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Effects of Ethnicity and Socioeconomic Status on Survival and Severity of Fibrosis in Liver Transplant Recipients With Hepatitis C Virus

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Abstract

The ethnicity and socioeconomic status of the host may affect the progression of hepatitis C virus (HCV). We aimed to compare survival and fibrosis progression in Hispanic white (HW) and non-Hispanic white (NHW) recipients of liver transplantation (LT) with HCV. All HW and NHW patients with HCV who underwent transplantation between January 2000 and December 2007 at 2 centers were retrospectively assessed. The primary outcomes were the time to death, death or graft loss due to HCV, and significant fibrosis [at least stage 2 of 4]. Five hundred eleven patients were studied (159 HW patients and 352 NHW patients), and the baseline demographics were similar for the 2 groups. NHW patients were more likely to be male, to have attended college, and to have private insurance, and they had a higher median household income (MHI). The unadjusted rates of survival (log-rank $P = 0.93$), death or graft loss due to HCV ($P = 0.89$), and significant fibrosis ($P = 0.95$) were similar between groups. In a multivariate analysis controlling for center, age [hazard ratio (HR) per 10 years = 1.43, $P = 0.01$], donor age (HR per 10 years = 1.25, $P = 0.001$), and rejection (HR = 1.47, $P = 0.048$) predicted death, whereas HW ethnicity (HR = 1.06, $P = 0.77$) was significant. Independent not predictors of significant fibrosis were HW ethnicity (HR = 2.42, $P = 0.046$), MHI (HR per \$10,000 = 1.11, $P = 0.01$), donor age (HR per 10 years = 1.13, $P = 0.02$), cold ischemia time (HR = 1.06, $P = 0.03$), and the interaction between ethnicity and MHI (HR = 0.82, $P = 0.03$). In conclusion, there is no difference in post-LT survival or graft loss due to HCV between HW patients and NHW patients. Socioeconomic factors may influence disease severity; this is suggested by our findings of more significant fibrosis in HW patients with a low MHI.

Host race and ethnicity may influence the natural history of a hepatitis C virus (HCV) infection, likely reflecting differences in a combination of biological and social determinants of disease progression and treatment response. It remains unknown, however, what proportion of these findings is due to environmental and/or genetic factors and how ethnicity and socioeconomic status (SES) affect the natural history of HCV after liver transplantation (LT).

Hispanic Americans are currently the largest minority population in the United States,¹ and chronic liver disease is the sixth leading cause of death in this population.² Hispanic

individuals have a higher prevalence of HCV disease than Caucasians (with the incidence increasing rather than declining)³ and perhaps more severe disease as measured by histological inflammation,⁴ liver enzyme elevations,^{5,6} the rate of fibrosis progression,^{4,6-8} and hepatocellular carcinoma (HCC)-related mortality.⁹ In addition, they respond to HCV therapy at a lower rate than non-Hispanic whites (NHWs), and they achieve less histological improvement with therapy.^{6,10,11} Despite this, Hispanic patients are underrepresented in HCV treatment and LT cohorts in comparison with Caucasians.^{12,13}

These natural history studies are largely limited to the extrapolation of disease progression from cross-sectional data, and they generally lack detailed measurements of important confounders, including disease duration, medical comorbidities, SES factors, and definitive determinations of the hepatic fibrosis stage at more than 1 point in time. In comparison with Caucasians, Hispanic patients have higher rates of several comorbid diseases known to contribute to hepatic fibrogenesis and HCV treatment nonresponse; these include hepatic steatosis,⁴ metabolic syndrome or its components,^{4,14} human immunodeficiency virus (HIV) coinfection,¹⁵ and excess alcohol use.¹⁶ In addition, a biological basis for differences in HCV treatment outcomes for Hispanic patients is supported by studies describing relatively high rates of the unfavorable interleukin-28B allele that is associated with lower HCV treatment responses in this population.¹⁷ Although some of the potential confounders that complicate the study of HCV can be more accurately measured or controlled in the LT population, little is known about post-LT outcomes for Hispanic LT recipients.

Many SES factors, such as access to care, income, education level, language barriers, and cultural beliefs, may also affect the time of presentation and the adherence to treatment regimens. However, these factors are very difficult to measure retrospectively in large cohorts and have not been definitively shown to affect the natural history of HCV in the nontransplant setting. In addition, there is evidence both for^{18,19} and against²⁰ the impact of SES variables on LT outcomes.

Therefore, we aimed to assess the association between Hispanic ethnicity and SES parameters and mortality and fibrosis progression in LT recipients with HCV in a retrospective, multicenter cohort with a detailed analysis of demographics, SES factors, medical comorbidities, and serial liver biopsy data.

PATIENTS AND METHODS

Patients

All patients who underwent LT for HCV-related end-stage liver disease at New York–Presbyterian Hospital (NYPH) or University of California San Francisco (UCSF) from 2000 to 2007 were retrospectively assessed. Patients who (1) had an HIV or hepatitis B virus coinfection, (2) had no detectable HCV RNA at the time of LT because of successful treatment or spontaneous clearance and were, therefore, not at risk for recurrent disease, or (3) died or underwent retransplantation within 30 days of LT were excluded. Patients whose race or ethnicity was other than Hispanic white (HW) or NHW were also excluded. Data were collected from the United Network for Organ Sharing (UNOS) database and chart and electronic medical record reviews at each center.

Predictors and Outcomes

The central independent variable that was tested was ethnicity (HW or NHW), which was identified with the UNOS database and was verified with a chart review. The primary outcome was overall time-dependent survival. Secondary outcomes included the development of significant fibrosis and death or graft failure requiring retransplantation due to recurrent HCV disease. Significant fibrosis was defined as at least stage 2 fibrosis on liver

biopsy according to the Scheuer (Batts-Ludwig) staging system (4 stages in all), fibrosing cholestatic hepatitis, or graft loss due to recurrent HCV. Liver biopsy staging was determined by a retrospective review of pathology reports, and biopsies were not restaged for the purposes of this study. Both NYPH and UCSF perform post-LT protocol liver biopsies annually and evaluate abnormal liver tests. Fifty-one patients (10%) with no posttransplant biopsy samples were excluded from the analysis of the fibrosis stage, but they were included in all survival analyses to prevent bias. A sensitivity analysis was performed under the assumption that all patients without biopsy samples either did or did not develop significant fibrosis.

Other independent variables that were tested in univariate and multivariate models included previously identified predictors of post-LT outcomes: the recipient's age and sex, the calculated Model for End-Stage Liver Disease (MELD) score at the time of LT, the presence of HCC on the explant, the donor's age, the cold ischemia time (CIT), the initial calcineurin inhibitor (CNI), the presence of a cytomegalovirus (CMV) infection, and the occurrence of rejection requiring high-dose therapy (an intravenous steroid bolus or a biological agent). In addition, SES factors such as the median household income (MHI), the highest level of education, and the insurance status at the time of LT were tested. The MHI was determined by the zip code at the time of transplantation and by extrapolation of 1999 US census data. The highest level of education and the insurance status at listing were obtained by a UNOS query and were confirmed by chart reviews at each center. Lastly, comorbid illnesses and features of metabolic syndrome [eg, body mass index (BMI) and the presence of diabetes mellitus, hypertension, and hyperlipidemia] at the time of LT and the last follow-up were also evaluated as predictors. All multivariate analyses controlled for center effects.

HCV treatment was defined as the patient receiving any interferon or ribavirin in the posttransplant period. Sustained virological response (SVR) was defined as a persistently undetectable viral load 6 or more months after the discontinuation of HCV antiviral therapy. Because significant fibrosis is a common indication for treatment, antiviral therapy was included as a time-varying predictor of death and graft failure due to advanced HCV and the development of stage 2 fibrosis.

Statistical Considerations

Between groups, continuous variables were compared with rank-sum tests, and categorical variables were compared with chi-square tests. Continuous variables are reported as medians and interquartile ranges (IQRs), which are presented as the difference between the third and first quartiles. Kaplan-Meier survival curves were compared with the log-rank test to evaluate overall time-dependent survival, death and graft loss due to HCV, and significant fibrosis in NHW and HW groups. Cox proportional hazards models were used to test multivariate models in a stepwise fashion. All variables with $P < 0.2$ in the univariate analysis and variables thought to be central to this analysis (eg, ethnicity) were included in the model building. Variables that were no longer significant at $P < 0.05$ or were not essential to the central hypothesis of the analysis were then sequentially eliminated. Prespecified interactions between ethnicity and SES factors, including the MHI, the highest level of education, and the insurance status at the time of transplantation, were also tested.

All analyses were performed with Stata 10.0 (Stata, Inc., College Station, TX). This protocol was approved by the institutional review boards of both NYPH and UCSF.

RESULTS

Five hundred eleven patients were included in the final analysis: 159 HW patients (31%) and 352 NHW patients (69%). Overall, the median age at LT was 54.5 years (IQR = 9.4

years), 73% were male, 79% of those with genotype data available ($n = 285$) had genotype 1 infection, the median laboratory MELD score at the time of transplantation was 19, and 14% received living donor grafts (Table 1). There were no significant differences in BMI, diabetes, laboratory MELD score, serum creatinine, HCC, donor age, CIT, or treated acute cellular rejection between the 2 groups. However, NHW patients were statistically more likely to be older and male, to have attended college, and to have private insurance, and they had a higher MHI than HW recipients. In addition, there was a nonsignificant trend toward higher rates of antiviral treatment and SVR in NHW patients versus HW patients. There were no significant differences between HW and NHW patients in the median (IQR) follow-up times [3.08 (3.89) years versus 3.26 (2.92) years, $P = 0.79$], median (IQR) times to first post-LT liver biopsy [0.36 (1.72) years versus 0.46 (1.93) years, $P = 0.46$] or the median IQR number of post-LT liver biopsies [3 (3) versus 3 (2), $P = 0.15$].

HW and NHW patients had similar overall survival rates (log-rank $P = 0.93$; Table 2 and Fig. 1). For HW and NHW recipients, the 1- (88% and 91%, $P = 0.30$) and 3-year survival rates (81% and 79%, $P = 0.60$) were similar. Recipient age [hazard ratio (HR) per 10 years = 1.34, $P = 0.01$], female sex (HR = 1.49, $P = 0.03$), donor age (HR per 10 years = 1.34, $P = 0.001$), HCV antiviral therapy (HR = 0.57, $P = 0.002$), and cyclosporine as the initial CNI (HR = 1.55, $P = 0.02$) were significant predictors of mortality in the univariate analysis. Controlling for center, the final model included recipient age (HR per 10 years = 1.43, $P = 0.01$), donor age (HR per 10 years = 1.25, $P < 0.001$), and treated acute rejection (HR = 1.47, $P = 0.048$); ethnicity was not statistically significant (HR = 1.06, $P = 0.77$; Table 3). No SES characteristics were significant in univariate or multivariate models, and there were no significant interactions between ethnicity and any SES factor tested. In addition, to control for differences in HW populations between centers, we added an interaction term for ethnicity and center to the model, but it was not statistically significant ($P = 0.85$). The most common causes of death were recurrent HCV and sepsis (Table 2). Recurrent HCC was common in NHW patients but was not found in HW patients.

The time to death or graft failure due to recurrent HCV also did not differ between the HW and NHW recipients (log-rank $P = 0.89$; Table 2). In univariate analyses, female sex (HR = 2.06, $P = 0.01$), donor age (HR per 10 years = 1.51, $P < 0.001$), initial cyclosporine use (HR = 2.7, $P < 0.001$), and CMV infection (HR = 2.20, $P = 0.03$) were predictive of death or graft failure due to HCV. In the final model, which controlled for centers, significant independent predictors included female sex (HR = 2.37, $P = 0.01$), donor age (HR per 10 years = 1.51, $P = 0.001$), and CIT (HR per hour = 1.12, $P = 0.03$), whereas ethnicity (HR = 1.04, $P = 0.92$) was not significant (Table 3). No significant interactions between ethnicity and SES factors or centers ($P = 0.21$) were observed.

Post-LT biopsy data were available for 460 patients (91%) in the cohort: a HW patients (91%) and 316 NHW patients (90%). Overall, the time to significant fibrosis at least stage 2 of 4 did not differ between the HW and NHW groups in the unadjusted analysis (log-rank $P = 0.95$; Table 2). For HW and NHW patients, the 1- (20% and 22%, $P = 0.59$) and 3-year rates of significant fibrosis (57% and 57%, $P = 1.0$) were similar. The only significant predictors of significant fibrosis in the univariate models were donor age (HR per 10 years = 1.18, $P < 0.001$), CMV infection (HR = 1.6, $P = 0.01$), and initial cyclosporine use (HR = 2.15, $P = 0.001$). In the multivariate models, a significant interaction was found between ethnicity and MHI (Table 3 and Fig. 2). Therefore, controlling for center, the final model included HW ethnicity (HR = 2.42, $P = 0.046$), MHI (HR per \$10,000 = 1.11, $P = 0.01$), the interaction term for ethnicity and MHI (HR = 0.82, $P = 0.03$), donor age (HR per 10 years = 1.13, $P = 0.02$), and CIT (HR per hour = 1.06, $P = 0.03$). A graphic interpretation of this interaction between ethnicity and MHI is shown in Fig. 2, which reveals that patients of HW ethnicity with a low MHI experienced more rapid progression to stage 2 fibrosis. No other

interaction terms, including the interaction between ethnicity and center ($P = 0.76$), were significant, and other SES and metabolic syndrome predictors were not significant individually or in multivariate models. In the sensitivity analysis, there were no differences in the overall rates of significant fibrosis between the groups when we assumed that all patients without biopsy samples developed minimal ($P = 0.39$) or significant fibrosis ($P = 0.57$).

DISCUSSION

In this large and detailed multicenter cohort, HW and NHW patients had similar rates of survival and patient/graft loss due to HCV. In addition, SES measures, including insurance and highest education level, were not predictive of overall outcomes in unadjusted or adjusted models. However, although the time to significant fibrosis was similar for the HW and NHW LT recipients overall, HW patients with a low MHI appeared to experience more rapid fibrosis.

Host race and ethnicity have been postulated to influence the natural history of HCV in transplant and nontransplant settings. Hispanic Americans are the largest minority population in the United States,¹ and they have a high incidence and prevalence HCV disease.³ In addition they may suffer from more severe liver disease as measured by liver tests,^{5,6} liver histology,^{4,6-8} and treatment responses.^{6,10,11} Few studies, however, have evaluated the influence of Hispanic ethnicity on HCV recurrence after LT. In the limited previous work including Hispanic ethnicity, there is no evidence that HW patients with all types of liver disease suffer from diminished post-LT survival in comparison with NHW patients.^{13,21} In a disease-specific analysis of the UNOS database, diminished patient and graft survival rates were seen for African American recipients with HCV but not for HW recipients.²² However, this analysis did not have the benefit of the liver biopsy information available for our multicenter cohort and could not, therefore, evaluate fibrosis severity.

Many biological hypotheses for differences in disease progression and treatment response exist; these include the relatively high prevalence of the unfavorable interleukin-28B allele in Hispanic patients¹⁷ and an excess prevalence of hepatic steatosis and metabolic syndrome,^{4,14} HIV coinfection,¹⁵ and alcohol abuse.¹⁶ In contrast to findings in the non-LT setting, medical comorbidities such as the components of metabolic syndrome (individually or in combination) did not significantly affect mortality or fibrosis in our cohort. However, it is possible that this analysis was limited by the complexities of measuring BMI in patients with cirrhosis and by the accuracy of the UNOS database in the reporting of comorbid illnesses. In addition, there are several mechanisms by which race and ethnicity might specifically affect post-LT outcomes. For example, there may be genetic differences in immune function or the pharmacokinetics of immunosuppressant agents that lead to variations in rates of rejection or other immunosuppression-related medical complications.²³⁻²⁵ In our cohort, there were no differences in rates of acute rejection requiring high-dose therapy, but chronic rejection and other immunosuppressive complications were not assessed.

Race and ethnicity in many studies may also be a surrogate for social and cultural factors such as income, access to care, medical literacy, and language barriers. Minority patients may present with more advanced HCV disease,²⁶ have diminished access to antiviral therapy and LT,^{12,23} have different cultural beliefs about organ transplantation,²⁷⁻²⁹ and face physician biases about transplantation in minority patients.³⁰ There are clearly limitations to the evaluation of transplant outcomes with global measures of SES,^{31,32} and attempts to evaluate the effect of SES on post-LT outcomes are hindered by inconsistent definitions and difficulties in achieving complete data in national databases. Yoo and Thuluvath¹⁸

investigated the potential confounding nature of SES; they found that the neighborhood income and the level of education had no impact on mortality in the UNOS data, and African American race remained a risk factor for diminished outcomes when they controlled for income, insurance, education, and other confounders. However, this study did not focus on HCV-positive recipients, biopsy data were not available, and fibrosis outcomes could not be assessed.

In our more detailed cohort, there appeared to be no difference in all-cause or HCV-related mortality or graft loss between HW and NHW patients, even when we adjusted for SES factors such as the insurance status, the highest level of education, and the neighborhood income. However, there did appear to be an interaction between ethnicity and neighborhood income, in that HW patients with low incomes experienced more severe fibrosis. Although this finding must be confirmed in larger prospective studies, we hypothesize that language may play an important role in this interaction, which is perhaps mediated by higher rates of medication noncompliance and chronic rejection and/or lower rates of successful post-LT HCV treatment. In kidney transplantation, there may be differential rates of chronic rejection among ethnic groups,²³ and one could postulate that language barriers play a role in the involuntary medication non-compliance associated with late rejection and diminished outcomes for kidney transplant³³ and LT recipients.³⁴ In addition, in comparison with HW patients, a higher percentage of NHW patients were treated for recurrent HCV in our cohort, although this difference did not reach statistical significance. The English language proficiency of LT recipients and their caregivers and the Spanish language proficiency of the transplant center staff would have been informative and potentially important because these factors are modifiable through interventions at the level of the staff of each center.

The main limitations of this analysis are due to the retrospective nature of the study design. The identification of patient ethnicity was of central importance to this study. In order to have some uniformity in this matter, we elected to use UNOS data, which are entered by the staff at each center, and to confirm this ethnicity assignment through chart reviews. Because these distinctions are difficult to make, especially in the retrospective setting, we thought that using the standardized UNOS definition would lead to the most uniformity and allow comparisons with other transplant outcome literature. It is likely that the HW patients in this study are from various countries of origin in different proportions at each site (one in New York City and the other in San Francisco). Unfortunately, it was not possible to determine the country of origin for each patient, and this may be very important in terms of both genetic polymorphisms and cultural beliefs that affect health care delivery. We attempted to control for the different populations seen at each site by controlling for center in all of our analyses and by evaluating for interactions between centers and ethnicity (which were all nonsignificant). In addition, it was not possible to accurately characterize donor ethnicity in this retrospective cohort. Because there are conflicting data about whether race mismatch affects LT outcomes,^{35,36} this mismatch will be an interesting avenue of future research.

There were several predictor variables that were not available or were not encountered with enough frequency to enter into models, including the pretransplant viral load and the HCV genotype. The interleukin-28B status of donors and recipients has been shown to correlate with post-LT liver tests and treatment responses,^{37,38} but these data were also not available. Furthermore, biopsy samples were not reread by a central pathologist, and this perhaps affected the reliability of fibrosis staging between centers. Also, almost 10% of the patients had no post-LT liver biopsy samples, although sensitivity analyses led to similar overall findings for the groups. Lastly, the relatively short follow-up of this study (median of approximately 3 years) may have limited our ability to detect differences in disease progression in this cohort. Although we used an important surrogate of mortality and graft

loss through our analysis of significant fibrosis, our findings should be verified with more prolonged posttransplant observation.

In conclusion, HCV research in Hispanic patients is essential for elucidating and modifying potential factors affecting disease outcomes. Chronic liver disease is among the leading causes of death for Hispanic Americans,² and with the rapid growth of this segment of our population, a focus on reducing HCV-related morbidity and mortality by increasing rates of HCV treatment before LT, increasing access to LT if end-stage liver disease is present, and optimizing post-LT outcomes should remain a priority.

Abbreviations

BMI	body mass index
CI	confidence interval
CIT	cold ischemia time
CMV	cytomegalovirus
CNI	calcineurin inhibitor
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HW	Hispanic white
IQR	interquartile range
LT	liver transplantation
MELD	Model for End-Stage Liver Disease
MHI	median household income
NHW	non-Hispanic white
NYPH	New York-Presbyterian Hospital
SES	socioeconomic status
SVR	sustained virological response
UCSF	University of California San Francisco
UNOS	United Network for Organ Sharing

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Figure 1.
Cumulative survival by ethnicity.

Figure 2.
Survival free of significant fibrosis by ethnicity and MHI category.

TABLE 1
Patient Characteristics

Variable	HW Patients (n = 159)	NHW Patients (n = 352)	P Value
Male [n (%)]	96 (60.4)	277 (78.7)	<0.001
Age at LT (years) *	52.6 (9.5)	55 (9.0)	0.03
Highest level of education [n (%)] [†]			
Less than high school graduation	84 (66.1)	129 (45.3)	<0.001
High school graduation	37 (29.1)	124 (43.5)	
College/graduate school	6 (4.7)	32 (11.2)	
Insurance status [n (%)] [‡]			
Medicaid	44 (27.7)	37 (10.8)	<0.001
Medicare	22 (13.8)	24 (7.0)	
Private/self-pay	93 (58.5)	283 (82.3)	
Household income (\$) *	37,417 (37,416)	54,780 (25,649)	<0.001
Metabolic factors at LT			
BMI (kg/m ²) *	25.4 (5.7)	26.0 (6.0)	0.36
Diabetes mellitus [n (%)]	39 (24.5)	73 (20.7)	0.33
Hypertension [n (%)]	45 (28.3)	98 (27.8)	0.97
HCC [n (%)]	47 (29.6)	147 (41.8)	0.10
MELD score at LT *	19 (13)	19 (10)	0.44
Serum creatinine at LT (mg/dL) *	1.0 (0.6)	1.1 (0.7)	0.05
Living donor [n (%)]	26 (16.4)	47 (13.4)	0.37
CIT (hours) *	8.5 (3.9)	8.5 (4.1)	0.67
Donor age (years) *	46 (25)	43 (22)	0.36
Acute cellular rejection [n (%)]	33 (20.8)	69 (19.6)	0.76
Tacrolimus as initial CNI [n (%)]	81 (50.9)	194 (55.1)	0.45
HCV antiviral therapy after LT [n (%)]	63 (39.6)	173 (49.1)	0.09
SVR [n (%)]	12 (7.6)	42 (11.9)	0.16
CMV infection [n (%)]	18 (11.3)	37 (10.5)	0.74
Time to first biopsy (years) *	0.36 (1.72)	0.46 (1.93)	0.46
Number of biopsies *	3 (3)	3 (2)	0.15
Follow-up (years) *	3.08 (3.89)	3.26 (2.92)	0.79

* The data are reported as medians and IQRs, which are presented as the difference between the third and first quartiles.

[†] Education data were available for 127 HW patients and 285 NHW patients.

[‡] Insurance status data were available for 159 HW patients and 344 NHW patients.

TABLE 2

Overall Patient Outcomes

Measure	HW Patients (n = 159)	NHW Patients (n = 352)	Log- Rank P Value
Patient survival [n (%)]	117 (74)	265 (75)	0.93
Death or graft failure due to HCV [n (%)]	17 (11)	37 (11)	0.89
Stage 2 or higher fibrosis [n (%)] *	77 (53)	156 (49)	0.95
Cause of death [n (%)]			
Recurrent HCV	13 (31)	25 (29)	
Sepsis	11 (26)	23 (26)	
HCC	0 (0)	13 (15)	
Other	18 (43)	19 (22)	
Unknown	0 (0)	7 (8)	

* Biopsies available for 316 NHW and 144 HW patients.

TABLE 3
Final Multivariate Cox Proportional Hazards Models for Predicting Mortality, Death or Graft Loss Due to HCV, and Significant Fibrosis

Predictor	HR	95% CI	P Value
Mortality			
HW ethnicity	1.06	0.71-1.60	0.77
Age (per 10 years)	1.43	1.09-1.87	0.01
Donor age (per 10 years)	1.25	1.10-1.87	<0.001
Treated acute rejection	1.47	1.01-2.29	0.048
Death or Graft Loss Due to HCV			
HW ethnicity	1.04	0.53-2.05	0.91
Female sex	2.37	1.21-4.64	0.01
Donor age (per 10 years)	1.51	1.19-1.91	0.001
CIT (per hour)	1.12	1.01-1.23	0.03
Significant Fibrosis			
HW ethnicity	2.42	1.01-5.78	0.046
MHI (per \$10,000)	1.11	1.03-1.19	0.01
Ethnicity-MHI interaction	0.82	0.68-0.98	0.03
Donor age (per 10 years)	1.13	1.02-1.25	0.02
CIT (per hour)	1.06	1.01-1.11	0.03

NOTE: The variables evaluated in the univariate and multivariate models included ethnicity, age at transplantation, sex, MHI, highest level of education, insurance status, BMI, diabetes, hypertension, hyperlipidemia, MELD score, donor type, HCC, donor age, CIT, cyclosporine use, post-LT HCV treatment (as a time-varying covariate), CMV treatment, treated acute rejection, and interaction terms (between ethnicity and MHI, highest level of education, insurance status, and center). All multivariate models were controlled for the center.