Rapid Decline Rather Than Absolute Level of HBsAg Predicts Its Seroclearance in Untreated Chronic Hepatitis B Patients From Taiwanese Communities

Hsin-Che Lin, MD[1,2], Jessica Liu, MPH, PhD[3], Mei-Hung Pan, MPH[1], Mei-Hsuan Lee, PhD[4], Richard Batrla-Utermann, MD, PhD[5], Sheng-Nan Lu, MD, PhD[6], Wen-Juei Jeng, MD[7,8], Hwai-I Yang, PhD[1,4,9,10] and Chien-Jen Chen, MPH, ScD, PhD[1]

INTRODUCTION: **Hepatitis B surface antigen (HBsAg) clearance leads to favorable outcomes in patients with chronic hepatitis B. HBsAg levels <200 IU/mL with HBsAg decline >0.5 $\log_{10}$ IU/mL in 1 year have been reportedly predictive of HBsAg loss. This study aimed to use the REVEAL-hepatitis B virus cohort to validate and simplify this prediction rule and verify whether the simplified algorithm can be used among various clinical subgroups.**

METHOD: **We analyzed 707 patients with untreated chronic hepatitis B who had 3 or more HBsAg measurements within 5 years before HBsAg seroclearance or last visit, greater than 1 year apart from one another. Rapid HBsAg decline was defined as HBsAg decline >0.5 $\log_{10}$ IU/mL in 1 year or >1 $\log_{10}$ IU/mL in 2 years. Sensitivity, specificity, positive predictive values, and negative predictive values were compared to assess the predictability of HBsAg seroclearance.**

RESULTS: **During a median follow-up of 10.7 years, 41 of the 707 patients cleared serum HBsAg. HBsAg levels at all measurements were lower ($P < 0.0001$) and HBsAg decline was greater ($P < 0.0001$) in patients with seroclearance compared with non-seroclearance patients. The predictive accuracy of predicting 1-year HBsAg loss using only the rapid decline algorithm (sensitivity = 0.4412, specificity = 0.9792, positive predictive value = 0.5172, negative predictive value = 0.972) was the same as the model combining rapid HBsAg decline and HBsAg levels <200 IU/mL. The simplified algorithm including only the rapid decline performed similarly among various levels of HBsAg, hepatitis B virus DNA, and alanine aminotransferase and was independent of inactive carrier state.**

DISCUSSION: **HBsAg decline >0.5 $\log_{10}$ IU/mL/yr was a practical predictor of HBsAg seroclearance within 1 year in our community-based untreated cohort.**

KEYWORDS: functional cure; hepatocellular carcinoma; inactive carrier; dynamic change

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A929

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INTRODUCTION

Chronic hepatitis B virus (HBV) infection is a global health burden. Worldwide, more than 257 million people are infected (1), and at least 68,000 people die from liver-related diseases each year (2), most of which are secondary to cirrhosis, liver failure, and hepatocellular carcinoma. Clinical transition to an inactive carrier state and, in some patients, further hepatitis B surface antigen (HBsAg) seroclearance lead to more favorable outcomes (3). Patients who achieve HBsAg seroclearance are at the lowest risk of hepatocellular carcinoma development and a decreased

[1]Genomics Research Center, Academia Sinica, Taipei, Taiwan; [2]Chang Gung Memorial Hospital, Linkou Branch, Taoyuan City, Taiwan; [3]Perinatal Epidemiology and Health Outcomes Research Unit, Division of Neonatology, Department of Pediatrics, School of Medicine, Stanford University and Lucile Packard Children's Hospital, Palo Alto, California, USA; [4]Institute of Clinical Medicine, National Yang Ming Chiao Tung University, Hsinchu, Taiwan; [5]Roche Diagnostics, Ltd, Basel, Switzerland; [6]Department of Gastroenterology and Hepatology, Chang-Gung Memorial Hospital, Kaohsiung Branch, Kaohsiung, Taiwan; [7]Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital, Linkou Branch, Taoyuan City, Taiwan; [8]Chang Gung University College of Medicine, Taoyuan City, Taiwan; [9]Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan; [10]Biomedical Translation Research Center, Academia Sinica, Taipei, Taiwan. **Correspondence:** Hwai-I Yang, PhD. E-mail: hiyang@gate.sinica.edu.tw.

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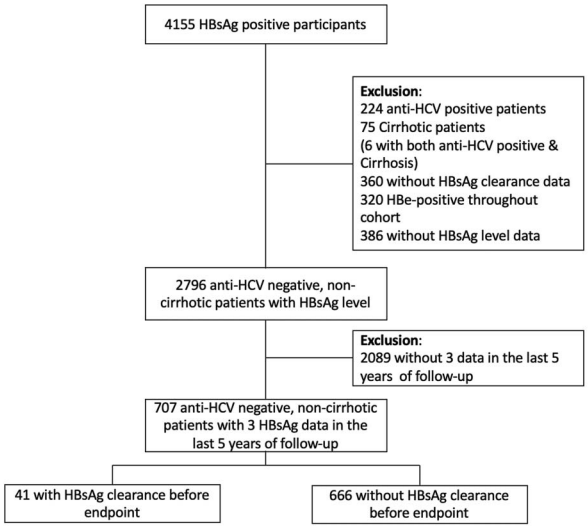

Figure 1. Flowchart of participant selection. HBe, hepatitis B e; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

risk of hepatic decompensation (4,5). However, the annual rate of spontaneous HBsAg seroclearance is low, ranging from 0.21% to 2.13% per year in different cohorts (6–10).

Serum HBsAg is a useful marker reflecting the levels of both actively transcribed covalently closed circular DNA and integrated DNA. A previous case-control study based in a tertiary hospital showed that a 0.5 log HBsAg reduction per year was predictive of HBsAg seroclearance in patients with serum HBsAg <200 IU/mL over 3 years of follow-up (11). Another tertiary hospital-based study showed that HBsAg decline >0.5 $\log_{10}$ IU/mL in 1 year or >1 $\log_{10}$ IU/mL in 2 years, accompanied by absolute HBsAg levels <200 IU/mL, could predict HBsAg seroclearance within 1 year (12). However, these studies had strict inclusion criteria and only included patients with persistently normal alanine aminotransferase (ALT) levels and low HBsAg levels. This prediction rule has not been validated in community cohorts with relatively loose follow-up intervals; its accuracy for predicting HBsAg loss in different settings, such as patients with HBsAg >200 IU/mL or abnormal ALT levels, has not been studied. This study aimed to explore these issues in the community-based untreated REVEAL-HBV cohort.

PATIENTS AND METHODS

Study cohort

This study was derived from the REVEAL-HBV cohort, which consisted of individuals with untreated chronic HBV infection aged 30–65 years recruited from 7 townships in Taiwan between 1991 and 1992. At enrollment, all participants were interviewed in person with a structured questionnaire administered by trained public health nurses. A 10 mL blood sample was collected at study entry, and participants were contacted and invited to return for follow-up visits every 6–12 months with blood samples collected at each visit. No participants received antiviral treatment during the follow-up period because antiviral therapy was not yet reimbursed by the National Health Insurance during the study period. All participants provided written informed consent to participate in the study, and the study was approved by the Institutional Review Board of Academia Sinica, Taipei, Taiwan.

Figure 1 shows a flowchart of how participants were selected. The REVEAL-HBV cohort contains 4,155 participants who were HBsAg-seropositive at enrollment. In this study, those who were cirrhotic and seropositive for anti-hepatitis C virus or who remained hepatitis B e antigen (HBeAg)-seropositive throughout the study period were excluded. To evaluate the dynamic changes in HBsAg levels before HBsAg seroclearance, only those with 3 or more quantitative HBsAg measurements within 5 years before HBsAg seroclearance or their last visit were included for analysis. Levels of ALT, HBV DNA, and HBsAg at study entry were not inclusion or exclusion criteria.

Table 1. Characteristics at study enrollment and at the first follow-up measurement within the study period for participants with or without HBsAg seroclearance

Characteristics	HBsAg seroclearance		*P* value
	No (N = 666)	Yes (N = 41)	
At enrollment			
Age (yr)	44.36 ± 8.89	45.02 ± 10.5	0.6465
Male	514 (77.18)	32 (78.05)	0.8972
Alcohol drinker	70 (10.53)	5 (12.20)	0.7923
HBV genotype[a]			0.1401
B	335 (52.34)	14 (35.90)	
C	166 (25.94)	14 (35.90)	
B + C	15 (2.34)	0	
Undetermined	124 (19.38)	11 (28.21)	
HBsAg level (IU/mL)	1,196 (261–3,439)	282 (135–1,172)	0.0004
HBV DNA level (IU/mL)	3,300 (437–36,100)	4,330 (0–40,200)	0.6494
AFP (U/L)	2.7 (0.9–5.4)	3.8 (0.2–7.1)	0.5972
AST (U/L)	15 (12–20)	17 (12–22)	0.4178
ALT (U/L)	12 (7–21)	19 (7–23)	0.4093
Follow-up time (yr)	11.06 ± 1.13	9.97 ± 1.92	0.0008
At the first measurement[b]			
Age (yr)	55.42 ± 8.92	54.98 ± 8.92	0.767
HBsAg level (IU/mL)	419.25 (60.53–1,356)	2.72 (0.05–17.79)	<0.0001
HBV DNA level (IU/mL)[c]	6,256.5 (467–45,978)	155 (0–1,507)	<0.0001
Time to the end of follow-up	2.09 ± 0.58	2.25 ± 0.66	0.0989

AFP, alpha-fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.
[a]HBV genotype: 26 missing data in the non-clearance group and 2 missing data in the clearance group.
[b]Within 5 years before HBsAg seroclearance or the last visit.
[c]HBV DNA level at first measurement: 12 missing in the non-clearance group and 5 missing in the clearance group.

Table 2. Three measurements of HBsAg levels during the 5-year study period in participants with or without HBsAg seroclearance

	HBsAg seroclearance		
	No (N = 666)	Yes (N = 41)	*P* value
Follow-up time (yr), mean ± SD			
From first measurement	2.93 ± 0.67	3.23 ± 0.67	0.0133
From second measurement	1.8 ± 0.52	2.02 ± 0.62	0.0162
From third measurement	0.83 ± 0.41	0.98 ± 0.6	0.0373
HBsAg levels (log_{10} IU/mL), median (IQR)			
At first measurement	2.62 (1.783 to 3.13)	0.43 (−1.3 to 1.25)	<0.0001
At second measurement	2.55 (1.653 to 3.09)	−0.62 (−1.33 to 0.35)	<0.0001
At third measurement	2.49 (1.643 to 3.07)	−1.1 (−1.33 to 0.52)	<0.0001
Decrease in HBsAg levels (log_{10} IU/mL), median (IQR)			
First to second	0.06 (−0.033 to 0.17)	0.46 (03 to 0.96)	<0.0001
Second to third	0.03 (−0.053 to 0.139)	0.26 (03 to 0.78)	<0.0001
First to third	0.08 (−0.053 to 0.24)	0.95 (03 to 1.88)	<0.0001
Decrease of HBsAg levels per year (log_{10} IU/mL), median (IQR)			
First to second	0.05 (−0.033 to 0.15)	0.38 (03 to 0.69)	<0.0001
Second to third	0.03 (−0.063 to 0.15)	0.26 (03 to 0.79)	<0.0001
First to third	0.04 (−0.023 to 0.12)	0.43 (03 to 0.72)	<0.0001

HBsAg, hepatitis B surface antigen; IQR, interquartile range.

Ascertainment of outcomes

The primary end point of this study was HBsAg seroclearance. The first instance at which a participant tested negative for HBsAg was determined to be the date of HBsAg seroclearance. For those who did not achieve HBsAg seroclearance during follow-up, the censor date was defined as the date of the participant's last visit before June 2004, when the National Health Insurance started to reimburse for antiviral treatment.

Laboratory methods

Serostatus of HBsAg and HBeAg and serum levels of ALT and alpha-fetoprotein were assayed by commercial kits (13,14). Abnormal ALT levels were defined as >45 U/L per the manufacturer's protocol. Serum HBV DNA levels were assayed using the Roche Cobas TaqMan HBV test (Roche Diagnostics, Indianapolis, IN; detection limit: 300 copies/mL, conversion factor of 0.190 IU/mL for 1 copies/mL). Serum HBsAg levels were measured by the Roche Elecsys HBsAg II Quant assay (Roche Diagnostics, Mannheim, Germany; lower detection limit: 0.05 IU/mL). HBV genotype was determined by the melting curve analysis (15).

Statistical analysis

We presented continuous data as median (interquartile range [IQR]) or mean ± SD and categorical groups as number of persons (percent). Differences between groups were compared with the Wilcoxon or Student *t*-tests, and categorical variables were analyzed with χ^2 or Fisher exact tests. We assessed the performance of various algorithms in predicting HBsAg seroclearance within 1 year using sensitivity, specificity, positive predictive values (PPVs), and negative predictive values (NPVs). Statistical analyses were performed using SAS software version 9.4, and statistical significance was determined by 2-tailed tests, with a *P* value less than 0.05 deemed as significant.

RESULTS

Characteristics of the study cohort at enrollment

Among 2,796 participants whose follow-up HBsAg seroclearance data were available, 707 participants with 3 or more measurements in the past 5 years were enrolled in the analysis. The characteristics of the enrolled 707 participants and the rest 2089 participants who failed to meet the inclusion criteria are listed in Supplementary Table 1 (Supplementary Digital Content 1, http://links.lww.com/CTG/A929). During a mean of 11.06 (SD: 1.13) years of follow-up, most of the participants (666/707, 94.2%) remained HBsAg-seropositive until their last visit while 41 participants (5.8%) achieved HBsAg seroclearance after a mean duration of 9.97 ± 1.92 years (Table 1). The mean intervals between these 3 measurements were comparable between participants with and without HBsAg loss (Supplementary Table 2, Supplementary Digital Content 1, http://links.lww.com/CTG/A929). Participants who achieved HBsAg seroclearance had lower HBsAg levels at study entry (median [IQR]: 282 [135–1,172] vs 1,196 [261–3,439] IU/mL; $P = 0.0004$) and a shorter follow-up duration (mean ± SD: 9.97 ± 1.92 vs 11.06 ± 1.13 years; $P = 0.0008$) than those who did not (Table 1). There were no differences in sex proportion (male: 78.05% vs 77.18%; $P = 0.8972$), age (mean ± SD: 45.02 ± 10.5 vs 44.36 ± 8.89 years;

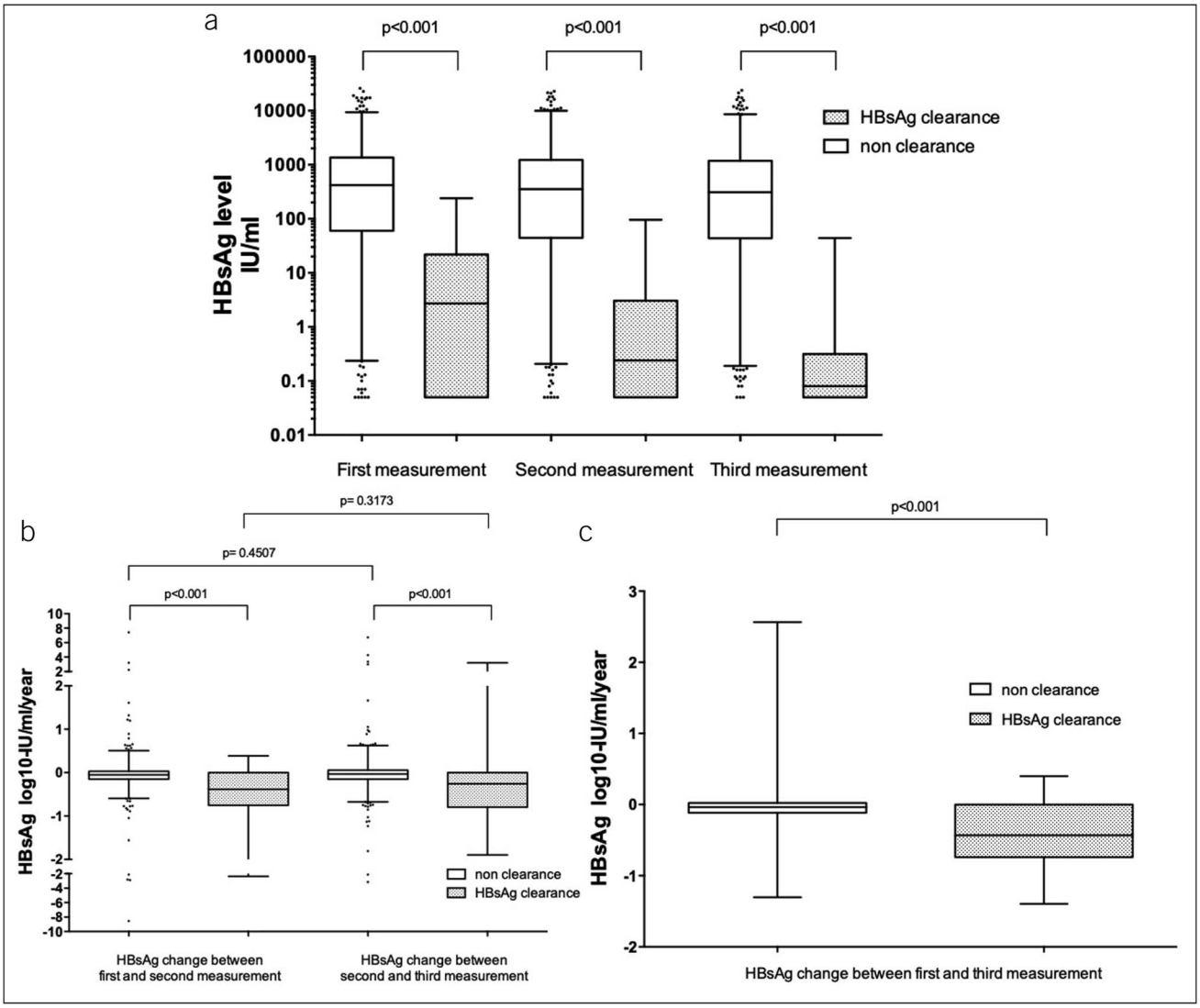

Figure 2. (**a**) Box plot of HBsAg levels among the clearance and non-clearance groups: HBsAg levels were significantly higher in the non-clearance group for all measurements ($P < 0.001$). (**b** and **c**) Box plot of HBsAg decline rates in the clearance and non-clearance groups: The decline rate was greater in the clearance group ($P < 0.001$), but decline rates were not different within groups ($P = 0.4507$ for the non-seroclearance group; $P = 0.3173$ for the seroclearance group). HBsAg, hepatitis B surface antigen.

$P = 0.6465$), HBV DNA levels (median [IQR]: 4,330 [0–40,200] IU/mL vs 3,300 [437–36,100] IU/mL; $P = 0.6494$), or ALT levels (median [IQR]: 19 [7–23] U/L vs 12 [7–21] U/L; $P = 0.4093$) at study entry between participants with and without HBsAg seroclearance.

Dynamic changes in surface antigen levels

We compared 3 quantitative HBsAg measurements during the past 5 years of follow-up between the non-clearance and clearance groups (Table 2). These measurements were classified into the first, second, and third measurements. Age at the first measurement was similar between the 2 groups (mean ± SD: 55.42 ± 8.92 vs 54.99 ± 8.92, $P = 0.0999$). The median (IQR) HBsAg levels at the first, second, and third measurements in the non-clearance group were 2.62 (1.78–3.13), 2.55 (1.65–3.09), and 2.49 (1.64–3.07) $\log_{10}$ IU/mL, respectively, all higher than corresponding measurements in the clearance group (0.43 [−1.3 to 1.25], −0.62 [−1.3 to 0.35], and −1.1 [−1.3 to 0.52] $\log_{10}$ IU/mL, respectively; Figure 2a).

The rate of HBsAg decline between each follow-up time point was compared between patients with and without HBsAg loss (Figure 2b,c and Table 2). The clearance group had a greater rate of decline from the first to second measurement (first-to-second) and from the second to third measurement (second-to-third) when compared with the non-clearance group (median [IQR]: 0.38 [0–0.69] vs 0.05 [−0.03 to 0.15] $\log_{10}$ IU/mL/yr for the first-to-second measurement and 0.26 [0–0.79] vs 0.03 [−0.06 to 0.15] $\log_{10}$ IU/mL/yr for the second-to-third measurement; $P < 0.0001$). Similar results were found for the rate of decline from the first to third measurement (first-to-third) (median [IQR]: 0.43 [0–0.72] vs 0.04 [−0.02 to 0.12] $\log_{10}$ IU/mL/yr; $P < 0.0001$). The annual rate of HBsAg decline in the clearance group was consistently higher than the non-clearance group in all first-to-second, second-to-third, and first-to-third measurements (all $P < 0.0001$).

Table 3. Performance of various algorithms for predicting HBsAg seroclearance within 1 year

	HBsAg <200 IU/mL with annual HBsAg decline rate >0.5 $\log_{10}$ IU/mL		Annual HBsAg decline rate >0.5 $\log_{10}$ IU/mL		HBsAg <200 IU/mL	
	Yes	No	Yes	No	Yes	No
HBsAg seroclearance in 1 year	15	19	15	19	34	0
No HBsAg seroclearance in 1 year	14	659	14	659	291	382
Sensitivity (95% CI)	0.4412 (0.2743–0.6081)		0.4412 (0.2743–0.6081)		1 (1–1)	
Specificity (95% CI)	0.9792 (0.9684–0.9900)		0.9792 (0.9684–0.9900)		0.5676 (0.5302–0.6050)	
PPV (95% CI)	0.5172 (0.3354–0.6691)		0.5172 (0.3354–0.6691)		0.1046 (0.0713–0.1379)	
NPV (95% CI)	0.9720 (0.9596–0.9884)		0.9720 (0.9596–0.9884)		1 (1–1)	

The decline rate of HBsAg was calculated between the first and third measurements.
CI, confidence interval; HBsAg, hepatitis B surface antigen; NPV, negative predictive value; PPV, positive predictive value.

Prediction of surface antigen seroclearance using various prediction algorithms

A total of 34 patients achieved HBsAg seroclearance in 1 year. We validated the algorithm (11,12) combining HBsAg levels <200 IU/mL and a decline rate of >0.5 $\log_{10}$ IU/mL/yr for predicting HBsAg seroclearance using our community-based cohort (Table 3). The sensitivity, specificity, PPV, and NPV were 0.4412, 0.9792, 0.5172, and 0.9720, respectively.

We further investigated the performance of using solely annual HBsAg decline rate >0.5 $\log_{10}$ IU/mL to predict HBsAg seroclearance within 1 year and obtained the same performance metrics (sensitivity: 0.4412, specificity: 0.9792, PPV: 0.5172, and NPV: 0.9720). Further examining the relationship between HBsAg levels and the HBsAg decline rate, we found that all patients with annual HBsAg decline >0.5 log10 IU/mL occurred in HBsAg <200 IU/mL (Supplementary Table 3, Supplementary Digital Content 1, http://links.lww.com/CTG/A929), which explains why the same performance was yielded using the simplified algorithm. In addition, using HBsAg <200 IU/mL only as the prediction criterion can achieve perfect sensitivity at the expense of specificity (0.5676); the NPV was almost the same as the previous 2 prediction algorithms, but the PPV was much lower (Table 3).

Predicting HBsAg seroclearance by annual HBsAg decline in various subgroups

We further evaluated the performance of using an HBsAg decline rate of >0.5 $\log_{10}$ IU/mL/yr to predict HBsAg seroclearance in 1 year stratified by various levels of HBsAg, ALT, and HBV DNA and inactive carrier state (Supplementary Table 4, Supplementary Digital Content 1, http://links.lww.com/CTG/A929). Among the patients with the first measurement of HBsAg level >10 IU/mL, the sensitivity, specificity, PPV, and NPV with corresponding 95% confidence interval (CI) were 0.8889 (0.6836–1), 0.9808 (0.9695–0.9920), 0.4211 (0.1990–0.6431), and 0.9982 (0.9947–1), respectively, and 0.28 (0.1040–0.4560), 0.9703 (0.9372–1), 0.7 (0.4160–0.9840), and 0.8448 (0.7789–0.9107), respectively, in patients with the first measurement of HBsAg level ≤10 IU/mL.

The performance for predicting 1-year HBsAg loss using an annual HBsAg decline rate of >0.5 $\log_{10}$ IU/mL was similar between patients with and without abnormal ALT during follow-up (abnormal ALT group, sensitivity [95% CI]: 0.5 [0.1901–0.8099], specificity [95% CI]: 0.9822 [0.9623–1], PPV [95% CI]: 0.6250 [0.2895–0.9605], and NPV [95% CI]: 0.9708 [0.9455–0.9960]; normal ALT group, sensitivity [95% CI]: 0.28 [0.1040–0.4560], specificity [95% CI]: 0.9703 [0.9372–1], PPV [95% CI]: 0.7 [0.4160–0.9840], and NPV [95% CI]: 0.8448 [0.7789–0.9107]) (Supplementary Table 4, Supplementary Digital Content 1, http://links.lww.com/CTG/A929).

When stratified according to consecutive HBV DNA levels (<2,000 IU/mL, 2,000–20,000 IU/mL, and >20,000 IU/mL) during the 5-year study period, only the group with HBV DNA levels lower than 2,000 IU/mL had enough cases of HBsAg seroclearance to generate valid estimates. Among this subgroup, sensitivity, specificity, PPV, and NPV with corresponding 95% CIs were 0.4444 (0.2570–0.6319), 0.9628 (0.9413–0.9844), 0.5217 (0.3176–0.7259), and 0.9500 (0.9253–0.9747), respectively. When combining HBV DNA levels <2,000 IU/mL with persistently normal ALT levels to define the inactive carrier state, it could be found that regardless of whether patients were inactive carriers, using the annual HBsAg decline rate to predict HBsAg seroclearance in 1 year had similar performance.

DISCUSSION

Our study has several novel findings. First, we validated the previously developed prediction algorithm for predicting 1-year HBsAg loss using a combination of HBsAg level <200 IU/mL and a decline rate of >0.5 $\log_{10}$ IU/mL per year, confirming that it is applicable in our community cohort. Second, we modified the prediction rule to only use an annual HBsAg decline rate of >0.5 $\log_{10}$ IU/mL and showed the same prediction accuracy as the

existing algorithm. The overall rate of HBsAg decline in the HBsAg seroclearance group was 0.43 $\log_{10}$ IU/mL/yr in our study, which is consistent with previous studies (0.53–0.751 $\log_{10}$ IU/mL/yr) (11,12) and higher than that (0.04 $\log_{10}$ IU/mL/yr) in the non-HBsAg seroclearance group. Third, we showed that the simplified algorithm was applicable in patients with various levels of HBsAg, ALT, and HBV DNA and regardless of inactive carrier status.

In a previous study, a decrease of 1 $\log_{10}$ IU/mL in the HBsAg level reflected an enhanced host immune control to HBV, especially in patients with HBeAg-seronegative chronic hepatitis B (16). However, this study did not investigate the predictability of HBsAg levels on the occurrence of HBsAg clearance. In antiviral treatment studies (17–19), a rapid decline in HBsAg levels has been considered as a reduction or inactivation of covalently closed circular DNA transcriptional activity and a favorable predictor of functional cure or sustained response. However, there has not been much discussion regarding the untreated population. Our study fills this data gap, showing that a rapid decline in HBsAg leads to a quicker and higher possibility of functional cure and can be considered a clinical marker of immune control for HBV, as well as a surrogate for HBsAg seroclearance.

In this community-based study, ALT levels did not significantly affect whether participants experienced a rapid decline in HBsAg. During the 5-year study period, among the 179 participants with abnormal ALT levels, only 8 (4.47%) showed a rapid HBsAg decline while 21 of 528 participants (3.98%) with persistently normal ALT levels showed a rapid decline in HBsAg ($P = 0.7743$).

Previous studies on the prediction of HBsAg seroclearance mainly focused on participants who were inactive carriers (HBV DNA levels <2,000 IU/mL and persistently normal ALT levels) (12). In this study, we found that the predictability of rapid HBsAg decline on seroclearance in participants with HBeAg-negative hepatitis was not inferior to that in inactive carriers (Supplementary Table 4, Supplementary Digital Content 1, http://links.lww.com/CTG/A929).

This study has some limitations. Patients were followed up less frequently than in hospital-based studies, and a less stringent follow-up may have led to an underestimation of the incidence of ALT abnormalities and rapid HBsAg decline. It is difficult to estimate the impact of hepatitis flares on HBsAg reduction in this cohort because of the relatively loose follow-up intervals. However, even with the potential for underestimation, rapid HBsAg decline was still predictive to HBsAg loss with high NPV, suggesting it as a reliable tool for routine clinical use. Second, the limited number of participants who achieved surface antigen seroclearance precluded further subgroup analyses. Further large-scale community-based studies are necessary to validate our findings. With growing interest in achieving functional cure in the era of treatment, the concept of rapid decline could further be applied and verified in patients receiving novel antivirals and immunomodulatory therapies as a treatment predictor or surrogate end point (20).

In conclusion, using a community-based cohort, we demonstrated that HBsAg >0.5 $\log_{10}$ IU/mL/yr alone can be used for predicting surface antigen seroclearance within 1 year without the need of incorporating additional absolute HBsAg levels. The application of this algorithm does not need to be limited by ALT and HBV DNA levels or whether patients are inactive carriers. In routine practice, serial measurement of HBsAg helps predict surface antigen seroclearance. More importantly, an annual HBsAg reduction rate of >0.5 $\log_{10}$ IU/mL can potentially be used as a sentinel indicator of functional cure.

CONFLICTS OF INTEREST

Guarantor of the article: Hwai-I Yang, PhD.

Specific author contributions: H.-C.L. contributed to study planning, data interpreting, and manuscript drafting. J.L. contributed to study planning and manuscript revising. M.-H.P., M.-H.L., R.B.-U., and C.-J.C. contributed to data collection. H.-I.Y. and W.-J.J. contributed to study planning and manuscript drafting and revising. All authors approved the final draft submitted.

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Potential competing interests: None to report.

Study Highlights

WHAT IS KNOWN

✓ Absolute HBsAg level and rapid decline of hepatitis B surface antigen (HBsAg) can predict HBsAg clearance.

WHAT IS NEW HERE

✓ HBsAg rapid decline is a predictor of HBsAg seroclearance within 1 year in our community-based untreated cohort.

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