**Applicability of BALAD score in prognostication of hepatitis B-related hepatocellular carcinoma**

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**Abstract**

**Background and Aims**

The BALAD score is developed to provide an objective determination of prognosis for hepatocellular carcinoma (HCC) by incorporating five serum markers including albumin, bilirubin, AFP, AFP-L3 and DCP. We aim to study the applicability of BALAD score and prognostication of the three tumor markers in hepatitis B-virus (HBV)-related HCC.

**Methods**

Patients with newly diagnosed HCC were prospectively enrolled. All of the baseline characteristics and serum albumin and bilirubin level were documented at baseline. The levels of the three tumor markers (AFP, AFP-L3 and DCP) were determined in archival serum samples. Patients were followed up for survivals according to local practice. The prognostic performances of the three markers and BALAD score were studied in association with overall survival (OS).

**Results**

Total 198 patients with hepatitis B-related HCC were recruited. AFP and AFP-L3 levels were independent prognostic factors. The number of elevated tumor markers was also predictive of worse OS. BALAD score could stratify the cohort into different patient groups with distinct median OS. The median OS of BALAD score of 0, 1, 2, 3 and 4 was not reached, 26.6, 8.3, 2.6 and 1.9 months, respectively (p<0.0001). BALAD score could further stratify outcomes in each BCLC subgroup. In particular, BALAD score of 3-4 had median OS of 2.6 months only in BCLC stage C patients.

**Conclusions**

BALAD score is applicable in the population of HBV-related HCC. The combined use of BALAD score and BCLC staging system could help identify more suitable candidates for clinical trial.

***Introduction***

The prognostication of hepatocellular carcinoma (HCC) differs from other cancer types because the outcomes of patients are not only influenced by tumor factors but also by multiple additional factors, including hepatic function, patients’ performance status, tumor markers and treatment modality. For the past decade, a number of staging systems have been developed for prognostication of HCC by different combinations of above prognostic factors. For examples, the Cancer of the Liver Italian Program (CLIP) score consists of four parameters including serum alpha-fetoprotein (AFP), tumor morphology and extent, Child-pugh stage and portal vein thrombosis.[1](#_ENREF_1) Barcelona Clinic Liver Cancer (BCLC) staging system considers factors including performance status, Child-pugh stage, tumor size and number, treatment modality, the presence of extra-hepatic disease and portal vein thrombosis.[2](#_ENREF_2) One of the common problems encountered in applying these staging systems is that some of the clinical factors, such tumor morphology and the presence of ascites, could be subjective and variable amongst different clinicians.[3](#_ENREF_3) This issue has led to difficulty in comparing prognoses of HCC patients in multi-centered clinical trials, even when the same staging system is applied.

In 2006, Japanese investigators proposed a staging model which was built on purely objective clinical parameters for HCC.[4](#_ENREF_4) The system, also known as the bilirubin, albumin, *Lens culinaris* agglutinin A–reactive fraction of alphafeto-protein, alphafeto-protein, and des-γ-carboxy prothrombin (BALAD) score, was built on a formula using a total of five objective parameters, namely the level of serum albumin and bilirubin, together with three serological tumor markers, AFP, Lens culinaris agglutinin-reactive alpha-fetoprotein (AFP-L3) and des-γ-carboxy prothrombin (DCP).[4](#_ENREF_4) The score could stratify the Japanese population of HCC into six groups with distinct survivals. Its objective nature could also allow uniform comparison of prognoses of patients in different centers, as well as enable the retrospective determination of patients’ prognoses without bias in recall or interpretation of medical record. Further, the BALAD score has the advantage of being a simple test by requiring only a plasma sample for analysis. The BALAD score has been validated in an independent cohort of Japanese population of HCC as well as in the Caucasian population of HCC, and the score is consistently able to stratify the outcome of HCC into six groups of patient with distinct median overall survival (OS).[5](#_ENREF_5), [6](#_ENREF_6)

In previous studies on the BALAD score, the etiology of HCC population is mainly due to hepatitis C virus infection and alcoholic cirrhosis. Hepatitis B virus (HBV) infection is under-represented in those studies with proportion lower than 15% of the study population. In Hong Kong and most of parts of China, HBV infection is the predominant etiology of HCC, accounting for more than 80% of the caseload.[7](#_ENREF_7), [8](#_ENREF_8) From year 2009 to 2013, our group has composed a prospective cohort of newly diagnosed HCC with a full record of baseline characteristics as well as paired serum sample. By measuring the levels of the three tumor markers in the serum samples, we aim to study the performance of BALAD score and each serological marker in prognostication of outcome of HCC of which HBV infection is the main etiology. At same time, because BCLC is a commonly applied staging system in clinical practice, we also aim to compare BALAD score to BCLC system, and explore the clinical value of combining both BALAD score and BCLC staging system for prognostication of HCC.

***Methods***

**Patients**

The patient cohort is composed of consecutive treatment-naïve patients attending the joint hepatoma clinic at the Prince of Wales Hospital, Hong Kong, from December 2009 to July 2013. The joint hepatoma clinic is the primary referral clinic for HCC in New Territories East of Hong Kong, which serves a population of approximately 2 million. The diagnosis of HCC was confirmed either by histological evidence when surgery or biopsy had been performed, or by radiologic criteria according to the international guidelines for diagnosis of HCC.[9](#_ENREF_9) Serum sample was obtained at the time of consent and before commencement of any treatment. The recruitment of patients was approved by the ethics committee, and all patients provide informed consent before their data were collected at the time of recruitment. In the joint clinic, the decision of treatment for HCC is decided by a multi-disciplinary team consisting of surgeon, oncologist and interventional radiologist. All patients are followed in the joint clinic according to the routine local practice.

**Clinical parameters and staging system**

Clinical parameters including baseline demographics (e.g. age, sex, ECOG performance status), etiology of HCC, tumorous features (maximal diameter and number of tumor; presence of vascular invasion), hepatic reserves (including ascites, liver function parameters; Child-pugh stage) and tumor staging were recorded at the time of consent. The modality of first-line treatment was documented after the treatment plan was decided after the clinical assessment.

**Determination of serological tumor markers and BALAD score**

The methodologies of measurements of AFP, AFP-L3 and DCP were described as previously. In brief, assays of AFP, AFP-L3, and DCP were conducted in the same serum sample by using a microchip capillary electrophoresis and liquid-phase binding assay on a μTAS Wako i30 analyzer (Wako Pure Chemical Industries, Ltd, Osaka, Japan).[10](#_ENREF_10) The precision of the assay for the two levels of the three markers were lower than 5% coefficient of variations with detection range of 0.3-1000ng/ml for AFP and 5-5000 AU/L for DCP. Analytical sensitivity is 0.3ng/ml for AFP and the percentage of AFP-L3 can be measured when AFP-L3 is over 0.3ng/ml. The computation of BALAD score was described previously[4](#_ENREF_4). In brief, the serum albumin was categorized as

>3.5, 2.8 –3.5, or <2.8 and scored as 0, 1, and 2, respectively, while the serum total bilirubin was categorized as <17.1, 17.1-34.2, or >34.2 and scored as 0, 1, and 2, respectively. The component of liver function was then categorized by the sum of these 2 scores as 0-1, 2-3, or 4 (Table 1). The final BALAD score was computed as described in Table 1.

**Statistical analysis**

All analyses were carried out with the use of SAS® version 9.3 [SAS Institute Inc., Cary NC]. Baseline demographic and clinical factors were summarized as the frequency and percentage, and continuous variables were expressed as median and range. Overall Survival (OS) was defined as the time from diagnosis of HCC to death by any cause or the date of last follow-up. Survival curves were estimated using the Kaplan-Meier method and inter-group comparisons were performed with the log-rank test. The median survival time and the corresponding 95% confidence will be provided. The cut-off date of the dataset for analysis was 30 June 2014.

Univariate was performed using Cox proportional hazard model to estimate the hazard ratios. The corresponding 95% confidence interval (CI)s were calculated. A stepwise model building procedure was used for multivariate analysis, based on a significance value of 0.05 for both inclusion and exclusion of prognostic factors. Proportional hazards assumptions were tested graphically.

Comparison of BCLC system and BALAD score was assessed by Harrell’s concordance-index (c-index).[11](#_ENREF_11) The Harrell’s C-index is equivalent to the area under the receiver operator characteristic curve, and ranges from 0.0 to 1.0. It estimates the proportion of correct predictions. A c-index of 1.0 indicates perfect concordance between the two variables (i.e. the order of survival time and the magnitude of various staging) while a c-index of 0.5 indicates a chance association. The c-index were calculated by using the SAS macro program[12](#_ENREF_12) and compared by using the bootstrap method with 500 replications.

***Results***

**Baseline characteristics**

Total 198 patients have been analyzed. The median duration of follow-up was 37.3 months (95% CI 33.1-42.6 months). The date of data cut-off for analysis was 30 June 2014. The baseline characteristics were listed in Table 2. In summary, close to 70% of patients had liver function of Child-pugh class A, and 95 (48.0%) of the patient cohort had radiological or clinical evidence of cirrhosis. Approximately 60% of patients suffered from multifocal HCC. The proportion of BCLC stage was as following: stage A (35; 17.7%), stage B (41, 20.7%), stage C (104; 52.5%) and stage D (18; 9.1%). Thirty-seven patients underwent treatment of curative intent, including surgery and locoablation, while another 161 patients received treatment of palliative intent, including TACE, systemic treatment or supportive care. The mean bilirubin and albumin level was 20µmol/L and 38g/dL, respectively.

**Prognostic role of AFP, AFP-L3 and DCP**

The median value of AFP, AFP-L3 and DCP was 228.2ng/ml, 25.2% and 48.2 ng/ml, with corresponding range of 0.7-1359304 ng/ml, 0.5-99.5% and 0.1-16930 ng/ml, respectively (Table 2). According to the cut-off value set by the BALAD score (i.e. AFP > 400ng/ml; AFP-L3 >15% or DCP>100ng/ml), the elevation of each single marker was associated with a worse OS with statistical significance (Table 3). For examples, the median OS of patients with serum AFP >400ng/ml was 3.1 months, which was significantly shorter than the median OS of 23.7 months in patients with AFP ≦ 400ng/ml (p<0.0001). Patients with elevation of AFP-L3 or DCP also had extremely poor prognosis with median OS of shorter than 5 months. On the other hand, the number of elevated markers was also a prognostic factor. The median OS of patients without elevation of any markers was not reached at the time of data-cut off, while the median OS of patients with elevation of one, two and three markers was 23.2, 4.0 and 3.0 months respectively (Table 3). Multivariate analyses found that AFP and AFP-L3 were both independent prognostic factors (AFP: hazard ratio=3.11, p<0.0001; AFP-L3: hazard ratio=2.14, p<0.0001). Other independent prognostic factors were listed in Table 4, which included conventional prognostic factors such as Eastern Cooperative Oncology Group (ECOG) performance status, bilirubin, vascular invasion, tumor size and number.

**Validation of BALAD score**

The breakdown and survival figures of BALAD score were listed in Table 5. There were no patients with BALAD score 5. The median OS of BALAD score 0 was not reached while the median OS of score 1, 2, 3 and 4 was 26.6, 8.3, 2.6, 1.9 months respectively (Figure 1). The BALAD score could divide patients into five groups with different median OS (p<0.0001). In general, the median OS of BALAD score of 0 to 1 was longer than 2.5 years, while the median OS of score 2 was 8.3 months. Patients with BALAD score 3 to 4 had median OS shorter than 3 months.

**Clinical use of BALAD score and BCLC staging system**

BALAD score was directly compared to BCLC staging system with the c-index of BCLC and BALAD score of 0.75 and 0.73, respectively. There was no statistically significant difference in c-index between the two systems (p=0.5098). On the other hand, we aim to determine the clinical value of BALAD score in the determination of median OS in each BCLC stage of patients. The results showed that BALAD score could subdivide each BCLC category of patients into different prognostic groups (Table 5). For examples, amongst the 104 BCLC Stage C patients, patients with BALAD score 3-4 had median OS of shorter than 3 months, while patients with BALAD score of 0-2 had median OS of longer than 5 months (Figure 2).

***Discussion***

The current study validates BALAD score in a Chinese patient population of HCC in Hong Kong. Patients with BALAD score of 0 to 1 have optimal outcome with median OS of longer than 2 years, while BALAD score 2 indicates intermediate prognosis with median OS of approximately 9 months. Patients with BALAD score of 3 or above have extremely poor prognosis with median OS shorter than 3 months. The survival data of BALAD score in our study cohort are comparable to the previous study in United Kingdom but appear shorter than Japanese cohorts.[4-6](#_ENREF_4) This difference could be due to the adoption of national screening program of HCC in Japan which enables diagnosis of the cancer at earlier stage.[13](#_ENREF_13) This is evidenced by higher than 50% of patients receiving treatment of curative intent in previous Japanese studies but only lower than 20% of patients in our cohort underwent curative treatment.[4-6](#_ENREF_4) The results of current study demonstrate the versatility of the BALAD score in prognostication of HCC population regardless of the disease burden or treatment modality.

Although some common staging systems, such as BCLC or CLIP systems, are frequently used to determine the prognoses of patients in international studies, the staging process is known to be subjective to variation by different clinicians’ judgment. For examples, ECOG performance status is one of the key factors to differentiate between BCLC stage B and C disease. However, the distinction between ECOG 0 and 1 is difficult for both the patient and physician in practice. This difficulty is tacitly acknowledged in the clinical trial setting where ECOG performance 1 and 0 are invariably lumped together. In addition, CLIP system requires investigators to determine the macroscopic tumor extent but the decision as to whether or not 50% of the liver is also highly subjective as there is no specification as to whether involvement refers to uni-dimensional, bi-dimensional measurement or volume. The BALAD score is characterized by the judgment of patients’ prognoses via the use of purely objective serum parameters. Our study also shows that the BALAD score could provide unbiased evaluation of prognoses of patients with HCC predominantly due to chronic HBV infection. Together with studies on other HCC populations, the current results indicate that BALAD score is suitable for multi-centered studies involving both Western and Eastern centers.

Currently, clinical trials routinely require investigators to exclude patients with OS of shorter than 3 months, who are believed to have more aggressive disease and be less suitable for the clinical trial[14](#_ENREF_14). According to the American Association for the study of Liver Disease guidelines, BCLC stage C patients are recommended to be the target population for drug testing. Nevertheless, BCLC stage C category is composed of heterogeneous groups of patients with different survivals and, therefore, less informative for clinicians to identify patients with OS shorter than 3 months.[15](#_ENREF_15) In the present study, it is shown that BALAD score could provide additional prognostic information on BCLC staging system by further subdividing patients in each BCLC category into various groups with different survivals. In particular, within the BCLC stage C subgroup, patients with BALAD score of 3 or higher have median OS of shorter than 3 months. The combined use of both BCLC and BALAD score could help identify a more homogeneous group of patients for drug testing.

In the study population, it is shown that the three serological markers, namely AFP, AFP-L3 and DCP, are prognostic factors. Notably, the prognostic effects of both AFP and AFP-L3 are independent of conventional prognostic factors for HCC such as ECOG performance status, albumin, bilirubin, vascular invasion, tumor size and number. Our study is in accordance with previous clinical studies showing that AFP and AFP-L3 as markers are important prognostic factors[16-20](#_ENREF_16). Robust epidemiological studies show that AFP-positive HCC tends to be associated with larger tumor size, more poorly differentiated histology, vascular invasion and distant metastases.[16](#_ENREF_16), [18](#_ENREF_18), [20](#_ENREF_20) Furthermore, meta-analysis of trancriptome in tumor reveals that the HCC with higher AFP level belong to a disease subtype featured by high rate of *TP53* mutation and worse poor prognosis.[21](#_ENREF_21) Together with data in the current study, the results suggest that serum AFP level may help signify a subgroup of patients with biologically more aggressive HCC, thereby supporting the incorporation of AFP into the staging system for HCC. Apart from the three tumor markers, hepatocarcinogenesis is characterized by chronic inflammatory reaction in the liver, and emerging evidences suggest that inflammatory markers including C-reactive protein and interleukins are independent prognostic factors for HCC.[22-26](#_ENREF_22) It is, therefore, worthwhile to evaluate the use of combined serum tumor and inflammatory markers for accurate estimation of prognosis. This process could be facilitated by the availability of a one-stop multiple essay to measure multiple cytokines and tumor markers with a small amount of serum sample.

There are several limitations about this study. First, there are no patients with BALAD score 5 in the cohort, which may undermine the generalization of the data to those patients. This is partly because all patients need to be able to give consent in the clinic to be enrolled in the study cohort, and patients with poor performance status may not be fit enough to attend the outpatient clinic. The lack of patients with BALAD score 5 in our study is not likely to affect the conclusion significantly because BALAD score 5 category only accounts for lower than 1% of HCC patients in previous studies, and the prognoses of these patients are invariably extremely poor[4-6](#_ENREF_4). Second, because of the referral network of hospital system, there are no patients receiving liver transplantation in the study population. This may limit the application of our finding to those patients who receive liver transplantation as the primary treatment for HCC. According to previous studies, the prognostication of serological tumor markers and BALAD score are not remarkably affected by treatment modality including liver transplantation.[4](#_ENREF_4) Thirdly, although serum DCP level is a prognostic factor in univariate analysis, it does not turn out to be the independent prognosticator in the multivariate analysis. This could be due to suboptimal statistical power in the study and future studies with larger sample size, especially with patients with disease of multiple etiologies, may help clarify whether the marker is an independent factor for HBV-related HCC. Finally, an international group led by Johnson et al. recently reported a novel model, known as the ALBI grade, to evaluate the hepatic function in patients with HCC.[27](#_ENREF_27) The ALBI grade has the advantage of high objectivity by involving only serum albumin and albumin to divide the prognoses of patients into three distinct categories. Further studies are required to determine whether BALAD score, ALBI grade or the combination is better to identify suitable patients for clinical trials for HCC.

In conclusion, BALAD score is useful in prognostication of HCC population due to chronic HBV infection. The combined use of BALAD score and BCLC staging system could help identify more suitable candidates for clinical trial. In particular, patients with BCLC stage C disease but with BALAD score of 3 or higher have survival of shorter than 3 months, which are not suitable for enrollment into clinical trial.

**Captions**

Figure 1: Kaplan Meier survival curve of BALAD score in the whole cohort

Figure 2: Kaplan Meier survival curve of BALAD score in the BCLC stage C subgroup

**Table 1: Calculation of the BALAD score**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Parameters** | **Bilirubin-albumin score** | | |  |
|  | 0 points | 1 point | 2 point |  |
| Serum bilirubin (µmol/L) | <17.1 | 17.1-34.2 | >34.2 |  |
| Serum albumin (g/L) | >35 | 28-35 | <28 |  |
|  | **BALAD score** | | | |
|  | Score 0 | Score 1 | Score 2 | 3 |
| Bilirubin-albumin score | 0-1 point | 2-3 point | 4 point |  |
| Number of elevated tumor markers | 0 | 1 | 2 | 3 |

**Table 2: Baseline characteristics**

|  |  |
| --- | --- |
| **Characteristics** | **Number (N=198)** |
| Age (years):   * Median; range | 57.5; 27-86 |
| Sex (Male: Female) | 178:20 |
| ECOG performance status (%):   * 0 * 1 * 2 * 3 | 67 (33.8)  120 (60.6)  8 (4.0)  3 (1.5) |
| Etiology (%)   * HBV | 198 (100.0) |
| Cirrhosis (%) | 95 (48.0) |
| Ascites (%) | 53 (26.8) |
| Symptomatic at presentation (%) | 139 (70.2) |
| Bilirubin (µmol/L)   * Median; range | 20; 3-548 |
| Albumin (g/L)   * Median; range | 38; 22-48 |
| INR  - Median; range | 1.13; 0.91-1.99 |
| ALP (IU/L)   * Median; range | 151; 41-2123 |
| Child-pugh class (%)   * A * B * C | 135 (68.2)  56 (28.3)  7 (3.5) |
| Vascular invasion (%) | 71 (35.9) |
| Tumor number (%)   * Unifocal * Multifocal | 78 (39.4)  120 (60.6) |
| Maximal tumor diameter (centimeters)   * median; range | 8.7; 1.3-20.7 |
| First-line treatment (%)  Curative intent   * Hepatectomy * Locoablative therapy   Palliative intent   * TACE * Systemic therapy (sorafenib or clinical trial) * Best supportive care | 37 (18.7)  27 (73.0)  10 (27.0)  161 (81.3)  25 (15.5)  62 (38.5)  74 (46.0) |
| TNM staging (%)   * I * II * III * IV | 11 (5.6)  43 (21.7)  26 (13.1)  118 (59.6) |
| BCLC staging (%)   * 0/A * B * C * D | 35 (17.7)  41 (20.7)  104 (52.5)  18 (9.1) |
| Serological markers  AFP (ng/ml)   * Median; range   AFP-L3 (%)   * Median; range   DCP (ng/mL)   * Median; range | 228.2; 0.7-1359304  25.2; 0.5-99.5  48.2; 0.1-16930 |

(Abbreviations: AFP, alpha-fetoprotein; AFP-L3, Lens culinaris agglutinin-reactive alpha-fetoprotein; ALP; alkaline phosphatase; BCLC, Barcelona Clinic Liver Cancer; DCP, des-γ-carboxy prothrombin; ECOG, Eastern Cooperative Oncology Group; INR, international normalized ratio; TACE, transarterial chemoembolization; TNM, Tumor-node-metastases staging)

**Table 3: Prognostication of the serological marker and BALAD score**

|  |  |  |  |
| --- | --- | --- | --- |
| **Tumor markers** | **Number (%)** | **Median OS (months; 95% C.I.)** | **p-value (log-rank)** |
| AFP (ng/ml)  <=400  >400 | 142 (57.5)  105 (42.5) | 25.6 (16.0-33.5)  3.3 (2.6-4.4) | <0.0001 |
| AFP-L3 (%)  <=15  >15 | 109 (44.1)  138 (55.9) | 27.1 (15.8-44.9)  4.8 (3.4-6.1) | <0.0001 |
| DCP (ng/ml)  <=100  >100 | 155 (62.8)  92 (37.3) | 24.6 (14.3-32.3)  3.7 (2.8-5.1) | <0.0001 |
| Number of elevated marker  0  1  2  3 | 69 (27.9)  62 (25.1)  75 (30.4)  41 (16.6) | 42.3 (27.1-nr)  24.7 (13.2-34.4)  4.1 (2.6-5.3)  3.0 (2.1-3.6) | <0.0001 |

(Abbreviations: AFP, alpha-fetoprotein; AFP-L3, Lens culinaris agglutinin-reactive alpha-fetoprotein; C.I., confidence interval; DCP, des-γ-carboxy prothrombin; nr; not reached; OS, overall survival)

**Table 4: Univariate and multivariate analyses**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Univariate analysis** | | | | **Multivariate analysis** | | |
| Factors | p-value | HR | 95% C.I. | p-value | HR | 95% C.I. |
| Age | 0.2050 | 0.990 | 0.975-1.005 |  |  |  |
| Sex (Male) | 0.2011 | 1.471 | 0.814-2.657 |  |  |  |
| ECOG (0-1 v.s. > 1) | <0.0001 | 4.323 | 2.308-8.095 | 0.0052 | 3.206 | 1.417-7.256 |
| Bilirubin | <0.0001 | 1.012 | 1.009-1.015 | <0.0001 | 1.009 | 1.005-1.012 |
| Albumin | <0.0001 | 0.920 | 0.893-0.947 | 0.0294 | 0.962 | 0.929-0.996 |
| AFP > 400 ng/mL | <0.0001 | 3.109 | 2.211-4.371 | 0.0002 | 2.095 | 1.417-3.098 |
| AFP-L3 > 15 (%) | <0.0001 | 2.138 | 1.498-3.052 | 0.0018 | 1.895 | 1.268-2.831 |
| DCP > 100 ng/mL | <0.0001 | 2.696 | 1.922-3.781 |  |  |  |
| LN ALP | <0.0001 | 2.402 | 1.951-2.959 | 0.0002 | 1.781 | 1.312-2.418 |
| Vascular Invasion | <0.0001 | 3.461 | 2.443-4.902 | 0.0068 | 1.726 | 1.163-2.562 |
| Tumor size | <0.0001 | 1.125 | 1.089-1.162 | 0.0021 | 1.062 | 1.022-1.103 |
| Tumor number (multiple vs. single) | <0.0001 | 2.978 | 2.059-4.308 | <0.0001 | 2.428 | 1.646-3.582 |

(Abbreviations: AFP, alpha-fetoprotein; AFP-L3, Lens culinaris agglutinin-reactive alpha-fetoprotein; ALP, alkaline phosphatase; DCP, des-γ-carboxy prothrombin; ECOG, Eastern Cooperative Oncology Group; LN, natural logarithm)

**Table 5: Survival figures of BALAD score and BCLC system**

|  |  |  |  |
| --- | --- | --- | --- |
| **Staging system** | **Number (%)** | **Median OS (months; 95% C.I.)** | **p-value (log-rank)** |
| BALAD score  0  1  2  3  4 | 30 (15.2)  49 (24.7)  53 (26.8)  44 (22.2)  22 (11.1) | nr (29.9-nr)  26.6 (14.1-nr)  8.3 (4.9-13.6)  2.6 (1.8-3.9)  1.9 (0.5-3.0) | <0.0001 |
| BCLC system  0/A  B  C  D | 35 (17.7)  41 (20.7)  104 (52.5)  18 (9.1) | nr (42.3-nr)  23.7 (14.2-nr)  3.6 (2.8-4.9)  1.1 (0.5-2.3) | <0.0001 |
| Whole population  BALAD score  0-1  2  3-4 | 79 (39.9)  53 (26.8)  66 (33.3) | 42.2 (24.6-nr)  8.3 (4.9-13.6)  2.5 (1.6-3.1) | <0.0001 |
| BCLC Stage A  BALAD score  0-1  2  3-4 | 29 (82.9)  4 (11.4)  2 (5.7) | nr (nr-nr)  33.4 (15.9-35.8)  nr (17.1-nr) | 0.0025 |
| BCLC Stage B  BALAD score  0-1  2  3-4 | 23 (56.1)  13 (31.7)  5 (12.2) | nr (23.7-nr)  13.6 (4.0-22.7)  6.1 (3.0-14.8) | 0.0008 |
| BCLC Stage C  BALAD score  0-1  2  3-4 | 26 (25.0)  33 (31.7)  45 (43.3) | 6.7 (2.2-13.2)  5.4 (3.4-9.4)  2.6 (1.9-3.1) | <0.0001 |
| BCLC stage D  BALAD score  0-1  2  3-4 | 1 (5.6)  3 (16.7)  14 (77.8) | nr (nr-nr)  2.6 (1.1-5.4)  0.7 (0.3-1.6) | 0.1398 |

(Abbreviations: BALAD, bilirubin, albumin, *Lens culinaris* agglutinin A–reactive fraction of alphafeto-protein, alphafeto-protein, and des-γ-carboxy prothrombin; BCLC, Barcelona Clinic Liver Cancer; nr, not reached)

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