CLINICAL STUDY

Nomograms for Predicting Outcomes after Chemoembolization in Patients with Nonmetastatic Hepatocellular Carcinoma

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ABSTRACT

Purpose: To construct prognostic nomograms capable of estimating individual probabilities of tumor progression and overall survival (OS) at specific time points during serial transarterial chemoembolization for hepatocellular carcinoma (HCC).

Materials and Methods: The study included 1,181 consecutive patients with nonmetastatic HCC undergoing repeated transarterial chemoembolization at a single tertiary referral center. Patients were assigned to 2 cohorts according to the first transarterial chemoembolization date: derivation (2004–2006; n = 854) and validation (2007; n = 327) sets. Multivariate Cox proportional hazards models were developed based on covariates derived before transarterial chemoembolization and assessed for their association with 5-year OS and 3-year progression-free survival (PFS). The accuracy of the models was internally and externally validated.

Results: The 5-year OS of the derivation set was 25.4%, and 3-year PFS was 20.8%. Nomograms for OS and PFS were built into the derivation set incorporating the following factors: log [tumor volume] calculated as $4/3 \times 3.14 \times$ (maximum radius of tumor in cm^3); tumor number; tumor type (nodular or infiltrative); Child-Pugh class (A or B); (model for end-stage liver disease score/10)$^{-2}$; log [α-fetoprotein]; and portal vein invasion. The models had good discrimination and calibration abilities with C-indexes of 0.80 (5-y survival) and 0.77 (3-y progression). The results of external validation confirmed that these models performed well in terms of discrimination and goodness-of-fit (C-indexes 0.77 for 5-y survival and 0.73 for 3-y progression).

Conclusion: Nomograms quantifying the survival and progression outcomes in patients treated with transarterial chemoembolization are useful clinical aids in providing personalized care.

ABBREVIATIONS

AFP = α-fetoprotein, CI = confidence interval, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, MELD = model for end-stage liver disease, OS = overall survival, PFS = progression-free survival, TTV = total tumor volume

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Appendix A and Appendix B are available online at *www.jvir.org*.

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Hepatocellular carcinoma (HCC) is one of the most common lethal malignancies worldwide (1). Despite increased clinical surveillance, only 30% of cases of HCC are diagnosed in the early stages (2). In other words, 70% are still detected in the late stages, in which curative treatments such as surgical resection, percutaneous ablation, or liver transplantation are not feasible (3). Some patients with early-stage disease are not eligible for curative management because of their general medical condition, the location of the tumor, or the shortage of liver donors. Palliative treatments are often required.

Transarterial chemoembolization has been shown to be a life-prolonging treatment and has been used in practice for a wide spectrum of HCCs including unresectable, untransplantable, and unablatable tumors at an early stage (4–6). However, because of the heterogeneity of the patient populations that underwent transarterial chemoembolization, variable survival outcomes have been reported, with a 2-year survival rate ranging from 20% to 60% among patients with intermediate-stage HCC for whom transarterial chemoembolization is the current standard recommendation (3,7). In certain subsets of patients who had decompensated liver disease, advanced liver dysfunction, macroscopic vascular invasion, or extrahepatic spread, this procedure was regarded as essentially detrimental (8). Many studies have been performed to identify prognostic factors using these heterogeneous populations, and variables such as liver function, tumor-node-metastasis stage, performance status, presence of hepatitis B virus (HBV), and α-fetoprotein (AFP) have been identified (9–14). However, the factors identified varied considerably from study to study, so that comprehensive predictions of patient outcomes have been difficult to make. To obtain per-patient prognoses and help physicians decide on treatment options by identifying more homogeneous subsets of patients, we constructed and validated comprehensive risk-scoring models in the form of nomograms consisting of easily accessible variables predicting overall survival (OS) and progression-free survival (PFS) in patients treated with transarterial chemoembolization.

MATERIALS AND METHODS

Study Design

This was a retrospective cohort study undertaken to construct risk-scoring models for patients who receive transarterial chemoembolization secondary to unresectable HCC, in whom the derivation and validation cohorts from the gastroenterology department of a single tertiary referral center were temporarily separated.

Derivation and Validation Sets

Consecutive data were collected for patients with a new diagnosis of HCC who were treated with transarterial chemoembolization as initial therapy at a single center between January 2004 and December 2007. The diagnosis of HCC based on the American Association for the Study of Liver Diseases practice guidelines was reconfirmed in all included patients (3). Transarterial chemoembolization was the optimal treatment, and curative surgical or locoregional modalities were impossible or contraindicated at the time of enrollment of these patients. The following patients were excluded: patients who (*a*) were lost to follow-up after the first transarterial chemoembolization session without evaluation of the treatment response, (*b*) had extrahepatic metastases at the time of diagnosis, or (*c*) had other histologically confirmed malignancies before or within 5 years of the diagnosis of HCC. There were 1,181 patients enrolled, and these patients were divided into a derivation set and a validation set, according to the date of initial transarterial chemoembolization (15,16). The derivation set for the primary analysis consisted of 854 patients (72.3%) who underwent their first transarterial chemoembolization between January 2004 and December 2006, and the temporal validation set consisted of the remaining 327 patients (27.7%) (15,16).

Data Collection

At the time of diagnosis, demographic and clinical variables including age, sex, tumor size, tumor number, tumor type (nodular or infiltrative), portal vein invasion, hepatic vein invasion, extrahepatic metastases, presence of cirrhosis, bilobar involvement, Child-Pugh class, model for end-stage liver disease (MELD) score, AFP level, and presence of HBV were collected for each patient from the database of our center. Total tumor volume (TTV), which had been initially proposed by Toso et al (17), was calculated from the sum of tumor volumes ($4/3 \times 3.14 \times$ [maximum radius of the tumor in cm^3]). All of the enrolled cases were confirmed as HCC by liver protocol computed tomography or magnetic resonance imaging or liver biopsy according to current American Association for the Study of Liver Diseases guidelines (3). Before the initial transarterial chemoembolization, chest computed tomography and bone scans were checked on a routine basis, and, if indicated, positron emission tomography was performed to exclude extrahepatic metastases.

Transarterial Chemoembolization Procedure

The routine protocol of our hospital has been described elsewhere (18). Details of the procedure are provided in **Appendix A** (available online at *www.jvir.org*) (19–23).

Study Endpoints

The primary endpoint was OS, which was defined as the interval between the date of the first transarterial chemoembolization and death or last follow-up visit. During follow-up, data were censored at the time when a treatment strategy of curative intent, such as surgical resection, liver transplantation, or percutaneous ablation, was attempted. Patients lost to follow-up were censored at the time of their last visit, and living patients were censored on December 31, 2012. The secondary endpoint was PFS estimated from the date of the first transarterial chemoembolization session to progression or the last follow-up visit. Progressive disease was confirmed according to the modified Response Evaluation Criteria in Solid Tumors (24). Death and follow-up