rate after 15 min; PT, prothrombin time activation rate; T-bil, total bilirubin.

To minimize the influence for prognosis being related to tumor factors, patients were divided according to their TNM stage classification: the number of patients in stages I, II, III, and IV-A was 265 (20.9%), 532 (41.9%), 363 (28.6%), and 110 (8.7%), respectively (Table 1). Up to the TNM stage III groups, both the ALBI and ALICE grades stratified the overall survival well; however, no statistical difference was found in the TNM stage IV-A group; the ability of both grading systems to stratify prognosis based on the estimated liver function became inconspicuous owing to the strong prognostic impact of the most advanced HCC (Fig. 3).

Comparison of the suitability of the models

The AUROC for the 5-year survival in the C-P, ALBI, and ALICE grades were 0.543, 0.602, and 0.614, respectively. The area under the curves of the ALBI and ALICE grades were similar ($P = 0.402$), whereas those of the two new grading systems were statistically higher than those of the C-P grade ($P < 0.001$; Fig. 4). The likelihood ratios χ^2 calculated using the Cox regression model, which indicates homogeneity, of the C-P, ALBI, and ALICE grades were 21.6, 65.7, and 73.8, respectively. The discriminatory ability of each system from the linear trend χ^2-test was 13.9, 34.9, and 43.4, respectively. The AIC of each grading system was 7254.3, 7212.3, and 7204.1, respectively. These results suggested that the prognostic power of the ALICE grade was superior to that of the ALBI and C-P grades for patients with resectable HCC (Table 3).

Relationship between the scoring systems and postoperative complications

Severe complications after hepatectomy, classified as Clavien–Dindo grade ≥III, occurred in 8.4% of all patients,

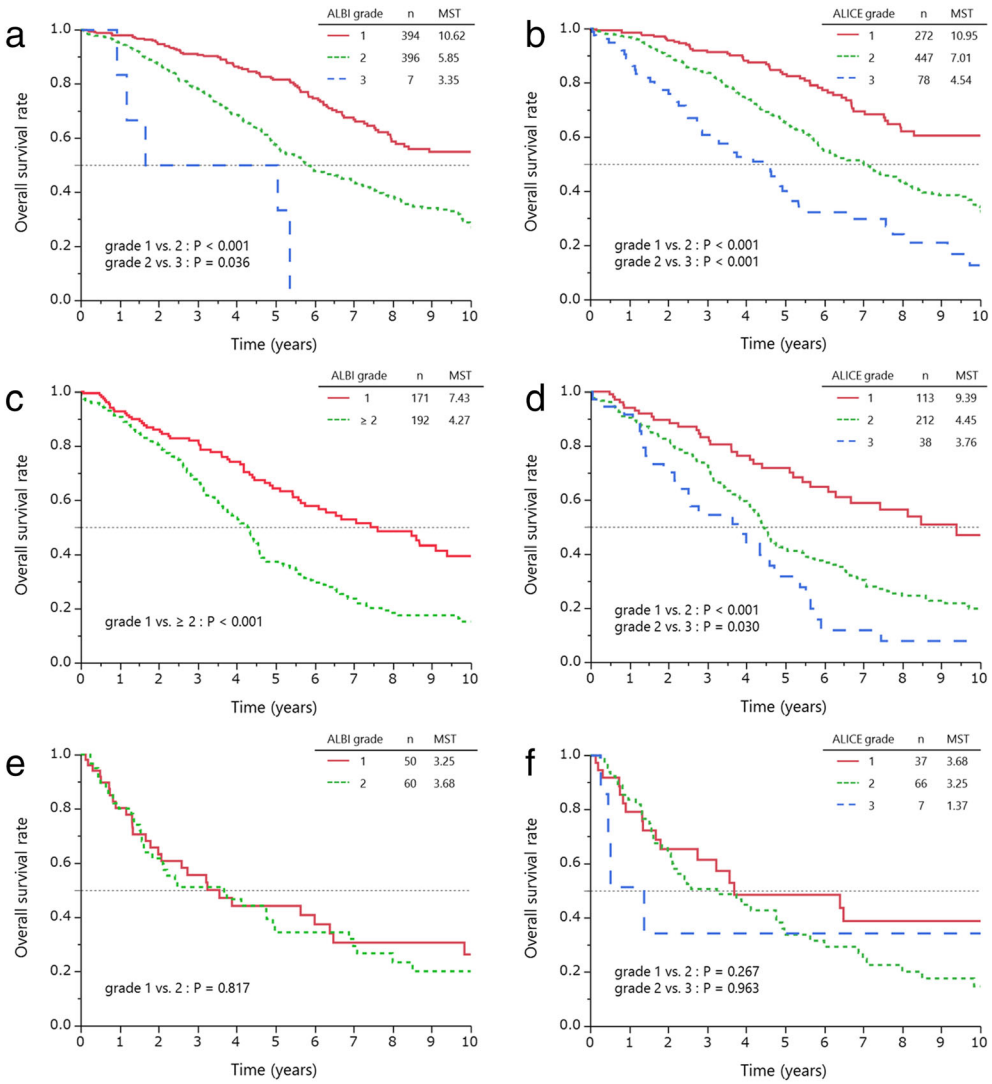
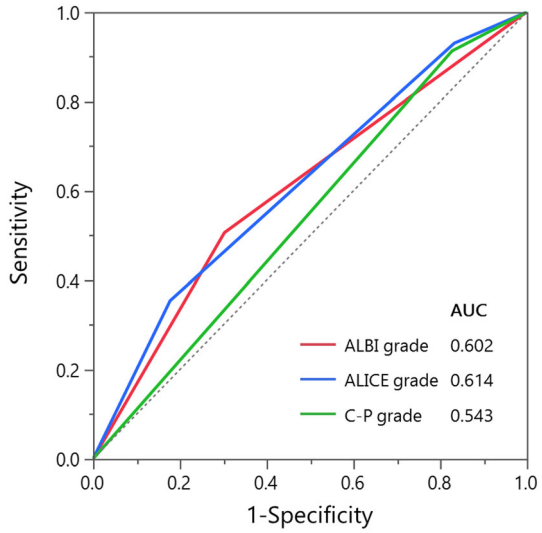


Figure 3 Survival curves of the subgroups divided according to the TNM stage. Kaplan–Meier curves were depicted according to the (a,c,e) Albumin-Bilirubin (ALBI) and (b,d,f) Albumin-Indocyanine Green Evaluation (ALICE) grades in (a,b) TNM stage I or II, (c,d) stage III, and (e,f) stage IV-A. [Color figure can be viewed at wileyonlinelibrary.com]

and the 90-day mortality rate was 1.6% (Table 1). Age, albumin and cholinesterase levels, prothrombin time activation rate, ICG R15, C-P grade, liver damage, ALBI and ALICE scores, operation time, blood loss, major hepatecomy, multiple tumors, and the existence of vascular invasion were associated with the development of severe complications on univariate analysis. Multivariate analysis including the removal of correlated variables and confounding factors showed that both the ALBI and ALICE scores, as well as prothrombin time activation rate and operation time, were independent risk factors for severe complications in the ALBI model and in the ALICE model, respectively (Table 4).

DISCUSSION

THE PROGNOSIS AND selected treatments of most malignancies are mainly predicted using the tumor stages; however, the assessment for patients with HCC is more complex, because chronic hepatitis and cirrhosis underlie HCC, and the liver function of patients strongly affects prognosis and treatment selection.[17] There are



	ΔAUC	P value
ALBI vs. C-P	0.059	< 0.001
ALICE vs. C-P	0.071	< 0.001
ALICE vs. ALBI	0.012	0.402

Figure 4 Receiver operating characteristic curve for 5-year survival of patients who underwent hepatectomy for hepatocellular carcinoma. ALBI, Albumin-Bilirubin; ALICE, Albumin-Indocyanine Green Evaluation; AUC, area under the curve; C-P, Child–Pugh. [Color figure can be viewed at wileyonlinelibrary.com]

several prognostic classification systems for patients with HCC: Okuda,[18] Cancer of the Liver Italian Program,[14] Barcelona Clinic Liver Cancer,[19] Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire,[20] Chinese University Prognostic Index,[21] and Japan Integrated Staging score.[22] All these systems combine tumor factors and liver function. Their utility has been investigated worldwide; however, no model is perfect.[17] The method used in evaluating liver function varies among these systems. Okuda includes ascites, albumin, and bilirubin;[18] Groupe d'Etude et de Traitement du Carcinome Hepatocellulaire[20] and Chinese University Prognostic Index[21] estimate bilirubin and alkaline phosphatase; and Cancer of the Liver Italian Program,[14] Barcelona Clinic Liver Cancer,[19] and Japan Integrated Staging score[22] use the C-P grade. A non-unified evaluation method for liver function might complicate the prediction of the prognosis of patients with HCC. The ALBI grade and/or ALICE grade, which are constructed by objective factors and through an evidence-based approach, would likely be a standard method in evaluating liver function.

The first published report that compared the ability of the ALBI and ALICE grading systems for predicting morbidity after hepatectomy showed that the ALICE grading system can assess liver function and predict postoperative outcomes comparable to the ALBI grading system.[10] Most recently, Shirata *et al.* suggested in their study that the ALICE score was the strongest predictor for large-volume ascites and liver failure after hepatectomy.[12] In the present study, we evaluated these new systems in terms of their homogeneity, discriminatory ability, AIC, and AUROC regarding overall survival. This method is similar to that used in previous studies comparing the staging of digestive cancer.[23–25] According to the present results, the ALICE grade was slightly superior to the ALBI grade in terms of homogeneity, discriminatory ability, and AIC. As described in Figure 1, the ALBI and ALICE scores have a strong correlation, because the linear predictors of both scoring systems are strongly related to the albumin level. Therefore, the difference in grade evaluation might be considered to be simply due to the difference in the cut-off value. It is common in either grading system that the linear predictors were conducted from independent prognostic factors in training sets, and cut-off values were determined at the 25th and 90th percentiles. However, the ALBI grade was based on a study targeting patients with HCC,

Table 3 Performance evaluation of Albumin-Bilirubin and Albumin-Indocyanine Green Evaluation grades

Grading system	Homogeneity (likelihood ratio χ^2)	Discriminatory ability (linear trend χ^2)	AIC
C-P grade	21.6	13.9	7254.3
ALBI grade	65.7	34.9	7212.2
ALICE grade	73.8	43.4	7204.1

Higher discriminatory ability and homogeneity, and lower Akaike information criterion (AIC) statistics were associated with better performance of the grading system. AIC, Akaike information criterion; ALBI, Albumin-Bilirubin; ALICE, Albumin-Indocyanine Green Evaluation; C-P, Child–Pugh.

Table 4 Risk factors for postoperative complications classified as Clavien–Dindo grade ≥III

	Univariate analysis		Multivariate analysis			
			ALBI model		ALICE model	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (years)	1.02 (0.999–1.04)	0.064	1.02 (1.00–1.05)	0.043	1.02 (0.999–1.05)	0.057
Male sex	0.79 (0.51–1.23)	0.290	-	-	-	-
Viral hepatitis	0.79 (0.51–1.22)	0.295	-	-	-	-
T-bil (mg/dL)	1.31 (0.77–2.22)	0.322	-	-	-	-
Albumin (g/dL)	0.48 (0.32–0.71)	<0.001				
ChE (IU/L)	0.996 (0.99–0.998)	0.001				
PT (%)	0.97 (0.96–0.98)	<0.001	0.98 (0.96–0.99)	0.002	0.98 (0.96–0.99)	0.002
PLT ($\times 10^3/\mu L$)	0.99 (0.96–1.02)	0.401	-	-	-	-
ICG R15 (%)	1.02 (1.00–1.04)	0.017	-	-		
Child–Pugh B	1.86 (1.09–3.16)	0.022			-	-
Liver damage ≥B	1.91 (1.28–2.84)	0.002	-	-		
ALBI score	2.30 (1.46–3.60)	<0.001	1.87 (1.10–3.20)	0.021		
ALICE score	2.26 (1.46–3.51)	<0.001			1.74 (1.02–2.95)	0.040
Operation time (min)	1.01 (1.00–1.01)	<0.001	1.004 (1.00–1.01)	<0.001	1.004 (1.00–1.01)	<0.001
Blood loss (ml)	1.00 (1.000–1.001)	<0.001	1.00 (0.9999–1.001)	0.160	1.00 (0.9999–1.001)	0.147
Major hepatectomy	1.64 (0.95–2.80)	0.074	–	–	–	–
Tumor size (mm)	1.002 (0.99–1.01)	0.684	–	–	–	–
Multiple tumors	1.77 (1.18–2.66)	0.006	1.51 (0.98–2.35)	0.064	1.51 (0.97–2.33)	0.067
Vascular invasion	1.42 (0.94–2.16)	0.099	–	–	–	–

AFP, alpha-fetoprotein; ALBI, Albumin-Bilirubin; ALICE, Albumin-Indocyanine Green Evaluation; ChE, cholinesterase; CI, confidence interval; ICG R15, indocyanine green retention rate after 15 min; OR, odds ratio; PLT, platelet count; PT, prothrombin time activation rate; T-bil, total bilirubin.

including those who underwent treatments apart from hepatectomy, whereas the ALICE grade included patients who only underwent treatment with liver resection.[1,2] Therefore, the above-mentioned results are natural, because the targets in the present study are patients with post-hepatectomy HCC. An advantage of both systems is that the ALBI and ALICE scores are continuous variables. In future cohorts, the usefulness of indicators using these scores is expected, because the cut-off value can be decided arbitrarily.

The present results suggested that both the ALBI and ALICE grades are independent prognostic factors, and the prognostic power was significantly superior in these systems than in the C-P grade. In patients with the most advanced HCC, TNM stage IV-A, neither the ALBI grade nor the ALICE grade could predict the overall survival, which might be because the prognostic influence of tumor factors is more powerful than that of the liver function. Conversely, it seems that both systems well reflected their influence on the prognosis of liver function.

There are several inherent limitations to our study. First, the patient data were retrospectively collected from the shared multi-institutional database; hence, some information might have been lost. Second, this study included a number of patients in a 30-year period, which could include historical bias due to the improvement of surgical techniques, perioperative management, therapy for recurrence, anti-virus treatment, and imaging technology.

In conclusion, both the ALBI and ALICE grades have a prognostic ability and are available to evaluate the liver function of patients with all, but the most advanced, stages of HCC. Regarding patients who underwent hepatectomy, the ALICE grade is likely to be a more suitable model than the ALBI grade.

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