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Risk of Advanced Fibrosis with Grafts from Hepatitis C Antibody Positive Donors: A Multicenter Cohort Study (CRUSH-C)

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for the ConsoRtiUm to Study Health Outcomes in HCV Liver Transplant Recipients (CRUSH-C)

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Abstract

Over the last decade, use of liver grafts from hepatitis C (HCV) antibody positive donors [HCV(+D)] has tripled in the U.S. Although prior studies demonstrated no association between HCV(+D) status and graft loss, the effects of HCV(+D) on *histologic* outcomes are not well known. HCV-infected recipients at 5 U.S. centers from 2002–2007 surviving >30 days with 1 post-transplant biopsy were included. Cox regression was used to examine the association between HCV(+D) status and advanced fibrosis (stage 3/4). Of 1,206 patients, 99 (8%) received a HCV(+D) graft. Recipients of HCV(+D) versus HCV(–)D grafts were older ($p=0.03$), but otherwise similar. HCV(+D) were of significantly lower quality as measured by the donor risk index ($p<0.001$). Advanced fibrosis occurred in 32% of HCV(+D) versus 28% of HCV(–)D graft recipients ($p=0.39$). Unadjusted 1- and 3-year rates of advanced fibrosis were significantly higher for HCV(+D) (14 and 48%) compared to HCV(–)D (7 and 33%) graft recipients ($p=0.01$). Transplantation with HCV(+D) grafts was associated with a 58% increased risk of advanced fibrosis (95% CI:1.05–2.36; $p=0.03$). However, in an analysis stratified at the mean donor age of 45 years, HCV(+D) status was only associated with advanced fibrosis with donors ≥ 45 years (HR, 1.76; 95%CI, 1.06–2.93; $p=0.03$) and not with donors <45 years (HR, 0.94; 95%CI:0.47–1.87; $p=0.85$). In conclusion, careful consideration of risk-benefit is needed with use of HCV(+D) grafts. Recipients of HCV(+D) grafts, especially from older donors, should undergo close monitoring for more rapidly progressive fibrosis. Studies are needed to determine whether early HCV therapy modifies this risk.

Introduction

In an effort to expand the supply of donor livers, transplant centers have increasingly utilized expanded criteria donors, including those from older donors, donors after cardiac death, and donors at risk for transmission of viral diseases. For hepatitis C (HCV) infected candidates awaiting transplantation, a liver from an HCV antibody positive donor [HCV(+D)] is an option. Over the last five years, approximately 3% of all deceased donor liver grafts in the United States have been procured from HCV(+D) (1). Although this

represents a small percentage of the total donors, the number of liver transplants from HCV(+)D has tripled over the last decade (2), making it imperative to understand the precise risk, if any, associated with these grafts.

Several studies have evaluated the association between donor HCV status and graft loss using data from the United Network for Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) registry (2–4). Although no effect was seen, these studies did not capture critical factors known to be associated with graft loss in HCV-infected recipients including acute rejection or cytomegalovirus (CMV) infection. In addition, these studies were not able to evaluate HCV disease severity, an outcome of particular importance given the morbidity and costs associated with management of recurrent HCV. Among the single center studies that have included histologic follow-up, some (3, 5), but not all (6, 7), studies reported more advanced fibrosis in recipients of HCV(+)D liver grafts compared with HCV(–)D grafts. One of these studies suggested that the risk of advanced fibrosis was further increased among older (> 50 years) compared to younger (<50) HCV(+)D (5), but all of these studies were limited by small sample sizes and relatively short duration of follow-up.

Given the limitations of these prior studies, we utilized the multi-center ConsoRtiUm to Study Health Outcomes in HCV Liver Transplant Recipients (CRUSH-C) database to evaluate the association between donor HCV-antibody status, donor age, and the development of advanced fibrosis after liver transplantation.

Methods

Patient Population and Data Definitions

The cohort included in CRUSH-C has been previously described (8). In brief, CRUSH-C is a multi-center study group that includes five high-volume experienced transplant centers in the U.S. – 1) University of California, San Francisco, 2) Baylor University Medical Center, 3) New York Presbyterian Hospital-Columbia, 4) Virginia Commonwealth University, and 5) University of Colorado. Data from all adult patients with HCV mono-infection who received a primary liver transplant from March 1, 2002 through December 31, 2007 were retrospectively collected from electronic health records and manual chart review. Donor data was obtained from the UNOS/OPTN registry. For this study, patients were excluded from the analyses if they had graft loss within 30 days of transplant (n=44), a negative HCV RNA immediately post-transplant in the absence of post-transplant antiviral treatment (n=61), or missing or “not reported” donor HCV-antibody status in the UNOS/OPTN registry (n=58).

Donor HCV antibody testing was performed at the donor’s local hospital, and the method of HCV antibody testing was not recorded in the UNOS/OPTN registry. Post-transplant variables were obtained from manual chart review performed by each center and included: acute cellular rejection treated with high-dose bolus corticosteroids or anti-lymphocyte therapy, treated CMV infection, receipt of post-transplant HCV treatment, and sustained virologic response (SVR).

Histologic data

Standard protocol at each of the five centers included annual liver biopsies for HCV-infected liver transplant recipients. However, in the event that a patient required a liver biopsy “for-cause”, the protocol liver biopsy may have been deferred beyond the annual patient’s transplant anniversary date. Therefore, both protocol and for-cause biopsy data were included in the analyses. Four centers used the Batts-Ludwig staging system (9) and one center used the Ishak staging system (10) for fibrosis.

Although biopsies of HCV(+)D grafts was routine, given the retrospective nature of this study, these data were inconsistently recorded in the medical record and therefore, not accessible for the purposes of this study. However, the standard practice at each of the five centers during the study period was to accept only livers from HCV(+)D without any evidence of fibrosis on frozen section. Acceptance of grafts from HCV(+)D with minimal fibrosis was considered if the donor did not have any additional characteristics that might confer a greater risk of poor post-transplant outcomes (e.g., older age, donation after cardiac death).

Immunosuppression

Each center used a standard immunosuppression regimen, however, immunosuppression regimens were not uniform among the sites. Data regarding the use of a) calcineurin inhibitor (tacrolimus or cyclosporine) at last follow-up and b) low-dose corticosteroids as maintenance immunosuppression (>3 months after transplant) were recorded. None of the sites routinely used induction therapy.

Primary Predictor and Endpoints

The primary predictor was donor HCV-antibody status, which was obtained from the UNOS/OPTN registry. The primary endpoint was recipient advanced fibrosis, defined as the first date of bridging fibrosis or cirrhosis on biopsy (Batts-Ludwig Stage 3–4 or Ishak Stage 4–6) post-transplant. Biopsies were read locally by each institution's pathologist. Patients without a single post-transplant liver biopsy (n=108) were excluded from the analyses for only this outcome. Patient mortality and graft loss were also assessed.

Statistical Analysis

Characteristics were described as a mean [$\pm$ standard deviation (SD)] for continuous variables or number (proportion) for categorical variables. The Student t-test and chi-square tests were used to compare baseline characteristics between HCV(+)D and HCV(-)D groups. Unadjusted survival rates were calculated using Kaplan-Meier methods and compared using the logrank test. Cox regression analysis evaluated the association between donor HCV-antibody status and the outcome of interest. Other variables that were associated with a $p < 0.2$ in univariable analysis were then evaluated in the multivariable model. To build the final multivariable model, variables with the highest p-value were eliminated in backwards step-wise fashion until all the remaining variables yielded a $p < 0.05$.

Post-transplant HCV treatment and episodes of treated acute cellular rejection were evaluated in the Cox models as time-varying covariates. Immunosuppression medications (e.g., cyclosporine, tacrolimus, and/or low-dose steroids for maintenance immunosuppression) were tested separately in the final model and included if significant at $p < 0.05$. All final models were adjusted for center effect to account for any potential unmeasured center-specific confounders.

Statistical analyses were performed using STATA version 11 software (Stata Corporation, College Station, Texas). This study was approved by the institutional review boards at each of the five centers.

Results

Baseline Characteristics

Among the five centers, 1,206 patients met the inclusion criteria for this study – 99 (8%) recipients received an HCV(+)D graft. Mean ($\pm$ SD) follow-up time was shorter for HCV(+)D compared to HCV(-)D graft recipients [2.6 ($\pm$ 1.5) vs. 3.3 ($\pm$ 1.8) years; $p < 0.001$].

Characteristics of the cohort and their donors are displayed in Table 1 by donor HCV-antibody status. Compared to HCV(–)D graft recipients, recipients of HCV(+)D grafts were older, but otherwise were similar with respect to gender, race, laboratory MELD score, and percent with hepatocellular carcinoma. HCV(+)D graft recipients were less likely to be on a tacrolimus-based immunosuppression regimen at last follow-up. With respect to *donor* characteristics, HCV(+)D were older, more likely to be African-American, more likely to die of stroke or other causes, and experienced longer cold ischemic time resulting in a donor risk index that was significantly higher for HCV(+)D versus HCV(–)D.

Eight (8%) HCV(+)D and 100 (9%) HCV(–)D graft recipients did not have a single post-transplant biopsy ($p=0.75$). Among those who had at least one post-transplant biopsy, the mean number of biopsies was 3 for both groups ($p=0.38$). The mean time to first biopsy for recipients of grafts from HCV(+)D and HCV(–)D was 5.1 (± 6) and 7.1 (± 8) months, respectively ($p=0.02$).

Donor HCV Status and Advanced Fibrosis

Advanced fibrosis occurred in 29 (32%) recipients of HCV(+)D grafts compared to 278 (28%) recipients of HCV(–)D grafts ($p=0.39$). Unadjusted 1- and 3-year rates of advanced fibrosis for recipients of HCV(+)D grafts were 14% and 48% compared with 7% and 33% for recipients of HCV(–)D grafts ($p=0.01$ logrank) [Figure 1A].

In univariable analysis, transplantation with a HCV(+)D graft was associated with an overall 62% increased risk of advanced fibrosis (95% CI, 1.10–2.38; $p=0.01$; Table 2). Other donor factors that were associated ($p<0.2$) with advanced fibrosis in univariable analysis were age, height, and stroke or other cause of death; African-American race was associated with a decreased hazard (Table 2). In a multivariable model evaluating only donor factors, donor HCV-antibody status, age, and African-American race remained significantly associated with the primary outcome ($p<0.05$; Table 2). Further adjustment for significant recipient characteristics again did not substantially change the increased hazard associated with HCV(+)D status on advanced fibrosis (HR, 1.58; 95% CI, 1.05–2.36; $p=0.03$; Table 2; Figure 1B).

Given prior single-center data suggesting worse outcomes with older HCV(+)D (5), we next performed a stratified analysis evaluating the association between donor age and donor HCV-antibody status. Using the mean donor age of 45 years, there was no significant difference in the cumulative rate of advanced fibrosis among HCV(+)D versus HCV(–)D graft recipients (HR, 1.34; 95% CI, 0.70–2.54; $p=0.38$; Figure 2A) in recipients of grafts from donors ≤ 45 years. While adjustment for the other significant predictors of advanced fibrosis among donors ≤ 45 years, including recipient African-American race and donor cause of death, decreased the hazard associated with donor HCV-antibody status, this was not statistically significant (HR, 0.94; 95% CI, 0.47–1.87; $p=0.85$). In contrast, among recipients of grafts from donors > 45 years, there was a higher rate of advanced fibrosis (HR, 1.78; 95% CI, 1.10–2.88; $p=0.02$; Figure 2B). Multivariable adjustment with other significant predictors of advanced fibrosis among donors > 45 years, including donor African-American race, post-transplant HCV treatment, and treated CMV infection, did not substantially change the increased hazard of advanced fibrosis associated with donor HCV-antibody status (HR, 1.76; 95% CI, 1.06–2.93; $p=0.03$).

Donor HCV-Antibody Status and Patient and Graft Survival

By the end of follow-up, 30 (30%) and 295 (27%) experienced graft loss ($p=0.43$). There was no difference in the proportion of HCV(+)D and HCV(–)D recipients who underwent retransplantation (3% vs. 4%; $p=0.64$). Unadjusted patient survival rates for recipients of

HCV(+)D versus recipients of HCV(-)D grafts were 90% and 91% at 1-year and 73% and 79% at 3-years ($p=0.11$). Unadjusted graft survival rates for recipients of HCV(+)D versus HCV(-)D were 89% and 90% at 1-year and 69% and 77% at 3-years ($p=0.10$). In multivariable analysis, donor HCV-antibody status was not an overall independent predictor of either mortality (HR, 1.28; 95% CI, 0.85–1.94; $p=0.24$) or graft loss (HR, 1.17; 95% CI, 0.79–1.72; $p=0.44$).

Donor HCV Status and Response to HCV Treatment

A total of 374 (31%) patients – 34 (34%) HCV(+)D and 340 (31%) HCV(-)D recipients ($p=0.45$) – received HCV treatment after transplant. Among those who were treated, overall rates of SVR were similar between HCV(+)D and HCV(-)D graft recipients (18% vs. 24%; $p=0.38$). Of the treated patients, 26/34 (77%) HCV(+)D and 257/340 (76%) HCV(-)D graft recipients received HCV treatment prior to the onset of advanced fibrosis ($p=0.91$). Three of 26 (12%) HCV(+)D compared to 60 of 252 (24%) HCV(-)D graft recipients who received HCV treatment prior to advanced fibrosis progressed to advanced fibrosis after treatment ($p=0.16$). In multivariable analysis, receipt of HCV treatment was associated with a decreased hazard of advanced fibrosis (HR, 0.72; 95%CI, 0.53–0.97; $p=0.03$), death (HR, 0.54; 95%CI, 0.40–0.73; $p<0.001$), and graft loss (HR, 0.63; 95%CI, 0.48–0.82; $p=0.001$).

Discussion

Our multicenter cohort study demonstrates that HCV(+)D are not “risk-free”. Although prior UNOS-based studies found no association between donor HCV-antibody status and survival (2–4, 6), these studies could not evaluate the clinically significant outcome of fibrosis progression or account for key post-transplant events (i.e., acute rejection, HCV treatment). Specifically, we found that liver transplantation with HCV(+)D grafts was associated with an overall 58% increased adjusted risk of advanced fibrosis compared to HCV(-)D grafts.

Importantly, this increased risk of advanced fibrosis associated with HCV(+)D grafts was most apparent among recipients of grafts from donors > 45 years – a finding that persisted even after adjustment for other independent predictors of advanced fibrosis. This substantiates findings from a prior single-center study that reported more severe fibrosis in the recipients of older (> 50 years; $n=9$) compared to younger HCV(+)D grafts (<50 years; $n=20$) (5). As regenerative capacity of hepatocytes is age-dependent (11), hepatocytes that have previously been injured by chronic inflammation in an older donor may have decreased ability to repair and proliferate compared to a younger donor. Additionally, age may be a surrogate for the presence of hepatic fibrosis in HCV(+)D, which has recently been reported to be an important predictor of severe HCV recurrence (12). Lastly, older donor livers may have higher rates of baseline clinical fibrosis prior to implantation.

Consistent with UNOS-registry based studies (2–4, 6), rates of mortality and graft loss did not differ significantly by HCV-antibody status in our cohort. One explanation is that recipients of HCV(+)D grafts live for several years after the development of advanced recurrent disease so that differences in patient and graft survival require a longer duration of follow-up to become apparent. Alternatively, increased attention on the part of the provider to post-transplant management of HCV(+)D graft recipients with rapid recurrence, including changes in immunosuppression, less aggressive treatment of acute rejection, and early initiation or longer duration of antiviral treatment, may attenuate differences in graft survival between HCV(+)D and HCV(-)D graft recipients. Additional studies with long-term follow-up and more granular post-transplant event data are needed to further explore these hypotheses.

Consistent with prior UNOS-based studies, we found that there were significant differences in baseline characteristics of HCV(+)D versus HCV(-)D. This perhaps reflects the demographics of the HCV-antibody positive individuals in the United States, as African-Americans, relative to individuals of other race/ethnicities, have a disproportionately higher prevalence of HCV-antibody positivity and rates of tobacco use (i.e., may be at increased risk of cerebrovascular death) (13, 14). In addition, a recent study demonstrated that HCV-antibody positive individuals (with or without viremia) experience a higher mortality rate ratio in all groups above 30 years (e.g., 30–44, 44–59, 60) compared to HCV-antibody negative individuals (13). These factors, in addition to their high proportion of national-share distribution likely due to their HCV-antibody positivity, explain the higher DRI associated with grafts from HCV(+)D.

Unlike in the DRI, however, grafts from African-American donors are associated with a *decreased* risk of advanced fibrosis in our analyses. Although these grafts were associated with a higher risk of graft loss in the donor risk index (15) – which included recipients of all etiologies of liver disease – there is a growing body of evidence to suggest that the donor risk index may not be predictive of graft loss in HCV-infected liver transplant recipients (16, 17). In the non-transplant setting, African-Americans with chronic HCV infection experience slower rates of progression to cirrhosis (18, 19), and whether these same protective immunologic and genetic factors play a role in the post-transplant setting warrant more detailed investigation.

One limitation of our study is the lack of detailed donor data, including donor biopsies and donor HCV RNA. Unfortunately, data on donor fibrosis were not reported in the UNOS registry, the source of our donor data; only macrovesicular and microvesicular steatosis was reported, and these data were available for <20% of our entire cohort. In a European-based multi-center study, 43% of the 63 HCV(+)D were aviremic and over 50% had stage 1 fibrosis (12). However, the mean donor age in their cohort was 57.3 years, over a decade older than the donors in our cohort, so these findings may not be applicable in a U.S.-based cohort. In addition, the standard practice at each of the five centers was to accept only grafts from HCV(+)D without any evidence of fibrosis. Acceptance of grafts from HCV(+)D with minimal fibrosis was considered only for donors without any additional risk factors for poor post-transplant outcome such as older donor age or donation after cardiac death. Therefore, we believe that it is unlikely that there was a *substantial* difference in baseline fibrosis between younger and older HCV(+)D. A second limitation is our lack of donor HCV viremic status. Since some proportion of the HCV(+)D in our study were not viremic and not at risk for potentially affecting HCV disease progression in the recipient, we would expect that reclassification of these aviremic HCV(+)D graft recipients would further strengthen the association between donor HCV-antibody status and post-transplant fibrosis severity.

Our study has important implications for the use of HCV(+)D grafts. We advise caution when using grafts from HCV(+)D, especially older ones. Recipients of HCV(+)D grafts should undergo close monitoring for the early development of advanced fibrosis, and this monitoring approach may be tailored if future studies demonstrate that donor fibrosis or donor HCV viremia further modify recipient outcomes. In light of more effective HCV therapy with direct-acting antiviral agents, further studies are warranted to determine whether early HCV treatment modifies this risk and whether recipients of HCV(+)D grafts should be selected based upon their genotype and ability to tolerate antiviral therapy. Most importantly, given the negative impact of advanced recurrent disease on health-related quality of life post-transplant (20) and the higher risk with use of HCV(+)D, our study reminds us of the need to carefully balance the risk of wait-list mortality with the risk of post-transplant complications when utilizing HCV(+)D organs.

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Figure 1.

(A) Unadjusted and (B) adjusted cumulative hazard of advanced fibrosis by donor HCV status.

Figure 2. Unadjusted cumulative hazard of advanced fibrosis by donor HCV status among (A) donors 45 years and (B) donors > 45 years.

Table 1

Characteristics of HCV-infected Liver Transplant Recipients and Their Donors

Characteristics	HCV(+)D (n=99)	HCV(-)D (n=1,107)	p value
Recipient Characteristics			
Female, n (%)	22 (22)	268 (24)	0.66
Age, mean (SD), years	54.6 (6.6)	53.0 (7.1)	0.03
Race			0.19
Caucasian, n (%)	68 (69)	704 (64)	
African-American, n (%)	9 (9)	114 (10)	
Other, n (%)	22 (22)	289 (26)	
Laboratory MELD at transplant, mean (SD)	19 (6)	19 (8)	0.32
Hepatocellular carcinoma, n (%)	34 (34)	463 (42)	0.15
Post-transplant Characteristics			
Maintenance immunosuppression medications			
Tacrolimus use at last follow-up, n (%)	50 (51)	699 (63)	0.01
Cyclosporine use at last follow-up, n (%)	33 (33)	286 (26)	0.11
# Episodes of treated acute rejection *			0.10
0, n (%)	82 (83)	827 (75)	
1, n (%)	15 (15)	206 (19)	
2, n (%)	2 (2)	74 (6)	
Cytomegalovirus infection, n (%)	18 (18)	131 (12)	0.07
Donor Characteristics			
Donor age, mean (SD), years	45 (11)	40 (17)	0.004
Donor African-American race, n (%)	25 (26%)	142 (13%)	<0.001
Donor cause of death, n (%)			0.03
Anoxia	14 (14%)	136 (14%)	
Cerebrovascular	54 (56%)	431 (43%)	
Trauma	26 (27%)	421 (42%)	
Other	3 (3%)	22 (2%)	
Share region, n (%)			<0.001
Local	46 (48%)	822 (79%)	
Regional	12 (13%)	142 (14%)	
National	38 (40%)	81 (8%)	
Cold ischemic time, mean (SD), hours	8 (3)	7 (3)	0.03
Donor risk index, mean (SD)	1.6 (0.4)	1.4 (0.4)	<0.001

Abbreviations: SD, standard deviation; n, number; MELD, Model for End-Stage Liver Disease

* Treated with either pulse-dosed steroids or anti-lymphocyte therapies

Table 2

Univariable and multivariable models evaluating the association between DONOR factors and advanced fibrosis.

Factors*	UNIVARIABLE HR (95%CI) p-value	MULTIVARIABLE HR (95%CI) p-value	
		Model with only donor factors [†]	Model with donor, recipient, & post-transplant factors [†]
Positive donor HCV antibody	1.62 (1.10–2.38) 0.01	1.55 (1.03–2.32) 0.04	1.58 (1.05–2.36) 0.03
Donor age, per 10 years	1.22 (1.14–1.32) <0.001	1.23 (1.15–1.33) <0.001	1.24 (1.15–1.33) <0.001
Donor African-American race	0.66 (0.45–0.97) 0.03	0.56 (0.38–0.82) 0.003	0.52 (0.35–0.76) 0.001
Recipient female gender	1.21 (0.94–1.56) 0.133	--	1.31 (1.01–1.69) 0.04
Post-transplant HCV treatment	0.62 (0.47–0.82) 0.001	--	0.72 (0.53–0.97) 0.03
Treated CMV infection	1.80 (1.34–2.41) <0.001	--	1.70 (1.25–2.32) 0.001

* Donor height, stroke/other cause of death, and split/partial liver were also associated with the pre-specified $p < 0.20$ in univariable analysis but were not statistically significantly associated with advanced fibrosis in multivariable analyses. Recipient obesity, donation after cardiac death, cold ischemia time, and share region were also evaluated but were not significantly associated with advanced fibrosis in univariable or multivariable analysis.

[†] Adjusted for center effect.