The Prognostic Model and Risk Stratification for HCC Development

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Chronic hepatitis B virus (HBV) infection is the leading cause of progression of liver disease to liver cirrhosis or hepatocellular carcinoma (HCC), therefore it is critically important to identify subgroup at high risk for HCC occurrence.1,2 To date, factors associated with HBV-related HCC occurrence, such as male gender, old age, advanced liver fibrosis or cirrhosis, and a high serum HBV-DNA level, have been extensively studied.3,5 On the basis of these findings, several risk prediction models composed of multiple parameters for HCC development, such as CU-HCC...
score, GAG-HCC score, REACH-B score, and LSM-HCC score, have been developed with promising results. However, several points should be addressed from the current viewpoint. In the first place, in the era of antiviral therapy where the appropriate antiviral therapy should be commenced, if necessary, to reduce the risk of progressive liver disease and the use of potent antiviral agents such as entecavir and tenofovir are recommended, the prognostic values of these models had not been validated sufficiently. Since antiviral therapy is an important disease modifier, when the HCC risk scores are applied among patients undergoing antiviral therapy in the real life, the expected HCC incidences might be overestimated in comparison with the actual ones. In the same context, the prognostic significance of a biological gradient of serum HBV-DNA levels measured at given time points during the disease course has substantially diminished, because most treated patients will eventually achieve virological responses (VR). Consequently, it is uncertain whether the earlier risk prediction models relying heavily on serum HBV-DNA levels can accurately determine the risk of HCC development. More importantly, considering that the risk of developing HCC cannot be totally eliminated even in those patients who achieve complete VRs, another predictive factor determining the long-term prognosis such as HCC development are required. So, the potential role of the pre-existing or residual fibrotic burden has become important nowadays. Among several non-invasive methods to assess the status of fibrosis, the liver stiffness (LS) value using transient elastography (TE) has been validated for its usefulness in not only diagnosing the fibrosis degree but also predicting the clinical outcomes. Moreover, the LS value which can disclose the fibrosis status precisely might be more appropriate as an integral component of the risk prediction models for HCC development. However, in previous risk prediction models, a crude, albeit simple and convenient, categorization of “liver cirrhosis” that is based on either the clinical manifestations or the subjective ultrasonographic findings had been applied. Accordingly, “modified REACH-B score” (mREACH-B score) had been proposed to predict the prognosis during the follow-up for patients who had achieved complete VR through entecavir therapy, on the assumption that the remaining fibrotic burden would finally affect the prognosis when both viral replication and necro-inflammation became maximally suppressed through antiviral therapy. So, in mREACH-B model, the same backbone of REACH-B score was adopted, but the serum HBV-DNA levels were substituted with LS values, which weighed 0, 2, and 4 points for LS values of <8.0 kPa, 8.0-13.0 kPa, and >13.0 kPa, respectively. Expectedly and interestingly, among those successfully treated with antiviral therapy, mREACH-B score showed the better prognostic performance compared to the original REACH-B score among those with VR through antiviral therapy.

However, in order to confirm whether mREACH-B score may be generalizable to the entire spectrum of subjects with chronic HBV infection, further validation would be necessary. LS values may be usually overestimated during active hepatic necroinflammation, for example, the phase with high serum alanine aminotransferase (ALT) level. However, as serum ALT level becomes normalized with antiviral therapy, LS values become decreased. So, LS values obtained when such a confounding milieu is appropriately excluded should be adopted as a component of the risk prediction models. In the similar context, the optimal timing of acquisition of LS values should be determined in the future studies, considering that suppression of HBV through long-term antiviral therapy can lead to regression of fibrotic burden. Furthermore, the application of such kinds of risk scoring models in other ethnic groups should be evaluated in the future studies. Papatheodoridis et al. reported the poor or modest prognostic values of HCC risk scores developed in Asian patients among Caucasian patients. So, differences in the natural courses of patients with chronic HBV infection according to ethnic groups and regions should be considered accordingly.

To establish the more refined risk prediction models, other viral or host factors should be evaluated as the major
component of the equations. For example, serum quantitative HBsAg level might be the promising component for the more refined risk prediction models at least in a subgroup with viral load of low to intermediate level, since high serum quantitative HBsAg level itself might indicate the relatively unfavorable host immune status against HBV infection, associated with a higher risk of HCC development among patients with low viral load. In addition, use of other non-invasive tests using serological or radiological parameters to assess fibrotic burden should be also studied.

In conclusion, individual risks should be assessed more effectively based on fibrotic burden rather than serum HBV-DNA level as a biological gradient assessed at one time point in the era of antiviral therapy. Given the importance of serum HBV-DNA level shown in the previous reports, it should be handled cautiously in accordance with status of viral activity and antiviral therapy of each individual.

References


