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Letter to the Editor: HBcrAg and Prediction of Hepatocellular Carcinoma Risk

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We wish to respond to the comments received from Drs. Wu, Tseng and Kao. Our analysis was focused on comparing HBV RNA and hepatitis B core related antigen (HBcrAg) levels with existing markers of hepatitis B virus (HBV) replication (HBV DNA and hepatitis B surface antigen)

and whether the two novel markers could improve distinguishing the different phases of infection.

Drs. Wu, Tseng and Kao are correct that we did not dilute samples that exceeded the upper limit of detection and that the absolute titers may have differentiated the immune tolerant (IT) and the hepatitis B e antigen (HBeAg) positive immune active (IA) phases. Indeed, two studies that examined HBcrAg levels among different phases of infection and diluted samples above the upper limit of detection found a statistically significant difference in HBcrAg levels between the IT and HBeAg positive IA phases.(*1, 2*) This point highlights a limitation of the HBcrAg assay, namely, its narrow linear detection range of 3.0-6.8 log U/L. Improved assays with a wider dynamic range may be of utility in making this clinical distinction.

As the analysis was cross-sectional in design, we did not explore the utility of HBV RNA and HBcrAg to predict clinical outcomes such as hepatocellular carcinoma (HCC). We agree with the authors that HBcrAg had been shown to be an independent predictor of HCC, but the preponderance of evidence suggests that it performs similarly to HBV DNA in predicting HCC risk among untreated patients.(*3, 4*) Thus, while the authors showed that HBcrAg may further stratify HCC risk among patients with low HBV DNA levels (2,000-19,999 IU/mL), this finding has not been confirmed in other studies and non-Asian cohorts.(*4*) We also agree with Drs. Wu, Tseng and Kao that more studies are needed to assess the role of HBcrAg in monitoring untreated patients with chronic HBV infection and in evaluating risk of cirrhosis and HCC, particularly in those with low HBV DNA levels, before it can be recommended for clinical use.

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