Research Article

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Liver stiffness-based optimization of hepatocellular carcinoma risk score in patients with chronic hepatitis B

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Background & Aims: CU-HCC score is accurate to predict hepatocellular carcinoma (HCC) in chronic hepatitis B (CHB) patients. However, diagnosis of cirrhosis may be incorrect based on ultrasonography, leading to some errors in HCC prediction. This study aimed to evaluate the accuracy of LSM-HCC score, refined from CU-HCC score with liver stiffness measurement (LSM) using transient elastography to predict HCC.

Methods: A prospective cohort study of 1555 consecutive CHB patients referred for transient elastography examination; 1035 and 520 patients randomly assigned to training and validation cohorts, respectively. Clinical cirrhosis of CU-HCC score was substituted by LSM and analyzed with multivariable Cox regression analysis with other parameters.

Results: During a mean follow-up of 69 months, 38 patients (3.7%) in the training cohort and 17 patients (3.4%) in the validation cohort developed HCC. A new LSM-HCC score composed of LSM, age, serum albumin and hepatitis B virus (HBV) DNA levels were derived, which ranges from 0 to 30. Areas under receiver operating characteristic curves of LSM-HCC score were higher than those of CU-HCC score (0.83–0.89 *vs.* 0.75–0.81). By applying the cutoff value of 11, the score excluded future HCC with high negative predictive value (99.4%–100%) at 5 years.

Conclusions: LSM-HCC score constructed from LSM, age, serum albumin and HBV DNA level is accurate to predict HCC in CHB patients.

Keywords: HBV DNA; Liver-related mortality; Predication score; Transient elastography.

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Abbreviations: ALT, alanine aminotransferase; Anti-HBe, antibody against hepatitis B e antigen; AUROC, area under the receiver operating characteristics curve; CHB, chronic hepatitis B; CI, confidence intervals; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HR, hazard ratios; IQR, interquartile range; LSM, liver stiffness measurement.

Introduction

Chronic hepatitis B (CHB) is the leading cause of liver cirrhosis and hepatocellular carcinoma (HCC) in Asia [1]. Advanced age, cirrhosis and high viral load are the most important predictors of HCC in CHB patients who are treatment-naïve [2,3] or receiving antiviral therapy [4,5]. CU-HCC was developed according to these parameters and validated in the clinic settings [3,4]. However, heavy weighting was assigned to cirrhosis in these scores. A group of Taiwanese investigators has developed a risk score based on non-cirrhotic patients [6], and liver cirrhosis was excluded based on ultrasonographic criteria. As early cirrhosis may be missed by ultrasonography, this limitation may lead to substantial errors of the prediction if the presence or absence of cirrhosis is misclassified [7].

Transient elastography is one of the most widely validated non-invasive tools to detect early liver cirrhosis in various chronic liver diseases [8,9]. Liver stiffness measurements (LSM) cutoff values 12.0 kPa and 13.4 kPa were found to be specific to detect histologic cirrhosis in CHB patients [10,11]. LSM was also found to be useful to predict HCC [12] and complications after hepatic resection [13]. LSM and other serum markers of liver fibrosis could also predict 5-year survival of patients with CHB [14]. Whether LSM can refine the diagnosis of cirrhosis and substitute clinical cirrhosis as a component of the risk score to predict HCC remains to be defined.

In this large-scale real-life prospective cohort study, we aimed to evaluate the accuracy of the risk score refined with LSM to predict HCC in CHB patients.

Patients and methods

Study population

This was a prospective cohort study. We included consecutive CHB patients who were referred to Prince of Wales Hospital for transient elastography examination from August 2006 to June 2008 [15–17]. We received referrals from primary care and hospital clinics in Hong Kong. All patients had positive hepatitis B surface antigen (HBsAg) for at least 6 months. Patients with co-infection with hepatitis C virus, other chronic liver diseases, pre-existing HCC and other serious concurrent illness were excluded. This study was approved by the Clinical

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Research Ethics Committee of the Chinese University of Hong Kong. All patients provided informed written consent.

Clinical and laboratory evaluation

Baseline visit was defined as the time of transient elastography examination. At baseline, patients received evaluation including a full medical history, physical examination, complete blood count, prothrombin time and international normalized ratio, liver and renal biochemistries, HBsAg, hepatitis B e antigen (HBeAg) and antibodies (anti-HBe), HBV DNA, quantitative HBsAg and trans-abdominal ultrasonography. In our laboratory, HBV DNA was measured by Taqman real-time polymerase chain reaction assay validated against the EUROHEP standard with a linear range of detection from 20–2 $\times$ 10^8 IU/ml [18]. HBsAg was quantified by Architect HBsAg QT (Abbott Diagnostic), with 1:500 autodilution according to the manufacturer's instruction. The sensitivity of the Architect assay was 175 to 124,950 IU/ml. Those below 175 IU/ml were repeated by undiluted detection (sensitivity from 0.05 to 250 IU/ml) [19].

The patients were followed up once every 3 to 12 months. During each visit, patients' symptoms and clinical events were recorded. Liver biochemistry and alpha fetoprotein were checked every visit. Antiviral therapy might be prescribed during the follow-up visits according to international guidelines and patient preference. In most patients receiving antiviral therapy for CHB, HBV DNA was checked 6 to 12-monthly. Maintained virologic response was defined as undetectable serum HBV DNA till the last visit [20]. Ultrasonography of the abdomen was performed every 1 to 2 years for surveillance of hepatocellular carcinoma, or more frequently if alpha fetoprotein rose above 20 μg/L. Clinical cirrhosis was defined as shrunken small liver with nodular surface noted on liver imaging and clinical features of portal hypertension (e.g., ascites, splenomegaly, and varices) [3].

Liver stiffness measurement (LSM) by transient elastography

LSM was performed using transient elastography (Fibroscan) according to the instructions and training provided by the manufacturer. Details of the technical background and examination procedure have been previously described [21]. The LSM was considered reliable only if 10 successful acquisitions were obtained and the ratio of interquartile range over LSM (IQR/LSM) $\leqslant$0.3 [22]. The liver stiffness was expressed in kiloPascal (kPa).

CU-HCC score

CU-HCC score were estimated at the time of transient elastography examination. CU-HCC score is composed of 5 parameters: age, albumin, bilirubin, HBV DNA, and clinical cirrhosis; it ranges from 0 to 44.5 [3]. A cutoff value at 5 of CU-HCC score is recommended to predict the 3-year and 5-year risks of HCC.

Clinical outcomes

The primary outcome of this study was the 3-year and 5-year incidence rates of HCC. The diagnosis of HCC was established based on histopathological confirmation; detection of a positive lesion with at least two imaging techniques (trans-abdominal ultrasonography, triphasic computed tomography, magnetic resonance imaging, or hepatic angiogram); or detection with one imaging technique coupled with an alpha-fetoprotein concentration greater than 400 ng/ml [23].

Statistical analyses

Statistical analysis was performed by Statistical Package for Social Science (SPSS version 20.0, Chicago, IL, USA). Patients were randomly assigned into a training cohort and a validation cohort in a 2:1 ratio. Continuous variables were expressed in mean ± standard deviation. Cox proportional hazard model was performed to determine the relationship of LSM and other clinical variables with HCC. The risks were expressed in hazard ratios (HR) and 95% confidence interval (CI). The clinical cirrhosis of CU-HCC score was substituted by LSM; this was analyzed with multivariable Cox regression analysis together with the other four parameters (age, albumin, bilirubin, HBV DNA) of CU-HCC score. The new score (LSM-HCC score) was the weighted sum of those significant variables, of which the new weights were defined as the quotient (rounded to nearest integer) of corresponding estimated coefficient from a Cox regression analysis divided by the smallest χ^2 coefficient. The score was then categorized into low risk and high risk groups with a cutoff value of highest sum of sensitivity and specificity value. The final model was applied to the validation cohort in predicting the risk of HCC. The overall accuracy of CU-HCC score, LSM-HCC score and LSM alone was estimated using the receiver operating characteristics (ROC) curve and its 95% CI. Areas under ROC (AUROC) were compared by DeLong test [24]. The Kaplan–Meier method was used to estimate the cumulative incidence of HCC of different risk groups. The log-rank test was used to compare time-to-event curves between different groups of patients. Sensitivity analysis was performed by repeating all the analyses in the subsets of patients who did or did not receive antiviral therapy. All statistical tests were two-sided. Statistical significance was taken as p <0.05.

Results

Patient characteristics

During the study period, 1643 CHB patients underwent transient elastography examination at our center. After excluding 81 patients who had unreliable LSM, 3 patients with pre-existing HCC at baseline, and 4 patients co-infected with hepatitis C, the final analysis included 1555 CHB patients; 1035 and 520 patients were randomly assigned to training and validation cohorts, respectively. The baseline characteristics of patients were shown in Table 1. Patients in two cohorts had similar baseline characteristics.

Thirty eight patients (3.7%) and 17 patients (3.4%) of training and validation cohort developed HCC during the follow-up period of 69 ± 8 months. In both cohorts, patients who developed HCC were older, had lower platelet counts, longer prothrombin time, lower serum albumin, higher serum alanine aminotransferase (ALT), were more likely to be cirrhotic, and had higher baseline LSM (Table 1). While more patients who developed HCC received antiviral therapy during the follow-up period, they were less likely to achieved maintained virologic response and had shorter duration of virologic remission.

Cumulative probability of HCC and deaths

In the training cohort, 38 patients and 17 patients developed HCC and liver-related mortality (14 patients died of HCC, 3 patients died of liver failure), respectively. The 3- and 5-year cumulative incidences of HCC were 2.3% (1.8%–2.8%) and 3.3% (2.7%–3.9%); those of liver-related mortality were 0.8% (0.5%–1.1%) and 1.3% (1.0%–1.6%), respectively. The incidences were similar in the validation cohort: HCC 1.5% (1.0%–2.0%) and 2.9% (2.2%–3.6%); liver-related mortality 0.8% (0.4%–1.2%) and 1.4% (0.9%–1.9%) at 3 years and 5 years, respectively.

Factors associated with HCC in the training cohort

Table 2 shows the analysis by Cox proportional hazards model concerning the parameters associated with HCC in CU-HCC score. The cutoff values of 8.0 kPa and 12.0 kPa were chosen to define three strata of LSM because these values had the highest sum of sensitivity and specificity, and specificity above 90% for HCC, respectively. By univariate analysis, age above 50 years, serum albumin 35 g/L or below, baseline serum HBV DNA above 200,000 IU/ml, LSM above 8.0 kPa were associated with HCC. Higher LSM at 12.0 kPa was associated with a higher risk of HCC. Serum bilirubin fell short of statistical significance after LSM was used to replace clinical liver cirrhosis in the analysis. All these factors remained the independent risk factors on multivariable analysis, after adjusting for antiviral drug use (Table 2).