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

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ABSTRACT

Background: 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 for predicting OS following curative liver resection.

Methods: The nomogram was built to estimate the probabilities of 1, 3, and 5-y OS based on training cohort of 709 HCC, which was validated in an international independent dataset. The prognostic value of the nomogram was determined by 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 the 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 normogram 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.

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer deaths worldwide [1]. 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]. 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, 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], the Barcelona Clinic Liver Cancer (BCLC) staging system [6], Okuda staging system [7], and the seventh edition of the Tumor Node Metastasis (TNM

Abbreviations: ALBI, Albumin–bilirubin; ALT, Alanine transaminase; ANN, Artificial neural network; AST, Aspartate transaminase; BCLC, The Barcelona Clinic Liver Cancer; C-index, Concordance index; CLIP, The Cancer of the Liver Italian Program; CP, Child-Pugh; GGT, Gamma-glutamyl transferase; HCC, Hepatocellular carcinoma;; MVI, Microvascular invasion;; NA, Nucleotide/nucleoside analogues;; OS, Overall survival;; PTA, Prothrombin activity;; tdROC, Time-dependent receiver operating characteristics;; TNM, The Tumor Node Metastasis

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7th) system [8]. Unfortunately, their criteria vary greatly, and no single system has consistently emerged as the optimal predictor of post-operative survival [9], including the BCLC or CLIP systems.

The albumin-bilirubin (ALBI) scoring model for evaluation of hepatic reserve in patients with HCC was reported, recently [10]. 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] and sorafenib [3, 12]. The ALBI score not only provides superior prognostic information to Child-Pugh (CP) class in patients with HCC but also obviates the need to assess subjective parameters such as ascites and hepatic encephalopathy [13, 14]. Modification of the BCLC system and CLIP score with the incorporation of the ALBI grade retains and, might have improved prognosis prediction for advanced HCC [15–18]. However, BCLC and CLIP systems are excessively complex, which are clearly impractical in a busy clinical practice.

Nomograms are graphical depictions of predictive statistical models for individual patients, and have been developed for various diseases, which have consistently shown better performance characteristics than other options [19, 20]. Moreover, nomograms provide a user-friendly interface, which does not require computer software for interpretation/prediction [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]. The nomograms have been proposed as an alternative method or even as a new standard to guide treatment allocation for critical diseases [23].

2. Materials and methods

2.1. 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, retrospectively. 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 non-curative resections were also excluded from the 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], 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 by 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 y, every 6 months until 5 y, and once a year thereafter.

Two international independent cohorts of patients with similar clinical characteristics recruited from the Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong, China between Nov 20, 2005 and Dec 31, 2014, and Ogaki Municipal Hospital, Ogaki, Gifu, Japan between Jan 10, 1990 and Sep 4, 2014 formed the validation cohort. The outcome of each patient with HCC was recorded as survival or death. 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.

2.2. Clinical information and laboratory examinations

A detailed history of all the patients was taken upon admission and during follow-up. Baseline patient characteristics were recorded 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-glutamyltransferase (GGT), creatinine, prothrombin activity (PTA), international normalized ratio (INR), white blood cell (WBC), platelet and alpha-fetoprotein (AFP). TB, ALB, ALT, AST, GGT, and AKP was detected by Beckman AU5800 analyzer. Blood routine examination (WBC, red blood cell, lymphocyte etc.) was tested by Sysmex XE-2100 analyzer. AFP was measured by UniCel DxI-800 analyzer.. Coagulation function (PTA, INR) was measured by Diagnostica Stago analyzer.

2.3. Score systems

The CLIP staging system incorporates measures of hepatic function, tumor morphologic characteristics, AFP level, and presence of portal vein thrombosis into a scoring system [5].

The BCLC staging system has been used to triage HCC patients into appropriate treatment modalities and incorporates functional status, extent of liver dysfunction, and oncologic variables [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].

ALBI score $= -0.085 \times$ (albumin g/l) $+ 0.66 \times \lg$(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].

2.4. Statistical analysis

Continuous variables were expressed as mean ± standard deviation; and categorical values were expressed by absolute and relative frequencies. Differences in variables were analyzed using Student's *t*-tests. The χ^2 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% CI were calculated. The endpoints in building the nomogram were 1, 3, 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]. 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]. 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]. Statistical analyses to identify risk factors were performed using SPSS 22.0, and the nomogram was computed with the rms package in R vers 3.1.2 (http://www.r-project.org/). A $P < 0.05$ were considered to be statistically significant.