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EZ-ALBI score as a new prognostic predictor in hepatocellular carcinoma

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Abstract

Background: Liver functional reserve is a major prognostic determinant in patients with hepatocellular carcinoma (HCC). The albumin-bilirubin (ALBI) score is an objective method to assess the severity of cirrhosis in this setting. However, the calculation of ALBI score is complex and difficult to access in clinical practice. Recently, the EZ (easy)-ALBI score was proposed as an alternative biomarker of liver injury. We aimed to evaluate the prognostic role of EZ-ALBI score in HCC from early to advanced stages.

Methods: A total of 3,794 newly diagnosed HCC patients were prospectively enrolled and retrospectively analyzed. Independent prognostic predictors were determined by using the multivariate Cox proportional hazards model.

Results: The EZ-ALBI score showed good correlation with ALBI score (correlation coefficient: 0.965, $p< 0.001$). The correlation of EZ-ALBI score was highly preserved in different Child-Turcotte-Pugh (CTP) classification, treatment modality, and BCLC stage (correlation coefficients: 0.90-0.97). In the Cox multivariate analysis, age > 65 years, male, serum α-fetoprotein > 20 ng/mL, large or multiple tumors, total tumor volume > 100 cm^3, vascular invasion or distant metastasis, ascites, poor performance status, EZ-ALBI grade 2 and 3, and non-curative treatments were independently associated with increased mortality (all $p< 0.05$). Moreover, EZ-ALBI grade can stratify long-term survival in patients with different CTP class, treatment strategy and BCLC stage.

Conclusions: The EZ-ALBI score is an easy and feasible method to evaluate liver functional reserve. As a new prognostic biomarker in HCC, the predictive power of EZ-ALBI grade is independent across different cancer stage and treatment modality.

Key words: EZ-ALBI score; hepatocellular carcinoma; prognosis

Introduction

Hepatocellular carcinoma (HCC) is the most common liver malignancy and the fourth leading cause of cancer-associated death worldwide in 2018, with the highest incidence in Southeast Asia and sub-Saharan Africa.[1] Chronic hepatitis B and C virus (HBV, HCV) infection, alcohol and metabolic liver disease are main etiologies of HCC.[2, 3] According to American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) HCC practice guidelines, curative treatments such as surgical resection, liver transplantation and radiofrequency ablation were recommended for early stage HCC with good liver function.[4, 5] For unresectable or advanced stage HCC, transarterial chemoembolization (TACE) and systemic therapy (including targeted/immunotherapy) are major treatment options.[4, 6, 7]

The management and prognosis of HCC largely depend on tumor burden and liver functional reserve.[8] Traditionally, the Child-Turcotte-Pugh (CTP) score, including serum albumin, bilirubin, international normalized ratio (INR) of prothrombin time (PT), ascites and hepatic encephalopathy, are utilized to assess the severity of liver dysfunction. The CTP score has limitations because some variables are interrelated and the cut-off values of the parameters are arbitrarily defined.[9, 10] Alternatively, the albumin-bilirubin (ALBI) score, which is based only on serum albumin and bilirubin, was proposed to assess liver reserve in HCC patients.[11] In this regard, several other noninvasive liver reserve models, such as aspartate aminotransferase-to-platelet ratio (APRI), cirrhosis discriminant index (CDS), Child-Turcotte-Pugh (CTP), fibrosis index based on 4 factors (FIB-4), Göteborg University Cirrhosis Index (GUCI), Lok index, model for end-stage liver disease (MELD) and King's score, have also been proposed to assess liver dysfunctions.[12] Notably, the ALBI score is a more objective tool to evaluate liver reserve and has been validated by independent research groups,[11, 13-17] but a major shortcoming of the score is the complexity of calculation.

More recently, Kariyama and colleagues introduced EZ(easy)-ALBI score which is a

new prognostic model to evaluate liver functional reserve in more than 5,000 Japanese patients from 8 collaborating hospitals. The development of EZ-ALBI score is primarily based on the regression coefficients of serum albumin and bilirubin levels by using multivariate Cox proportional hazards model. They showed that the EZ-ALBI score is a feasible prognostic model to evaluate liver dysfunction in HCC.[18] However, the prognostic role of EZ-ALBI score has not been validated in other centers. In this study, we aimed to assess the role of EZ-ALBI score as a potentially new prognostic biomarker in HCC.

METHODS

Patients

A total of 3,794 prospectively identified, newly diagnosed HCC patients in Taipei Veterans General Hospital were retrospectively analyzed in this study. Their baseline characteristics, clinical information and staging were collected at the time of diagnosis. This study was approved by the Institutional Review Board (IRB) of Taipei Veterans General Hospital and complies with the standards of Declaration of Helsinki and current ethical guidelines. Informed consent was waived by the IRB due to retrospective nature of this study. Patients were followed up every 3 to 6 months until death or drop-out from the follow-up program.

Diagnosis

The diagnosis of HCC was through the detection of typical imaging findings (early arterial enhancement in arterial phase and delayed wash-out in portal venous phase) by contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI), or confirmed by pathology if the image finding was not typical.[4, 8] Performance status was evaluated by the Eastern Cooperative Oncology Group of performance scale.[19] Vascular invasion was denoted as radiological evidence of tumor invasion to intrahepatic vasculature, portal trunk or inferior vena cava.[20] Distant metastasis such as lung, bone, lymph was diagnosed by CT, MRI or bone scan.[21] The calculation and equation of noninvasive liver reserve models such as APRI, CDS,

FIB-4, GUCI, Lok index, MELD, King's score have been prescribed in detail in our previous study.[12]

Albumin-bilirubin (ALBI) score and grading

The ALBI score is calculated using the following equation as previously defined:[11, 13, 22]

ALBI score= 0.66 x $\log_{10}$ bilirubin (umol/L)-0.085 x albumin (g/L)

ALBI grade was defined as ALBI grade 1 (score ≤ -2.60), grade 2 (score > -2.60 and ≤ -1.39), and grade 3 (score > -1.39).

EZ (easy)-ALBI score and grading

The formula for EZ-ALBI score is as follows:[18]

EZ-ALBI score = Total bilirubin (mg/dL) – (9 × albumin (g/dL))

The EZ-ALBI grade was classified into 3 groups as previously defined:

Grade 1 (score ≤ -34.4), grade 2 (score between -34.4 and -22.2) and grade 3 (score ≥ -22.2)

Statistics

The categorical variables were analyzed by the Chi-squared test or Fisher exact test. The comparison of continuous variables was assessed by the Mann-Whitney U test. The overall survival was evaluated by Kaplan-Meier analysis with log-rank test. Factors that were possibly associated with survival were analyzed in the univariate survival analysis. Multivariate Cox proportional hazards model was used to identify independent prognostic predictors and the adjusted hazard ratio (HR) with 95% confidence interval (CI).

The discriminatory ability of different models to predict survival was examined by using the Cox proportional hazards model, and the consequences of the Cox model were expressed with the corrected Akaike information criterion (AICc), which reveals how the model affects the dependent variable (patient survival) and represents an overall assessment of the model.[23, 24] The lower the AIC, the more explanatory and informative the model is.[25] A p value < 0.05

was considered statistically significant. All statistical analyses were performed by using the IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient characteristics

The baseline characteristics of the 3,794 patients and their comprehensive clinical data are summarized in Table 1. The mean age was 65 years, and patients were predominantly (76%) male. HBV and HCV were the main etiologies of HCC. Of all, 64% of patients had single tumor and 65% of patients had tumor diameter larger than 3 cm. Vascular invasion or distant metastasis occurred in 27% of patients. The majority (73%) of patients belonged to CTP class A, and 37% were EZ-ALBI grade 1, 54% were grade 2, and 9% were grade 3. About half (48%) of patients received curative treatments such as surgical resection, liver transplantation and percutaneous ablation, and others (52%) received non-curative treatments including TACE, chemotherapy, targeted or immuno-therapy, and best supportive care as their primary therapy.

The prognostic performance of the 10 noninvasive liver reserve models for HCC was analyzed (Table 2). Among these models, ALBI and EZ-ALBI ranked the first two highest homogeneity along with the lowest AICc, suggesting a better prognostic performance of these two models; the difference of the AICc between ALBI (41218.535) and EZ-ALBI (41224.867) score was small.

Correlation of ALBI and EZ-ALBI score

The correlation coefficient between the ALBI and EZ-ALBI score was 0.965 (95% CI: 0.957-972, $p< 0.001$) for all patients (Figure 1). In subgroup analysis of CTP class A and class B/C patients, the correlation coefficient between ALBI score and EZ-ALBI score were 0.970 and 0.907, respectively. When stratified by treatment modality, the correlation coefficient among those undergoing curative and non-curative treatments were 0.98 and 0.953,

respectively. According to the Barcelona Clinic Liver Cancer (BCLC) stage, the correlation coefficient for BCLC stage 0/A and stage B/C/D patients were 0.97 and 0.961, respectively; the coefficient for subgroup patients with total bilirubin < 3 mg/dL and > 3mg/dL were 0.982 and 0.853, respectively.

Survival of patients based on ALBI grade

The medium overall survival (OS) was 65 (95% CI: 58.3-71.6) months, 19 (95% CI: 16.9-21.1) months, and 3 (95% CI: 2.4-3.6) months for ALBI grade 1, 2 and 3, respectively. The 1-, 3-, 5-year OS rates were 85%, 65%, 52% for ALBI grade 1, 60%, 37%, 25% for ALBI grade 2, and 26%, 12%, 9% for ALBI grade 3 patients, respectively.

Survival of patients according to EZ-ALBI grade

The survival distribution of all study patients according to EZ-ALBI grade is shown in Figure 2. The medium OS was 65 (95% CI: 58.5-71.5) months, 19 (95% CI: 16.9 -21.1) months, and 3 (95% CI: 2.4-3.6) months for EZ-ALBI grade 1, 2 and 3 patients, respectively. The 1-, 3-, 5-year OS rates were 85%, 66% and 52% for EZ-ALBI grade 1, 60%, 37% and 25% for EZ-ALBI grade 2, and 24%, 11% and 9% or EZ-ALBI grade 3 patients, respectively.

In subgroup analysis for CTP class A patients, the medium OS was 65 (95% CI: 58.4-71.5) months for EZ-ALBI grade 1, and 28 (95% CI: 24.7-31.3) months for grade 2-3 patients, respectively. The 1-, 3-, 5-year OS rates were 85%, 66%, 52% for EZ-ALBI grade 1, and 69%, 45%, 30% for grade 2-3 patients, respectively ($p< 0.001$, Figure 3A). For CTP class B or C patients, the medium OS rates were 31 (95% CI: 0-93.6) months, 6 (95% CI: 4.5-7.5) months, and 3 (95% CI: 2.4-3.6) months for EZ-ALBI grade 1, 2 and 3 patients, respectively. There 1-, 3-, 5- years OS rates were 75%, 50%, 19% for EZ-ALBI grade 1, 41%, 21%, 13% for grade 2, and 24%, 11%, and 8% for grade 3 patients, respectively ($p<0.001$, Figure 3B).

The analysis of HCC patients was further stratified by treatment modality. For patients undergoing curative treatments, the medium OS was 98 (95% CI: 88.8-107.2) months, 55

(95% CI: 50.2-60) months, and 17 (95% CI: 5.2-26.7) months for EZ-ALBI grade 1, 2 and 3 patients, respectively. The 1-, 3-, 5-years OS rates were 93%, 78%, 65% for EZ-ALBI grade 1, 85%, 64%, 46% for grade 2, and 59%, 35%, 30% for grade 3 patients, respectively ($p< 0.001$, Figure 4A). For non-curative treatments, the medium OS was 25 (95% CI: 20.4-30) months, 8 (95% CI: 7.0-9.0) months, and 2 (95% CI: 1.5-2.5) months for EZ-ALBI grade 1, 2 and 3 patients, respectively. The 1-, 3-, 5-year OS rates were 70%, 42%, 27% for EZ-ALBI grade 1, 42%, 19%, 10% for grade 2, and 17%, 6%, 4% for grade 3 patients, respectively ($p< 0.001$, Figure 4B).

When the analysis was stratified for BCLC stage 0/A patients, the medium OS was 104 (95% CI: 93-114.9) and 62 (95% CI: 56.9-67.1) months for EZ-ALBI grade 1 and grade 2-3 patients, respectively. The 1-, 3-, 5-year OS rates were 96%, 81%, 70% for EZ-ALBI grade 1, and 92%, 69%, 51% for grade 2-3 patients, respectively ($p< 0.001$, Figure 5A). For BCLC stage B/C/D patients, the medium OS rates were 41 (95% CI: 35.5 -46.5) months, 10 (95% CI: 8.7-11.3) months, and 3 (95% CI: 2.5-3.5) months for EZ-ALBI grade 1, 2 and 3 patients, respectively. The 1-, 3-, 5-year OS rates were 77%, 53%, 38% for EZ-ALBI grade 1, 47%, 24%, 14% for grade 2, and 20%, 9%, 7% for grade 3 patients, respectively ($p< 0.001$, Figure 5B).

Cox multivariate survival analysis

In univariate analysis, age, gender, serum albumin, bilirubin, ALT, platelet count, INR of PT, serum AFP, tumor size, tumor nodules, total tumor volume (TTV), vascular invasion or distant metastasis, ascites, performance status, EZ-ALBI grade and non-curative treatment were associated with a decreased survival. In Cox multivariate proportional hazards model, age > 65 years (HR: 1.281, 95% CI: 1.281-1.385, $p< 0.001$), male (HR: 1.144, 95% CI: 1.044-1.253, $p=0.004$), serum AFP > 20 ng/mL (HR: 1.591, 95% CI: 1.466-1.727, $p< 0.001$), tumor size > 3 cm (HR: 1.414, 95% CI: 1.-1.253, $p< 0.001$), multiple tumors (HR: 1.085, 95% CI: 1.002-1.174, $p=0.016$), TTV > 100 cm^3 (HR:1.413, 95% CI: 1.276-1.566, $p< 0.001$),

vascular invasion or distant metastasis (HR: 2.268, 95% CI: 2.067-2.488, p< 0.001), ascites (HR: 1.458, 95% CI: 1.325-1.605, p< 0.001), performance status 1 (HR: 1.215, 95% CI: 1.098-1.344, p< 0.001), performance status 2-4 (HR: 1..678, 95% CI: 1.509-1.867, p< 0.001), EZ-ALBI grade 2 (HR: 1.600, 95% CI: 1.464-1.748, p< 0.001), EZ-ALBI grade 3 (HR: 2.407, 95% CI: 2.080-2.784, p< 0.001) and non-curative treatments (HR: 2.059, 95% CI: 1.882-2.253, p< 0.001) were independent predictors associated with increased mortality (Table 3).

Multivariate analysis in different subgroups

In subgroup analysis of CTP class A patients, those with EZ-ALBI grade 2-3 had a worse survival compared with grade 1 patients in multivariate analysis (HR: 1.596, 95% CI: 1.450-1.758, p< 0.001). In CTP class B/C patients, multivariate analysis revealed that EZ-ALBI grade 2 (HR: 2.024, 95% CI: 1.186-3.456, p< 0.001) and grade 3 (HR: 2.609, 95% CI: 1.515-4.492, p< 0.001) was associated with an increased risk of mortality.

For patients undergoing curative treatment, EZ-ALBI grade 2 (HR: 1.563, 95% CI: 1.371-1.781, p< 0.001) and grade 3 (HR: 2.370, 95% CI: 1.704-3.294, p< 0.001) predicted an increased risk of mortality in multivariate analysis. In non-curative treatment group, EZ-ALBI grade 2 (HR: 1.597, 95% CI: 1.415-1.802, p< 0.001) and grade 3 patients (HR: 2.371, 95% CI: 1.995-2.819, p< 0.001) had a decreased long-term survival.

In subgroup analysis of BCLC stage O/A patients, EZ-ALBI grade 2-3 patients had an increased mortality risk compared with grade 1 patients (HR: 1.781, 95% CI: 1.525-2.079, p< 0.001). For BCLC stage B/C/D patients, EZ-ALBI grade 2 (HR: 2.060, 95% CI: 1.861-2.280, p< 0.001) and grade 3 (HR: 4.055, 95% CI: 3.508-4.686, p< 0.001) predicted a decreased survival (Table 4).

DISCUSSION

Liver functional reserve plays a crucial role in the management of HCC.[26] Our results show

that EZ-ALBI score, a simplified and updated version of the ALBI score, is closely correlated with the original version in different clinical scenarios. Importantly, the EZ-ALBI grade can adequately stratify the survival in HCC patients from early to far-advanced stage. In addition, the EZ-ALBI grade is an independent prognostic predictor in both entire cohort and variable clinical entities including different CTP classification, treatment modality and BCLC stage. Consistent with a previous study,[18] our study suggests that EZ-ALBI score is a new model to evaluate the severity of liver dysfunction in HCC patients.

Kariyama *et al*. proposed EZ-ALBI score to assess liver dysfunction in HCC patients in Japan.[18] The correlation coefficient of EZ-ALBI and ALBI score was high as 0.981. This trend was well preserved across different BCLC stages (regression coefficient, 0.93-0.98) and different hospitals (regression coefficient, 0.98-0.99). In our study, the correlation coefficient of EZ-ALBI and ALBI score was consistently high (0.965), and was highly preserved in different CTP classification (coefficient: 0.90-0.97), treatment modality (coefficient: 0.95-0.98), and BCLC stage (coefficient: 0.96-0.97). More importantly, the EZ-ALBI score can accurately stratify long-term survival in patients with different clinical scenarios. Our data confirm that the EZ-ALBI score is a feasible prognostic model to evaluate the severity of liver dysfunction in HCC.

A high linear correlation between EZ-ALBI and ALBI score was observed in the entire cohort and different subgroups. Notably, the EZ-ALBI score may outperform ALBI score in several reasons. First, the calculation of the EZ-ALBI score is much easier compared with ALBI score which is difficult to estimate due to the complexity of formula. Second, EZ-ALBI score maintains fairly good prognostic performance in discriminating long-term survival in HCC patients. Third, the EZ-ALBI score is a more friendly and readily available surrogate marker to assess liver dysfunction at bedside in daily practice. These features make EZ-ALBI grade a feasible prognostic biomarker for HCC. Furthermore, although there are multiple cancer staging systems nowadays for HCC,[27-29] most models are based on CTP

classification to indicate the degree of liver dysfunction. An EZ-ALBI grade-based prognostic model should be considered to better reflect the outcome of HCC patients across all cancer stages.

In multivariate Cox analysis, EZ-ALBI grade 2 and grade 3 patients were associated with 1.6- to 2.4-fold increased risk of mortality compared with grade 1 patients, suggesting EZ-ALBI can stratify patients into different risk groups. In addition, tumor-related parameters such as tumor size, number, vascular invasion or distant metastasis are all independent prognostic factors in the Cox model in our study. These results are mostly consistent with previous studies.[20, 21, 30] In addition, patients with poor performance status had a decreased overall survival. Taken together, along with tumor burden and performance status, we show that the assessment of EZ-ALBI grade is a crucial step in the management of HCC.

There are a few limitations in this study. First, more than half of our patients had chronic hepatitis B infection. This feature is quite different from Western countries where chronic hepatitis C is the main etiology of HCC. Second, the study design is retrospective in nature and the selection bias cannot be completely avoided. Third, since this is a single center study at a tertiary referral hospital, the prognostic role of EZ-ALBI grade requires external validation from independent research groups.

In conclusion, our results show that EZ-ALBI score, a feasible and easy-to-use method to evaluate liver functional reserve, can discriminate survival in HCC patients from early to advanced stage. The EZ-ALBI score could thus potentially replace ALBI score in clinical practice. As a new prognostic biomarker in HCC, the predictive power of EZ-ALBI grade is independent of the severity of cirrhosis, cancer stage and treatment modality. An EZ-ALBI grade-based prognostic model should be considered to better stage the outcome of these patients. Further studies are required for confirmation.

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Figure legend

Figure 1. The correlation between EZ(easy)-ALBI and ALBI score. There is good linear correlation between EZ-ALBI and ALBI score.

Figure 2. Kaplan-Meier survival analysis of patients according to EZ-ALBI grade. Patients with EZ-ALBI grade 1 had better overall survival than EZ-ALBI grade 2 and grade 3 patients ($p < 0.001$).

Figure 3. Kaplan-Meier survival analysis according to EZ-ALBI grade in (A) Child-Turcotte-Pugh classification (CTP) A patients (B) CTP class B/C patients. Patients with higher EZ-ALBI grade had decreased overall survival in CTP class A ($p<0.001$) and class B/C patients ($p<0.001$).

Figure 4. Kaplan-Meier survival analysis according to EZ-ALBI grade in patients undergoing (A) curative treatments (B) non-curative treatments. Patients with higher EZ-ALBI grade had increased mortality rate in both curative and non-curative treatment group (both $p< 0.001$).

Figure 5. Kaplan-Meier survival analysis according to EZ-ALBI grade in (A) BCLC stage 0/A patients (B) BCLC stage B/C/D patients. There was significant overall survival difference between different EZ-ALBI grade in early ($p<0.001$) and intermediate-advanced stage patients ($p<0.001$).

Table 1. Baseline characteristics of hepatocellular carcinoma patients (n=3794)

Variables	All patients
Age (years, mean±SD)	65±13
Male/Female, n (%)	2895/899 (76/24)
Etiologies of liver disease	
HBV, n (%)	1513 (40)
HCV, n (%)	824 (21)
HBV+HCV, n (%)	135 (4)
Others, n (%)	1322 (35)
Laboratory values (mean±SD)	
Albumin (g/dl)	3.7±0.6
Bilirubin (mg/dl)	1.5±2.8
ALT (IU/L)	70±92
Creatinine (mg/dL)	1.1±1.0
Sodium (mmol/L)	138±4
INR of PT	1.1±0.2
Platelet (1000 ul/L)	170±96
AFP (ng/mL) Median [IQR]	44 [8-806]
Tumor nodules (single/multiple), n (%)	2437/1357 (64/36)
Tumor size, Mean ±SD	6.0±4.5
Tumor size > 3 cm, n (%)	2447 (65)
Vascular invasion or distant metastasis n (%)	1038 (27)
Ascites, n (%)	861 (23)
DM, n (%)	972 (26)
CTP class (A/B/C), n (%)	2787/831/176 (73/22/5)
CTP score (mean±SD)	6.0±1.5
ALBI score (mean±SD)	-2.30±0.65
ALBI grade (1/2/3), n (%)	1444/1970/380 (38/52/10)
EZ-ALBI score (mean±SD)	-31.31±7.0
EZ-ALBI grade (1/2/3)	1411/2038/345 (37/54/9)
Performance status (0/1/2/3-4), n (%)	2226/780/431/357 (59/21/11/9)
BCLC (0/A/B/C/D), n (%)	295/932/640/1504/423 (8/25/16/40/11)
Treatment	
Surgical resection	1107 (29)
Liver transplantation	20 (1)
Percutaneous ablation	680 (18)
TACE	1034 (27)
Chemotherapy or targeted therapy	303 (8)
Best supportive care	896 (17)

Abbreviations: ALBI, albumin-bilirubin; ALT, alanine aminotransferase; AST, aspartate aminotransferase;

AFP, α-fetoprotein; BCLC, Barcelona clinic liver cancer; CTP, Child-Turcotte-Pugh; DM, diabetes mellitus; EZ-ALBI, easy- albumin-bilirubin ; INR of PT, international normalized ration of prothrombin time; HBV, hepatitis B virus; HCV, hepatitis C virus; TACE, transarterial chemoembolization; SD, standard deviation

Table 2. Prognostic performance of noninvasive liver reserve models in 3794 HCC patients

	Homogeneity (Wald $\chi 2$)	Corrected Akaike information criteria (AICc)
ALBI	593.295	41218.535
APRI	189.181	41622.648
CDS	28.797	41783.032
CTP	565.506	41246.323
EZ-ALBI	586.962	41224.867
FIB-4	183.909	41627.920
GUCI	189.215	41622.615
King's score	187.975	41623.855
Lok index	336.527	41475.302
MELD	374.513	41437.317

ALBI, albumin-bilirubin; APRI, Aspartate aminotransferase-to- platelet ratio; CDS, cirrhosis discriminant index; CTP, Child-Turcotte-Pugh; EZ-ALBI, easy-albumin-bilirubin; FIB-4, fibrosis index based on 4 factors; GUCI, Göteborg University Cirrhosis Index; MELD, model for end-stage liver disease.

Table 3. Univariate and multivariate survival analysis of HCC patients (n=3794)

		Univariate analysis			Multivariate analysis		
Overall survival	Number	3-year survival (%)	5-year survival (%)	*p*	HR	CI	*p*
Age (≦65/>65 years)	1880/1914	48/43	38/29	<0.001	1.281	1.185-1.385	<0.001
Sex (male/female)	2895/899	44/50	32/37	0.004	1.144	1.044-1.253	0.004
Albumin level (≥3.5/<3.5g/dL)	2468/1326	57/24	43/16	<0.001			
Bilirubin level (≦1.1/>1.1mg/dL)	2453/1341	54/30	40/21	<0.001			
ALT (≦40/>40 IU/L)	1604/2190	49/43	38/30	<0.001			
Platelet (≥150,000/<150,000/μL)	1961/1833	41/50	31/36	<0.001			
INR of PT (≦1.1/>1.1)	2467/1326	53/31	40/22	<0.001			
AFP (≦20/>20 ng/mL)	1539/2255	62/34	48/24	<0.001	1.591	1.466-1.727	<0.001
Tumor size (≦3cm/>3cm)	1347/2447	68/33	51/24	<0.001	1.414	1.290-1.549	<0.001
Tumor nodules (single/multiple)	2437/1357	50/36	39/23	<0.001	1.085	1.002-1.174	0.016
TTV (≦100/>100 cm^3)	269/331	58/22	46/15	<0.001	1.413	1.276-1.566	<0.001
Vascular invasion or distant metastasis	2756/1038	58/12	43/7	<0.001	2.268	2.067-2.488	<0.001
Ascites (no/yes)	2933/861	53/19	39/13	<0.001	1.458	1.325-1.605	<0.001
Performance status							
0	2226	60	46		1		

1	780	33	23	<0.001	1.215	1.098-1.344	<0.001
2-4	788	12	9	<0.001	1.678	1.509-1.867	<0.001
EZ-ALBI grade							
Grade 1	1411	66	52		1		
Grade 2	2038	37	25	<0.001	1.600	1.464-1.748	<0.001
Grade 3	345	11	9	<0.001	2.407	2.080-2.784	<0.001
Curative/non-curative treatments	1807/1987	70/22	55/13	<0.001	2.059	1.882-2.253	<0.001

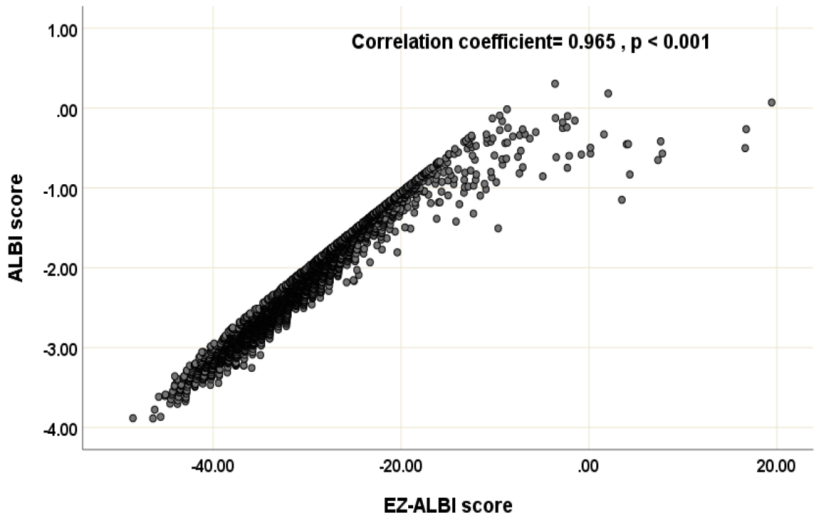
The forepart of the parentheses was set as the reference group in the univariate and multivariate analysis.

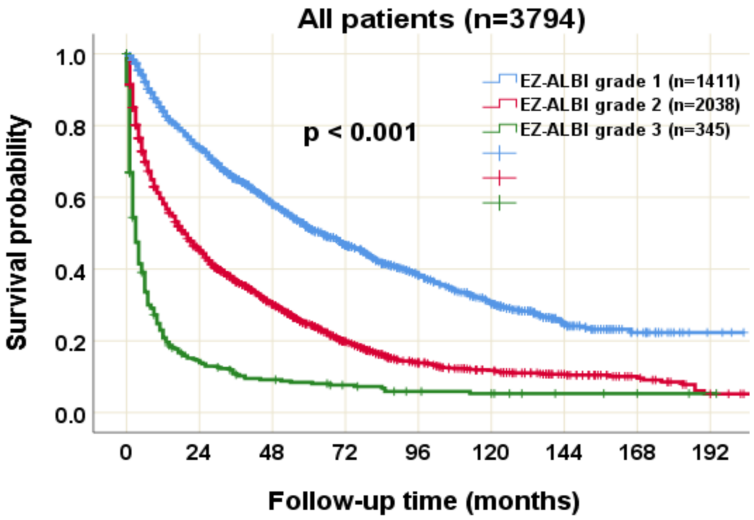
Abbreviations: AFP, α-fetoprotein; ALBI, albumin-bilirubin; ALT, alanine aminotransferase; INR of PT, international normalized ratio of prothrombin time, EZ-ALBI, easy-albumin-bilirubin

Table 4. Multivariate analysis of EZ-ALBI-based survival risk according to CTP classification, treatments and BCLC stage

		mutivariate analysis		
	Number	HR	CI	*p*
CTP A (n=2787)				
EZ-ALBI grade 1	1391	1		
EZ-ALBI grade 2-3	1396	1.596	1.450-1.758	<0.001
CTP B-C (n=1007)				
EZ-ALBI grade 1	482	1		
EZ-ALBI grade 2	1216	2.024	1.186-3.456	0.010
EZ-ALBI grade 3	289	2.609	1.515-4.492	0.001
Curative treatments (n=1807)				
EZ-ALBI grade 1	929	1		
EZ-ALBI grade 2	822	1.563	1.371-1.781	<0.001
EZ-ALBI grade 3	56	2.370	1.704-3.294	<0.001
Non-curative treatments (n=1987)				
EZ-ALBI grade 1	482	1		
EZ-ALBI grade 2	1216	1.597	1.415-1.802	<0.001
EZ-ALBI grade 3	289	2.371	1.995-2.819	<0.001
BCLC stage 0/A (n=1227)				
EZ-ALBI grade 1	634	1		
EZ-ALBI grade 2-3	593	1.781	1.525-2.079	<0.001
BCLC stage B/C/D (n=2567)				
EZ-ALBI grade 1	777	1		
EZ-ALBI grade 2	1470	2.060	1.861-2.280	<0.001
EZ-ALBI grade 3	320	4.055	3.508-4.686	<0.001

BCLC, Barcelona clinic liver cancer; CTP, Child-Turcotte-Pugh; EZ-ALBI, easy-albumin-bilirubin





No. at risk									
EZ-ALBI grade 1	1411	994	688	456	280	187	71	23	3
EZ-ALBI grade 2	2038	893	518	259	132	85	48	21	6
EZ-ALBI grade 3	345	45	26	18	11	9	4	3	1