Hepatocellular carcinoma risk scores: ready to use in 2015?

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Hepatic Oncology

Hepatocellular carcinoma (HCC) is one of the most common cancers in the world, with more than 0.6 million deaths annually [1,2]. The incidence of liver cancer is highest in sub-Saharan Africa, and Central and Southeast Asia, where the prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection is high [1,2]. However, only a proportion of patients with chronic infection of HBV and/or HCV will develop HCC. The lifetime risk of developing HCC from 30 to 75 years, for men and women, was 27.38 and 7.99% in chronic hepatitis B patients, and 23.73 and 16.71% in chronic hepatitis C patients [3]. Hepatocarcinogenesis is a multistage process with the involvement of a multifactorial etiology [4]. The individual variation in disease risk implies the existence of various risk factors that drive the progression from hepatitis through cirrhosis to HCC in the natural history of chronic hepatitis B and C [5,6]. These risk predictors include viral, host and environmental factors that may be used to triage chronic viral hepatitis patients into groups with high and low risk of HCC for referral to different clinical managements.

The predictors of HCC development for chronic hepatitis B and C patients have been well documented in many case-control and cohort studies [1]. Most important findings for the accurate prediction of HCC risk come from long-term prospective studies. In the community-based REVEAL-HBV/HCV study, HCC risk predictors for chronic hepatitis B patients include male gender, increasing age, family history of HCC, habitual alcohol consumption, HBeAg serostatus, genotype C (versus genotype B) and basal core promoter A1762T/G1764A mutant of HBV, co-infection with HCV, and elevated serum levels of HBV DNA, HBsAg and ALT [4,7–10]. The long-term HCC risk predictors for chronic hepatitis C patients include increasing age, cirrhosis status, HCV genotype 1, elevated serum levels of HCV RNA and ALT, increased ratio between serum AST and ALT level (AST/ALT ratio), and co-infection with HBV [5,11–12].

Risk calculators, which integrate several independent risk predictors through the conversion of a risk function into a single easy-to-use measure of disease risk,

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are widely used in many clinical fields. Many risk calculators have been developed for the prediction of HCC in patients with chronic hepatitis B and C based on community or hospital cohorts [13,14]. Most of them were hospital-based [15–20] with limited sample sizes, follow-up period, and insufficient external validation. Chronic viral hepatitis patients from hospitals are obviously symptomatic and more severely affected with the disease than patients in the community. The risk of HCC based on hospital cohorts is very likely overestimated. Small sample size and short follow-up periods may result in a small number of HCC cases and wide confidence intervals of regression coefficients for assessing associations between predictors and HCC risk. Some risk calculators for HBV-related HCC included unique predictors that are uncommonly used clinically, and that might not be applicable to most patients in the population. The best approach is to derive an HCC risk calculator using clinical parameters from a large community cohort and to validate the calculator using the data from large hospital cohorts, especially from different countries.

We have developed HCC risk calculators for chronic hepatitis B patients from our REVEAL-HBV study. Several REVEAL-HBV nomograms incorporating risk predictors, including age, gender, family HCC history, alcohol consumption, HBeAg serostatus, HBV genotype, and serum levels of ALT and HBV DNA, into the risk functions have been derived and internally validated [21]. Two-thirds of the REVEAL-HBV cohort members were allocated for the model derivation with another one-third for the model validation. For the prediction of HCC risk, the correlation coefficients between the observed and nomogram-predicted HCC risk were greater than 0.90 in all model derivation and validation sets. All the areas under the receiver operating characteristic curve (AUROC) for risk prediction nomograms ranged 0.83–0.89 and 0.82–0.85 in the derivation and validation sets, respectively, indicating a high predictive accuracy.

The risk calculators derived from the REVEAL-HBV study have been further validated internationally using clinical cohorts enrolled from hospitals in East Asia [22]. This new HCC risk calculator, called REACH-B score, was derived from 3584 patients without cirrhosis from the REVEAL-HBV study, and validated by 1505 patients from three hospitals in Hong Kong and South Korea. The 17-point REACH-B

score included only five risk predictors, which were sex, age, HBeAg status, and serum levels of ALT and HBV DNA, because data of family HCC history, alcohol consumption and HBV genotype were not available in all three hospital cohorts. The predicted HCC risk ranged from 0–23.6% at 3 years, 0–47.4% at 5 years, and 0–81.6% at 10 years for patients with the lowest to highest risk score. The AUROCs to predict risk were 0.81, 0.80 and 0.77, respectively, at 3, 5 and 10 years in the validation cohort; and 0.90, 0.78 and 0.81, respectively, after exclusion of 277 cirrhosis patients from the validation cohort. This accurate and simple-to-use REACH-B score is ready to use for untreated chronic hepatitis B patients in East Asia, where HBV is mainly transmitted in early childhood and prevalent HBV genotypes are B and C. The REACH-B score has already been used to assess the efficacy of anti-viral therapy of chronic hepatitis B to prevent the occurrence of HCC.

Risk calculators may be upgraded continuously once new independent risk predictors are identified. After the discovery of quantitative serum level of HBsAg as an independent risk predictor of HCC, new nomograms including serum HBsAg level in the risk function have been further developed and internally validated in the REVEAL-HBV study [23]. The addition of serum HBsAg level into the risk calculator may predict HCC risk of chronic hepatitis B patients with serum HBV DNA levels $<10^6$ copies/ml more precisely. The AUROC for predicting 5-year, 10-year and 15-year risk of HCC ranged 0.86–0.89 and 0.84–0.87 in the derivation and validation sets, respectively. Further analysis incorporating serum HBsAg level into the internationally validated REACH-B score is undergoing. The updated REACH-B calculators are expected to provide more precise risk prediction for patients with low viral load.

Nowadays, there are several risk prediction models for end-stage liver diseases among HCV infected patients [16–18,24–26]. Some of the risk calculators were designed to predict the risk for HCC development [16–18]. However, the algorithms have not yet been validated for the performance of the predictability to the risk for HCC.

HCC risk calculators have also been developed using the REVEAL-HCV cohort and validated by a community-based patient cohort in Taiwan recently [14]. The model derivation and validation cohorts consisted of 975 and 572 patients infected with HCV, respectively. The

predictors included in the risk functions were age, cirrhosis status, serum ALT level, serum AST/ALT ratio, serum HCV RNA level, and HCV genotype. Two risk calculators were developed: one for all HCV-infected patients, and the other for HCV-infected patients with detectable serum HCV RNA levels. The AUROC for predicting 5-year HCC risk in the validation cohort for the two calculators was 0.73 and 0.70, respectively. The low AUROCs may be due to the small sample size of HCV-infected patients and HCC cases in model derivation and validation sets. However, the HCC risk calculators are considered satisfactory for the triage of HCV-infected patients into groups with high and low risk of HCC. They are ready to use for HCV-infected patients in East Asia, where the HCV transmission routes are mainly iatrogenic and prevalent HCV genotypes are 1 and 2.

The HCC risk calculators derived from REVEAL-HBV/HCV might not be applicable to patients infected with other genotypes of HBV/HCV at different ages through different transmission routes. For examples, the HCC risk of drug abusers infected with HBV/HCV in adulthood might not be predictable by the above-mentioned risk calculators. These risk calculators may also not be applicable to patients coinfecting with HBV and HCV, who have an extremely high risk of HCC [3], nor to immunosuppressed patients due to HIV infection or chemotherapy of cancer. HCC risk calculators may not be applicable either to young patients who are in the immune tolerance phase.

Treatments of chronic viral hepatitis patients with antiviral agents may lower both viral load

and serum ALT levels, which may result in the regression of fibrosis and cirrhosis and the prevention of HCC. However, the risk profile could be highly dynamic, both during and after treatment, due to the variable responses in treated patients. It is recommended to apply current risk calculators to treated patient cohorts in order to assess whether the treatment-modified risk profile actually corresponds to the reduction in HCC risk.

In conclusion, several HCC risk calculators have been developed and internationally or externally validated for patients affected with chronic hepatitis B or C. These simple-to-use risk calculators are ready to use in most patients from East Asia. They need to be further assessed for applicability to patients of other ethnic origin, viral genotype, and age at infection. Further investigation and validation of risk calculators for patients undergoing therapy would also be beneficial. It is worth reaching an international consensus on the incorporation of risk calculators in clinical guidelines to improve patient management through appropriate and timely intervention.

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