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Predicting the severity of liver cirrhosis through clinical parameters

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ARTICLE INFO

Article history:
Received 6 December 2015
Received in revised form
17 March 2016
Accepted 15 April 2016
Available online 23 April 2016

Keywords:
Hepatocellular carcinoma
Cirrhosis
Histological staging
Hepatitis B virus
Portal hypertension

ABSTRACT

Background: Severity of liver cirrhosis plays a vital role in determining an appropriate surgical strategy for HCC treatment. However, preoperative evaluation of the severity of cirrhosis has not been established in a surgical setting. This study aims to develop a model to predict the severity of cirrhosis.

Methods: Overall, 604 patients with hepatocellular carcinoma (HCC) and hepatitis B virus–related cirrhosis undergoing liver resection from Jan 2005 to Jun 2013 were randomly divided into either the model building group (n = 304) or the test group (n = 300). The severity of cirrhosis of the resected specimens was pathologically staged according to the Laennec scoring system, which sub-classified cirrhosis into either stage F4A, F4B, or F4C.

Results: A logistic regression analysis showed that varicosity, portal vein diameter, spleen thickness, and platelet count were significantly associated with the histologic sub-classification of cirrhosis in the model building group. Based on these four parameters, a scoring model for predicting the severity of cirrhosis was established. The model was then verified in the test group, the areas under the ROC (AUROC) for predicting mild (F4A), moderate (F4B), and severe cirrhosis (F4C) were 0.861 (95% confidence interval [CI], 0.810-0.911), 0.860 (95% CI, 0.819-0.901), and 0.968 (95% CI, 0.951-0.985), respectively. The accuracy of this model in predicting mild, moderate, and severe cirrhosis is 79.3%, 81.0%, and 85.3%, respectively.

Conclusions: By using this model, the severity of cirrhosis can be reliably staged preoperatively, which will provide more information on cirrhotic livers in surgical settings for the treatment of hepatitis B virus–related HCC.

Introduction

Liver cirrhosis is an increasing cause of morbidity and mortality in patients with chronic hepatitis B virus (HBV), which is partly due to the portal hypertension and hepatocellular carcinoma (HCC) that occur secondary to different stages of cirrhosis.[1,2] In China, >80% of HCCs arises from varied degrees of cirrhosis, which plays a key role in the selection of the

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0022-4804/$ – see front matter
http://dx.doi.org/10.1016/j.jss.2016.04.036

surgical modality for child A HCC.[3,4] Histologically, cirrhosis is characterized by nodular regeneration surrounded by extensive fibrotic septa with subsequent parenchymal extinction and collapse of the liver structure.[5] This distortion results in increased resistance to portal blood flow and portal hypertension with the signs of hypersplenism such as low platelet count and large spleen size.[6] Additionally, with the progression to cirrhosis, portal pressure increases and dilatation of the portal vein system can occur. In recent years, the Child-Pugh and Model for End-Stage Liver Disease scores have been widely used to determine the prognosis by modeling hepatic dysfunction. Cirrhotic stage is previously classified into noncirrhotic, compensated, and decompensated cirrhosis according to the measurement of hepatic venous pressure gradient.[7] However, these methods do not provide direct evidence of dynamic process of cirrhosis or prognostic information for the bulk of cirrhotic HCC patients who are compensated. Moreover, recent prospective studies revealed that the severity of cirrhosis was closely associated with liver-related event occurrence and tumor recurrence after liver resection for HCC patients.[2,8,9] Antivirus/antifibrotic treatments could reverse fibrosis and then decrease the incidence of HCC occurrence and recurrence after resection.[10,11] Therefore, a simple one-stage description of liver cirrhosis cannot stratify patients for treatment assignment or evaluation of treatment response.[7] Thus, there is an urgent need to redefine cirrhosis in a manner that more faithfully evaluates its progression and clinical outcomes and that is also essential for the individualization of surgical modalities.[4]

According to the Laennec scoring system, liver cirrhosis can be subdivided into three groups (F4A, F4B, and F4C) based on liver biopsy.[1] However, the clinical feasibility of the liver biopsy can be severely limited due to its invasiveness which prevents the collection of histologic information from all patients at any given time. In recent years, several noninvasive methods using laboratory tests, scores and indices to predict liver fibrosis have been proposed, such as S-index,[12] PAHA (which refers to as platelet count, AST, haptoglobin, and Apo-A1),[13] and RPR (red cell distribution width to platelets ratio).[14] However, these methods were originally used to predict the severity of liver fibrosis, and they have not been applied to the evaluation of the severity of liver cirrhosis.[15,16] Transient elastography (TE, by using FibroScan), which is a noninvasive method that can be performed preoperatively, is becoming the state-of-the-art for evaluation of liver stiffness. However, optimal TE cutoffs for the diagnoses of cirrhosis vary from study to study and remain in debate. Additionally, cirrhosis has not been reported to be sub classified by TE cutoffs.[17-20]

In the present study, we aimed to develop a scoring model using noninvasive parameters to predict histologic severity of cirrhosis in HBV-related HCC patients.

Materials and methods

Patients and clinical parameters

The participants included consecutive patients with chronic hepatitis B who underwent liver resection for the first time. All patients' detailed information was all obtained before liver resection. The patients with the following conditions were excluded: (1) tumor diameters >10 cm or multiple tumors; (2) tumors that oppressed the main portal vein; (3) main portal vein thrombus; (4) any etiologies other than HBV and regular antivirus treatment; (5) Child-pugh B or C liver function; and (6) incomplete data. Finally, 604 patients were randomly divided into the model building group and the test group according to a computer-generated randomization schedule. All patients provided written informed consent for the liver resection and further research. This study was approved by the Ethics Committee of our hospital and complies with the standards of the Declaration of Helsinki and current ethical guidelines.

Before liver resection, all patients underwent an ultrasound examination of the upper abdomen performed by a professional sonographer in our hospital. Spleen thickness is defined as the vertical distance between the porta lienis and the point of tangency of the lateral border. Portal vein diameter was measured as the largest antero-posterior diameter at the crossing point with the hepatic artery, during suspended respiration.[21] Endoscope examination was conducted preoperatively for all the patients. The grades of esophageal varices were classified as: F1, straight varices not disappearing with insufflations; F2, enlarged tortuous, occupying <1/3 of the lumen; and F3, coil-shaped, occupying >1/3 of the lumen.

Assessment of the histologic severity of cirrhosis

The severity of the excised specimens was blindly and independently assessed twice by two histopathologists according to the Laennec scoring system. The inter-rater agreement was excellent (Kappa = 0.754). The samples were re-examined to analyze for discrepancies and reached a consensus when the two pathologists did not obtain the same results. Cirrhosis was scored on four scales: <F4, no cirrhosis; F4A, mild cirrhosis (most septa are thin, one broad septum allowed); F4B, moderate cirrhosis (at least two broad septa); and F4C, severe cirrhosis (at least one very broad septum or many minute nodules).[1]

Statistical analysis

All statistical analyses were performed with SPSS, version 15.0, software (SPSS Inc, Chicago, IL, United States). Continuous variables were expressed as the mean ± standard deviation and were compared with student t test or nonparametric test depending on their distribution. Categorical variables were compared with χ^2 or the Fisher exact tests. We used the logistic analyses to select parameters associated with the histologic severity of cirrhosis. Correlation was evaluated by Spearman rank correlation coefficients. The accuracy of the generated scoring system was evaluated by constructing the area under receiver operating characteristic (ROC) curve analyses. Thereafter, in subsequent validation group, we tested the diagnostic value of this scoring system that was derived from the estimation group and calculated the sensitivity (Sen), specificity (Spe), positive predictive values, and diagnosis accuracy (DA). The probability cutoff points for the optimal combination of sensitivity and specificity were determined by