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MAJOR ARTICLE

# Hepatitis B Surface Antigen Levels Can Be Used to Rule Out Cirrhosis in Hepatitis B e Antigen-Positive Chronic Hepatitis B: Results From the SONIC-B Study

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***Background.*** Serum hepatitis B surface antigen (HBsAg) levels correlate with the duration of chronic hepatitis B virus (HBV) infection and may predict the extent of hepatic fibrosis.

***Methods.*** We analyzed data from the SONIC-B database, which contains data from 8 global randomized trials and 2 large hepatology centers. Relationship between HBsAg levels and presence of significant fibrosis (Ishak 3–4) or cirrhosis (Ishak 5–6) were explored, and clinically relevant cutoffs were identified to rule out cirrhosis.

***Results.*** The dataset included 2779 patients: 1866 hepatitis B e antigen (HBeAg)-positive; 322 with cirrhosis. Among HBeAg-positive patients, lower HBsAg levels were associated with higher rates of significant fibrosis (odds ratio [OR], 0.419; $P < .001$) and cirrhosis (OR, 0.435; $P < .001$). No relationship was observed among HBeAg-negative patients. Among HBeAg-positive patients, genotype-specific HBsAg cutoffs had excellent negative predictive values (>97%) and low misclassification rates (≤7.1%) and may therefore have utility in ruling out cirrhosis. Diagnostic performance of the HBsAg cutoffs was comparable among patients in whom cirrhosis could not be ruled out with fibrosis 4 (FIB-4).

***Conclusions.*** Hepatitis B virus genotype-specific HBsAg cutoffs may have utility in ruling out presence of cirrhosis in HBeAg-positive patients with genotypes B, C, and D and can be an adjunct to FIB-4 to reduce the need for further testing.

**Keywords.** cirrhosis; fibrosis; hepatitis B; HBsAg.

Assessment of the extent of hepatic fibrosis is essential for the management of chronic hepatitis B (CHB), because it is a recognized indication for commencing antiviral therapy, and it also influences decisions on therapy discontinuation strategies and eligibility for enrollment in clinical trials [1, 2]. Liver biopsy is considered the gold standard for determining the extent of hepatic fibrosis, but it is used infrequently because it is associated with considerable risks to the patient. Liver stiffness-based assessment of hepatic fibrosis is increasingly being used but is not widely available. Several noninvasive indices of hepatic fibrosis have gained popularity, but we recently showed these should be used with caution due to prohibitively high rates of misclassification [3, 4]. Novel predictors of the extent of hepatic fibrosis, preferably in serum, are therefore required. Various natural history studies have shown that serum hepatitis B surface antigen (HBsAg) levels decline in hepatitis B e antigen (HBeAg)-positive patients during active hepatic inflammation. Lower serum HBsAg levels are therefore considered to reflect a longer duration of hepatitis B virus (HBV)-related liver disease. Previous studies have suggested that lower HBsAg levels are associated with more severe hepatic fibrosis, but findings have been conflicting, and clinically applicable cutoffs have not been established [5–8]. The aims of the current study were therefore to study the relationship between serum HBsAg levels and presence of significant fibrosis and/or cirrhosis in a large global cohort of CHB patients.

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## PATIENTS AND METHODS

### Patients

The current study enrolled HBeAg-positive and HBeAg-negative patients with available liver biopsy and HBsAg data from the SONIC-B database. This dataset includes patients from 8 global randomized trials that required baseline liver biopsy and all consecutive CHB patients who underwent liver biopsy in the liver clinics of the Erasmus MC University Hospital in Rotterdam, the Netherlands and the University Health Network, Toronto, Canada. The included trials consisted of 3 studies coordinated by the Foundation for Liver and Gastrointestinal Research from Rotterdam (HBV-9901 study [9], PARC study [10], and ARES study [11]), and we also used data from the 2 phase 3 studies of peginterferon alfa-2a (PEG-IFN) for HBeAg-positive [12] and HBeAg-negative patients [13], the Neptune study [14], and the tenofovir disoproxil fumarate phase 3 trials [15]. The data were subsequently pooled to compile the SONIC-B database. For the current study, only patients with available HBsAg levels were eligible (Supplementary Figure 1). For the clinical trials, HBsAg levels were measured at baseline before commencement of antiviral therapy.

### Hepatitis B Surface Antigen Quantification and Liver Biopsy Assessment

Standard biochemical and virological assessments were previously performed according to the study protocols. Hepatitis B surface antigen levels were measured using the Abbott Architect or Roche Elecsys (Roche Diagnostics, Mannheim, Germany). Liver biopsy was a requisite for study enrollment, and biopsy samples were scored by experienced pathologists who either applied the Ishak or METAVIR systems. Liver fibrosis was defined as no significant fibrosis (Ishak 0–2), significant fibrosis (Ishak 3–4/METAVIR F2–F3), or cirrhosis (Ishak 5–6/METAVIR F4).

**Table 1. Patient Characteristics**

| Characteristics | HBeAg Positive (n = 1866) | HBeAg Negative (n = 913) |
|---|---|---|
| Demography | | |
| Mean (SD) age, years | 32.7 (10.4) | 41.6 (10.8) |
| Male | 1372 (74%) | 728 (80%) |
| Race | | |
| Caucasian | 454 (24%) | 462 (51%) |
| Asian | 1315 (71%) | 404 (44%) |
| Other | 96 (5%) | 47 (5%) |
| Laboratory Values | | |
| HBV DNA (log IU/mL) | 9.73 (1.7) | 7.41 (1.66) |
| HBsAg (log IU/mL) | 4.19 (0.7) | 3.59 (0.62) |
| ALT (×ULN) | 3.41 (3.0) | 2.87 (2.8) |
| HBV Genotype | | |
| A | 197 (11%) | 85 (9%) |
| B | 465 (25%) | 165 (18%) |
| C | 865 (46%) | 222 (24%) |
| D | 291 (16%) | 406 (45%) |
| Other | 47 (3%) | 35 (4%) |
| Missing | 1 (0.1%) | 0 (0%) |
| Biopsy Score | | |
| Ishak 0–2 | 987 (53%) | 435 (48%) |
| Ishak 3–4 | 693 (37%) | 342 (38%) |
| Ishak 5–6 | 186 (10%) | 136 (15%) |

Abbreviations: ALT, alanine aminotransferase; DNA, deoxyribonucleic acid; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis b virus; SD, standard deviation; ×ULN, times upper limit of normal.

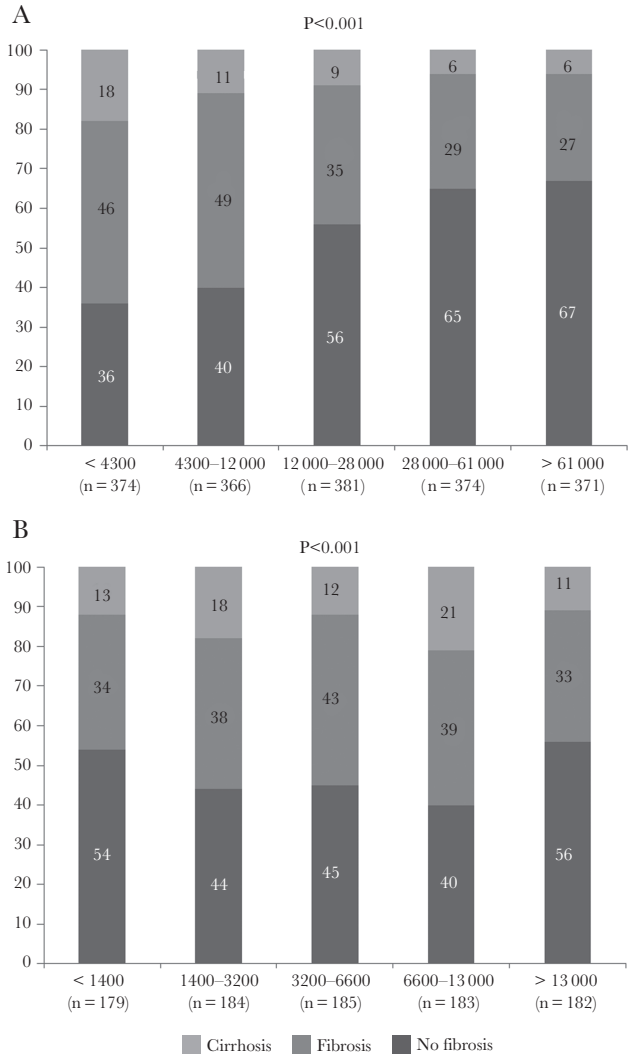


**Figure 1.** Relationship between hepatitis B surface antigen (HBsAg) level and liver fibrosis and/or cirrhosis among hepatitis B e antigen (HBeAg)-positive (A) or HBeAg-negative (B) patients. Liver fibrosis was graded as no significant fibrosis (Ishak 0–2), significant fibrosis (Ishak 3–4), or cirrhosis (Ishak 5–6). The HBsAg levels are given as quintiles.

### Statistical Analysis

SPSS version 21 was used for statistical analyses. Diagnostic performance was assessed with positive predictive values and negative predictive values (NPVs), sensitivity and specificity, and areas under the receiver operator characteristic curve (AUROC). We used a grid search of cutoff point to identify cutoffs for quantitative HBsAg that would be clinically relevant; meaning that at least 10% of patients would have to be captured by the cutoff, with less than 10% misclassification (ie, sensitivity

>90%) and an NPV of >95%. We then assessed performance of these cutoffs in the overall population and in patients for whom cirrhosis could not be ruled out using the recently published optimized fibrosis 4 (FIB-4) cutoffs (ie, those aged <30 or with a FIB-4 of >0.70) [4].

## RESULTS

### Patient Characteristics

A total of 2779 patients could be analyzed (Supplementary Figure 1). An overview of the characteristics of the study cohort is shown in Table 1, stratified by HBeAg status. The majority of patients in the cohort were either Asian (61.9%) or Caucasian (33.0%), and all major genotypes were represented. A total of 1357 patients (48.8%) had at least significant fibrosis, and 322 (11.6%) had cirrhosis.

### Relationship Between Hepatitis B Surface Antigen Levels and Presence of Significant Fibrosis or Cirrhosis

#### *Hepatitis B e Antigen-Positive Patients*

Among HBeAg-positive patients, mean HBsAg levels were 4.34, 4.05, and 3.89 log IU/mL among patients with Ishak 0–2, 3–4, and 5–6, respectively ($P < .001$ by analysis of variance [ANOVA]). The relationship between HBsAg level (in quintiles) and rates of significant fibrosis or cirrhosis are shown in Figure 1A; lower levels were associated with a higher rate of significant fibrosis or cirrhosis ($P < .001$). This was confirmed by logistic regression: lower serum HBsAg levels were associated with higher rates of significant fibrosis (OR adjusted for genotype: 0.419 [95% confidence interval {CI}, 0.357–0.492; $P < .001$]) (Figure 2A) and cirrhosis (OR adjusted for genotype: 0.435 [95% CI, 0.350–0.541; $P < .001$]) (Figure 2B). Similar results were obtained in multivariate logistic regression adjusted for potential confounders (Table 2).

#### *Hepatitis B e Antigen-Negative Patients*

Among HBeAg-negative patients, mean HBsAg levels were 3.59, 3.61, and 3.57 log IU/mL among patients with Ishak 0–2, 3–4, and 5–6, respectively ($P = .771$ by ANOVA). The relationship between HBsAg level (in quintiles) and rates of significant fibrosis or cirrhosis are shown in Figure 1B for the overall population. Although the rates of significant fibrosis and cirrhosis did vary according to HBsAg level, no clear linear relationship could be observed. This was confirmed by logistic regression: serum HBsAg levels were not associated with significant fibrosis (OR adjusted for genotype: 0.937 [95% CI, 0.741–1.185;

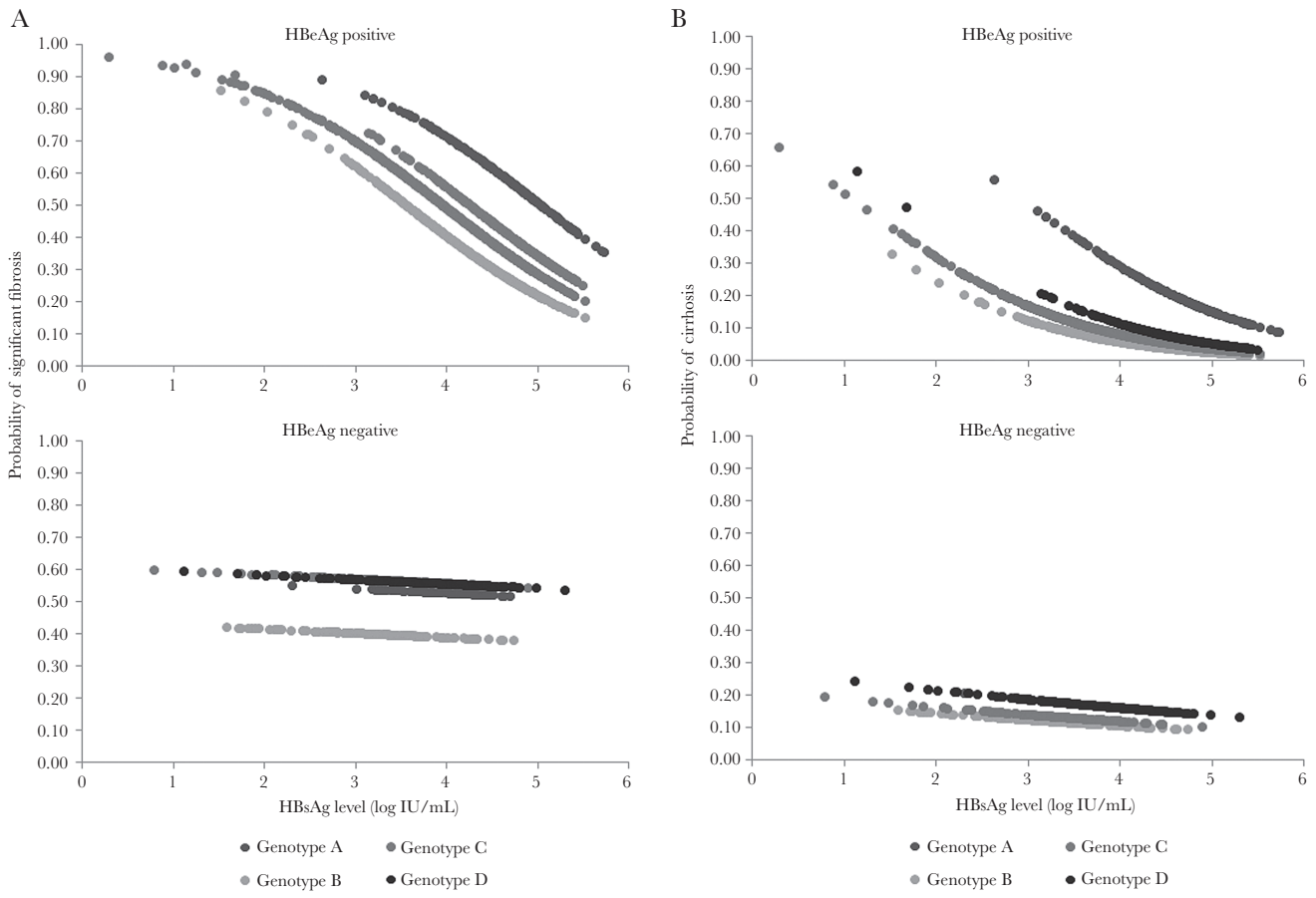


**Figure 2.** Predicted probability of significant fibrosis (Ishak 3–6 [A]) or cirrhosis (Ishak 5–6 [B]) according to hepatitis B surface antigen (HBsAg) level and stratified by hepatitis B e antigen (HBeAg) status. Estimates were derived by logistic regression adjusted for hepatitis B virus genotype.

**Table 2. Association Between HBsAg Levels and Presence of Cirrhosis in Multivariable Logistic Regression**

| HBeAg Positive | | | HBeAg Negative | | |
|---|---|---|---|---|---|
| Variable | OR (95% CI) | *P* | Variable | OR (95% CI) | *P* |
| Age | 1.043 (1.026–1.060) | <.001 | Age | 1.021 (1.001–1.042) | .040 |
| Sex (male) | 0.676 (0.435–1.049) | .081 | Sex (male) | 0.613 (0.353–1.062) | .081 |
| HBV genotype | | .127 | HBV genotype | | .526 |
| A | Reference | | A | Reference | |
| B | 0.537 (0.296–1.109) | .098 | B | 0.859 (0.362–2.042) | .731 |
| C | 0.505 (0.287–0.888) | .018 | C | 0.819 (0.364–1.843) | .629 |
| D | 0.838 (0.441–1.593) | .590 | D | 1.258 (0.619–2.556) | .525 |
| Other | 1.059 (0.397–2.828) | .908 | Other | 0.605 (0.152–2.413) | .477 |
| ALT (×ULN) | 0.987 (0.914–1.065) | .730 | ALT (×ULN) | 0.882 (0.753–1.033) | .120 |
| AST (×ULN) | 1.088 (0.995–1.190) | .064 | AST (×ULN) | 1.152 (0.919–1.443) | .219 |
| AP (×ULN) | 3.390 (1.826–6.292) | <.001 | AP (×ULN) | 3.444 (1.499–7.915) | .004 |
| Bilirubin, mmol/L | 0.956 (0.910–1.024) | .241 | Bilirubin, mmol/L | 0.935 (0.480–1.824) | .845 |
| Albumin, g/L | 0.869 (0.828–0.912) | <.001 | Albumin, g/L | 0.912 (0.861–0.966) | .002 |
| Platelets, $10^9$/mm$^3$ | 0.990 (0.987–0.994) | <.001 | Platelets, $10^9$/mm$^3$ | 0.991 (0.987–0.995) | <.001 |
| HBV DNA, log IU/mL | 0.786 (0.688–0.897) | <.001 | HBV DNA, log IU/mL | 0.900 (0.783–1.034) | .138 |
| HBsAg, log IU/mL | 0.649 (0.486–0.868) | .003 | HBsAg, log IU/mL | 1.037 (0.714–1.507) | .848 |

Abbreviations: ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; CI, confidence interval; DNA, deoxyribonucleic acid; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; OR, odds ratio; ULN, upper limit of normal.

*P* = .588]) (Figure 2A) or cirrhosis (OR adjusted for genotype: 0.811 [95% CI, 0.590–1.115, *P* = .197]) (Figure 2B). Similar results were obtained in multivariate logistic regression (Table 2).

### Ruling Out Cirrhosis Using Hepatitis B Surface Antigen Levels in Hepatitis B e Antigen-Positive Patients

Because serum HBsAg levels were independently associated with presence of cirrhosis among HBeAg-positive patients, we attempted to identify a clinically relevant cutoff that could be used to rule out presence of cirrhosis in this population, applying our preset criteria (cutoff identifies at least 10% of patients, with a sensitivity >90% and NPV >95%). Because HBsAg levels varied significantly across the HBV genotypes, we performed HBV genotype-specific analyses.

As shown in Table 3, HBsAg levels could discriminate between presence or absence of cirrhosis in patients with genotypes B (n = 465), C (n = 865), or D (n = 291), with AUROCs of 0.662–0.712 ($P \leq .009$). Genotype-specific cutoffs had excellent NPVs ( ≥97.7%) and low misclassification rates (≤7.1%) (Table 3). Discrimination was suboptimal in patients with genotype A (n = 197, AUROC = 0.576, *P* = .133), and no clinically relevant cutoff could be identified for this subgroup because of a high rate of cirrhosis even among the patients with the highest HBsAg levels (NPV 89.5%).

### Prediction of Cirrhosis in Hepatitis B e Antigen-Positive Patients in Whom Cirrhosis Could Not Be Ruled Out With the Optimized Fibrosis-4 Score

In the subset of HBeAg-positive patients with HBV genotypes B, C, or D, cirrhosis could not be confidently ruled out using FIB-4 in 1457 patients (either because of an age <30 or FIB-4 >0.70). Application of the optimized HBsAg cutoffs identified 20.8%–35.4% of patients, with excellent NPVs (>97%) and low misclassification rates (<10%), as shown in Table 4.

## DISCUSSION

Serum HBsAg levels have been shown to decrease as a result of immune activity and immune-mediated clearance of infected hepatocytes [16, 17]. Because this immune response is also considered the main cause of liver

**Table 3. Ruling Out Cirrhosis Using Serum HBsAg Levels in HBeAg-Positive Patients[a]**

| Genotype | AUROC | *P* | Cutoff | No Identified | NPV | Misclassification[b] |
|---|---|---|---|---|---|---|
| A (n = 197) | 0.576 | .133 | >182 620 | 19 (9.6%) | 89.5% | 2/41 (4.9%) |
| B (n = 465) | 0.702 | .001 | >55 000 | 95 (20.4%) | 97.9% | 2/26 (7.7%) |
| C (n = 865) | 0.712 | <.001 | >18 000 | 310 (35.8%) | 98.1% | 6/85 (7.1%) |
| D (n = 291) | 0.662 | .009 | >75 000 | 88 (30.2%) | 97.7% | 2/24 (8.3%) |

Abbreviations: AUROC, area under the receiver operator characteristic curve; CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; NPV, negative predictive value.

[a]Genotype-specific cutoffs for ruling out cirrhosis in patients with HBeAg-positive CHB. Optimized cutoffs were identified through a grid search stratified by HBV genotype. For a cutoff to be clinically useful it had to identify >10% of patients, with a sensitivity of >90% and an NPV of >95%.

[b]Misclassification is the number of patients with cirrhosis incorrectly classified as no cirrhosis.

**Table 4. Ruling Out Cirrhosis Using Serum HBsAg Levels in HBeAg-Positive Patients in Whom Cirrhosis Could Not Be Excluded Using FIB-4[a]**

| Genotype | Cutoff | No Identified | NPV | Misclassification[b] |
|---|---|---|---|---|
| B (n = 414) | >55 000 | 86 (20.8%) | 97.7% | 2/24 (8.3%) |
| C (n = 779) | >18 000 | 276 (35.4%) | 97.8% | 6/79 (7.6%) |
| D (n = 264) | >75 000 | 81 (30.7%) | 97.5% | 2/21 (9.5%) |

Abbreviations: CHB, chronic hepatitis B; FIB-4, fibrosis 4; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen.

[a]Performance of genotype-specific HBsAg cutoffs for ruling out cirrhosis in patients with HBeAg-positive CHB who were either aged <30 or had an FIB-4 score of >0.70.

[b]Misclassification is the number of patients with cirrhosis incorrectly classified as no cirrhosis.

inflammation and fibrosis, it was previously suggested that patients with lower HBsAg levels could be at higher risk of significant liver fibrosis. However, a study from Europe failed to confirm such an association [5–8]. These conflicting findings might be explained by differences in HBV genotype distribution (mainly genotypes B/C in the Asian studies, whereas none of the patients in the European study had B/C genotype), sex (the European study enrolled exclusively women), or HBeAg status (HBeAg-negative patients were the vast majority in the European study). The previous studies had been unable to perform stratified analyses due to sample size limitations or enrollment from single geographic areas. In our study, in a pooled analysis of 2779 patients enrolled from 8 global randomized trials, we found a strong association between serum HBsAg levels and presence of fibrosis and/or cirrhosis among HBeAg-positive patients, but not HBeAg-negative patients. The absence of a relationship in HBeAg-negative patients may have multiple explanations. One might be that although most of the patients were probably infected perinatally, the duration of immune activity, which is the main driver of HBsAg decrease rather than duration of infection, may vary widely across patients. Furthermore, recent studies have shown that much of the HBsAg produced in HBeAg-negative patients may in fact be derived from HBV deoxyribonucleic acid (DNA) integrated in host DNA rather than viral covalently closed circular DNA (cccDNA). This integrated DNA may not elicit an immune response and may therefore be associated with less inflammatory activity or fibrosis [18, 19]. At this time, options for noninvasive fibrosis assessment in HBeAg-negative patients thus remain limited to FIB-4 and elastography-based methods.

It is important to note that the observed relationship between lower HBsAg levels and higher rates of fibrosis and cirrhosis was consistent across the 4 major genotypes in the HBeAg-positive subset, but that the association was most pronounced among patients with HBV genotypes B, C, and D. A possible explanation might be differences in duration of infection and immune activity: most of the genotype B, C, and D patients were probably infected perinatally, whereas the genotype A subgroup comprised both non-Caucasians (11%), most likely infected perinatally, and Caucasians (who could have been infected perinatally or horizontally). Other contributing factors may be the previously observed much higher HBsAg levels in HBeAg-positive genotype A patients when compared with the other genotypes [16], and the varying frequency of presence of precore and core promoter mutants, which are more frequently detected in non-A genotypes and are both associated with lower serum HBsAg levels and a higher probability of developing cirrhosis [20, 21].

We next performed a grid search of cutoff points to identify optimized cutoffs that could be used to rule out cirrhosis. We applied predefined criteria based on both NPV (>95%) and sensitivity (>90%) thresholds, because a search based on NPV alone may identify cutoffs that still have high rates of misclassification. We recently showed that this is a clinically relevant issue that severely hampers the use of other noninvasive indices of hepatic fibrosis [4]. Our grid search identified genotype HBsAg cutoffs (>55 000 IU/mL for genotype B; >18 000 IU/mL for genotype C; >75 000 IU/mL for genotype D) that had excellent NPVs and low rates of misclassification. Our findings may have important clinical implications, because these cutoffs could be used to reliably rule out cirrhosis in 20%–36% of patients depending on the HBV genotype.

The diagnostic performance of the optimized HBsAg cutoffs compares well with those recently reported for a FIB-4 score of <0.70, which identified approximately 32% of patients with an NPV of 97% and a misclassification rate of 5.8% [4]. However, we previously showed that the optimized FIB-4 score has suboptimal performance in the young (those aged below 30). This is a major limitation of FIB-4, because many patients, especially those with HBeAg-positive disease, are in this age group. Therefore, we specifically studied the performance of our novel HBsAg cutoffs in the patients who did not meet the FIB-4 rule. In our cohort, the optimized HBsAg cutoffs had high diagnostic accuracy for ruling out cirrhosis in this population, and they could thus be used as an adjunct before further testing is required. Figure 3 shows a flowchart depicting the potential application of our findings in clinical practice to rule out cirrhosis in HBeAg-positive patients. In combination, FIB-4 and HBsAg may thus be used as a first step to rule out cirrhosis, which may impact decision making regarding hepatocellular carcinoma surveillance, treatment strategies aiming at finite treatment, and even participation in trials exploring the efficacy of new compounds.

Although our study is the largest to date, it does have some caveats. First, our study pooled patients from randomized trials, which could potentially influence external, but not internal, validity. In addition, stratification by HBV genotype reduced sample size per subgroup, introducing uncertainty. Therefore, external validation of our findings is required before they can be applied in clinical practice.

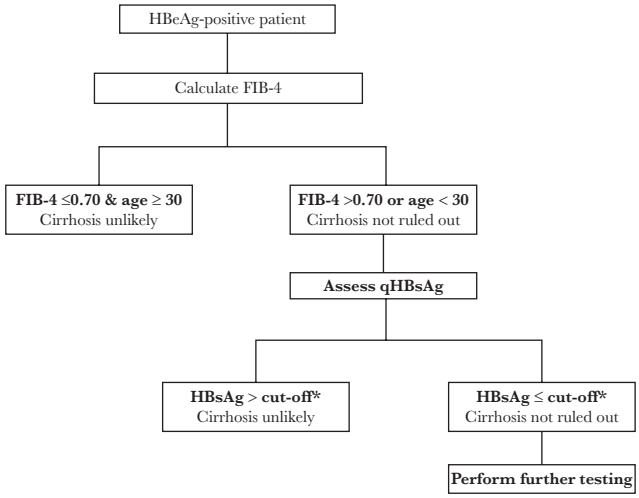


**Figure 3.** Potential application of quantitative hepatitis B surface antigen (HBsAg) to rule out cirrhosis in clinical practice. *, Genotype-specific cutoffs: genotype B >50 000 IU/mL, genotype C >18 000 IU/mL, and genotype D >75 000 IU/mL. FIB-4, fibrosis 4; qHBsAg, quantitative HBsAg.

## CONCLUSIONS

In conclusion, lower serum HBsAg levels are associated with a higher rates of significant fibrosis or cirrhosis in HBeAg-positive, but not HBeAg-negative, CHB patients. Genotype-specific HBsAg cutoffs can be used to rule out presence of cirrhosis in patients with HBV genotypes B, C, and D and are complementary to established FIB-4 cutoffs.

### Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

**Supplementary Figure 1.** Patient disposition.

### Notes

***Author contributions.*** M. J. S., W. P. B., B. E. H., R. J. d. K., R. A. d. M., and H. L. A. J. contributed to study design, collection of data, data analysis, and writing of the manuscript and approved the final version. H. L.-Y. C., T. P., J.-D. J., S. Z., R. N. C., H. L.-Y. C., C. W., V. P., A. G., Q. X., and M. B. contributed to study design, collection of data, and critical review of the manuscript and approved the final version: All authors approve submission of the manuscript.

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