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Disparities in presentation and management of chronic hepatitis B among Hispanics in a diverse safety net system

Allison E. Wang[1] | **Norah A. Terrault**[2] | **Tse-Ling Fong**[2,3] | **Kali Zhou**[2]

[1]Department of Medicine, LAC+USC Medical Center, Los Angeles, California, USA

[2]Division of Gastrointestinal and Liver Diseases, Department of Medicine, University of Southern California, Los Angeles, California, USA

[3]Liver Program, Hoag Memorial Hospital Presbyterian, Newport Beach, California, USA

Correspondence
Kali Zhou, 2250 Alcazar St., CSC Room 135H, Los Angeles, CA 90033, USA.
Email: kalizhou@usc.edu

Abstract

Background: Chronic hepatitis B (HBV) prevalence is highest in foreign-born Asian and African individuals in the US, though Hispanics make up the largest proportion of the immigrant population. Differences in the diagnosis and management of chronic HBV in Hispanics might exist due to the lower awareness of risk. We aim to examine racial/ethnic disparities in the diagnosis, presentation, and immediate management of chronic HBV in a diverse safety net system enriched for Hispanics.

Methods: In a large urban safety-net hospital system, we retrospectively identified patients with chronic HBV by serological data and categorized them into mutually exclusive self-identified racial/ethnic groups: Hispanics, Asians, Blacks, and Whites. We then examined differences in screening, disease phenotype and severity, follow-up testing, and referral by race/ethnicity.

Results: Among 1063 patients, 302 (28%) were Hispanics, 569 (54%) Asians, 161 (15%) Blacks, and 31 (3%) Whites. More Hispanics (30%) were screened in the acute setting (defined as inpatient or emergency department encounters) than Asians (13%), Blacks (17%), or Whites (23%) ($p < 0.01$). Hispanics also had lower rates of follow-up testing after HBV diagnosis than Asians including HBeAg status (43% vs. 60%, $p < 0.01$) and HBV DNA levels (42% vs. 58%, $p < 0.01$) and lower rates of linkage to specialty care (32% vs. 55%, $p < 0.01$). Among those with available testing, however, the presence of immune-active chronic HBV was infrequent and similar across racial/ethnic groups. 25% of Hispanics had cirrhosis at initial presentation, proportionally higher than other groups ($p < 0.01$).

Conclusion: Our results underscore the importance of raising chronic HBV awareness and increasing both screening and linkage to care among Hispanic immigrants in addition to the existing risk groups, with the goal of mitigating downstream liver-related complications.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AFP, alpha-fetoprotein; APRI, AST-to-platelet ratio; AUD, alcohol use disorder; FIB-4, Fibrosis-4 score; GI, gastroenterology; HBeAb, Hepatitis B e-antibody; HBeAg, Hepatitis B e-antigen; IQR, interquartile range; LAC DHS, Los Angeles County Department of Health Services.

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INTRODUCTION

The World Health Organization estimates that ~257 million people worldwide have chronic hepatitis B (HBV) infection.[1] In the US, there are an estimated 880,000–1.89 million people living with chronic HBV,[2–4] with a prevalence of 8 times higher in foreign-born than US-born individuals.[4] Of those in the US with chronic HBV, it is estimated that only 35% of individuals have been diagnosed.[5] The American Association for the Study of Liver Diseases (AASLD) recommends screening persons born in countries with intermediate to high HBV endemicity (HBsAg prevalence > 2%).[6] As HBV endemicity rates fluctuate by region, and often countries within regions, this nuanced recommendation may play a role in suboptimal identification rates of HBV infection in immigrant populations. Other barriers that lead to a delay in or even lack of diagnoses include poor public understanding of HBV and its long-term sequelae, patients opting out of screening, difficulty reaching populations at higher risk for HBV infection (ie, immigrants, persons who inject drugs, and the undomiciled), the asymptomatic nature of chronic HBV until late stage, and poor provider understanding of HBV treatment indications.[7–9] In addition to underdiagnosis, downstream completion of HBV metrics are also lacking; up to half of patients who are eligible for HBV treatment do not receive treatment in the first year following diagnosis.[5,7,10,11] Delays in diagnosis and treatment places an estimated 15%–25% of undiagnosed chronic HBV patients at risk of premature death from cirrhosis, HCC, or liver failure necessitating liver transplant.[12,13]

While there are some data on the management and outcomes of HBV infection among immigrants in the US, primarily Asian-born,[14,15] there is very little on the epidemiology and outcomes of HBV infection in Hispanics. This is an important knowledge gap as Hispanic immigrants are currently the largest racial/ethnic group of foreign-born in the US,[16] and are projected to comprise ~22.8% of the total US population by 2035. Importantly, Hispanics, compared with Whites, have a 50% greater death rate due to chronic liver disease,[10,11] and are projected to have the highest rate of liver cancer by 2030.[17] The sharp increase in HCC in Hispanics has been largely attributed to higher rates of NAFLD and high-risk alcohol use[18]; however, the presence of other etiologies of liver disease, such as chronic HBV, may be relevant, particularly among the foreign-born.

We hypothesized that delays in screening and subsequent HBV management may be more frequent among Hispanics than other racial groups, especially Asians, due to the lower recognition of Hispanics as a risk group. Herein, we compared chronic HBV presentation and initial management of Hispanics with other racial/ethnic groups in a large, urban safety net population predominantly of Hispanic immigrants, with a focus on clinical setting of screening and subsequent downstream testing and linkage to care.

METHODS

Case selection

We performed a retrospective analysis of persons with chronic HBV infection within the Los Angeles County Department of Health Services (LAC DHS) safety net health care system between December 29, 2016 and December 31, 2019. The LAC DHS system is an integrated health care system of 26 health centers and 4 acute-care hospitals, caring for more 750,000 unique patients yearly. Nationally, it is the second largest municipal health system, serving the most populous county in the US. More than 80% of patients served have public insurance or are uninsured.[19] Gastroenterology (GI) and hepatology subspecialty clinics serve as the referral clinic for primary care providers within the DHS system and received referrals from other federally qualified health centers and community health centers who provide care for publicly insured or uninsured patients.

HBV diagnosis was defined as a positive HBsAg or detectable hepatitis B DNA (HBV DNA) (due to possibility of HBsAg testing outside of our system). Index date or time of diagnosis was considered the date of first positive test. Figure 1 provides a diagrammatic explanation of cohort selection. All cases 18 years of age and older were included. Patients with an ALT > 250 U/L or reactive HBV Core IgM at the time of diagnosis were excluded from the study to avoid inclusion of patients with acute HBV. Those with missing or insufficient data to assign ethnicity were excluded. Patients with positive HBV testing before December 29, 2016 or were on HBV treatment before positive testing within the study time period were excluded. This study was approved and informed consent waived by the Institutional Review Board at the University of Southern California.

Race/ethnicity classification

Patients were classified into the following groups using self-reported race and ethnicity: Hispanics (all races), non-Hispanic Whites, non-Hispanic Blacks, non-Hispanic Asians, and non-Hispanic Others (Pacific Islander, Alaskan Native, Native American). Those identifying as non-Hispanic Others were not included in the analysis due to the small sample size (n = 30). Further disaggregation by country of origin is presented in Supplemental Figure 1 (http://links.lww.com/HC9/A189).

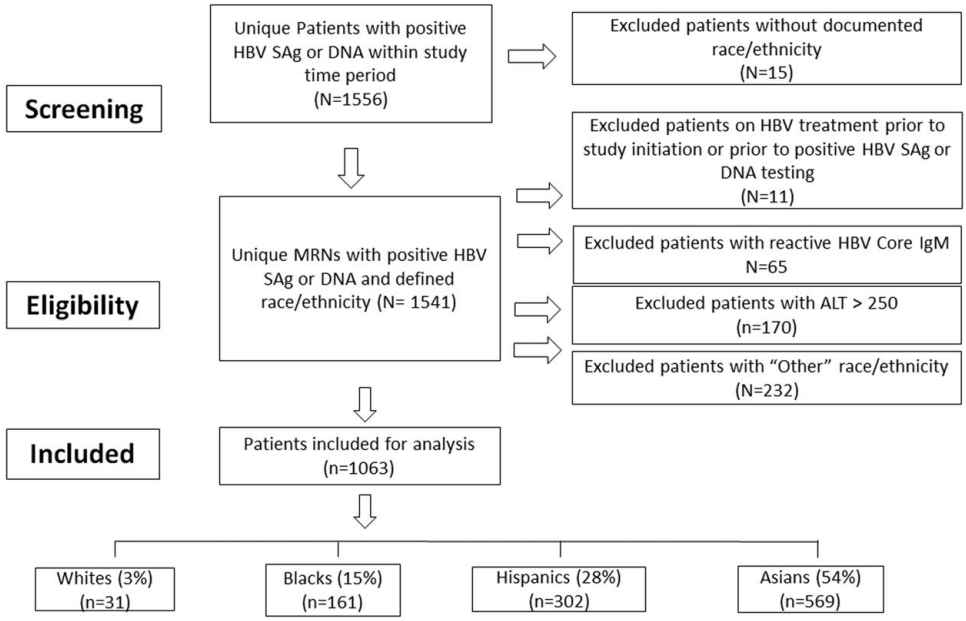

FIGURE 1 Defining the chronic hepatitis B cohort.

Demographic and clinical covariates

After identification of our final patient population, we extracted relevant data from the electronic medical record through our institution's Clinical Data Warehouse up until December 31st, 2020 to allow for at least 1-year of follow-up time for all patients. All data were aligned to entry into the cohort (date of initial HBsAg/HBV DNA testing). Patient demographics were obtained, including age, gender, insurance, country of birth, and preferred language. Insurance was categorized as Medicare, Medicaid, Subsidized (federally or state subsidized), Commercial, Self-Pay (no insurance or out of network for insurance), and Other (none of the above).

We obtained the following baseline clinical data: medical comorbidities by ICD-10 coding (Supplemental Table 1, http://links.lww.com/HC9/A190) and closest laboratory data to date of diagnosis including platelet count, AST, ALT, HBeAg/Ab testing, alpha-fetoprotein, HBV DNA, HIV, and hepatitis C antibody (HCV) testing. The upper limit of normal for ALT was 25 U/L for females and 35 U/L for males.[6] Fibrosis-4 (FIB-4) scores were calculated using the formula: age (years) × AST [U/L]/(platelets [10^9/L] × (ALT [U/L])$^{1/2}$), using age at cohort entry.[20] AST-to-platelet ratio (APRI) scores were calculated using the formula: [(AST level/AST upper limit of normal)/(platelet counts 10^9/L)] × 100.[21] Cirrhosis was defined by ICD-10 coding, and/or FIB-4 score >3.25[20,22] and APRI score >2.[21,22] Decompensated cirrhosis was defined by the presence of any ICD-10 code for decompensation (Supplemental Figure 1, http://links.lww.com/HC9/A189). Cirrhosis and HCC definitions and all ICD-10 diagnosis codes were limited to 365 days before and after initial diagnosis date to reflect patient's disease severity at initial presentation. To determine the baseline HBV phenotype, we first identified patients who had the minimum laboratory tests (ie, HBeAg, HBV DNA, and ALT) needed to determine the baseline phenotype, then categorized as immune-tolerant, immune-active, inactive carrier, or indeterminate as defined by AASLD guidelines (Supplemental Table 1, http://links.lww.com/HC9/A190).[6] We also collected data on abdominal imaging performed within 365 days of initial HBV diagnosis.

Screening and management covariates

To examine differences in the identification and management of patients with chronic HBV, we obtained additional details related to patient encounter and clinic visits. First, we identified the ordering provider and their location (categorized as inpatient, outpatient, or emergency department) of initial diagnostic testing, and if applicable, the outpatient department where testing was ordered (categorized as primary care, GI or hepatology, obstetrics, or other specialty clinics).

Among those diagnosed in the outpatient setting ($n=858$) or those diagnosed in the acute care setting with outpatient follow-up in our system ($n=205$), we examined rates of referral and linkage to subspecialty care for chronic HBV. Linkage to care could have occurred as (1) direct scheduling into the subspecialty clinic (more common after an acute care visit) or (2) as an outpatient GI/hepatology referral through the DHS E-consult referral system. The E-consult system allows

TABLE 1 Demographic and clinical characteristics at initial diagnosis of patients with chronic HBV stratified by race/ethnicity

	Hispanic N = 302	Asian N = 569	Black N = 161	White N = 31	*p*
Demographics					
Age, y	49 (39–58)	56 (47–62)	52 (43–59)	56 (53–62)	< 0.01
Male sex	54%	42%	65%	61%	< 0.01
Insurance					< 0.01
Medicaid	69%	74%	63%	72%	
Medicare	8%	7%	12%	3%	
Subsidized	7%	2%	3%	6%	
Commercial	1%	0%	3%	3%	
Self-pay	3%	1%	5%	6%	
Other	11%	16%	14%	9%	
Non-English language	75%	56%	4%	23%	< 0.01
Foreign born	83%	93%	30%	42%	< 0.01
Clinical comorbidities					
Hypertension	8%	10%	20%	4%	< 0.01
Hyperlipidemia	17%	17%	11%	16%	0.28
Diabetes	15%	11%	8%	10%	0.17
Obesity	37%	27%	22%	35%	< 0.01
AUD or ALD	22%	9%	22%	26%	< 0.01
	N = 186	N = 290	N = 88	N = 23	
HIV coinfection	10%	1%	7%	17%	< 0.01
	N = 237	N = 373	N = 127	N = 29	
HCV coinfection	8%	3%	10%	21%	< 0.01
	N = 12	N = 42	N = 5	N = 1	
HDV co-infection	0%	5%	0%	100%	< 0.01
Laboratory values at presentation					
	N = 122	N = 329	N = 57	N = 17	
HBeAg-positive (IU/mL)	8%	9%	25%	12%	< 0.01
	N = 115	N = 321	N = 90	N = 16	
Median HBV DNA (log IU/mL)	458 (60–3755)	1070 (135–8660)	573 (116–17800)	1126 (186–11350)	0.05
	N = 289	N = 555	N = 156	N = 30	
Median ALT (U/mL)	25 (18–39)	25 (19–38)	25 (17–38)	27 (19–45)	< 0.01
% with ALT > 2× ULN[a]	14%	10%	8%	13%	0.11
Median platelet count (/cmm)	207 (151–263)	220 (179–265)	208 (174–246)	194 (148–237)	0.03
	N = 112	N = 372	N = 51	N = 10	
AFP > 9	9%	8%	10%	30%	0.34
Median APRI	0.34 (0.22–0.67)	0.31 (0.24–0.46)	0.33 (0.25–0.48)	0.32 (0.25–0.68)	0.27
Median FIB-4	1.35 (0.84–2.59)	1.39 (0.97–1.89)	1.99 (1.00–2.19)	1.3 (0.88–2.96)	0.84
Liver-related complications at the time of presentation (±1 year of diagnosis)					
Cirrhosis					
By ICD codes[b]	15%	11%	3%	10%	< 0.01
FIB-4 > 3.25	19%	9%	9%	23%	< 0.01
APRI > 2	9%	3%	3%	6%	< 0.01
Cirrhosis by ICD codes and/or FIB-4/APRI	25%	15%	11%	23%	< 0.01
HCC	2%	4%	2%	0%	0.54

[a] For women ≥ 50 U/L, for men ≥ 70.
[b] Any ICD code for cirrhosis or decompensated cirrhosis (esophageal varices, ascites, encephalopathy, SBP, portal hypertension).
Abbreviations: AFP, alpha-fetoprotein; ALD, alcohol-associated liver disease; APRI, AST-to-platelet ratio; AUD, alcohol use disorder; FIB-4, Fibrosis-4 score; ULN, upper limit of normal.

primary care physicians to directly message specialist reviewers about potential patient referrals through an online portal; specialists then triage the request to the hepatology clinic or back to the primary care. Patients who are triaged back to primary care are provided with standardized guidance on further workup and monitoring. Based on internal E-consult guidance documents, patients who meet treatment criteria have cirrhosis or have a first-degree family member with HCC are recommended for a subspecialty appointment. Patients, whose referrals were accepted are then contacted by schedulers to schedule a subspecialty appointment within the time frame recommended by the specialist reviewer. In this study, we collected the frequency of direct scheduling, E-consult referral (requested and accepted), and dates of initial E-consult request and first liver clinic appointment to determine the time elapsed between initial referral and initial appointment as a proxy for timely care.

To examine treatment patterns within our population, we first identified the proportion eligible for HBV treatment based on AASLD guidelines (presence of cirrhosis, HIV coinfection, or immune-active disease).[6] Finally, we identified the number of patients who had at least 2 GI appointments and were prescribed HBV treatment, and proportion who were not prescribed treatment despite potential eligibility.

Statistical analysis

Descriptive statistics by race/ethnicity were reported as median with interquartile ranges or mean with SD and compared using the Kruskal-Wallis test. Categorical variables were reported as total number and proportion and were compared using a chi-square test. All data were analyzed using Python Data Analysis Library[23] and SciPy.[24] Statistical significance was defined as $p < 0.05$. This study was approved and informed consent waived by the Institutional Review Board at the University of Southern California.

RESULTS

Demographic and clinical characteristics of Hispanics with chronic hepatitis B

A total of 1063 patients met the inclusion criteria: 89% by positive HBsAg and 11% by positive HBV DNA. Demographic and clinical characteristics stratified on race/ethnicity are presented in Table 1. The study population was made up of 28% Hispanics, 54% Asians, 15% Blacks, and 3% Whites. Hispanics were diagnosed at a median age of 49 years [interquartile range (IQR) 39–58], younger than a median age of 56 (IQR 47–62) for Asians; 54% of Hispanics with chronic HBV were male, compared with 42% of Asians. A higher proportion of Hispanics preferred non-English language (75%), followed by Asians (56%), Whites (23%), and Blacks (4%) ($p < 0.01$). High proportions of both Hispanics (82%) and Asians (93%) were foreign-born as compared with 42% of Whites and 30% of Blacks ($p < 0.01$). In this safety net setting, a majority of patients across all racial/ethnic groups had Medicaid insurance (ranging 63%–74% across ethnicity groups).

In terms of comorbidities, 15% of Hispanics had diabetes compared with 11% of Asians; 37% of Hispanics were obese compared with 27% of Asians. Hispanics had higher rates of alcohol use disorder or alcohol-associated liver disease (22%) as compared with Asians (9%), but similar rates of alcohol use disorder/alcohol-associated liver disease to Blacks (22%) and Whites (26%) ($p < 0.01$).

Median HBV DNA at presentation was lower in Hispanics at 458 IU/mL (IQR 60–3755) compared with 1070 IU/mL (IQR 135–8660) for Asians (Table 1). Conversely, 14% of Hispanics had an ALT > 2× upper limit of normal compared with 10% of Asians. Of the Hispanics who received HBeAg testing, 8% were positive, similar to 9% of Asians. The median platelet count differed slightly between racial/ethnic groups; however, APRI and FIB-4 did not.

Liver-related complications at initial presentation

The following patterns were observed with regard to liver-related complications within the first year of an HBV diagnosis (Table 1). Hispanics had the highest frequency of cirrhosis (15%) by ICD-10 coding, followed by Whites (10%), Asians (11%), and Blacks (3%). The proportion of Hispanic patients with cirrhosis within 1 year of HBV diagnosis increased to 25% when the definition of cirrhosis was expanded to include noninvasive fibrosis scores (ie, FIB-4 > 3.25 or APRI > 2), compared with an increase to only 15% in Asians ($p < 0.01$). Rates of HCC diagnosis within the first year of HBV diagnosis were low and similar across groups, ranging from 0 to 4% ($p = 0.54$). Overall, Hispanics were the racial/ethnic group most likely to have any liver-related complication at presentation (cirrhosis by ICD-10 coding, fibrosis scores, and/or HCC).

Racial/ethnic differences in diagnosis setting

A higher proportion of Hispanics (25%) were diagnosed in the acute care setting (inpatient or emergency room), as compared with Whites (23%), Blacks (16%), and Asians (10%) ($p < 0.01$) (Figure 2A). Among those diagnosed in the acute-care setting, reason for testing

was as follows: 61 (30%) with a known risk factor for HBV, 15 (7%) with symptoms or a history of possible exposure, 41 (20%) with abnormal imaging findings or elevated liver tests, and 88 (43%) with no discernable reason identified in the chart. Among those with known risk factors, 31 (51%) had a self-reported history of HBV or HCV, 12 (20%) had HIV, 12 (20%) were on dialysis, and 6 (10%) were from a high prevalence region. Most patients in this study across all groups received HBV screening in the outpatient setting and majority of diagnoses were made in the primary care. Among Hispanics diagnosed in the outpatient setting, 71% were diagnosed in the primary care, 15% in the GI/hepatology clinic, 10% in non-GI subspecialty clinics, and 4% by obstetrics (Figure 2B). Blacks were more often diagnosed by non-GI subspecialty clinics (27%).

Follow-up testing and determination of the HBV phenotype for patients seen in the outpatient setting

A total of 906 patients had either outpatient diagnoses (95%) or acute care diagnoses with the outpatient follow-up (5%) in our system. Median follow-up time was 12.5 (3.8–25.3) months for Hispanics, 18.9 (9.2–32.9) months for Asians, 16.4 (6.7–24.3) months for Blacks, and 9.8 (3.2–21.6) months for Whites. There were differences in receipt of subsequent laboratory testing after an HBV diagnosis (Figure 3). Overall, 49% of patients did not have HBV DNA testing in our system. Only 38% of Hispanics had follow-up HBV DNA testing compared with 56% of Asians. Nearly all (96%–97%) of the patients had AST and ALT testing. Only 43% of Hispanics received HBeAg testing, much lower than Asians (60%) or Whites (58%) ($p < 0.01$).

Of all coinfection testing, HCV screening was most likely to be performed, with 92% of Whites, 64% Asians, 76% Hispanics, and 79% of Blacks receiving HCV screening. Asians had the lowest rates of HCV co-infection (3%), followed by Hispanics (8%), Blacks (10%), and Whites (21%) ($p < 0.01$). There were suboptimal rates of HIV testing (51%–74%) and very low rates of HDV testing (3%–7%) among all ethnicities. Of the 60 patients overall tested for HDV antibody, only 3 patients tested antibody positive, and 5 (8%) had HDV RNA testing, none of which were positive.

Baseline HBV disease phenotype could only be ascertained in 25% of patients who had minimum sufficient testing (ie, HBeAg, HBV DNA, and ALT) within the first year of diagnosis (Table 2). Across all groups, patients were most likely to have an indeterminate phenotype (ranging from 50% to 64%), followed by an inactive carrier (ranging from 28% to 44%), immune tolerant (ranging from 3% to 11%), and immune active (ranging from 0 to 6%) ($p < 0.01$). Of the Hispanics, 3% were immune-tolerant, 5% immune-active, 28% inactive carriers, and, the largest group, 64% indeterminate. Asians had proportionally more immune-tolerant (11%) and inactive carrier (33%), with less indeterminate (50%), but similar proportion of immune-active (6%) phenotypes.

Of all patients, 66% received some type of abdominal imaging within the first year of initial HBV diagnosis; however, variation was seen by race/ethnicity: 73% of Hispanics, 87% of Asians, 50% of Blacks, and 64% of Whites (Table 2). The most common imaging modality was an abdominal ultrasound for all groups. Only 51% of subjects received alpha-fetoprotein screening, with a higher proportion of Asians (65%) receiving testing as compared with Hispanics (37%), Whites (32%), and Blacks (32%) ($p < 0.01$).

Referral rates and linkage to care

Figure 4 shows the care cascade from diagnosis to linkage to subspecialty care in this safety-net system. Few patients diagnosed in the acute care setting had outpatient follow-up in our system (lowest 14% of Whites to 28% of Asians). Among those diagnosed in the outpatient setting and those diagnosed in the acute-care setting with outpatient follow-up (n = 906), linkage to specialty care also differed by race/ethnicity. Overall, all other racial/ethnic groups had lower rates of linkage to care with GI/hepatology clinic as compared with Asians (32% of Hispanics, 20% of Blacks, 32% of Whites vs. 55% of Asians). In total, 28% were directly scheduled with a subspecialty clinic (ranging 9%–39% by race/ethnicity), while 34% of all patients had a provider request for GI/hepatology subspecialty care sent through the E-consult system. E-consult referral rates were lower for Hispanics compared with Asians (33% vs. 46%), but similar rates of E-consult acceptance (47% vs. 51%) and slightly lower rates of completion of initial clinic appointment (78% vs. 89%). Among those with at least 2 subspecialty follow-up appointments, 10% of Hispanics versus 33% of Asians were prescribed HBV treatment.

DISCUSSION

Appropriate screening and management for chronic HBV is crucial to modifying the risk of liver-related complications. In this study, we examined the role of race/ethnicity in disease presentation and initial management of chronic HBV in a safety net setting, with a specific focus on Hispanics as there is little research on HBV among the large and growing Hispanic demographic in the US. In fact, due to the high proportion of Hispanic immigrants in our safety net catchment area, Hispanics were the second largest race/ethnicity group in our study with HBV. Within this study, we identified notable disparities in initial

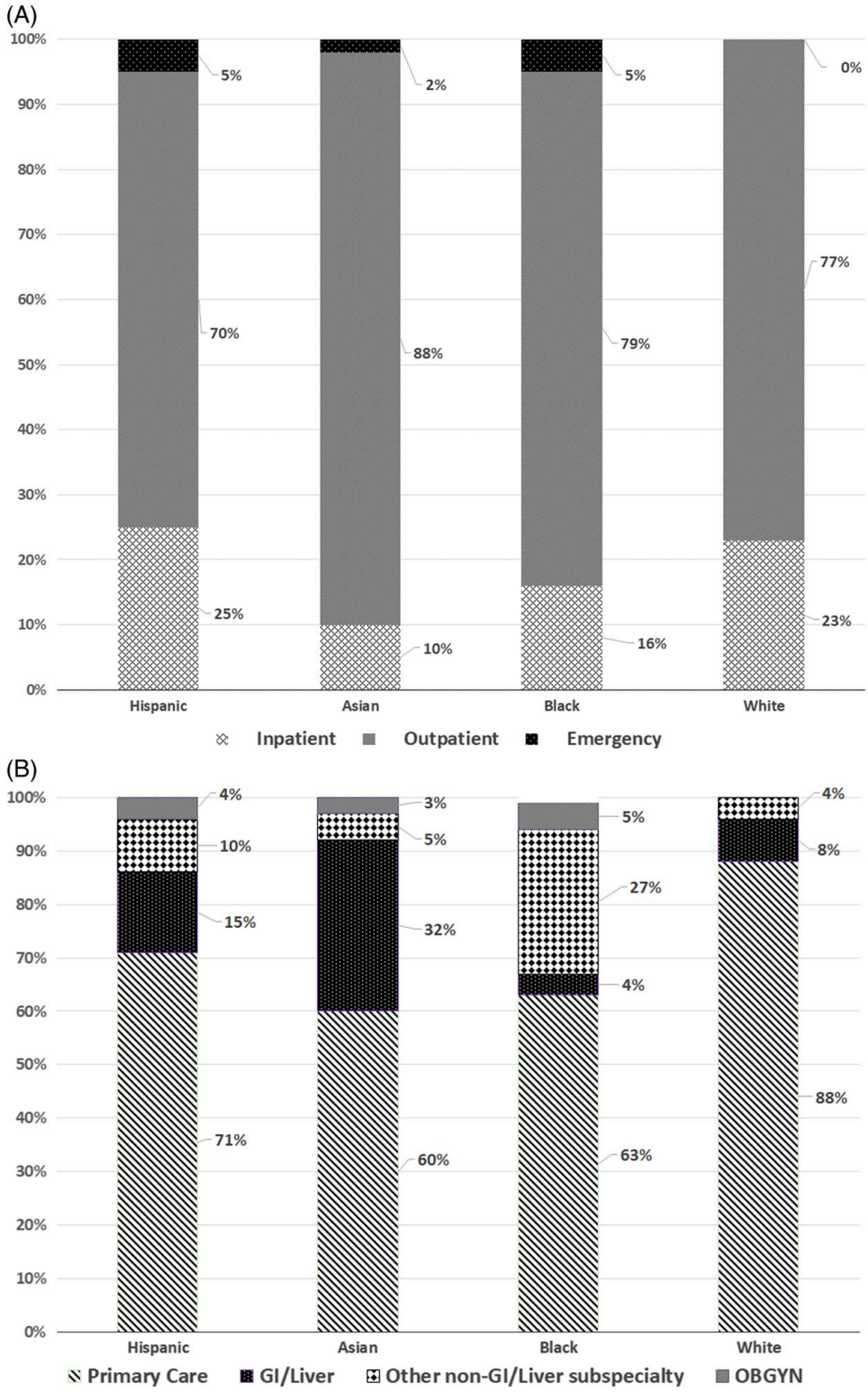

FIGURE 2 (A) Initial screening setting by ethnicity. (B) Outpatient screening location by ethnicity.

presentation and management for Hispanics, including more screening performed in the inpatient or emergency room setting, lower proportion with minimum testing to determine the HBV phenotype, lower rates of subspecialty referral, and higher rates of advanced liver disease.

There were clear differences in the physical location of initial HBV screening/diagnosis across racial/ethnic groups. Hispanics had higher rates of diagnosis in inpatient or emergency room settings when compared with Asians, suggesting that Hispanics are less likely to

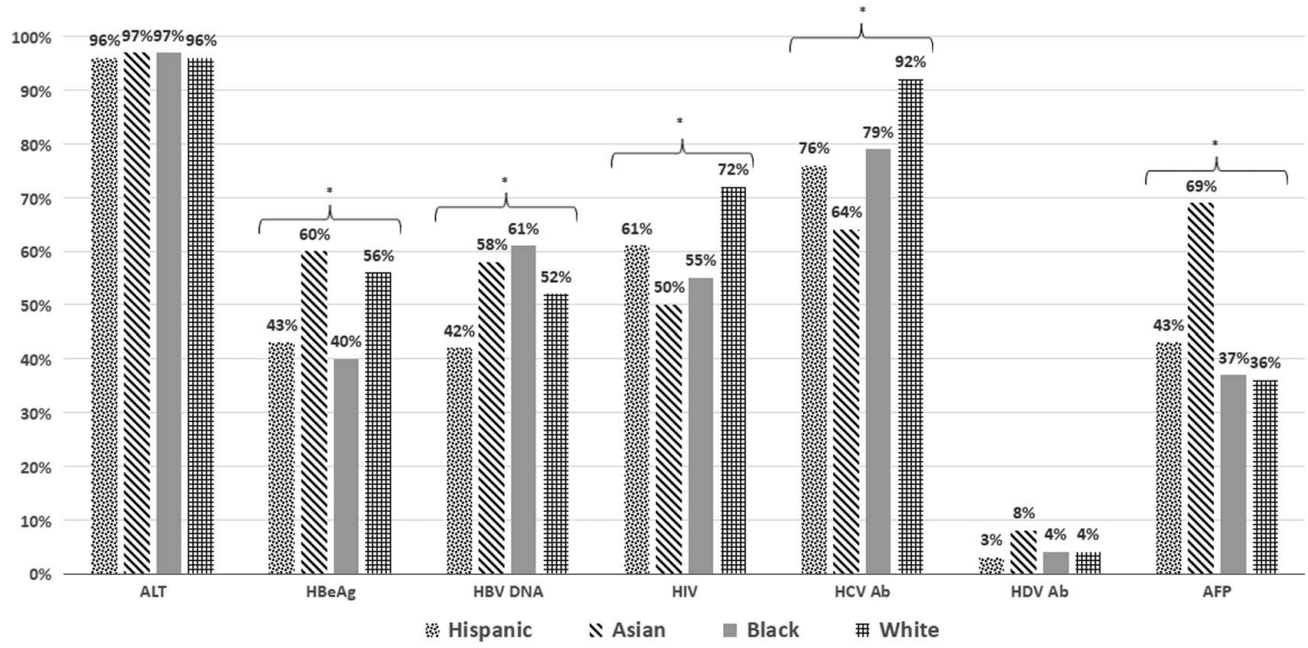

FIGURE 3 Initial laboratory testing received by ethnicity group for patients who received outpatient care. *$p < 0.05$.

receive risk-based screening for HBV in the outpatient setting as per AASLD and US Preventative Services Taskforce guidelines,[6,25] and are instead screened in an acute-care setting presumably guided by symptoms, examination findings, or abnormal laboratory or imaging results. This finding could be partially explained by differential utilization of health care, including how likely a patient is to establish care with a primary care provider and regularly attend outpatient visits and phlebotomy lab draws. Studies have shown that Hispanics are less likely to get preventative care due to lack of health insurance (related to immigration status, employers), financial burdens, previous poor medical provider interactions, and the desire to not be given an official diagnosis for an illness.[26–28] Our study found that although Hispanics had the highest rates of cirrhosis among all ethnicity groups, they had the lowest rates of outpatient follow-up (at primary care or gastroenterology clinics) after initial positive HBsAg or HBV DNA test in our system (77%) and E-consult referrals (33%). As expected, patients diagnosed with HBV in acute-care settings (inpatient or emergency settings) have lower rates of outpatient follow-up appointment attendance than for patients diagnosed in the outpatient setting. While perhaps some patients hospitalized in our healthcare system may establish care outside our system, we suspect that these rates are low and that education around HBV in the acute-care setting is inadequate, such that most of these patients remain unaware of their infection upon discharge. Low overall outpatient follow-up rates underscore the point that while increasing HBV screening overall is extremely important, we also must ensure that patients diagnosed with HBV are appropriately linked to further care.

It is also plausible that poor provider familiarity with risk-based HBV screening guidelines and HBV prevalence in Latin American countries plays a role in the lower frequency of outpatient screening in Hispanics compared with Asians. HBV prevalence fluctuates greatly between the countries of Central America, from 0.20% in Mexico and Guatemala, 0.55% in Nicaragua, 0.62% in Costa Rica, 4.71% in Belize, and 1.68% in Panama.[29] Even within Mexico specifically, one study found that Mexico City had higher rates of HBV infection than other regions,[30] while another study found that residents in Southern Mexico had higher rates of HBV exposure than those in Central Mexico.[31] The high frequency of representation of Mexico as a country of origin of the Hispanics in this study (~50%) suggests that current screening guidelines that do not include Mexico as a country with $\geq$ 2% HBV prevalence may be leading to underdiagnosis. One way to overcome this barrier would be a recommendation for one-time universal HBV screening for all US adults (or at least all foreign-born), identical to the universal screening guidelines for HIV and HCV, to ultimately simplify screening guidelines and ensure broader diagnosis coverage for HBV. A recent Markov modeling study has shown that the implementation of universal HBV screening in the US would not only prevent 23,000 liver-related deaths, but also be a cost-savings of 596 million dollars,[32] further demonstrating that timely diagnosis of HBV by increasing HBV screening is not only potentially lifesaving, but also a judicious use of health care resources. Recent release of universal HBV vaccination recommendations by the Advisory Committee on Immunization Practices[33] has paved the way for the evaluation of a universal screening recommendation

TABLE 2 HBV phenotype and initial management characteristics of those with outpatient diagnosis or follow-up by race/ethnicity (n = 906)

	Hispanic N = 231	Asian N = 518	Black N = 132	White N = 25	*p*
HBV phenotype[a]					
	N = 39	N = 178	N = 41	N = 9	< 0.01
Immune tolerant	3%	11%	7%	0%	
Immune active	5%	6%	2%	0%	
Inactive carrier	28%	33%	29%	44%	
Indeterminate	64%	50%	61%	56%	
Indeterminate subclassification:	N = 25	N = 90	N = 25	N = 5	< 0.01
ALT > 2× ULN with high HBV DNA	0%	0%	0%	20%	
ALT > 2× ULN with low HBV DNA	20%	13%	4%	0%	
ALT 1–2× ULN with high HBV DNA	20%	28%	20%	0%	
ALT 1-2× ULN with low HBV DNA	44%	27%	28%	60%	
ALT < ULN with high HBV DNA	12%	32%	40%	20%	
ALT < ULN with low HBV DNA	4%	0%	8%	0%	
Management					
Median follow-up time (mo)	12.5 (3.8-25.3)	18.9 (9.2-32.9)	16.4 (6.7-24.3)	9.8 (3.2-21.6)	0.01
Minimum sufficient set of labs to determine treatment eligibility within 1 y of diagnosis[b]	17%	34%	31%	36%	< 0.01
	N = 47	N = 208	N = 42	N = 12	
% patients with minimum sufficient set ever and liver clinic visit	70%	58%	48%	58%	0.19
% with abdominal imaging	73%	87%	50%	64%	< 0.01
Total treatment eligibility[c]	22%	15%	11%	24%	0.01
% eligible not initiated on HBV treatment	68%	38%	60%	83%	< 0.01
% patients with 2 outpatient GI appointments and prescription for HBV treatment	10%	33%	7%	3%	< 0.01

[a]Phenotype definitions: immune tolerant = HBeAg+, viral load $\geq 10^5$ IU/mL, normal ALT. Immune active = HBeAg+, ALT ≥ 2× ULN and HBV DNA ≥ 20000 OR HBeAg−, ALT ≥ 2x ULN & HBV DNA ≥ 2000. Inactive carrier = HBeAg−, normal ALT and HBV DNA < 2000. Indeterminate = everyone else who has minimum sufficient lab testing: ALT > 2× ULN with normal HBV DNA = ALT < 50 for women or ALT <70 for men with HBV DNA <2000 OR normal ALT with elevated HBV DNA = ALT <26 for women or ALT <36 for men with HBV DNA > 2000 OR elevated ALT with elevated HBV DNA = ALT 26–49 for women or ALT 36–69 for men with HBV DNA > 2000.
[b]Minimum sufficient set defined as HBeAG, HBV DNA, and ALT testing.
[c]Total treatment eligibility was defined as immune active phenotype with HBV Eag positive and HBV DNA > 20,000 IU/mL, immune-active phenotype with HBV Eag negative and HBV DNA > 2000 IU/mL, presence of cirrhosis (compensated or decompensated) by ICD-10 coding, AST-to-platelet ratio > 1.5, or Fibrosis-4 score > 3.25, or HIV coinfection.
Abbreviations: GI, gastroenterology; ULN, upper limit of normal.

—which if implemented could have substantial public health impact.[34]

When examining the severity of liver disease at the time of HBV diagnosis, we found that Hispanics had higher rates of advanced fibrosis or cirrhosis by ICD-10 coding and fibrosis scores within the first year of diagnosis compared with all other races. These findings suggest that Hispanics may present with more advanced liver disease upon initial HBV diagnosis than other racial/ethnic groups. There are several possible explanations. The first is that the phenotype of HBV is more aggressive in Hispanics, but this is less likely as viral parameters such as HBV DNA and proportion with immune-active HBV were similar by race/ethnicity in our cohort; prior studies have also suggested a more benign disease course.[35] More likely, we believe the more advanced fibrosis in Hispanics with HBV may be a result of higher rates of coexisting liver disease such as fatty liver disease and alcohol-associated liver disease in this population, as both metabolic comorbidities and alcohol use disorder/alcohol-associated liver disease, in particular, were more common among Hispanics in this cohort, especially when compared with Asians. Hispanics have high rates of mortality due to liver disease and are expected to have the highest rates of HCC in the US by 2030,[17] largely due to the preponderance of NAFLD found in Hispanics, typically linked to diabetes and obesity.[18] Therefore, given the potential heightened risk of cofactors for fibrosis progression in Hispanics specifically, it is even more important to identify potential modifiable risk factors, such as HBV, as early as possible to avert liver-related complications.

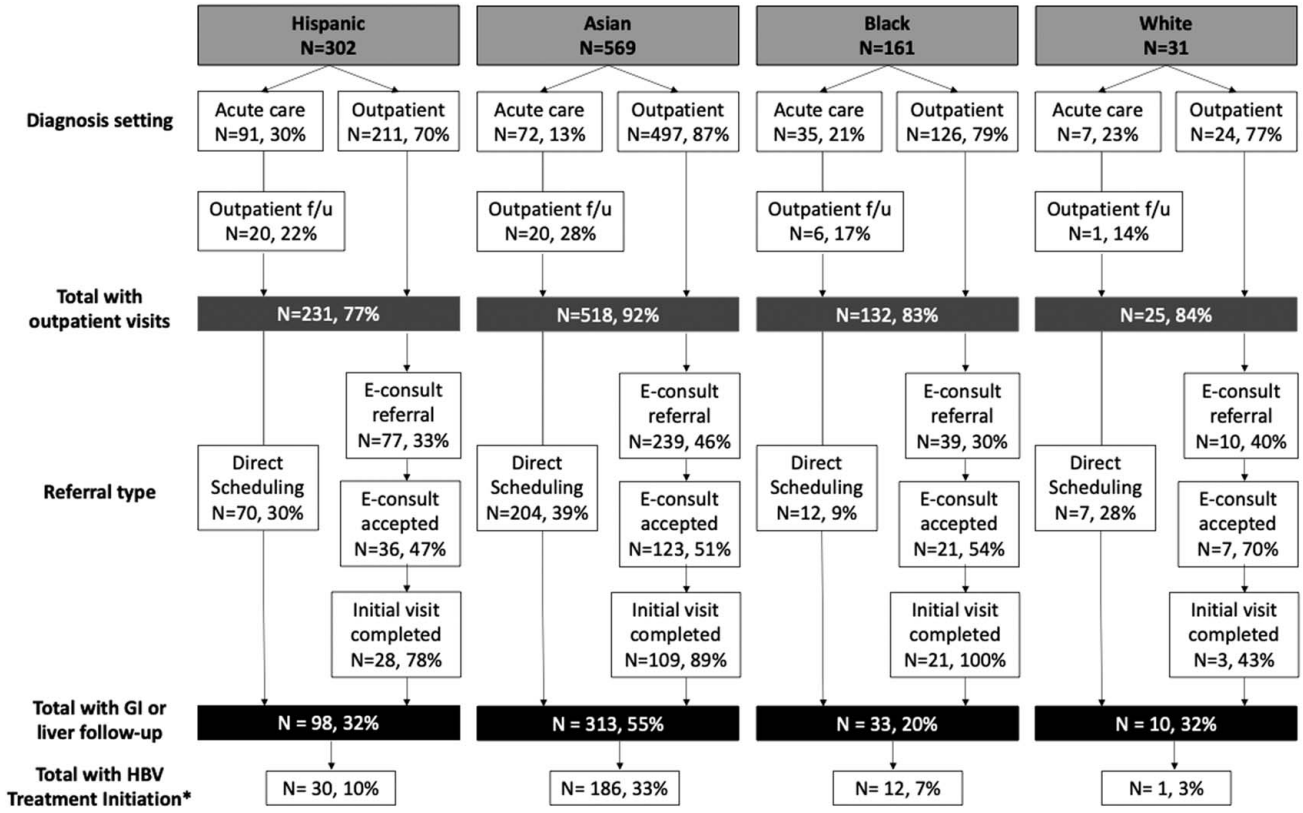

FIGURE 4 HBV care cascade by ethnicity group. *Patients with at least 2 outpatient gastroenterology (GI)/hepatology appointments.

In a US-based cross-sectional study on the rates of treatment initiation in patients aware of their chronic hepatitis B diagnosis, 28% of patients were initiated on treatment.[36] Similarly, in our study, only 26% study participants were ever started on treatment for chronic HBV during the study period, with Asians initiating treatment nearly twice as frequently as Hispanics among eligible. The determination of HBV phenotype and treatment eligibility was based on a single set of labs, a notable limitation of this study as patients with chronic HBV need continued monitoring and reassessment for treatment eligibility. In this study, follow-up testing for HBV DNA, HBeAg, and HIV were suboptimal, which points toward lapses in HBV care, but also a potential barrier to receiving treatment. The minimum sufficient set of testing to determine HBV phenotype within 1 year of diagnosis, including HBeAg status, was only available in 17% of Hispanics (vs. 34% of Asians), which may be directly correlated with lower subspecialty referral and visits. Thus, the inequities in receiving referrals and secondary screening tests may lead to a smaller proportion of patients appearing eligible for treatment.[37]

In addition, overall screening for coinfections were inadequate; of the Hispanic population, only 62% received HIV testing, 78% received HCV testing, and 4% received HDV testing. Unlike HCV and HIV coinfection testing which is recommended for all patients with HBV infection, the 2018 AASLD HBV guidance currently recommend risk-based HDV testing, which undoubtedly contributes to the low rates of HDV testing observed in this study.[6] Low testing for HDV overall is consistent with other studies from other health systems.[38–41] However, guidance from other organizations such as the 2017 European Association for the Study of Liver diseases Hepatitis B guidelines recommend testing for HDV in all patients with positive HBsAg.[42] True HDV prevalence, especially in the US is currently unclear given the low screening rates, which makes it difficult to determine the true impact of HDV infection has on chronic HBV patients' treatment eligibility and outcomes. Lack of complete testing for HBV phenotype and coinfections ultimately hinders an accurate determination of treatment eligibility and is an area of postdiagnosis management that needs to be optimized in clinical practice.

Our study highlights the need for provider-level education and interventions around HBV diagnosis and management targeted to foreign-born Hispanics. For example, one US health system first prioritized accurate recording of patients' birthplaces, then developed an electronic health record alert to prompt medical providers to screen patients born in countries with $>2\%$ HBV endemicity who had not yet received HBV screening.[43] A Mayo Clinic quality improvement study increased HBV testing in at-risk immigrants by reminder emails to primary care providers 1 week before patient appointments to discuss HBV screening at patient's upcoming appointment.[44] Interventions increasing

linkage to care amongst patient diagnosed with HBV in emergency department settings might be implemented in safety net systems serving populations with high HBV prevalence and a patient population that may not regularly engage in outpatient primary care.[45]

This is an administrative dataset, thus biases related to misclassification due to coding or lack of validated codes may be present. In particular, we could not independently stage liver disease with standard tools (i.e. elastrography) due to unavailability in our healthcare system, so surrogate measures such as ICD-10 coding or fibrosis estimate scores were utilized. Our data on abdominal imaging was limited to the imaging type and date of imaging; therefore, we cannot comment on the reasons why patients received abdominal imaging. ICD-10 codes as surrogate for a clinical diagnosis of cirrhosis have been used in other administrative studies to describe the burden of liver disease and comorbid conditions.[46] The small sample size of Whites and Blacks in this study makes it more likely that estimates in these smaller groups, especially Whites, were biased or inaccurate. As our system is a referral base for community clinics and federally qualified health centers, we may be underestimating the proportion receiving appropriate testing and follow-up if performed in primary care outside of our system, but we are likely accurately capturing linkage to specialty care. Further, due to resource constraints, only patients that will likely require treatment are recommended for specialty follow-up, so rates of linkage to specialty care within this system should not be directly compared with other systems with less restrictive referral policies. While our study population is not generalizable to the entire US population and potentially other geographic regions, it is the ideal population in which to study HBV in Hispanic immigrants, who often access care in safety net facilities and are a vulnerable population that has been poorly characterized in the literature to date.

In conclusion, we demonstrate notable differences in initial diagnosis, linkage to care, and management for Hispanics with chronic HBV in a safety net healthcare system, including lower frequency of appropriate viral testing and subspecialty referrals. These deficiencies are important as we simultaneously found a higher rate of liver-related complications among Hispanics at the time of their HBV diagnosis. Our findings underscore the importance of scaling up HBV screening in less well-recognized risk groups to mitigate the potential negative outcomes related to delays in the identification of chronic HBV infection.

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CONFLICT OF INTEREST

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ORCID

Allison E. Wang https://orcid.org/0000–0001–8221–6670
Norah A. Terrault https://orcid.org/0000–0003–4143–1950
Tse-Ling Fong https://orcid.org/0000–0001–9020–4880
Kali Zhou https://orcid.org/0000–0001–8554–2906

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