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Hepatitis C Genotype Influences Post-Liver Transplant Outcomes

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Abstract

Background—In non-transplant patients with chronic hepatitis C virus (HCV), HCV genotype has been linked with a differential response to antiviral therapy, risk of steatosis and fibrosis, as well as all-cause mortality, but the role of HCV genotypes in post-transplant disease progression is less clear.

Methods—Using the multicenter CRUSH-C cohort, genotype-specific rates of advanced fibrosis, HCV-specific graft loss and, response of antiviral therapy were examined.

Results—Among 745 recipients [605 (81%) genotype 1, 53 (7%) genotype 2, and 87 (12%) genotype 3] followed for a median of 3.1 years (range 2.0-8.0) the unadjusted cumulative rate of advanced fibrosis at 3 years was 31%, 19% and 19% for genotypes 1, 2 and 3 (p=0.008). After multivariable adjustment, genotype remained a significant predictor, with genotype 2 having a 66% lower risk (p=0.02) and genotype 3 having a 41% lower risk (p=0.07) of advanced fibrosis compared to genotype 1 patients. The cumulative 5-year rates of HCV-specific graft survival were 84%, 90% and 94% for genotypes 1, 2 and 3, p=0.10. A total of 37% received antiviral therapy, with higher rates of sustained virologic response in patients with genotype 2 (HR=5.10; p=0.003) and genotype 3 (HR=3.27; p=0.006) compared to patients with genotype 1.

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Conclusion—Risk of advanced fibrosis and response to therapy are strongly influenced by genotype. LT recipients with HCV genotype 1 have the highest risk of advanced fibrosis and lowest SVR rate. These findings highlight the need for genotype-specific management strategies.

Keywords

fibrosis progression; recurrence; antiviral treatment; genotype 2; genotype 3

Introduction

In Western world countries, hepatitis C virus (HCV) infection is the most common indication for liver transplantation (LT) (1). In the US, persons born between 1940-1965 have the highest prevalence of HCV and this birth cohort accounted for 81% of all new wait-list registrants with HCV between 1995 and 2010 (2). These “baby boomers” are expected to continue to have a high need for LT over the next decade, with a rising proportion having hepatocellular carcinoma (HCC) as their primary indication for LT (2). Optimizing the post-LT outcomes of patients with HCV remains a critically important goal (3, 4).

Natural history studies in LT recipients with chronic HCV have identified several key risk factors for liver disease progression post-LT, including older donor age, treated acute rejection, African-American recipient race, and donor/recipient interleukin 28B (IL28B) types (5-7). Prior studies in non-transplant patients report an association between HCV genotype and the risk of advanced fibrosis, HCC and all-cause mortality (8-15) but HCV genotype has not been consistently linked with HCV disease outcomes in LT recipients, except in the context of treatment (16). Achievement of a sustained virologic response (SVR) is associated with improved LT survival in HCV recipients (4) and genotype is a strong determinant of SVR (16-20). Prior studies addressing the association between HCV genotype and post-LT outcomes, have largely focused on HCV genotype 1 subtype differences (21, 22), have grouped genotypes 3 and 2 together (23, 24), or had insufficient numbers of non-1 genotypes to perform statistically robust comparisons between genotypes (25). Thus, the role of HCV genotype in the outcomes of LT recipients is incompletely known.

The large U.S. multicenter Consortium to Study Health Outcomes in HCV Liver Transplant Recipients (CRUSH-C) cohort, with representation of all the major HCV genotypes in the U.S., provides an opportunity to evaluate genotype-specific differences in HCV-related outcomes in LT patients. Our results highlight genotype differences in fibrosis progression and response to treatment and suggest the need for genotype-specific algorithms for management of transplant recipients.

Results

Cohort Characteristics

Of the 1364 patients in the CRUSH-C cohort, a total of 745 patients met the inclusion criteria and 690 (93%) had at least one liver biopsy (Supplementary Figure 1). Excluded

patients were similar to included patients except excluded patients were more likely to have CMV infection or died, and less likely to have acute rejection or antiviral therapy (Supplementary Table 1). The study cohort included 605 (81%) with HCV genotype 1, 53 (7%) with HCV genotype 2 and 87 (12%) with HCV genotype 3. The median follow up was 3.1 years (range 2.0-8.0). The characteristics of the transplant cohort and their donors are shown in Table 1. Genotype groups were comparable, except for median age at transplantation, recipient race, donor gender, median warm ischemia time, and length of follow-up.

Genotype and Advanced Disease

Biopsy data were available in 563 (93%) recipients with genotype 1, 45 (85%) for genotype 2 and 82 (94%) for genotype 3 (p=0.08). The median number of biopsies per recipient was 3 (IQR 2-4), without differences among genotype groups (p=0.11). The median time to first biopsy was 4.3, 6.1 and 8.0 months, respectively for recipients with genotype 1, 2 and 3 (p=0.06) with the same proportion in each genotype group having advanced fibrosis at first biopsy (p=0.73). With censoring of patients at the start of antiviral therapy, the unadjusted cumulative rates of advanced disease at 1, 3 and 5 years post-LT were 8%, 31% and 46% for patients with HCV genotype 1 compared with 0%, 19% and 19% for HCV genotype 2 and 2%, 19% and 32% for HCV genotype 3 (log rank=0.008) (Figure 1). After adjustment for covariates associated with fibrosis, compared to genotype 1, HCV genotype 2 (HR=0.34; 95% CI: 0.14-0.84; p=0.02) remained at significantly lower risk of advanced fibrosis and HCV genotype 3 (HR=0.59, 95% CI: 0.33-1.05; p=0.07) was of borderline significance. Other independent predictors of advanced fibrosis were older donor age (HR=1.02; 95% CI: 1.01-1.03; p<0.001), and CMV infection (HR=1.59; 95% CI: 1.01-2.50; p=0.04), whereas older recipient age (HR=0.96; 95% CI: 0.94-0.99; p=0.01), donor African American race (HR=0.57; 95% CI: 0.33-0.98; p=0.04) were protective (Table 2).

To evaluate the effect of antiviral therapy in the fibrosis progression, a sub-analysis that included receipt of post-LT therapy as a covariate was performed. HCV genotype 2 (HR=0.29; 95% CI: 0.12-0.71; p=0.007) and HCV genotype 3 (HR=0.55; 95% CI: 0.33-0.92; p=0.02) had a significantly lower risk of advanced fibrosis compared to HCV genotype 1. Other independent predictors of advanced fibrosis in this analysis were female recipient gender (HR=1.48; 95% CI: 1.07-2.04; p=0.02), older donor age (HR=1.02; 95% CI: 1.01-1.03; p<0.001), and CMV infection (HR=1.68; 95% CI: 1.13-3.52; p=0.01), whereas older recipient age (HR=0.96; 95% CI: 0.94-0.99; p=0.002), donor African American race (HR=0.44; 95% CI: 0.26-0.76; p=0.003) as well as receipt of post-LT antiviral treatment prior to advanced fibrosis (HR=0.56; 95% CI: 0.38-0.83; p=0.003) were protective (Supplementary Table 2).

Genotype and Response to HCV Treatment

A total of 273 (37%) patients received peginterferon-based treatment post-LT: 219 (36%), 19 (36%) and 35 (40%) with HCV genotypes 1, 2 and 3, respectively. Among the patients who were treated, 69% HCV genotype 1 patients, 73% of the HCV genotype 2 patients and 65% of HCV genotype 3 patients received antiviral treatment before the presence of advanced fibrosis (p=0.87). The rate of SVR was 19%, 47% and 40% for patients with HCV

genotype 1, 2 and 3, respectively (p=0.001). In multivariable analysis, HCV genotype 2 (HR=5.10; 95% CI:1.77-14.71; p=0.003) and HCV genotype 3 (HR=3.27; 95% CI: 1.42-7.56; p=0.006) compared to genotype 1, were independently associated with SVR whereas older donor age (HR=0.98; 95% CI: 0.96-0.99; p=0.04), treated acute rejection episodes (HR=0.30; 95% CI: 0.13-0.67; p=0.004) and advanced fibrosis at the time of antiviral treatment (HR=0.35; 95% CI: 0.15-0.83; p=0.02) were negatively associated with SVR (Table 3).

Genotype and Survival

Graft failure occurred in 152 (20%) patients overall, 128 (21%), 11 (21%) and 13 (15%) patients with HCV genotypes 1, 2 and 3, respectively (p=0.40). The unadjusted cumulative rates of overall graft survival at 1, 3 and 5 years post-LT were 95%, 81% and 73% for HCV genotype 1, 98%, 87% and 75% for HCV genotype 2 and 94%, 87% and 87% for HCV genotype 3 infected patients in unadjusted analysis (log rank= 0.35) (Supplementary Figure 2). The cumulative HCV-specific graft survival post-LT did not differ significantly by HCV genotype: 91%, 95% and 96% at 3 years for genotypes 1, 2 and 3, respectively (log rank= 0.10). In adjusted analysis, HCV-specific graft loss was associated with older donor age (HR=1.03, 95% CI: 1.01-1.04; p=0.003) and absence of SVR (HR=0.17, 95% CI: 0.04-0.71; p=0.01).

Death occurred in 137 (18%) patients, HCV-related deaths tended to be more frequent in patients with HCV genotype 1 (n=55, 48%) compared with genotype 3 (n=3, 25%) and 2 (n=3, 27%) and HCC-related deaths tended to be more frequent among HCV genotype 3 infected patients (n=4, 33%) in comparison with genotype 1 (n=10, 9%) and genotype 2 (n=1, 9%), (p=0.06), (Figure 2). The unadjusted cumulative patient survival at 1, 3 and 5 years post-LT were 94%, 84% and 76% for HCV genotype 1, 98%, 87% and 75% for genotype 2 and 95%, 90% and 86% for genotype 3 infected patients (log rank=0.50). In multivariable analysis, recipient African-American race (HR=2.38; 95% CI: 1.30-4.36; p=0.005) and older donor age (HR=1.20; 95% CI: 1.005-1.03; p=0.006) were associated with mortality and achievement of SVR was strongly protective (HR=0.16; 95% CI: 0.04-0.70; p=0.011). HCV genotype was not associated with overall mortality (HR=0.91, 95% CI: 0.45-1.85; p=0.79 for genotype 2 and HR=0.90, 95% CI: 0.46-1.76; p=0.76 for genotype 3). In a sensitivity analysis, expanded to patients with death <30 days, no differences were founded in unadjusted and adjusted analysis regarding HCV genotype (log-rank 0.23).

Discussion

In this large multicenter cohort of HCV-infected transplant recipients, we demonstrate the importance of HCV genotype in post-transplant outcomes. Genotype 1, the most common genotype in the U.S. (26), has the highest risk of advanced fibrosis and the lowest rate of SVR. Rates of advanced fibrosis are similar to previously published studies (27, 28). Uniquely, we found that genotype 2 had the lowest risk of advanced fibrosis and the highest rate of sustained viral clearance and genotype 3 had an intermediate risk of advanced fibrosis and SVR. These genotype differences are relevant in identifying patients for more

intensive monitoring for disease progression post-transplantation and for future preventive and treatment strategies. Specifically, since patients with genotypes 1 and 3 are at higher risk of fibrosis progression, monitoring of disease progression with at least annual biopsy or elastography is critical to assist in determining the optimal timing of HCV treatment. Also, since treatment responses are reduced in patients with advanced fibrosis and those with genotypes 1 and 3, earlier consideration of HCV therapy for these genotypes may be of particular importance.

With the recent approval of sofosbuvir and RBV and increasing off-label use of other antivirals for treatment of post-LT HCV disease, a greater proportion of LT recipients are expected to undergo HCV treatment post-transplant. We confirmed that achievement of SVR was a strong predictor of graft and patient survival and influenced rates of advanced fibrosis progression. As more tolerable therapies become available, more patients can be expected to be treatment-eligible and to achieve sustained viral clearance. However, differences in success of antiviral therapy by genotype are still apparent, even in this new era of HCV treatment. For example, with sofosbuvir-based therapy the highest SVR rates among immunocompetent patients are seen with genotype 2 and lower rates in genotypes 1 and 3. Among LT recipients with compensated recurrent disease, SVR4 rates with 24 weeks treatment with sofosbuvir and ribavirin are 77% overall, but with no data on genotype-specific responses (29). It is likely that genotypic differences in SVR will play an important role in HCV outcomes in LT recipients and more data on genotype-specific responses in the LT population are urgently awaited. Additionally, the impact of these new antiviral therapies in preventing fibrosis progression and graft loss, while expected to be positive, has not been demonstrated (18-20, 29-32), highlighting the need for large cohort studies to assess these “hard” endpoints.

Given the significant effect of HCV genotype on fibrosis progression and SVR rates, it is surprising that the rates of graft loss and mortality did not differ significantly among genotypes. We believe this is likely due to an insufficient duration of follow-up after advanced fibrosis to detect a mortality difference. The median follow-up time after advanced fibrosis was 0.90 years for the entire cohort and 0.84, 1.13 and 1.0 years for genotype 1, 2 and 3 respectively, ($p=0.43$), a duration too short to expect a large proportion of those with advanced fibrosis to experience graft loss.

The main limitation of this study is its retrospective nature, and the lack of detailed data on immunosuppression, donor and recipient IL28B genotypes and HCC characteristics which may further elucidate the causes for the genotype differences identified. However, this is the largest study to address outcomes by genotype and the geographic diversity and representativeness (distribution of genotype 1, 2 and 3) of a US population of LT recipients are particular strengths. Further, recognizing that there may be unmeasured differences between clinical centers, all analyses were adjusted for center effect.

In conclusion, HCV genotype is an important determinant of advanced recurrent HCV disease and achievement of SVR. Our results would support a genotype-specific algorithm for post-LT management, and will be useful as a comparator as we assess new treatment options. In particular, the timing of HCV therapy will likely strongly influence future post-

LT outcomes in HCV-infected patients, and genotypic differences in response to antiviral therapies and risk of progression without successful therapy will be of critical importance.

Patients and Methods

The Strengthening the Report of Observational Studies recommendations for reporting observational Studies (33) were applied.

Patient Population and Variables—All adult patients undergoing primary liver transplant for HCV-related liver disease from March 1, 2002 through December 31, 2007 at five experienced U.S. transplant centers: the University of California-San Francisco, New York Presbyterian Hospital-Columbia, Baylor University Medical Center, the University of Colorado, and Virginia Commonwealth University were included. Patients were excluded if they had negative HCV RNA findings immediately after transplantation in the absence of posttransplant antiviral treatment, graft loss < 90 days as such losses were unlikely to be HCV-related, coinfection with human immunodeficiency virus, receipt of an anti-HCV positive donor, or HCV genotypes other than 1, 2 or 3.

Donor characteristics, warm and cold ischemia times were obtained from the United Network for Organ Sharing/Organ Procurement and Transplantation Network registry. Recipient demographic, virologic, and clinical data, including immunosuppressive medications at last follow-up and HCV treatment, were collected by review of medical records. HCV treatment was defined as receipt of any peginterferon or RBV in the post-transplant period. Although, the timing of treatment initiation was not protocolized, patients generally received HCV treatment for recurrent disease of fibrosis stage ≥F2 or fibrosing cholestatic hepatitis. The achievement of SVR was based on documented undetectable HCV RNA at least 6 months after treatment discontinuation. CMV infection was defined as CMV infection requiring anti-CMV therapy. Acute cellular rejection was defined as biopsy-proven rejection requiring treatment with high-dose bolus corticosteroids or antilymphocyte therapy.

Histological Data—All five centers assessed HCV disease severity using annual liver biopsies. However, annual biopsies were deferred if patients had a recent liver biopsy for cause or if there was a contraindication to liver biopsy. Both protocol and for-cause biopsy data were included in the analyses. Four centers used the Batts-Ludwig staging system to assess fibrosis severity (34), and 1 center used the Ishak staging system (35). For the purposes of this analysis, advanced fibrosis was defined as Batts-Ludwig stage 3-4 or Ishak stage 4-6.

Immunosuppression—Each center used a standard immunosuppression regimen; however, immunosuppression regimens were not uniform among the sites. The immunosuppression-related variables collected were use of tacrolimus versus cyclosporine at last follow-up and use of corticosteroids at last follow-up. None of the sites routinely used induction therapy.

Study Predictors and Endpoints—The primary predictor was recipient HCV genotype. The primary endpoint of the study was advanced recurrent HCV disease, which was defined

as the first date of bridging fibrosis or cirrhosis on biopsy. For the main analysis, patients were censored at the time of initiation of antiviral treatment. The secondary outcome measures were (1) SVR and (2) overall and HCV-specific graft loss, defined as graft loss from cirrhosis-related complications with documented advanced fibrosis; and (3) mortality. Patients without histologic follow-up (n=55) were excluded from the analysis for the primary outcome, but included in the analyses for all other outcomes.

Statistical Analysis—Quantitative variables are presented as medians and interquartile range, and categorical variables as frequency and percentage. Differences between categorical variables were assessed by Chi-square test or Fisher's exact test. Continuous variables were compared using Mann-Whitney test. Any baseline characteristic that was significantly different between the three genotypes groups (1, 2 and 3) was evaluated in the final multivariable models.

Survival rates were computed using Kaplan-Meier methods and compared using log rank test. Univariable Cox proportional hazards analysis was first performed to identify factors independently associated with the outcome of interest. Those variables that yielded a hazard ratio associated with $p < 0.2$ were evaluated in the final multivariable model. Multivariable Cox stepwise regression models were built using backward elimination of variables that were not significantly associated with the outcome of interest using $p < 0.05$ criterion. Clinically relevant interactions were examined. Results are expressed as hazard ratios (HR) with 95% CIs. HCV genotype, the primary predictor of interest, was forced into all models as were variables with well-established associations with the outcome of interest. Post-LT HCV treatment, achievement of SVR, episodes of treated acute rejection, and advanced fibrosis were evaluated as time-varying covariates. Since antiviral therapy may influence fibrosis progression, a sub-analysis was performed in which patients who received antiviral therapy were censored at the time of treatment initiation. Assessment of proportional hazards was performed. All final models were adjusted for the center effect to account for any potential unmeasured center-specific confounders.

Data were analyzed with SPSS software (21.0, SPSS Inc., Chicago IL, USA). The Institutional Review Boards at each center approved this study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

CI	confidence interval
CMV	cytomegalovirus

CRUSH-C	Consortium to Study Health Outcomes in HCV Liver Transplant Recipients
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HR	hazard ratio
IL28B	interleukin 28B
IQR	interquartile range
LT	liver transplantation
RBV	ribavirin
SVR	sustained virologic response

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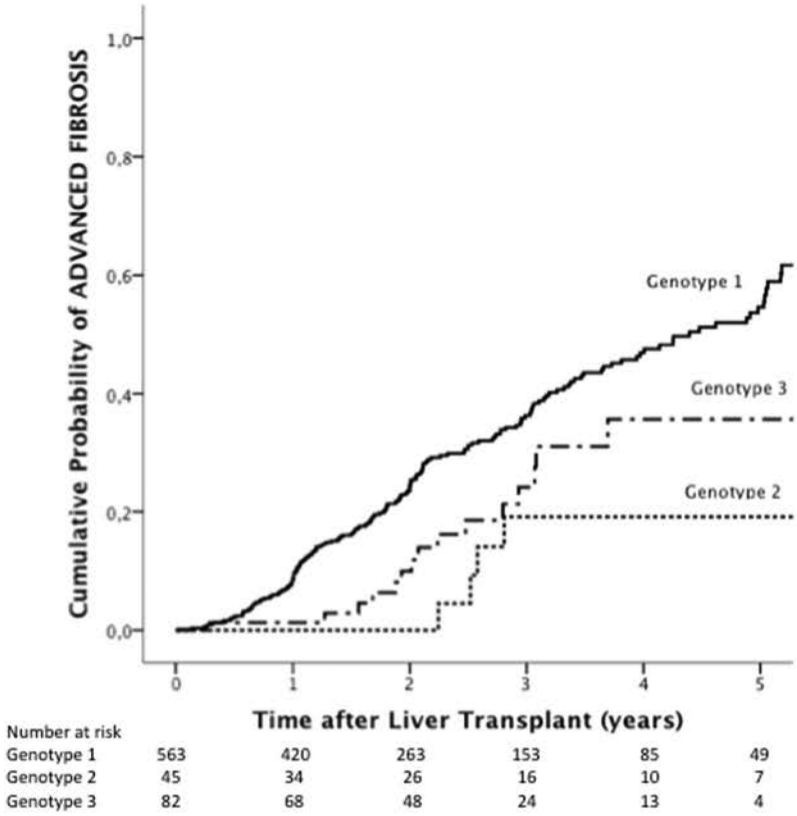

Fig. 1.

Unadjusted Cumulative Rate of Advanced Fibrosis by HCV-genotype in HCV-infected liver transplant recipients.

The unadjusted cumulative rates of advanced fibrosis at 1, 3 and 5 years post-LT were 8%, 31% and 46% for patients with HCV genotype 1; 0%, 19% and 19% for HCV genotype 2; and 2%, 19% and 32% for HCV genotype 3 (log rank=0.008).

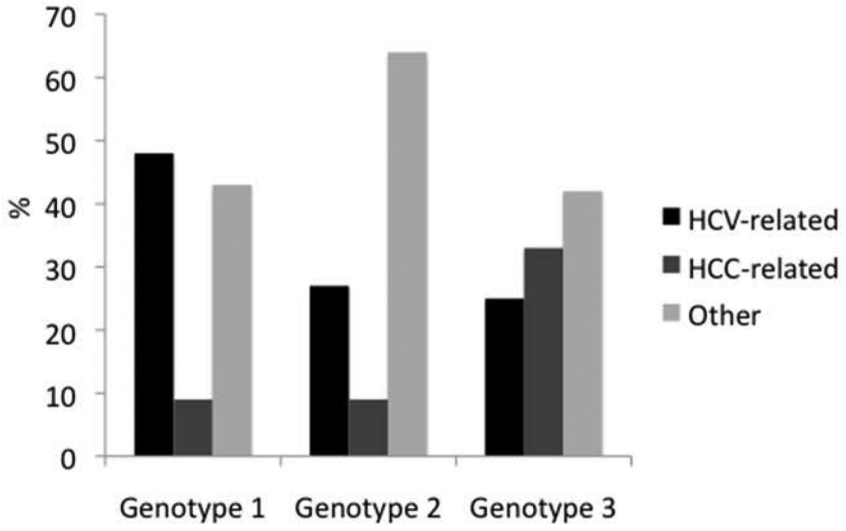

Fig. 2.

Causes of Death by HCV-genotype in HCV-infected liver transplant recipients.

HCV-related deaths were 55 (48%), 2 (27%) and 3 (25%) for genotype 1, 2 and 3 respectively. HCC-related deaths were 10 (9%), 1 (9%) and 4 (33%) for genotypes 1, 2 and 3 respectively; (p=0.06).

Table 1

Characteristics of HCV-infected Liver Transplant Recipients and Their Donors, By HCV Genotype

Characteristic	Total (n=745)	Genotype 1 n=605 (81%)	Genotype 2 n=53 (7%)	Genotype 3 n=87 (12%)	p value
Recipient					
Female recipient, n (%)	180 (24)	139 (23)	15 (28)	26 (30)	0.28
Recipient age (years), median (IQR)	53 (49-57)	53 (49-57)	56 (51-61)	52 (48-55)	0.001
African American race, n (%)	64 (9)	63 (10)	2 (4)	0	0.002
Body mass index at LT (kg/m^2), median (IQR)	27 (25-31)	27 (25-31)	29 (24-33)	27 (24-30)	0.17
Laboratory MELD at LT, median (IQR)	18 (13-24)	18 (13-24)	17 (13-20)	17 (12-22)	0.40
Hepatocellular carcinoma, n (%)	324 (43)	263 (43)	26 (49)	35 (40)	0.59
DM at LT, n (%)	140 (20)	109 (20)	17 (32)	14 (16)	0.06
Donor					
Donor age (years), median (IQR)	41 (25-53)	41 (25-53)	42 (30-52)	41 (26-53)	0.75
African American race, n (%)	100 (14)	82 (14)	6 (11)	12 (14)	0.87
Female donor, n (%)	265 (36)	206 (35)	17 (32)	42 (49)	0.02
Cold ischemia time (hour), median (IQR)	7.6 (5.4-9.5)	7.7 (5.5-9.5)	7.3 (5.6-9.4)	7.5 (5.2-8.7)	0.67
Warm ischemia time (minuts), median (IQR)	42 (35-50)	42 (36-50)	45 (40-56)	42 (31-47)	0.04
Split/Partial transplant, n (%)	24 (4)	20 (4)	0	4 (5)	0.34
Donor risk index, median (IQR)	1.1 (1.0-1.6)	1.3 (1.0-2.2)	1.3 (1.0-2.2)	1.0 (1.0-1.6)	0.42
Post-LT					
Calcineurin inhibitor at last follow up, n (%)					
Tacrolimus based	436 (59)	342 (56)	31 (58)	63 (73)	0.22
Cyclosporine based	163 (22)	134 (22)	14 (26)	15 (17)	
Corticosteroids at last follow up, n (%)	325 (44)	261 (43)	25 (47)	39 (45)	0.83
Post-LT HCV-treatment, n (%)	273 (37)	219 (36)	19 (36)	35 (40)	0.76
Post-LT HCV-treatment before advanced fibrosis, n (%)†	163 (69)	135 (69)	11 (73)	17 (65)	0.87
Treated acute rejection, n (%)	205 (27)	167 (28)	15 (28)	23 (26)	0.97
DM, at last follow up, n (%)	246 (36)	202 (37)	16 (30)	28 (32)	0.50
CMV infection, n (%)	78 (10)	66 (11)	5 (9)	7 (8)	0.69
Follow up (years), median (IQR)	3.1 (2.0-4.5)	3.0 (2.0-4.5)	4.0 (2.3-5.1)	3.4 (2.2-4.5)	0.02

CMV: Cytomegalovirus; DM: Diabetes Mellitus; HBV: HCV: Hepatitis C Virus; IQR: interquartile range; LT: Liver Transplantation; MELD: Model of End-Stage Liver Disease

†Among patient receiving HCV-treatment.

Table 2

Univariable and Multivariable Analyses of Factors Associated with Advanced Fibrosis*

	Advanced Fibrosis Univariable predictors		Advanced Fibrosis Multivariable predictors	
	HR (95% CI)	**p value**	**HR (95% CI)**	**p value**
HCV genotype 1	ref		ref	
HCV genotype 2	0.34 (0.14-0.83)	0.02	0.34 (0.14-0.84)	0.02
HCV genotype 3	0.57 (0.32-1.01)	0.05	0.59 (0.33-1.05)	0.07
Recipient age (per year)	0.96 (0.94-0.98)	0.001	0.96 (0.94-0.99)	0.01
Recipient DM at LT	0.64 (0.40-1.02)	0.06	-	
Donor age (per year)	1.02 (1.01-1.03)	<0.001	1.02 (1.01-1.03)	<0.001
Donor African American race	0.66 (0.39-1.11)	0.11	0.57 (0.33-0.98)	0.04
CMV infection	1.83 (1.21-2.78)	0.004	1.59 (1.01-2.50)	0.04

† HCV genotype 1 was used as the reference genotype.

‡ Adjusted for center effect.

§ Other covariates that were evaluated: recipient and donor sex, BMI, MELD at LT, recipient race, episodes of treated acute rejection, immunosuppression at last follow-up (tacrolimus or cyclosporine).

CMV: Cytomegalovirus; DM: Diabetes Mellitus; HCV: Hepatitis C Virus; LT: Liver Transplantation.

* Recipients receiving antiviral therapy were censored at time of treatment initiation.

Table 3

Factors Associated with Sustained Virologic Response

	Sustained Virologic Response Univariable predictors		Sustained Virologic Response Multivariable predictors	
	HR (95% CI)	**p value**	**HR (95% CI)**	**p value**
HCV genotype 1	ref		ref	
HCV genotype 2	3.79 (1.45-9.92)	0.007	5.10 (1.77-14.71)	0.003
HCV genotype 3	2.81 (1.32-5.98)	0.007	3.27 (1.42-7.56)	0.006
Recipient age (per year)	1.04 (1.01-1.09)	0.04	-	
African American recipient race	0.32 (0.09-1.11)	0.07	-	
Donor age (per year)	0.99 (0.97-1.01)	0.15	0.98 (0.96-0.99)	0.04
Treated acute rejection before treatment	0.29 (0.13-0.65)	0.003	0.30 (0.13-0.67)	0.004
Advanced Fibrosis at the time of treatment	0.36 (0.16-0.79)	0.01	0.35 (0.15-0.83)	0.02

*HCV genotype 1 was used as the reference genotype.

†Adjusted for center effect.

‡Other covariates that were evaluated were: donor and recipient sex, BMI, MELD at LT, donor race, diabetes, CMV infection, calcineurin inhibitor used at last follow-up (tacrolimus or cyclosporine).

HCV: Hepatitis C Virus