Published in final edited form as:

Clin Gastroenterol Hepatol. 2008 December ; 6(12): 1403–1411. doi:10.1016/j.cgh.2008.08.006.

Fibrosis Progression in African Americans and Caucasian Americans with Chronic Hepatitis C

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Abstract

Background & Aims—Prior studies suggest the rate of liver fibrosis progression is slower in African-Americans (AA) than Caucasian-Americans (CA) with chronic hepatitis C virus (HCV) infection.

Methods—Using a multi-state Markov model, fibrosis progression was evaluated in a well-characterized cohort of 143 AA and 157 CA adults with untreated chronic HCV genotype 1 infection. In subjects with a history of injection drug use, duration of infection was imputed from a fitted risk model rather than assumed to be the reported first year of use.

Results—The distribution of Ishak fibrosis stages were 0 (8.7%), 1/2 (55.7%), 3/4 (29.3%) and 5/6 (6.3%), and was similar in AA and CA ($p = 0.22$). After adjusting for biopsy adequacy, AA had a 10% lower rate of fibrosis progression than did CA, but the difference was not statistically significant (hazard ratio = 0.90, 95% confidence intervals = 0.72, 1.12). The overall 20-year estimates of probabilities of progression from stage 0 to stages 1/2, 3/4 and 5/6 were 59.3%, 28.8% and 4.7%. The estimated median time from no fibrosis to cirrhosis was 79 years for the entire cohort, and 74 and 83 years for CA and AA, respectively. In 3-variable models including race and biopsy adequacy, the factors significantly associated with fibrosis progression were age when infected, steatosis, ALT level, and necroinflammatory score.

Conclusions—The rates of fibrosis progression were slow and did not appear to differ substantially between AA and CA.

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There are no conflict of interests to disclose.

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INTRODUCTION

Individuals with chronic hepatitis C virus (HCV) infection are at variable risk for developing cirrhosis and liver-related complications. The factors most consistently associated with developing cirrhosis are age, duration of infection, age of onset of infection, heavy use of alcohol, human immunodeficiency virus coinfection, and male sex (1–4). African-American (AA) race has been associated with less severe histological disease and slower rate of progression compared to Caucasian-Americans (CA) in several single center cross-sectional studies (5–7). At apparent odds with these results, however, is the finding that AAs with HCV infection have a higher risk of hepatocellular carcinoma than CAs (8, 9). Virahep-C was a multicenter cohort study designed to identify the potential immunological, genetic, virological and therapeutic factors associated with resistance to peginterferon and ribavirin therapy in treatment-naïve AAs and CAs with HCV genotype 1 infection (10). In the current study, a subset of patients enrolled in the Virahep-C cohort was used to evaluate the association of race with HCV fibrosis progression. This cohort had several advantages over prior published studies, including a geographically diverse U.S. population of untreated HCV-infected patients, a large number of African-American patients, a standardized assessment of disease cofactors, and detailed evaluation of liver histology by one pathologist including assessment of biopsy adequacy.

A second goal of this study was to estimate race-specific rates of fibrosis progression and examine the association of selected covariates with the progression rates. Prior studies estimating fibrosis progression in AAs and CAs used the commonly employed method of dividing the current fibrosis stage by the estimated duration of HCV infection. However, this method has several limitations that may lead to biased estimates of fibrosis progression. First, the exact duration of infection is frequently unknown. For example, HCV-infected persons with a history of injection drug use often have an extended period of risk with multiple exposures to HCV (11–13), whereas others with a single parenteral risk factor for HCV acquisition with a more accurate estimate of date of infection (e.g., those whose only risk factor is blood transfusion or needle stick). In this study, we evaluate the bias related to assuming the time of infection in drug users is the reported first year of use. Actual first year of drug use may be earlier or later. Second, the exact time of entry to a given fibrosis state is unknown, and prior studies assumed entry was at time of biopsy. That assumption leads to an underestimation of progression rates. In this study, the analysis avoids these sources of bias. Third, prior models assumed that the duration of time to change from one fibrosis stage to another was the same, so that the time of progression from stage 0 to 1 was equivalent to the time of change from 3 to 4 (5–7, 14). In the present analysis, a discrete-time multi-state model was used to permit estimation of the rates of progression between states without assuming equal time in each state. The final fitted models are provided as an aid to clinicians in making decisions influenced by the rate of fibrosis progression, such as the timing of HCV treatment and the frequency of liver biopsy in untreated patients,

STUDY METHODS

Study Population

The Virahep-C study cohort included adult patients from 8 clinical centers in the United States who self-identified as either Black/African American or White/Caucasian American. All but 7 patients had a pretreatment liver biopsy within 18 months of the study enrollment and those with cirrhosis or transition to cirrhosis (i.e. Ishak stage 5 or 6) were required to have compensated liver disease and no evidence of hepatocellular carcinoma. Patients with detectable hepatitis B surface antigen, anti-HIV or consuming more than 2 alcoholic beverages per day during the 6 months prior to the screening visit were excluded. There were no exclusion criteria based on aminotransferase levels; patients with normal serum

alanine aminotransferase levels were eligible for enrollment. However, subjects with significant cytopenias (platelet count less than 100,000/mm³ and total white cell count <3.0/mm³) or abnormal indices of liver synthetic function (albumin, prothrombin time and total bilirubin) were excluded. All subjects entering the Virahep-C study signed a written informed consent document approved by the local site Institutional Review Board.

A total of 401 subjects (196 AA and 205 CA) were enrolled and treated in the Virahep-C study. The current study was limited to the 300 (143 AA and 157 CA) Virahep-C participants who reported a known risk factor for HCV infection, had a probable year of onset of infection determined by their physician, and a pretreatment biopsy specimen that was scored for fibrosis. Patients were specifically queried regarding known parenteral risk factors for HCV infection and after review of all the medical information, the principal investigator at each study site provided a “most probable mode of infection” and a “probable year of onset of infection”. Patients who lacked one or more of these assessments (N=101) were excluded from the current analysis.

Histological Methods

Liver biopsy specimens were stained for hematoxylin and eosin, and Masson trichrome, and read under code by one pathologist without knowledge of the subject’s race and other clinical characteristics. Liver biopsy length and width were measured by a hand ruler, and the portal triads counted to assess for biopsy adequacy. Portal triads were categorized as either <11 or ≥11. Width was categorized in 3 groups: < 0.55 mm, 0.55 to 1.1 mm or > 1.1 mm. Histology was graded and staged using the modified hepatitis activity index scoring system (15). The activity was graded for portal inflammation (0 to 4), lobular inflammation and necrosis (0 to 4), bridging necrosis (0 to 6) and periportal inflammation and necrosis (0 to 4), for a total necroinflammatory score ranging from 0 to 18. For the purposes of this analysis, Ishak fibrosis scores were grouped into fibrosis states as follows: none (fibrosis stage 0), portal/periportal (fibrosis stages 1 and 2), bridging (fibrosis stages 3 and 4) or cirrhosis (fibrosis stages 5 and 6). Steatosis was graded on a scale of 0 to 4 based upon the percentage of hepatocytes with fat, with 0 = none, 1 = 5% to <25%, 2 = 25% to <50% 3 = 50% to <75%, and 4 = 75% to 100%.

Statistical Methods

Racial differences in the distributions of continuous baseline laboratory results and demographic factors were tested using Student’s t-test or the Wilcoxon rank sum test. Racial differences in categorical variables were tested using the Pearson chi-square test. For the main analysis of fibrosis progression, the primary predictor variable was race (AA versus CA), with examination of the effects of selected covariates on the estimates of fibrosis progression including estimated age of onset of infection (continuous), alcohol use (ever drinker versus never), risk factor for HCV acquisition (injection drug use versus other parenteral risk factors), sex (male versus female), BMI (less than 25 kg/m² versus at least 25 kg/m² [i.e., overweight]), steatosis (present or absent), and biopsy adequacy (less than 11 versus at least 11 portal triads).

Methods to Estimate Duration of Infection—For patients with a history of blood transfusion, the onset of infection was assumed to be the year of transfusion. For patients with a history of occupational exposure, the onset of infection was assumed to be the first year of a needlestick exposure. For subjects with a history of injection drug use, the time of infection was estimated using a multiple imputation approach. Prior studies had assumed the reported “first year of injection” was the onset of infection, but injection drug users may inaccurately report year of first injection and may acquire HCV infection at any time during the actual period of injection drug use. To reflect the uncertainty in the actual year of

infection, we obtained progression estimates and confidence intervals that account for the uncertainty of unknown infection times by multiple imputations with 10 independent imputations (16). We computed estimated duration of infection for participants whose exposure to HCV was most likely injection drug use by randomly selecting, for each such participant, an age of infection from a distribution of the probability of getting infected at each age given reported age at first injection drug use, sex and race. These probability distributions were obtained from an analysis of the HCV antibody status and risk factor histories of 4600 injection drug users from the San Francisco Urban Health Study {Bacchetti, 2007 #9891}. Randomly selected ages of infection were generated 10 times to create 10 datasets containing estimated ages of infection for the Virahep-C participants whose most likely exposure to HCV was injection drug use. We then analyzed each of the 10 resulting data sets and synthesized the results to obtain the final estimates and confidence intervals (16). Duration of infection was calculated by subtracting the estimated age at infection from age at biopsy.

Methods to Estimate Probability of Fibrosis Progression—A multi-state Markov model was used to study disease progression (17–22). This is a useful way to describe a process in which an individual moves through a series of states over time. In this study, the progression of chronic HCV disease is described by stages of severity defined by Ishak score. The transition intensities between different fibrosis states were determined under the following assumptions: (i) all patients had Ishak fibrosis =0 at the time of HCV infection; (ii) fibrosis state cannot improve over time (all subjects were untreated); and (iii) transition intensities are constant over time (the Markov assumption). Variances of the estimated transition intensities were calculated taking into account the multiple imputations (23). These models estimate the effect of a covariate as a hazard ratio (HR). A HR of 0.90, for example, for AA vs CA means that the rate at which AA's transition is 10% lower than the rate for CA's. The relationship between race and fibrosis progression was examined in both constrained and unconstrained models. In the former, the HR of the transition intensities for race were assumed to be the same for different transitions between states, whereas in the unconstrained models, the hazard ratios for race were allowed to be different for different transitions. Subsequent analyses (Tables 3–5) utilized constrained models. The 5-, 10- and 20-year probabilities of fibrosis progression were calculated from the transition intensities. Covariates, including age of infection, race and biopsy adequacy, were evaluated in the models, and we report their estimated multiplicative effects on the transition intensities as hazard ratios (24).

We computed median time to cirrhosis two ways. The first, more consistent with prior studies, was to calculate the median progression rate (fibrosis state/duration of disease) and invert it (5–7). The second approach used numerical methods to get the median from our model. We generated random individual histories for 10,000 simulated patients assuming exponential distributions with parameters equal to the estimated fibrosis progression rates. This yielded a generated time to transition to the next state for each simulated person. That is, for each of the 10,000 generated observations, time to cirrhosis (T_C) was calculated as $T_{0,12} + T_{12,34} + T_{34,56}$ where $T_{0,12}$ was the time to transition from fibrosis state 0 to 1/2, $T_{12,34}$ was the time to transition from fibrosis state 1–2 to 3–4 and $T_{34,56}$ was the time to transition from fibrosis state 3–4 to 5–6. The median time to cirrhosis was the 50th percentile of the distribution of the 10,000 T_C .

Statistical analyses used msm: Multi-state Markov and hidden Markov models in continuous time. R package version 0.6. (Christopher Jackson, 2005, available at <http://CRAN.R-project.org/>) and SAS 8.02 (Statistical Analysis Software, SAS Institute, Cary NC).

RESULTS

Baseline Characteristics of the Cohort

The clinical and demographic features of the African American (n = 143) and Caucasian American (n = 157) subjects are shown in Table 1. The groups were comparable in age, sex, alcohol use, adequacy of liver biopsy, presumed sources of hepatitis C, and physician-estimated duration of disease. The physician-estimated age of onset of HCV was significantly older in AAs than CAs. AAs also had a significantly higher body mass index than CAs, but the prevalence of hepatic steatosis was similar. The participants included in this study were similar to Virahep-C participants excluded from this study in terms of age, sex, body mass index, HCV viral load, HCV genotype, risk factors for HCV acquisition (if known) and fibrosis scores (data not shown).

The proportion of patients with Ishak fibrosis stages 0, 1/2, 3/4 and 5/6 were 8.7%, 55.7%, 29.3% and 6.3%, respectively. The distributions of fibrosis scores by racial group were similar, $p = 0.22$ (Figure 1). There were no statistically significant differences in biopsy length, width or number of portal triads in CAs versus AAs (Table 1). To control for inaccuracy in assessing the state of fibrosis related to biopsy adequacy (25–27) all models included number of portal triads (less than 11 versus at least 11). The correlations among length, width, and number of portal triads were high and the models that adjusted for biopsy length or width, respectively, yielded qualitatively the same results (data not shown).

Estimation of Disease Duration

The overall mean duration of HCV infection until biopsy, based on physician assessment, was 23.9 years (median 25 years, IQR 17 to 31 years). The overall mean duration of infection, based upon the estimated probabilities of infection using the multiple imputations method, was 23.5 years (median 24.1, IQR 18 to 29.4 years). Models were fit using these randomly generated, less uncertain, imputed values of duration of infection.

The differences between imputed age of infection and physician-estimated age of infection varied by subject age (Figure 2). For subjects with a physician-estimated age of infection <24 years, imputed ages of infection were older than physician-estimated values in 79% of subjects. For subjects with a physician-estimated age of infection >28 years, imputed ages of infection were younger than physician-estimated values in 86% of subjects. The smallest differences in imputed versus physician-estimated values were seen in subjects in their mid-20s (specifically, ages 24–28 years).

Race and Fibrosis Progression

To determine whether the association of race with fibrosis progression may differ for different fibrosis states, we examined race as a predictor of fibrosis progression in both constrained (Table 2A) and unconstrained models (Table 2B), controlling for biopsy adequacy. In constrained models adjusted for biopsy adequacy, the risk of progression was 10% lower in AA compared with CA but the 95% CI included 1, the value corresponding to equal hazards for AA and CA (HR=0.90, 95% CI 0.72–1.12) (Table 2A). In the unconstrained models controlling for race and biopsy adequacy, the risk of fibrosis progression was slightly higher for AA than CA for the early transition (stage 0 to stage 1/2) and lower in AA than CA for later transitions (stage 1/2 to stage 3/4 and stage 3/4 to stage 5/6) (Table 2B). In all subsequent multivariable analyses, the simplifying assumption that HRs are the same for all transitions (constrained model) was used to reduce the number of parameters to be estimated.

Race-Specific Transition Probabilities for Fibrosis Progression

The 5-year and 20-year transition probabilities for fibrosis progression for AA and CA determined using the constrained model with race and biopsy adequacy are shown in Tables 3A–D. The slightly lower probabilities of progression for AA reflect the overall estimated HR of 0.90. For example, the 5-year probability of a patient with fibrosis stages 1/2 progressing to fibrosis stages 3/4 is 13.8% for AA and 15.2% for CA, and the 20-year probability of a patient with fibrosis stages 3/4 progressing to fibrosis stages 5/6 is 29.0% for AA and 31.8% for CA.

Effect of Covariates on Transition Probabilities

Covariates were examined individually in constrained tri-variable models that included race (CA versus AA) and total portal tracts (less than 11 versus at least 11) (Table 4). Older age when infected, higher steatosis score, higher necroinflammatory score, and higher ALT were significantly ($p < 0.05$) associated with increased probability of fibrosis progression. In all of these tri-variable models, the estimates for race and biopsy adequacy remained similar to those shown in Table 2A.

Comparison of Estimates of Fibrosis Progression Rates Using Transition Probabilities versus Traditional Methods

Figure 3 shows estimated 5- and 20-year transition probabilities in persons with an adequate biopsy. The estimated percentages of individuals without fibrosis (fibrosis stage 0) progressing to bridging fibrosis or cirrhosis (fibrosis stage 5/6) were 0.13% (95% CI: 0.11% – 0.16%) at 5 years and 4.7% (95% CI: 4.0% – 5.4%) at 20 years. The percentages of individuals with mild fibrosis (fibrosis stage 1/2) progressing to bridging fibrosis or cirrhosis (fibrosis stage 5/6) was 0.70% (95% CI: 0.59%–0.81%) at 5 years and 8.7% (95% CI: 7.4%–9.9%) at 20 years. Finally, the percentages of patients with bridging fibrosis (stage 3/4) progressing to cirrhosis (stage 5/6) in 5 and 20 years were 8.8% (95% CI: 7.5%, 10.1%) and 30.7% (95% CI: 26.7%–34.4%), respectively. A likelihood ratio test of whether the transition intensities between states are all equal produced a p -value < 0.0001 .

Using the traditional formula to estimate fibrosis progression (i.e. individual progression rates = fibrosis state/estimated duration of infection) yielded a median estimated rate of progression of 0.056 of our collapsed states per year using physician-estimated age of infection so that the median time from no fibrosis to Ishak state 5/6 (incomplete cirrhosis or cirrhosis) was 54 years. If imputed ages of infection were used, the median time to cirrhosis remained the same. In contrast, using the model-based approach, the median time to cirrhosis was 79 years using clinician estimated age of infection and 78 years using imputed age of infection. The race-specific estimates of median time to cirrhosis from no fibrosis (stage 0), based upon our method of using transition probabilities and imputed age of infection, were 83 years for AA and 74 years for CA.

Discussion

African-Americans had an estimated 10% lower risk of fibrosis progression than did CA, but this difference was not statistically significant. Race-specific fibrosis progression rates for AA and CA, adjusting for biopsy adequacy and the uncertain time of infection were developed. In these models, the probability of progressing from no fibrosis to mild fibrosis (fibrosis stage 0 to 1/2) was the most rapid transition, with subsequent transitions occurring more slowly. These models provide less biased estimates of fibrosis progression than more traditional models and may be useful to clinicians in their discussions with patients regarding prognosis and the need for repeat biopsy or other interventions. Overall, these models show a slower rate of progression than earlier models (14) and are more consistent

with several prospective and retrospective-prospective studies of the natural history of hepatitis C (28–31).

Prior models of fibrosis progression assumed the effect of race on rate of progression was the same for all stages of disease. Our methods permitted estimation of different effects of race on transitions between different fibrosis states. An interesting but not statistically significant trend in the relative risk of fibrosis progression was evident. AA had a 7% higher risk of transition from no fibrosis to portal fibrosis but a 26% and 48% lower risk of transitioning to the two higher states of fibrosis than CA. Overall, however, the rate of progression was slow in both races with an estimated median time to cirrhosis of 74 years and 83 years in CA and AA, respectively. Older age at infection, higher ALT levels, greater necroinflammatory activity, and higher grades of steatosis were associated with more rapid progression of fibrosis.

Prior studies estimating time to cirrhosis computed the average rate of progression of patients within the cohort and then inverted that value to obtain the time to cirrhosis. Technically, this is the harmonic mean of the time to cirrhosis. This measure differs from the arithmetic mean time to cirrhosis, the mean value of the individual times to cirrhosis, and both measures can be distorted by extreme values. For this reason, we used median rather than mean values to calculate the time to cirrhosis. We believe this approach is more useful to clinicians, as the median value is such that half the HCV-infected patients will progress more rapidly than the median value and half will progress more slowly.

Clinicians interpreting these results should bear in mind that they are for people with adequate biopsies. Patients with small biopsies may be in a more advanced stage of the disease than indicated by the biopsy. Also, the results are specific to this sample; see below for discussion of possible biases. Additionally, this cohort only included subjects who were candidates for antiviral treatment and excluded patients with advanced portal hypertension or hypersplenism. Therefore, not surprisingly, the proportion of patients with advanced fibrosis was relatively low. The lower prevalence of advanced fibrosis may have affected the estimates of fibrosis progression for those with more advanced disease.

Previous studies comparing CA and AA failed to adjust for biopsy adequacy (5–7). The importance of biopsy quality in assessing fibrosis progression is highlighted by our study. Recent studies have shown that shorter biopsies (25, 26), of narrower width (26, 32), and with a limited number of portal tracts (26) underestimate both inflammatory and fibrosis scores and thereby, can lead to an underestimation of rates of fibrosis progression. Within the Virahep-C study, we also found that fibrosis scores tended to be lower in biopsies with less than 11, compared to at least 11, portal triads (27). Given the important effect of biopsy adequacy on estimates of fibrosis progression, models failing to assess or control for this bias must be interpreted with caution. We generated estimates of fibrosis progression adjusted for a biopsy of at least 11 portal triads, as this would be predicted to be more reflective of patient's actual fibrosis state.

The duration of HCV infection in patients with chronic disease is frequently unknown. Prior models of fibrosis progression assumed a specific year of onset of infection based upon risk factors, namely the year of blood transfusion or reported first year of injection drug use. Epidemiologic studies indicate a high rate of HCV acquisition during the first year of injection drug use, but more recent studies suggest time to seroconversion can be longer than a year and age is an important determinant of the time to seroconversion (11–13). In addition, treating presumed or imputed dates the same as known dates can lead to exaggeration of the accuracy of resulting estimates. To assess the potential inaccuracy of assuming that HCV infection occurs in the reported first year of drug use, we estimated

HCV infection using a probability model. We found that imputed age of infection based on our probability model was older than the physician-estimated age of infection in younger injection drug users (<24 years), and younger than the physician-estimated age of infection in older users (>28 years). Thus, duration of infection may be over- or underestimated based on the individual's reported year of first use of injection drugs.

The strengths of our study include relatively large numbers of CA and AA from multiple U.S. centers with a broad and representative spectrum of HCV-infected patients. However, since patients in this cohort were, at time of biopsy, previously untreated with interferon or ribavirin, eligible for antiviral therapy, infected with HCV genotype 1, and HIV uninfected, these results are not generalizable to *all* HCV patients. Additionally, patients with cirrhosis and significant portal hypertension or decompensation or those with liver cancer or who had died from complications of cirrhosis were excluded, eliminating the more severe end of the disease spectrum and making our estimates for transition rates to the final state lower than they would otherwise have been. Indeed, only 12% of the subjects in this study had advanced fibrosis (Ishak stages 5 and 6). This small number resulted in greater uncertainty in the estimates of transition to advanced fibrosis states, as evidenced by the wider confidence intervals. On the other hand, patients had to be known to have chronic HCV, which could have preferentially excluded completely asymptomatic patients (33). Application of these models to a larger population-based cohort is needed to further refine the progression estimates. Another potential limitation is the lack of quantitative data on lifetime alcohol intake. Heavy alcohol use, typically at levels of 40–80 gms per day, has been consistently linked with higher risk of advanced liver disease in patients with HCV (1–3). Heavy alcohol use was a contraindication to enrollment in the Virahep-C Study, though prior heavy use was allowed but not measured.

In summary, the estimated rates of fibrosis progression in the HCV-infected persons in this cohort were slow, with the median time to cirrhosis estimated to be 78 years. The differences in rates of fibrosis progression between AA and CA were not statistically significant but ALT activity, age of infection, necroinflammatory scores and steatosis were associated with risk of progression. We provide a model for predicting the risk of fibrosis progression for CA and for AA that may be useful to clinicians, both in discussions regarding prognosis and in guiding the need for repeat liver biopsy and other interventions amongst untreated HCV-infected patients

Acknowledgments

The clinical study was a cooperative agreement funded by the NIDDK and co-funded by the National Center on Minority Health and Health Disparities (NCMHD), with a Cooperative Research and Development Agreement (CRADA) with Roche Laboratories, Inc. Grant numbers: U01DK60329, U01 DK 60340, U01 DK60324, U01 DK60344, U01 DK60327, U01 DK60335, U01 DK60352, U01 DK60342, U01 DK60345, U01 DK60309, U01 DK60346, U01 DK60349, U01 DK60341. Other support: National Center for Research Resources (NCRR) General Clinical Research Centers Program grants: M01 RR00645 (New York Presbyterian), M02 RR000079 (University of California, San Francisco), M01 RR16500 (University of Maryland), M01 RR000042 (University of Michigan), M01 RR00046 (University of North Carolina). The study was also funded by R01 AI069952 from the National Institutes of Health and was supported in part by the Intramural Research Program of the National Cancer Institute.

Abbreviations

HCV	hepatitis C virus
IQR	interquartile range
HR	hazard ratio
CI	confidence interval

Virahep-C The Viral Resistance to Antiviral Therapy of Chronic Hepatitis C

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Appendix

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Figure 1.
The distribution of Ishak fibrosis scores on pre-treatment liver biopsies in African-Americans (N=143) and Caucasian-Americans (N=157) was similar (P=0.22).

Figure 2.

Differences between imputed age of infection (among subjects with injection drug use as risk factor) and physician-estimated age of infection are depicted by the open circles, with the smallest differences among subjects with a physician-estimated age of infection of 24–28 years (bracketed by in the vertical broken lines). The solid line represents the smoothed plot of these differences across clinician-estimated ages.

Figure 3A

Figure 3B

Figure 3.

This figure graphically depicts the overall 5-year (Figure 3A) and 20-year transition (Figure 3B) probabilities for the different states of fibrosis, adjusted for biopsy adequacy. Four states were modeled using Markov methods: F0 = no fibrosis, F1–2 = portal fibrosis, F3–4 = bridging fibrosis, and F5–6 = cirrhosis (including incomplete cirrhosis).

Table 1

Baseline Characteristics of Study Cohort

	Caucasian-Americans (n=157)	African-Americans (n=143)	P-Value
Male	101 (64.3%)	95 (66.4%)	0.70
Female	56 (35.7%)	48 (33.6%)	
Age (yrs) at biopsy			0.32
mean (SD)	46.6 (8.8)	47.9 (6.9)	
median (IQR)	47.0 (42.0,51.0)	48.0 (44.0,51.0)	
Estimated age (yrs) when infected*			0.006
mean (SD)	21.9 (8.5)	24.8 (8.3)	
median (IQR)	20.0 (17.0,25.0)	22.0 (18.0,32.0)	
Estimated duration of infection (yrs)*			0.13
mean (SD)	25.2 (9.8)	24.0 (9.3)	
median (IQR)	26.0 (19.0,32.0)	24.0 (17.0,32.0)	
Risk Factor for Infection			0.15
IDU	97 (61.8%)	82 (57.3%)	
Blood transfusion	42 (26.8%)	33 (23.1%)	
Other parenteral/percutaneous	18 (11.5%)	28 (19.6%)	
BMI (kg/m²)			0.016
<25	46 (29.7%)	25 (17.7%)	
≥25	109 (70.3%)	116 (82.3%)	
HCV RNA (IU/ml)			0.77
≤800,000	47 (29.9%)	45 (31.5%)	
>800,000	110 (70.1%)	98 (68.5%)	
Genotype (%)			0.036
1a	89 (56.7%)	73 (51.1%)	
1b	48 (30.6%)	61 (42.7%)	
1 other[§]	20 (12.7%)	9 (6.3%)	
Alcohol use at time of evaluation			0.46
No	121 (78.6%)	114 (82.0%)	
Yes	33 (21.4%)	25 (18.0%)	
Steatosis			0.22
no steatosis	54 (34.4%)	59 (41.3%)	
any steatosis	103 (65.6%)	84 (58.7%)	
ALT (IU/L)			<0.0001
mean (SD)	110.4 (90.3)	66 (35.1)	

	Caucasian-Americans (n=157)	African-Americans (n=143)	P-Value
median (SD)	75.0 (53.0–139.0)	57.0 (40.0, 82.0)	
Histologic inflammatory score [¶]			
mean (SD)	8.7 (2.8)	8.4 (2.5)	0.29
median (IQR)	9.0 (7.0, 11.0)	8.0 (7.0,10.0)	
Number of total portal areas			
<11	42 (26.8%)	33 (23.1%)	0.46
≥11	115 (73.3%)	110 (76.9%)	
Biopsy Length (mm)			
mean (SD)	15.7 (8.3)	16.9 (9.0)	0.26
median (IQR)	14.0 (9.0,22.5)	15.0 (10.0,22.0)	
Biopsy Width (mm)	n=156	n=142	
<0.55	27 (17.3%)	17 (12.0%)	0.27
0.55–1.1	123 (78.9%)	122 (85.9%)	
>1.1	6 (3.9%)	3 (2.1%)	

* Based on physician's assessment of when infected until age at biopsy

[¶] Sum of portal inflammation, lobular inflammation and necrosis scores

[§] Includes HCV genotype unspecified and mixed 1a/1b

Table 2A

Relationship Between Race and Biopsy Adequacy and Fibrosis Progression (Constrained Model*)

Variable	Univariate		Bivariate	
	HR	95% CI	HR	95% CI
AA vs CA	0.90	0.73, 1.13	0.90	0.72, 1.12
Total Portal Tracts (≥ 11 versus <11)	1.48	1.13, 1.94	1.49	1.14, 1.95

AA: African-American; CA: Caucasian-American; HR: hazard ratio, CI: confidence intervals

* Constrained model assumes the effect of explanatory variables to be the same for fibrosis progression from any state to the next

Univariate results are for race or portal tracts considered separately; bivariate results are for a model with both terms at once. Total portal tracts included to control for bias related to biopsy adequacy.

Table 2BRelationship Between Race and Fibrosis Progression (Unconstrained Model^{1**})

	Univariate [*]		Bivariate [*]	
	HR	95% CI	HR	95% CI
AA versus CA	--	---	--	---
F0-F1/2	1.07	0.77, 1.49	1.07	0.77, 1.50
F1/2-F3/4	0.77	0.51, 1.17	0.74	0.49, 1.13
F3/4-F5/6	0.53	0.18, 1.53	0.52	0.18, 1.49
Total Portal Tracts (≥ 11 versus < 11)	--	---	--	---
F0-F1/2	1.29	0.89, 1.88	1.30	0.89, 1.88
F1/2-F3/4	1.78	1.03, 3.09	1.82	1.05, 3.16
F3/4-F5/6	3.56	0.46, 27.51	3.70	0.48, 28.73

AA: African-American; CA: Caucasian-American

* Univariate results are for race or portal tracts considered separately; bivariate results are for a model with both terms included at once. Total portal tracts is included to control for bias related to biopsy adequacy.

** Unconstrained models assume the effect of explanatory variables could be different for each transition

Table 3A5-Year Transition Probabilities [with 95% Confidence Intervals[†]] for CA with Adequate Biopsy

	Fibrosis 0	Fibrosis 1/2	Fibrosis 3/4	Fibrosis 5/6
Fibrosis 0	0.501 [0.460, 0.523]	0.454 [0.434, 0.489]	0.044 [0.041, 0.051]	0.0015 [0.001, 0.002]
Fibrosis 1/2		0.840 [0.829, 0.851]	0.152 [0.142, 0.163]	0.008 [0.006, 0.009]
Fibrosis 3/4			0.909 [0.895, 0.922]	0.091 [0.078, 0.105]
Fibrosis 5/6				1.000

[†] based on 2.5% and 97.5% percentile interval of 1000 bootstrap replications

Table 3B20-Year Transition Probabilities [with 95% Confidence Intervals[†]] for CA with Adequate Biopsy

	Fibrosis 0	Fibrosis 1/2	Fibrosis 3/4	Fibrosis 5/6
Fibrosis 0	0.063 [0.048, 0.078]	0.582 [0.560, 0.600]	0.303 [0.284, 0.326]	0.052 [0.043, 0.062]
Fibrosis 1/2		0.498 [0.473, 0.525]	0.408 [0.385, 0.431]	0.094 [0.079, 0.107]
Fibrosis 3/4			0.682 [0.645, 0.725]	0.318 [0.275, 0.355]
Fibrosis 5/6				1.000

[†] based on 2.5% and 97.5% percentile interval of 1000 bootstrap replications

Table 3C5-Year Transition Probabilities [with 95% Confidence Intervals[†]] for AA with Adequate Biopsy

	Fibrosis 0	Fibrosis 1/2	Fibrosis 3/4	Fibrosis 5/6
Fibrosis 0	0.538 [0.505, 0.556]	0.424 [0.408, 0.454]	0.037 [0.034, 0.041]	0.001 [0.0009, 0.0014]
Fibrosis 1/2		0.855 [0.845, 0.866]	0.138 [0.128, 0.148]	0.006 [0.005, 0.007]
Fibrosis 3/4			0.918 [0.906, 0.930]	0.082 [0.070, 0.094]
Fibrosis 5/6				1.000

[†] based on 2.5% and 97.5% percentile interval of 1000 bootstrap replications

Table 3D20-Year Transition Probabilities [with 95% Confidence Intervals[†]] for AA with Adequate Biopsy

	Fibrosis 0	Fibrosis 1/2	Fibrosis 3/4	Fibrosis 5/6
Fibrosis 0	0.084 [0.067, 0.098]	0.604 [0.585, 0.624]	0.272 [0.253, 0.293]	0.041 [0.034, 0.048]
Fibrosis 1/2		0.535 [0.511, 0.563]	0.386 [0.362, 0.408]	0.078 [0.066, 0.090]
Fibrosis 3/4			0.710 [0.676, 0.749]	0.290 [0.251, 0.324]
Fibrosis 5/6				1.000

[†] based on 2.5% and 97.5% percentile interval of 1000 bootstrap replications

Table 4

Estimated Associations with Fibrosis Progression, from 3-Predictor Models that Control for Race and Biopsy Adequacy*

Covariates Examined in 3-Variable Models	Hazard Ratio	95% Confidence Interval
Age when infected (continuous, per decade)	1.54	1.32, 1.81
Risk factor for HCV Acquisition (IDU vs non-IDU)	1.10	0.87, 1.38
Alcohol use (ever vs none)	1.12	0.84, 1.49
Sex (male versus female)	1.15	0.90, 1.46
BMI (≤ 25 kg/m ² vs >25 kg/m ²)	1.31	0.99, 1.72
Diabetes	1.42	0.95, 2.14
Smoking (ever vs none)	1.10	0.81, 1.49
Steatosis (continuous)	1.22	1.02, 1.47
Necroinflammatory score (HAI) (continuous)	1.23	1.16, 1.30
ALT (continuous, per 10 IU/L)	1.02	1.004, 1.04

BMI, body mass index; IDU, injection drug use

* 3-variable models were evaluated including race, biopsy adequacy, and each of the variables shown above tested in turn.

Table 5

Comparison of Methods to Estimate Median Time to Cirrhosis

	Median Time to Cirrhosis	
	Clinician Assessed Age at Infection	Imputed Age at Infection
Traditional Method (arithmetic mean of individual fibrosis scores/ duration of infection)	54 years	54 years
Transition Probability - Model Based [†]	79 years	78 years

[†] Based on 3 transitions (F0 to F1–2, F1–2 to F3–4, and F3–4 to F5–6 Ishak score). 10,000 random samples were generated from exponential distributions with the model estimated progression rates for each transition.