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Ethnic Differences in Incidence of Hepatitis B Surface Antigen Seroclearance in a Real-Life Multicenter Clinical Cohort of 4,737 Chronic Hepatitis B Patients

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Abstract

BACKGROUND—Hepatitis B surface antigen (HBsAg) positivity is associated with increased risk for cirrhosis and hepatocellular carcinoma (HCC). HBsAg seroclearance is thought to be rare in general, but cohort data from U.S. patients is limited. **AIM:** Our objective is to determine the incidence of HBsAg seroclearance in a real-life U.S. cohort.

METHODS—In total, 4,737 consecutive chronic hepatitis B (CHB) patients from five primary care, gastroenterology, and multispecialty centers, and a university medical center were retrospectively enrolled between 2001-2014 with data obtained by manual review of individual patient medical records. Seroclearance was determined by loss of HBsAg seropositivity. Persistent

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AUTHOR STATEMENT/STATEMENT OF INTERESTS

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1) substantial contributions to conception and design (LN, MN)

2) acquisition of data (LN, JH, NN, VV, CW, HT, JL, JZ, MN)

3) analysis and interpretation of data (LN, MN)

4) drafting and revising manuscript critically for important intellectual content (LN, MN)

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HBsAg was confirmed by direct serology or by proxy with positive hepatitis B e-antigen (HBeAg) or HBV DNA levels.

RESULTS—HBsAg seroclearance occurred in 52 patients over 16,844 person-years (0.31% annually, 1.2% overall). Median follow-up was 32 months, and mean age 45±14 years. Incidence of HBsAg seroclearance was higher in non-Asians, age>45, males, and those with baseline HBV DNA ≤ 10,000 IU/mL. On multivariate Cox proportional modeling, non-Asian ethnicity (HR 2.8), male sex (HR 2.1), baseline HBVDNA≤10,000 (HR 2.0), and age>45 (HR 1.8) were significant independent predictors of seroclearance.

DISCUSSION—HBsAg seroclearance rates were lower than previously described in in this real-life cohort of CHB patients, especially among Asian, female, and younger patients.

Keywords

hepatitis B; viral hepatitis; outcomes research; epidemiology

INTRODUCTION

Hepatitis B virus (HBV) affects approximately 250 million people worldwide, with 850,000 individuals in the United States (U.S.) alone, and chronic hepatitis B (CHB) is a major cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC) [1, 2]. The number infected in the U.S. may be underreported and rising with the increased immigration from the Asia/Pacific region where HBV is endemic [3, 4].

Spontaneous seroclearance of hepatitis B surface antigen (HBsAg), a detectable serologic indicator of active infection, is defined as the loss of serum HBsAg on two occasions at least 6 months apart and is a rare event. Most studies from Asia and Europe suggest an annual seroclearance rate between 0.12-2.4% [5-12].

Current treatment guidelines favor anti-viral treatment in those with biochemical evidence of inflammation which justifiably prioritizes treatment of those with more severe disease and active viral replication as evidenced by positive hepatitis B e-antigen (HBeAg) status. However, mounting evidence suggests that even those with normal or minimally elevated transaminases may harbor significant hepatic fibrosis while those who achieve treatment-induced HBeAg seroconversion may have recurrent HBV viremia[13-17]. In contrast, long-term complications following successful HBsAg seroclearance, including cirrhosis and HCC, appear to be greatly decreased compared to those who remain HBsAg positive, making HBsAg seroclearance a desirable, measureable, and durable outcome[18-21]. Additionally, some data suggest patients hospitalized with HBV may have higher mortality and charges and longer length of stay than those with hepatitis C virus (HCV) or alcoholic liver disease, possibly due to the heterogeneous nature of chronic HBV where previously inactive carriers may experience severe, acute reactivations requiring higher level of care, further evidence that complete cure may be more desirable than viral suppression alone[22].

Given the difficulties in assembling a sizable cohort for such a rare event, studies in North American patients have either been small or in specialized populations (blood donors and inactive carriers) and have observed annual seroclearance rates between 0.54-1.7% [23-25].

Treatment with interferon (IFN)-based therapies appear to result in dramatic increases in seroclearance rates, estimated between 2.6-4.4% per person-year, but IFN-based therapies are not used frequently in routine practice due to their side effects [26-31]. Results with oral nucleos(t)ide analogues have been variable with higher HBsAg seroclearance rates with newer oral nucleotides such as tenofovir but these were seen in cohorts of highly selected clinical trial patients and almost exclusively in non-Asian patients.[31-42]. Our objective is to determine the incidence of HBsAg seroclearance in a diverse real-life clinical cohort of both university and community adult CHB patients in the United States.

MATERIALS and METHODS

Study Population

Using ICD-9 electronic query for patient identification followed by manual chart review by research assistants for each study location over a two-year period with data abstraction applied to a standardized case report form for data collection, all consecutive patients with confirmed chronic HBV infection from a community GI clinic (San Jose Gastroenterology, San Jose, CA), two community primary care clinics (Chinese Hospital, San Francisco, CA), one community multispecialty medical center (Palo Alto Medical Foundation, Mountain View, CA), and one university medical center (Stanford University, Stanford, CA) were retrospectively enrolled from 2001-2014. Study inclusion criteria included 18 years of age or older and confirmed HBV infection for ≥6 months (at least two lab values demonstrating persistently positive HBsAg, detectable HBV DNA, or positive HBeAg). Patients with HIV co-infection or HCV/HDV dual infection as well as prior treatment or treatment during follow up with an IFN-based regimen were excluded. All 21 patients previously treated with IFN also had HCV dual infection.

End Points

Research personnel at each study location manually reviewed in their entirety the paper and/or electronic charts of individual patients. HBsAg seroclearance was determined by documented loss of HBsAg through direct serologic testing. Persistence of HBsAg was verified either directly with HBsAg serology or by proxy with positive HBeAg results or detectable HBV DNA levels indicating continued HBsAg positivity. Patients who did not have at least two data points confirming positive chronic HBV infection for six months or greater using the criteria above were not included.

Follow Up

Date of study entry was determined by initial laboratory data confirming diagnosis or date of presentation to clinic, whichever occurred first. Patients were censored either at time of HBsAg seroclearance, date of last confirmed ongoing infection as above, or study termination, whichever occurred first.

The study was approved by the institutional review board at Stanford University with informed consent exempted (Stanford, CA).

Statistical Analysis

Patient clinical and viral characteristics were compiled, compared, and analyzed using standard statistical tests. Categorical variables were analyzed by chi-squared (X^2) or Fisher's exact testing where appropriate. The student *t*-test was applied to normally distributed, non-categorical variables, and nonparametric statistics, including the Wilcoxon rank sum test, were applied to all others. Differences with two-tailed $p \leq 0.05$ were considered significant.

The Kaplan-Meier method was used to calculate HBsAg seroclearance incidence rate, and group comparison was performed using the log-rank test. The Cox proportional hazard regression model was used to estimate univariate and multivariate hazard ratios (HR) relating sex, age, practice setting, baseline HBV DNA level, and ethnicity as determined by self or physician identification to achievement of HBsAg seroclearance. Statistical analyses were performed using Stata MP 11 (Stata Corporation, College Station, TX).

RESULTS

Among the 5,650 patients screened from 2001-2014 for retrospective enrollment, 3 were excluded for documented acute HBV infection, 65 for HCV dual-infection, 15 for HDV dual infection, 6 for HIV co-infection, and 824 for either age <18 years or insufficient data, typically a lack of serial laboratory data confirming chronic infection. In total, 4,737 CHB patients were included in the final analysis.

Baseline Clinical and Laboratory Characteristics

Of the 4,737 patients enrolled, 57% were male, mean age was 45±14 years, and 36% were seen in the university setting compared to 64% from the various community primary care, gastroenterology, and multispecialty centers collectively comprising our community cohort. Only 11% were treatment-experienced at the time of presentation (none with IFN-based regimens). The majority of the cohort were of Asian ethnicity (95%). Median follow-up length was 32 (13-61) months, and few (<5%) of patients either presented with or had interval development of either cirrhosis or HCC. Patients had HBsAg testing with a median of 2 times during the course of follow up (IQR 2-4), while lab surveillance indicating ongoing infection (positive HBsAg, positive HBeAg, or detectable HBV DNA) was obtained a median of every 5 months (IQR 2-14). For both HBsAg and laboratory surveillance testing rates, there was no difference in frequency between the seroclearance and non-seroclearance groups.

In total, 52 patients, or 1.2% of the cohort, ultimately went on to achieve HBsAg seroclearance. When comparing those who did and did not achieve HBsAg seroclearance, patients achieving HBsAg seroclearance were more likely to be non-Asian (13% of seroclearance patients were non-Asian vs. 5%), male (75% vs 56%), older (49±12 vs. 45±14 years), and more likely to be followed in a university setting (58% of seroclearance patients were university vs. 42%). This data was summarized in Table 1.

At presentation, 26% of all patients were HBeAg positive, 20% in the seroclearance group vs. 26% in the non-seroclearance group, $p=0.37$). Baseline HBV DNA levels were lower in the seroclearance group compared to persistently positive patients (3.7±2.5 vs. 4.5±2.4

log_{10}IU/mL, p=0.02) as well as university vs. community patients (4.1±2.6 vs. 4.8±2.2 log_{10}IU/mL, p<0.0001). Other laboratory values for seroclearance and non-seroclearance as well as university vs. community patients were mostly similar and summarized in Table 1 and Supplementary Table 1. Asian patients tended to drink less frequently, were more commonly seen in a community practice, and had lower rates of cirrhosis at presentation and during follow up compared to non-Asian patients (Table 2).

Annual and cumulative incidence of HBsAg seroclearance

Overall, annual seroclearance rate for all 4,737 patients followed over 16,844 person-years was 0.31% per person-year (Figure 1). When compared by log-rank testing, males had more than double the rate of HBsAg seroclearance compared to their female counterparts (0.44% vs. 0.18% per person-year, p=0.009), while non-Asian patients achieved HBsAg seroclearance three times more frequently than did Asian patients (0.84% vs. 0.28% per person-year, p=0.006, Figure 2) and those age >45 years doubling the rate of their younger counterparts (0.44% vs. 0.20% per person-year, p=0.006). Similarly, those who presented with HBV DNA ≤ 4 log_{10}IU/mL were more likely to achieve HBsAg seroclearance than their counterparts who presented with higher HBV DNA levels (0.41% vs. 0.21% per person-year, p=0.03, Figure 3). There was no statistically significant difference between patients and their rate of HBsAg seroclearance on the basis of practice setting or baseline HBeAg status. Among those who had achieved seroclearance, 10 patients would go on to achieve documented hepatitis B surface antibody (anti-HBs) development at a median time of 27 months after presentation (IQR 11-60).

Predictors of HBsAg seroclearance

On univariate Cox proportional modeling, the followings were found to predict successful HBsAg seroclearance: non-Asian compared to Asian ethnicity (HR 2.9, p=0.009), male compared to female sex (HR 2.3, p=0.01), and age >45 at presentation (HR 2.2, p=0.008). HBV DNA>4 log_{10}IU/mL at presentation was associated with lower seroclearance rates (HR 0.5, p=0.03), while university vs. community practice setting did not significantly impact seroclearance (Table 3). Antiviral therapy, presence of cirrhosis, as determined by characteristic imaging findings or evidence of portal hypertension such as thrombocytopenia, encephalopathy, ascites, or varices, or HCC, whether at baseline or during follow-up, were not significant predictors on univariate analysis.

Using multivariate modeling also inclusive of practice setting, significant independent predictors for HBsAg seroclearance were non-Asian ethnicity (HR 2.8, p=0.02), male sex (HR 2.1, p=0.03) and age>45 years (HR 1.8, p=0.04). On the other hand, high baseline HBV DNA level significantly predicted failure to achieve HBsAg seroclearance (HR 0.5, p=0.04).

DISCUSSION

In summary, HBsAg seroclearance occurred in 52 patients over 16,844 person-years, a 0.31% annual seroclearance rate or just 1.2% of our real-life cohort of CHB patients. In addition, annual incidence of HBsAg seroclearance was three times higher in non-Asian compared to Asian patients and approximately two times more frequent in the following:

patients aged >45 compared to those younger at presentation, males compared to females, and those with baseline HBV DNA ≤ 10,000 IU/mL compared to their counterparts with higher HBV DNA levels. On multivariate Cox proportional modeling also inclusive of practice setting, non-Asian ethnicity, male sex, baseline HBV DNA ≤ 10,000 IU/mL, and age >45 were each significant independent predictors of HBsAg seroclearance.

To our knowledge, this study represents the largest assembled real-life cohort in the Western hemisphere specifically examining HBsAg seroclearance rates, an important yet understudied determinant in disease progression and outcomes in CHB patients. McMahon et al found a 0.54% annual HBsAg seroclearance rate in their investigation of 1,536 HBV carriers in Alaska, the largest investigation of U.S. HBV patients prior to our work, though their findings may reflect a population significantly younger than most other comparable studies (median age 19.9 years) [24]. A Brazillian cohort found an HBsAg seroclerance rate of 0.7% in their 548 patients in a study strengthened by their quarterly serologic testing [43].

Large-scale investigations on this subject have been conducted predominantly in Asia. Kim et al found an annual seroclearance rate of 0.33% among their 5,409 Korean CHB patients [20]. Kobayashi et al reported a rate of 1.75% in their long-term investigation of 2,112 patients in Japan, results that appear higher due to the apparent acceleration of seroclearance at more than ten years of follow up, a trend observed in this study as well as in Chu et al's investigation of 1,965 inactive HBV carriers in Taiwan (overall HBsAg seroclearance rate 1.15%) [8, 44]. Finally, the REVEAL-HBV study group led by Liu et al discovered a 2.3% annual seroclearance rate in their study of community cohort of 3,087 patients from Taiwan [45].

Patients of the current study were recruited from several diverse clinical settings including primary care clinics, community specialty clinics, multispecialty community and university medical centers in the San Francisco Bay Area, which are all consecutive patients from real-life practice rather than selected patients from a clinical trial setting or epidemiologic cohort with younger patients. Given the variety of clinical settings from which our patient cohort was drawn from, we believe we have assembled a fairly representative U.S. study population for CHB.

Also, with the unique multi-ethnic population of the surrounding area, a head-to-head comparison between Asian and non-Asian HBV patients was possible and largely corroborated the body of literature in Asia that appears to suggest a lower seroclearance rate from what has been observed in prior European or non-Asian studies, but a direct comparison between the two ethnicities had not been previously possible. This is a crucial assessment given the well-studied and established differences in the epidemiology of HBV acquisition, subsequent duration of infection—with Asians believed to have a higher rate of perinatal infection compared to non-Asian patients—and the current body of literature from Europe and Asia that separately reported higher rates of HBsAg seroclearance in non-Asian patients, findings that are now confirmed in the current study with head-to-head comparisonAdditionally, our study appears to reinforce the conclusions of prior investigations that indicate older age, lower HBV DNA, and male gender are significant predictors of spontaneous HBV cure[8, 24, 43, 45-52].

This investigation was not without limitations—given the retrospective nature of this study, we are limited by the type of data we can collect and do not have data on quantitative HBsAg, a documented predictor of successful seroclearance, especially in the setting of treatment with pegylated IFN since IFN treatment can positively affect rates of HBsAg seroclearance. However, we excluded all patient with prior treatment with IFN-based therapies and this is a very small minority of our screening cohort (<1%). Treated patients in our study cohort received only oral anti-HBV nucleos(t) analogs including older agents such as lamivudine and did not show significantly higher rates of HBsAg seroclearance. In highly selected clinical trial populations, modestly higher rates of HBsAg seroclearance have been reported in patients treated with newer and more potent agents such as entecavir and tenofovir but not in studies of older oral anti-HBV agents [36-42, 53, 54]. Moreover, patients achieving HBsAg seroclearance in such clinical trials were also predominantly non-Asians. In a large, real-life cohort of treatment-naïve Asian patients with chronic hepatitis B, 5-year cumulative probability of HBsAg loss on entecavir was comparable to our study at 5%, possibly attributable to both the differences in viral acquisition between Asian and non-Asian patients as well as non-adherence in routine clinical practice[55-57]. In regards to differences between clinical trial and real-life cohorts, lower HBeAg seroconversion rates have also been observed in real-life cohort studies compared to results reported by registration trials[58, 59]. Patients who achieved HBsAg seroclearance in our study also had longer follow up than non-seroclearance patients, but we used Kaplan-Meier methods to account for this difference. Lastly, though there are some conflicting data on HBV genotype and its effect on both spontaneous and treatment-induced HBsAg seroclearance, this information was not available for the majority of patients and thus not presented [53, 60-63].

In summary, in this real-life cohort of CHB patients from several diverse clinical centers, HBsAg seroclearance rates may be lower than previously described, especially in Asian, female and younger patients compared to their comparable counterparts. This head-to-head comparison of the two ethnic groups corroborated international data that suggests Asian patients have lower rates of spontaneous HBV cure with or without antiviral therapy compared to non-Asian counterparts. Since HBsAg seroclearance is the ultimate goal for anti-HBV therapies and this event occurs so rarely in both treated and untreated patients, newer agents that can lead to higher rates of HBsAg seroclearance are urgently needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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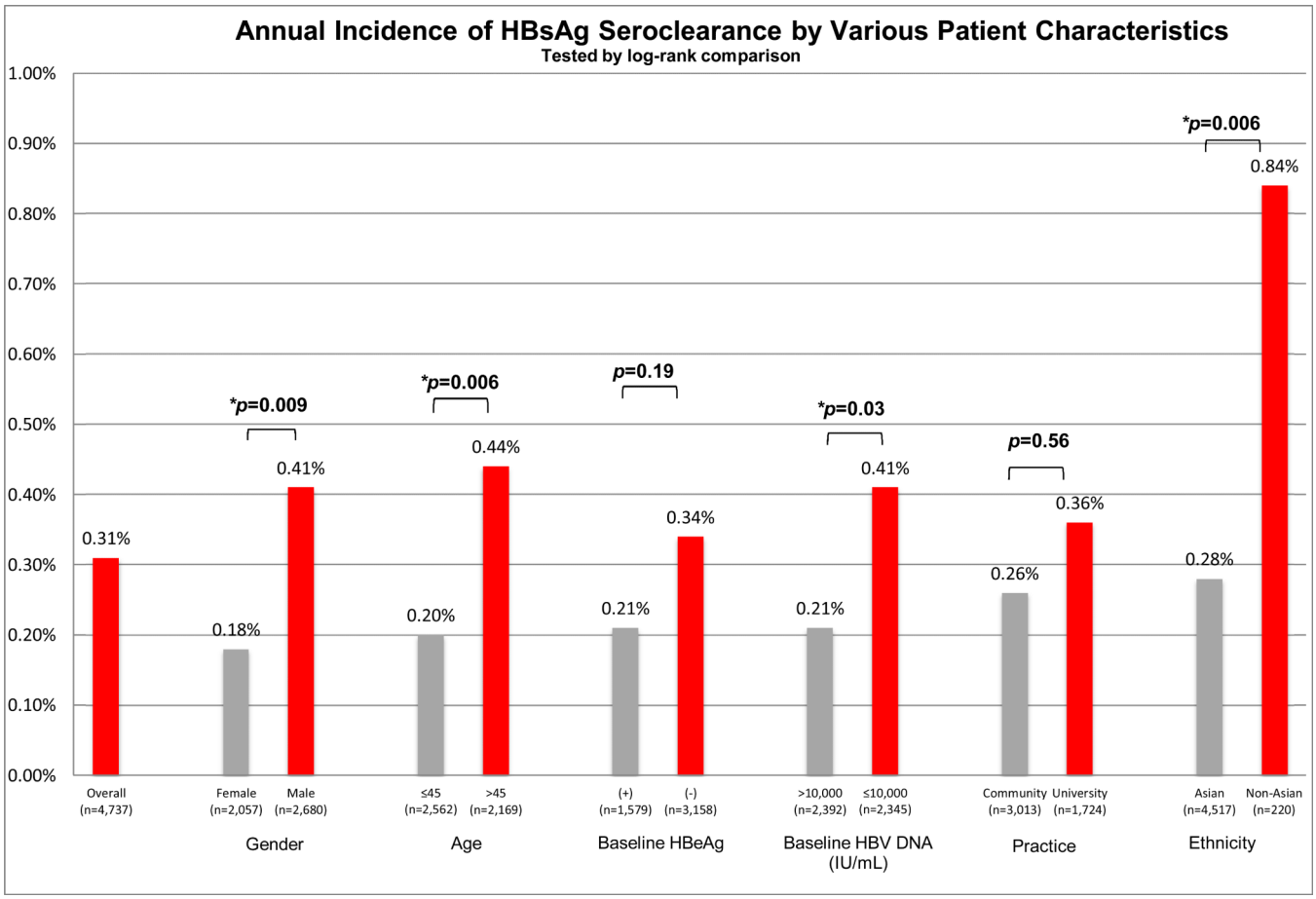

Figure 1.

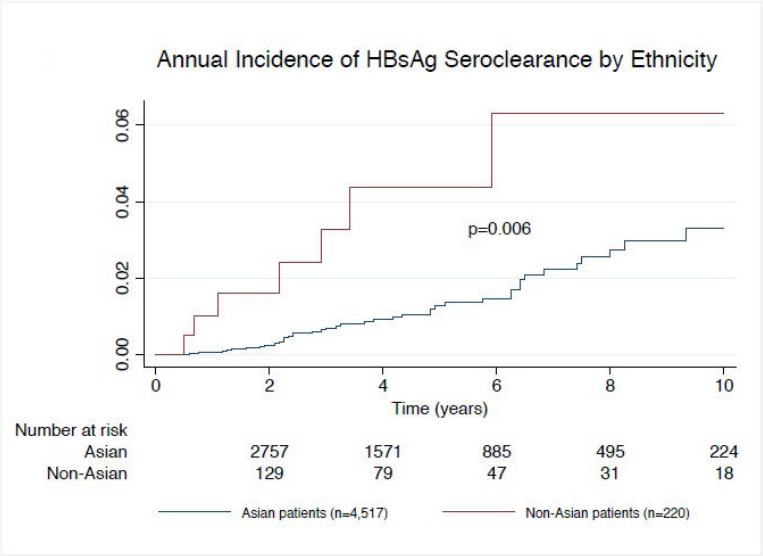

Figure 2.

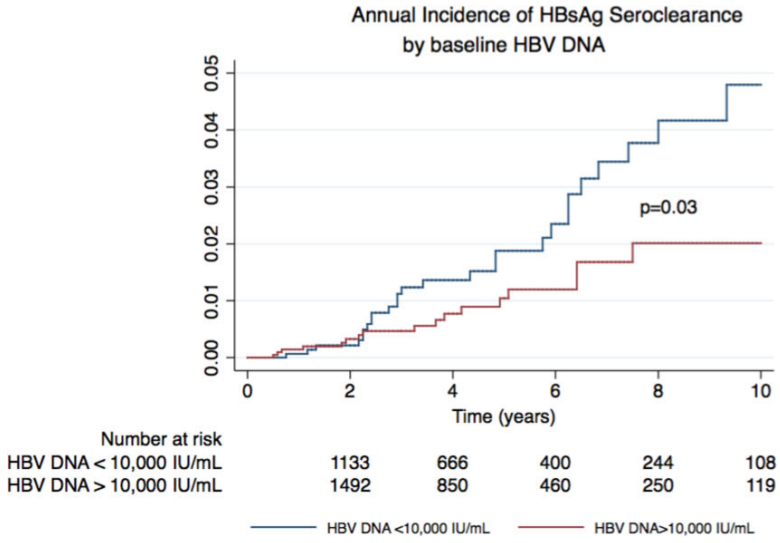

Figure 3.

Table 1

Baseline Demographic, Clinical, and Laboratory Characteristics of Patients by Seroclearance Status

	Seroclearance (n=52)	Positive HBsAg Throughout (n=4,685)	*p*-value
Male	39 (75%)	2641 (56%)	0.007
Age (years)	49±12	45±14	0.03
<45	19 (37%)	2543 (54%)	0.01
Ethnicity			0.002
Asian	45 (87%)	4,472 (95%)	
Non-Asian	7 (13%)	213 (5%)	
Smoking	9 (17%)	825 (18%)	0.96
Drinking	18 (35%)	1,131 (24%)	0.08
Practice Type			0.001
University	30 (58%)	1694 (36%)	
Community	22 (42%)	2991 (64%)	
Any Treatment at Any Point	15 (29%)	1,718 (37%)	0.24
Treatment-Experienced at Presentation	4 (8%)	533 (11%)	0.41
Follow Up Length (months)	45 (27-81)	32 (13-61)	0.006
Any Cirrhosis at Any Point	2 (4%)	245 (5%)	0.49
Cirrhosis at Presentation	0 (0%)	202 (4%)	0.17
Any HCC at Any Point	1 (2%)	195 (4%)	0.72
HCC at Presentation	0 (0%)	20 (1%)	0.8
Platelets ($\times 10^3$/mL)	202±59	220±71	0.11
International Normalized Ratio	1.1±0.2	1.1±0.2	0.87
Total Bilirubin (mg/dL)	0.8 (0.6-1)	0.7 (0.5-0.9)	0.03
Aspartate Aminotransferase (AST, U/L)	31 (22-49)	29 (22-44)	0.6
Alanine Aminotransferase (ALT, U/L)	41 (26-73)	38 (24-66)	0.55
Alpha Fetoprotein (AFP, mg/dL)	3.2 (2-6.8)	3 (2-4.8)	0.41
Hepatitis B e-Antigen(+)	9 (20%)	1,087 (26%)	0.37
Log_{10}HBVDNA (IU/mL)	3.7±2.5	4.5±2.4	0.02

Values presented as n (%), mean±SD, or median (IQR)

Table 2

Baseline Demographic, Clinical, and Laboratory Characteristics of Patients by Ethnicity

	Asian (n=4,517)	Non-Asian (n=220)	*p*-value
Male	2542 (56%)	138 (63%)	0.06
Age (years)	45±14	46±15	0.27
<45	2456 (54%)	106 (48%)	0.07
Smoking	792 (18%)	42 (19%)	0.55
Drinking	1069 (24%)	80 (36%)	<0.001
Practice Type			
University	1571 (35%)	153 (70%)	<0.001
Community	2946 (65%)	67 (30%)	
Any Treatment at Any Point	1659 (37%)	74 (34%)	0.35
Treatment-Experienced at Presentation	518 (11%)	19 (9%)	0.20
Follow Up Length (months)	32 (13-61)	34 (12-67)	0.78
Any Cirrhosis at Any Point	219 (5%)	28 (12%)	<0.001
Cirrhosis at Presentation	182 (4%)	20 (9%)	<0.001
Any HCC at Any Point	189 (4%)	7 (3%)	0.45
HCC at Presentation	17 (1%)	3 (1%)	0.30
Platelets ($\times 10^3$/mL)	220±70	211±83	0.09
International Normalized Ratio	1.1±0.3	1.1±0.2	0.17
Total Bilirubin (mg/dL)	0.7 (0.5-0.9)	0.7 (0.5-1)	0.13
Aspartate Aminotransferase (AST, U/L)	29 (22-44)	32 (25-56)	<0.001
Alanine Aminotransferase (ALT, U/L)	38 (24-65)	45 (32-69)	<0.001
Alpha Fetoprotein (AFP, mg/dL)	3 (2-5)	3 (2-5)	0.70
Hepatitis B e-Antigen(+)	1039 (26%)	57 (28%)	0.44
Log_{10}HBVDNA (IU/mL)	4.5±2.4	4.1±2.6	0.006

Values presented as n (%), mean±SD, or median (IQR)

Table 3

Univariate and Cox Proportional Modeling for Predictors of HBsAg Seroclearance

	Univariate		Multivariate	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Male Sex	2.3 (1.2-4.3)	0.01	2.1 (1.1-4.0)	0.03*
Age >45	2.2 (1.2-23.8)	0.008	1.8 (1.02-3.35)	0.04*
Community Practice	0.8 (0.5-1.5)	0.56	1.1 (0.6-2.1)	0.77
HBV DNA > $\log_{10}$4 IU/mL	0.5 (0.3-0.9)	0.03	0.5 (0.3-0.9)	0.04*
Non-Asian Ethnicity	2.9 (1.3-6.5)	0.009	2.8 (1.2-6.5)	0.02*
Positive HBeAg	0.6 (0.3-1.33)	0.19	N/A	N/A
Any Treatment	0.7 (0.4-1.2)	0.19	N/A	N/A
Treatment at Baseline	0.6 (0.2-1.6)	0.27	N/A	N/A
Cirrhosis at Any Point	0.67 (0.2-2.7)	0.57	N/A	N/A
HCC at Any Point	0.4 (0.6-3.0)	0.4	N/A	N/A