**A nomogram integrating hepatic reserve and tumor characteristics for hepatocellular carcinoma following curative liver resection**

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**List of Abbreviations**

ALT, alanine transaminase; ANN, artificial neural network; AST, aspartate transaminase; AUROC, area under receiver operating characteristics; CI, confidence interval; C-index, concordance index; GGT, gamma-glutamyl transferase; HR, hazard ratio; NA, [nucleotide/nucleoside analogues](http://www.ncbi.nlm.nih.gov.bakerezproxy.palnet.info/pubmed/27083430); PTA, prothrombin activity; ROC, receiver operating characteristics; tdROC, time-dependent receiver operating characteristics

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**Abstract**

**BACKGROUND AND AIMS:**

Because of the mutual influence of liver dysfunction and malignancy, overall survival (OS) is a composite clinical endpoint in hepatocellular carcinoma (HCC). We developed a nomogram integrating albumin–bilirubin (ALBI) grade, a new index of hepatic reserve, and tumor characteristics of HCC patients for predicting OS following curative liver resection.

#### METHODS:

The nomogram was built to estimate the probability of 1-year, 3-year and 5-year OS based on a training cohort of 709 HCC, which was validated in an international independent dataset. The prognostic value of nomogram were determined by a concordance index (C-index), time-dependent receiver operating characteristics (tdROC), and decision curves, comparing with ALBI grade alone, the Cancer of the Liver Italian Program (CLIP), the Barcelona Clinic Liver Cancer (BCLC), and Okuda staging systems.

#### RESULTS:

Independent factors derived from multivariable Cox analysis of the training cohort to predict OS were tumor grade, microvascular invasion, tumor size and ALBI grade which were assembled into nomogram. The calibration curves for probability of OS showed optimal agreement between nomogram prediction and actual observation, which was tested in validation cohort. The C-index, tdROC and decision curves showed that nomogram was superior to CLIP, ALBI grade, BCLC and Okuda. The patients could also be stratified into low, intermediate risk and high risk of the mortality by the,nomogram in both development and validation cohorts..

#### CONCLUSIONS:

The nomogram integrating hepatic reserve and tumor characteristics provided a highly accurate estimation of OS in patients with HCC after curative liver resection, contributing to assess patient prognosis.

**Keywords:** hepatocellular carcinoma, nomogram, time-dependent receiver operating characteristics, decision curves, prediction

**Introduction**

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer deaths worldwide [1](#_ENREF_1" \o "Forner, 2012 #1218). Hepatic resection remains the best therapeutic option for potential curative outcomes, although less than a third of HCC cases are suitable for it at the time of diagnosis [2](#_ENREF_2" \o "Bruix, 2016 #1222). Unlike other solid tumors, the prognosis and treatment options for patients with HCC depend not only on the tumor stage but also on residual liver function[3](#_ENREF_3), [4](#_ENREF_4). In an attempt to stratify expected survival outcomes for HCC patients treated by partial hepatectomy, several staging systems have been developed, including the Cancer of the Liver Italian Program (CLIP) staging system [5](#_ENREF_5), the Barcelona Clinic Liver Cancer (BCLC) staging system [6](#_ENREF_6), Okuda staging system[7](#_ENREF_7), and the seventh edition of the Tumor Node Metastasis (TNM 7th) system [8](#_ENREF_8). Unfortunately, their criteria vary greatly, and no single system has consistently emerged as the optimal predictor of postoperative survival [9](#_ENREF_9" \o "Guglielmi, 2008 #1229), including the BCLC system or CLIP systems.

The albumin-bilirubin (ALBI) scoring model for evaluation of hepatic reserve in patients with HCC was reported, recently [10](#_ENREF_10" \o "Johnson, 2015 #1230). The ALBI grade offers a simple, evidence-based, objective, and discriminatory method of assessing hepatic reserve in HCC that has been extensively tested in an international setting, including patients treated with transarterial chemo-embolisation[11](#_ENREF_11) and sorafenib [3](#_ENREF_3), [12](#_ENREF_12). The ALBI score not only provides superior prognostic information to CP class in patients with HCC but also obviates the need to assess subjective parameters such as ascites and hepatic encephalopathy [13](#_ENREF_13), [14](#_ENREF_14). Modification of BCLC system and CLIP score with incorporating ALBI grade retains and might have improved prognosis prediction for advanced HCC [15-18](#_ENREF_15" \o "Shao, 2016 #1219). However, BCLC and CLIP systems are excessively complex, they are clearly impractical in busy clinical practice.

Nomograms are graphical depictions of predictive statistical models for individual patients, and they have been developed for various diseases, which have consistently shown better performance characteristics than other options [19](#_ENREF_19), [20](#_ENREF_20). Moreover, nomograms provide a user-friendly interface, which does not require computer software for interpretation/prediction [21](#_ENREF_21). In addition, the use of nomograms has a demonstrated advantage over the traditional staging systems used to predict patient outcomes for many diseases [22](#_ENREF_22). The nomograms have been proposed as an alternative method or even as a new standard to guide treatment allocation for critical diseases [23](#_ENREF_23).

**Materials and methods**

**Study design and participants**

We enrolled patients treated with liver resection for HCC from the First Affiliated Hospital of Wenzhou Medical University between Jan 1, 2007, and Dec 31, 2015. Patients who met the following criteria were excluded: liver transplantation; preoperative anticancer therapy or intraoperative radiofrequency ablation; other simultaneous malignancies; cardiopulmonary, renal or cerebral dysfunction before liver resection. Patients undergoing repeat or noncurative resections were excluded from analysis. Repeat pathologic analysis was performed to confirm the histologic diagnosis of HCC; because of oncologic and staging discrepancies that have been described between fibrolamellar and nonfibrolamellar variants of HCC [24](#_ENREF_24), patients with fibrolamellar HCC were also excluded. The start date of the follow-up was the date of curative liver resection. All patients were prospectively followed up consisted of clinical examination and imaging studies (CT scan of abdomen and thorax and ultrasound or MRI according to the specific scenario) once every 3 months for the first 2 years, every 6 months until 5 years, and once a year thereafter.

Two international independent cohorts of patients with similar clinical characteristics recruited from Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong, China between Jan 1, 2012, and Dec 31, 2015, and Ogaki Municipal Hospital, Ogaki, Gifu, Japan between Jan 1, 2012, and Dec 31, 2015 formed the validation cohort. The outcome of each patient with HCC was recorded as survival or death. Written informed consent was obtained from each patient included in the study and the research protocol of the study was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical University, Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong, China and Ogaki Municipal Hospital, Ogaki, Gifu, Japan.

**Clinical information and laboratory examinations**

A detailed history of all the patients was taken upon admission and during follow-up. Baseline patient characteristics were detected before the resection of HCC for patients, including age, sex, survival time, body mass index (BMI), Tumor size, TNM stage, total bilirubin (TB), albumin (ALB), alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (AKP), gamma-glutamyl transferase (GGT), creatinine, prothrombin activity (PTA), international normalized ratio (INR), white blood cell (WBC), platelet, alpha-fetoprotein (AFP).

**Score systems**

The CLIP staging system incorporates measures of hepaticfunction, tumor morphologic characteristics, AFP level, and presence of portal vein thrombosis into a scoring system [5](#_ENREF_5" \o "Ueno, 2001 #1225).

The BCLC staging system has been used to triage HCC patients into appropriate treatment modalities and incorporates functionalstatus, extent of liver dysfunction, and oncologic variables [6](#_ENREF_6).

The Okuda staging system categorizes HCC patients based mostly on measures of functional hepatic reserve, with only 1 broad oncologic variable (tumor extension involving > 50% of the liver) [7](#_ENREF_7).

ALBI score = -0.085 × (albumin g/L) + 0.66×lg (TBil μmol/L). Patients were divided into 3 groups as grade 1 (ALBI score ≤ -2.60), grade 2 (ALBI score > -2.60, ≤ -1.39), and grade 3 (ALBI score > -1.39) [10](#_ENREF_10" \o "Johnson, 2015 #1230).

**Statistical analysis**

Continuous variables are expressed as mean ± standard deviation; and categorical values were expressed by absolute and relative frequencies. Differences in variables were analyzed using Student t-tests. The Chi-square test was used for categorical data. Survival estimates for the entire study population were generated using the Kaplan-Meier method calculated from the date of diagnosis to the date of last follow-up or death. The association of relevant variables with survival was assessed using Cox proportional hazards models. Variables with P < 0.05 in the univariate Cox regression analysis were progressed to a multivariate analysis using backward stepwise selection. Hazard ratio (HR) and 95% confidence interval (CI) were calculated.

The endpoints in building the nomogram were 1-year, 3-year, 5-year mortality. The prognostic nomogram was developed starting from a multivariable Cox model, which allowed us to obtain survival probability estimates. The total points of each patient were calculated according to the established nomogram. The performance of the nomogram was evaluated by the concordance index (C-index) and assessed by comparing nomogram-predicted vs observed Kaplan-Meier estimates of survival probability, and bootstraps with 1000 resamples were applied to these activities. Comparisons between the nomogram, and CLIP, ALBI grade, BCLC, Okuda staging system were performed with the rcorrp.cens function in the Hmisc package in R and were tested by the C-index. The time-dependent receiver operating characteristics curve (tdROC) evaluates the accuracy of quantitative markers for time-varying outcomes [25](#_ENREF_25). The area under time-dependent ROC curve (tdAUC) was also estimated for assessing the performance of the nomogram, CLIP, ALBI grade, BCLC, Okuda staging system with timeROC package in R [26](#_ENREF_26). A larger C-index and tdAUC indicated more accurate prognostic stratification. We also plotted decision curves to assess the net benefit of nomogram, CLIP, ALBI grade, BCLC, and Okuda -assisted decisions at different threshold probabilities, compared with the net benefit of treat all/treat none strategies [27](#_ENREF_27). Statistical analyses to identify risk factors were performed using SPSS 22.0 (SPSS, Chicago, IL), and the nomogram was computed with the rms package in R version 3.1.2 (http://www.r-project.org/). P values of less than 0.05 were considered to be statistically significant.

**Results**

**Patient Characteristics**

After exclusion of those who did not meet the inclusive criteria, 709 consecutive patients with HCC were finally included. The baseline characteristics of the patients in training cohort were listed in Table 1. Supplementary Table 1 summarized the baseline characteristics of 1022 patients with HCC following curative liver resection in the validation cohort (Japan cohort = 615; Hong Kong cohort = 407).

**Prognostic Factors**

Mortality was 16.9% at 1year, 32.9% at 3 years and 40.6% at 5 years follow-up. Univariate analysis indicated that tumor grade (P < 0.001), microvascular invision (P < 0.001), ALBI grade (P < 0.001), tumor size (P < 0.001), TNM stage (P < 0.001), TB (P < 0.001), ALB (P < 0.001), PTA (P < 0.001) and WBC (P = 0.001) were associated with the OS of the patients with HCC after curative liver resection (Supplementary Table 2). All significant factors in the univariable analysis were entered into the multivariable analysis based on the Cox regression. Multivariable analyses demonstrated that tumor grade, microvascular invision, ALBI grade and tumor size were independent prognostic factors for OS of the patients with HCC, respectively (Supplementary Table 3).

**Prognostic Nomogram Development and Validation**

A prognostic nomogram that incorporated the independent prognostic factors for 1 year, 3 year and 5 year mortality of the patients with HCC was established (Figure 1). Each subtype within these variables was assigned a score on the point scale. By adding up the total score and locating it on the total point scale, we were easily able to draw a straight line down to determine the estimated probability of survival at each time point. The nomogram scoring system (Table 2) could be used for a more precise calculation of the survival predictions than drawing lines on the nomogram.

The calibration plot for the probability of 1 year (Figure 2A), 3 years (Figure 2B) and 5 years (Figure 2C) survival showed excellent agreement between the prediction by nomogram and actual observation in training cohort. In the validation cohort, the calibration curve also showed optimal agreement between prediction and observation in the probability of survival in nomogram (Supplemental Figure 2). The tdROC also showed a good predictive value of nomogram, with 0.91 (0.883 - 0.937) for 1-year survival, 0.859 (0.828 - 0.890) for 3-year survival, and 0.796 (0.740 - 0.852) for 5-year survival (Table 4, Figure 3), which was tested in the validation cohort (Supplemental Figure 3).

**Comparison of Predictive Accuracy Between Nomogram and ALBI grade, CLIP, BCLC, and Okuda systems**

The predictive power for prognosis of HCC between nomogram and ALBI grade, CLIP, BCLC, and Okuda systems was compared. The C-indexes for 1-year, 3-year and 5-year survival prediction were 0.789 (95%CI, 0.758-0.821), 0.747 (95%CI, 0.721-0.773), 0.731 (95%CI, 0.706-0.756) by ALBI grade, 0.669 (95%CI, 0.621-0.717), 0.648 (95%CI, 0.613-0.683) and 0.636 (95% CI, 0.604-0.669) by CLIP, 0.673 (95%CI, 0.629-0.718), 0.649 (95%CI, 0.616-0.683), 0.647 (95%CI, 0.616-0.678) by BCLC, 0.647 (95%CI, 0.603-0.692), 0.640 (95%CI, 0.608-0.672), 0.641 (95%CI,0.612-0.670) by Okuda, statistically significantly lower than the C-index by nomogram, with the values of 0.875 (95%CI, 0.846-0.903, P<0.001), 0.829 (95%CI, 0.805-0.854, P<0.001) and 0.822 (95%CI, 0.799-0.845, P<0.001), respectively (Table 4).

We used tdROC to investigate the accuracy of nomogram, ALBI grade, CLIP, BCLC, and Okuda to predict OS at 1-year, 3-year and 5-year. Figure 3 showed the tdROC curves of nomogram, ALBI grade, CLIP, BCLC, and Okuda for predicting the mortality of HCC at 1-year, 3-year and 5year, respectively. The tdAUC also showed the predictive performances of nomogram were superior to ALBI grade alone, CLIP, BCLC, Okuda for determining OS within these time intervals. The results of our analyses were listed in Table 4. Consistent with the survival c-index and tdAUC, decision curve analysis also showed that the nomogram had the higher clinical net benefit than CLIP, ALBI grade, BCLC, Okuda across the entire range of threshold probabilities (Supplementary Figure 4).

**Performance of the Nomogram in Stratifying Risk of Patients**

We determined the cutoff values by grouping the patients evenly into three subgroups after sorting by total points (low risk: 0 to 10.0, intermediate risk: 11.0 to 60.0, and high risk: ≥61.0); each group represented a distinct prognosis (Figure 4). After applying the cutoff values of nomogram to group patients in the validation cohort, stratification into three risk subgroups also allowed significant distinction between Kaplan-Meier curves for survival outcomes (Supplementary Figure 5). Furthermore, the nomogram scoring system was used to stratify risk of mortality in HCC patients at different tumor characteristics, including tumor grade (low and high), MVI (absence and presence), tumor stage (low and high), and different CLIP (CLIP 0, 1, 2, 3), BCLC (BCLC A, B, C) and Okuda stages (Okuda I, II, III), and displayed its reliable ability to identify patients with different risk of HCC mortality in the different tumor characteristics (Figure 5), CLIP (Supplementary Figure 6), BCLC (Supplementary Figure 7) and Okuda stages (Supplementary Figure 8).

**Discussion**

Nomograms provide user-friendly, accurate and reproducible predictions for patients without requiring computer software for interpretation/prediction, which allow clinicians to standardize clinical decision-making. In current study, we developed and validated a prognostic nomogram integrating ALBI grade and tumor characteristic, which had a high accuracy for predicting OS of patients with HCC following curative liver resection. The prognostic value of the nomogram was superior to those of ALBI grade alone, CLIP, BCLC, and Okuda systems.

Like other solid tumors, HCC, even in an early stage, is in fact quite variable in tumor structure [28](#_ENREF_28), [29](#_ENREF_29). The prognosis of HCC strongly depends upon tumor grade and the presence of MVI [30](#_ENREF_30) which were integrated into the nomogram. Tumor size was modeled as an ordinal categorical variable with the cutoff values at 3 cm. The nomogram illustrated tumor size as the smallest contribution to prognostic prediction, in which only 10 points were gained with the size ≤ 3cm. This might be due to strict relationship reported between tumor size and tumor grade and MVI [31](#_ENREF_31), [32](#_ENREF_32).

In the current nomogram, hepatic reserve was considered as a prognostic variable. ALBI, as a novel surrogate marker of hepatic reserve, involved only 2 variables, albumin and serum bilirubin, hich could be easily acquired. The ALBI grade offers a simple, evidence-based, objective, and discriminatory method of assessing liver function in HCC that has been extensively tested in an international setting. With a higher ALBI grade, the liver function was worse and the prognosis was poorer 3. Similar to the Child score, the ALBI grade stratified patients into three categories. Several evidence-based approach and multicenter designed studies have identified ALBI grade had better performance than Child score on evaluating liver function, achieving stronger predictive ability in OS of patients with different HCC stages experiencing different treatments  [14](#_ENREF_14), [33](#_ENREF_33). The ALBI grade spread through the full range of point axis in the nomogram, which indicated that hepatic reserve was mainly associated with OS of HCC after liver resection.

Calibration plots showed optimal agreement between prediction and actual observation, which guaranteed the repeatability and reliability of the established nomogram. C-index, the time-dependent ROC analysis and decision curve analysis also found that nomogram was superior to ALBI grade, CLIP, BCLC, and Okuda score. Patients with HCC could be stratified into high risk, intermediate risk and low risk subgroups according to the nomogram scoring system. Furthermore, the nomogram scoring system could stratify risk of mortality at different tumor characteristics, including tumor grade (low and high), MVI (absence and presence), tumor stage (low and high), and different CLIP, BCLC and Okuda stages.

The current nomogram has several potential benefits. First, it had an accurate and reproducible prediction for OS of HCC. Second, the parameters in the nomogram could be easily obtained in standard hospitalization settings. Third, it provided user-friendly interface, without requiring computer software. The physicians could perform an individualized survival prediction through this easy-to-use scoring system 4. Identifying subgroups of patients at different risk for mortality might have an impact on the treatment or care option. This scoring system should help physicians to select patients who need additional therapy or intensive follow-up. In addition, this tool could provide information for patient stratification in the design of clinical study, gaining better equivalence between study arms.

In conclusion, the prognostic nomogram integrated hepatic reserve and tumor characteristics to provide an individualized risk estimation of OS in patients with HCC after liver resection. It could be offered to clinicians to improve their prognostication for patients and strengthen prognosis-based decision making for each patient.

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**Figure legends**

**Figure 1. Prognostic nomogram for predicting overall survival patients with hepatocellular carcinoma.**

This nomogram provided a method to calculate 1-year, 3-year, and 5-year probability of survival of hepatocellular carcinoma on the basis of a patient’s combination of covariates. To use, locate the ALBI grade, draw a line straight up to the points axis to establish the score associated with the grade. Repeat for the other three covariates (microvascular invasion, tumor grade, and tumor size). Add the scores for each covariate together and locate the total score on the total points axis. Draw a line straight down to the 1-year, 3-year, and 5-year survival axes to obtain the probability.

**Figure 2. Calibration plots of the prognostic nomogram in training cohort**

Calibration plots of the prognostic nomogram for 1-year survival (A), 3-year survival (B), and 5-year survival (C); The average predicted probability (predicted overall survival; x-axis) was plotted against the Kaplan-Meier estimate (observed overall survival; y-axis). Dashed line indicates the reference line, indicating where an ideal would lie.

**Figure 3. Time-dependent ROC of the prognostic nomogram, CLIP, ALBI grade, BCLC and Okuda score in training cohort**

Time-dependent ROC for 1-year survival (A), 3-year survival (B), and 5-year survival (C).

The time-dependent ROC curve was used to evaluate the prognostic performance for survival prediction. Performance comparison was assessed between the nomogram and CLIP, ALBI grade, BCLC, Okuda score by calculating the area under the ROC curves.

ALBI, albumin-bilirubin; CLIP, the Cancer of the Liver Italian Program; BCLC, the Barcelona Clinic Liver Cancer; ROC, receiver operating characteristics

**Figure 4. Kaplan-Meier survival curves and risk group stratification according to trisection of the nomogram predicted survival in training cohort.**

The scoring range of each risk group: low risk: 0 to 10.0, intermediate risk: 11.0 to 60.0, and high risk: ≥ 61.0.

**Figure 5. Risk group stratification within tumor characteristics according to trisection of the nomogram predicted survival.**

(A) Subgroup with low tumor grade, (B) Subgroup with high tumor grade, (C) Subgroup without MVI, (D) Subgroup with MVI, (E) Subgroup with high tumor stage, (F) Subgroup with high tumor stage

Subgroups fewer than 10 patients were omitted from the graphs.

**TABLES**

**Table 1.** Baseline demographics and clinical characteristics of patients in training cohort

**Table 2.** Nomogram Scoring System

Mortality predictions corresponding to total points not shown in thetable may be obtained by linear interpolation.

**Table 3.** The comparison of nomogram, CLIP, ALBI grade, BCLC and Okuda score for predicting overall survival using C-index and time-dependent ROC

BCLC, the Barcelona Clinic Liver Cancer; C-index, concordance index; CLIP, the Cancer of the Liver Italian Program; ROC,receiver operating characteristics

**SUPPLEMENTARY FILES**

**Supplementary Figure 1. Calibration plots of the prognostic nomogram in validation cohort**

Calibration plots of the prognostic nomogram for 1-year survival (A), 3-year survival (B), and 5-year survival (C); The average predicted probability (predicted overall survival; x-axis) was plotted against the Kaplan-Meier estimate (observed overall survival; y-axis). Dashed line indicates the reference line, indicating where an ideal would lie.

**Supplementary Figure 2. Time-dependent ROC of the prognostic nomogram in validation cohort**

Time-dependent ROC analysis for 1-year survival (A), 3-year survival (B), and 5-year survival (C).

The time-dependent ROC curve was used to evaluate the prognostic performance for survival prediction.

ROC, receiver operating characteristics; td-AUC, time dependent- area under receiver operating characteristics

**Supplementary Figure 3. Decision curve analyses demonstrating the net benefit associated with the use of the nomogram, CLIP, ALBI grade, BCLC and Okuda score in training cohort**

Decision curves for 1-year survival (A), 3-year survival (B), and 5-year survival (C). Solid thin line: net benefit of a strategy of treating all patients. Solid bold line: net benefit of treating no patients. Dotted line: net benefit of a strategy of treating patients according to the nomogram predictions or CLIP, ALBI grade, BCLC and Okuda score. Compared with CLIP, ALBI grade, BCLC and Okuda score, the nomogram had a higher clinical net benefit across the entire range of threshold probabilities.

CLIP, the Cancer of the Liver Italian Program; ALBI, albumin-bilirubin; BCLC, the Barcelona Clinic Liver Cancer

**Supplementary Figure 4. Kaplan-Meier survival curves and risk group stratification according to trisection of the nomogram predicted survival in validation cohort.**

The scoring range of each risk group: low risk: 0 to 10.0, intermediate risk: 11.0 to 60.0, and high risk: ≥ 61.0.

**Supplementary Figure 5. Risk group stratification within each CLIP stages (CLIP 0, 1, 2, 3) according to trisection of the nomogram predicted survival in training cohort.**

(A) Subgroup with CLIP 0; (B) Subgroup with CLIP 1; (C) Subgroup with CLIP 2; (D) Subgroup with CLIP 3

Subgroups fewer than 10 patients were omitted from the graphs.

CLIP, the Cancer of the Liver Italian Program;

**Supplementary Figure 6. Risk group stratification within each BCLC stages (BCLC A, B, C) according to trisection of the nomogram predicted survival in training cohort.**

1. Subgroup with BCLC A; (B) Subgroup with BCLC B; (C) Subgroup with BCLC C

Subgroups fewer than 10 patients were omitted from the graphs.

BCLC, the Barcelona Clinic Liver Cancer;

**Supplementary Figure 7. Risk group stratification within each Okuda stages (Okuda I, II, III) according to trisection of the nomogram predicted survival in training cohort.**

1. Subgroup with Okuda I; (B) Subgroup with Okuda II; (C) Subgroup with Okuda III

Subgroups fewer than 10 patients were omitted from the graphs.

**Supplementary Table 1**. Baseline characteristics of the patients with hepatocellular carcinoma following curative liver resection in the validation cohort

**Supplementary Table 2**. Univariable Cox proportional hazards analysis for survival of hepatocellular carcinoma

**Supplementary Table 3**. Multivariable Cox proportional hazard regression model-based (adjusted) factor for mortality at each time point in training cohort