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Original Paper

Validation of Modified ALBI Grade for More Detailed Assessment of Hepatic Function in Hepatocellular Carcinoma Patients: A Multicenter Analysis

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Keywords
Hepatocellular carcinoma · Albumin-bilirubin grade · Modified ALBI · Japan Integrated Staging score · ALBI-T score · mALBI-T score · Prognosis

Abstract
Background/Aim: The frequency of hepatocellular carcinoma (HCC) in patients with good hepatic reserve function has been increasing in Japan along with the progression of antiviral therapies and aging of the society. We evaluated the usefulness of modified albumin-bilirubin (ALBI) grade as a tool for assessment of hepatic reserve function. ***Materials/Methods:*** We enrolled 6,649 naïve HCC patients treated from 2000 to 2017 and divided them into training

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(Ehime Prefecture group: E group, *n* = 2,357) and validation (validation group: V group, *n* = 4,292) cohorts. Child-Pugh classification and ALBI and modified ALBI (mALBI) grading were compared using with Japan Integrated Staging (JIS), ALBI-TNM (ALBI-T), and mALBI-T scores, which were calculated based on TNM stage and each assessment tool, retrospectively. ***Results:*** In the E group, Akaike's Information Criterion (AIC) and c-index values for mALBI-T (13,725.2/0.744) were better as compared to those of ALBI-T (13,772.6/0.733) and JIS score (13,874.7/0.720), with similar results observed in the V group (mALBI-T: 27,727.4/0.760; ALBI-T: 27,817.8/0.750; JIS: 27,807.5/0.748). Although there were some significant differences between the groups with regard to clinical background factors (age, etiology, tumor size, tumor number, treatment modalities), for all patients the AIC and c-index values of mALBI-T (45,327.1/0.755) were also better than those of ALBI-T (45,467.7/0.744) and JIS scores (45,555.8/0.739), indicating its superior stratification ability and prognostic predictive value in patients with HCC. ***Conclusion:*** The detailed stratification ability of mALBI grade for hepatic reserve function is suitable for the recent trend of HCC patients, while mALBI-T may provide a more accurate predictive value than existing total staging scoring systems.

Introduction

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related death worldwide [1]. Recently, eradication of hepatitis C virus (HCV) and control of hepatitis B virus (HBV) with use of direct acting antivirals [2, 3] and nucleotide analogues [4, 5], along with progression in the development of low invasive therapeutic modalities such as ablative therapy (e.g., percutaneous ethanol injection therapy, radiofrequency ablation [RFA] [6–8]) have contributed to the improvement of hepatic reserve function and prognosis in HCC patients. However, an important remaining issue is lack of development of a suitable evaluation tool for hepatic reserve function in this era of hepatitis control. Although Child-Pugh classification [9] has traditionally been used for assessment of hepatic function, its effectiveness has not been established based on a statistical method, as classification is determined using both objective (ascites, hepatic coma) and semiquantitative factors. Previously, the albumin-bilirubin (ALBI) grade obtained with a statistical method was proposed as a new assessment tool [10], and some studies of its usefulness have reported its ability to predict prognosis and assist in decision making regarding treatment choices for HCC patients [11–14]. However, ALBI grade 2 includes patients with a wide range of hepatic function as well as those rated as Child-Pugh class B. In a recent report, a modification of ALBI grade (mALBI grade) into 4 subgrades (1, 2a, 2b, and 3) was proposed [15, 16]. The present validation study aimed to evaluate the usefulness of mALBI grade for predicting the prognosis of HCC patients.

Materials and Methods

We enrolled 7,898 patients with naïve HCC who were diagnosed and treated from 2000 to 2017 at 12 institutions in Japan (Ehime Prefectural Central Hospital [*n* = 1,627], Ogaki Municipal Hospital [*n* = 1,373], Teine Keijinkai Hospital [*n* = 943], Kagawa Prefectural Central Hospital [*n* = 894], Asahi General Hospital [*n* = 811], Okayama City Hospital [*n* = 400], Matsuyama Red Cross Hospital [*n* = 376], Toyama University Hospital [*n* = 368], Ehime University Hospital [*n* = 365], Otakanomori Hospital [*n* = 313], Saiseikai Niigata Daini Hospital [*n* = 284], Komaki City Hospital [*n* = 144]). After exclusion of those with no information regarding tumor node metastasis (TNM) stage, assessed according to the Liver Cancer Study Group of Japan (LCSGJ) criteria 6th edition (Table 1), or Child-Pugh classification, as well as 1 case treated with liver transplantation, we analyzed the clinical characteristics and prognosis of 6,649 patients. Of those, 2,357 were

Table 1. Tumor node metastasis stage of the Liver Cancer Study Group of Japan

T factor[a] for TNM stage of LCSGJ 6th edition	
T1	Fulfilling 3 factors
T2	Fulfilling 2 factors
T3	Fulfilling 1 factor
T4	Fulfilling 0 factors
TNM stages in LCSGJ 6th edition	
Stage I	T1N0M0
Stage II	T2N0M0
Stage III	T3N0M0
Stage IVa	T4N0M0, or any TN1M0
Stage IVb	Any TN0-N1M1

LCSGJ, Liver Cancer Study Group of Japan; TNM stage, tumor node metastasis stage. [a] The 3 factors are a single lesion, a lesion measuring <2 cm, and no vascular involvement.

Table 2. JIS, ALBI-T, and mALBI-T scoring systems

	Score 0	Score 1	Score 2	Score 3
JIS				
Child-Pugh class	A	B	C	
TNM stage	I	II	III	IV
ALBI-T				
ALBI grade	1	2	3	
TNM stage	I	II	III	IV
mALBI-T				
mALBI grade	1	2a	2b	3
TNM stage	I	II	III	IV

JIS, Japan Integrated Staging; TNM stage, tumor node metastasis according to the criteria of Liver Cancer Study Group of Japan, 6th edition; ALBI-T, albumin-bilirubin grade-TNM; mALBI-T, modified ALBI-TNM.

treated at 3 institutions in the Ehime Prefecture area (Ehime Prefectural Central Hospital, Ehime University Hospital, Matsuyama Red Cross Hospital) and analyzed as the training cohort (Ehime Prefecture group: E group), while the other 4,292 treated at 9 institutions in another area served as the validation cohort (validation group: V group).

Basal Hepatic Disease

Patients positive for anti-HCV were judged to have HCC due to HCV, and those positive for HBV surface antigen (HBsAg) were judged to have HCC due to HBV. Cases without anti-HCV or HBsAg were defined as negative for both HBV and HCV.

Methods for Assessment of Hepatic Reserve Function and Prognosis

Child-Pugh classification, and ALBI and mALBI grades were used as assessment tools for hepatic reserve function. ALBI grade was calculated based on serum albumin and total-bilirubin values using the following formula: ALBI-score: ($\log_{10}$ bilirubin (μmol/L) × 0.66) + (albumin (g/L) × –0.085); and ALBI grade was defined by the score of the following: ≤–2.60 = Grade 1, >–2.60 to ≤–1.39 = Grade 2, >–1.39 = Grade 3 [10]. ALBI grade 2 was further divided into 2 subgrades (2a and 2b) using a previously reported cut-off value (ALBI score –2.270) and the 4 ALBI grades were named as mALBI grade [15, 16].

Japan Integrated Staging (JIS), ALBI-TNM (ALBI-T), and mALBI-TNM (mALBI-T) scores were used for evaluation of prognosis, and their predictive ability in regard to prognosis was compared. JIS score was calcu-

Table 3. Characteristics of all patients

	Total (*n* = 6,649)	E group (*n* = 2,357)	V group (*n* = 4,292)	*p* value
Age, years	69.4 (9.9)	69.0 (10.2)	69.6 (9.8)	0.028
Gender, M/F	4,648/2,001	1,675/682	2,973/1,319	0.116
HCV/HBV/HBV & HCV/Alc/nonBnonC/UK	4,162/818/45/387/1,235/2	1,542/260/22/205/327/1	2,620/558/23/182/908/1	<0.001
Child-Pugh class, A/B/C	4,812/1,546/291	1,713/567/77	3,099/979/214	0.422
ALBI grade, 1/2/3	2,531/3,630/488	917/1,256/184	1,614/2,374/304	0.563
mALBI grade, 1/2a/2b/3	4,162/818/45/387/1,235/2	917/518/738/184	1,614/934/1,440/304	0.348
Tumor size, cm	3.6 (3.1)	3.5 (2.9)	3.7 (3.2)	0.012
Tumor number, single/multiple	3,934/2,715	1,438/919	2,496/1,796	0.024
TNM stage, I/II/III/IV	1,690/2,687/1416/856	601/995/479/282	1,089/1,692/937/574	0.093
JIS score, 0/1/2/3/4/5	1,337/2,364/1,581/886/374/107	469/873/570/302/114/29	868/1491/1011/584/260/78	0.101
ALBI-T score, 0/1/2/3/4/5	721/2,064/1,897/1,188/624/155	260/762/665/400/219/51	461/1,302/1232/788/405/104	0.087
mALBI-T score, 0/1/2/3/4/5/6	721/1,584/1,522/1,361/812/494/155	260/591/537/464/288/166/51	461/993/985/897/524/328/104	0.084
Treatment, SR/RFA/PEI/TACE/others/BSC	1,734/2,243/79/1,587/423/583	563/1,075/46/372/73/228	1,171/1,168/33/1,215/350/355	<0.001
Observation period, years	3.31 (3.11)	3.2 (3.01)	3.36 (3.17)	0.038

Values for age, tumor size, and observation period are expressed as mean (SD). HCV, hepatitis C virus; HBV, hepatitis B virus; Alc, alcohol; nonBnonC, both negative for HBV and HCV; UK, unknown; ALBI grade, albumin-bilirubin grade; mALBI grade, modified ALBI grade; JIS, Japan Integrated Staging; TNM stage, tumor node metastasis according to the criteria of the Liver Cancer Study Group of Japan, 6th edition; ALBI-T, ALBI-TNM; mALBI-T, mALBI-TNM; SR, surgical resection; RFA, radiofrequency ablation; PEI, percutaneous ethanol injection therapy; TACE, transcatheter arterial chemoembolization; BSC, best supportive care.

lated by summing up scores for Child-Pugh class and TNM stage. ALBI-T and mALBI-T were calculated using either ALBI or mALBI grade and TNM stage, and then calculated in the same manner as JIS (Table 2).

Diagnosis and Treatment of HCC

HCC was diagnosed based on an increasing course of alpha-fetoprotein (AFP), as well as dynamic CT [17], magnetic resonance imaging (MRI) [18, 19], contrast-enhanced US (CEUS) with perflubutane (Sonazoid®, Daiichi Sankyo Co., Ltd. Tokyo, Japan) [20, 21], and/or pathological findings. TNM stage was determined as previously reported in studies for staging of HCC conducted by the LCSGJ [22] (Table 1). From 2006, all treatments were performed following the Japanese practical guidelines for HCC [23, 24], whenever possible, after obtaining written informed consent from the patient. The present study protocol was approved by the Institutional Ethics Committee of Ehime Prefectural Central Hospital (No. 28–30).

Statistical Analysis

Data are expressed as the mean and standard deviation (SD). Statistical analyses were performed using Student's *t* test, a Mann-Whitney U test, a χ^2 test, and Kaplan-Meyer methods with a log-rank test. A *p* value <0.05 was considered to indicate statistical significance. For multiple comparisons, Holm's method was used. Akaike's Information Criterion (AIC) and c-index were used for evaluation of ability for stratification and prediction of prognosis by each method. All statistical analyses were performed using Easy R (EZR) (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [25], a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

The characteristics of the present cohort are shown in Table 3. Average age was 69.4 ± 9.9 years, males comprised 69.9% (*n* = 4,648), and the average observation period was 3.31 ± 3.11 years (TNM stage I, II, III, IV = 1,690, 2,687, 1,416, 856 cases, respectively; surgical resection, RFA, percutaneous ethanol injection, transcatheter arterial chemoembolization, other, best supportive care = 1,734, 2,243, 79, 1,587, 423, 583 cases, respectively).

In the E group, used as the training cohort (*n* = 2,357), the stratification ability regarding prognosis by each system was good (Fig. 1a), though the AIC and c-index values for mALBI-T

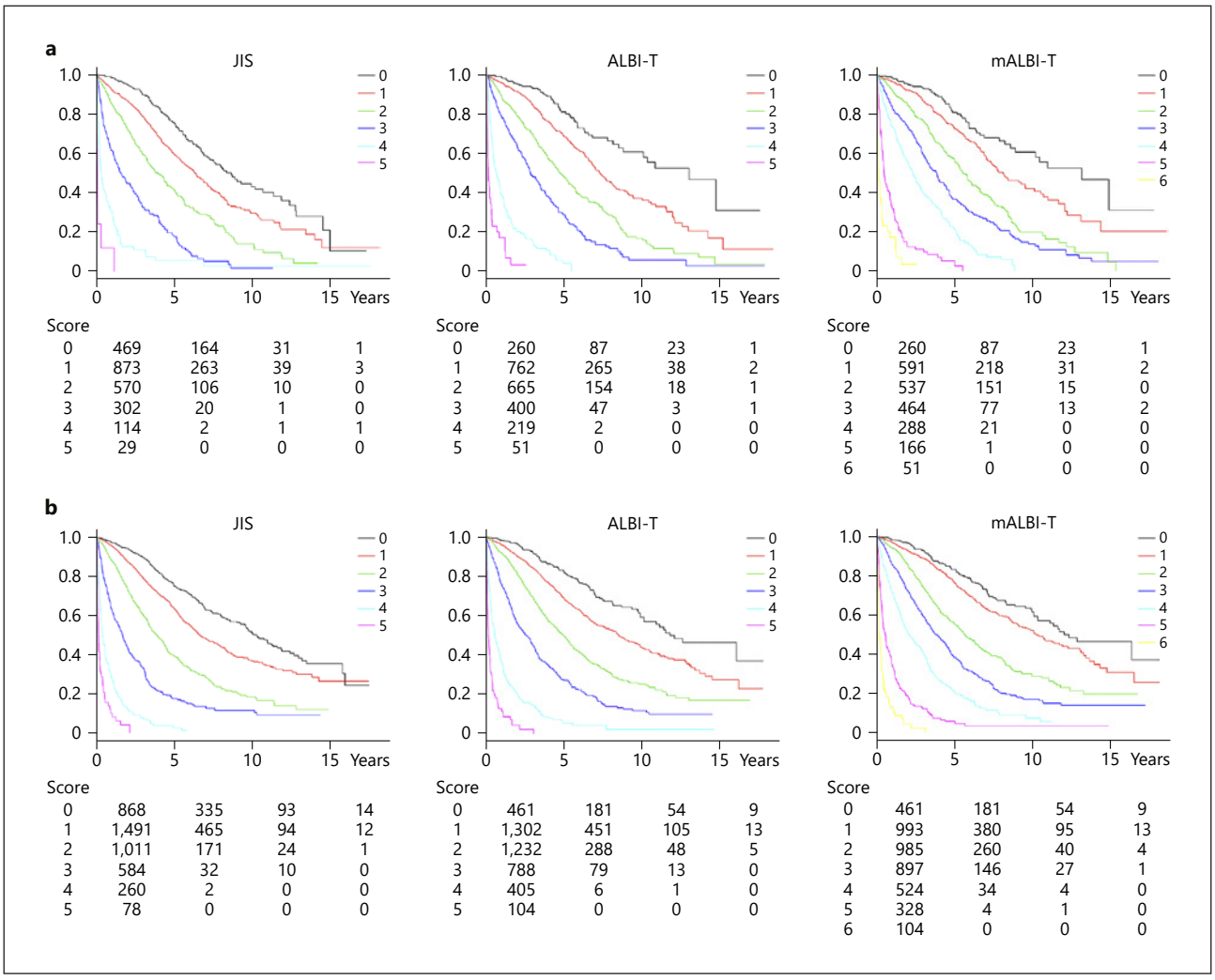

Fig. 1. JIS, ALBI-T, and mALBI-T scores for E and V groups. **a** The E group was used as a training cohort (n = 2,357). The AIC and c-index values for JIS were 13,874.7 and 0.720, respectively, for ALBI-T were 13,772.6 and 0.733, respectively, and for mALBI-T were 13,725.2 and 0.744, respectively. **b** The V group was used as a validation cohort (n = 4,292). The AIC and c-index values for JIS were 27,807.5 and 0.748, respectively, for ALBI-T were 27,817.8 and 0.750, respectively, and for mALBI-T were 27,727.4 and 0.760, respectively. **a**, **b** Values on the y axes represent estimation of cumulative survival probability.

(13,725.2 and 0.744, respectively) were superior to those of ALBI-T (13,772.6 and 0.733, respectively) and JIS (13,874.7 and 0.720, respectively). In the V group, used as the validation cohort (n = 4,292), similar results were observed (Fig. 1b), as the AIC values for JIS, ALBI-T, and mALBI-T were 27,807.5, 27,817.8, and 27,727.4, respectively, and their c-index values were 0.748, 0.750, and 0.760, respectively.

Although there were some significant differences observed regarding some of the clinical background factors between the E and V groups (age, etiology, tumor size, tumor number, treatment modalities) (Table 3), mALBI-T showed a better stratification ability and prognostic predictive value with both cohorts, as the AIC and c-index values for mALBI-T were also better than those of the others for all patients (Table 4). The prognosis of patients after dividing by TNM stage could be separated according to the order of mALBI grade (p < 0.001,

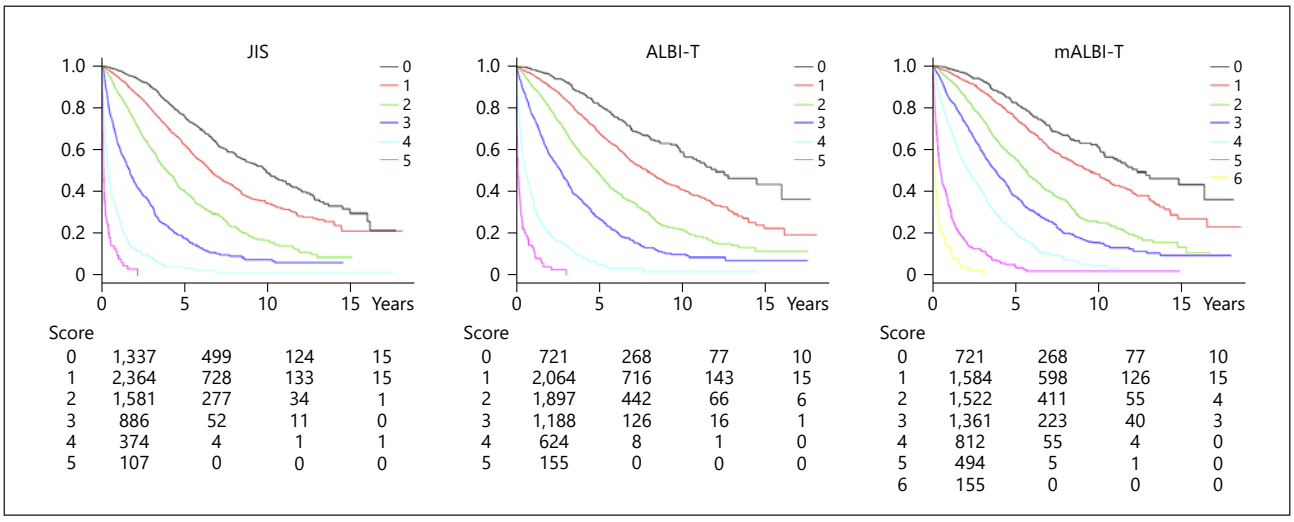

Fig. 2. JIS, ALBI-T, and mALBI-T scores in all patients. For all patients (n = 6,649), the AIC and c-index values for JIS were 45,555.8 and 0.739, respectively, for ALBI-T were 45,467.7 and 0.744, respectively, and for mALBI-T were 45,327.1 and 0.755, respectively. mALBI-T was superior in both stratification and prognostic predictive ability, followed in order by ALBI-T and JIS for both. Values on the y axes represent estimation of cumulative survival probability.

Table 4. Median survival time, AIC, and c-index for each scoring system

	Median survival time, years (95% CI)		
	JIS	ALBI-T	mALBI-T
Score 0	9.85 (8.70–10.88)	12.05 (10.16–NA)	12.05 (10.16–NA)
Score 1	6.53 (6.21–6.96)	7.89 (7.21–8.51)	9.26 (8.33–10.24)
Score 2	3.94 (3.56–4.32)	4.85 (4.53–5.18)	5.50 (5.16–5.89)
Score 3	1.66 (1.46–1.88)	2.72 (2.43–2.93)	3.70 (3.39–4.01)
Score 4	0.37 (0.31–0.46)	0.58 (0.49–0.71)	2.11 (1.86–2.43)
Score 5	0.09 (0.08–0.13)	0.14 (0.10–0.21)	0.48 (0.40–0.58)
Score 6	none	none	0.14 (0.10–0.21)
AIC	45,555.8	45,467.7	45,327.1
c-index	0.739	0.744	0.755

JIS, Japan Integrated Staging; ALBI-T, albumin-bilirubin grade-TNM; mALBI-T, modified ALBI-T; AIC, Akaike's information criterion.

Holm's method) (data not shown). As a result, ALBI-T scoring (grade 1–4) could be separated in a more detailed manner (mALBI-T grade 1–5) by division of ALBI grade 2 into 2 subgrades. The AIC and c-index values for JIS were 45,555.8 and 0.739, respectively, while those for ALBI-T were 45,467.7 and 0.744, respectively, and for mALBI-T were 45,327.1 and 0.755, respectively. The correlation of median survival time with mALBI-T score was good as compared to each corresponding JIS score (Fig. 2) (Table 4). The result of reevaluation of hepatic function using mALBI grade was shown in Figure 3. Thus, mALBI grade has a better assessment ability than ALBI grade and Child-Pugh classification, and mALBI-T showed the best stratification ability and prognostic predictive value, followed in order by ALBI-T and JIS for both values, as a result (Table 4).

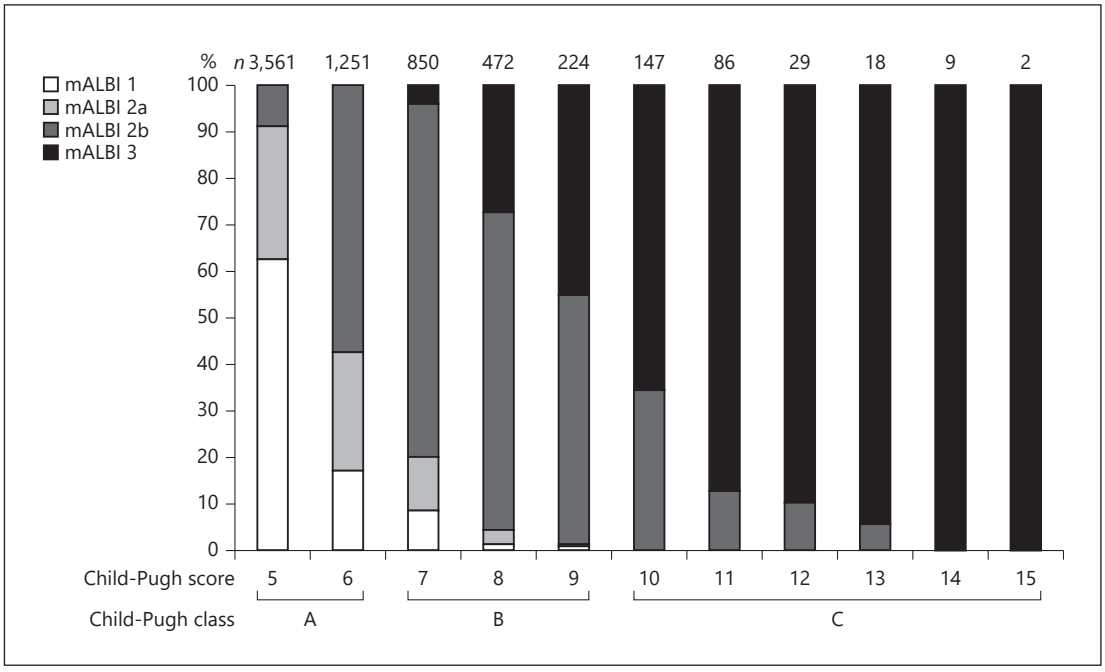

Fig. 3. Reevaluation of reserve function using modified albumin-bilirubin (mALBI) grade.

Discussion

It is well known that the prognosis of HCC patients is dependent on hepatic reserve function and tumor burden [26, 27]. Recently established treatment strategies for HCC [23, 24, 28], as well as progression of therapeutic and diagnostic modalities (e.g., resection, low invasive RFA [6–8], CEUS [20, 21], EOB-MRI [18, 19]) have contributed to improve the prognosis of affected patients. Moreover, improved antiviral therapies (interferon [29], direct acting antivirals [2, 3], nucleotide analogues [4, 5]) have been shown to be helpful for increasing hepatic reserve function in cases of viral-related HCC. In addition, there has been a rapid increase in the proportion of cases negative for HBV and HCV, so-called NBNC-HCC, with the rate of incidence increasing steadily from 8.7% in 2000 to 14.9% in 2007 in Japan [30], with a more recent report noting that the rate is now greater than 20% [31]. As a result, the frequency of patients with better Child-Pugh class has increased, which is considered to be a recent trend in HCC cases treated in Japan [32]. Thus, in this era, the necessity of a suitable assessment tool for hepatic function has been increasing, with ALBI grade based on a statistical method proposed for helping to meet the present clinical need [10]. In a recent study, the predictive ability of ALBI-T, determined using ALBI grade and TNM stage, for the prognosis of HCC patients was shown to be better than that of JIS, which is determined based on Child-Pugh class and TNM stage [11, 33]. ALBI grade is thought to be a suitable assessment tool for hepatic function.

On the other hand, ALBI grade has also a weak point as well as Child-Pugh classification. An issue with Child-Pugh classification is that hepatic function of the middle group (Child-Pugh B) has a wide range of scores [7–9]. However, division of class B is difficult because the factors used for this classification are not defined statistically and have variability. Although ALBI grade 2 also features a wide range similar to Child-Pugh class B, an advantage is that ALBI grade is defined by serial ALBI scores, which are calculated statistically using only serum

albumin and bilirubin levels. In previous reports, a cut-off value for ALBI score (–2.270) for dividing into subgrades 2a and 2b [15] was proposed based on indocyanine green retention rate after 15 min (ICG-R15) (cut-off value 30% or less), which is an indicator for use of a subsegmentectomy as a minimum anatomical resection in the Makuuchi criteria [34, 35]. In the present validation study, mALBI-T showed both a more detailed stratification ability and better predictive value for prognosis of HCC patients as compared to those shown by ALBI-T and JIS.

The present study has some limitations, including its retrospective nature. Furthermore, the participating institutions are high-volume treatment centers; thus, the number of patients not indicated for treatment for HCC was small at each. Findings from a prospective study are needed before definite conclusions can be made.

In summary, although mALBI grade is made of only 2 factors (albumin and total bilirubin), it showed an ability for more detailed stratification of hepatic reserve function, which is valuable for the recent trend seen in HCC patients. We consider that mALBI-T may provide more accurate prediction of prognosis of affected patients as compared to existing total staging scoring systems.

Disclosure Statement

The authors declare no conflicts of interest.

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