FIGURE 3E

Country	BALAD-2 score	N	Median survival (months)	95% Conf. Interval	
UK (BALAD-2)	1	111	26.1	18.6	35.8
	2	116	17.6	12.4	19.2
	3	91	7.0	5.6	9.5
	4	56	2.0	1.3	2.8
Japan (BALAD-2)	1	816	78.9	71.6	86.3
	2	379	30.0	26.9	34.4
	3	208	11.7	9.6	15.6
	4	111	2.0	1.6	3.1
Germany (BALAD-2)	1	90	26.1	18.7	38.8
	2	54	14.1	7.6	20.9
	3	67	6.7	5.3	8.1
	4	40	2.4	1.3	3.8
Hong Kong (BALAD-2)	1	68	Not reached	34.8	.
	2	67	15.0	11.3	25.8
	3	61	4.3	3.1	5.3
	4	50	1.6	1.1	2.6

Integration of Albumin-Bilirubin (ALBI) score into Barcelona Clinic Liver Cancer (BCLC) system for hepatocellular carcinoma

Running title: ALBI-based BCLC for HCC

Anthony W.H. Chan[1]

Takshi Kumada[2]

Hidenori Toyoda[2]

Toshifumi Tada[2]

Charing C.N. Chong[3]

Frankie K.F. Mo[4]

Winnie Yeo[4]

Philip J. Johnson[5]

Paul B.S. Lai[2,5]

Anthony T.C. Chan[4]

Ka-Fai To[1,6,7]

Stephen L. Chan[4,6]

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

[2]Department of Gastroenterology, Ogaki Municipal Hospital, Ogaki, Japan

[3]Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, The Chinese University of Hong Kong

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/jgh.13291

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

[5]Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Liverpool, United Kingdom

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

[7]Li 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, WY, PJJ, PBSL, ATCC, KFR

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

Data analysis: AWHC, SLC

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

Funding support

None

Disclosure/Conflict of interest

None

Abstract

Background and Aims

The albumin-bilirubin (ALBI) grade is a recently reported, simpler, more objective and evidence-based alternative to the Child-Pugh (CP) score for hepatocellular carcinoma (HCC). We aimed to study whether ALBI grade could substitute for CP score in Barcelona Clinic Liver Cancer (BCLC) for HCC.

Methods

An international multicentre cohort (n=3696) was accrued to compare the prognostic performance of the CP-based and ALBI-based BCLC system, in terms of homogeneity, discriminatory ability and monotonicity of gradients which were numerically reflected by homogeneity likelihood and linear trend chi-squares, and c-indices, respectively.

Results

ALBI grade performed as well as CP score when integrated into the BCLC staging system in terms of predicting clinical outcome of HCC regardless of regions, aetiology and treatment options. CP-based and ALBI-based BCLC systems were highly concordant with weighted kappa value of 0.917. All restaged patients showed significantly different clinical outcomes compared to their original stage classification. In particular, ALBI-based BCLC upstaged 83 (2.2%) patients from lower CP-based BCLC stages to ALBI-based BCLC stage D, whose median overall survival was only 3 months.

Conclusions

The overall prognostic performance of ALBI-based and CP-based BCLC system was similar. It also potentially allows more precise patient selection for clinical trials on systemic agents.

Keywords

albumin; Barcelona Clinic Liver Cancer (BCLC); bilirubin; Child-Pugh score; liver function; survival; prognosis; tumour staging

Introduction

Hepatocellular carcinoma (HCC) is the sixth commonest cancer and the second commonest cause of cancer-associated death worldwide in 2012.[1] The clinical outcome and therapeutic options depend not only on tumour burden but also on hepatic function. The Child-Pugh (CP) score is widely adopted to gauge the severity of hepatic dysfunction in patients with HCC; it assesses five clinical and laboratory parameters semiquantitatively, including the severity of ascites, degree of hepatic encephalopathy, international normalized ratio (INR), serum albumin and bilirubin levels. The CP score has therefore been incorporated into most HCC staging systems including the Barcelona Clinic Liver Cancer (BCLC) system, the Cancer of the Liver Italian Program (CLIP) score and the Japan Integrated Staging (JIS).[2-4] As endorsed by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL), the BCLC system is currently the most widely recognized staging system worldwide.[4, 5]

Despite its popularity, the CP score has several limitations including the arbitrary use of cut-off values for the parameters, the same weighting among all five parameters, and the subjective nature of ascites and hepatic encephalopathy assessment.[6, 7] In 2015, the albumin-bilirubin (ALBI) scoring model for evaluation of hepatic function in patients with HCC was reported.[7] The score was derived from a cohort of 1313 Japanese patients with HCC with the use of multivariable Cox regression and validation by multi-institutional cohorts of 5097 patients from different geographic regions. The score was also shown to provide prognostic information in patients with cirrhosis alone. The ALBI score not only provides similar prognostic information to CP class in patients with HCC but also obviates the need to assess subjective parameters such as ascites and hepatic encephalopathy. Nevertheless, how ALBI grade facilitates clinical management of patients with HCC in daily practice remains to be

addressed.[8] Before the generalized use of ALBI score, one of the key questions is whether ALBI grade could replace CP class in the existing tumour staging system for prognostication and management of HCC. To address this issue, we conducted a large international multicentre cohort study of patients with HCC to compare the prognostic performance of the original CP-based BCLC and an ALBI-based BCLC.

Methods

Patients

Patients from three geographical regions, namely Hong Kong, Japan and the United Kingdom, were studied. The cohort from Hong Kong was composed of surgical and non-surgical patients. The surgical cohort (n=525) is a retrospective one consisting of patients who underwent curative resection for primary HCC at the Prince of Wales Hospital from January 2001 to December 2012. The non-surgical cohort (n=1007) is a prospectively accrued cohort from the multi-disciplinary hepatoma clinic at the Prince of Wales Hospital from June 2003 to March 2012.[9, 10] The cohort from Japan (n=1502) was composed of patients with primary HCC who underwent treatment with follow up at Ogaki Municipal Hospital between 1998 and 2013. Patients in the cohort from the United Kingdom were recruited at the Queen Elizabeth Hospital, Birmingham, and from those who were approached and consented to the study between 2007 and 2012.

Treatment was classified as curative (liver transplantation, surgical resection and local ablative therapy) or palliative (transarterial embolization, systemic therapy or best supportive care). All parameters investigated were measured before any treatment and within 6 weeks of diagnosis. ALBI score is computed by the formula, $-0.085\times$(albumin g/l) + $0.66\times\log$(bilirubin μmol/l). Patients were stratified into three groups according to previously

described cut-offs resulting in three grades: ALBI grade 1 (≤−2.60), grade 2 (>−2.60 to −1.39) and grade 3 (>−1.39)..[7] Patients were then classified according to CP-based and ALBI-based BCLC staging systems (Table 1). 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

The Kaplan-Meier method was used to estimate the survival rates for different groups. The prognostic performance of staging systems 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 favourable group is longer than in a less favourable group).[11] The likelihood ratio test was applied to evaluate the homogeneity. The linear trend chi-square test was used to quantify both the monotonicity and discriminatory ability. The Harrell's concordance index (c-index) was calculated by bootstrapping with 100 resamples to estimate the discriminatory ability. The agreement between CP-based and ALBI-based BCLC systems was evaluated by weighted kappa statistics. 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

Baseline characteristics

The baseline characteristics of the three cohorts are summarized in Table 2. In summary, a total of 3696 patients were evaluated. The Hong Kong cohort was composed of 1532 patients with 81.7% attributable to chronic hepatitis B virus (HBV). The Japanese cohort comprised

1502 patients mainly (69.9%) attributable to chronic hepatitis C virus (HCV) infection. The United Kingdom cohort comprised 662 patients, of which half of them (49.8%) had neither HBV nor HCV infection. The rate of curative therapy was highest in the Japanese cohort (60.7%), followed by United Kingdom (39.9%) and Hong Kong (38.8%). The median OS of Japan, United Kingdom and Hong Kong cohort was 44.9, 20.1 and 13.7 months, respectively.

The prognostic performance of CP-based and ALBI-based BCLC systems

Kaplan-Meier curves for OS among all patients (n=3696) classified by CP-based and ALBI-based BCLC systems are shown in Fig. 1. Within each CP-based and ALBI-based BCLC systems, there were significant differences in the median OS of different groups of patients ($P<0.001$). The similarity in prognostic performance, in terms of homogeneity, discriminatory ability and monotonicity of gradients, between the two systems was numerically reflected by the homogeneity likelihood and linear trend chi-squares, and c-indices (Table 3). Overall, the ALBI score performed as well as the CP score when integrated into the BCLC staging system to predict the clinical outcome of patients with HCC. In subgroup analyses, the performance of CP-based and ALBI-based BCLC systems was similar, irrespective of region, aetiology or treatment intents (Table 3; Suppl. Fig. 1-3).

Stage redistribution by ALBI-based BCLC

The CP-based and ALBI-based BCLC systems were highly concordant with a weighted kappa of 0.917 ($P<0.001$). A total of 328 patients were upstaged, and 35 patients were downstaged with the use of ALBI-based staging system (Fig. 2). All restaged patients showed significantly different clinical outcomes compared to their original stage groups (Fig. 3). The median OS of unaltered and restaged patients among in CP-based BCLC stage 0, A, B, C and D was not reached vs. 96.2 months ($P<0.001$), 70.1 months vs. 23.8 months ($P<0.001$), 29.2

months vs. 9.2 months (P<0.001), 7.4 months vs. 4.1 months (P<0.001), and 3.0 months vs. 19.6 months (P=0.003), respectively. In particular, amongst the 328 patients with upstaging of disease, a large proportion (n=176) were upstaged from a lower CP-based BCLC stage to ALBI-based BCLC stage D. Almost half of these (n=83; 47.2%) received supportive care with a median OS of 3.0 months, whereas other patients undergoing treatment other than supportive care had a median OS of 15.2 months. On the other hand, 35 (0.9%) patients had disease downstaged from CP-based BCLC stage D to lower ALBI-based BCLC stage. Amongst this group of patients, 37.1% (n=13) underwent treatment other than supportive therapy, with a median OS of 28.2 months. The remaining 22 patients received supportive care had a median OS of 2.8 months only.

Discussion

In the current international study, we examined a large international multicentre cohort study of 3696 patients and compared the prognostic power of CP-based and ALBI-based BCLC systems. It is demonstrated that ALBI score provides similar prognostic discrimination as CP class when incorporating into BCLC regardless of aetiologies, regions and treatment intents. The findings indicate that the substitution of CP class by ALBI score does not influence the overall prognostic performance of the BCLC system. Compared to CP class, there are several advantages favoring the incorporation of the ALBI score in tumor staging. First, the two parameters, namely serum albumin and bilirubin, for the ALBI score, could objectively be obtained by readily-accessible blood tests. In contrast, the clinical assessment of ascites and hepatic encephalopathy for the CP score is difficult to score consistently. Moreover, the criteria for different grades of ascites are not uniform in different studies.[12, 13] Therefore, the ALBI score provides an entirely objective tool of assessing hepatic dysfunction during prognostication of HCC. Second, the two components of the ALBI score are selected on the

basis of a mathematical model but the five components of the CP score are selected empirically with arbitrary use of cut off values and same weighting among all parameters. Further, there were correlations between components of the CP score such as albumin and INR (both reflecting hepatic synthetic function), and albumin and ascites (decreased plasma osmotic pressure due to hypoalbuminaemia).[14, 15] Third, the CP score is designed primarily for cirrhotic patients but a certain proportion of HCC arises from the noncirrhotic liver.[16] Fourth, the cutoff values of bilirubin in the CP score is required to be modified for chronic cholestatic diseases such as primary biliary cirrhosis.[17] However, we demonstrated that the ALBI score can be applied in primary biliary cirrhosis without any modification.[18] In view of simplicity, objectivity, evidence-based and generalizability across different ethnic groups, the ALBI score is a promising alternative to the CP score to assess liver function within tumor staging system.

Despite the similarity in overall prognostic performance between the CP-based and the ALBI-based BCLC staging system, it is noted that the ALBI-based BCLC have upstaged a significant number of patients, as compared to the CP-based BCLC. Two CP class A and 194 CP class B patients were reclassified as ALBI grade 3, whereas only 38 CP class C patients were re-stratified as ALBI grade 2. As a result, 176 patients were upstaged from lower CP-based BCLC stages to ALBI-based BCLC stage D patients, and the median of OS of this group was 3 months only with almost half of them not suitable for any form of active treatment. This may be of clinical relevance because the BCLC system has been linked with treatment algorithm corresponding to each tumour stage. For examples, BCLC stage C and selected stage B patients are frequently recommended to be trial candidates for novel agents. Currently, most clinical trials on HCC have eligibility criteria of excluding patients with an expected OS of shorter than 3 months, who are believed to have more aggressive disease and

be less suitable for clinical trials.[19] However, the judgement on expected survival of patients mostly relies on clinicians' subjective assessments. The use of the ALBI-based staging system in identification of more suitable candidates is potentially helpful and requires further investigations.

Our study has few caveats. Firstly, patients did not receive treatment modalities strictly according to the BCLC treatment algorithm. For example, a significant portion of patients with early stage disease (19.4% of CP-based BCLC 0/A and 18.7% of ALBI-based BCLC 0/A) patients received palliative treatment only. Similarly, a certain portion of patients with terminal disease (10.6% of CP-based BCLC D and 14.8% of ALBI-based BCLC D) underwent curative treatments. Such discordance has also been observed in other studies,[20, 21] and in real-life practice, clinicians frequently consider multiple factors in addition to tumour stage for decision of treatment modality.[22] Secondly, some patients having relatively early tumours without vascular invasion or extrahepatic spread (i.e. CP-based BCLC A and B) were up-staged to the terminal stage D by ALBI. Their median survival rates (23.8 months and 9.2 months of originally CP-based BCLC A and B, respectively) were far above than that of terminal disease. Although they represented a small portion of their originally staged group (3.4% and 4.1% of CP-based BCLC A and B, respectively), they would be precluded for aggressive therapy according to the current guideline. Indeed, some groups have showed that liver transplantation could result in survival benefit for patients with HCC and advanced liver cirrhosis (BCLC stage D).[23, 24] Thirdly, some experts in the HCC field may hold a view that a completely novel staging system should be developed by combining ALBI score and other tumour-related factors for HCC, rather than substituting the CP class by ALBI score in existing staging systems. Our group is not opposed to this approach but consider the incorporation approach more acceptable and pragmatic to clinicians who are used to the

current staging system. Finally, both HCC cohorts in Hong Kong and Japan come from era whereas the potent HBV nucleot(s)ide analogues were not widely used or direct acting antivirals for HCV were not available. Since these antiviral agents could lead to improvement of hepatic function and potential downstaging of tumor, it is of value to validate the ALBI-BCLC staging system in a more modern cohort with wide-spread use of antivirals for HBV and HCV.

In conclusion, the ALBI score provides a similar overall prognostic discrimination as the CP score when incorporating into the BCLC tumour staging systems regardless of regions, aetiologies and treatment options. ALBI-based tumour staging system also potentially allow better patient selection for clinical trials on novel drugs.

References

[1] Ferlay J, Soerjomataram I, Ervik M, *et al.* GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. International Agency for Research on Cancer, Lyon, France.

[2] The Cancer of the Liver Italian Program (CLIP) investigators. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients. *Hepatology*. 1998; **28**: 751-5.

[3] 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.

[4] 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.

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

[6] Durand F, Valla D. Assessment of the prognosis of cirrhosis: Child-Pugh versus MELD. *J Hepatol*. 2005; **42 Suppl**: S100-7.

[7] 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.

[8] Knox JJ. Addressing the Interplay of Liver Disease and Hepatocellular Carcinoma on Patient Survival: The ALBI Scoring Model. *J Clin Oncol*. 2015; **33**: 529-31.

[9] 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.

[10] 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.

[11] 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.

[12] Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg*. 1973; **60**: 646-9.

[13] Infante-Rivard C, Esnaola S, Villeneuve JP. Clinical and statistical validity of conventional prognostic factors in predicting short-term survival among cirrhotics. *Hepatology*. 1987; **7**: 660-4.

[14] Fujii M, Yasunaga K, Uchino H. Correlation analysis of relationships between vitamin-K-dependent clotting factors and effective hepatic blood flow, albumin and other liver function tests. *Haemostasis*. 1980; **9**: 9-14.

[15] Arroyo V. Pathophysiology, diagnosis and treatment of ascites in cirrhosis. *Ann Hepatol*. 2002; **1**: 72-9.

[16] Trevisani F, Frigerio M, Santi V, Grignaschi A, Bernardi M. Hepatocellular carcinoma in non-cirrhotic liver: a reappraisal. *Dig Liver Dis*. 2010; **42**: 341-7.

[17] Chan AW, Chan RC, Wong GL, *et al.* Evaluation of histological staging systems for primary biliary cirrhosis: correlation with clinical and biochemical factors and significance of pathological parameters in prognostication. *Histopathology*. 2014; **65**: 174-86.

[18] 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.

[19] Chan SL, Yeo W. Selecting the right patients for testing novel agents in hepatocellular carcinoma: who, when and how? *Asia Pac J Clin Oncol*. 2013; **9**: 2-5.

[20] Marrero JA, Fontana RJ, Barrat A, *et al.* Prognosis of hepatocellular carcinoma: comparison of 7 staging systems in an American cohort. *Hepatology*. 2005; **41**: 707-16.

[21] Chan SL, Johnson PJ, Mo F, *et al.* International validation of the Chinese university prognostic index for staging of hepatocellular carcinoma: a joint United Kingdom and Hong Kong study. *Chin J Cancer*. 2014; **33**: 481-91.

[22] Roayaie S, Jibara G, Tabrizian P, *et al.* The role of hepatic resection in the treatment of hepatocellular cancer. *Hepatology*. 2015.

[23] D'Avola D, Inarrairaegui M, Pardo F, *et al.* Prognosis of hepatocellular carcinoma in relation to treatment across BCLC stages. *Ann Surg Oncol*. 2011; **18**: 1964-71.

[24] Vitale A, Morales RR, Zanus G, *et al.* Barcelona Clinic Liver Cancer staging and transplant survival benefit for patients with hepatocellular carcinoma: a multicentre, cohort study. *Lancet Oncol*. 2011; **12**: 654-62.

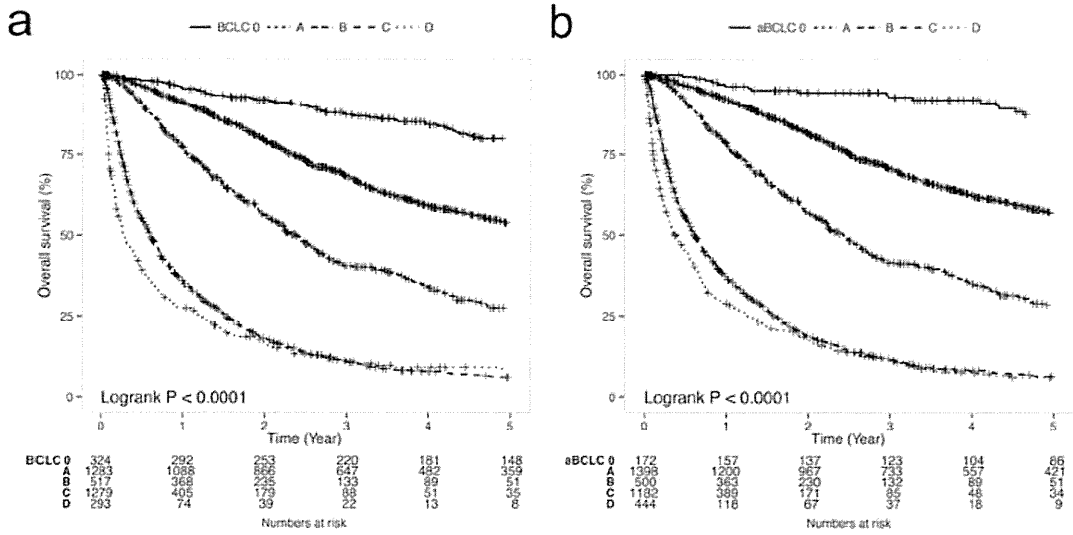

Figure 1: Kaplan-Meier survival plots comparing overall survivals for all 3696 patients stratified by (a) Child-Pugh-based BCLC and (b) ALBI-based BCLC staging systems.

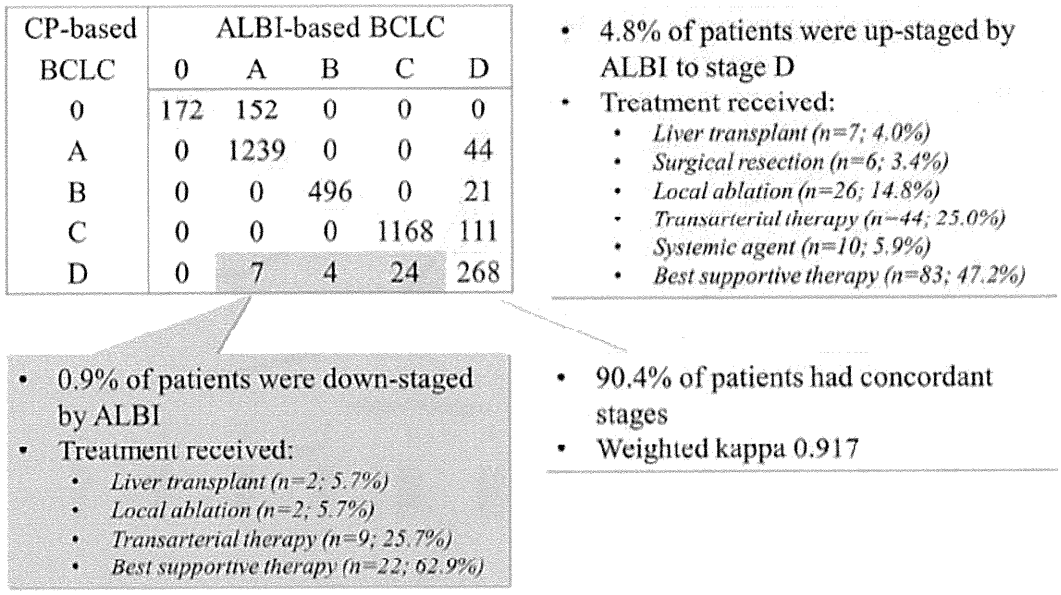

Figure 2: Stage distribution between Child-Pugh-based and ALBI-based BCLC systems.

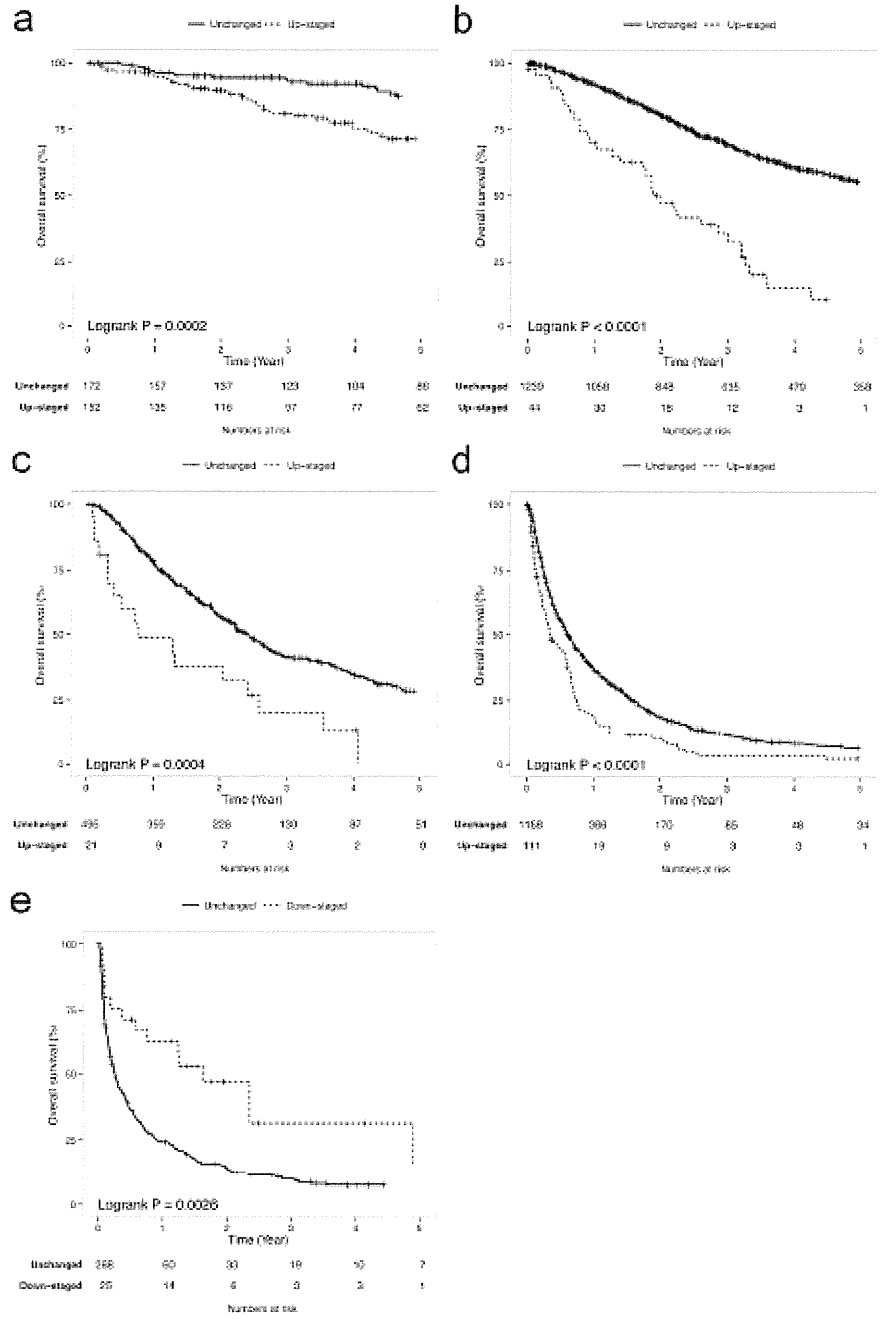

Figure 3: Kaplan-Meier survival plots comparing overall survivals for patients restaged by ALBI in (a) Child-Pugh-based BCLC 0, (b) Child-Pugh-based BCLC A, (c) Child-Pugh-based BCLC B, (d) Child-Pugh-based BCLC C, and (e) Child-Pugh-based BCLC D.