Racial Differences in the Progression to Cirrhosis and Hepatocellular Carcinoma in HCV-Infected Veterans

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OBJECTIVES: **The race of patients infected with hepatitis C virus (HCV) in the United States may be associated with the risk for cirrhosis and hepatocellular carcinoma (HCC). However, previous studies are too small to provide convincing data regarding the effect of race on cirrhosis and HCC risk after accounting for demographic, clinical, and virological factors.**

METHODS: **We used the Veterans Administration (VA) HCV Clinical Case Registry to identify patients with confirmed viremia between 2000 and 2009 and with at least 1 year of follow-up in the VA. We identified cirrhosis and HCC cases through early 2010. Cox proportional hazard regression models were performed to examine the effect of race on the risk for cirrhosis and HCC while adjusting for patients' age, gender, period of service (World War I/II, Vietnam era, post-Vietnam era), HIV coinfection, HBV coinfection, alcohol abuse, diabetes, body mass index, and antiviral treatment receipt and response.**

RESULTS: **There were 149,407 patients with active HCV viremia. Of them, 56.3% were non-Hispanic White (NHW), 36.1% were African American (AA), 6.0% were Hispanic, and 1.6% belonged to other racial groups. After an average follow-up of 5.2 years, 13,099 patients were seen to have a recorded diagnosis of cirrhosis and 3,551 had HCC. Hispanics had the highest annual incidence rates of cirrhosis and HCC (28.8 and 7.8%, respectively), whereas AAs had the lowest rates (13.3% and 3.9%, respectively) compared with NHWs (21.6 and 4.7%, respectively). There were differences among NHW, AA, and Hispanic patients in the rates of HIV infection (2.1, 2.5, and 6.0%, respectively), HCV genotype 1 (50.0, 50.6, and 64.2%, respectively), obesity (28.0, 25.4, and 30.9%, respectively), diabetes (8.7, 16.1, and 16.1%, respectively), and absence of antiviral treatment (81.1, 89.6, and 82.1%, respectively). However, adjusting for differences in demographic and clinical factors did not change the magnitude or direction of the race effect. Compared with NHWs, Hispanic patients had a higher risk of having cirrhosis recorded (adjusted hazard ratio (HR) = 1.28, 95% confidence interval (CI) = 1.21–1.37) and HCC (1.61, 95% CI = 1.44–1.80). In contrast, AAs had a lower risk of cirrhosis (HR = 0.58, 95% CI = 0.55–0.60) and HCC (0.77, 95% CI = 0.71–0.83) compared with NHWs.**

CONCLUSIONS: **Hispanics with HCV are at a significantly higher risk, whereas AAs are at a considerably lower risk of developing cirrhosis and HCC than are NHWs. These associations persisted even after adjusting for a range of factors including HCV genotype, HCV treatment, diabetes, and body mass index.**

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INTRODUCTION

There are remarkable racial and ethnic variations in several aspects of the epidemiology and clinical course of hepatitis C virus (HCV) infection in the United States. For example, population-based studies (e.g., The National Health and Nutrition Examination Survey (NHANES)) reported that the prevalence of HCV is higher in African Americans (AAs) than in Whites (3.2 vs. 1.5%, respectively), with AAs comprising approximately 22% of all HCV cases in the United States. The NHANES study also revealed a higher rate of chronic (vs. resolved) infection in

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AAs compared with Whites with HCV (86 vs. 68%; $P=0.02$). Other studies reported that AAs with HCV have a greater prevalence than do Whites with HCV genotype 1, and a higher prevalence of the TT interleukin 28B (IL28B) host genotype that is associated with lower rates of spontaneous viral clearance and sustained virological response following antiviral treatment.

In addition, the progression of liver disease among HCV-infected patients may differ among racial groups, although the magnitude and direction of these differences are unclear. Several (1–4) cross-sectional or case–control studies reported that HCV-infected AAs have significantly lower risk of cirrhosis and fibrosis progression compared with Whites. However, this finding has not been consistently found (5,6). Conversely, AAs with HCV and already established cirrhosis were reported in a few studies to have a twofold increased risk of developing hepatocellular carcinoma (HCC) compared with Whites (7). Studies have also reported that Hispanics with non-alcoholic fatty liver disease have disproportionately more advanced fibrosis, cirrhosis, or HCC compared with Whites. However, whether Hispanics with HCV have a different risk of advanced liver disease compared with other racial/ethnic groups (8–15) is unclear.

Longitudinal "cohort" studies including large multiracial groups of patients with well-defined HCV status and long-term follow-up data would be ideal to evaluate racial differences in the natural history of HCV infection. However, there is only one published US-based multicenter cohort study that followed up patients with HCV cirrhosis or advanced fibrosis and found a higher risk of progression to HCC in AAs than in Whites while adjusting for other demographic, clinical, and virological factors (16). However, this study is limited by the small numbers of patients who developed HCC during follow-up and included a few Hispanic patients to reliably estimate HCC risk in this subgroup.

More data from cohort studies are required to understand the magnitude and direction of differences in disease progression to cirrhosis or HCC, if any, between the various ethnic and racial groups infected with HCV in the United States. Information about racial differences in risk of cirrhosis or HCC is important for providing evidence-based prognosis estimates that are used for counseling patients regarding the intensity of follow-up visits. This information can also guide further examination of genetic and non-genetic explanations of ethnic and racial differences in disease severity (17). For example, the discovery of the IL28B polymorphism is a powerful genetic explanation of an important epidemiological observation, but this polymorphism has not been consistently implicated in HCV disease progression beyond affecting response to treatment or spontaneous viral clearance (18).

Therefore, we conducted a retrospective cohort study of 149,407 multiracial US veterans with confirmed chronic HCV infection and an average follow-up of 5.2 years to examine the differences between AA, Hispanics, and non-Hispanic Whites (NHWs) in the risk of progression to cirrhosis and HCC.

METHODS

Data sources

This study was approved by Baylor College of Medicine's Institutional Review Board and all procedures conformed to the ethical guidelines of the 1975 Declaration of Helsinki. We used data from the Veterans Administration (VA) HCV Clinical Case Registry (CCR), which contains health information of all known HCV-infected patients from 128 VA facilities nationwide. The CCR automatically identifies patients with positive HCV antibody tests as well as HCV-related ICD-9 codes. Data elements in the CCR include demographics, laboratory test results, outpatient and inpatient VA pharmacy data, and inpatient and outpatient diagnoses codes. Additional details of the CCR data are published elsewhere (19). We examined data sets obtained from the VA HCV CCR database for patients diagnosed with HCV in the VA between 1 October 1999 and 1 January 2010. For patients with missing race/ethnicity, we linked the CCR to the VA Patient Treatment File and the Outpatient Care File to identify additional race/ethnicity information.

Study population

To be included in the study cohort, patients had to have at least one positive HCV RNA test, at least one visit to a VA facility, an HCV index date between VA fiscal year 2000 and 2009, and at least 1 year of follow-up in the VA. The index date for HCV diagnosis reflected the date of the earliest positive HCV RNA test.

Study exposure

We identified and categorized the self-reported race/ethnicity from two variables (race and ethnicity) in the data set into four groups: NHW, AA, Hispanic, or other race. NHWs were defined as those of Caucasian race who were not of Hispanic ethnicity, whereas Hispanics were those with Hispanic ethnicity irrespective of race. We classified non-Hispanic patients with Black or African American race as AAs. We excluded patients without a documented race ($n=12,470$) from the analysis.

Study outcomes

Primary outcomes of interest were cirrhosis and HCC defined as the presence of ICD-9 codes for each condition (cirrhosis: 571.2, 571.5, and 571.6; and HCC: 155.0 and absent 155.1). Both of these definitions have been validated against detailed chart reviews and shown to have high positive predictive values in previous studies (20,21). Prevalent or coexisting cases of cirrhosis or HCC were defined as those recorded in the 3 years before up to 1 year after the HCV index date. Incident or newly diagnosed cirrhosis or HCC was defined as any cirrhosis or HCC present any time after 1 year of the HCV index date. The study follow-up ended at the time of diagnosis of HCC, patient's death, last visit as recorded in the VA, or 1 January 2010.

We also examined additional definitions of cirrhosis in sensitivity analyses. We defined cirrhosis on the basis of aspartate aminotransferase to platelet ratio index (APRI) ≥2 and on the

basis of diagnostic codes for hepatic decompensation (varices, encephalopathy, ascites). For APRI, we extracted lab data on platelets and alanine aminotransferase, and calculated APRI value on the basis of aspartate aminotransferase and platelet test results that were closest to the HCV index date (22). Where possible, we used the values from tests that were performed the same day. In the absence of concurrent testing, we combined information from the nearest available tests within 1 year of each other. The baseline APRI information was available for 92.1% of the current study population.

Potential confounders

We identified several potential confounders for the association between race and cirrhosis or HCC. These included age at the time of HCV diagnosis, gender, period of service (World War I/II, Vietnam era, post-Vietnam era), year of HCV diagnosis, HCV genotype, diabetes, alcohol abuse, body mass index, HIV coinfection, HBV coinfection, and receipt and success of antiviral treatment. We identified HIV, diabetes, and alcohol abuse by the presence of outpatient or inpatient ICD-9 diagnosis codes recorded 1 year before or after the HCV index date. We defined HBV coinfection by positive HBV surface antigen test. We used body mass index closest to the HCV index date and categorized it as <18.5, 18.5–24.9, 25.0–29.9, or ≥30. We defined antiviral treatment as at least two filled prescriptions (within 65 days) of any interferon and one filled prescription of ribavirin any time after the HCV index date, and sustained virologic response as all RNA tests being negative after treatment completion with one being recorded at least 12 weeks after treatment completion (23).

Data analysis

For the incidence estimates, we calculated incidence rates per 1,000 person-years (PY) for newly diagnosed cases of cirrhosis by racial groups after excluding prevalent cases of cirrhosis and HCC, and for newly diagnosed HCC after excluding patients who had a prevalent diagnosis of HCC. We generated Kaplan–Meier curves to illustrate and compare the cumulative incidence rates of cirrhosis and HCC in the racial groups beginning 12 months after baseline until the end of the follow-up period. We used the log rank test to evaluate the differences among these curves. All potential confounders defined above were compared across racial/ethnic groups, and chi-squared tests were used to assess significance for categorical variables, whereas the analysis of variance F-test was used for continuous variables. We then compared risk for cirrhosis and HCC between the racial groups using Cox proportional hazard regression, adjusting for era of military service (pre-Vietnam, Vietnam, post-Vietnam), number of inpatient and outpatient visits prior to baseline (a measure of use of VA medical services), and specific potential confounders defined above. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated.

For the prevalence estimates, we calculated the proportions (and their accompanying 95% CIs) of patients with prevalent cirrhosis and HCC for each racial group. We used two separate logistic regression analyses to examine the association between race and each of prevalent cirrhosis and HCC while adjusting for potential confounders described above. Odds ratios (ORs) and 95% CIs were calculated.

To examine the robustness of the findings, we conducted several sensitivity analyses. First, for the HCC incidence analysis we conducted several analyses stratified by age (50 or younger and >50), presence or absence of diabetes, and HCV genotype (genotype 1 or 3). Second, and in order to examine racial differences in HCC among patients with a somewhat uniform risk for HCC, we constructed regression models to examine the incidence of HCC among the subgroup of patients with prevalent cirrhosis. Third, and in order to evaluate for possible incidence/prevalence bias where racial imbalance among the excluded prevalent cases would lead to spurious racial differences in incidence cases, we repeated the regression analyses including all cirrhosis or HCC events following the HCV index date (i.e., post-baseline HCV RNA) and not just those that occurred after the first 12 months of follow-up as in the primary analyses. Fourth, we defined prevalent cirrhosis by the presence of cirrhosis ICD-9 codes and/or an APRI ≥ 2.0. Fifth, we defined incident cirrhosis by the presence of cirrhosis ICD-9 codes, APRI≥2, or hepatic decompensation. Finally, given that HCV infection affects certain birth cohorts and that these cohorts may differ among the different racial groups, we adjusted for birth year (instead of age at first HCV RNA).

Analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

The study cohort included 149,407 patients with HCV (**Table 1**) who were followed up for a mean duration of 5. 2 years (s.d. 2.5 years). The mean age was 52.5 years (s.d. 7.5 years) and almost all (97.2%) were male. Most patients were Vietnam era veterans (75.8%). Approximately 11.9% had diabetes, 27.3% had body mass index > 30, 53.1% had a diagnosis of alcohol abuse, and 4.3% had HIV coinfection. A total of 15.7% received antiviral treatment and only 5.1% achieved sustained virologic response.

A total of 84,065 (51.9%) patients were NHW, whereas 53,982 (33.4%) were AA, 8925 (5.5%) were Hispanic, and 1.5% patients belonged to other races (including 0.2% Asians). There were significant demographic and clinical differences among these racial groups (**Table 1**). Notably, AAs had significantly higher proportions of obesity, alcohol abuse, diabetes, and HCV genotype 1 and lower proportion of HCV genotype 3 and HCV antiviral treatment than did NHWs. On the other hand, Hispanics had greater proportions of diabetes, alcohol abuse, obesity, and HIV than did NHWs. A total of 29,266 patients (19.6%) had APRI≥2 within 1 year of the HCV index date.

Association between race and risk of incident cirrhosis and HCC

After an overall follow-up of 772,492 PY in 149,407 patients, 13,099 (8.7%) patients were seen to have a recorded diagnosis of cirrhosis for an incidence rate of 16.9 per 1,000 PY, and 3,551 (2.4%) patients developed HCC for an incidence rate of 4.6 per

Table 1. Demographic and clinical features of several racial groups of patients with hepatitis C virus (HCV) infection

Variables	Non-Hispanic Whites	African Americans	Hispanics	Other	*P* value
	84,065	53,982	8,925	2,435	
Demographics					
Age in years mean (s.d.)	52.3 (7.9)	52.8 (6.9)	52.3 (7.7)	52.5 (7.9)	<0.0001
Male gender, (%)	81,484 (96.9)	52,532 (97.3)	8,791 (98.5)	2,340 (96.1)	<0.0001
Period of service (%)					
World War I/II	5,701 (6.8)	3,229 (6.0)	636 (7.1)	169 (6.9)	<0.0001
Vietnam	58,138 (69.2)	37,875 (70.2)	5,907 (66.2)	1,628 (66.9)	
Post-Vietnam	20,226 (24.1)	12,878 (23.9)	2,382 (26.69)	638 (26.2)	
Years of birth (%)					
1900–1940	6,171 (7.3)	3,486 (6.4)	689 (7.7)	206 (8.5)	<0.001
1941–1950	30,394 (36.2)	20,661 (38.3)	3,286 (36.8)	875 (35.9)	
1951–1960	41,699 (49.6)	27,948 (51.8)	4,364 (48.9)	1,205 (49.5)	
1961–1987	5,801 (6.9)	1,887 (3.5)	586 (6.6)	149 (6.1)	
Clinical (%)					
Years of HCV diagnosis					
2000–2002	30,867 (36.7)	191,211 (35.6)	3,515 (39.4)	879 (36.1)	<0.0001
2003–2005	31,637 (37.6)	20,887 (38.7)	3,321 (37.2)	945 (38.8)	
2006–2009	21,561 (25.7)	13,884 (25.7)	2,089 (23.4)	611 (25.1)	
Diabetes	7,306 (8.7)	8,665 (16.1)	1,434 (16.1)	310 (12.7)	<0.0001
Alcohol abuse	41,638 (49.5)	31,969 (59.2)	4,496 (50.4)	1,180 (48.5)	<0.0001
HIV coinfection	1,794 (2.1)	4031 (2.5)	533 (6.0)	53 (2.2)	<0.0001
HBV coinfection	1,021 (1.2)	812 (1.5)	94 (1.1)	23 (0.9)	<0.001
Body mass index					
Less than 18.5	1,124 (1.3)	1,109 (2.1)	95 (1.1)	29 (1.2)	<0.0001
18.5–24	26,301 (31.3)	18,819 (34.9)	2,395 (26.8)	693 (28.5)	
25.0–29.9	32,740 (39.0)	20,095 (37.2)	3,642 (40.8)	951 (39.1)	
30 or higher	23,521 (28.0)	13,714 (25.4)	2,753 (30.9)	752 (30.9)	
Missing	379 (0.5)	245 (0.5)	40 (0.5)	10 (0.4)	
HCV genotype					
1	42,027 (50.0)	34,647 (64.2)	4,518 (50.6)	1,302 (53.5)	<0.001
2	9,402 (11.2)	1,319 (2.4)	1,002 (11.2)	241 (9.9)	
3	6,354 (7.6)	441 (0.8)	620 (7.0)	163 (6.7)	
4	484 (0.6)	403 (0.8)	102 (1.1)	14 (0.6)	
5/6	15 (0.0)	12 (0.0)	2 (0.0)	2 (0.1)	
Unknown	25,783 (30.7)	17,160 (31.8)	2,681 (30.0)	713 (29.3)	
Antiviral treatment					
No treatment	68,148 (81.1)	48,375 (89.6)	7,327 (82.1)	2,025 (83.2)	<0.0001
Sustained response	5,823 (6.9)	1,103 (2.0)	510 (5.7)	141 (5.8)	
No response	5,541 (6.6)	2,513 (4.7)	568 (6.4)	145 (6.0)	
Undeterminable	4,553 (5.4)	1,991 (3.7)	520 (5.8)	124 (5.1)	

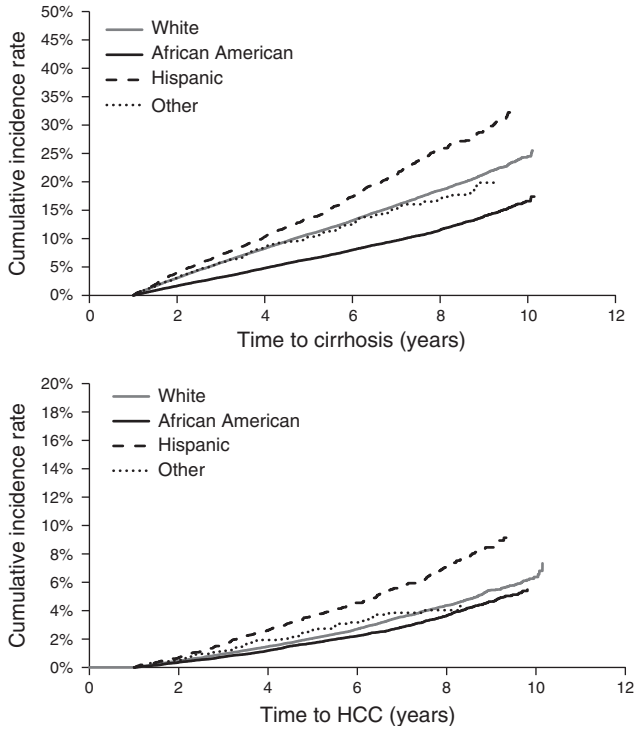

Figure 1. Cumulative incidence of cirrhosis (**a**) and hepatocellular cancer (HCC, **b**) in non-Hispanic White, African Americans, and Hispanic patients.

1,000 PY. The incidence rate of HCC was 20.1 and 19.1 per 1,000 PY in patients with all cirrhosis and prevalent cirrhosis, respectively.

The incidence rate of cirrhosis was highest in Hispanics (28.8/1,000 PY, 95% CI = 27.2–30.5) followed by NHWs (21.6/1,000 PY, 95% CI = 21.1–22.0), and the lowest in AAs (13.3/1,000 PY, 95% CI = 12.8–13.7). Similarly, the incidence rates for HCC were highest in Hispanics (7.8/1,000 PY, 95% CI = 7.0–8.6), followed by NHWs (4.7/1,000 PY, 95% CI = 4.5–4.9), and lowest in AAs with a rate of 3.9/1,000 PY (95% CI = 3.7–4.1).

Figure 1a,b display the cumulative incidence of cirrhosis and HCC, respectively stratified by race. Risk of having cirrhosis or HCC recorded was significantly different by racial group (log-rank test *P* value < 0.0001). The rates were consistently highest among Hispanics, followed by NHWs and lowest in AAs. In univariate Cox analyses, and similar to the Kaplan–Meier analysis, Hispanic race was associated with a higher risk for cirrhosis (unadjusted HR = 1.33, 95% CI = 1.25–1.41) and HCC (unadjusted HR = 1.64, 95% CI = 1.47–1.84) compared with NHW. In contrast, AAs had a significantly lower risk for cirrhosis (unadjusted HR, HR = 0.61, 95% CI = 0.0.59–0.64) and HCC (unadjusted HR = 0.83, 95% CI = 0.77–0.90) compared with NHWs.

We examined the independent association between race and risk for incident cirrhosis and HCC after adjusting for demographic and clinical factors (**Table 2**). The risk for cirrhosis in Hispanics with HCV was 28% greater (adjusted HR = 1.28, 95% CI = 1.21–1.37), and risk for HCC was 61% greater (adjusted HR = 1.61, 95% CI = 1.44–1.80), compared with NHWs. In contrast, the risks for cirrhosis and HCC were lower in AAs with HCV compared with NHWs, with adjusted HR = 0.58 (95% CI = 0.55–0.61) and 0.77 (95% CI = 0.71–0.83) for cirrhosis and HCC, respectively.

Reclassification of all cirrhosis or HCC events following the HCV index date (and not just those that occurred after the first 12 months of follow-up) as incident cases or using year of birth in lieu of age at diagnosis did not change the direction or magnitude of the race effect above.

The results of stratified analyses based on age, diabetes, and HCV genotype are shown in **Table 3**. AA race was associated with a significantly lower risk for HCC in all subgroup analyses. However, although Hispanic ethnicity was significantly associated with an increased risk for HCC in most subgroups, it was not significant when limited to HCV genotype 3 patients. Limiting the analysis to only patients with prevalent cirrhosis attenuated the associations between race and HCC but did not change the direction or significance of most of these associations. The largest attenuation affected Hispanics, wherein the HR dropped from 1.61 to 1.22 (0.995–1.507).

We found similar racial variations in a sensitivity analysis examining the incidence of cirrhosis defined by a combination of diagnostic codes for cirrhosis or hepatic decompensation or APRI ≥ 2 among 114,858 patients without these conditions at baseline. Compared with NHWs, Hispanics were significantly more likely (adjusted HR 1.22, 1.158–1.276) and AAs less likely (0.51, 0.495–0.524) to have cirrhosis recorded during follow-up.

Association between race and prevalent cirrhosis and HCC

A total of 11,214 (7.5%) and 773 (0.5%) patients had prevalent cirrhosis and HCC. **Table 4** displays the distribution of prevalent cases of cirrhosis and HCC stratified by racial groups. Similar to the results presented above for the incidence of cirrhosis or HCC, AAs with HCV were less likely to have cirrhosis or HCC (unadjusted OR = 0.42, 95% CI = 0.40–0.44 and unadjusted OR = 0.65, 95% CI = 0.55–0.77), whereas Hispanics were more likely (unadjusted OR = 1.17, 95% CI = 1.10–1.25 and unadjusted OR = 2.03, 95% CI = 1.63–2.52) to have prevalent cirrhosis or HCC, respectively, when compared with NHW patients. Adjusting for potential confounders did not change the magnitude or direction of the associations between race and cirrhosis or HCC for AAs and Hispanics (**Table 4**).

We also examined a broader definition of cirrhosis as either cirrhosis or hepatic decompensation codes (as defined above) or APRI≥2. A total of 34,415 (23.0%) patients had either APRI≥2 or cirrhosis diagnosis codes. The racial differences in distribution of APRI≥2 mirrored those of cirrhosis diagnosis. The highest proportion of APRI≥2 or cirrhosis was among Hispanics (30.6%), followed by NHWs (25.5%) and AAs (16.2%; *P* < 0.0001). In the multivariable logistic regression examining the expanded cirrhosis definition as the outcome variable, the adjusted OR for AAs was 0.57 (0.55–0.58), and 1.29 (1.23–1.36) for AAs as compared with NHWs (data not shown).

In the last sensitivity analysis, we repeated the analyses using birth year instead of age at first HCV RNA, and found similar

Table 2. Association between race and risk of incident cirrhosis (column 2) and hepatocellular cancer (HCC, column 3)—results of multivariable Cox regression analyses

Characteristics	Adjusted hazard ratio[a] (95% confidence interval)	
	Incident cirrhosis	Incident HCC
Race		
White	1.0	1.0
African American	0.576 (0.553–0.601)	0.770 (0.713–0.832)
Hispanic	1.283 (1.206–1.365)	1.610 (1.440–1.801)
Others	0.919 (0.807–1.047)	1.005 (0.782–1.292)
Demographics		
Age	1.023 (1.020–1.027)	1.063 (1.056–1.070)
Gender		
Female	1.0	1.0
Male	1.165 (1.034–1.313)	2.925 (1.936–4.419)
Period of service		
World War I/II	1.0	1.0
Vietnam	1.353 (1.226–1.493)	1.376 (1.173–1.614)
Post-Vietnam	1.161 (1.024–1.315)	0.956 (0.767–1.193)
Clinical factors		
Years of HCV diagnosis		
2000–2002	1.0	1.0
2003–2005	1.057 (1.015–1.101)	1.196 (1.104–1.295)
2006–2009	1.295 (1.215–1.380)	1.857 (1.637–2.107)
Diabetes		
No	1.0	1.0
Yes	1.324 (1.259–1.392)	1.400 (1.279–1.533)
Alcohol abuse		
No	1.0	1.0
Yes	1.187 (1.145–1.230)	1.229 (1.146–1.317)
HIV coinfection		
No	1.0	1.0
Yes	1.157 (1.065–1.257)	0.953 (0.802–1.132)
Body mass index (BMI)		
Less than 18.5	1.0	1.0
18.5–24	0.958 (0.815–1.126)	1.185 (0.870–1.612)
25–29	1.056 (0.899–1.240)	1.129 (0.830–1.536)
30 or higher	1.262 (1.074–1.483)	1.165 (0.854–1.588)
HCV genotype		
1	1.0	1.0
2	0.697 (0.652–0.746)	0.559 (0.481–0.650)
3	1.283 (1.201–1.371)	1.789 (1.586–2.018)
4	0.942 (0.771–1.151)	0.997 (0.677–1.468)
5/6	1.951 (0.931–4.089)	1.027 (0.144–7.292)
Antiviral treatment		
No treatment	1.0	1.0
Sustained response	0.752 (0.692–0.818)	0.400 (0.321–0.497)
No response	2.068 (1.968–2.178)	1.336 (1.194–1.495)
Undeterminable	1.554 (1.453–1.662)	0.956 (0.816–1.120)

[a]Adjusted for year of hepatitis C virus (HCV) diagnosis, age, gender, HCV genotype, BMI, alcohol use, HIV, Hep B coinfection, period of service, and HCV treatment response.

associations between race and risk for cirrhosis or HCC. For example, for AAs (vs. NHWs), the adjusted HR for cirrhosis was 0.77 (95% CI = 0.71–0.83) and for HCC the adjusted HR was 0.58 (95% CI = 0.55–0.60).

DISCUSSION

In this large US cohort of patients with HCV, we found that patients' race/ethnicity was independently associated with the risk of having cirrhosis and HCC recorded during follow-up. Specifically, we found that, compared with NHW patients with HCV, the odds of AAs being less likely to develop cirrhosis and HCC were 0.42 and 0.23, respectively. In contrast, Hispanics with HCV had a 28 and 61% increased risk of developing both cirrhosis and HCC, respectively, compared with NHWs. The effect of race persisted after we adjusted for confounders in the multivariable regression analyses and was consistent across several subgroups based on age, HCV genotype, and diabetes.

We considered several possibilities as explanations for the association between race and cirrhosis or HCC in patients with HCV. First, HCV treatment, especially one that results in sustained virologic response, is a known protective factor against the development of cirrhosis or HCC. Indeed, we found that NHWs and Hispanics were significantly more likely to receive and respond to antiviral treatment than were AAs. This therapeutic advantage in NHWs and Hispanics, however, did not counterbalance the observed negative impact of race on cirrhosis and HCC risk. Second, we considered the possibility of an incidence/prevalence bias introduced by our analytical technique where we excluded patients with prevalent cirrhosis or HCC from the main analyses. Specifically, it is possible that differential exclusion of AA patients from the main analysis could have spuriously magnified the inverse association between AA and study endpoints. To explore this possibility, we constructed separate models that examined the association between race and prevalent cirrhosis and HCC and found similar results to those for the incident cases. Third, it is plausible that lower diagnoses of cirrhosis and HCC in AAs reflect lower health-care utilization, resulting in suboptimal workup and evaluation in this subgroup. However, our main findings persisted

Table 3. Association between race and risk of incident hepatocellular cancer in subgroup analyses—table presents adjusted hazard ratios from Cox regression models under various scenarios

Defined subgroup	Adjusted hazard ratio (95% confidence interval)
Patients with prevalent cirrhosis (n=10,758)	
Non-Hispanic White	1.0
African American	0.804 (0.673–0.959)
Hispanic	1.224 (0.995–1.507)
Other	0.978 (0.595–1.608)
Patients with any cirrhosis (n=26,294)	
Non-Hispanic White	1.0
African American	1.095 (1.001–1.199)
Hispanic	1.287 (1.139–1.454)
Other	0.987 (0.736–1.647)
Younger patients (50 years and younger, n=64,858)	
Non-Hispanic White	1.0
African American	0.691 (0.599–0.796)
Hispanic	1.705 (1.407–2.065)
Other	0.808 (0.484–1.348)
Older patients (older than 50 years, n=83,776)	
Non-Hispanic White	1.0
African American	0.797 (0.727–0.873)
Hispanic	1.542 (1.343–1.771)
Other	1.098 (0.823–1.464)
HCV genotype 1 (n=82,108)	
Non-Hispanic White	1.0
African American	0.757 (0.690–0.830)
Hispanic	1.655 (1.428–1.919)
Other	1.138 (0.837–1.549)
HCV genotype 3 (n=7552)	
Non-Hispanic White	1.0
African American	0.493 (0.253–0.961)
Hispanic	1.299 (0.917–1.840)
Other	0.840 (0.393–1.795)
Patients without diabetes (n=131,069)	
Non-Hispanic White	1.0
African American	0.774 (0.711–0.843)
Hispanic	1.626 (1.435–1.843)
Other	0.987 (0.747–1.304)
Patients with diabetes (n=17,565)	
Non-Hispanic White	1.0
African American	0.732 (0.611–0.877)
Hispanic	1.495 (1.157–1.930)
Other	1.020 (0.570–1.825)

Models adjusted for year of hepatitis C virus (HCV) diagnosis, age, gender, HCV genotype, body mass index, alcohol use, HIV, Hep B coinfection, period of service, and HCV treatment response.

despite adjusting for the number of outpatient and inpatient visits in the VA as a surrogate measure of the quantity of health-care utilization. Furthermore, although possible, it is unlikely that racial differences in care may explain the higher risks of cirrhosis and HCC in Hispanic patients with HCV compared with NHWs (24). In fact, racial differences in care are often ameliorated in the VA because of the equal access system that provides care to a racially diverse veteran population without the financial restrictions generally associated with the private sector (25,26). Collectively, these data demonstrate that AAs have lower risk of cirrhosis and HCC in patients with HCV, whereas Hispanics have higher risks of these conditions.

Racial differences in the distribution of genetic and non-genetic risk factors not completely captured by our study may explain some of the observed racial differences in cirrhosis or HCC risk. For example, Hispanics are known to have high rates of fatty liver as well as high prevalence of PNPLA3 polymorphism, both of which may predispose to increased risk for cirrhosis and HCC (27,28); however, we did not have information on the presence or severity of fatty liver or any genetic data. Insulin resistance is also a risk factor for advanced fibrosis, cirrhosis, and HCC (29), and, although we adjusted for diabetes, we did not have information on insulin resistance (e.g., HbA1C or HOMA-IR) in nondiabetics. Furthermore, there are interethnic differences in adipose tissue amount and distribution where AAs may have significantly lower abdominal or visceral adiposity compared with other ethnic groups (30–34). Visceral abdominal adiposity is associated with increased risk for hepatic steatosis and fibrosis in HCV as well as non alcoholic fatty liver disease (30,31,35). We did not have information on the amount and distribution of body fat on patients in this study. Although HIV was more common among Hispanics, and thus may partly explain this group's higher risk for advanced liver disease, the adjusted analyses (for HIV) demonstrated the persistence of racial differences in risk for cirrhosis and HCC. Future studies should consider confirming our findings as well as explaining the racial variation in severity of HCV and non-HCV-related liver disease by addressing some of the risk factors described above.

Our study is limited by the observational retrospective nature of its design. However, this is the most efficient and feasible option because large prospective studies with long-term follow-up are not likely to be conducted because of cost and time constraints. Furthermore, the consistency of our results across several subgroups and in prespecified sensitivity analyses provides further internal validity to the findings. Underrecording of cirrhosis was possible, and this underrecording may have affected one or more racial groups compared with the rest. This likelihood is, however, lower for highly fatal conditions such as HCC. On the basis of known racial discrepancies in care, one would expect AAs and Hispanics to be disproportionately affected by underdiagnosis, and hence some of the observed findings (low rates in AAs) may be partly explained by that, but not the opposite, finding in Hispanics. Furthermore, some veterans in this study may have used non-VA care with the potential for missing information.

Table 4. Racial distribution of prevalent cases of cirrhosis and hepatocellular cancer (HCC) among veteran patients with HCV infection

Race	*N* (%)		Adjusted odds ratio[a] (95% confidence interval)	
	Prevalent cirrhosis	Prevalent HCC (%)	Prevalent cirrhosis	Prevalent HCC
White	7,775 (9.25)	467 (0.56)	1.0	1.0
African American	2,227 (4.13)	195 (0.36)	0.393 (0.374 0.413)	0.586 (0.492 0.697)
Hispanic	1,018 (11.41)	100 (1.12)	1.224 (1.141 1.313)	2.009 (1.613 2.502)
Others	194 (7.97)	11 (0.45)	0.826 (0.711 0.960)	0.790 (0.434 1.441)

[a]Adjusted for year of hepatitis C virus (HCV) diagnosis, age, gender, HCV genotype, body mass index, alcohol use, HIV, Hep B coinfection, period of service, and HCV treatment response.

Our results are derived from known HCV-infected patients who sought care in the VA health-care system, and, although the generalizability of the biologic process of cirrhosis progression probably extends from these veterans to other HCV-infected individuals in the VA, as well as to non-veterans, further research would be needed to confirm that. We are also limited by the ICD-9 coding system's sensitivity and specificity for our outcomes, which may vary between the VA and non-VA practitioners, thus limiting the generalizability of overall rates of cirrhosis and HCC to HCV patients outside of the VA. It is important to distinguish our data on the risk estimates of cirrhosis and HCC from the burden of these diseases. For example, AAs have a higher burden of HCV-related cirrhosis and HCC compared with NHWs because the prevalence of HCV in AAs is more than double that in NHWs. Finally, the increased HCC risk in Hispanics dropped in subgroup analysis limited to HCV genotype 3; although this may reflect the relatively small number of patients in this group, it is possible that steatosis effect related to insulin resistance, which is common in Hispanics, is attenuated in the presence of HCV genotype 3 viral-related steatosis (36).

In summary, patients' race was significantly associated with the risk for cirrhosis and HCC. This association is independent of patients' age, year of birth, or HCV genotype and persisted after adjusting for a range of factors including diabetes, body mass index, and antiviral treatment. These data are relevant to further the understanding of genetic as well as non-genetic differences that may explain the racial variations in the progression of liver disease, and can also guide physicians in counseling patients with HCV regarding the risk of disease progression. We also believe that individual-level clinical data, such as the present degree of hepatic fibrosis, presence of decompensation, and non-hepatic comorbidities, rather than distal events such as time of HCV acquisition or patients' race, should be employed in treatment decision making.

CONFLICT OF INTEREST

Guarantor of the article: Hashem B. El-Serag, MD, MSHS.

Specific author contributions: Hashem El-Serag conceived the research idea, obtained funding for the study, supervised the analyses, and wrote the paper; Duan Zhigang was involved in data-set cleaning, variable definition, and statistical analyses, as well as in the final approval of the manuscript; Fasiha Kanwal participated in the study design, analysis of data, and writing of the paper and approved the final manuscript; Jennifer Kramer participated in the study design, analysis of data, and writing of the paper and approved the final manuscript.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ There are known racial and ethnic variations in the prevalence of hepatitis C virus (HCV), spontaneous clearance, and response to antiviral therapy.
- ✓ There may be racial differences in the severity of HCV-related disease, specifically cirrhosis and hepatocellular carcinoma.
- ✓ Small studies, mostly case–control and cross-sectional studies, reported racial differences among Whites, African Americans, and Hispanics. However, neither the direction nor the magnitude of these differences is known.

WHAT IS NEW HERE

- ✓ We conducted a retrospective cohort study of 149,407 multiracial US veterans with confirmed chronic HCV infection and an average follow-up of 5.2 years.
- ✓ Hispanic patients have a significantly higher risk of developing cirrhosis and hepatocellular carcinoma compared with African Americans and non-Hispanic Whites.
- ✓ African Americans have a significantly lower risk of developing cirrhosis and hepatocellular carcinoma compared with Hispanics and non-Hispanic Whites.
- ✓ These associations persisted even after adjusting for a range of factors including HCV genotype, HCV treatment, diabetes, and body mass index.
- ✓ The reasons for the observed racial differences need to be examined.

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