Prognostic Nomograms for Pre- and Postoperative Predictions of Long-Term Survival for Patients Who Underwent Liver Resection for Huge Hepatocellular Carcinoma

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BACKGROUND: Liver resection is an effective treatment in select patients with huge hepatocellular carcinoma (HCC, diameter ≥10 cm). This study aimed to develop nomograms for pre- and postoperative predictions of overall survival (OS) for these patients.

STUDY DESIGN: There were 464 consecutive patients who underwent liver resection for huge HCC at the Eastern Hepatobiliary Surgery Hospital (EHBH) between January 2008 and December 2009. They were collected and divided into a training cohort (n = 310) and an internal validation cohort (n = 154). Another 90 patients who were operated on at the Fujian Medical University (FMU) between January 2008 and April 2010 served as an external validation cohort. The surgical morbidity, mortality, time to recurrence, and OS were observed. Two prognostic nomograms were developed based separately on the data obtained before and after surgery. Discrimination and predictive accuracy of the models were measured using concordance index (C-index), calibration curves, and validation study.

RESULTS: The postoperative 4-year tumor recurrence and OS rates were, respectively, 79.0% and 41.2% in the patients from the EHBH and 78.8% and 37.6% in those from the FMU. Independent predictors of OS on multivariable analysis using pre- and postoperative data were respectively incorporated into the 2 nomograms. In the training cohort, calibration curves for the probability of 4-year postoperative survival fitted well. The C-indexes of the pre- and postoperative nomograms in predicting OS were 0.75 (95% CI 0.72 to 0.78) and 0.78 (95% CI 0.75 to 0.81), respectively. The internal and external validation studies optimally supported these results.

CONCLUSIONS: The 2 nomograms achieved accurate pre- or postoperative predictions of long-term survival for patients with huge HCC after liver resection. (J Am Coll Surg 2015;221:962–974. © 2015 by the American College of Surgeons)

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Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the second leading cause of cancer-related mortality worldwide.[1] In China, its incidence and mortality account for more than 50% of all HCC patients in the world.[2] Because early symptoms are not obvious, the majority of patients with HCC are diagnosed at advanced stages. Some patients are not diagnosed until their tumors have grown to large sizes (≥10 cm).[3] Patients with huge HCCs are difficult to treat and the prognosis is relatively poor. Currently, these patients are commonly treated with liver resection, transarterial chemoembolization (TACE), cryoablation, chemotherapy, or sorafenib.[4,5] According to the currently recommended criteria, patients with huge HCC are usually not

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Abbreviations and Acronyms

AFP = alpha fetoprotein
EHBH = Eastern Hepatobiliary Surgery Hospital
FMU = Fujian Medical University
HBV-DNA = hepatitis B virus-deoxyribonucleic acid
HCC = hepatocellular carcinoma
HR = hazard ratio
MVI = microvascular invasion
OS = overall survival
PVTT = portal vein tumor thrombus
TACE = transarterial chemoembolization

suitable candidates for liver transplantation.[6,7] For patients who have resectable HCC with good liver functional reserve, liver resection remains the most effective treatment to improve long-term survival.[8]

However, the reported long-term survival of these patients varies. Tsoulfas and colleagues[9] reported that 5-year overall survival and disease-free survival rates range from 25% to 45% and from 15% to 35%, respectively; Miyoshi and associates[10] achieved a 5-year overall survival rate of 58.3%, while Shrager and colleagues[11] reported this rate to be only 18.8%. Moreover, because patients with huge HCC are frequently complicated with intrahepatic metastases, tumor compression, or direct invasion into major hepatic/portal veins or bile ducts, the R0 resection rate is low. In addition, surgical resection for these patients is relatively difficult and the perioperative mortality and morbidity rates are still high.[11,12] Because alternatives to hepatectomy are now available for huge HCC,[13] patients who are predicted to be unfavorable candidates for hepatectomy before surgery can choose other treatments. Therefore, a preoperative prognostic prediction is essential to properly select patients for liver resection. On the other hand, an accurate prognostic prediction after hepatectomy can guide postoperative monitoring and adjuvant therapy.

To the best of our knowledge, no prognostic tool currently exists to predict long-term survival of patients with huge HCC before and after liver resection. Conventional clinical staging systems generally classify a huge HCC as at an advanced stage of disease. The seventh edition of the Tumor Node Metastasis (TNM) system considers a huge HCC as stage III and above, which is similar to the other systems such as the Cancer of the Liver Italian Program (CLIP), the Japanese Integrated Staging (JIS) system, and the Okuda Scoring.[14,15] Therefore, a huge HCC is often given a high score and it is unable to be further classified into any prognostic subgroups by these systems. On the other hand, none of these systems are established to predict prognosis of surgically treated patients.

Currently, nomograms have been recognized to be accurate in prognostic predictions and can easily be applied in many cancers.[16,17] We have previously confirmed a nomogram to have a higher predictive accuracy than the currently used staging systems in predicting prognosis after liver resection for intrahepatic cholangiocarcinoma.[18] However, nomograms have not been widely applied in HCC. Recently, Shim and colleagues[19] reported on nomograms that showed good predictions for post-resectional recurrence and survival in patients with early stage HCC.[19] Based on the superiority of the nomogram in prognostic prediction, we hypothesized that the model could also serve as an ideal tool to predict long-term post-resectional outcomes in patients with huge HCC. In this study, we developed 2 prognostic nomograms based on the data obtained before or after liver resection for huge HCC. Performance of these models was tested and verified.

METHODS

Patients and study design

We retrospectively reviewed data on consecutive patients who underwent liver resection for huge HCC $\geq$ 10 cm in diameter, at the Eastern Hepatobiliary Surgery Hospital (EHBH) between January 2008 and December 2009 and the Fujian Medical University (FMU) between January 2008 and April 2010. Patients were included if they met the following inclusion criteria: no history of other malignancies; no distant metastasis; no preoperative anticancer therapy; preoperative Child-Pugh class A liver function; and histopathologically confirmed HCC with diameter $\geq$ 10 cm. Patients were excluded if they met the following exclusion criteria: non-R0 liver resection; missing data; and perioperative death. Qualified patients from the EHBH were randomly assigned at a 2:1 ratio into the training cohort to develop the prognostic nomograms and the internal validation cohort to validate the established predictive models. All qualified patients from the FMU served as the external validation cohort. The flow chart of the study is shown in Supplemental Figure 1 (available online).

This study was approved respectively by the Institutional Ethics Committee of the 2 hospitals, and informed consent was obtained from all patients for their data to be used for research.

Diagnosis and treatment

After history taking and physical examination, the patients underwent routine serologic examination, which included liver and renal function tests, alpha-fetoprotein (AFP), prothrombin time (PT), white blood cell count (WBC), platelet (PLT), hepatitis B virus deoxyribonucleic