Ethnic Differences in Viral Dominance Patterns in Patients with Hepatitis B Virus and Hepatitis C Virus Dual Infection

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Studies of hepatitis B virus (HBV)/hepatitis C virus (HCV) dual infection are limited. Most are small, conducted outside the United States, and compare dual infection with HCV monoinfection. The goal of this study was to characterize HBV/HCV dual infection in a large multiethnic, matched, case-control study of dual-infected and HBV-monoinfected patients at two United States centers. Using an International Classification of Disease Version 9 electronic query and chart review, we identified 115 HBV/HCV dual-infected patients with serial HBV DNA, HCV RNA, and alanine aminotransferase (ALT) levels. As a control, 115 HBV-monoinfected patients were chosen randomly and matched with cases by age ±10 years, sex, Asian versus non-Asian ethnicity, and study site. Both groups had similar sex, ethnic, and age distributions (68% male, 83% Asian, age 52 ± 14 years). The median follow-up times were 33 and 38 months for the dual-infected and monoinfected groups, respectively. More monoinfected patients received HBV antiviral therapy than dual-infected patients (43% versus 24%; $P = 0.002$). No significant difference was detected between the proportion of monoinfected versus dual-infected patients with ALT above 40 U/L at presentation or during follow-up. Dual infection patients exhibited very little HBV/HCV codominance at baseline and throughout follow-up: patients had either HBV viremia with low or absent HCV RNA or detectable HCV RNA with low or absent HBV DNA. Asian ethnicity was predictive of HBV dominance after adjusting for sex, age, and baseline ALT elevation (odds ratio 7.35; $P = 0.01$). *Conclusion:* HBV/HCV dual-infected and HBV-monoinfected patients had similar clinical characteristics. Asian ethnicity is a major independent predictor of HBV-dominant disease, and HCV dominance with undetectable HBV DNA is more common in non-Asian individuals. Larger studies are needed to further characterize the natural history of HBV/HCV dual infection in Asian and non-Asian individuals. (HEPATOLOGY 2011;53:1839-1845)

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the two most common causes of chronic liver disease globally. Worldwide, approximately 350 million and 170 million people are infected with HBV and HCV, respectively.[1,2] Dual infection with HBV and HCV is possible because of common routes of infection and is frequently found in several high-risk populations, such as injection drug users, hemodialysis patients, organ transplant recipients, and human immunodeficiency virus–positive individuals.[3] Thus, dual infection with both viruses is not uncommon, with a review of prevalence data suggesting that 2%-10% of hepatitis C antibody (anti-HCV)–positive patients are hepatitis B surface antigen (HBsAg)-positive and that anti-HCV is found in 5%-20% of patients with chronic hepatitis B.[3]

Abbreviations: ALT, alanine aminotransferase; anti-HCV, hepatitis C antibody; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; OR, odds ratio; PCR, polymerase chain reaction; ULN, upper limit of normal.

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The prevalence of HBV and HCV dual infection is likely to vary depending on different geographic areas and may depend on the ethnic makeup of a given population. Investigators in Eastern Europe found a dual infection rate of nearly 1% in a healthy cohort.[4] A European study of 59 dual-infected patients found that geographic region, age >42 years, prior history of blood transfusion, and injection drug users were independently associated with HBV/HCV dual infection compared with a control group of HBV-monoinfected patients.[5] The HBV/HCV dual infection rate in the United States may be both underreported and potentially on the rise. In recent years, the number of immigrants from Asia and the Pacific region, an area where HBV is endemic, has increased substantially to approximately 14 million individuals.[6,7]

Patients infected with both HBV and HCV are generally more likely to develop fulminant hepatitis in the acute phase or more advanced disease such as cirrhosis and hepatocellular carcinoma (HCC) with chronic dual infection and are also at a greater risk to fail interferon-based antiviral treatment.[8-14] Although HBV/HCV dual infection has been shown to lead to more severe forms of liver disease, the interaction between the hepatitis B and C viruses appears to be one of reciprocal inhibition, each preventing or greatly decreasing the ability of the other virus to replicate.[11,15-22] In general, the most common pattern of viral interaction is for HCV to be dominant with detectable HCV RNA in combination with very low or undetectable levels of HBV DNA and negative hepatitis B e antigen (HBeAg) with detectable HBeAg antibody.[3] However, this pattern of HCV dominance is not uniform, and some studies have reported that HBV may be dominant.[23-25]

Additionally, the reciprocal inhibition of each virus on the other virus may prevent identification of dual-infected patients because of negative serum HBV DNA and/or HCV RNA by polymerase chain reaction (PCR) tests. The goal of this study was to characterize the demographic, clinical, and viral characteristics of all HBV/HCV dual-infection patients in a large, multiethnic, matched case-control study of HBV/HCV dual-infected and HBV-monoinfected patients at two large liver centers in the United States.

Patients and Methods

Study Design and Data Collection. Using an electronic query of International Classification of Disease Version 9 codes and comprehensive chart review, we identified 2,612 patients with chronic hepatitis B seen at a major university medical center and a community gastroenterology clinic from January 1994 to March 2009. A total of 115 dual-infected patients with serial HBV DNA, HCV RNA, and alanine aminotransferase (ALT) test results were identified during the study period. For a control group, 115 HBV-monoinfected patients were chosen randomly and matched with the dual-infected cases by age ±10 years, sex, Asian versus non-Asian ethnicity, and study site. Diagnosis of HBV-monoinfected patients was based on the presence of positive serum HBsAg. When HBsAg results were unavailable, detectable serum HBV DNA PCR was also used to confirm the diagnosis of HBV infection. Diagnosis of HBV/HCV dual-infected patients was based on the presence of either positive serum HBsAg or detectable serum HBV DNA PCR in combination with either positive serum anti-HCV or detectable serum HCV RNA PCR.

Patients were either self-identified or identified by their physicians as either Asian or non-Asian. Both study sites serve a large Asian American patient population in the San Francisco Bay Area, many of whom emigrated from regions where chronic HBV infection is endemic. The medical records of all study patients were reviewed in their entirety. Laboratory tests were performed by several local community clinical laboratories operated by either Quest Diagnostics (San Juan Capistrano, CA) or Stanford University Medical Center Laboratories (Palo Alto, CA). Over the 15-year period of this study, serum HCV RNA and HBV DNA were measured by various generations of commercial assays with variable lower limits of detection. Where applicable, HBV DNA viral load measurements reported in either picograms per milliliter or copies per milliliter were converted to international units per milliliter using standard conversion rates, whereas HCV RNA viral load measurements reported in copies per milliliter were converted using laboratory-specific conversion rates.[26,27] The histological grade of inflammation and stage of fibrosis on liver biopsy specimens were determined using the Batts-Ludwig scoring system as reported in pathology reports from patient clinical records. A case report form was created and used for data abstraction. The Stanford Institutional Review Board (Stanford, CA) and the Western Institutional Review Board (Olympia, WA) approved the study protocol.

Statistical Analysis. Patient clinical and viral characteristics were compiled, compared, and analyzed using standard statistical tests. Categorical variables were evaluated using a chi-squared test. The Student *t* test was applied to normally distributed noncategorical 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. We determined odds ratios (ORs) and their 95% confidence intervals relating HBV or HCV viral dominance to sex, age, ethnicity, and monoinfection versus dual infection status using both uncontrolled univariate logistic regression and adjusted multivariate logistic regression. All statistical analyses were performed using Stata version 10.0 software (StataCorp LP, College Station, TX).

Results

Patient Characteristics by Study Cohort. A total of 115 consecutive HBV/HCV dual-infected patients with serial HBV DNA, HCV RNA, and ALT test results from January 1994 through March 2009 were included in the data analysis along with an age-, sex-, ethnicity-, and site-matched HBV-monoinfected cohort. Both groups had an identical mean age (52 ± 14 years), sex distribution (68% male), and ethnic distribution (83% Asian versus non-Asian). The HBV-monoinfected control patients had a lower prevalence of smoking (21% versus 34%; $P = 0.09$) and alcohol consumption (17% versus 32%; $P = 0.03$) compared with dual-infected patients.

No significant differences were found at the time of presentation when comparing monoinfected patients with dual-infected patients for the following clinical and laboratory characteristics: body mass index (24 ± 5.3 versus 24 ± 3.5; $P = 0.89$), HBeAg (18% versus 12%; $P = 0.28$) or antibody to HBeAg (79% versus 88%; $P = 0.08$), family history of either HBV or HCV (19% versus 19%; $P = 0.99$), family history of HCC (9% versus 9%; $P = 0.99$), and median follow-up duration (38 months versus 33 months; $P = 0.85$). There was no difference in the rate of preexisting HCC (6% versus 4%; $P = 0.36$). These data are summarized in Table 1.

HBV genotype and the presence of HBV viral mutations were also evaluated, and no significant differences between monoinfected and dual-infected patients were found at the time of presentation: 78% of monoinfected patients had genotype B and 22% had genotype C, whereas 71% of dual-infected patients had genotype B and 29% had genotype C (n = 32/17; $P = 0.66$). HBV precore mutations were found in 71% of monoinfected patients and 75% of dual-infected patients (n = 28/16; $P = 0.8$) and basal core promoter mutations in 46% versus 44%, respectively ($P = 0.86$). No DNA polymerase mutations were found in either study group.

Table 1. Patient Baseline Demographic Characteristics

	HBV Monoinfection (n = 115)	HBV/HCV Dual Infection (n = 115)	*P* Value
Male sex	78 (68)	78 (68)	
Ethnicity			
Asian	95 (83)	95 (83)	
Non-Asian	20 (17)	20 (17)	
Age, years	52 ± 14	52 ± 14	0.75
Body mass index	24 ± 5.3	24 ± 3.5	0.89
Time in United States, years	16 ± 12	42 ± 22	0.31
Alcohol use	19 (17)	34 (32)	0.03
Smoking	23 (21)	35 (34)	0.09
Family history			
HBV or HCV infection	20 (19)	20 (19)	0.99
HCC	10 (9)	10 (9)	0.99
HBeAg (n = 98/95)	19 (18)	11 (12)	0.28
HBeAg antibody (n = 98/95)	79 (79)	84 (88)	0.08
Follow-up time, months	38 (5-86)	33 (5-106)	0.85
HCC	7 (6)	5 (4)	0.36

Data are presented as n (%), mean ± SD, or median (5%-95% range).

The baseline hepatic inflammation and fibrosis scores were also measured and compared in the two populations. Among HBV-monoinfected patients, 77% had grade 1 or 2 inflammation and 23% had grade 3 or 4 inflammation, whereas dual-infected patients had scores of 66% and 34% for mild to moderate versus more advanced inflammation, respectively (n = 22/30; $P = 0.44$). The fibrosis scores showed that 77% of monoinfected patients had stage 1 or 2 fibrosis and 23% had stage 3 or 4 fibrosis, whereas 57% and 43% of HBV/HCV dual-infected patients had mild to moderate versus advanced fibrosis scores, respectively ($P = 0.21$).

HBV/HCV dual-infected patients most often presented with evidence of dual infection at baseline (88%), as determined by either dual positivity of HBV DNA and HCV RNA and/or serologic findings of HBsAg and anti-HCV. The remaining 12% were found to have become dual-infected with the second virus at least 3 months after the initial diagnosis of the first viral infection during the course of follow-up (8% had HBV before HCV, and 4% had HCV before HBV). The HCV genotype distribution was as follows: 55% genotype 1, 20% genotype 2 or 3, 25% genotypes 4-6 (n = 51).

Proportion of Patients Receiving Treatment. Monoinfected patients were significantly more likely to receive anti-HBV therapy during the course of their follow-up than patients with HBV and HCV dual infection (43% versus 24%; $P = 0.002$). Among those who received HBV antiviral therapy, the average duration of treatment was similar between the two study groups (38 ± 24 months versus 40 ± 29 months;

Table 2. Laboratory Values at Presentation and During Follow-up

	HBV Monoinfection (n = 115)	HBV/HCV Dual Infection (n = 115)	*P* Value
At presentation			
Alpha-fetoprotein (ng/mL)	4 (1.7-238)	4.8 (1.5-165)	0.12
Albumin (g/dL)	4.1 ± 0.66	4.1 ± 0.68	0.47
Alkaline phosphatase (U/L)	70 (46-161)	76 (48-211)	0.15
ALT (U/L)	38 (12-130)	47 (17-165)	0.02
International normalized ratio	1.1 (1-1.5)	1.1 (1-1.7)	0.24
Total bilirubin (mg/dL)	0.8 (0.4-1.7)	0.8 (0.4-4.6)	0.63
HBV DNA (log_{10} IU/mL)	4.7 ± 1.6	4.6 ± 1.9	0.71
HCV RNA (log_{10} IU/mL)	NA	5.7 ± 1.0	
During follow-up			
Alpha-fetoprotein (ng/mL)	3.8 (1.7-29)	4.8 (1.7-116)	0.04
Albumin (g/dL)	4.1 ± 0.6	4 ± 0.7	0.28
Alkaline phosphatase (U/L)	71 (47-202)	75 (49-184)	0.25
ALT (U/L)	39 (14-108)	49 (19-195)	0.009
International normalized ratio	1.1 (1-2.7)	1.1 (1-2)	0.29
Total bilirubin (mg/dL)	0.7 (0.5-4.8)	0.8 (0.5-4)	0.35
HBV DNA (log_{10} IU/mL)	4.6 ± 1.7	4.5 ± 1.9	0.81
HCV RNA (log_{10} IU/mL)	NA	5.3 ± 1.2	

Abbreviation: NA, not available.
Data are presented as the mean ± SD or median (5%-95% range).

$P = 0.77$). Dual-infected patients received anti-HCV therapy 28% of the time for 9 ± 3 months.

Laboratory Findings at Presentation and During Follow-up. Laboratory measurements evaluated at presentation including several markers of overall liver function were similar: alpha-fetoprotein, albumin, alkaline phosphatase, international normalized ratio for prothrombin time, total bilirubin, and HBV DNA and remained similar during the course of follow-up. These results are summarized in Table 2.

Viral Dominance Patterns Among Dual-Infected Patients at Baseline. At presentation, HBV/HCV dual-infected patients were categorized as negative for both viruses (dual-negative viral load results) or having an HBV-dominant infection (HBV DNA level greater than HCV RNA) or HCV-dominant infection (HCV RNA level greater than HBV DNA). Among dual-infected Asian patients, 14% presented with a negative viral load results for both viruses, whereas 25% of non-Asian patients presented with no detectable HBV or HCV ($P = 0.21$) (Table 3). HBV-dominant disease was found in 38% of Asian patients and 10% of non-Asian patients ($P = 0.02$). Of the 38% of Asians with HBV-dominant infection, 83% had complete dominance (defined as negative HCV RNA with detectable HBV DNA), and 17% had partial HBV dominance (detectable HBV and HCV viral loads, but with HBV DNA level being greater than HCV RNA). All of the non-Asian patients with HBV-dominant disease displayed complete HBV dominance.

Infection characterized by HCV dominance was found in 48% of Asian patients and 65% of non-Asian patients ($P = 0.18$). In this category, 70% of Asian patients had undetectable HBV DNA coupled with a positive HCV RNA, and 30% had detectable viral loads for both viruses. Similar results were found in non-Asian patients, with 62% of those with HCV-dominant disease having undetectable HBV DNA and 38% having detectable viral loads for both HBV and HCV.

Proportion of Patients with Abnormal ALT Levels. At baseline, HBV-monoinfected patients had a lower median ALT level than their HBV/HCV dual-infected counterparts (38 U/L versus 47; $P = 0.02$). During the course of follow-up, ALT remained lower in monoinfected patients compared with dual-infected patients (39 U/L versus 49; $P = 0.009$). Among HBV-monoinfected patients, 44% presented with an ALT level >40 U/L, the upper limit of normal (ULN), compared with 54% of dual-infected patients ($P = 0.17$). During the course of follow-up, 64% of the entire HBV-monoinfected population and 75% of the dual-infected population had at least one elevated ALT result ($P = 0.09$).

There was no significant difference between the proportion of monoinfected patients and dual-infected patients who presented with an ALT 1-2× ULN at baseline (29% versus 28%; $P = 0.8$) and during follow-up (40% versus 36%; $P = 0.50$). However, 16% of monoinfected patients and 23% of dual-infected patients presented with ALT 2-5× ULN ($P = 0.17$) and 23% versus 35% over the course of their follow-up ($P = 0.04$). No HBV-monoinfected patients presented with ALT >5× ULN compared with 3% of the HBV/HCV dual-infected patients ($P = 0.08$), and the difference between the two study groups during follow-up was not significant (1% versus 4%; $P = 0.79$).

Table 3. Proportion of all HBV/HCV Dual-Infected Patients with HBV or HCV Viral Dominance Patterns at Presentation

	Asian (n = 95)	Non-Asian (n =20)	*P* Value*
Both viruses negative	13 (14)	5 (25)	0.21
HBV > HCV	36 (38)	2 (10)	0.02
HBV (+), HCV (−)	30 (32)	2 (10)	
Both (+), HBV > HCV	6 (6)	0 (0)	
HBV < HCV	46 (48)	13 (65)	0.18
HCV (+), HBV (−)	32 (34)	8 (40)	
Both (+), HCV > HBV	14 (14)	5 (25)	

Data are presented as n (%).
*$P = 0.11$ between all three groups (both negative, HBV-dominant, HCV-dominant).

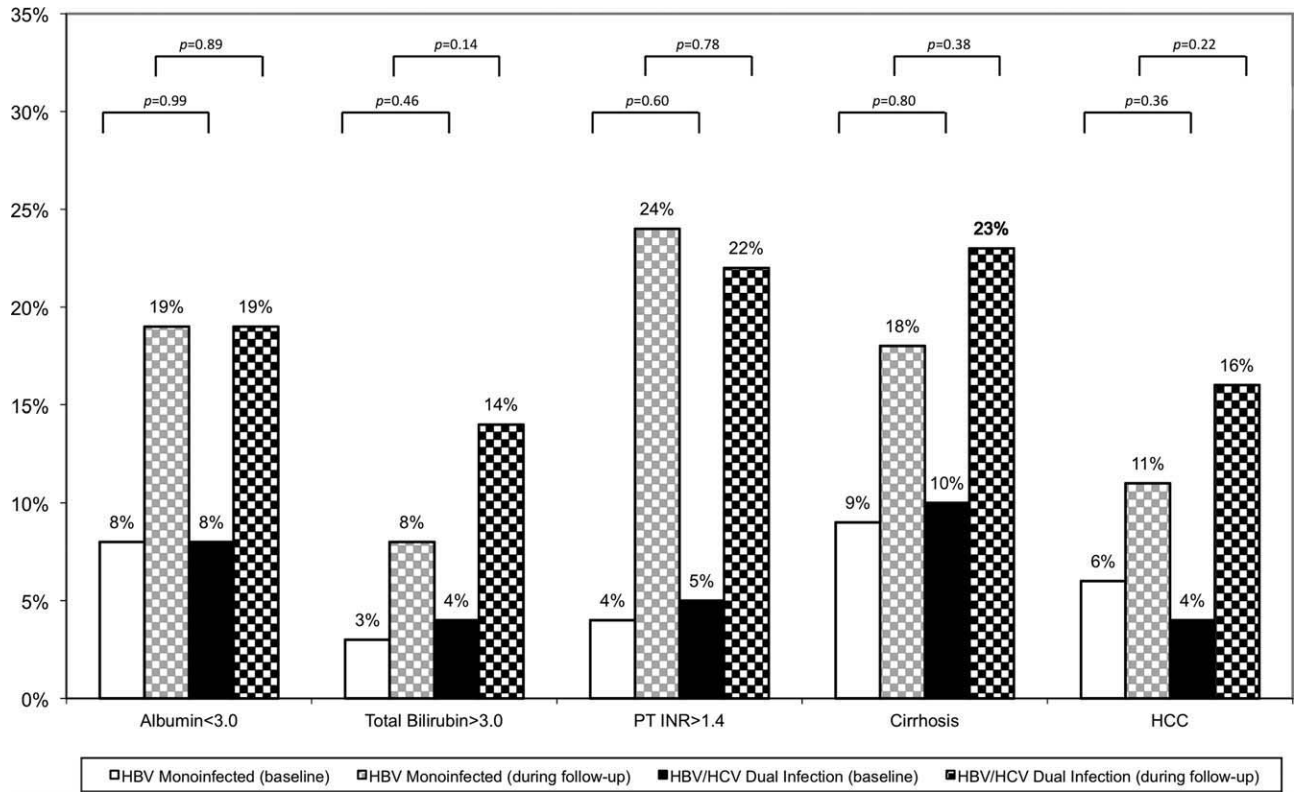

Fig. 1. Proportion of patients with signs of advanced liver disease.

Signs of Advanced Liver Disease at Baseline and During Follow-up. There were no significant differences between the proportion of HBV-monoinfected patients compared with the HBV/HCV dual-infected patients achieving the following benchmarks for advanced liver disease at either baseline or during follow-up: albumin <3.0 g/dL, total bilirubin >3.0 mg/dL, international normalized ratio >1.4, diagnosis of cirrhosis, or detection of HCC (Fig. 1).

Predictors of HBV and HCV Dominance. Univariate and adjusted multivariate logistic regression analyses were performed to determine whether sex, age, ethnicity, or baseline ALT were independent predictors of either HBV-dominant disease or HCV-dominant disease. Among all dual-infected patients, Asian ethnicity predicted HBV dominance after adjusting for sex, age, and baseline ALT elevation (OR 7.35; $P = 0.01$) (Table 4). Examining the entire dual-infected study group, both female sex and baseline ALT elevation independently predicted HCV-dominant disease at baseline after adjusting for age and ethnicity (OR 4.20, $P = 0.002$ and OR 2.63, $P = 0.02$, respectively) (Table 5). Non-Asian ethnicity as an independent predictor also trended toward significance (OR 3.00; $P = 0.052$).

Discussion

The current study is the largest to compare HBV-monoinfected patients with HBV/HCV dual-infected patients in the United States. Patients were drawn from both a university tertiary care facility and a large community gastroenterology group practice. The results demonstrate that Asian ethnicity can be a predictor for HBV-dominant dual infection, and female sex and baseline ALT level can predict HCV-dominant disease, with non-Asian ethnicity trending toward

Table 4. Predictors of HBV Dominance at Baseline Among HBV/HCV Dual-Infected Patients

	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Sex		0.17		0.13
Female	1		1	
Male	1.84 (0.76-4.44)		2.1 (0.82-5.27)	
Age	0.98 (0.95-1.01)	0.18	0.97 (0.94-1.00)	0.1
Ethnicity		0.03		0.01
Non-Asian	1		1	
Asian	5.49 (1.20-25.1)		7.35 (1.52-35.5)	
Baseline ALT		0.47		0.26
>40	1		1	
≤40	1.33 (0.61-2.93)		1.64 (0.70-3.82)	

Abbreviation: CI, confidence interval.

Table 5. Predictors of HCV Dominance at Baseline Among HBV/HCV Dual-Infected Patients

	Unadjusted OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Sex		0.006		0.002
Male	1		1	
Female	3.22 (1.4-7.4)		4.2 (1.7-10.4)	
Age	1.02 (0.99-1.05)	0.18	1.02 (0.99-1.05)	0.15
Ethnicity		0.18		0.052
Asian	1		1	
Non-Asian	1.98 (0.73-5.39)		3.0 (0.99-9.22)	
Baseline ALT		0.1		0.02
≤40	1		1	
>40	1.88 (0.89-3.96)		2.63 (1.14-6.10)	

Abbreviation: CI, confidence interval.

significance. We are unaware of prior studies linking ethnicity to HBV or HCV dominance in the setting of dual infection. In the current study, HBV-monoinfected patients had a lower mean ALT level at baseline than did dual-infected patients, and the ALT level stayed lower over the course of follow-up. This difference was small and likely not clinically important. In fact, the proportion of patients with an ALT level >40 U/L in both groups at baseline and during follow-up was similar.

The findings of the current study support the literature that suggests dual-infected patients often have a disease course characterized by dominance of one virus over the other (i.e., either HBV over HCV or HCV over HBV).[19,24,28-30] In contrast to other studies, the dual-infected patients in the current study did not have increased rates of advanced liver disease or HCC compared with their HBV-monoinfected counterparts.[8-10,23,29,30,31-33] In fact, a recent systematic review and meta-analysis suggested that HBV/HCV dual infection is not an increased risk for HCC compared with HBV or HCV monoinfection.[34] However, our median follow-up for each group was only 38 months for the HBV-monoinfected patients and 33 months for the HBV/HCV dual-infected patients, making any comparisons between groups with respect to end-stage liver disease and HCC either premature or beyond the scope of this study.

This study is not without its limitations. There is evidence that genotype distribution, and as a corollary, country of origin may predict natural history and clinical outcome of HBV-monoinfected patients.[35-38] Unfortunately, HBV and HCV genotype and mutation data, as well as histological data, were only available in a minority of our patients, limiting our observations in this regard. Furthermore, we compared patients with HBV/HCV dual infection with patients with HBV monoinfection but not HCV monoinfection. The study design was based in part on the relative lack of comparative studies of dual infection with HBV monoinfection. The 15-year period of study may introduce some variability in the data interpretation based on the number of hepatologists and gastroenterologists involved in the care of these patients and the different generations of HBV DNA and HCV RNA assays used over this time interval. Although it is likely that different types of molecular tests with varying sensitivities were used over the course of the study period, it is unlikely these methodological differences would have led to significant variation in levels of viremia in most cases. The viral dominance pattern in the vast majority (≈80%) of study cases was fairly clear in which one virus was completely undetectable and was therefore less likely to be affected by variations produced by such factors. Finally, the number of non-Asian patients in the case group was few, and subsequently so was their ethnicity-matched control group (≈20% of the study population). Nevertheless, they were among the consecutive patients who met our inclusion and exclusion criteria during the specified study period.

Additionally, the dual-infected patients did not differ significantly from the monoinfected patients in proportion of patients with elevated ALT at either mildly elevated or higher levels of aminotransferases. One potential explanation for this is that in our study population, the vast majority of HBV/HCV dual-infected patients have one virus dominating the viral profile, either HBV over HCV or HCV over HBV. Because only 22% of the dual-infected patients have positive viral load results for both viruses at the time of presentation, their clinical course may more closely reflect their monoinfected counterparts.

HBV/HCV dual infection is not uncommon, particularly among populations in which HBV is endemic and may in fact be underestimated due to the existence of both occult dual infection and viral dominance patterns that may hinder detection.[3] Our findings suggest that ethnicity may predict for the dual infection viral dominance profile—specifically, that Asian ethnicity is an independent predictor for HBV-dominated dual infection. Further studies are needed to characterize HBV/HCV dual infection and the effect of viral dominance on dual infection.

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