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Original Article

A detailed assessment of liver function in patients with hepatocellular carcinoma via the modified albumin-bilirubin (mALBI) grade

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Abstract: Recently, the albumin-bilirubin (ALBI) score, a continuous index consisting of only albumin and bilirubin, has been developed for objectively assessing liver function in patients with hepatocellular carcinoma (HCC). However, the ALBI score was arbitrarily categorized into three ALBI grades based on two artificially predetermined cutoff points with no explanation and statistical grounds, causing a considerable loss of discriminatory ability. This study aims to propose a modified ALBI (mALBI) grade for offering a detailed evaluation of hepatic reserve and specify its role during clinical practice in the HCC setting. The study population comprised 3540 HCC patients treated with mainstream therapies including hepatectomy (n=2056), thermal ablation (n=550), and transcatheter arterial chemoembolization (n=934) from 2002 to 2017. The ALBI score was stratified into four mALBI grades through a recently proposed statistical method aiming to select the optimal cutoff points of a continuous predictive variable by maximizing the discriminative ability in a multivariable Cox regression model. The mALBI grade had an overall better discriminatory ability than the ALBI grade in predicting overall survival through Harrell's C-index (0.614 vs. 0.598, P<0.001). Both visual inspections of Kaplan-Meier curves and calculation of hazard ratios displayed a more subtle evaluation of liver function using the mALBI grade. Moreover, the newly identified cut-point (ALBI score = -2.29) between the mALBI grade 2a and 2b was much closer to a 30% retention rate of indocyanine green at 15 minutes, an indicator for the performance of a subsegmentectomy. The newly proposed mALBI grade provides a more subtle assessment of liver function to guide clinical decision-making and predicts the prognosis of HCC patients more accurately than the original ALBI grade.

Keywords: Liver function, hepatocellular carcinoma, ALBI grade, mALBI grade, prognosis

Introduction

Hepatocellular carcinoma (HCC) was reported to be the fourth leading cause of cancer deaths worldwide in 2018, especially in less developed countries [1]. It is widely acknowledged that, unlike other cancer types, the survival of HCC patients mainly depends on underlying liver function in addition to tumor stage. In recent years, with emerging effective therapies against viral hepatitis and wider implementation of HCC screening, an increasing proportion of patients are diagnosed with adequate liver function and can undergo more effective HCC therapies. For better decision-making on treatment strategies for these patients, an objective, accurate, inexpensive, and readily available assessment of hepatic reserve function is urgently needed. In 2015, an international collaboration team developed an objective measure of liver function, the ALBI score, based on a simple model including only serum bilirubin and albumin levels [2]. For the convenience of clinical exposition, Johnson et al. split the continuous ALBI score into three categories of ALBI grade 1, 2, and 3, representing good, moderate, and poor liver function, respectively, using the 25th and 90th percentiles as cut-offs [2]. However, this stratification of ALBI score has the following drawbacks: (a) Failure to follow the

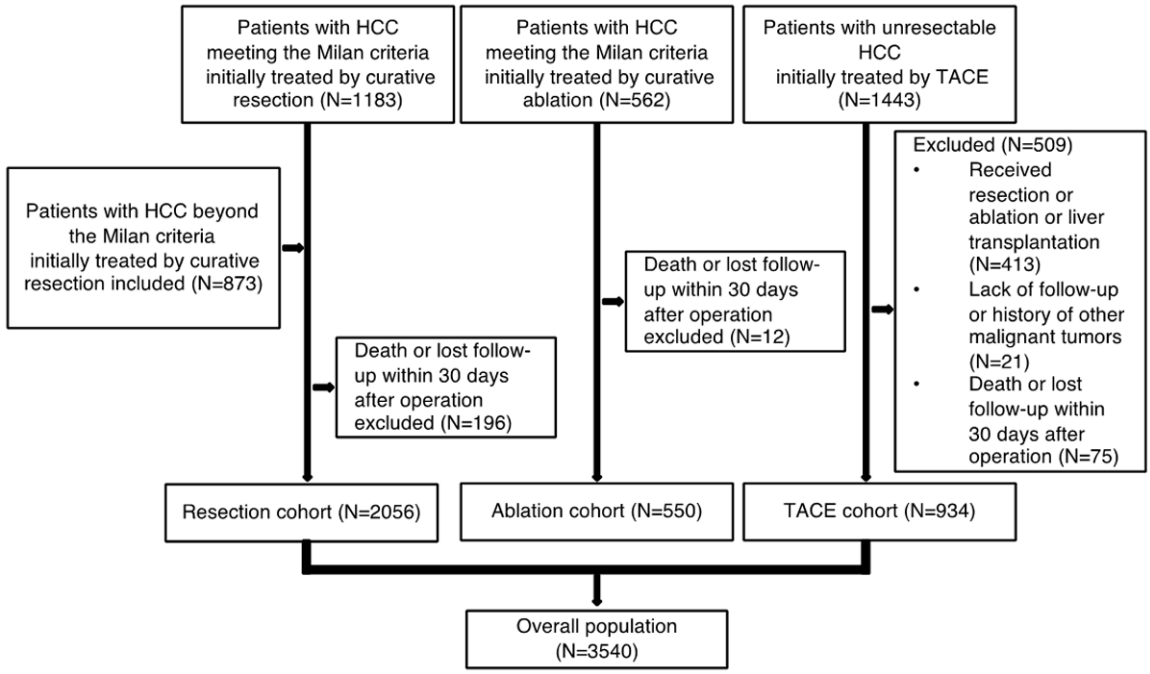

Figure 1. Flow chart illustrating the patient cohorts included in the study.

STROBE guidelines which suggest that authors should "Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why [3]. (b) ALBI grade 2 has a very wide range of risk scores (65 percentiles) which should be divided into subgrades for a more precise assessment of liver function [4, 5]. (c) Finally, the cutoff points for generating ALBI grade were arbitrarily selected with no statistical ground. Hence, to maximize the discriminatory ability of the ALBI score and for easy clinical exposition and practice, we attempt to find the optimal cutoff points to categorize the ALBI score using the concordance probability, based on the Cox proportional hazards regression model [6, 7].

Materials and methods

Patients

The study population was a combination of three cohorts of HCC patients, consecutively recruited and treated with three mainstream therapies including surgical resection [8], thermal ablation [9] and transcatheter arterial chemoembolization (TACE) [10] (shown in **Figure 1**). Patients were recruited from the Sun Yat-sen University Cancer Center with a multidisciplinary team of surgeons, physicians, and radiologists specializing in the diagnosis and management of hepato-pancreato-biliary diseases according to international guidelines [11, 12]. Sex, age, macroscopic vascular invasion, albumin, bilirubin, tumor size, and tumor number were identified as statistically significant prognostic variables of overall survival (OS) in the study that initially developed the ALBI score model [2]. Hence, these variables were extracted from our datasets [8-10] (shown in **Table 1**). Demographic data and biochemical tests were mainly measured within the week before treatment. Enhanced computerized tomography and/or magnetic resonance imaging were all conducted within 6 weeks before treatment and used to derive the number of focal hepatic lesions, maximum tumor diameter, and macroscopic vascular invasion. To mainly explore the impact of liver function on long-term survival, patients who died or were lost to follow-up within 30 days after treatment were excluded to reduce the impact of severe complications on patient survival. OS was measured from the date of primary operation (first treatment with resection or ablation or TACE) to the date of any cause of death or last follow-up. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and obtained

Table 1. Baseline demographic and clinical characteristics of the entire cohort and its subgroups according to treatments

Characteristic	Overall (N=3540)	Resection (N=2056)	Ablation (N=550)	TACE (N=934)
Gender				
Male	3166 (89.4%)	1796 (87.4%)	495 (90.0%)	875 (93.7%)
Female	374 (10.6%)	260 (12.6%)	55 (10.0%)	59 (6.3%)
Age, years	52.0 (43.0, 60.0)	51.0 (42.0, 59.0)	55.0 (46.0, 64.0)	51.0 (42.0, 58.0)
Presence of macroscopic vascular invasion				
Absent	2825 (79.8%)	1891 (92.0%)	550 (100.0%)	384 (41.1%)
Present	715 (20.2%)	165 (8.0%)	0 (0.0%)	550 (58.9%)
Tumor number	1.0 (1.0, 2.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	2.0 (1.0, 2.0)
Tumor size, cm	4.5 (2.8, 8.9)	4.0 (2.8, 6.0)	2.3 (1.8, 3.0)	10.0 (7.6, 12.5)
ALB, g/L	41.7 (38.8, 44.5)	42.5 (39.9, 45.0)	41.7 (38.6, 44.5)	39.7 (36.5, 42.6)
TBIL, μmol/L	14.3 (10.8, 18.8)	13.6 (10.4, 17.5)	14.9 (11.5, 20.6)	15.7 (11.7, 20.6)
ALBI grade				
1	2445 (69.1%)	1621 (78.8%)	365 (66.4%)	459 (49.1%)
2	1086 (30.7%)	435 (21.2%)	184 (33.5%)	467 (50.0%)
3	9 (0.3%)	0 (0.0%)	1 (0.2%)	8 (0.9%)
mALBI grade				
1	2306 (65.1%)	1547 (75.2%)	345 (62.7%)	414 (44.3%)
2a	797 (22.5%)	380 (18.5%)	110 (20.0%)	307 (32.9%)
2b	431 (12.2%)	129 (6.3%)	94 (17.1%)	208 (22.3%)
3	6 (0.2%)	0 (0.0%)	1 (0.2%)	5 (0.5%)

Median (interquartile range) for continuous variables; frequency (%) for categorical variables. Abbreviations: TACE, transcatheter arterial chemoembolization; ALBI, Albumin-Bilirubin; mALBI, modified Albumin-Bilirubin.

approval from the Institutional Review Board of Sun Yat-Sen University Cancer Center. The need to obtain written informed consent from patients was waived.

Number of categories of ALBI score

Although categorization of continuous risk score is not advisable from a statistical point of view due to loss of information and power, individuals in a population are usually graded into k groups for the convenience of exposition and clinical practice [13]. Dichotomization is strongly advised against due to a considerable loss of statistical power [14, 15]. However, statistical common sense dictates that five or fewer risk groups are preferable to a large number (e.g., 6 or more) in the case of unstable survival curves or poor discrimination between neighboring groups [16]. Indeed, a large recent survey of the published epidemiological literature demonstrated that most studies (78%) categorized the primary continuous predictor into 3-5 groups [17]. Elston and Ellis suggested that the number of risk groups should also be related to the available treatment options [18], and the widely recognized Barcelona Clinic Liver Cancer (BCLC) staging system divides HCC patients into four groups with different survival of prognoses [11]. Therefore, we aimed to explore whether categorizing the ALBI score to four groups, now named the modified ALBI (mALBI) grade, performs better than the original ALBI grade of three groups.

ALBI score, ALBI grade, and mALBI grade

The continuous ALBI score was calculated using the following formula: $\log_{10}$ bilirubin (μmol/L) × 0.66 + albumin (g/L) × -0.085. Then, the ALBI grade was defined by two predetermined cutoff points (the 25th and 90th percentile of risk score) as follows: ≤ -2.60 (grade 1), more than -2.60 to ≤ -1.39 (grade 2), and more than -1.39 (ALBI grade 3) [2]. For a given number of groups (k=4), it is desired that the optimal cutoff points be chosen to retain the discriminative ability of the risk score as much as possible. As a survival model, it is common to measure its discriminative ability by the concordance probability proposed by F E Harrell Jr, the so-called Harrell's C-index, which is defined as

"the proportion of all pairs of patients for which we could determine the ordering of survival times such that the predictions are concordant" [19, 20]. Recently, Barrio et al. proposed a new approach for the selection of optimal cut-points by maximizing the discriminative ability in a multivariable Cox regression model, which also allows for more than one cut-point to be selected [6, 7]. An accompanying R package (CatPredi, Version 1.1) leading to easy use of this methodology in practice was subsequently developed [21]. As previously described by Johnson et al. [2], we included the same variables (sex, age, macroscopic vascular invasion, tumor size, tumor number, and ALBI score) to construct the multivariable Cox regression analyses when implementing the CatPredi R package to find the optimal cutoff points. Therefore, we categorized the continuous ALBI score into four grades instead of three to retain as much discriminatory ability as possible, giving two extreme groups with excellent (mALBI grade 1) and poor (mALBI grade 3) liver function and two intermediate groups with good (mALBI grade 2a) and moderate (mALBI grade 2b) liver function. Specifically, the newly discovered and statistics-based cutoff points were as follows: ≤ -2.65 (mALBI grade 1), more than -2.65 to ≤ -2.29 (mALBI grade 2a), more than -2.29 to ≤ -1.33 (mALBI grade 2b), and more than -1.33 (mALBI grade 3).

Statistical analysis

All statistical analyses were performed using R version 4.0.3 software (R Foundation for Statistical Computing, Vienna, Austria). The discriminatory performance of the mALBI grade and the ALBI grade was calculated and compared using Harrell's C-index and assessed visually via Kaplan-Meier (KM) plots. Log-rank tests were conducted between risk groups. Unlike *P*-value for comparing risk groups, reporting hazard ratios (HRs) is a more straightforward assessment of discrimination. The more widely separated the two survival curves are, the larger the hazard ratio. We used a forest plot to demonstrate the adjusted HRs and their confidence intervals (CIs) of the ALBI and the mALBI grade accompanying the KM curves discussed above. To investigate whether the mALBI grade could offer a more detailed assessment of liver function, we used KM plots to detect variation in survival curves across each ALBI grade. Clinical application of the mALBI grade was evaluated across each treatment cohort.

Results

Stratification of patients by the ALBI and mALBI grade

The characteristics of the enrolled HCC patients are shown in **Table 1**. The median OS was 14.6 years for the resection cohort, compared with 9.3 years in the ablation cohort, and 0.7 years in the TACE cohort (shown in **Figure 2A**). When hepatic function was assessed by the ALBI grade, 69.1% of the overall population was ALBI grade 1 (ALBI score ≤ -2.60), 30.7% of patients were ALBI grade 2 (-2.60 < ALBI score ≤ -1.39), and 0.3% of patients were ALBI grade 3 (ALBI score > -1.39). When stratified by the mALBI grade, 65.1% of all patients had the best liver function (mALBI grade 1, ALBI score ≤ -2.65), and 0.2% of patients had the worst liver function (mALBI grade 3, ALBI score > -1.33). In addition, the rest of the patients with moderate hepatic reserve could be further divided into two different prognostic groups, with 22.5% graded as mALBI grade 2a (-2.65 < ALBI score ≤ -2.29) and 12.2% graded as mALBI grade 2b (-2.29 < ALBI score ≤ -1.33). Either stratification of prognosis according to the ALBI or the mALBI grade showed clear deterioration in the 1-, 3-, and 5-year OS rates and median OS (shown in **Table 2**). Visual inspection of the resulting Kaplan-Meier survival curves showed good discrimination between the three ALBI (P<0.001; Harrell's C index =0.598) and the four mALBI (P<0.001; Harrell's C index =0.614) prognostic groups (shown in **Figure 2B** and **2C**).

Multivariable Cox analysis

The ALBI and mALBI grades were adjusted by the same covariates in two separate Cox regression models, and multivariable analyses confirmed those patients with advanced ALBI or mALBI grades were associated with higher hazard ratios of death (shown in **Figure 3**).

Performance of mALBI grade

Visual inspection of the survival curves indicated that the mALBI grade could reveal two different prognostic groups across each ALBI grade (within ALBI grade 1: mALBI grade 1 vs. mALBI grade 2a, P<0.001; within ALBI grade 2: mALBI

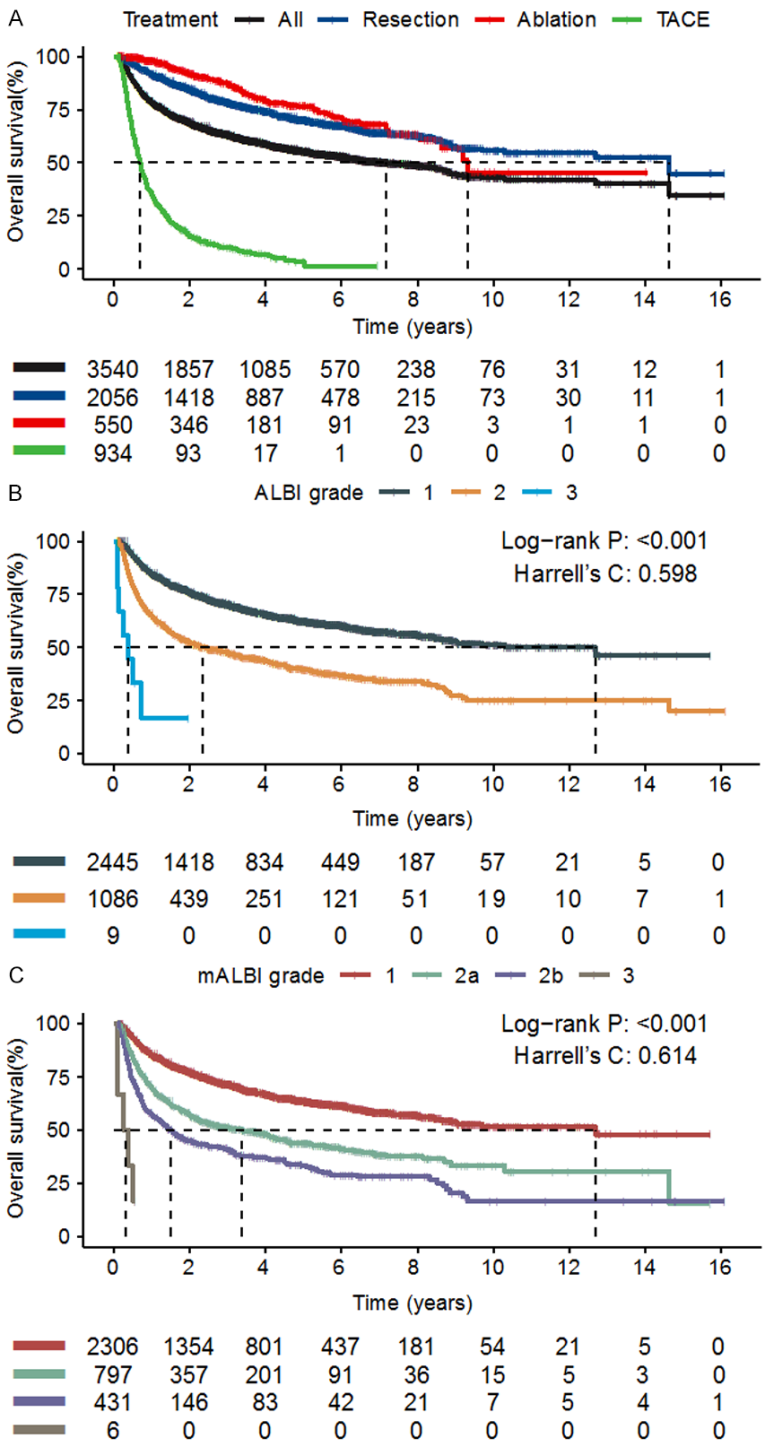

Figure 2. Kaplan-Meier curve analysis showing the overall survival of the individual patient cohorts included in the study. (A) Overall survival of the entire cohort and each cohort with different primary treatments. Kaplan-Meier curves depict the overall survival of the entire cohort according to (B) the albumin-bilirubin (ALBI) grade and (C) the modified albumin-bilirubin (mALBI) grade, associated with corresponding Harrell's C-index.

grade 2a vs. mALBI grade 2b, P<0.001; within ALBI grade 3: mALBI grade 2b vs. mALBI grade 3, P=0.2; shown in **Figure 4A-C**, respectively).

When applying the mALBI model to the patient cohorts treated with surgical resection, thermal ablation, or locoregional TACE (shown in **Figure 5A-C**, respectively), visual inspection of the survival curves again demonstrated that the mALBI grade could effectively distinguish different prognostic groups among patients receiving the same treatments, especially in curative settings.

Discussion

Using appropriate statistical methods, we categorized the ALBI score into four grades instead of three to retain as much discriminatory ability as possible, giving two extreme groups with excellent (mALBI grade 1) and poor (mALBI grade 3) liver function and two intermediate groups with good (mALBI grade 2a) and moderate (mALBI grade 2b) liver function. Overall, the mALBI grade proposed in this study offered a more precise stratification of liver function than the original ALBI grade and thus might assist in clinical decision-making and predict prognosis more accurately.

It is well known that underlying hepatic dysfunction has an important impact on the optimal treatment strategies and long-term outcomes of individual HCC patients and thus needs to be accurately evaluated. The Child-Pugh classification is the earliest and most commonly used bedside tool for evaluating liver function in cirrhotic patients. However, it has poor performance as a prognostic predic-

Table 2. Descriptive survival statistics of the cohorts according to ALBI and mALBI grade

Cohorts	1-year OS rate (95% CI)	3-year OS rate (95% CI)	5-year OS rate (95% CI)	Median OS (years)
ALBI grade				
1	85% (83%, 86%)	70% (68%, 72%)	62% (60%, 65%)	13 (8.9, -)
2	65% (62%, 68%)	47% (44%, 51%)	40% (36%, 43%)	2.3 (1.9, 3.1)
3	17% (3.2%, 88%)	- (-, -)	- (-, -)	0.38 (0.13, -)
mALBI grade				
1	85% (84%, 87%)	71% (69%, 73%)	63% (61%, 66%)	13 (9.0, -)
2a	70% (67%, 73%)	51% (48%, 55%)	44% (40%, 48%)	3.4 (2.4, 4.3)
2b	58% (53%, 63%)	41% (36%, 46%)	33% (28%, 39%)	1.5 (1.2, 2.1)
3	- (-, -)	- (-, -)	- (-, -)	0.32 (0.11, -)

Abbreviations: OS, overall survival; ALBI, Albumin-Bilirubin; mALBI, modified Albumin-Bilirubin; CI, confidence interval.

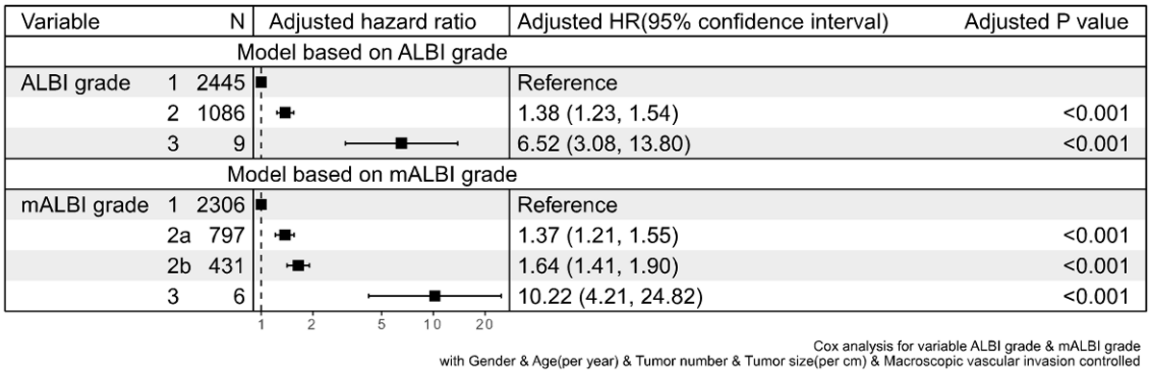

Figure 3. Multivariable Cox regression analysis of overall survival in the entire study population based on albumin-bilirubin (ALBI) model and modified albumin-bilirubin (mALBI) model. Both models are adjusted with the same covariates as follows: gender, age, tumor number, tumor size, and macrovascular invasion according to Johnson et al. (2).

tion tool or indeed a decision-making tool [22]. To fill this gap, a recent model, the ALBI score, comprising albumin and bilirubin, was proposed and validated as an objective measurement of liver function and a good predictor of survival in the HCC setting [2]. Although the ALBI score has the clear advantage of a continuous variate in predicting mortality risk, categorization is a more commonly used strategy in biomedical research, where clinical decisions are usually based on the risk classification of patients [23]. Since no universal methods have been proposed for categorizing a continuous predictor in a survival model so far [17], the original ALBI grade was generated according to two predetermined cutoff points and without formal statistical grounding [2]. Notably, the ALBI grade had unsatisfactory discrimination among patients with moderate liver function due to a wide range of ALBI score from the 25th to 90th percentile in ALBI grade 2. Hence, a greater discriminatory ability of the ALBI score in evaluating liver function can be attained by stratification into four groups instead of three. Recently, Barrio et al. developed and validated a methodology to categorize a continuous risk-score by maximizing the concordance probability based on a multivariable Cox regression model [6, 7]. When applying the proposed approach to the ALBI score model, three optimal cutoff points were identified, and the resulting mALBI grade was defined as follows: mALBI grade 1 (score ≤ -2.65), mALBI grade 2a (-2.65 < score ≤ -2.29), mALBI grade 2b (-2.29 < score ≤ -1.33) and mALBI grade 3 (score > -1.33). The mALBI grade had an overall better discriminatory ability than the ALBI grade in predicting OS through Harrell's C-index (0.614 vs. 0.598). Additionally, both visual inspection of K-M curves and calculation of HRs displayed a more subtle evaluation of liver function using the mALBI grade. Unsurprisingly, when patients

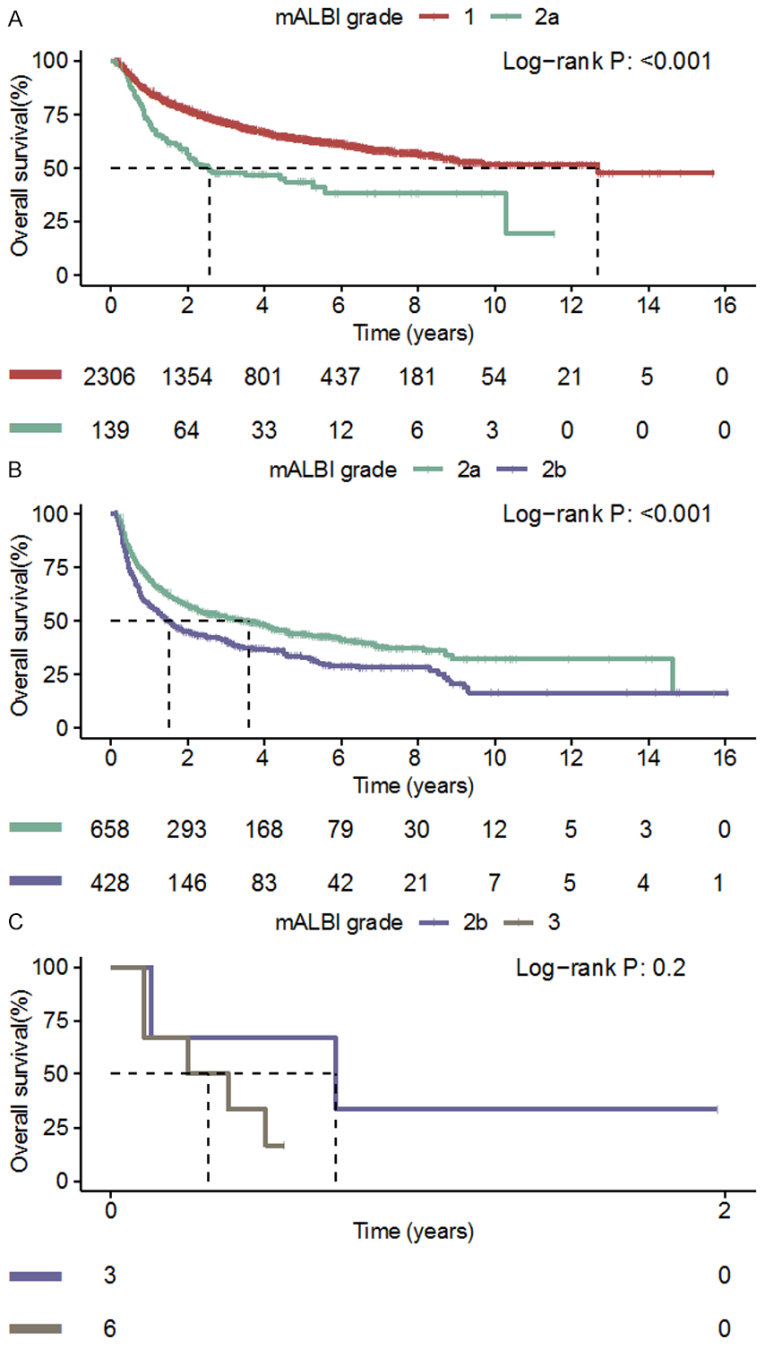

Figure 4. Prognostic performance of the modified albumin-bilirubin (mALBI) grade across each ALBI grade. A. Kaplan-Meier curves depict the different overall survival of patients with liver function of ALBI grade 1 according to the mALBI grade. B. Kaplan-Meier curves depict the different overall survival of patients with liver function of ALBI grade 2 according to the mALBI grade. C. Kaplan-Meier curves depict the different overall survival of patients with liver function of ALBI grade 3 according to the mALBI grade.

were roughly classified into ALBI grade 1 or grade 2 cohorts, two distinct prognostic groups could be identified in each cohort according to the mALBI grade. Among patients with ALBI grade 1, patients with mALBI grade 1 had a nearly 10 year longer median OS than those with mALBI grade 2a. Among patients with ALBI grade 2, patients with mALBI grade 2a had nearly 2 year longer median OS than those with mALBI grade 2b. Additionally, with better discriminatory ability in evaluating liver function, the mALBI grade is superior to the ALBI grade in discovering real differences in therapeutic effects in clinical trials because hepatic reserve is an important competing cause of death.

The HCC guideline from the European Association for the Study of the Liver (EASL) points out that although the ALBI grade outperforms the traditional Child-Pugh grade in discriminative capacity, its role in clinical decision-making or stratification in research trials is not defined [11]. Studies confirmed a strong positive and significant statistical correlation between the ALBI score and the retention rate of indocyanine green (ICG) at 15 minutes (ICG-R15) [24, 25], which is also a continuous index in evaluating liver function and is widely used in Asian countries for hepatectomy decision-making [26]. In a nationwide study in Japan, Hiraoka et al. discovered a special threshold of ALBI score (-2.27), which was approximate to a 30% ICG-R15, an indicator for the performance of a subsegmentectomy [4, 5, 24]. Notably, the newly identified cut-point (ALBI score = -2.29) in generating the mALBI grade in this study was quite in line with the clinically meaningful value (ALBI score -2.27) [24]. Hence, unlike the ALBI grade, the mALBI grade can assist in clinical decision-making, e.g., patients

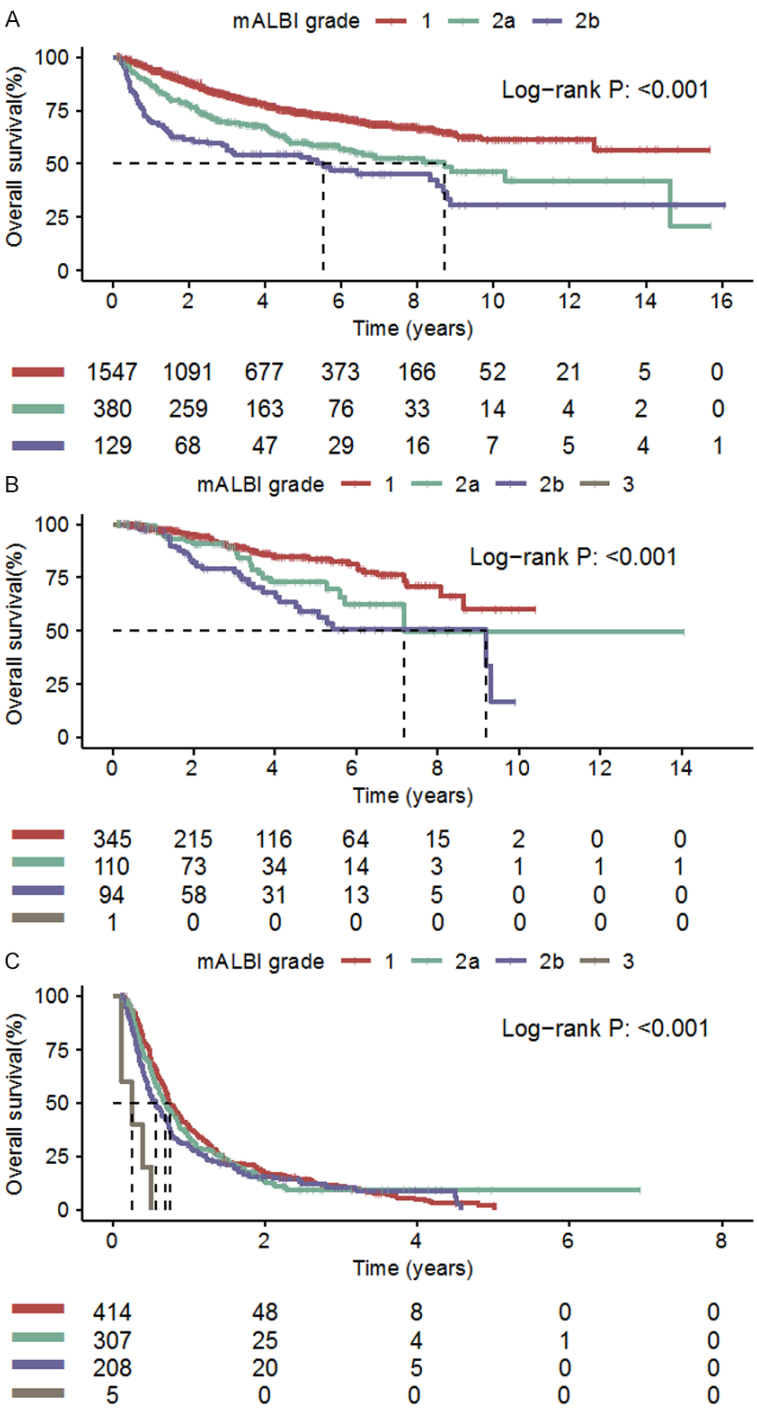

Figure 5. Prognostic performance of the modified albumin-bilirubin (mALBI) grade across each cohort with different primary therapies. Kaplan-Meier curves depict overall survival according to the mALBI grades within (A) surgically resected patients, (B) thermally ablated patients, and (C) patients treated with transcatheter arterial chemoembolization.

with liver function of mALBI grade 1 or 2a are likely to tolerate subsegmentectomy or a greater extent of hepatectomy, while liver function of mALBI grade 2b or 3 are strong indications of intolerance of surgical resection.

Underlying liver dysfunction plays a more important role than liver malignancy in predicting the survival of early-stage HCC patients who receive curative therapies, while it plays a less important role in the prognosis prediction with increased HCC stages. That is why the performance of the mALBI in predicting survival was different across the three studied cohorts, being worse in TACE cohorts (mainly consisting of advanced HCC) compared to the resection and ablation cohorts (mainly consisting of early-stage HCC).

One of the limitations in this study is that patients with terminal liver cancer who received medical care or supportive care were not included in this study. Another limitation is that there were only nine patients with liver function of ALBI grade 3, resulting in compromised power to detect the different prognoses of subgroups of grades 2b and 3 when subdivided according to the mALBI grade. The retrospective nature and the prolonged enrollment period in our study should also be acknowledged as limitations. However, one of the strengths of this study is that the three cutoff points (ALBI score: -2.65, -2.29, and -1.33) identified by appropriate statistical methods matched up with those reported in the literature such as the two cutoff points (ALBI score: -2.60 and -1.39) proposed by Johnson et al. [2] and a clinically meaningful cut-point (ALBI score: -2.27) discovered by Hiraoka et al. [4, 5].

However, prospective validation studies of the mALBI grade are warranted in real-world clinical practice.

Compared with the original ALBI grade, the newly proposed mALBI grade has a better discriminatory ability in stratifying HCC patients into different prognostic groups and is more informative in clinical decision-making due to a reasonable categorization of the ALBI score.

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Disclosure of conflict of interest

None.

Abbreviations

HCC, hepatocellular carcinoma; ALBI, albumin-bilirubin; mALBI, modified ALBI; TACE, transcatheter arterial chemoembolization; OS, overall survival; HRs, hazard ratios; KM, Kaplan-Meier; CIs, confidence intervals; EASL, European Association for the Study of the Liver; ICG, indocyanine green; BCLC, Barcelona Clinic Liver Cancer.

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