**Applicability of Albumin-Bilirubin-based Japan Integrated Staging (ALBI-T) score in hepatitis B-associated hepatocellular carcinoma**

Running title: Applicability of ALBI-T score

Anthony W.H. Chan1

Charing C.N. Chong2

Frankie K.F. Mo3

John Wong2

Winnie Yeo3

Philip J. Johnson4

Shuangni Yu5

Paul B.S. Lai2,6

Anthony T.C. Chan3

Ka-Fai To1,6,7

Stephen L. Chan3,7

1Department of Anatomical and Cellular Pathology, State Key Laboratory in Oncology in South China, Prince of Wales Hospital, The Chinese University of Hong Kong

2Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, The Chinese University of Hong Kong

3Department of Clinical Oncology, State Key Laboratory in Oncology in South China, Prince of Wales Hospital, The Chinese University of Hong Kong

4Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Liverpool, United Kingdom

5Department of Pathology, Peking Union Medical College Hospital, Beijing, China

6Institute of Digestive Disease, Partner State Key Laboratory of Digestive Disease, The Chinese University of Hong Kong

7Li Ka Shing Institute of Health Science, Sir Y.K. Pao Centre for Cancer, The Chinese University of Hong Kong

Address correspondence and reprint request to

Dr. Stephen L. Chan

Department of Clinical Oncology, Prince of Wales Hospital, The Chinese University of Hong Kong, 30-32 Ngan Shing Street, Shatin, NT, Hong Kong

Phone: (852) 2632-2118

Fax: (852) 2648-7097

Email: chanlam\_stephen@cuhk.edu.hk

**Author contribution**

Study design: AWHC, SLC

Drafting of the manuscript: AWHC, SLC

Critical revision of the manuscript: FKFM, CCNC, JW, WY, PJJ, SY, PBSL, ATCC, KFT

Data retrieval and database construction: AWHC, CCNC, SLC, FKFM, WY, PJJ

Data analysis: AWHC, SLC

Clinical managements of the patients: SLC, CCNC, JW, WY, PBSL, ATCC

**Word count**: 240 (abstract); 1842 (main text)

**Number of figures**: 3 figures, 1 supplementary figure

**Number of tables**: 3 tables

**Funding support**

None

**Disclosure/Conflict of interest**

None

**Abstract**

*Background & Aims*

The Japan Integrated Staging (JIS) for hepatocellular carcinoma (HCC) has been extensively studied in hepatitis virus C-endemic Japanese population but seldom evaluated outside Japan, while Albumin-Bilirubin (ALBI)-based JIS (ALBI-T) has never been externally validated. We evaluate the prognostic significance of the ALBI-T score among Chinese patients with hepatitis virus B (HBV)-related HCC, and to explore its potential therapeutic application in selecting patients for appropriate treatments in addition to the Barcelona Clinic Liver Cancer (BCLC) recommendation.

*Methods*

A cohort of 1222 HBV-associated HCC patients was evaluated to compare the prognostic performance of JIS and ALBI-T scores by homogeneity likelihood chi-square and corrected Akaike information criterion (AICc). In the subgroup analysis of each BCLC stage, Kaplan-Meier method and log-rank statistics were used to compare overall survival of patients undergoing different treatment options.

*Results*

The ALBI-T score showed better prognostic performance than the JIS score, which were indicated by homogeneity likelihood chi-squares (ALBI-T 580.12 vs. JIS 536.35) and AICs (ALBI-T 9836.57 vs. JIS 9880.23). Treatment options significantly influenced prognosis amongst patients of the same BCLC stage. With the use of ALBI-T score 4 as the cutoff, the current study identified that 14.7%, 25.2% and 28.6% of patients undergoing unnecessary therapy without survival advantage in BCLC stage B, C and D, respectively.

*Conclusions*

The ALBI-T score is applicable to Chinese patients with HBV-related HCC to provide reasonable prognostic information as well as potentially helping clinicians to avoid offering non-beneficial aggressive treatments.

**Keywords (not in the title)**

Barcelona Clinic Liver Cancer (BCLC), liver neoplasm, staging, survival

**Introduction**

The prognostication of hepatocellular carcinoma (HCC) is much more complex than other malignancy. Tumor burden is not the exclusive factor affecting the clinical outcome. Liver function as well as treatment modality also substantially influences the survival of patients. The Child-Pugh grade is one of the most common parameter to assess hepatic function. Albumin-Bilirubin (ALBI) score is a newly emerging alternative of traditional Child-Pugh grade.[1](#_ENREF_1), [2](#_ENREF_2) It not only provides predictive value comparable to the Child-Pugh grade among HCC patients but also surpasses the Child-Pugh grade by eliminating subjective clinical assessment of ascites and hepatic encephalopathy for Child-Pugh grade, and subdividing Child-Pugh A patients into two prognostically different groups (ALBI grade 1 and 2).[2](#_ENREF_2) The ALBI grade has been recently shown to successfully replace the Child-Pugh grade in two of existing HCC staging systems, Barcelona Clinic Liver Cancer (BCLC) and Japan Integrated Staging (JIS). The ALBI-based BCLC and ALBI-based JIS (also known as ALBI-T score) showed similar or even better prognostic performance than the Child-Pugh-based BCLC and JIS.[3](#_ENREF_3), [4](#_ENREF_4) The JIS system has been extensively studied in hepatitis virus C (HCV)-endemic Japanese population but seldom evaluated outside Japan, while the latest ALBI-T score has never been externally validated yet.

Treatment modality is one of the essential prognostic factors because different treatment modalities could offer different clinical outcomes among HCC patients with similar tumor burden and liver function.[5](#_ENREF_5), [6](#_ENREF_6) The BCLC system, which is endorsed by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL), predicts clinical outcome as well as allocating treatment.[7](#_ENREF_7), [8](#_ENREF_8) However, in real practice, therapeutic modalities provided to patients are not uncommonly deviated from the BCLC recommendations.[9-11](#_ENREF_9) Moreover, the BCLC staging system has been challenged for its capacity to provide precise classification of patients, especially amongst BCLC stages B and C disease, for clinical trials.[8](#_ENREF_8) Further stratification of patients within individual BCLC stage is warranted to assist clinicians to select the most appropriate effective treatment.

 We therefore conducted a cohort study to evaluate the prognostic significance of the ALBI-T score among Chinese patients with hepatitis virus B (HBV)-related HCC, and to explore its potential therapeutic application in selecting patients for appropriate treatments in addition to the BCLC recommendation.

**Methods**

*Patients*

The cohort was composed of surgical and non-surgical patients with HBV-associated HCC. The surgical cohort was a retrospective one consisting of patients who underwent curative resection for primary HCC at the Prince of Wales Hospital, Hong Kong from January 2001 to December 2013. The non-surgical cohort was a prospectively accrued cohort from the multi-disciplinary hepatoma clinic at the Prince of Wales Hospital from June 2003 to March 2012.[12](#_ENREF_12), [13](#_ENREF_13) Patients with incomplete data for constructing various staging systems were excluded. Treatment was classified as curative (liver transplantation, surgical resection and local ablation), palliative (transarterial embolization and systemic therapy) and best supportive care. Non-curative treatments included palliative treatment and best supportive care. Systemic therapy included sorafenib or other systemic chemotherapeutic agents. Best supportive care referred to symptomatic treatment without active antineoplastic intervention. All parameters investigated were measured before any treatment and within 6 weeks of diagnosis. The ALBI score was computed by the formula, −0.085×(albumin g/l) + 0.66×log(bilirubin µmol/l). Patients were stratified into 3 groups according to previously described cut-offs resulting in 3 grades: ALBI grade 1 (≤−2.60), grade 2 (>−2.60 to −1.39) and grade 3 (>−1.39).[2](#_ENREF_2) Alternatively, the ALBI grade could be derived from the heatmap or normogram provided in the original article by Johnson et al. without calculation.[2](#_ENREF_2) Patients were then classified according to BCLC,[4](#_ENREF_4) JIS and ALBI-T scores (Table 1[)](#_ENREF_5).[3](#_ENREF_3) Overall survival (OS) was defined as the date of first diagnosis to the time of death, or last follow-up if death had not occurred.

*Statistical analyses*

Continuous variables were expressed in mean ± standard derivation or median with interquartile range (IQR). The Kaplan-Meier method was used to estimate the survival rates for different groups. The equivalences of the survival curves were tested by log-rank statistics. The prognostic performance of JIS and ALBI-T scores was evaluated by the following: (1) homogeneity within classification (differences in survival time among patients classified in the same group); (2) discriminatory ability (greater differences in survival time among patients in different groups); and (3) monotonicity of gradients (mean survival time in a more favorable group is longer than in a less favorable group).[14](#_ENREF_14) The likelihood ratio chi-square test was applied to evaluate the homogeneity and monotonicity of gradients. A larger value of the likelihood ratio chi-square test indicates a system with better homogeneity and monotonicity. The corrected Akaike information criterion (AICc) was employed to estimate the discriminatory ability.[15](#_ENREF_15) A smaller value of AICs signifies a system with higher discriminatory ability. All statistical analyses were performed by R version 3.02 (R Foundation for Statistical Computing, Vienna, Austria). A 2-tailed *P*-value <0.05 was regarded as statistically significant.

**Results**

*The prognostic performance of JIS and ALBI-T scores*

The surgical and non-surgical cohorts recruited 565 and 1306 patients, respectively. After excluding patients with incomplete data (n=372), co-infection of HBV/HCV (n=8), HCV infection (n=79) and non-B/non-C etiology (n=190), a total of 1222 patients were evaluated in the study. The baseline characteristics of patients are summarized in Table 2. Only 303 patients received antiviral treatment and 40.5% of them received before the diagnosis of HCC. The median OS of the entire cohort was 16.8 months, whereas that of patients receiving curative, palliative and best supportive treatments was not reached, 10.3 months and 2.7 months, respectively.

Kaplan-Meier curves for OS classified by JIS and ALBI-T scores are shown in Fig. 1. Significant differences in survival distributions were found across all stages of JIS and ALBI-T systems (all P<0.005) except JIS score 4/5 (P=0.130). Patients in ALBI-T score 1-4 had better median OS than patients in corresponding JIS score (P=0.043, <0.001, 0.001and 0.005 for score 1, 2, 3 and 4, respectively), whereas patients in ALBI-T score 0 and 5 showed similar clinical outcome to those in the corresponding JIS score (Table 3). The ALBI-T score showed better prognostic performance than the JIS score in terms of homogeneity, discriminatory ability and monotonicity of gradients, which were indicated by homogeneity likelihood chi-squares (ALBI-T 580.12 vs. JIS 536.35) and AICs (ALBI-T 9836.57 vs. JIS 9880.23). The homogeneity likelihood chi-square and AIC of BCLC was 711.42 and 9705.16, respectively.

*The therapeutic implications of ALBI-T score*

Treatment options significantly influenced prognosis amongst patients of the same BCLC stage (Fig. 2). In BCLC stage 0/A, patients undergoing curative therapy had better OS than those receiving non-curative treatments (P<0.001) (Fig. 2a). For those BCLC stage 0/A patients who underwent curative therapy, 20 patients (5.6%, 20/357) had ALBI-T score 3 or more, and did not show any prognostic superiority to patients who received non-curative treatments (Fig. 3a). Similarly, in BCLC stage B, curative therapy did not offer any survival advantage to patients with ALBI-T score 4/5 (n=13; 14.7% of 88 BCLC stage B patients treated with curative therapy) compared to palliative treatment (Fig. 3b). In BCLC stage C, patients undertaking palliative treatment had longer OS than those provided with best supportive care (P<0.001) (Fig. 2c). The outcome of patients with ALBI-T score 4/5 undertaking palliative treatment (25.2%, 69/273) was similar to that provided with best supportive care (Fig. 3c). Likewise, in BCLC stage D, palliative therapy did not provide any survival benefit to patients with ALBI-T score 4/5 (n=4; 28.6% of 14 BCLC stage D patients treated with palliative therapy) compared to best supportive care (Fig. 3d). In brief, ALBI-T score potentially provided an additional objective measure for clinicians to avoid unnecessary non-beneficial treatments to patients. In contrast, JIS score identified much fewer patients undergoing ineffective treatment among patients in BCLC stage 0/A (1.2%, 3/257), C (6.6%, 18/273) and D (21.4%, 3/14) (Supplementary Fig. 1), and failed to highlight those BCLC stage B patients receiving unnecessary curative therapy.

**Discussion**

We externally validates the prognostication of the ALBI-T score in 1222 Chinese patients with HBV-related HCC in Hong Kong. The ALBI-T score is feasibly applied among HBV-associated HCC patients as it could stratify patients into 6 prognostically distinguishing subgroups. It also showed better prognostic performance than the JIS score, which reemphasizes that the ALBI grade is not only a simple substitute but also a superior alternative of the Child-Pugh grade. However, there are two major discrepancies between the original report of the ALBI-T score and our present study. Firstly, Hiraoka et al. demonstrated that the ALBI-T score outperformed BCLC and CLIP.[3](#_ENREF_3) We found that both JIS and ALBI-T scores did not outweigh BCLC. In fact, the ancestor of the JIS score was shown to be superior to other staging systems (including BCLC and CLIP) by various Japanese cohorts,[3](#_ENREF_3), [16](#_ENREF_16), [17](#_ENREF_17) but the finding was not reproduced by other non-Japanese studies.[10](#_ENREF_10), [15](#_ENREF_15), [18](#_ENREF_18) This is likely because HCC is highly heterogeneous in tumor burden, etiology, liver function, treatment option and ethnicity. Secondly, the clinical outcome of ALBI-T score 2 and 3 in our cohort were poorer than that of corresponding score in the Japanese cohort (25.0 months vs. 53.4 months for ALBI-T score 2; 8.4 months vs. 27.4 months for ALBI-T score 3).[3](#_ENREF_3) These findings could be explained by the allocation of curative therapy among patients in these 2 subgroups: ALBI-T score 2 (49.7% in Hong Kong vs. 67.8% in Japan) and score 3 (27.5% in Hong Kong vs. 40.0% in Japan). Within the ALBI-T subgroup, more Japanese patients tended to receive curative treatment than Hong Kong patients likely as a result of successful national screening program which could diagnose tumor at smaller size amongst the ALBI-T score 2 and 3 category.[19](#_ENREF_19)

Although BCLC system is designed to guide treatment to each stage category, it has been shown by multiple studies that more aggressive treatment could offer better outcome in Stage B, C or even D patients. In current study, surgical resection provided the best survival benefit for patients in BCLC stage 0, A, even B and C,[9](#_ENREF_9), [11](#_ENREF_11) whereas transarterial chemotherapy could offer survival advantages in selected patients in BCLC stage C and D.[9](#_ENREF_9) Our study reiterated that treatment options could influence clinical outcome of patients in the same BCLC stage. On the other hand, apart from administering aggressive treatment to suitable patients, non-beneficial treatments should also be avoided. With the use of ALBI-T score 4 as the cutoff, the current study identified that 14.7%, 25.2% and 28.6% of patients undergoing unnecessary therapy without survival advantage in BCLC stage B, C and D, respectively. The ALBI-T score could help select patients who are not expected to derive benefit from the treatment despite the recommendation by BCLC system.

Our study has few limitations. Firstly, our cohort did not recruit any patients undergoing liver transplantation due to the local referral policy. However, there were also lack of patients undergoing liver transplantation in the study population on ALBI-T by Hiraoka et al.[3](#_ENREF_3) The generalizability of the ALBI-T score to HCC population who received liver transplantation as the primary treatment requires further investigations. Secondly, our cohorts included patients before the era of widely use of the potent HBV nucleot(s)ide analogues. As antiviral agents could improve liver function and potentially downstage tumor,[20](#_ENREF_20), [21](#_ENREF_21) it is important to validate the ALBI-T score in a more modern cohort with wide-spread use of antivirals for HBV.

In summary, the ALBI-T score is applicable to Chinese patients with HBV-related HCC to provide reasonable prognostic information as well as potentially helping clinicians to avoid offering non-beneficial aggressive treatments.

**References**

[1] 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.

[2] 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.

[3] Hiraoka A, Kumada T, Michitaka K*, et al.* Usefulness of albumin-bilirubin (ALBI) grade for evaluation of prognosis of 2584 Japanese patients with hepatocellular carcinoma. *J Gastroenterol Hepatol*. 2015.

[4] Chan AW, Kumada T, Toyoda H*, et al.* Integration of albumin-bilirubin (ALBI) score into Barcelona clinic liver cancer (BCLC) system for hepatocellular carcinoma. *J Gastroenterol Hepatol*. 2016.

[5] Guo Z, Zhong JH, Jiang JH, Zhang J, Xiang BD, Li LQ. Comparison of survival of patients with BCLC stage A hepatocellular carcinoma after hepatic resection or transarterial chemoembolization: a propensity score-based analysis. *Ann Surg Oncol*. 2014; **21**: 3069-76.

[6] Yin L, Li H, Li AJ*, et al.* Partial hepatectomy vs. transcatheter arterial chemoembolization for resectable multiple hepatocellular carcinoma beyond Milan Criteria: a RCT. *J Hepatol*. 2014; **61**: 82-8.

[7] Bruix J, Sherman M, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology*. 2011; **53**: 1020-2.

[8] European Association for the Study of the Liver, European Organisation For Research and Treatment of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2012; **56**: 908-43.

[9] Wang JH, Changchien CS, Hu TH*, et al.* The efficacy of treatment schedules according to Barcelona Clinic Liver Cancer staging for hepatocellular carcinoma - Survival analysis of 3892 patients. *Eur J Cancer*. 2008; **44**: 1000-6.

[10] Kim BK, Kim SU, Park JY*, et al.* Applicability of BCLC stage for prognostic stratification in comparison with other staging systems: single centre experience from long-term clinical outcomes of 1717 treatment-naive patients with hepatocellular carcinoma. *Liver Int*. 2012; **32**: 1120-7.

[11] Torzilli G, Belghiti J, Kokudo N*, et al.* A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: is it adherent to the EASL/AASLD recommendations?: an observational study of the HCC East-West study group. *Ann Surg*. 2013; **257**: 929-37.

[12] Chan SL, Mo FK, Johnson PJ*, et al.* Prospective validation of the Chinese University Prognostic Index and comparison with other staging systems for hepatocellular carcinoma in an Asian population. *J Gastroenterol Hepatol*. 2011; **26**: 340-7.

[13] Chan AW, Chan SL, Mo FK*, et al.* Albumin-to-Alkaline Phosphatase Ratio: A Novel Prognostic Index for Hepatocellular Carcinoma. *Dis Markers*. 2015; **2015**: 10.

[14] Ueno S, Tanabe G, Sako K*, et al.* Discrimination value of the new western prognostic system (CLIP score) for hepatocellular carcinoma in 662 Japanese patients. Cancer of the Liver Italian Program. *Hepatology*. 2001; **34**: 529-34.

[15] Liu PH, Hsu CY, Hsia CY*, et al.* Prognosis of hepatocellular carcinoma: Assessment of eleven staging systems. *J Hepatol*. 2015.

[16] Kudo M, Chung H, Haji S*, et al.* Validation of a new prognostic staging system for hepatocellular carcinoma: the JIS score compared with the CLIP score. *Hepatology*. 2004; **40**: 1396-405.

[17] Kitai S, Kudo M, Izumi N*, et al.* Validation of three staging systems for hepatocellular carcinoma (JIS score, biomarker-combined JIS score and BCLC system) in 4,649 cases from a Japanese nationwide survey. *Dig Dis*. 2014; **32**: 717-24.

[18] Hsu CY, Hsia CY, Huang YH*, et al.* Selecting an optimal staging system for hepatocellular carcinoma: comparison of 5 currently used prognostic models. *Cancer*. 2010; **116**: 3006-14.

[19] Kudo M. Japan's Successful Model of Nationwide Hepatocellular Carcinoma Surveillance Highlighting the Urgent Need for Global Surveillance. *Liver Cancer*. 2012; **1**: 141-3.

[20] Chan SL, Mo FK, Wong VW*, et al.* Use of antiviral therapy in surveillance: impact on outcome of hepatitis B-related hepatocellular carcinoma. *Liver Int*. 2012; **32**: 271-8.

[21] Chan SL, Wong VW, Qin S, Chan HL. Infection and Cancer: The Case of Hepatitis B. *J Clin Oncol*. 2016; **34**: 83-90.

**Figure legends**

Figure 1: Kaplan-Meier survival plots comparing overall survivals for all 1222 patients stratified by (a) JIS score and (b) ALBI-T score.

Figure 2: Kaplan-Meier survival plots comparing overall survivals stratified by treatment modalities among patients in (a) BCLC stage 0/A, (b) BCLC stage B, (c) BCLC stage C, and (d) BCLC stage D.

Figure 3: Kaplan-Meier survival plots comparing overall survivals among (a) BCLC stage 0/A patients: Non-curative vs. curative (ALBI-T score 3/4/5); (b) BCLC stage B patients: Non-curative vs. curative (ALBI-T score 4/5); (c) BCLC stage C patients: best supportive care vs. palliative (ALBI-T score 4/5); and (d) BCLC stage D patients: best supportive care vs. palliative (ALBI-T score 4/5).

Supplementary Figure 1: Kaplan-Meier survival plots comparing overall survivals among (a) BCLC stage 0/A patients: Non-curative vs. curative (JIS score 3/4/5); (b) BCLC stage C patients: best supportive care vs. palliative (JIS score 4/5); and (c) BCLC stage D patients: best supportive care vs. palliative (JIS score 4/5).