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ORIGINAL ARTICLE

Performance status as a prognostic surrogate in hepatocellular carcinoma: Role of albumin–bilirubin and easy-albumin–bilirubin grade

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Abstract

Background: Performance status (PS) is associated with the severity of liver cirrhosis and is also an important survival determinant in hepatocellular carcinoma (HCC). Albumin–bilirubin (ALBI) grade and easy (EZ)-ALBI grade have been proposed to evaluate liver dysfunction in HCC, but their role in patients with different PS is unclear. We aimed to investigate the prognostic role of ALBI and EZ-ALBI grade in a large HCC cohort with variable PS.

Methods: A total of 3355 newly diagnosed HCC patients between 2002 and 2018 were identified and retrospectively analyzed. Independent prognostic predictors associated with survival were investigated using the Cox proportional hazards model.

Results: Patients with poor PS had decreased survival compared with those with good PS. In the Cox model, creatinine ≥1.2 mg/dL, α-fetoprotein (AFP) ≥20 ng/mL, vascular invasion, distant metastasis, total tumor volume >100 cm^3, presence of ascites, ALBI grades 2 and 3, EZ-ALBI grade 2 and grade 3, PS 1–4, and noncurative treatment were independently associated with higher mortality in the entire cohort (all $p < 0.001$). ALBI grade and EZ-ALBI grade can well stratify overall survival in subgroup patients with PS 0, PS 1–2, and PS 3–4 (all $p < 0.001$).

Conclusion: Patients with good PS have better long-term survival compared with those with poor PS. ALBI and EZ-ALBI grade can discriminate long-term outcome in the entire cohort as well as in patients with different PS. ALBI and EZ-ALBI are objective and feasible prognostic models to evaluate liver dysfunction in HCC patients independent of PS.

Keywords: Alpha-fetoprotein; Hepatocellular carcinoma; Liver cirrhosis; Prognosis; Survival

1. INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer and the third leading cause of cancer-related deaths worldwide in 2020.[1] The underlying causes of HCC are chronic hepatitis B and C, alcoholism, and nonalcoholic fatty liver disease.[2] According to current HCC practice guidelines, liver resection, local ablation therapy, and liver transplantation are recommended for very early or early-stage HCC. For intermediate or advanced-stage HCC, transarterial chemotherapy embolization (TACE), systemic therapy, targeted- and immunotherapy are usually suggested.[3–5]

The extent of tumor burden, severity of liver injury, and performance status (PS) are important prognostic factors for HCC. The PS scale, developed by the Eastern Cooperative Oncology Group (ECOG), is used to determine general condition of cancer patients. This scale ranges from 0 (fully active with no limitations in pre-disease activities) to 5 (deceased).[6] Notably, PS is closely associated with tumor burden and severity of cirrhosis,[7] and thus plays a critical role in treatment selection and long-term survival of HCC patients. Also, it is included in the Barcelona Clinic Liver Cancer (BCLC) staging system for HCC.

The severity of liver dysfunction is known to heavily impact patient outcome in HCC. The Child-Turcotte-Pugh (CTP) score is used to assess the status of liver cirrhosis. However, CTP has limitations because of the use of arbitrary cut-off objective variables, and ascites and serum albumin are interrelated.[8] Albumin–bilirubin (ALBI) score is a more objective tool to evaluate liver dysfunction in HCC and has been validated by several research groups.[9–13] Despite its objectivity, the calculation of ALBI score is quite complicated. Recently, Kariyama et al[14] introduced the easy (EZ)-ALBI score, which is easier to calculate and highly correlated with the original ALBI score in estimating liver functional reserve. Furthermore, EZ-ALBI score is able to determine long-term outcome from early to advanced stages of HCC.[15,16]

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Although PS is highly linked with the severity of liver injury, the role of ALBI and EZ-ALBI score has not been evaluated in HCC patents with varying PS. In this study, we aimed to examine the prognostic role of ALBI and EZ-ALBI grade in a large HCC cohort with different PS.

2. METHODS

2.1. Patient characteristics

From 2002 to 2018, a total 3355 of newly diagnosed HCC patients at Taipei Veterans General Hospital were retrospectively analyzed. Their baseline characteristics, including demographic data, serum biochemistry, tumor burden (size and nodules, vascular invasion, distant metastasis), severity of liver functional reserve, cancer stage, and treatments were recorded at the time of diagnosis. The patients were monitored every 3 to 6 months until death or withdrawal from the follow-up program. The study has been approved by the Institutional Review Board of Taipei Veterans General Hospital.

2.2. Diagnosis and treatment

HCC was diagnosed by typical image finding of computed tomography (CT) scan or magnetic resonance imaging (MRI) according to current HCC practice guidelines.[3,5] Vascular invasion was defined as the presence of tumor invasion into the branch or main portal vein or inferior vena cava as described previously.[15] PS was evaluated by using the ECOG scale.[6,17] Patients were evaluated by a team of experts including hepatologists, oncologists, surgeons, pathologists, and radiologists to determine the diagnosis and appropriate treatment plan.

Surgical resection, liver transplantation, and local ablation therapy were categorized as curative treatment, whereas TACE, targeted- or immunotherapy, and systemic therapy were grouped as noncurative treatment.

2.3. Total tumor volume

The calculation of total tumor volume (TTV) involved the following formula:

Tumor volume (cm^3) = 4/3 × π × (maximum radius of the tumor nodule in cm)^3

TTV was determined by adding up the volume of all nodules:

TTV (cm^3) = sum of the volumes of each tumor nodule (nodule 1 + nodule 2 +…nodule *N*)[18]

Albumin-bilirubin (ALBI)

The equation of ALBI score is as follows:

ALBI score = ($\log_{10}$ bilirubin (μmol/L) × 0.66) – (albumin [g/L] × 0.085)

The cut-off value of ALBI grade1/2 and ALBI grade 2/3 were ≤–2.60 and >–1.39.[9]

Easy-ALBI (EZ-ALBI) score

The EZ-ALBI score was calculated by using the following equation:

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

The cut-off values of EZ-ALBI grade 1/2 and EZ-ALBI grade 2/3 were ≤–34.4 and >–22.2.[14]

2.4. Statistics

The statistical analysis was performed using IBM SPSS Statistics software version 25.0 (IBM Corp., Armonk, NY). Continuous variables were compared by the Mann-Whitney test, and categorical variables were compared with the chi-squared test or Fisher's exact test. The overall survival was assessed by the Kaplan-Meier analysis with a log-rank test. Factors that were significant in univariate survival analysis were further analyzed through a Cox proportional hazards model to determine the hazard ratio (HR) and 95% CI.

3. RESULTS

3.1. Patient characteristics

The baseline characteristics of the study patients are shown in Table 1. Their mean age was 66 years, and the majority were male. The most common underlying liver disease was hepatitis B (52%), followed by hepatitis C (30%). About 62% of patients had single tumor and mean tumor diameter was 6.6 cm. Vascular invasion was present in 29% of patients, and 12% of patients had distant metastasis. Most (62%) HCC patients were CTP class A and 26% of patients had ascites formation. The distribution of PS was as follows: 1823 (54%) patients were PS 0, 701 (21%) patients were PS 1, 468 (14%) patients were PS 2, 241 (7%) patients were PS 3, and 122 (4%) patients were PS 4.

Table 1

Baseline characteristics of HCC patients (n = 3355)

Number of patients	3355
Age (y, mean ± SD)	66 ± 13
Male/female, n (%)	2584/771 (23/77)
Etiology of liver disease	
HBV, n (%)	1753 (52)
HCV, n (%)	1008 (30)
HBV + HCV, n (%)	156 (5)
Others, n (%)	755 (23)
Laboratory values (mean ± SD)	
Albumin (g/dL)	3.6 ± 0.6
Bilirubin (mg/dL)	1.7 ± 3.1
ALT (IU/L)	72.8 ± 110.7
Creatinine (mg/dL)	1.2 ± 1
Sodium (mmol/L)	138.1 ± 4.2
INR of PT	1.1 ± 0.3
Platelets (1000 μL/L)	176 ± 99
Serum AFP (ng/mL), median (IQR)	64 (9.3-1554.5)
Tumor nodules (single/multiple), n (%)	2066/1290 (62/38)
Tumor size (cm, mean ± SD)	6.6 ± 4.8
Tumor size >3 cm, n (%)	2353 (70)
Vascular invasion, n (%)	983 (29)
Distant metastasis, n (%)	407 (12)
Ascites, n (%)	877 (26)
DM, n (%)	893 (27)
CTP class, A/B/C, n (%)	2326/846/183 (69/25/6)
CTP score (mean ± SD)	6 ± 2
ALBI score (mean ± SD)	–2.22 ± 0.66
ALBI grade, 1/2/3, n (%)	1088/1862/404 (32/56/12)
EZ-ALBI score (mean ± SD)	–30.5 ± 7.2
EZ-ALBI grade, 1/2/3, n (%)	1075/1916/363 (32/57/11)
Performance status, 0/1–2/3–4, n (%)	1823/1170/362 (54/35/11)
BCLC, 0/A/B/C/D, n (%)	206/673/565/1480/431 (6/20/17/44/13)
Treatment, n (%)	
Surgical resection	751 (22)
Liver transplantation	6 (0.1)
Percutaneous ablation	557 (17)
TACE	1068 (32)
Chemotherapy or targeted therapy	347 (10)
Best supportive care	626 (19)

Data are shown as n (%), mean ± SD, or median (IQR).

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; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; INR = international normalized ratio; IQR = interquartile range; PT = prothrombin time; TACE = transarterial chemoembolization.

3.2. Comparison of HCC patients based on different PS

The comparison of the baseline characteristics of patients based on their PS is shown in Table 2. Patients with worse PS had lower levels of serum albumin, higher levels of serum bilirubin and creatinine, prolonged prothrombin time, larger TTV, vascular invasion, distant metastasis, and ascites formation compared with patients with better PS (all $p < 0.001$). Patients with PS 0 had significantly lower levels of serum α-fetoprotein (AFP), better liver functional reserve (including CTP A, ALBI grade 1, and EZ-ALBI grade 1), and higher chance to undergo curative treatment (all $p < 0.001$).

3.3. Multivariable Cox analysis in the entire cohort

In Cox multivariable model 1 which includes ALBI grade, positive for HCV antibody, lower serum albumin level, higher serum bilirubin, creatinine, ALT, and AFP level, thrombocytopenia, prolonged international normalized ratio (INR), vascular invasion, distant metastasis, presence of diabetes mellitus, ALBI grade 2 and grade 3, larger TTV, multiple tumor nodules, ascites, poor PS, and noncurative treatment were associated with decreased overall survival in univariate analysis. Multivariate Cox analysis revealed that creatinine ≥1.2 mg/dL (HR: 1.133, $p < 0.001$), AFP ≥20 ng/mL (HR: 1.344, $p < 0.001$), vascular invasion (HR: 1.675, $p < 0.001$), distant metastasis (HR: 1.268, $p < 0.001$), tumor size >3 cm (HR: 1.155, $p = 0.006$), TTV > 100 cm^3 (HR: 1.432, $p < 0.001$), ascites (HR: 1.196, $p < 0.001$), ALBI grades 2 (HR: 1.327, $p < 0.001$) and ALBI grade 3 (HR: 1.580, $p < 0.001$), PS 1 (HR: 1.201, $p < 0.001$), PS 2 (HR: 1.402, $p < 0.001$), PS 3 (HR: 1.576, $p < 0.001$), PS 4 (HR: 1.238, $p = 0.05$), and noncurative treatment (HR: 1.696, $p < 0.001$) were independent prognostic predictors associated with increased mortality. In Cox multivariate model 2 which includes EZ-ALBI grade, EZ-ALBI grade 2 (HR: 1.363, $p < 0.001$) and EZ-ALBI grade 3 (HR: 1.536, $p < 0.001$) were independent predictors associated with increased mortality (Table 3).

3.4. Multivariable analysis of ALBI and EZ-ALBI grade in different PS

The prognostic role of ALBI and EZ-ALBI stratified by the PS is shown in Table 4. In Cox model 1, ALBI grade 2 (HR: 1.535, $p < 0.001$) and ALBI grade 3 (HR: 2.656, $p < 0.001$) were linked with increased risk of mortality compared with ALBI grade 1 in PS 0 group. In Cox model 2, EZ-ALBI grade 2 (HR: 1.516, $p < 0.001$) and EZ-ALBI grade 3 (HR: 2.493, $p < 0.001$) were significantly associated with decreased survival compared with EZ-ALBI grade 1 in PS 0 patients.

In Cox model 1 of patients with PS 1-2, ALBI grade 2 (HR: 1.472, $p < 0.001$) and ALBI grade 3 (HR: 2.493, $p < 0.001$) patients had decreased long-term survival compared with ALBI grade 1 patients. In Cox model 2, EZ-ALBI grade 2 (HR: 1.534, $p < 0.001$) and EZ-ALBI grade 3 (HR: 2.268, $p < 0.001$) were

Table 2

Comparison of HCC patients according to performance status

	Performance status					
	0 (n = 1823)	1 (n = 701)	2 (n = 468)	3 (n = 241)	4 (n = 121)	*p*
Sex (male, %)	77	79	74	82	74	0.074
Age (y)	65 ± 13	64 ± 14	69 ± 13	68 ± 15	70 ± 14	<0.001
HBV (%)	55	52	48	46	48	0.016
HCV (%)	32	28	27	28	28	0.040
Serum biochemistries						
Albumin level (g/dL)	3.8 ± 0.5	3.5 ± 0.6	3.3 ± 0.6	3.1 ± 0.6	3.0 ± 0.6	<0.001
Bilirubin level (mg/dl)	1.2 ± 2.3	1.6 ± 2.4	2.0 ± 3.1	3.6 ± 5.3	4.3 ± 6.7	<0.001
Creatinine (mg/dL)	1.1 ± 0.9	1.1 ± 1.0	1.4 ± 1.3	1.5 ± 1.3	1.6 ± 1.4	<0.001
Platelet (1000 μL)	164 ± 89	181 ± 107	187 ± 106	207 ± 127	213 ± 104	<0.001
ALT (IU/L)	69 ± 99	74 ± 124	73 ± 80	88 ± 187	88 ± 88	0.073
INR of PT	1.1 ± 0.4	1.1 ± 0.2	1.2 ± 0.2	1.2 ± 0.4	1.2 ± 0.3	<0.001
AFP (ng/mL), median (IQR)	39 (8-410)	130 (12-3410)	167 (9.7-7543)	402 (13-7921)	1094 (11-12502)	<0.001
CTP classification A/B/C (%)	85/14/1	63/33/4	52/39/9	27/45/28	15/57/27	<0.001
CTP score	5.6 ± 1.0	6.4 ± 1.5	6.9 ± 1.8	8.2 ± 2.2	8.4 ± 1.9	<0.001
ALBI (%)						
Grade 1	45	24	18	8	3	
Grade 2	51	65	60	55	52	
Grade 3	4	11	22	37	45	
EZ-ALBI (%)						
Grade 1	45	23	17	8	3	
Grade 2	51	67	64	59	55	
Grade 3	4	10	19	33	42	
Tumor size (≤3 cm/>3 cm, %)	40/60	21/79	19/81	12/88	7/93	<0.001
Tumor nodules (single/multiple, %)	65/35	58/42	60/40	48/52	60/40	<0.001
TTV (cm^3; mean ± SD)	282 ± 638	613 ± 931	625 ± 877	670 ± 1128	875 ± 526	<0.001
Ascites (%)	9	36	45	66	67	<0.001
Vascular invasion (%)	17	41	42	51	65	<0.001
Distant metastasis (%)	6	18	18	25	29	<0.001
Diabetes mellitus (%)	24	28	32	29	29	0.005
Treatment (curative/noncurative, %)	54/46	30/70	19/81	11/89	3/97	<0.001

AFP = α-fetoprotein; ALBI = albumin–bilirubin; ALT = alanine aminotransferase; CTP = Child-Turcotte-Pugh; DM = diabetes mellitus; EZ-ALBI = easy ALBI; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; INR = international normalized ratio; IQR = interquartile range; PT = prothrombin time; TTV = total tumor volume.

Table 3

Univariate and multivariable survival analyses of patients with HCC (n = 3355)

				Univariate analysis			Multivariable analysis		
Overall survival	Number	1-y survival (%)	3-y survival (%)	HR	95% CI	*p* value	HR	95% CI	*p*
Sex (male/female)	2584/771	51/58	29/33	1.089	1.000-1.186	0.051			
Age (≤65/>65 y)	1563/1792	50/55	29/31	0.966	0.899-1.038	0.347			
HBV (negative/positive)	1603/1752	54/51	30/30	0.958	0.892-1.030	0.245			
HCV (negative/positive)	2347/1008	49/60	29/34	0.870	0.805-0.941	<0.001			
Platelet (≥150 000/<150 000/μL)	1769/1586	44/62	24/36	0.781	0.727-0.839	<0.001	0.914	0.841-0.994	0.035
Bilirubin level (≤1.1/>1.1 mg/dL)	2071/1284	61/38	37/18	1.749	1.625-1.883	<0.001	1.177	1.080-1.283	<0.001
Albumin level (≥3.5/<3.5 g/dL)	2036/1319	65/34	40/17	2.086	1.936-2.247	<0.001	1.220	1.108-1.344	<0.001
Creatinine (<1.2/≥1.2 mg/dL)	2430/925	55/47	32/25	1.205	1.113-1.304	<0.001	1.133	1.044-1.230	0.003
ALT (≤40/>40 IU/L)	1369/1986	56/36	50/28	1.127	1.047-1.212	0.001			
INR of PT (≤1.1/>1.1)	2058/1297	60/40	47/18	1.673	1.554-1.801	<0.001			
Serum AFP (<20/≥20 ng/mL)	1225/2130	69/43	44/22	1.709	1.584-1.844	<0.001	1.344	1.242-1.454	<0.001
Vascular invasion (no/yes)	2373/982	67/17	39/6	3.362	3.095-3.652	<0.001	1.675	1.518-1.849	<0.001
Distant metastasis (no/yes)	2497/408	58/16	33/4	2.888	2.584-3.327	<0.001	1.268	1.125-1.429	<0.001
Diabetes mellitus (no/yes)	2461/894	53/51	31/27	1.098	1.013-1.190	0.023			
Tumor size (≤3 cm/>3 cm)	1003/2352	79/41	51/21	1.976	1.823-2.142	<0.001	1.155	1.042-1.282	0.006
Tumor nodules (single/multiple)	2066/1289	56/46	33/25	1.289	1.198-1.387	<0.001			
TTV (≤100/>100 cm^3)	1780/1575	73/29	45/12	2.435	2.262-2.622	<0.001	1.432	1.295-1.585	<0.001
Ascites (no/yes)	2479/876	62/24	37/10	1.644	1.572-1.718	<0.001	1.196	1.133-1.262	<0.001
Performance status									
0	1823	70	43	1			1		
1	701	41	20	1.875	1.709-2.058	<0.001	1.201	1.089-1.325	<0.001
2	468	31	12	2.498	2.243-2.782	<0.001	1.402	1.248-1.575	<0.001
3	241	16	6	3.684	3.203-4.239	<0.001	1.576	1.347-1.843	<0.001
4	122	13	3	5.005	4.144-6.046	<0.001	1.238	1.000-1.533	0.05
Curative/noncurative treatment	1313/2042	80/35	53/14	2.675	2.478-2.889	<0.001	1.696	1.556-1.848	<0.001
Cox model 1									
ALBI									
Grade 1	1088	73	47	1			1		
Grade 2	1862	48	25	1.805	1.663-1.959	<0.001	1.327	1.201-1.466	<0.001
Grade 3	405	18	6	3.996	3.536-4.516	<0.001	1.580	1.332-1.874	<0.001
Cox model 2									
EZALBI									
Grade 1	1075	75	48	1			1		
Grade 2	1916	47	24	1.838	1.694-1.994	<0.001	1.363	1.237-1.503	<0.001
Grade 3	364	17	5	4.101	3.608-4.662	<0.001	1.536	1.299-1.816	<0.001

AFP = α-fetoprotein; ALBI = albumin–bilirubin; ALT = alanine aminotransferase; CTP = Child-Turcotte-Pugh; DM = diabetes mellitus; EZ-ALBI = easy ALBI; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HR = hazard ratio; INR = international normalized ratio; PT = prothrombin time; TACE = transarterial chemoembolization; TTV = total tumor volume.

associated with decreased survival compared with EZ-ALBI grade 1 patients.

In Cox model 1 of patients with PS 3-4, ALBI grade 2 (HR: 1.966, $p < 0.001$) and ALBI grade 3 (HR: 1.811, $p < 0.001$) were associated with increased risk of death compared with ALBI grade 1. In Cox model 2, EZ-ALBI grade 2 (HR: 2.177, $p < 0.001$) and EZ-ALBI grade 3 (HR: 2.855, $p < 0.001$) patients were linked with higher mortality compared with EZ-ALBI grade 1 patients.

3.5. Survival analysis based on different PS

Patients with better PS tended to have a longer survival (Fig. 1, $p < 0.001$). Their median OS was 29 (95% CI, 27-31), 9 (95% CI, 7.6-10), 5 (95% CI, 3.8-6.2), 2 (95% CI, 1.5-2.5), and 1 (95% CI, 0.8-1.2) months for patients with PS 0, 1, 2, 3, and 4, respectively.

3.6. Survival analysis based on different ALBI and EZ-ALBI grade

Patients with ALBI grade 1 had better OS compared to those with ALBI grade 2 and grade 3 (Fig. 2A, $p < 0.001$). Their median OS for ALBI grades 1, 2, and 3 were 34 (95% CI, 30.6–37.4), 11 (95% CI, 9.6–12.4), and 2 (95% CI, 1.5–2.5) months, respectively. Patients with EZ-ALBI grade 2 and grade 3 had worse survival compared to those with EZ-ALBI grade 1 (Fig. 2B, $p < 0.001$). Their median OS for EZ-ALBI grades 1, 2, and 3 were 34 (95% CI, 30.1–37.2), 11 (95% CI, 9.7–12.3), and 2 (95% CI, 1.5–2.6) months, respectively.

3.7. Survival analysis in HCC patients with varying PS stratified by ALBI and EZ-ALBI grade

The survival analysis was primarily based on different PS groups of the entire cohort. To enhance statistical robustness, three groups (PS 0, PS 1–2, and PS 3–4) were allocated to investigate the independent role of ALBI/EZ-ALBI in the Cox model. In subgroup analysis of PS 0, patients with ALBI grade 1 had better survival compared with ALBI grade 2 and grade 3 (Fig. 3A, $p < 0.001$). The median OS was 41 (95% CI, 36.4-45.6), 23 (95% CI, 20.3-25.7), and 10 (95% CI, 6.2-13.8) months for ALBI grades 1, 2, and 3 patients, respectively. In subgroup analysis of PS 1–2, ALBI grade 2 and grade 3 patients had decreased survival compared to ALBI grade 1 group (Fig. 3B, $p < 0.001$). The median OS for ALBI grades 1, 2, and 3 were 16 (95% CI, 11.7-20.3), 7 (95% CI, 5.9-8.1), and 2 months (95% CI, 1.3-2.7),

Table 4

Multivariable analysis ALBI grade and EZ-ALBI grade based on different performance status

	Multivariable analysis		
	HR	95% CI	*p*
PS 0 (n = 1823)			
Cox model 1			
ALBI grade 1	1		
ALBI grade 2	1.535	1.379-1.708	<0.001
ALBI grade 3	2.656	2.060-3.425	<0.001
Cox model 2			
EZ-ALBI grade 1	1		
EZ-ALBI grade 2	1.516	1.362-1.687	<0.001
EZ-ALBI grade 3	2.493	1.903-3.264	<0.001
PS 1–2 (n = 1170)			
Cox model 1			
ALBI grade 1	1		
ALBI grade 2	1.472	1.257-1.724	<0.001
ALBI grade 3	2.064	1.657-2.571	<0.001
Cox model 2			
EZ-ALBI grade 1	1		
EZ-ALBI grade 2	1.534	1.313-1.794	<0.001
EZ-ALBI grade 3	2.268	1.830-2.810	<0.001
PS 3–4 (n = 362)			
Cox model 1			
ALBI grade 1	1		
ALBI grade 2	1.966	1.190-3.248	0.008
ALBI grade 3	2.811	1.660-4.762	<0.001
Cox model 2			
EZ-ALBI grade 1	1		
EZ-ALBI grade 2	2.177	1.354-3.498	0.001
EZ-ALBI grade 3	2.855	1.727-4.722	<0.001

ALBI = albumin–bilirubin; EZ-ALBI = easy ALBI; HR = hazard ratio; PS = performance status.

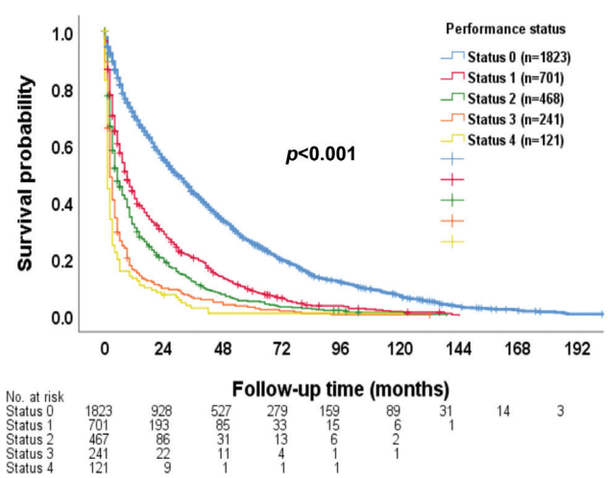

Fig. 1 Survival distribution stratified by performance status among HCC patients. Patients with poor performance status had decreased overall survival compared to those with good performance status ($p < 0.001$). HCC = hepatocellular carcinoma.

respectively. In subgroup analysis of PS 3–4, ALBI grade 2 and grade 3 patients had an increased risk of mortality compared with ALBI grade 1 patients (Fig. 3C, $p < 0.001$). The median OS were 19 (95% CI, 5.8-32.1), 2 (95% CI, 2.5-1.5), and 1 (95% CI, 0.7-1.4) months for ALBI grade 1, 2 and 3, respectively.

Using a similar approach, in subgroup analysis of PS 0, patients with EZ-ALBI grade 1 had better survival compared with EZ-ALBI grade 2 and grade 3 patients (Fig. 4A, $p < 0.001$). The median OS were 40 (95% CI, 35.7-44.3), 22 (95% CI, 19.5-24.5), and 10 (95% CI, 6.2-13.8) months for EZ-ALBI grade 1, 2, and 3 patients, respectively. In subgroup analysis of PS 1–2, patients with EZ-ALBI grade 2 and grade 3 had decreased survival compared with EZ-ALBI grade 1 patients (Fig. 4B, $p < 0.001$). The median OS were 18 (95% CI, 17.8-23.2), 7 (95% CI, 5.9-8.1), and 3 (95% CI, 2.4-3.7) months for EZ-ALBI grade 1, 2, and 3, respectively. In subgroup analysis of PS 3–4, EZ-ALBI grade 2–3 patients had an increased risk of mortality compared with EZ-ALBI grade 1 patients (Fig. 4C, $p < 0.001$). The median OS were 12 (95% CI, 5.3-32.7), 2 (95% CI, 1.5-2.5), and 1 (95% CI, 0.8-1.2) months for EZ-ALBI grade 1, 2, and 3, respectively.

4. DISCUSSION

PS is the parameter assessing the general condition of cancer patients.[19,20] It does not only estimate long-term outcome but also plays a critical role in treatment selection for HCC.[20,21] The association between PS and ALBI/EZ-ALBI grade in HCC is unclear. A previous study reported that PS was associated with the severity of liver cirrhosis in HCC patients.[7] In this study, we found that worse PS is often linked with larger tumor burden, poor liver reserve, vascular invasion, and ascites formation compared with those of good status. Importantly, patients with poor PS had 2 to 4 times increased risk of mortality compared with those with good status. Consistent with previous studies,[22,23] our results demonstrate that PS is a surrogate predictor for long-term survival in HCC patients.

PS is also correlated with the severity of liver cirrhosis in HCC. The CTP classification is traditionally used to evaluate the severity of liver dysfunction in HCC, but it has some shortcomings due to interrelated and subjective variables. The ALBI score and EZ-ALBI score are more objective models to evaluate liver dysfunction in HCC. Our study shows that both ALBI and EZ-ALBI grade can discriminate different overall survival in the entire cohort. Consistently, patients with ALBI grade 2 and grade 3 had 1.3 to 1.5 times increased risk of mortality compared with those with ALBI grade 1 in multivariate analysis.[24–26] Similarly, patients with EZ-ALBI grade 2 and grade 3 had 1.3 to 1.5 times increased risk of death compared with EZ-ALBI grade 1.[15,27] Our results indicate that ALBI grade and EZ-ALBI grade are feasible models to determine long-term outcome in HCC patients.

In subgroup analysis of patients with different PS, ALBI grade 1 consistently predicted a better survival compared with ALBI grade 2 and 3. Patients with ALBI grade 2 and grade 3 had 1.2 to 2.0 times increased risk of mortality compared with those of ALBI grade 1. Alternatively, EZ-ALBI grade 1 was also associated with increased mortality risk compared with EZ-ALBI grade 2 and grade 3 patients. Notably, patients with EZ-ALBI grade 2 and grade 3 had 31% to 90% increased risk of death compared with EZ-ALBI grade 1 among patients with different PS. There results further indicate that ALBI and EZ-ALBI grade are useful models to evaluate liver dysfunction and predict long-term outcome in HCC patients independent of PS.

In addition to the severity of cirrhosis and PS, the extent of tumor burden is also an important prognostic predictor in HCC.[28] In multivariate analysis, we found that the extent of tumor burden including tumor size and nodules, vascular invasion, and distant metastasis were all independent prognostic predictors. Consistent with this notion is that patients with elevated serum AFP level also had poor survival in multivariate

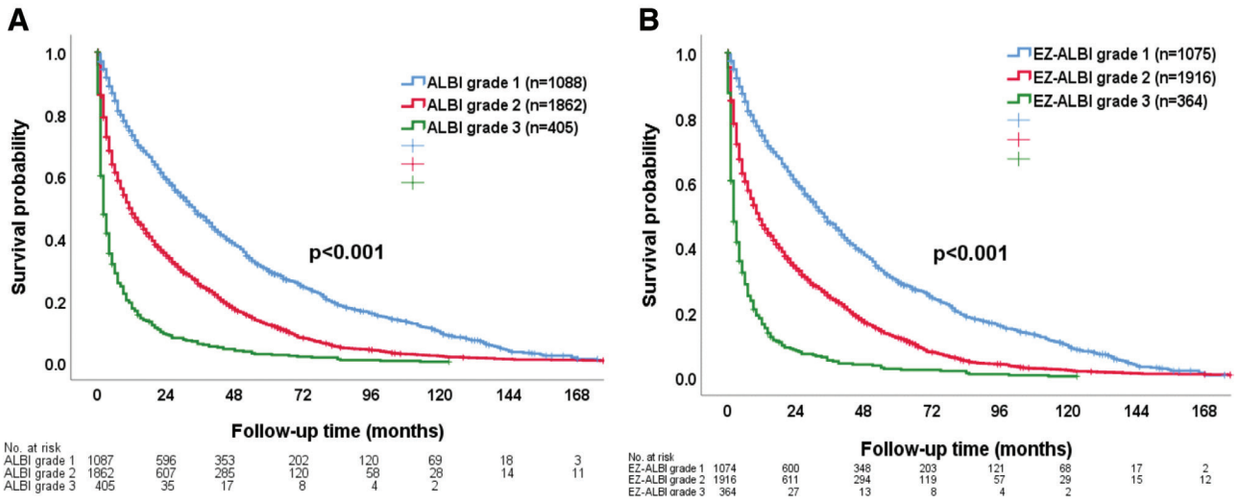

Fig. 2 Survival distribution of ALBI grade and EZ-ALBI grade in the entire cohort. There was a significant survival difference in (A) ALBI grade ($p < 0.001$) and (B) EZ-ALBI grade ($p < 0.001$). ALBI = albumin–bilirubin; EZ = easy.

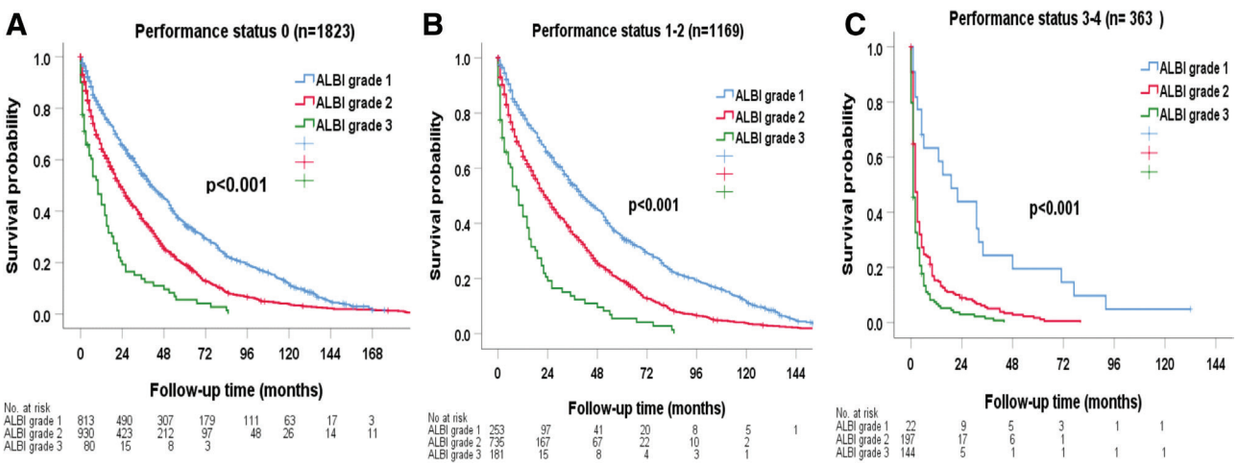

Fig. 3 Survival distribution according to ALBI grade in HCC patients with different PS. There were significant survival differences of ALBI grade in (A) PS 0 ($p < 0.001$), (B) PS 1–2 ($p < 0.001$), and (C) PS 3–4 ($p < 0.001$) groups. ALBI = albumin–bilirubin; HCC = hepatocellular carcinoma; PS = performance status.

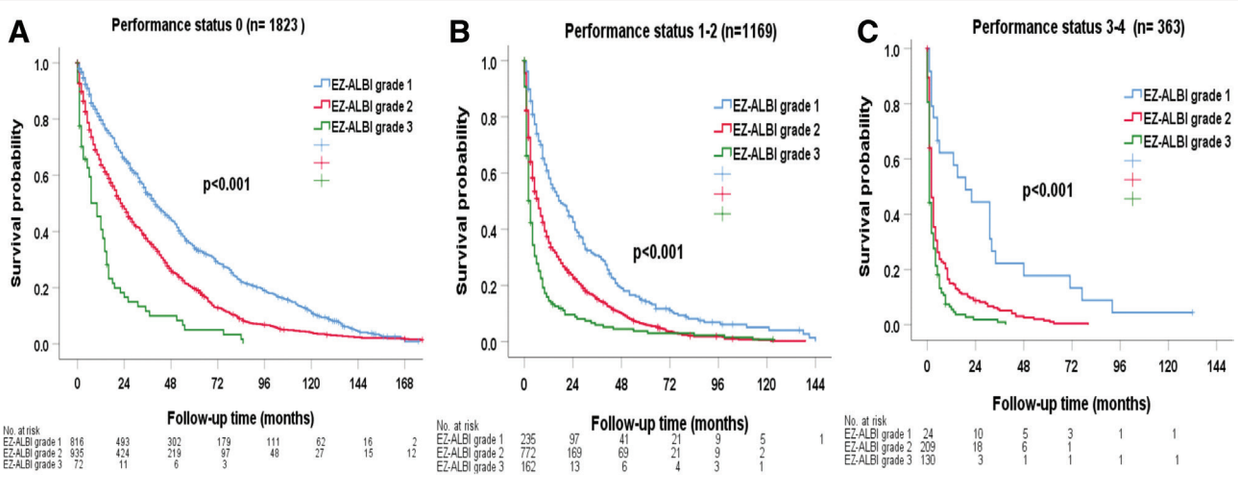

Fig. 4 Survival distribution according to EZ-ALBI grade in HCC patients with different PS. There were significant survival differences of EZ-ALBI grade in (A) PS 0 ($p < 0.001$), (B) PS 1–2 ($p < 0.001$), and (C) PS 3–4 ($p < 0.001$) groups. ALBI = albumin–bilirubin; HCC = hepatocellular carcinoma; PS = performance status.

analysis. Taken together, ALBI grade, EZ-ALBI grade, PS, and tumor burden are all crucial makers to determine long-term prognosis in HCC.

There are several limitations of this study. Firstly, this study was performed in an endemic area of hepatitis B that is different from most Western countries. Secondly, this is a single-center retrospective study, thus the selection bias cannot be completely eliminated. Finally, although PS was determined at the time of diagnosis according to the ECOG criteria, its scale was mostly based on clinician's subjective judgment.

In conclusion, patients with good PS have better long-term survival compared with those of poor status. ALBI and EZ-ALBI grade can discriminate long-term outcome in the entire cohort as well as in patients with different PS. ALBI and EZ-ALBI are robust prognostic models to evaluate liver dysfunction in HCC patients independent of PS.

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