

Impact of Modified Albumin–Bilirubin Grade on Survival in Patients With HCC Who Received Lenvatinib: An Analysis Using Time-Dependent ROC

Toshifumi Tada (✉ tadat0627@gmail.com)

Himeji Red Cross Hospital

Takashi Kumada

Gifu Kyoritsu University

Atsushi Hiraoka

Ehime Prefectural Central Hospital

Masanori Atsukawa

Nippon Medical School

Masashi Hirooka

Ehime University

Kunihiko Tsuji

Teine Keijinkai Hospital

Toru Ishikawa

Saiseikai Niigata Hospital

Koichi Takaguchi

Kagawa Prefectural Central Hospital

Kazuya Kariyama

Okayama City Hospital

Ei Itobayashi

Asahi General Hospital

Kazuto Tajiri

Toyama University Hospital

Noritomo Shimada

Otakanomori Hospital

Hiroshi Shibata

Tokushima Prefectural Central Hospital

Hironori Ochi

Matsuyama Red Cross Hospital

Satoshi Yasuda

Ogaki Municipal Hospital

Hidenori Toyoda

Ogaki Municipal Hospital

Shinya Fukunishi

Osaka Medical College

Hideko Ohama

Osaka Medical College

Kazuhito Kawata

Hamamatsu University School of Medicine

Joji Tani

Kagawa University

Shinichiro Nakamura

Himeji Red Cross Hospital

Kazuhiro Nouse

Okayama City Hospital

Akemi Tsutsui

Kagawa Prefectural Central Hospital

Takuya Nagano

Kagawa Prefectural Central Hospital

Tanaka Takaaki

Ehime Prefectural Central Hospital

Norio Itokawa

Nippon Medical School

Tomomi Okubo

Nippon Medical School

Taeang Arai

Nippon Medical School

Michitaka Imai

Saiseikai Niigata Hospital

Kouji Joko

Matsuyama Red Cross Hospital

Yohei Koizumi

Ehime University

Yoichi Hiasa

Ehime University

Research Article

Keywords: lenvatinib, modified albumin–bilirubin grade, Child–Pugh classification, hepatocellular carcinoma, time-dependent receiver operating characteristic

Posted Date: June 9th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-580189/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Scientific Reports on July 14th, 2021. See the published version at <https://doi.org/10.1038/s41598-021-93794-5>.

Abstract

We investigated the impact on survival of modified albumin–bilirubin (mALBI) grade vs. Child–Pugh classification in patients with hepatocellular carcinoma (HCC) who received lenvatinib. A total of 524 patients with HCC who received lenvatinib were included. Univariate analysis showed that mALBI grade 2b/3 and Child–Pugh class B/C were significantly associated with survival (hazard ratio [HR], 2.471; 95% confidence interval [CI], 1.944–3.141 and HR, 2.178; 95%CI, 1.591–2.982). In patients with a Child–Pugh score of 5, multivariate analysis showed that mALBI grade 2b/3 was independently associated with survival (HR, 1.814; 95%CI, 1.083–3.037). Conversely, among patients with mALBI grade 1/2a, there was no difference in survival between those with a Child–Pugh class of 5 or 6 ($p = 0.735$). Time-dependent receiver operating characteristic analysis showed that the ALBI score predicted survival better than the Child–Pugh score. The optimal cut-off value of the ALBI score for predicting survival was nearly the same as the value separating mALBI grades 2a and 2b. In conclusion, the mALBI grade was a better predictor of survival than the Child–Pugh classification in patients with unresectable HCC who received lenvatinib therapy.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver. It is also one of the most prevalent malignancies globally and the cause of significant health-related problems, making it the third most frequent cause of cancer-related deaths worldwide [1–3]. Curative treatments such as liver resection, liver transplantation, and radiofrequency/microwave ablation are indicated in only 30–40% of patients with HCC. Most patients for whom curative treatment is not indicated undergo transarterial chemoembolization or systemic treatment for palliation [4].

Molecularly targeted agents such as sorafenib [5, 6], regorafenib [7, 8], and ramucirumab [9] have been developed for the systemic treatment of patients with unresectable HCC. In the past 10 years, no first-line systemic treatments other than sorafenib were approved for unresectable HCC in Japan [5–8]. Lenvatinib [10], a newly developed tyrosine kinase inhibitor, has recently become available not only as a first-line treatment in patients with unresectable HCC, but also as a later-line therapeutic option [11, 12]. More recently in Japan, the combination of atezolizumab plus bevacizumab has been approved as a first-line systemic therapy in patients with unresectable HCC [13].

The Child–Pugh classification system [14] is the most extensively used method worldwide for assessing hepatic function in patients being treated for HCC. However, this system includes subjective components such as encephalopathy and ascites, and interrelated factors such as serum albumin and ascites. Therefore, accurate and more objective methods to evaluate hepatic function are needed. A new assessment tool for hepatic function, known as the albumin–bilirubin (ALBI) grade, was recently developed [15]. In addition, several studies have shown that the modified ALBI (mALBI) grade is effective for assessing hepatic function in patients with HCC [16–18]. Furthermore, we recently reported that liver function in patients with naïve HCC has improved remarkably in the last 30 years, and in the last 5 years

over 80% of patients reached Child–Pugh class A, including 65% who attained a Child–Pugh score of 5 [19]. Since lenvatinib therapy is mainly indicated in HCC patients with Child–Pugh class A disease, it is necessary to elucidate the ability of the mALBI grade to assess hepatic function as an alternative to the Child–Pugh classification system.

In this study, we investigated the association between the ALBI score and survival, with a particular focus on the mALBI grade vs. the Child–Pugh score, in patients with unresectable HCC who received lenvatinib at multiple centers in Japan. To further compare the ability of the mALBI grade and Child–Pugh score in predicting survival, we generated time-dependent receiver operating characteristic (ROC) curves [20] for censored data and compared the areas under the ROC curves (AUROCs).

Results

Patient characteristics

Table 1 shows the characteristics of the study patients at the start of follow-up. There were 126 (24.0%) females and 398 (76.0%) males, with a median age of 73.0 (68.0–79.0) years. The median follow-up was 11.6 (6.0–18.5) months. There were 277 (52.9%) patients with a Child–Pugh score of 5, 171 (32.6%) with a score of 6, 56 (10.7%) with a score of 7, 15 (2.9%) with a score of 8, 2 (0.4%) with a score of 9, 2 (0.4%) with a score of 10, and 1 (0.2%) with a score of 13, corresponding to 448 (85.5%) patients with Child–Pugh class A disease, 73 (13.9%) with class B disease, and 3 (0.6%) patients with class C disease. The median ALBI score was -2.36 (-2.68 to -1.99). There were 165 (31.5%) patients with mALBI grade 1, 131 (25.0%) with grade 2a, 210 (40.1%) with grade 2b, and 18 (3.4%) with grade 3.

Table 1
Patient characteristics

	Overall (n = 524)	Child-Pugh score of 5 (n = 277)
Age (years)*	73.0 (68.0–79.0)	73.0 (68.0–79.0)
Sex (female/male)	126/398	59/218
ECOG-PS (0/1/2/3)	420/91/12/1	233/40/3/1
Body mass index (kg/m ²)*	22.9 (20.6–25.4)	23.1 (20.9–25.4)
Etiology of HCC (hepatitis B/C/B + C/non-B, non-C)	75/214/2/233	49/105/2/121
Albumin (g/dL)*	3.6 (3.3–4.0)	3.9 (3.7–4.2)
Total bilirubin (mg/dL)*	0.8 (0.6–1.1)	0.7 (0.6–1.0)
Platelet count ($\cdot 10^3/m^3$)*	13.5 (10.0–18.6)	14.3 (10.8–18.5)
Prothrombin time (%)*	87.0 (78.0–97.0)	90.0 (83.0–100.0)
α -fetoprotein (ng/mL)*	40.9 (6.8–668.7)	25.7 (5.6–426.0)
ALBI score*	-2.36 (- 2.68 to - 1.99)	-2.65 (- 2.86 to - 2.44)
mALBI grade (1/2a/2b/3)	165/131/210/18	153/95/28/1
Child–Pugh score (5/6/7/8/9/10/13)	277/171/56/15/2/2/1	
Child–Pugh class (A/B/C)	448/73/3	
BCLC stage (0/A/B/C/D)	4/8/225/285/2	3/7/126/140/1
Vascular invasion (yes/no)	116/408	51/226
Extrahepatic spread (yes/no)	186/338	96/181
Post-treatment of lenvatinib (yes/no/ongoing)	188/253/83	125/101/51
Follow-up duration (months)*	11.6 (6.0–18.5)	14.3 (10.8–18.5)
* Values are expressed as medians (interquartile range).		
ECOG-PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; ALBI, albumin–bilirubin; mALBI, modified albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer.		

The cumulative overall survival rates at 6, 12, 18, and 24 months were 82.7%, 61.6%, 47.3%, and 37.0%, respectively. The median survival was 17.1 months (95% confidence interval [CI], 15.0–19.6).

Overall Survival By Malbi Grade And Child–pugh Class

Figure 1a shows that cumulative survival curves differed significantly according to mALBI grade ($p < 0.001$). Multiple comparisons using the Bonferroni method showed significant differences between each grade, except between mALBI grades 1 and 2a, and grades 2b and 3. Figure 1b shows a significant difference between the cumulative survival curves of patients with mALBI grades of 1/2a vs. 2b/3 ($p < 0.001$). Univariate analysis with a Cox proportional hazards model showed that mALBI grade 2b/3 was significantly associated with poor survival (HR, 2.471; 95%CI, 1.944–3.141; $p < 0.001$; c-index, 0.625).

Figure 1c shows that cumulative survival curves differed significantly according to Child–Pugh class ($p < 0.001$). Multiple comparisons using the Bonferroni method showed a significant difference only between Child–Pugh classes A and B. Figure 1d shows a significant difference between cumulative survival curves for Child–Pugh class A vs. B/C ($p < 0.001$). Univariate analysis with a Cox proportional hazards model showed that Child–Pugh class B/C was significantly associated with poor survival (HR, 2.178; 95%CI, 1.591–2.982; $p < 0.001$; c-index, 0.555).

Subgroup Analysis

Table 1 shows the characteristics of patients with a Child–Pugh score of 5 at the start of follow-up ($n = 277$). There were 59 females and 218 males, with a median age of 73.0 (68.0–79.0) years. There were 153 (55.2%) patients with mALBI grade 1, 95 (34.3%) with grade 2a, 28 (10.1%) with grade 2b, and 1 (0.4%) with grade 3. Figure 2 shows a significant difference between cumulative survival curves for mALBI grade 1/2a vs. 2b/3 ($p = 0.032$). Univariate analysis with a Cox proportional hazards model showed that mALBI grade 2b/3 was significantly associated with poor survival (HR, 1.740; 95%CI, 1.040–2.909; $p = 0.035$). Multivariate Cox proportional hazards models that included the covariates of age, sex, ECOG-PS, etiology, α -fetoprotein, HCC stage, and mALBI grade showed that mALBI grade was independently associated with overall survival (HR, 1.814; 95%CI, 1.083–3.037; $p = 0.024$) (Table 2). There were 116 (58.0%) and 84 (42.0%) patients with mALBI grade 1/2a who received post-treatment of lenvatinib and not, and 9 (34.6%) and 17 (65.4%) patients with mALBI grade 2b/3 who received post-treatment of it and not, respectively ($p = 0.035$).

Table 2
Multivariate analysis in patients with Child–Pugh score of 5

	HR	95% CI	p value
Age (years)			
< 75 (n = 161)	1	0.899–1.945	0.155
≥ 75 (n = 116)	1.322		
Sex			
Female (n = 59)	1	0.675–1.680	0.786
Male (n = 218)	1.065		
ECOG-PS			
0 (n = 233)	1	0.506–1.562	0.682
≥ 1 (n = 44)	0.889		
Etiology of HCC			
Viral (n = 156)	1	0.497–1.079	0.115
Non-viral (n = 121)	0.732		
α-fetoprotein (ng/mL)			
< 400 (n = 205)	1	0.938–2.120	0.099
≥ 400 (n = 71)	1.410		
mALBI grade			
1/2a (n = 248)	1	1.083–3.037	0.024
2b/3 (n = 29)	1.814		
BCLC stage			
≤B (n = 136)	1	0.969–2.209	0.070
≥C (n = 141)	1.463		
HR, hazard ratio; CI, confidence interval ECOG-PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; mALBI, modified albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer.			

Figure 3 shows that in patients with mALBI grade 1/2a (n = 295), there was no significant difference in cumulative survival curves according to Child–Pugh scores of 5 vs. 6 (p = 0.735). Univariate analysis with Cox proportional hazards model showed that a Child–Pugh class of 6 was not associated with poor survival (HR, 1.088; 95%CI, 0.666–1.777; p = 0.736).

Time-dependent Roc Analysis Of Overall Survival

Figure 4 shows AUROC plots of the ALBI and Child–Pugh scores for overall survival from 3 to 24 months after the start of follow-up, as determined using time-dependent ROC analysis. The ALBI score had better predictive power for overall survival than the Child–Pugh score at all time points.

Table 3 shows the sensitivity, specificity, and cut-off values of the ALBI and Child–Pugh scores at 6, 12, 18, and 24 months based on time-dependent ROC analysis for overall survival. The optimal cut-off values of the ALBI score for predictive survival at each month were nearly identical to the value that separated mALBI grades 2a and 2b. The optimal cut-off value of the Child–Pugh score for predictive survival was 5 at each month.

Table 3
Sensitivity, specificity, and cut-off values based on time-dependent ROC analysis

	ALBI score			Child-Pugh score		
	Cut-off value	Sensitivity	Specificity	Cut-off value	Sensitivity	Specificity
At 6 months	-2.19	70.0%	67.8%	5	73.9%	58.5%
At 12 months	-2.24	61.3%	71.9%	5	63.1%	62.8%
At 18 months	-2.24	54.4%	74.3%	5	58.1%	65.1%
At 24 months	-2.31	56.8%	73.9%	5	55.2%	66.6%
ROC, receiver operating characteristic						

Discussion

In this multicenter study of a large number of patients with unresectable HCC who received lenvatinib therapy, Cox proportional hazards modeling that included age, sex, ECOG-PS, HCC etiology, mALBI grade, α -fetoprotein, and BCLC stage as covariates showed that mALBI grade (1/2a vs. 2b/3) was independently associated with overall survival in patients with a Child–Pugh score of 5. Conversely, the survival analysis of patients with mALBI grade 1/2a and Child–Pugh class A showed no difference between patients with Child–Pugh class 5 vs. 6. In addition, the predictive power of the ALBI score for overall survival was superior to that of the Child–Pugh score in time-dependent ROC analysis. Furthermore, the optimal cut-off values of the ALBI score for predicting good survival in the 2 years from the start of lenvatinib treatment were nearly equal to the value separating mALBI grades 2a and 2b. These results suggest that the ALBI score is a better predictive marker for overall survival than the Child–Pugh score in patients with unresectable HCC who are treated with lenvatinib. In addition, the mALBI grade was able to predict good vs. poor prognosis in patients with a Child–Pugh score of 5, even though these patients are generally considered to have a good prognosis. Furthermore, patients with a mALBI grade of 1 or 2a had a similar prognosis regardless of whether their Child–Pugh score was 5 or 6.

Recently, Ueshima et al. [21] investigated the association between baseline liver function, as determined by the Child–Pugh score and ALBI grade, and the outcomes of 82 patients with unresectable HCC who were treated with lenvatinib. Their study patients were divided into four groups: (1) Child–Pugh score 5 and ALBI grade 1 (group 1; n = 27); (2) Child–Pugh score 5 and ALBI grade 2 (group 2; n = 19); (3) Child–Pugh score 6 (group 3; n = 30); and (4) Child–Pugh score ≥ 7 (group 4; n = 6). They found that the median times to treatment failure (i.e., time from the initial administration of lenvatinib to treatment discontinuation for any reason, including disease progression, treatment toxicity, patient preference, and any cause of death) were 8.9, 5.3, 5.9 and 0.3 months in groups 1, 2, 3, and 4, respectively (HR, 0.38; 95%CI, 0.18–0.80; $p < 0.001$) [21]. In addition, overall survival was significantly better in patients with ALBI grade 1 than in those with ALBI grade 2 (HR, 0.12; 95%CI, 0.02–0.97); $p < 0.01$) [21]. Although our study did not investigate the time to treatment failure, we showed that patients with mALBI grade 1, as well as those with 2a, had better overall survival than patients with mALBI grade 2b/3. In addition, we used time-dependent ROC analysis to demonstrate that the optimal cut-off values of the ALBI score during the 2 years after initiating lenvatinib treatment were nearly equal to the value that separated mALBI grades 2a and 2b, as opposed to that separating ALBI grades 1 and 2. One advantage of this study relative to that by Ueshima et al. is that the former included more patients with unresectable HCC who received lenvatinib therapy. In addition, this study statistically confirmed the optimal cut-off values of the ALBI score for predicting good overall survival in patients treated with lenvatinib.

Ando et al. [22] reported that mALBI grade 1/2a (odds ratio, 5.18; 95%CI, 1.465–18.31; $p = 0.011$) was an independent factor for possible treatment with second-line molecularly targeted agents in 141 HCC patients who received lenvatinib as first-line therapy. In addition, in a study by Hiraoka et al. [23] using a Japanese hospital-based administration database, the overall duration of systematic treatment in patients with advanced HCC was shorter in those with a baseline ALBI grade of 2b or 3 than in those with grade 1 or 2a (medians: 7.1, 6.7, 4.5, and 3.0 months for grades 1, 2a, 2b, and 3, respectively). In this study, we clarified that there was a significant difference in the post-treatment of lenvatinib rate between patients with mALBI grade 1/2a and those with grade 2b/3, even among those with good liver function as defined by a Child–Pugh score of 5.

The Child–Pugh classification system comprises five factors, specifically serum albumin, total bilirubin, prothrombin time, ascites, and encephalopathy [14]. This system has been widely used to evaluate hepatic function and has been incorporated into the HCC staging system [24]. However, the Child–Pugh classification is limited by the subjectivity involved in evaluating encephalopathy and ascites, and serum albumin levels are correlated with the severity of ascites [14]. Furthermore, this system was originally developed for patients with cirrhosis, not HCC. The ALBI grade, which was recently developed as an objective parameter for liver function, is calculated using only serum albumin and total bilirubin levels. It has been shown to accurately assess the prognosis of patients with HCC, and is superior not only to the Child–Pugh classification [25, 26], but also to the liver damage classification system [27].

Hiraoka et al. [16] developed the new mALBI grading system, which divides ALBI grade 2 into 2a and 2b, by analyzing 46,681 HCC patients in a nationwide survey conducted in Japan. The mALBI grade showed

a good ability to stratify prognosis in each TNM stage of the Liver Cancer Study Group of Japan [28], and there was a statistically significant difference between each mALBI grade in all TMN stages ($p < 0.01$). This study confirmed the utility of subdividing ALBI grade 2 into 2a and 2b for predicting survival in advanced HCC patients who received systemic therapy.

ROC analysis is generally used to evaluate the discriminatory power of a continuous variable for a binary disease outcome (e.g., disease positive or negative). However, many chronic disease outcomes, including the prognosis of patients with malignancy, are time dependent. Therefore, time-dependent ROC curve analysis has been introduced to evaluate the predictive power of assessment markers for time-dependent disease outcomes [20]. No previous studies have used this approach to evaluate parameters of liver function in terms of their association with survival in patients with unresectable HCC who received lenvatinib therapy. In this study, we used time-dependent ROC analysis to show that the ALBI score was superior to the Child–Pugh score in terms of predicting overall survival up to 2 years after the start of lenvatinib therapy in patients with unresectable HCC.

The main limitations of this study are its hospital-based subject population and retrospective nature. Although the study included a large number of patients with unresectable HCC from multiple centers in Japan, future prospective studies with community-based populations are warranted. An additional limitation was that the study only enrolled patients with unresectable HCC who were treated with lenvatinib. Future studies of patients with HCC should include those who receive atezolizumab plus bevacizumab, a recently approved, first-line, systemic combination therapy, as well as those who receive lenvatinib.

In conclusion, the mALBI grade is a new, simple, objective parameter that was a better predictor of survival in HCC patients who received lenvatinib therapy than the Child–Pugh classification, even among individuals with good liver function as defined by a Child–Pugh score of 5. Further studies in other populations are warranted to confirm these findings.

Methods

Patients

The protocol used in the present study was approved by the Institutional Ethics Committee of Ehime Prefectural Central Hospital (IRB No. 30-66), based on the Guidelines for Clinical Research issued by the Ministry of Health and Welfare of Japan.

We enrolled 524 patients with unresectable HCC who received lenvatinib between March 2018 and February 2021 at 19 institutions in Japan (Himeji Red Cross Hospital [n=126], Nippon Medical School Hospital Group [Sendagi Hospital, Chiba Hokusoh Hospital, and Musashi Kosugi Hospital] [n=75], Ehime Prefectural Central Hospital [n=53], Ogaki Municipal Hospital [n=38], Kagawa University Hospital [n=33], Asahi General Hospital [n=26], Ehime University Hospital [n=23], Osaka Medical College Hospital [n=22], Okayama City Hospital [n=21], Teine Keijinkai Hospital [n=20], Saiseikai Niigata Hospital [n=18], Kagawa

Prefectural Central Hospital [n=17], Hamamatsu University Hospital [n=17], Matsuyama Red Cross Hospital [n=16], Otakanomori Hospital [n=9], Toyama University Hospital [n=6], and Tokushima Prefectural Central Hospital [n=4]).

The start of the follow-up period was defined as the date when lenvatinib therapy began. The end of follow-up was defined as the date of the final visit for patients who remained alive or the date of death for patients who died during the follow-up period.

The etiology of HCC was considered to be hepatitis B virus in patients positive for hepatitis B virus surface antigen, and hepatitis C virus in those positive for hepatitis C virus antibodies.

Diagnosis and treatment of HCC

HCC was diagnosed based on increases in α -fetoprotein levels, pathological findings, or the use of imaging modalities such as dynamic computed tomography, magnetic resonance imaging, and contrast-enhanced ultrasonography with perflubutane [29, 30]. HCC stage was based on the Barcelona Clinic Liver Cancer (BCLC) classification system [24].

The most appropriate treatment modality for HCC in each patient was selected through discussion between surgeons, hepatologists, and radiologists in each institution, based on Japanese practice guidelines for HCC [31, 32].

Liver function assessment

We assessed liver function using the Child–Pugh classification system [14] and albumin–bilirubin (ALBI) score [15]. The ALBI score was calculated based on serum albumin and total bilirubin values using the following formula: $\text{ALBI score} = (\log_{10} \text{ total bilirubin } (\mu\text{mol/L}) \times 0.66) + (\text{albumin (g/L)} \times -0.085)$. ALBI grades were assigned as follows: ≤ -2.60 = ALBI grade 1, -2.60 to -1.39 = ALBI grade 2, and > -1.39 = ALBI grade 3. For more detailed evaluation of hepatic function, we used the mALBI grade, which was calculated by subdividing ALBI grade 2 into 2a and 2b based on a cut-off score of -2.27 [16].

Lenvatinib treatment

Lenvatinib (Lenvima®; Eisai, Tokyo, Japan) treatment was started after written informed consent was obtained from each patient. The dose of oral lenvatinib was 8 mg/day in patients who weighed <60 kg and 12 mg/day in those who weighed ≥ 60 kg. However, the initial dose of lenvatinib was reduced at the discretion of the physician in patients with any of the following: advanced age; non–Child–Pugh A disease; low body weight; and pleural effusion, ascites, or gastrointestinal varices at risk of bleeding.

Lenvatinib was discontinued when any unacceptable or serious adverse event or clinical tumor progression occurred. Based on the drug manufacturer's guidelines, the lenvatinib dose was reduced or treatment was interrupted when a patient developed any grade ≥ 3 [33] severe adverse events, if any unacceptable treatment-related adverse events occurred, or if there was clinical evidence of tumor

progression. In cases of treatment-related adverse events, dosing was reduced or temporarily interrupted until symptoms diminished to grade 1 or 2, based on the manufacturer's guidelines.

Statistical analysis

Continuous variables are expressed as medians (interquartile range). The chi-square test was used for categorical variables. Actuarial analysis of cumulative survival was performed using the Kaplan–Meier method, and differences were tested using the log-rank test with Bonferroni correction. Univariate and multivariate Cox proportional hazards models were used to calculate hazard ratios (HRs) for survival. The concordance (C)-index was used to determine the predictability of survival. We performed multivariate analysis using the following covariates that were previously reported to be risk factors for HCC or predictors of liver prognosis: age, sex, Eastern Cooperative Oncology Group performance status (ECOG-PS), HCC etiology, α -fetoprotein, HCC stage, and mALBI grade [4, 13, 34, 35]. We used cut-off values for clinical data as defined in previous reports regarding the risk or prognosis of HCC [4, 13, 34, 35]. In this study, we analyzed clinical data obtained at the start of follow-up. Time-dependent ROC curves for overall survival were obtained with the Kaplan–Meier method using the Child–Pugh score and ALBI score. We calculated the sensitivity and specificity at each survival time using the maximum Youden index (sensitivity+specificity–1) as the cut-off level [36].

Statistical significance was defined as $p < 0.05$. Statistical analyses were performed with EZR Ver. 1.53 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [37]. More precisely, it is a modified version of the R commander designed to add statistical functions frequently used in biostatistics.

List Of Abbreviations

HCC, hepatocellular carcinoma; ALBI, albumin–bilirubin; mALBI, modified albumin–bilirubin; ROC, receiver operating characteristic; AUROC, area under the receiver operating characteristic curve; HR, hazard ratio; C-index, concordance index; ECOG-PS, Eastern Cooperative Oncology Group performance status; CI, confidence interval.

Declarations

Acknowledgments

Conflicts of interest: The authors declare no conflicts of interest.

Financial support: There was no grant support or other financial support for this study.

Availability of data and material: The datasets are available from the corresponding author on reasonable request.

Authors' contributions:

Concept and study design: Toshifumi Tada and Atsushi Hiraoka

Data acquisition: All authors,

Analyses of the data: Toshifumi Tada

Statistics: Toshifumi Tada,

Supervise: Takashi Kumada,

Preparing manuscript: Toshifumi Tada,

Review and approval: All authors.

Ethics approval: The protocol used in the present study was approved by the Institutional Ethics Committee of Ehime Prefectural Central Hospital (IRB No. 30-66), based on the Guidelines for Clinical Research issued by the Ministry of Health and Welfare of Japan.

Consent to participate: Written informed consent was obtained from each patient.

Consent for publication: Written informed consent was obtained from each patient.

References

1. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet*. 391, 1301-1314 (2018).
2. Kim DY, Han KH. Epidemiology and surveillance of hepatocellular carcinoma. *Liver Cancer*. 1, 2-14 (2012).
3. Nault JC, Galle PR, Marquardt JU. The role of molecular enrichment on future therapies in hepatocellular carcinoma. *Hepatology*. 69, 237-247 (2018).
4. European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *Hepatology*. 56, 908-943 (2012).
5. Llovet JM, et al; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N. Engl. J. Med.* 359, 378-390 (2008).
6. Cheng AL, et al. Safety and efficacy of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol.* 10, 25-34 (2009).
7. Bruix J, et al; RESORCE Investigators. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 389, 56-66 (2017).
8. Finn RS, et al. Outcomes of sequential treatment with sorafenib followed by regorafenib for HCC: Additional analyses from the phase III RESORCE trial. *J. Hepatology*. 69, 353-358 (2018).

9. Zhu AX, et al; REACH-2 study investigators. Ramucirumab after sorafenib in patients with advanced hepatocellular carcinoma and increased α -fetoprotein concentrations (REACH-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 20, 282-296 (2019).
10. Kudo M, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *Lancet.* 391, 1163-1173 (2018).
11. Hiraoka A, et al; Real-life Practice Experts for HCC (RELPEC) Study Group and the HCC 48 Group (hepatocellular carcinoma experts from 48 clinics in Japan). Therapeutic potential of lenvatinib for unresectable hepatocellular carcinoma in clinical practice: Multicenter analysis. *Res.* 49, 111-117 (2019).
12. Hiraoka A, et al; Real-life Practice Experts for HCC (RELPEC) Study Group, HCC 48 Group (hepatocellular carcinoma experts from 48 clinics in Japan); GLSG (Gunma Liver Study Group). Therapeutic efficacy of lenvatinib as third line treatment following regorafenib for unresectable hepatocellular carcinoma progression. *Res.* 2021 Apr 10. doi: 10.1111/hepr.13644. Online ahead of print.
13. Finn RS, et al; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *Engl. J. Med.* 382, 1894-1905 (2020).
14. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *J. Surg.* 60, 646-649 (1973).
15. Johnson PJ, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. *J. Clin. Oncol.* 33, 550-558 (2015).
16. Hiraoka A, et al. Validation and Potential of Albumin-Bilirubin Grade and Prognostication in a Nationwide Survey of 46,681 Hepatocellular Carcinoma Patients in Japan: The Need for a More Detailed Evaluation of Hepatic Function. *Liver Cancer.* 6, 325-336 (2017).
17. Hatanaka T, et al. The Role of the Albumin-Bilirubin Score for Predicting the Outcomes in Japanese Patients with Advanced Hepatocellular Carcinoma Treated with Ramucirumab: A Real-World Study. 99, 203-214 (2021).
18. Chen HY, et al. Predicting outcomes for recurrent hepatocellular carcinoma within Milan criteria after complete radiofrequency ablation. *PLoS One.* 15, e0242113 (2020).
19. Kumada T, Toyoda H, Tada T, Yasuda S, Tanaka J. Changes in Background Liver Function in Patients with Hepatocellular Carcinoma over 30 Years: Comparison of Child-Pugh Classification and Albumin Bilirubin Grade. *Liver Cancer.* 9, 518-528 (2020).
20. Heagerty PJ, Zheng Y. Survival model predictive accuracy and ROC curves. *Biometrics.* 61, 92-105 (2005).
21. Ueshima K, et al. Impact of Baseline ALBI Grade on the Outcomes of Hepatocellular Carcinoma Patients Treated with Lenvatinib: A Multicenter Study. *Cancers (Basel).* 11, 952 (2019).
22. Ando Y, et al. Analysis of Post-Progression Survival in Patients with Unresectable Hepatocellular Carcinoma Treated with Lenvatinib. 98, 787-797 (2020).

23. Hiraoka A, Tanizawa Y, Huang YJ, Cai Z, Sakaguchi S. Association of Albumin-Bilirubin Grade and Sequential Treatment with Standard Systemic Therapies for Advanced Hepatocellular Carcinoma: A Retrospective Cohort Study Using a Japanese Administrative Database. *Drugs Real World Outcomes*. 2021 Apr 1. doi: 10.1007/s40801-021-00245-8. Online ahead of print.
24. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. *Semin Liver Dis*. 19, 329-338 (1999).
25. Marrero JA, et al. Diagnosis, Staging, and Management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 68, 723-750 (2018).
26. Tada T, et al. Impact of albumin-bilirubin grade on survival in patients with hepatocellular carcinoma who received sorafenib: An analysis using time-dependent receiver operating characteristic. *Gastroenterol. Hepatol*. 34, 1066-1073 (2019).
27. Hiraoka A, et al; Real-Life Practice Experts for HCC (RELPEC) Study Group and HCC 48 Group (hepatocellular carcinoma experts from 48 clinics). Albumin-Bilirubin (ALBI) Grade as Part of the Evidence-Based Clinical Practice Guideline for HCC of the Japan Society of Hepatology: A Comparison with the Liver Damage and Child-Pugh Classifications. *Liver Cancer*. 6, 204-215 (2017).
28. Liver Cancer Study Group of Japan: The General Rules for the Clinical and Pathological Study of Primary Liver Cancer, ed 6. Tokyo, Kanehara (2015).
29. Bruix J, Sherman M. Management of hepatocellular carcinoma. *Hepatology*. 42, 1208-1236 (2005).
30. Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology*. 53, 1020-1022 (2011).
31. Kudo M, et al; Liver Cancer Study Group of Japan. JSH Consensus-Based Clinical Practice Guidelines for the Management of Hepatocellular Carcinoma: 2014 Update by the Liver Cancer Study Group of Japan. *Liver Cancer*. 3, 458-468 (2014).
32. Kokudo N, et al. Evidence-based Clinical Practice Guidelines for Hepatocellular Carcinoma: The Japan Society of Hepatology 2013 update (3rd JSH-HCC Guidelines). *Hepatol. Res*. 2015; 45. doi: 10.1111/hepr.12464.
33. National Cancer Institute, Protocol Development Cancer Therapy. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm-ctc_40. Accessed April 1, 2021.
34. Kaibori M, et al; Liver Cancer Study Group of Japan. Impact of Advanced Age on Survival in Patients Undergoing Resection of Hepatocellular Carcinoma: Report of a Japanese Nationwide Survey. *Surg*. 269, 692-699 (2019).
35. Tada T, et al. Neutrophil-to-lymphocyte ratio is associated with survival in patients with unresectable hepatocellular carcinoma treated with lenvatinib. *Liver Int*. 40, 968-976 (2020).
36. Youden W. J. Index for rating diagnostic tests. *Cancer*. 3, 32-35 (1950).
37. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant*. 48, 452-458 (2013).

Figures

Figure 1

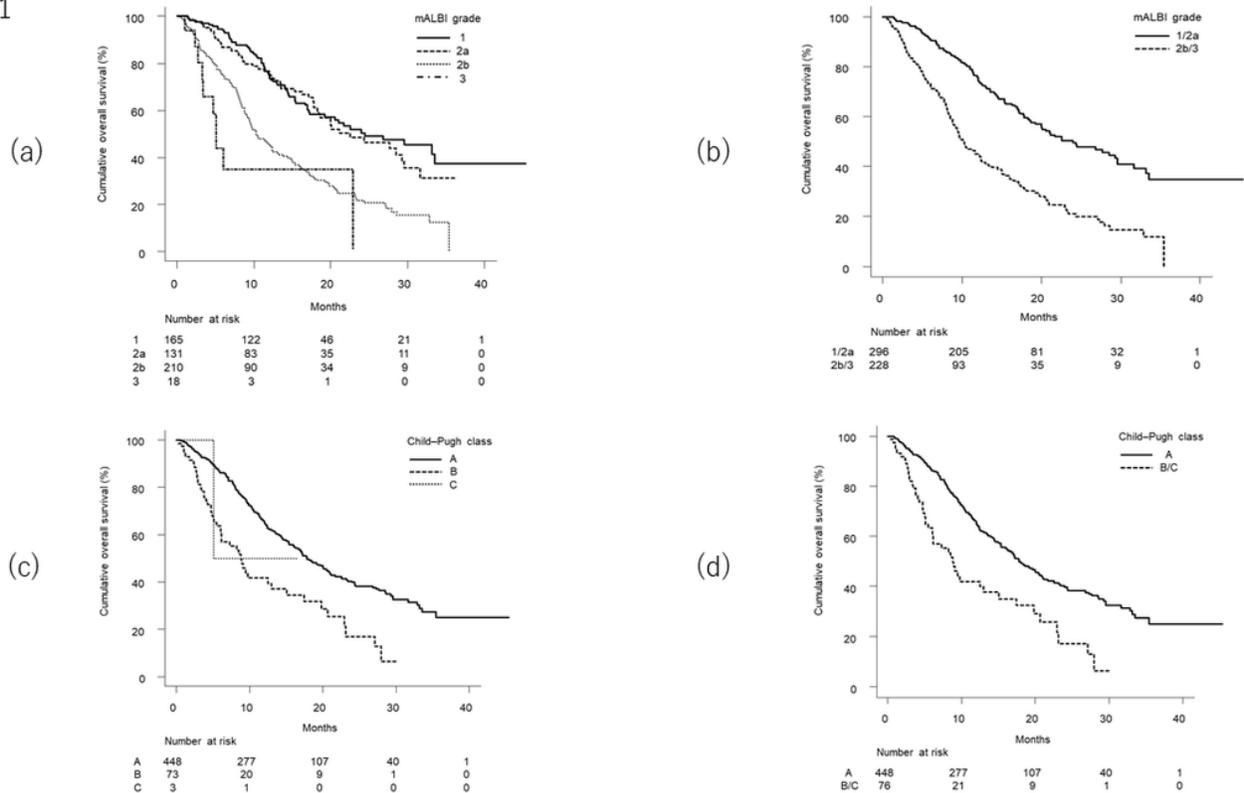


Figure 1

Cumulative survival curves for all study patients a: By mALBI grade There was a significant difference in cumulative overall survival among patients grouped by mALBI grade ($p < 0.001$). The median survival times of patients with mALBI grades 1, 2a, 2b, and 3 were 24.4 (95%CI, 17.2– not available), 22.5 (95%CI, 18.3–29.5), 10.3 (95%CI, 9.1–12.5), and 5.1 (95%CI, 3.3– not available) months, respectively. Multiple comparisons between mALBI grades 1 and 2a, 1 and 2b, 1 and 3, 2a and 2b, 2a and 3, and 2b and 3 demonstrated p values of 1.000, < 0.001 , < 0.001 , < 0.001 , < 0.001 , and 0.654, respectively. b: By mALBI grade divided into 1/2a and 2b/3 There was a significant difference in cumulative overall survival between patients with mALBI grades 1/2a and 2b/3 ($p < 0.001$). The median survival times in patients with mALBI grades 1/2a and 2b/3 were 23.9 (95%CI, 20.0–29.5) and 10.1 (95%CI, 8.9–12.4) months, respectively. c: By Child–Pugh classification There was a significant difference in cumulative overall survival among patients stratified by Child–Pugh classification ($p < 0.001$). The median survival times in patients with Child–Pugh classes A, B, and C were 17.8 (95%CI, 16.0–20.8), 8.8 (95%CI, 6.0–12.9), and 5.1 (95%CI, 5.1– not available) months, respectively. Multiple comparisons between Child–Pugh classes A and B, A and C, and B and C demonstrated p values of < 0.001 , 1.000, and 1.000, respectively. d: By Child–Pugh classification divided into A and B/C There was a significant difference in cumulative overall survival between patients with Child–Pugh classes A and B/C ($p < 0.001$). The median survival times in patients with Child–Pugh classes A and B/C were 17.8 (95%CI, 16.0–20.8) and 8.8 (95%CI, 6.0–15.0) months, respectively. mALBI, modified albumin–bilirubin; CI, confidence interval.

Figure 2

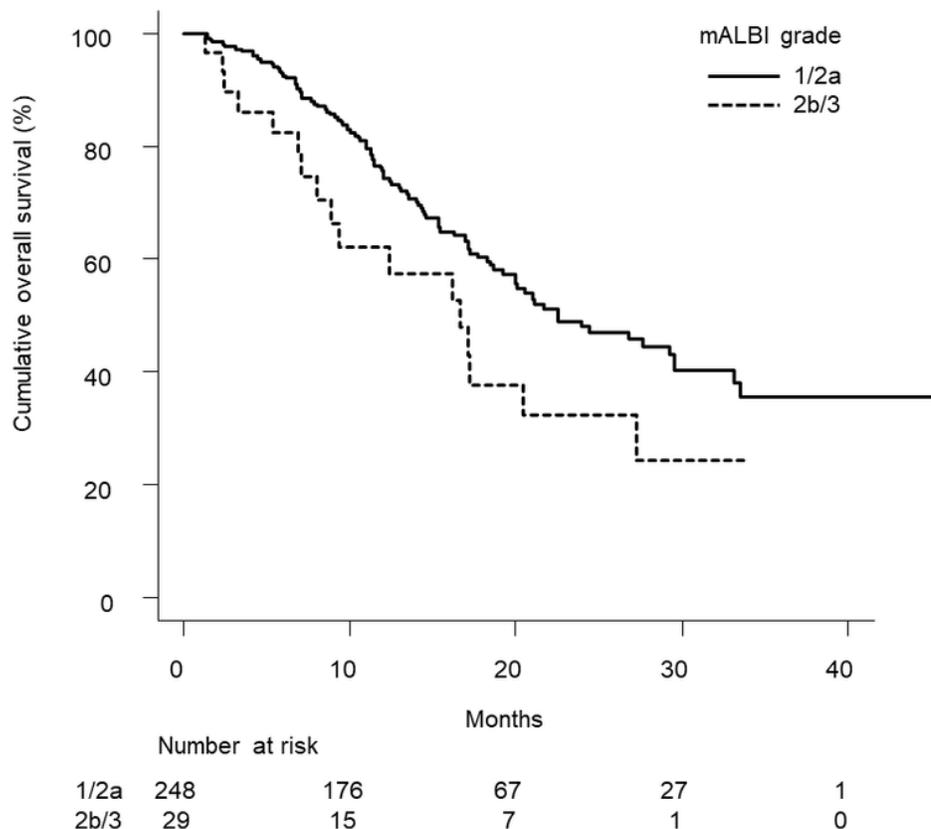


Figure 2

Cumulative survival curves in patients with Child–Pugh score of 5. There was a significant difference in cumulative overall survival between patients with mALBI grades 1/2a and 2b/3 ($p=0.032$). The median survival times in patients with mALBI grades 1/2a and 2b/3 were 22.5 (95%CI, 19.2–29.5) and 16.6 (95%CI, 8.0–27.3) months, respectively.

Figure 3

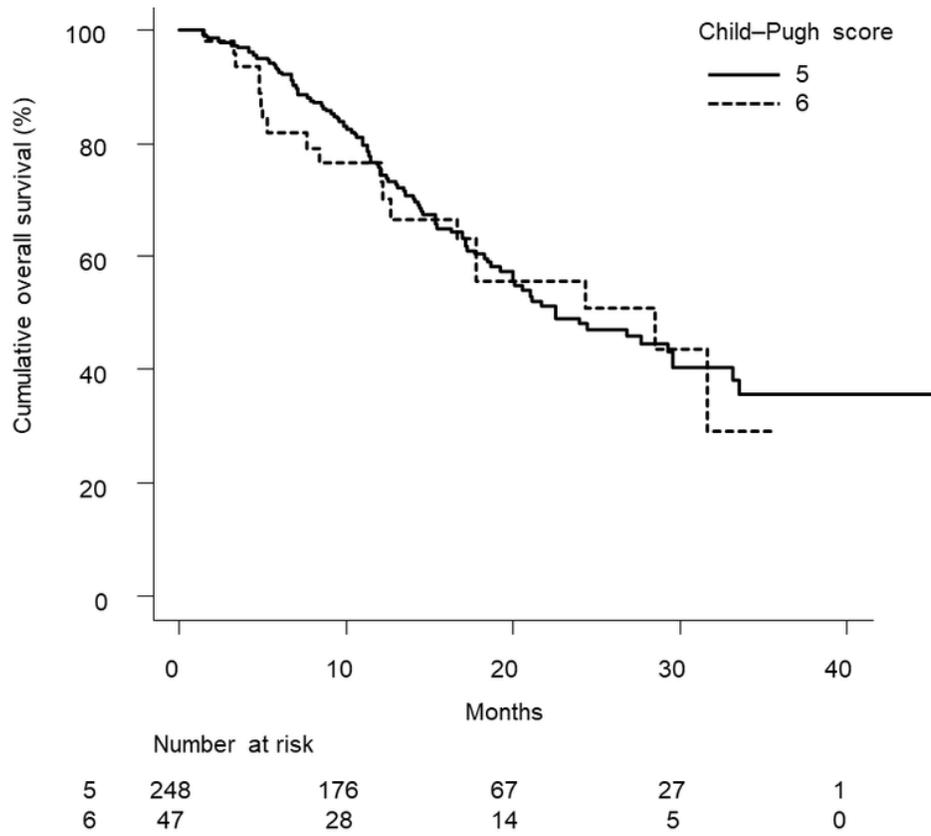


Figure 3

Cumulative survival curves in patients with mALBI grade 1/2a and Child-Pugh class A There was no difference in cumulative overall survival between patients with mALBI grade 1/2a and Child-Pugh classes 5 and 6 ($p=0.735$). The median survival times in patients with mALBI grade 1/2a and Child-Pugh classes 5 and 6 were 22.5 (95%CI, 19.2–29.5) and 28.5 (95%CI, 12.7– not available) months, respectively. mALBI, modified albumin–bilirubin

Figure 4

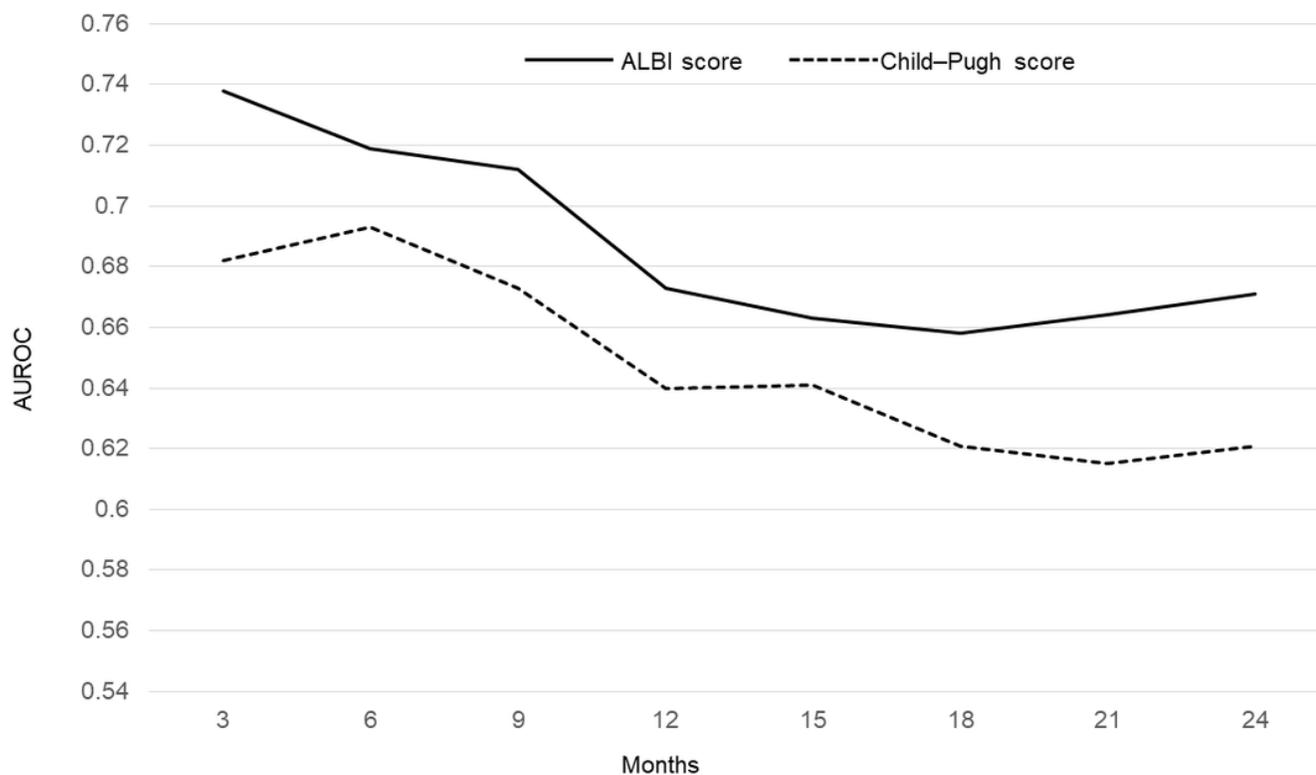


Figure 4

Time-dependent AUROCs of the ALBI and Child-Pugh scores for overall survival after the start of follow-up Based on time-dependent ROC analysis, the AUROCs of the ALBI and Child-Pugh scores for overall survival at 3, 6, 9, 12, 15, 18, 21, and 24 months were 0.738 and 0.682, 0.719 and 0.693, 0.712 and 0.673, 0.673 and 0.640, 0.663 and 0.641, 0.658 and 0.621, 0.664 and 0.615, and 0.671 and 0.621, respectively. Based on time-dependent AUROCs, the ALBI score had a higher predictive power for overall survival than the Child-Pugh score. AUROC, area under the receiver operating characteristic curve; ALBI, albumin-bilirubin.