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Easy albumin–bilirubin 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, calculation of the 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 the EZ-ALBI score in HCC from early to advanced stages.

Methods: A total of 3794 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 the ALBI score (correlation coefficient, 0.965; $p < 0.001$). The correlation of the EZ-ALBI score was highly preserved in different Child–Turcotte–Pugh (CTP) classifications, treatment methods, and Barcelona Clinic Liver Cancer (BCLC) stages (correlation coefficients, 0.90–0.97). In the Cox multivariate analysis, age >65 years, male sex, 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 noncurative 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 the EZ-ALBI grade is independent across different cancer stages and treatments.

KEYWORDS

EZ-ALBI score, hepatocellular carcinoma, prognosis

Abbreviations: AICc, corrected Akaike information criterion; ALBI, albumin–bilirubin; APRI, aspartate aminotransferase-to-platelet ratio index; BCLC, Barcelona Clinic Liver Cancer; CDS, cirrhosis discriminant score; CI, confidence interval; CT, computed tomography; CTP, Child–Turcotte–Pugh; EZ-ALBI, easy ALBI; GUCI, Göteborg University Cirrhosis Index; FIB-4, fibrosis index based on four factors; HCC, hepatocellular carcinoma; HR, hazard ratio; INR, international normalized ratio; IRB, institutional review board; MELD, Model for End-stage Liver Disease; MRI, magnetic resonance imaging; OS, overall survival; PT, prothrombin time; TACE, transarterial chemoembolization; TTV, total tumor volume.

INTRODUCTION

Hepatocellular carcinoma 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 infection, alcohol, and metabolic liver disease are the main etiologies of HCC.[2,3] According to American Association for the Study of Liver Diseases and European Association for the Study of the Liver HCC practice guidelines, curative treatments such as surgical resection, liver transplantation, and radiofrequency ablation are recommended for early stage HCC with good liver function.[4,5] For unresectable or advanced stage HCC, 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 CTP score, including serum albumin, bilirubin, INR of 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 ALBIscore, 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 APRI, CDS, CTP, FIB-4, GUCI, Lok index, 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 the EZ-ALBI score, which is a new prognostic model to evaluate liver functional reserve using data from more than 5000 Japanese patients from eight collaborating hospitals. The development of the EZ-ALBI score is primarily based on the regression coefficients of serum albumin and bilirubin levels by using a multivariate Cox proportional hazards model. The researchers showed that the EZ-ALBI score is a feasible prognostic model to evaluate liver dysfunction in HCC.[18] However, the prognostic role of the EZ-ALBI score has not been validated in other centers. In this study, we aimed to assess the role of the EZ-ALBI score as a potentially new prognostic biomarker in HCC.

METHODS

Patients

A total of 3794 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 IRB of Taipei Veterans General Hospital and complies with the standards of the Declaration of Helsinki and current ethical guidelines. Informed consent was waived by the IRB due to the retrospective nature of this study. Patients were followed up every 3–6 months until death or drop-out from the follow-up program.

Diagnosis

The diagnosis of HCC was based on typical imaging findings (early arterial enhancement in arterial phase and delayed wash-out in portal venous phase) by contrast-enhanced CT or MRI, or confirmed by pathology if the image finding was not typical.[4,8] Performance status was evaluated by the Eastern Cooperative Oncology Group performance scale.[19] Vascular invasion was identified as radiological evidence of tumor invasion to the intrahepatic vasculature, portal trunk, or inferior vena cava.[20] Distant metastasis such as lung, bone, or lymph node was diagnosed by CT, MRI, or bone scan.[21] The calculation and equations of noninvasive liver reserve models such as APRI, CDS, FIB-4, GUCI, Lok index, MELD, and King's score have been described in detail in our previous study.[12]

Albumin–bilirubin score and grading

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

$$\text{ALBI score} = 0.66 \times \log_{10}\text{bilirubin (μmol/L)} - 0.085 \times \text{albumin (g/L)}.$$

The 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-ALBI score and grading

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

$$\text{EZ-ALBI score} = \text{total bilirubin (mg/dl)} - (9 \times \text{albumin [g/dl]}).$$

The EZ-ALBI grade was classified into three 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 χ^2-test or Fisher's 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 the 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 HR with 95% 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 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 undertaken using SPSS Statistics for Windows, version 21.0 (IBM).

RESULTS

Patient characteristics

The baseline characteristics of the 3794 patients and their comprehensive clinical data are summarized in Table 1. The mean age was 65 years, and patients were predominantly (76%) male. Hepatitis B and C virus were the main etiologies of HCC. Of all patients, 64% had a single tumor and 65% 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; 37% were EZ-ALBI grade 1, 54% were grade 2, and 9% were grade 3. Approximately half (48%) of patients received curative treatments such as surgical resection, liver transplantation, and percutaneous ablation, and others (52%) received noncurative treatments including TACE, chemotherapy, targeted or immunotherapy, 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 in the AICc between ALBI (41 218.535) and EZ-ALBI (41 224.867) scores was small.

Correlation of ALBI and EZ-ALBI scores

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 the 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, the correlation coefficients among those undergoing curative and noncurative treatments were 0.98 and 0.953, respectively. According to the BCLC stage, the correlation coefficients for BCLC stage 0/A and stage B/C/D patients were 0.97 and 0.961, respectively; the coefficients for subgroup patients with total bilirubin <3 mg/dl and >3 mg/dl were 0.982 and 0.853, respectively.

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

Variable	All patients
Age, years	65 ± 13
Gender, male/female	2895/899 (76/24)
Etiology of liver disease	
HBV	1513 (40)
HCV	824 (21)
HBV + HCV	135 (4)
Others	1322 (35)
Laboratory values	
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
Platelets, 1000 μl/L	170 ± 96
AFP, ng/ml	44 (8–806)
Tumor nodules (single/multiple)	2437/1357 (64/36)
Tumor size, cm	6.0 ± 4.5
Tumor size > 3 cm	2447 (65)
Vascular invasion or distant metastasis	1038 (27)
Ascites	861 (23)
DM	972 (26)
CTP class, A/B/C	2787/831/176 (73/22/5)
CTP score	6.0 ± 1.5
ALBI score	−2.30 ± 0.65
ALBI grade, 1/2/3	1444/1970/380 (38/52/10)
EZ-ALBI score	−31.31 ± 7.0
EZ-ALBI grade, 1/2/3	1411/2038/345 (37/54/9)
Performance status, 0/1/2/3–4	2226/780/431/357 (59/21/11/9)
BCLC, 0/A/B/C/D	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)

(Continues)

TABLE 1 (Continued)

Variable	All patients
Chemotherapy or targeted therapy	303 (8)
Best supportive care	896 (17)

Note: Data are shown as *n* (%), mean ± SD, or median (interquartile range).
Abbreviations: AFP, α-fetoprotein; ALBI, albumin–bilirubin; ALT, alanine aminotransferase; BCLC, Barcelona Clinic Liver Cancer; CTP, Child–Turcotte–Pugh; DM, diabetes mellitus; EZ-ALBI, easy ALBI; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; PT, prothrombin time; TACE, transarterial chemoembolization.

TABLE 2 Prognostic performance of noninvasive liver reserve models in 3794 patients with hepatocellular carcinoma

	Homogeneity (Wald χ^2)	Corrected Akaike information criteria
ALBI	593.295	41 218.535
APRI	189.181	41 622.648
CDS	28.797	41 783.032
CTP	565.506	41 246.323
EZ-ALBI	586.962	41 224.867
FIB-4	183.909	41 627.920
GUCI	189.215	41 622.615
King's score	187.975	41 623.855
Lok index	336.527	41 475.302
MELD	374.513	41 437.317

Abbreviations: ALBI, albumin–bilirubin; APRI, aspartate aminotransferase-to-platelet ratio; CDS, cirrhosis discriminant score; CTP, Child-Turcotte-Pugh; EZ-ALBI, easy ALBI; FIB-4, fibrosis index based on four factors; GUCI, Göteborg University cirrhosis index; MELD, Model for End-stage Liver Disease.

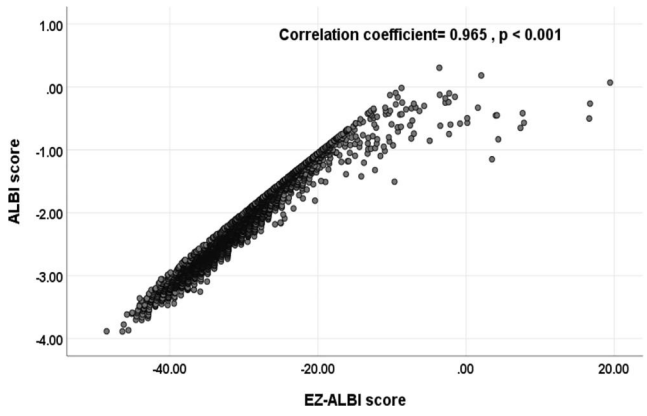

FIGURE 1 Correlation between EZ albumin–bilirubin (EZ-ALBI) and ALBI scores. Good linear correlation is shown between EZ-ALBI and ALBI scores in 3794 patients with hepatocellular carcinoma

Survival of patients based on ALBI grade

The median 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%, and 52% for ALBI grade 1, 60%, 37%, and 25% for ALBI grade 2, and 26%, 12%, and 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 median 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-, and 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% for EZ-ALBI grade 3 patients, respectively.

In the subgroup analysis for CTP class A patients, the median 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-, and 5-year OS rates were 85%, 66%, and 52% for EZ-ALBI grade 1, and 69%, 45%, and 30% for grade 2–3 patients, respectively ($p < 0.001$, Figure 3a). For CTP class B or C patients, the median 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. The 1-, 3-, and 5-year OS rates were 75%, 50%, and 19% for EZ-ALBI grade 1, 41%, 21%, and 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. For patients undergoing curative treatments, the median 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-, and 5-year OS rates were 93%, 78%, and 65% for EZ-ALBI grade 1, 85%, 64%, and 46% for grade 2, and 59%, 35%, and 30% for grade 3 patients, respectively ($p < 0.001$, Figure 4a). For noncurative treatments, the median 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-, and 5-year OS rates were 70%, 42%, and 27% for EZ-ALBI grade 1, 42%, 19%, and 10% for grade 2, and 17%, 6%, and 4% for grade 3 patients, respectively ($p < 0.001$, Figure 4b).

When the analysis was stratified for BCLC stage 0/A patients, the median 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-, and 5-years OS rates were 96%, 81%, and 70% for EZ-ALBI grade 1, and 92%, 69%, and 51% for grade 2–3 patients, respectively ($p < 0.001$, Figure 5a). For BCLC stage B/C/D patients, the median 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

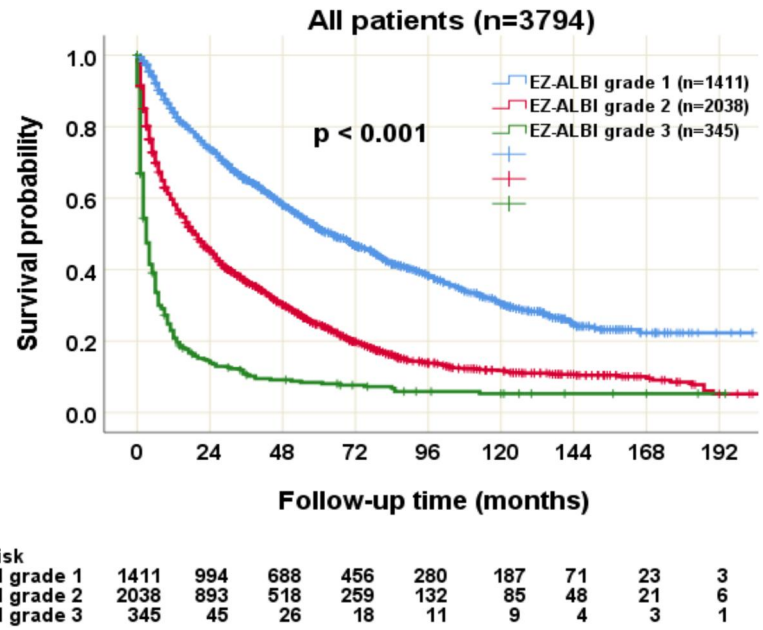

FIGURE 2 Kaplan–Meier survival analysis of 3794 patients with hepatocellular carcinoma according to EZ albumin–bilirubin (EZ-ALBI) grade. Patients with EZ-ALBI grade 1 had better overall survival than EZ-ALBI grade 2 and grade 3 patients ($p < 0.001$) [Colour figure can be viewed at wileyonlinelibrary.com]

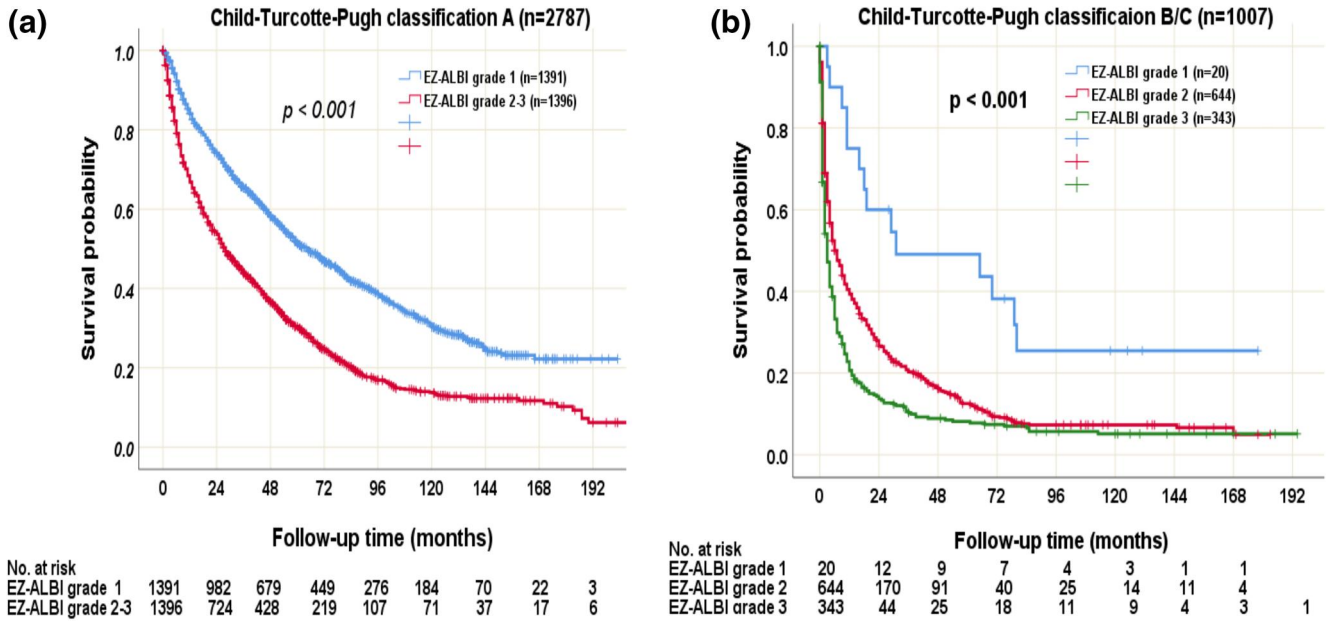

FIGURE 3 Kaplan–Meier survival analysis in 3794 patients with hepatocellular carcinoma according to EZ albumin–bilirubin (EZ-ALBI) grade in (a) Child–Turcotte–Pugh (CTP) class A patients and (b) CTP class B/C patients. Patients with higher EZ-ALBI grade had decreased overall survival in CTP class A ($p < 0.001$) and class B/C patients ($p < 0.001$) [Colour figure can be viewed at wileyonlinelibrary.com]

grade 1, 2, and 3 patients, respectively. The 1-, 3-, and 5-year OS rates were 77%, 53%, and 38% for EZ-ALBI grade 1, 47%, 24%, and 14% for grade 2, and 20%, 9%, and 7% for grade 3 patients, respectively ($p < 0.001$, Figure 5b).

Cox multivariate survival analysis

In the univariate analysis, age, gender, serum albumin, bilirubin, ALT, platelet count, INR of PT, serum AFP, tumor size, tumor nodules, TTV, vascular invasion or distant metastasis, ascites, performance status, EZ-ALBI grade, and noncurative treatment were associated with decreased survival. In the Cox multivariate proportional hazards model, age more than 65 years (HR, 1.281; 95% CI, 1.185–1.385; $p < 0.001$), 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, 1.290–1.549; $p < 0.001$), 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; $p < 0.001$),

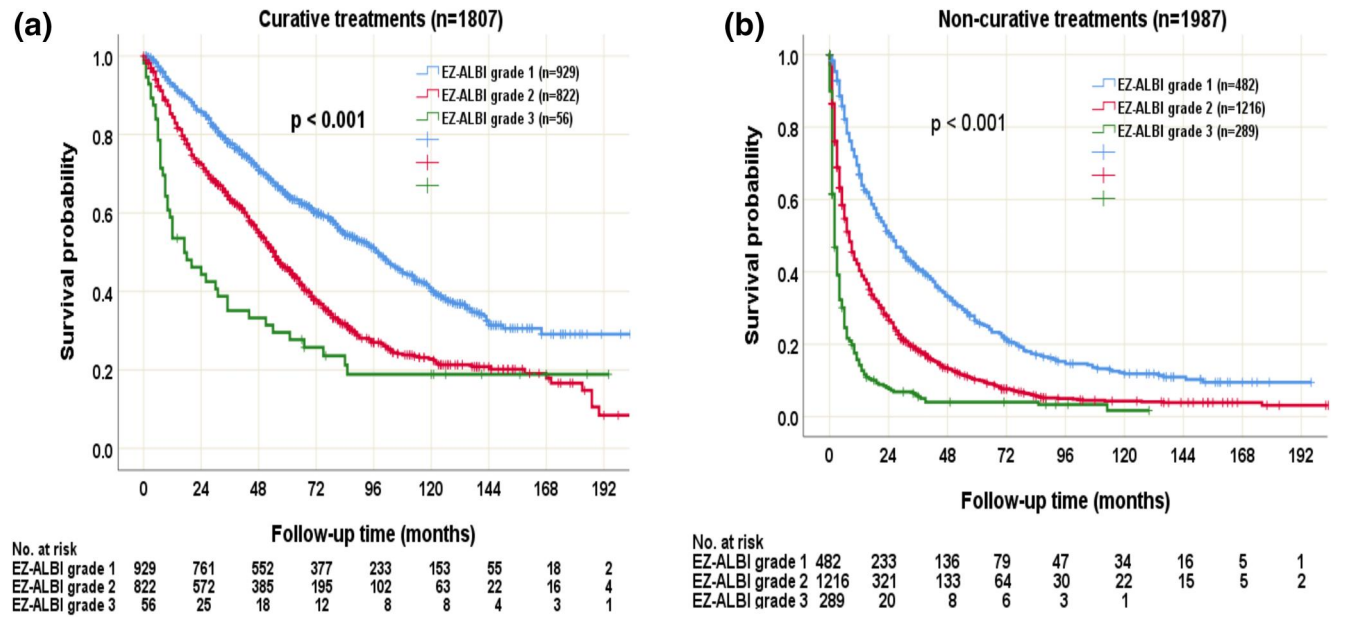

FIGURE 4 Kaplan–Meier survival analysis in 3794 patients with hepatocellular carcinoma according to EZ albumin–bilirubin (EZ-ALBI) grade in patients undergoing (a) curative or (b) noncurative treatment. Patients with higher EZ-ALBI grade had increased mortality rate in both curative and noncurative treatment groups (both $p < 0.001$) [Colour figure can be viewed at wileyonlinelibrary.com]

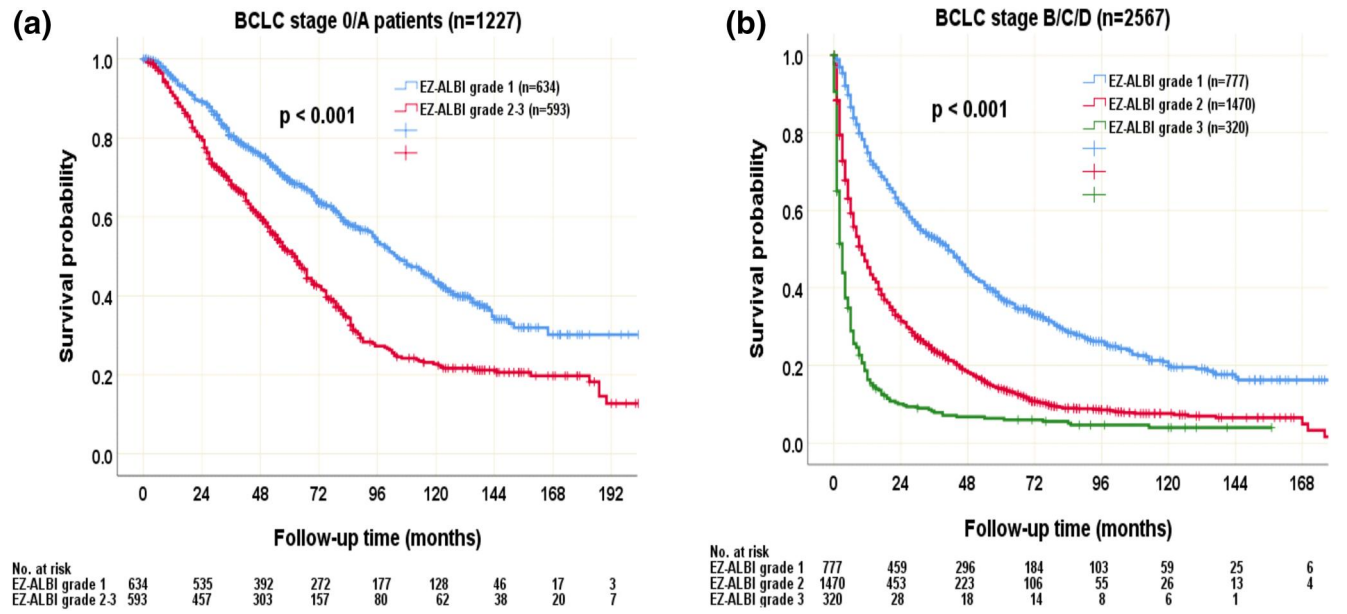

FIGURE 5 Kaplan–Meier survival analysis in 3794 patients with hepatocellular carcinoma according to EZ albumin–bilirubin (EZ-ALBI) grade in (a) Barcelona Clinic Liver Cancer (BCLC) stage 0/A patients and (b) BCLC stage B/C/D patients. There was significant overall survival difference between different EZ-ALBI grade in early ($p < 0.001$) and intermediate-advanced stage patients ($p < 0.001$) [Colour figure can be viewed at wileyonlinelibrary.com]

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 the subgroup analysis of CTP class A patients, those with EZ-ALBI grade 2–3 had 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;

TABLE 3 Univariate and multivariate survival analyses of patients with hepatocellular carcinoma (n = 3794)

		Univariate analysis			Multivariate analysis		
Overall survival	**Number**	**3-year survival (%)**	**5-year survival (%)**	***p*-value**	**HR**	**CI**	***p*-value**
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/<3.5 g/dl)	2468/1326	57/24	43/16	<0.001			
Bilirubin level (≤1.1/>1.1 mg/dl)	2453/1341	54/30	40/21	<0.001			
ALT (≤40/>40 IU/L)	1604/2190	49/43	38/30	<0.001			
Platelets (≥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 (≤3 cm/>3 cm)	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 (no/yes)	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		1.000		
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		1.000		
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/noncurative treatment	1807/1987	70/22	55/13	<0.001	2.059	1.882–2.253	<0.001

Note: The forepart of the parentheses was set as the reference group in the univariate and multivariate analyses.

Abbreviations: AFP, *α*-fetoprotein; ALT, alanine aminotransferase; CI, confidence interval; EZ-ALBI, easy albumin–bilirubin; HR, hazard ratio; INR, international normalized ratio; PT, prothrombin time; TTV, total tumor volume.

$p < 0.001$) 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 the noncurative 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 decreased long-term survival.

In the subgroup analysis of BCLC stage 0/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 decreased survival (Table 4).

DISCUSSION

Liver functional reserve plays a crucial role in the management of HCC.[26] Our results show that the 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 survival in HCC patients from early to advanced stage. In addition, the EZ-ALBI grade is an independent prognostic predictor in both entire cohort and variable clinical entities including different CTP classifications, treatments, and BCLC stages. 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 the EZ-ALBI score to assess liver dysfunction in HCC patients in Japan.[18] The correlation coefficient of EZ-ALBI and ALBI scores was as high as 0.981. This

TABLE 4 Multivariate analysis of EZ albumin–bilirubin (EZ-ALBI)-based survival risk in patients with hepatocellular carcinoma according to Child–Turcotte–Pugh (CTP) classification, treatment, and Barcelona Clinic Liver Cancer (BCLC) stage

		Multivariate analysis		
	Number	HR	CI	*p*-value
CTP A (n = 2787)				
EZ-ALBI grade 1	1391	1.000		
EZ-ALBI grade 2/3	1396	1.596	1.450–1.758	<0.001
CTP B–C (n = 1007)				
EZ-ALBI grade 1	482	1.000		
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 treatment (n = 1807)				
EZ-ALBI grade 1	929	1.000		
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
Noncurative treatment (n = 1987)				
EZ-ALBI grade 1	482	1.000		
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	1.000		
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	1.000		
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

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 scores was consistently high (0.965), and was highly preserved in different CTP classifications (coefficient, 0.90–0.97), treatments (coefficient, 0.95–0.98), and BCLC stages (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 scores was observed in the entire cohort and different subgroups. Notably, the EZ-ALBI score could outperform the ALBI score in several respects. First, the calculation of the EZ-ALBI score is much easier compared with the ALBI score, which is difficult to determine due to the complexity of the formula. Second, the EZ-ALBI score maintains fairly good prognostic performance in discriminating long-term survival in HCC patients. Finally, the EZ-ALBI score is a more user-friendly and readily available surrogate marker to assess liver dysfunction at the 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 outcomes of HCC patients across all cancer stages.

In the multivariate Cox analysis, EZ-ALBI grade 2 and grade 3 patients were associated with 1.6–2.4-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 decreased OS. Taken together 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 non-Asian 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. Finally, as 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 the 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 the ALBI score in clinical practice. As a new prognostic biomarker in HCC, the predictive power of the EZ-ALBI grade is independent of the severity of cirrhosis, cancer stage, and treatment. 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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CONFLICT OF INTEREST

The authors have no conflict of interest.

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