

Albumin-bilirubin (ALBI) score at admission predicts possible outcomes in patients with acute-on-chronic liver failure

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Abstract

The albumin-bilirubin (ALBI) score is a new model for assessing the severity of liver dysfunction. The purpose of the present study is to investigate the prognostic value of the ALBI score in predicting the 3-month outcome of patients with hepatitis B virus (HBV)-related acute-on-chronic liver failure (AoCLF).

This study included 84 patients with HBV-AoCLF, 56 chronic hepatitis B (CHB) patients, and 48 healthy controls (HCs). The virological parameters and biochemical examination of blood were obtained after 12 hours of fasting. The follow-up of AoCLF patients lasted for at least 3 months, and the relationships between the prognosis and ALBI score were analyzed.

A significantly higher ALBI score was detected in AoCLF patients than in the HC and CHB groups (both $P = .001$). The ALBI score was positively correlated with the model of the end-stage liver disease (MELD) score and Child–Pugh score. Moreover, ALBI scores were higher among non-survivors than survivors in AoCLF patients. Multivariate analysis suggested that both the ALBI and MELD scores were independent predictors of the 3-month mortality in AoCLF patients ($P < .001$).

A high ALBI score measured at admission may be used as a predictor for the 3-month mortality rate in patients with HBV-AoCLF.

Abbreviations: ALBI = albumin-bilirubin score, ALT = alanine aminotransferase, AoCLF = acute-on-chronic liver failure, AUCs = areas under the curve, CHB = chronic hepatitis B, HBV = Hepatitis B virus, HCs = healthy controls, INR = International normalized ratio, MELD score = model for end-stage liver disease score, ROC = receiver operating characteristic.

Keywords: acute-on-chronic liver failure, albumin-bilirubin score, mortality

1. Introduction

Hepatitis B virus (HBV)-related acute-on-chronic liver failure (AoCLF) accounts for most cases of liver failure in China. AoCLF features acute deterioration of liver function over a period of 2 to 4 weeks in patients whose liver functions were well-compensated despite chronic liver disease. This failure is usually induced by a precipitating event, such as variceal bleeding, infection, surgical procedures, or hepatotoxic drugs, and it is associated with progressive jaundice, coagulopathy, and hepatic encephalopathy (HE).^[1] HBV-AoCLF is associated with a mortality rate that ranges from 32% to 68%, which mainly occurs in the first 3 months after diagnosis.^[2,3] Therefore, new potential biomarkers that could promptly and accurately predict the outcome and inspire appropriate medical decision-making could reduce the complications and improve patient survival.

The albumin-bilirubin (ALBI) score, by combining the serum albumin and bilirubin, is a new model for assessing the severity of

liver dysfunction. Recently, Johnson and colleagues reported that the ALBI score more accurately predicts patients' mortality without requiring subjective determinants of liver failure, including ascites and encephalopathy, in patients with hepatocellular carcinoma.^[4] A retrospective study also investigated the prognostic significance of the ALBI score among patients with primary biliary cirrhosis.^[5] The authors found that the ALBI score seems to be superior to other scores (such Child–Pugh and MELD score) for predicting the occurrence of hepatic events in such patients. Furthermore, Chen et al^[6] demonstrated that ALBI score had a significantly better performance for long-term survival prediction in patients with HBV-related cirrhosis than the Child–Pugh or MELD scores. However, to the best of our knowledge, there are no studies on the ALBI score in HBV-related AoCLF patients. We hypothesized that ALBI is potentially associated with clinical outcomes in AoCLF patients. Based on this background, we investigated the relationship between the ALBI score and AoCLF and then evaluated the prognostic value of ALBI in HBV-AoCLF patients.

2. Materials and methods

2.1. Patients

One hundred and forty patients, including 56 chronic hepatitis B (CHB) and 84 AoCLF patients, were enrolled from the Department of Infectious Diseases, the First Affiliated Hospital of Zhejiang University College of Medicine from August 1, 2014 to August 1, 2016. None of the patients had prior liver or other organ transplantation. All patients received standard medical therapy during hospitalization for primary prevention of spontaneous bacterial peritonitis according to the guidelines,^[3] including absolute resting, intravenous infusion of albumin and plasma, and nutritional and energy supplements. Forty-eight

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age- and sex-matched individuals were selected as healthy controls (HCs), who presented for their annual physical examinations and required no medical attention. The diagnoses of HBV-related CHB and AoCLF were performed according to the guidelines and recommendations of the Asian Pacific Association for the Study of the Liver.^[3] Briefly, CHB patients were defined as positive for hepatitis B surface antigen (HBsAg) for at least 6 months prior to this study and abnormal alanine aminotransferase (ALT) levels (>40 U/L) without evidence of cirrhosis or hepatocellular carcinoma. The diagnostic standard for HBV-related AoCLF mainly includes a history of CHB or liver cirrhosis with serum HBsAg positivity for more than 6 months, jaundice (serum bilirubin ≥ 10 mg/dL), and coagulopathy (international normalized ratio [INR] ≥ 1.5), which is quickly complicated by ascites and/or encephalopathy. Patients who meet the following criteria were excluded: acute hepatitis; current hepatitis virus (A, C, D, and E) or human immunodeficiency virus (HIV) infection, or other chronic liver diseases related to alcohol, drugs, or autoimmune diseases; malignancies, such as HCC; and pregnancy. During follow-up, all patients received nucleotide/nucleoside analogue antiviral treatment with entecavir, telbivudine, lamivudine, or lamivudine combined with adefovir dipivoxil, which could prevent disease progression and would not affect the short-term prognosis for patients in the current study.^[7,8] All patients were followed up for 3 months or longer to assess the 3-month mortality.

The study was performed in accordance with the Declaration of Helsinki, and the procedures were approved by the ethics committee of the First Affiliated Hospital of Zhejiang University College of Medicine. Oral informed consent was obtained from each study participant prior to enrolment.

2.2. Laboratory analysis

After a fasting period of 12 hours, a peripheral venous blood sample was collected from all patients within the first 24 hours after admission. Biochemical indicators, such as serum albumin, total protein, total bilirubin, creatinine, and ALT, were determined using a Hitachi 7600 Clinical Analyzer (Hitachi, Tokyo, Japan), and the INR was analyzed using the coagulation method with a Sysmex CS-2000i Analyzer (Sysmex, Kobe, Japan). At baseline, for each patient, demographic and clinical data, including the age; sex; and complications of ascites, variceal bleeding, hepatorenal syndrome (HRS), or HE and clinical course, were obtained from the medical files and recorded in a specified liver disease document. In addition, the model for end-stage liver disease (MELD) score, Child–Pugh score, ALBI score, and serological indexes (HBsAg, HBeAg, anti-HBc, and HBV DNA levels) were collected at baseline.

2.3. Calculation of scores

The Child–Pugh score was calculated from 5 variables, including bilirubin, albumin, prothrombin, ascites status, and degree of encephalopathy.^[9]

$$\text{MELD score} = 3.78 \times \ln(\text{Tbil } \mu\text{mol/L}) + 11.2 \times \ln(\text{INR}) + 9.57 \times \ln(\text{creatinine mg/dL}) + 6.4.$$
^[10]

$$\text{ALBI score} = -0.085 \times (\text{albumin/g}) + 0.66 \times \lg(\text{Tbil } \mu\text{mol/L}).$$
^[4]

2.4. Statistical analysis

Statistical analysis was performed by SPSS software version 12.0 (SPSS Inc., Chicago, IL). Continuous variables were expressed as

the mean \pm standard deviation (SD) or medians (range), and categorical data were expressed as percentages. Differences in variables were analyzed using a one-way ANOVA and Student *t* tests or the Kruskal–Wallis and Mann–Whitney *U* tests. Categorical data were evaluated by the χ^2 -test or Fisher exact test, as appropriate. The correlation between two variables was assessed using the Spearman rank correlation test. The diagnostic accuracy of prognostic variables was examined by receiver operating characteristic (ROC) analysis. Logistic regression analysis was employed to demonstrate the independent predictors for the 3-month mortality rate of patients with AoCLF. A two-tailed $P < .05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics

One hundred and forty patients, including patients with CHB ($n=56$), patients with AoCLF ($n=84$), and 48 HCs, were enrolled in the current study. The ages in the study cohort ranged from 20 to 67 years with a mean of 45.3 years. The age and sex were well balanced among the 3 study groups. This study showed that the ALBI score in AoCLF patients was significantly higher than in HCs and CHB patients (both $P < .001$), and CHB patients had a higher ALBI score than HCs ($P < .001$) (Fig. 1). Significant positive correlations between the ALBI score and both the Child–Pugh score ($r = .576$, $P < .001$) and MELD score ($r = .254$, $P = .020$) were detected in AoCLF patients (Fig. 2). The baseline characteristics of all participants are listed in Table 1.

3.2. Comparison of ALBI score between non-surviving and surviving patients with HBV-related AoCLF

HBV-related AoCLF patients were divided into non-surviving ($n=41$) and surviving groups ($n=43$). The clinical and laboratory characteristics of these patients are listed in Table 2. The non-surviving patients had a higher MELD score, ALBI score, total bilirubin, Child–Pugh score, and INR compared with those in surviving patients. However, a much lower albumin was observed in the non-surviving group compared with that in the

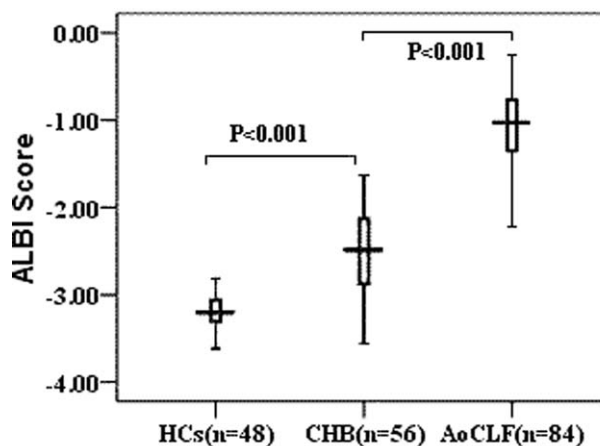


Figure 1. ALBI score in HBV-infected patients and HCs at admission. In the box plots, the horizontal lines illustrate the 25th, 50th, and 75th percentiles for the LMR values. The vertical lines represent the 5th and 95th percentiles. ALBI = albumin-bilirubin score, HBV = Hepatitis B virus, HCs = healthy controls.

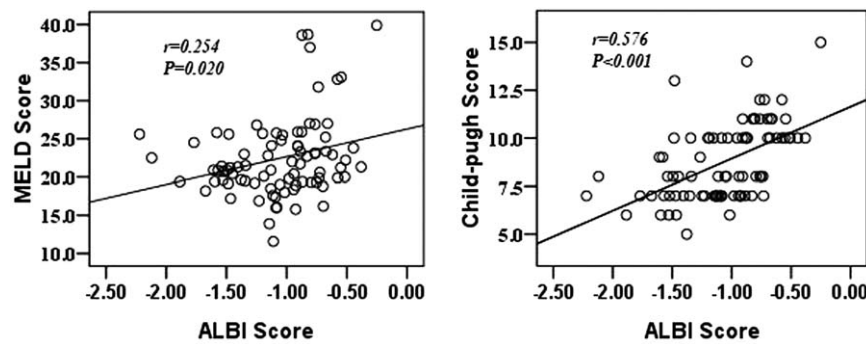


Figure 2. Scatter diagram showing a positive correlation between the ALBI and MELD scores in AoCLF patients. AoCLF = acute-on-chronic liver failure, ALBI = albumin-bilirubin score, MELD score = model for end-stage liver disease score.

surviving patients. No significant differences in the total protein, ALT, sex, or age were detected.

3.3. Increased ALBI score as a predictor of prognosis in HBV-AoCLF patients

The follow-up of HBV-AoCLF patients lasted for 3 months to at least evaluate the short-term mortality. The median follow-up period was 64 days (range: 22–109 days). Forty-one patients died due to upper gastrointestinal bleeding (n=22), HE (n=15), or HRS (n=4). Univariate logistic regression analysis showed that a high MELD score, Child–Pugh score, and ALBI score were independent risk factors for the 3-month mortality in AoCLF patients. Multivariate logistic regression analysis identified both the MELD and ALBI scores as related to this mortality (Table 3). ROC curves were established to evaluate the relative efficiencies of the ALBI and MELD scores for predicting the 3-month mortality (Fig. 3). The areas under the curve (AUC) values were

0.837 ± 0.043 for the MELD score and 0.784 ± 0.049 for the ALBI score (both $P < .001$). The cut-off values, sensitivity and specificity of the MELD, were 22.7%, 68.3%, and 88.4% and the ALBI score values were -0.95% , 65.9%, and 81.4%, respectively. When the ALBI and MELD scores were combined; the AUC was 0.912 ± 0.054 ($P < .001$), which is higher than the AUC of the MELD score ($P = .020$), and the specificity (76.7%) and sensitivity (90.9%) were improved.

4. Discussion

It is well known that there are several scoring systems available to evaluate the severity of liver dysfunction and predict the prognosis of patients with liver disease, such as the MELD and Child–Pugh scores. The Child–Pugh score contains five parameters, including the total bilirubin, serum albumin, prothrombin time, ascites, and hepatic encephalopathy. However, the highly subjective evaluation of ascites and encephalopathy

Table 1
Baseline demographic and clinical characteristics of the study participants.

	AoCLF patients (n=84)	CHB patients (n=56)	HCs (n=48)	P
Age, y	46.0 ± 10.5	43.8 ± 10.0	43.3 ± 10.9	.187
Gender (male/female)	70/14	38/18	36/12	.101
Total protein, g/L	58.9 ± 7.7 ^{***}	67.6 ± 6.8 ^{**}	70.5 ± 4.0	<.001
Albumin, g/L	32.0 ± 4.6 ^{***}	40.6 ± 4.4 ^{**}	45.6 ± 3.2	<.001
Total bilirubin, μmol/L	318.5 (236.0–444.0) ^{***}	22.0 (12.0–53.0) ^{**}	12.0 (9.0–15.0)	<.001
ALT, U/L	100.5 (53.0–202.0) ^{**}	167.0 (51.0–333.5) ^{**}	20.0 (16.0–27.0)	<.001
INR	2.07 ± 0.55 ^{***}	1.06 ± 0.12	0.90 ± 0.12	<.001
MELD score	21.3 (19.3–24.7)	4.1 (2.0–7.1)	—	<.001 [*]
ALBI score	-1.02 (-1.35 to -0.76) ^{***}	-2.48 (-2.90 to -2.13) ^{**}	-3.20 (-3.31 to -3.06)	<.001
HBsAg positive	84	56	0	—
HBeAg positive	78	50	0	—
HBcAb IgM positive	0	0	0	—
HBV-DNA, log copies/mL	6.2 (3.9–8.1)	6.9 (4.9–8.5)	—	.372
Ascites (n)	40	0	—	—
HE (n)	15	0	—	—
Variceal bleeding (n)	45	0	—	—
HRS (n)	6	0	—	—
Child–Pugh score	8.0 (7.0–10.0)	—	—	—

Data are expressed as n, mean ± SD, or median (interquartile range). ALBI score = albumin-bilirubin score, ALT = alanine aminotransferase, AoCLF = acute-on-chronic liver failure, CHB = chronic hepatitis B, HCs = healthy controls, HE = hepatic encephalopathy, HRS = hepatorenal syndrome, HBsAg = hepatitis B surface antigen, INR = International normalized ratio, MELD score = model for end-stage liver disease score. P, comparison among the three groups. * $P < .05$, compared with the CHB group. ** $P < .05$, compared with the HC group.

Table 2

Comparison of clinical characteristics between non-surviving and surviving patients with acute-on-chronic liver failure at admission.

	Non-surviving patients (n=41)	Surviving patients (n=43)	P
Age, y	47.1 ± 11.2	45.0 ± 9.8	.345
Gender (male/female)	34/7	36/7	.922
Total protein, g/L	58.2 ± 7.0	59.6 ± 8.3	.310
Albumin, g/L	30.1 ± 4.0	33.8 ± 4.4	<.001
ALT, U/L	115.0 (66.8–272.0)	77.0 (39.5–175.0)	.060
Total bilirubin, μmol/L	369.0 (276.0–493.3)	288.0 (221.3–374.0)	.017
INR	2.22 ± 0.61	1.93 ± 0.46	.017
MELD score	24.0 (21.3–26.8)	19.60 (18.1–21.4)	.001
ALBI score	−0.87 (−1.06 to −0.67)	−1.24 (−1.53 to −0.96)	<.001
Child–Pugh score	9.7 ± 0.61	7.8 ± 1.5	<.001

Data are expressed as n, mean ± SD, or median (interquartile range). ALBI score = albumin-bilirubin score, ALT = alanine aminotransferase, INR = International normalized ratio, MELD score = model for end-stage liver disease score.

might reduce the accuracy of assessment.^[11] The MELD score incorporates 3 laboratory variables, TBil, INR, and creatinine, and it eliminates the subjective factors.^[12] The MELD score was widely used as a scoring system for organ allocation in liver transplantation and is the current standard prognostic tool for assessing the 3- to 6-month survival in patients with liver failure.^[13] The ALBI score only involves 2 common laboratory parameters, albumin and total bilirubin, and it has been used in patients with HCC for assessing the severity of liver dysfunction.^[4] Our study shows that patients with HBV-related AoCLF have significantly higher ALBI scores compared with CHB and HCs. Moreover, the ALBI score was higher for non-survivors than survivors, and it was positively correlated with the MELD and Child–Pugh scores in AoCLF patients. Furthermore, the ALBI score may be used for predicting AoCLF patient mortality, although the prediction power of the ALBI score was relatively lower than that of the MELD score. This result differs from the data from Chen’s group,^[6] and they showed that the ALBI score was effective in predicting the long-term prognosis for patients with HBV-related cirrhosis. Additionally, it was more accurate than Child–Pugh and MELD scores, and this difference may largely reflect differences in stages of liver diseases for patients recruited between studies. However, only 2 components are used to formulate the ALBI score, which is simpler and easier to calculate than the MELD and Child–Pugh scores. Moreover, the combination of the ALBI and MELD scores provided better prediction of the 3-month mortality than that of the MELD score alone (*P* = .020).

The underlying mechanisms enable the ALBI score to indicate that possible outcomes in AoCLF patients are not well established.

Table 3

Risk factors associated with 3-month mortality, as analyzed by Cox proportional hazards analysis.

	Univariate			Multivariate		
	Odds ratio	95% CI	P	Odds ratio	95% CI	P
ALBI score	27.361	5.524–140.598	.001	68.069	5.482–845.172	.001
MELD score	1.571	1.270–1.942	<.001	1.807	1.304–2.505	.001
Age, y	1.020	0.979–1.064	.341	—	—	.188
Total protein, g/L	0.972	0.919–1.032	.384	—	—	.357
ALT, U/L	1.002	1.000–1.003	.100	—	—	.747
Child–Pugh score	1.834	1.363–2.468	.001	0.926	0.591–1.452	.738

ALBI score = albumin-bilirubin score, ALT = alanine aminotransferase, CI = confidence interval, MELD score = model for end-stage liver disease score.

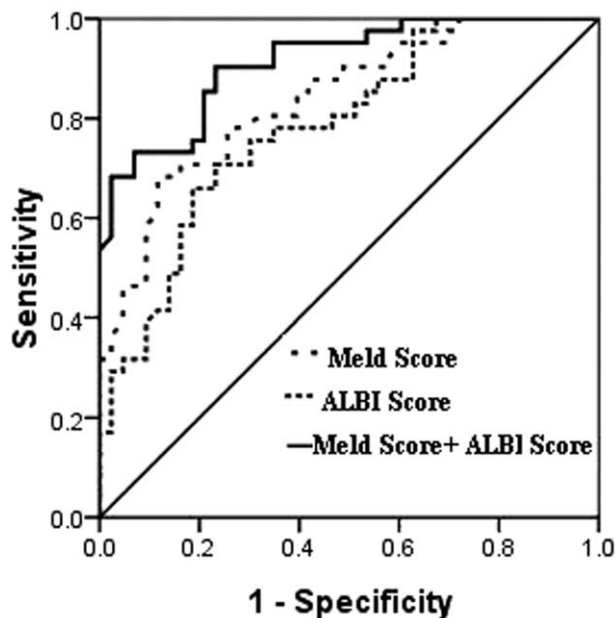


Figure 3. Receiver operating characteristic curve indicating the relative efficiencies for predicting 3-month mortality by the ALBI score (----), MELD score (- · -), and their combination (—) at admission. Data are plotted to generate the receiver operating characteristic curve. ALBI = albumin-bilirubin score, MELD score = model for end-stage liver disease score.

Several biochemical markers can reveal both liver function and the extent of liver injury. The ALBI score uses the bilirubin and albumin levels to reflect insufficient liver function and new liver damage. The usefulness of the ALBI score has been validated in several studies associated with HCC patients in different tumor stages.^[14–17] A previous study found that high levels of bilirubin can predict short-term mortality (1-week) in AoCLF patients.^[18] Additionally, albumin is produced by the liver, and the decreased albumin indicates there is dysfunction of liver synthesis and a higher risk of cirrhosis ascites. We found that a higher ALBI score in AoCLF patients was primarily the result of a decreased serum albumin and increased bilirubin compared with those in CHB patients and HCs. Furthermore, a much lower albumin and higher bilirubin appeared in the non-surviving group compared with the surviving patients. Therefore, high bilirubin levels combined with low albumin levels may be used to predict the severity and progression of liver injury in AoCLF patients.

Our study has several limitations. First, the present study was a single center investigation in China, and the sample size was relatively small. The findings need to be confirmed in large multi-

center, prospective studies. Second, the ALBI scores were not dynamically measured. Therefore, whether the ALBI score is stepwise elevated based on the progressive deterioration of liver function remains unclear.

5. Conclusion

The results from the present study show that the ALBI score determined on admission indicates the likelihood of survival of an AoCLF patient. The ALBI score is readily obtained by an easily accessible, non-invasive blood test and it is objectively evaluated. Further prospective studies are needed for a larger cohort of patients involving multiple centers to confirm the prognostic value of the ALBI score in AoCLF patients.

References

- [1] Jalan R, Williams R. Acute-on-chronic liver failure: pathophysiological basis of therapeutic options. *Blood Purif* 2002;20:252–61.
- [2] Moreau R, Arroyo V. Acute on chronic liver failure: A new clinical entity. *Clin Gastroenterol Hepatol* 2015;13:836–41.
- [3] Sarin SK, Kumar A, Almeida JA, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the study of the liver (APASL). *Hepatol Int* 2009;3:269–82.
- [4] Johnson PJ, Berhane S, Kagebayashi C, et al. Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach—the ALBI grade. *J Clin Oncol* 2015;33:550–8.
- [5] Chan AW, Chan RC, Wong GL, et al. New simple prognostic score for primary biliary cirrhosis: Albumin-bilirubin score. *J Gastroenterol Hepatol* 2015;30:1391–6.
- [6] Chen RC, Cai YJ, Wu JM, et al. Usefulness of albumin-bilirubin grade for evaluation of long-term prognosis for hepatitis B-related cirrhosis. *J Viral Hepat* 2017;24:238–45.
- [7] Lai J, Yan Y, Mai L, et al. Short-term entecavir versus lamivudine therapy for HBeAg-negative patients with acute-on-chronic hepatitis B liver failure. *Hepatobiliary Pancreat Dis Int* 2013;12:154–9.
- [8] Wang J, Ma K, Han M, et al. Nucleoside analogs prevent disease progression in HBV-related acute-on-chronic liver failure: validation of the TPPM model. *Hepatol Int* 2014;8:64–71.
- [9] Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973;60:646–9.
- [10] Durand F, Valla D. Assessment of the prognosis of cirrhosis: Child Pugh versus MELD. *J Hepatol* 2005;42:S100–7.
- [11] Durand F, Valla D. Assessment of prognosis of cirrhosis. *Semin Liver Dis* 2008;28:110–22.
- [12] Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001;33:464–70.
- [13] Freeman RBJr, Wiesner RH, Harper A, et al. The new liver allocation system: moving toward evidence-based transplantation policy. *Liver Transpl* 2002;8:851–8.
- [14] Pinato DJ, Sharma R, Allara E, et al. The ALBI grade provides objective hepatic reserve estimation across each BCLC stage of hepatocellular carcinoma. *J Hepatol* 2016;24:30535–9.
- [15] Toyoda H, Lai PB, O’Beirne J, et al. Long-term impact of liver function on curative therapy for hepatocellular carcinoma: application of the ALBI grade. *Br J Cancer* 2016;114:744–50.
- [16] Ma XL, Zhou JY, Gao XH, et al. Application of the albumin-bilirubin grade for predicting prognosis after curative resection of patients with early-stage hepatocellular carcinoma. *Clin Chim Acta* 2016;462:15–22.
- [17] Ogasawara S, Chiba T, Ooka Y, et al. Liver function assessment according to the Albumin-Bilirubin (ALBI) grade in sorafenib-treated patients with advanced hepatocellular carcinoma. *Invest New Drugs* 2015;33:1257–62.
- [18] López-Velázquez JA, Chávez-Tapia NC, Ponciano-Rodríguez G, et al. Bilirubin alone as a biomarker for short-term mortality in acute-on-chronic liver failure: an important prognostic indicator. *Ann Hepatol* 2014;13:98–104.