could be differentiated between these two chronological phases and provide more clinical information.

In summary, HBcrAg and HBV RNA were shown to add limited value in defining different clinical stages given that they are highly correlated with HBV-DNA levels. However, existing data from longitudinal cohorts have suggested that HBcrAg levels serve as complementary predictors in predicting long-term outcomes of CHB patients. More studies are needed to explore how to combine these novel biomarkers with HBV-DNA levels to guide physicians to implement precision medicine.

FUNDING INFORMATION

The work from the Taiwanese research team was supported by the grants from National Taiwan University Hospital (106-N3626, 107-S3816, and 107-N4041), the Ministry of Science and Technology, Executive Yuan, Taiwan (MOST 105-2314-B-303-008 and MOST 106-2314-B-002-136), National Health Research Institutes (NHRI-EX108-10807BC), and Gilead Sciences (IN-TW-988-5987)

CONFLICT OF INTEREST

Dr. Tseng is on the speakers' bureau for and received grants from Gilead. He is on the speakers' bureau for Fujirebio and Bristol-Myers Squibb.

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Reply

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 HBV replication (HBV DNA and HBsAg) and whether the two markers could improve distinguishing the different phases of infection.

Drs. Wu, Tseng, and Kao are correct in 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 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 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 (2000–19,999 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.

ACKNOWLEDGMENTS

The authors acknowledge the use of Hepatitis B Research Network (HBRN) samples and data as the sole contribution of the HBRN. The HBRN was funded as a Cooperative Agreement between the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the following investigators: Lewis R. Roberts, MB, ChB, PhD (U01-DK082843), Anna Suk-Fong Lok, MD (U01-DK082863), Steven H. Belle, PhD, MScHyg (U01-DK082864), Kyong-Mi Chang, MD (U01-DK082866), Michael W. Fried, MD (U01-DK082867), Adrian M. Di Bisceglie, MD (U01-DK082871), William M. Lee, MD (U01-DK082872), Harry L. A. Janssen, MD, PhD (U01-DK082874), Daryl T-Y Lau, MD, MPH (U01-DK082919), Richard K. Sterling, MD, MSc (U01-DK082923), Steven-Huy B. Han, MD (U01-DK082927), Robert C. Carithers, MD (U01-DK082943), and Mandana Khalili, MD (U01-DK082944); an interagency agreement with NIDDK: Lilia M. Ganova-Raeva, PhD (A-DK-3002-001); and support from the intramural program, NIDDK, National Institues of Health (NIH): Marc G. Ghany, MD. Additional funding to support this study was provided to Kyong-Mi Chang, MD, the Immunology Center (NIH/NIDDK Center of Molecular Studies in Digestive and Liver Diseases P30DK50306, NIH Public Health Service Research Grant M01-RR00040), Richard K. Sterling, MD, MSc (UL1TR000058, National Center for Advancing Translational Sciences, NIH), Mandana Khalili, MD, MAS (CTSA UL1TR000004), Michael W. Fried, MD (CTSA UL1TR001111), and Anna Suk-Fong Lok (CTSA UL1RR024986 and U54TR001959.) Additional support was provided by Gilead Sciences, Inc., and Roche Molecular Systems via a CRADA through the NIDDK.

CONFLICT OF INTEREST

Dr. Lau consults for Abbott and advises Gilead. Dr. King received grants from AbbVie. Dr. Lisker-Melman is on the speakers' bureau for AbbVie and Gilead. Dr. Terrault consults for EXIGO, ENYO, PPD Pharma, and Entourage. She received grants from Gilead, Genentech, and Roche. Dr. Janssen consults and received grants from Gilead, GlaxoSmithKline, Janssen, Roche, and Vir. He consults for Aligos, Antios, Arbutus, Eiger, Viroclinics, and VBI Vaccines. He received grants from AbbVie. Dr. Khalili consults and received grants from Gilead. She received grants from AbbVie. Dr. Chung received grants from Gilead, Bristol-Myers Squibb, Boehringer Ingelheim, Janssen, Merck, and Roche. Dr. Lee consults for Forma, SeaGen, Karuna, and Cortexyme. He received grants from Merck, Bristol-Myers Squibb, Intercept, Aurora, Novo Nordisk, Cumberland, and Meridian. Dr. Cloherty is employed and owns stock in Abbott. Dr. Sterling is on the data security monitoring board for AskBio and Pfizer. He received grants from Roche, Abbott, AbbVie, and Gilead.

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Letter to the editor: The addition of C-reactive protein and von Willebrand factor to Model for End-Stage Liver Disease-Sodium

To the editor,

With great interest, we read a study about a novel modification of Model for End-Stage Liver Disease-Sodium (MELD-Na).[1] Starlinger and colleagues concluded that the addition of C-reactive protein (CRP) and von Willebrand factor antigen (vWF-Ag) to MELD-Na improves the prediction of waitlist mortality. However, several crucial concerns attracted our due attention.

As was depicted in the authors' Table 1, some imbalances existed in patient characteristics between Vienna (Exploration) cohort and Mayo (Validation) cohort. For example, in terms of indication for transplant, alcohol-associated cirrhosis occurred in 33.1% of patients in Vienna (Exploration) cohort, whereas it occurred in 12.4% of patients in Mayo (Validation) cohort; tumor occurred in 23.0% of patients in Vienna (Exploration) cohort, whereas it occurred in 41.9% of patients in Mayo (Validation) cohort. Surprisingly, the authors ignored these aspects. Thus, Mayo (Validation) cohort may not be suitable for the validation of the novel model due to these imbalances. We strongly suggest that the authors better detect the difference between these two cohorts.[2,3]

Moreover, some imbalances also existed in patient characteristics between Vienna (Exploration) cohort and Vienna (Pathophysiology) cohort. For example, in terms of etiology, alcohol-associated cirrhosis occurred in up to 61% of patients in Vienna (Pathophysiology) cohort. Furthermore, the data of CRP was 0.80 (0.31 to 1.71) in Vienna (Exploration) cohort, whereas the data of CRP was 0.61 (0.25 to 1.51) in Vienna (Pathophysiology) cohort. Thus, Vienna (Pathophysiology) cohort maybe not suitable to further explore pathophysiological processes involved in the association of vWF-Ag, CRP, and Na with waitlist mortality.[2,3] In principle, the primary cohort would be the optimal choice.

Most notably, there may be a minor error in the authors' Table 1. We are unsure whether the data of vWF-Ag [419 (314 to 420)] are right or not in Vienna (Exploration) cohort. In addition, due to the availability of data, Vienna (Exploration) cohort solely included 32.41% (269/830) of patients, potentially producing selection bias.[4]

We thank Starlinger and colleagues for their efforts to modify the model for MELD. However, the