**Supplementary material**

Page 2-3: Viral and serological markers

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**Serological assays**

Serum HBsAg, HBeAg, anti-HBe, and anti-HCV were tested by commercial assays (Abbott Laboratories, Abbott Park, IL, USA and Abbott Laboratories, Tokyo, Japan) in both cohorts except HBeAg in Japan (HBeAg EIA; Institute of Immunology, Tokyo, Japan).

**Quantification of HBV DNA, HBsAg, and HBcrAg levels in serum**

HBV DNA, HBsAg, and HBcrAg levels were quantified retrospectively using stored sera in the discovery cohort and in the validation cohort when data was unavailable from the medical records. HBV DNA levels were determined using the commercial assays with a lower limit of detection being 15-20 IU/mL. HBsAg levels were determined using the Architect HBsAg QT (Abbott Laboratories, Abbott Park, IL, USA) according to the previous studies.1-3 HBcrAg levels were determined using the Lumipulse G HBcrAg assay and the Lumipulse G1200 Analyzer (Fujirebio, Tokyo, Japan) with a dynamic range from 1000 U/mL to 10,000,000 U/mL.

**Determination of HBV genotype**

In the discovery cohort, HBV genotype was determined by using a PCR-based assay.4 The lower detection limit of HBV-DNA levels is 20 IU/mL (100 copies/mL). IMMUNIS ® HBV Genotype EIA kit (Institute of Immunology Co. Ltd, Tokyo, Japan), which detects genotype-specific epitopes in the preS2 region, was used to determine HBV genotypes for the patients with low viral loads in the discovery cohort and for all the patients in the validation cohort.5 The detection limit of this assay is approximately 100 IU/mL of HBsAg.

**Calculation of FIB-4 index**

The FIB-4 index was calculated according to the formulas: FIB-4= age (years)×AST [U ⁄ L] ⁄ (platelet counts [109⁄ L]×(ALT [U ⁄ L])1 ⁄ 2).6

**Inverse probability of treatment weighting**

In addition to the treatment-naïve patients, sensitivity analysis was conducted by including HBeAg-negative patients who received antiviral treatment prior to HCC development in the discovery cohort. Antiviral treatment is known to lower HCC risk but the presence of HBeAg-negative chronic hepatitis or cirrhosis, which are the key to initiate antiviral treatment,7-9 is associated with the increased risk of HCC. To assess the controlled direct effect of baseline HBcrAg on HCC development, an inverse probability of treatment weighting (IPTW) approach in conjunction with the marginal structural model was applied to control the potential effect of time-dependent antiviral treatment.10-13 In brief, antiviral treatment, which was initiated due to emergence of HBeAg-negative chronic hepatitis or cirrhosis during follow-up, was incorporated in the systematic component of logistic regression model to derive the treatment probability for each subject at each time point. The treated patients were censored when receiving antiviral treatment and the untreated patients were weighted inversely based on the factors to initiate antiviral treatment in these treated patients. The marginal structural Cox proportional hazards regression model was applied for the derivation of causal inference of HBcrAg on HCC development.

**Supplementary figure legends**

Supplementary figure 1. Flow of study participants in the (A) discovery cohort and the (B) validation cohort.

Supplementary figure 2. Comparison of cumulative incidence of HCC between the discovery and validation cohorts.

Supplementary figure 3. HBcrAg level of 10,000 U/mL categorizes HCC risk in (A) group 1, (B) group 2, (C) group 3, (D) group 4, and (E) group 5.

Supplementary figure 4. In the HBeAg-negative patients with indeterminate CHB, HBcrAg level 10,000 U/mL stratifies HCC risk in the subgroup analysis of (A) 905 patients who did not reach AASLD treatment indication within 1 year and (B) 570 patients who had FIB-4 <1.29 at baseline.

Supplementary figure 5. In 1312 HBeAg-negative patients from the validation cohort, (A) HCC risk is categorized into 8 groups by HBV DNA and AASLD-defined ALT levels and (B) HBcrAg serves as a better HCC predictor than HBV DNA and HBsAg in indeterminate patients.

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