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ORIGINAL ARTICLE

Post-transplant survival is improved for hepatitis C recipients who are RNA negative at time of liver transplantation

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Summary

Hepatitis C virus (HCV) infection recurs universally in patients who are viremic at liver transplantation and likely accounts for the diminished post-transplant graft and patient survival. We evaluated whether undetectable HCV RNA pre-transplant improves graft and patient survival after transplantation. Cases, defined by HCV listing diagnosis and positive HCV antibody, were selected from the Scientific Registry of Transplant Recipients database and further grouped as HCV RNA-positive (n = 4978) or negative (n = 445) based upon pretransplant testing. Controls were non-HCV recipients (n = 2995). RNA-negative cases had significantly better 5-year graft (72% vs. 64%) and patient (79% vs. 69%) survival than RNA-positive cases ($P < 0.01$ for both), and similar survival as controls (Graft: 72% vs. 74%, Patient: 79% vs. 80%; $P > 0.05$ for both). Nonproportional hazards modeling of RNA-positive cases identified a subgroup with rapid progression leading to early graft loss and death. Multivariable analyses confirmed that a positive HCV RNA prior to transplantation was a significant independent predictor of graft loss and death. In conclusion, HCV patients who have undetectable RNA at the time of liver transplantation experience improved long-term graft and patient outcomes. We speculate that the post-transplant survival of HCV recipients could be improved by safe and tolerable pretransplant antiviral strategies.

Introduction

Cirrhosis due to hepatitis C virus (HCV) infection is the leading indication for liver transplantation in the US [1,2]. Hepatitis C recurs universally in patients who are viremic at the time of transplantation, and recurrent hepatitis C is associated with accelerated graft loss and decreased survival [3–6]. Recipients with high levels of HCV RNA prior to transplantation are more likely to experience rapid progression of fibrosis and poor outcome [7–11]. Despite these known relationships, data regarding the long-term graft and patient survival stratified by pretransplant HCV RNA status are lacking.

Aggressive post-transplant recurrence of hepatitis C has prompted investigators to advocate pretransplant antiviral therapy to clear HCV RNA, thereby preventing viral recurrence. Advocates assume that clearing HCV RNA will improve graft and patient survival. Indeed, a recent Markov analysis, incorporating this assumption, demonstrated that interferon-based treatment of either compensated or decompensated cirrhosis could potentially lower costs and reduce deaths compared to post-transplant or no-treatment strategies [12]. Studies demonstrating improved post-transplant outcomes in HCV RNA-negative patients are needed to corroborate the assumptions used in these analyses.

Graft outcome after liver transplantation for hepatitis C is dependent upon several factors beyond HCV recurrence [6,13,14]. Recipient factors include age, gender, ethnicity, body mass index (BMI), underlying disease, and severity of illness based on Model for End Stage Liver Disease (MELD) score. Donor demographics and type of donor graft, such as donation after circulatory death (DCD), also influence outcomes. Linking HCV RNA status to post-transplant graft and patient survival requires consideration of these and other variables that might determine outcomes.

In our study, we compared the long-term graft and patient survival of three groups of liver recipients based on listing diagnoses, pretransplant serology, and HCV RNA status using the Scientific Registry of Transplant Recipients (SRTR). All HCV cases required a listing diagnosis of hepatitis C infection. RNA-positive HCV cases had both a positive HCV antibody and positive HCV RNA. RNA-negative HCV cases had a positive HCV antibody and undetectable HCV RNA. Controls lacked a listing diagnosis of hepatitis C and had a negative HCV serology and undetectable HCV RNA. In addition to confirming the expected survival detriment after transplant for HCV recipients with HCV RNA positivity, our main aim was to understand how post-transplant survival was influenced by having a negative pretransplant HCV viral load.

Materials and methods

Patient data

The patients included in this study had results of pretransplant HCV RNA testing recorded in the SRTR and received their initial liver transplant between 1993 and 2007. Hepatitis C virus cases were defined by positive HCV antibody and indication for liver transplantation listed as either 'AHN: hepatitis C' ($n = 306$), 'cirrhosis: hepatitis C' ($n = 4226$), or 'ETOH cirrhosis with hepatitis C' ($n = 891$). Hepatitis C virus cases were further grouped as RNA-positive ($n = 4978$) or RNA-negative ($n = 445$) based on similar recordings in the database. Controls ($n = 2995$) were defined by negative HCV antibody, negative HCV RNA, and non-HCV listing diagnoses. Any case with missing data for any of the important factors (i.e., listing diagnosis, HCV antibody status, and HCV RNA status) was excluded. Exclusion criteria for all patients were recipient age less than 18 years, simultaneous multiple organ transplantation, and prior transplantation. Recipient and donor demographics at the time of liver transplantation and post-transplant recipient variables were recorded.

Outcomes measured

The main outcomes of interest were graft and patient survival for 5 years after liver transplantation. Graft survival was calculated from the time of first transplant to last follow up, re-transplantation, or death. Patient survival was calculated from the time of first transplant to last follow up or death and included time after re-transplantation (480 patients had two transplants and 17 patients had three). A total of 355 (7%) HCV RNA-positive cases, 42 (9%) HCV RNA-negative cases, and 153 (5%) non-HCV controls were lost to follow up. Cases and controls were censored for graft and patient survival at the time of last known follow-up.

Statistical analysis

Baseline characteristics were compared between groups using chi-square tests for categorical variables and *t*-tests for continuous variables. Continuous variables were assessed for normality by quantile–quantile plots and histograms. Unadjusted graft and patient survivals were calculated using the Kaplan–Meier method and compared between groups with log-rank tests.

The effect of HCV RNA status on graft loss and patient death was analyzed using Cox regression. Visual inspection of the complementary log–log survival plot suggested that the proportional hazards assumption had been violated. As a result, we applied a three-knot cubic spline function to the Cox regression model to control for an interaction between time and HCV RNA status [15]. Knot positions were chosen using the fifth, 25th, and 75th percentiles of all survival times, irrespective of censoring. A Wald test for the overall effect of HCV status was produced from the model as well as a test for change over time to determine whether that change was linear. A sensitivity analysis was performed using the cubic spline function, and adjustments were made for covariates listed in Table 1. Missing variables were coded as a separate risk group category for each missing covariate, with known values dichotomized into high- and low-risk categories and analyzed as class variables.

Multivariable logistic regression was used to assess risk factors for rapid graft loss or early death within 3 years among HCV RNA-positive cases.

All tests were two-sided and a *P*-value of less than 0.05 was considered statistically significant. Hazard ratios (HR) are presented with 95% confidence intervals. All analyses were performed with the use of SAS software, version 9.2 (SAS Institute, Cary, NC, USA).

Results

Characteristics of the HCV and non-HCV cohorts

There were 60 534 adult liver transplantations recorded in the SRTR database between 1993 and 2007. After the application of study criteria, our cohorts consisted of 5423 HCV cases and 2995 non-HCV controls. Baseline characteristics of the entire cohort were analyzed and found to be similar

Table 1. Baseline demographics, donor characteristics and transplant parameters of our three cohorts during 1993–2007: HCV RNA-positive cases, HCV RNA-negative cases, and non-HCV controls.

	HCV recipients		Non-HCV recipients	*P*-value		
	RNA-positive $n = 4978$	RNA-negative $n = 445$	Controls* $n = 2995$	HCV RNA-pos versus controls	HCV RNA-neg versus controls	HCV RNA-pos versus HCV RNA-neg
Demographics						
Mean age, years (SD)	51.4 (7.3)	51.8 (7.7)	52.4 (11.4)	**<0.01**	0.28	0.27
% Ethnicity				**<0.01**	**0.01**	**0.01**
White	73.5	79.2	75.9			
Black	9.2	4.7	7.9			
Hispanic	14.2	13.9	11.6			
Other	3.1	2.2	4.6			
% Male	74.8	73.8	61.2	**<0.01**	**<0.01**	0.63
Mean BMI, kg/m^2 (SD)	28.3 (5.3)	28.6 (5.7)	27.6 (5.8)	**<0.01**	**<0.01**	**<0.01**
% With diabetes	17.4	16.0	20.9	**<0.01**	**<0.01**	**0.04**
% With HCC at LT	13.2	9.0	9.3	**<0.01**	0.80	**0.01**
Mean MELD score (SD)	19.8 (8.6)	19.5 (8.3)	19.8 (9.1)	0.87	0.52	0.54
% On ventilator at LT	2.8	3.4	3.8	**0.01**	0.65	0.47
% On hemodialysis at LT	3.6	2.5	3.9	0.37	0.18	0.17
Donor						
Mean donor age, years (SD)	39.5 (16.5)	40.2 (17.0)	41.6 (18.2)	**<0.01**	0.13	0.43
Mean donor BMI, kg/m^2 (SD)	26.2 (5.4)	26.8 (6.3)	26.2 (5.5)	0.72	**0.02**	**0.03**
% DCD	5.1	3.9	4.6	0.21	**0.03**	**0.04**
Transplant						
Type of transplant, %				0.33	0.05	**0.03**
DDLT	94.5	96.9	95.0			
LDLT	5.5	3.1	5.0			
Mean cold ischemia, hours (SD)	7.2 (3.6)	7.5 (3.1)	7.2 (3.2)	0.81	**0.03**	0.06
Mean warm ischemia, min (SD)	41.5 (17.4)	38.4 (16.6)	39.7 (16.4)	**<0.01**	0.13	**<0.01**
% After March 1, 2002 at LT	68.2	70.4	73.7	**<0.01**	0.14	0.34
% Type of procedure				0.07	0.21	0.11
Whole liver	93.4	95.7	93.6			
Partial liver or LDLT	5.4	3.1	4.7			
Split liver	1.2	1.1	1.7			

*Most common indication for transplantation was Laennec Cirrhosis (26.6%).

Values in bold font denote a significant difference for the comparison. HCV, hepatitis C virus; SD, standard deviation; BMI, body mass index; HCC, hepatocellular carcinoma; MELD, Model for End-Stage Liver Disease; DCD, Death after cardiac death; DDLT, deceased-donor liver transplantation; LDLT, living donor liver transplantation; LT, liver transplantation.

to the cohort we analyzed, with the exception of the entire cohort more frequently receiving a transplant in the pre-MELD era (Table S1). The most frequent reason for exclusion (80%) was due to missing HCV RNA status, which may relate to the pre-MELD era when most of the cases were performed as well as transplant center-reporting practices. We then analyzed the included and excluded non-HCV controls and found that no significant difference between the groups existed except for the median year of transplant (Table S2). The median year of transplant for the non-HCV controls we analyzed was 2003 (1993–2007) and the most common listing diagnosis was alcohol-related cirrhosis (27%).

The included HCV cases consisted of 4978 RNA-positive and 445 RNA-negative patients. The median year of transplant was 2004 (range 1996–2007) and 2003 (range 1993–2007) for the RNA-positive and RNA-negative cases, respectively. An analysis of cases with HCV listing diagnosis but excluded from the HCV cohort due to missing HCV antibody or RNA status demonstrated that this excluded group had an earlier median year of transplant with significantly more cases performed in the pre-MELD era compared to the included HCV cases (Table S3).

Cohort demographics and other baseline variables are presented in Table 1. Hepatitis C virus cases, compared to controls, tended to be younger, were more often male, and had a higher BMI. Among the HCV cases, RNA-negative patients were less likely to be African American or have hepatocellular carcinoma.

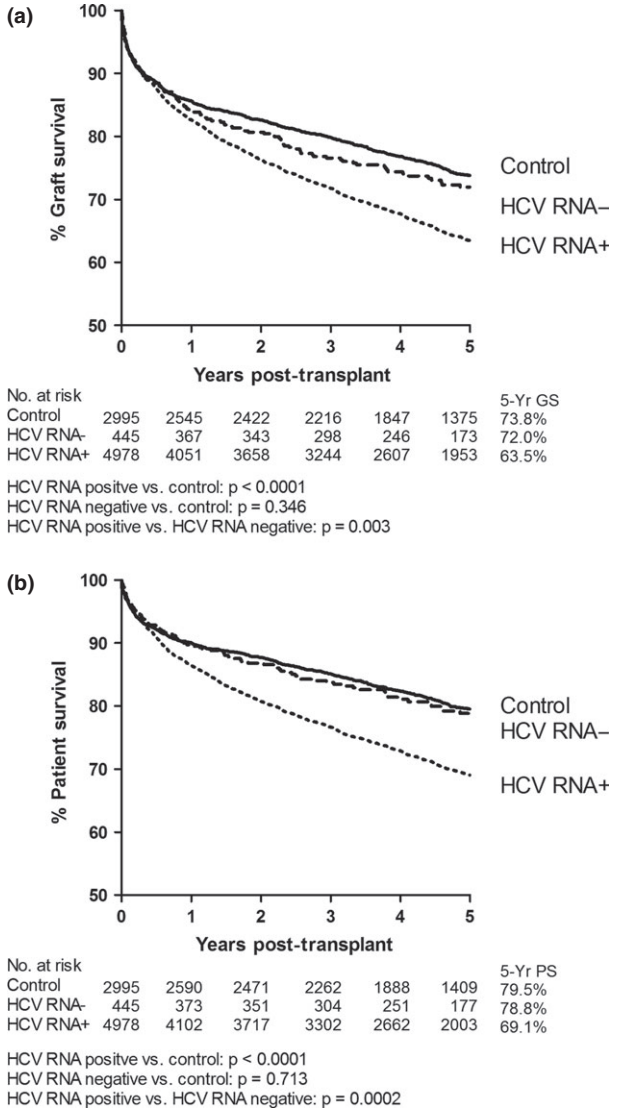

Figure 1 Unadjusted Kaplan–Meier curves comparing the 5-year graft survival (a) and patient survival (b) after liver transplantation between non-HCV controls, HCV RNA-positive cases, and HCV RNA-negative cases using the full cohort 1993–2007. HCV, hepatitis C virus; GS, Graft survival; PS, patient survival.

Graft and patient survival

Figure 1a, b demonstrates results of the unadjusted Kaplan–Meier graft and patient survival analyses. RNA-negative cases and controls had similar 5-year graft and patient survivals (RNA-negative cases vs. controls: Graft: 72.0% vs. 73.8%, $P = 0.346$; Patient: 78.8% vs. 79.5%, $P = 0.713$). RNA-positive cases had the worst 5-year graft (64%) and patient (69%) survivals, which were significantly inferior to controls and RNA-negative cases ($P < 0.01$ for all comparisons). We recognize that the quality and lower limit of detection of HCV PCR assays have changed over time. To account for this variability, we repeated the analyses of unadjusted Kaplan–Meier graft and patient survival using transplants that occurred between 2005 and 2007 (Fig. S1). This subanalysis demonstrated a similar statistically significant decrease in graft and patient survival for HCV RNA-positive cases compared to HCV RNA-negative and non-HCV cases.

The time-dependent effect of HCV RNA status on graft failure (Fig. 2a–c) and death (Fig. 2d–f) was determined by nonproportional hazards models. RNA-positive cases experienced accelerated graft loss and death for the first 3 years after transplantation compared to both controls (adjusted HR for graft loss at 3 years: 2.24, 95% CI: 1.91–2.63, $P < 0.001$ and adjusted HR for patient death at 3 years: 2.34, 95% CI: 1.95–2.80, $P < 0.001$) and HCV RNA-negative cases (adjusted HR for graft loss at 3 years: 1.69, 95% CI: 1.20–2.39, $P = 0.003$ and adjusted HR for death at 3 years: 1.72, 95% CI: 1.19–2.51, $P = 0.004$). In contrast, graft and patient survivals were similar between RNA-negative cases and controls (adjusted HR for graft loss at 3 years: 1.32, 95% CI: 0.92–1.90, $P = 0.13$ and adjusted HR for death at 3 years: 1.36, 95% CI: 0.91–2.02, $P = 0.13$). Neither retransplantation nor the time after retransplantation influenced the survival outcomes described above. A similar profile of the change in HR over time was shown when comparing the 2005–2007 cohort with the full 1993–2007 cohort (Fig. S2) suggesting our findings had little impact from the era of transplantation. As graft loss from recurrence of HCV typically evolves over months to years, we performed a *post hoc* sensitivity analysis by excluding patients whose grafts failed within the first 90 days. Results remained similar (adjusted HR for graft loss at 3 years after transplantation for RNA-positive cases vs. controls: 2.03, 95% CI 1.71–2.40, $P < 0.001$; RNA-positive vs. RNA-negative cases: 1.62, 95% CI 1.12–2.35, $P = 0.010$).

Figures 3 and 4 demonstrate several recipient and donor covariates that had a significant impact on graft and patient survival. Older recipient age, non-Caucasian ethnicity, diabetes, higher MELD score, and requiring mechanical ventilation or hemodialysis at the time of transplant were all associated with decreased survival. Older donors and prolonged cold ischemia times also led to poor survival. Performing a subanalysis in the newer era of transplantation demonstrated that the HR for HCV RNA-positive compared to HCV RNA-negative cases from the 2005–2007 cohort (Fig. S3) was similar to the HR for the full 1993–2007 cohort. The subanalysis showed a trend toward improved survival for HCV RNA-negative cases compared to HCV RNA-positive cases for graft survival ($P = 0.07$) with a similar magnitude of effect. We attribute the lack of statistical significance to a reduction in power due to the smaller sample size in the HCV RNA-negative group.

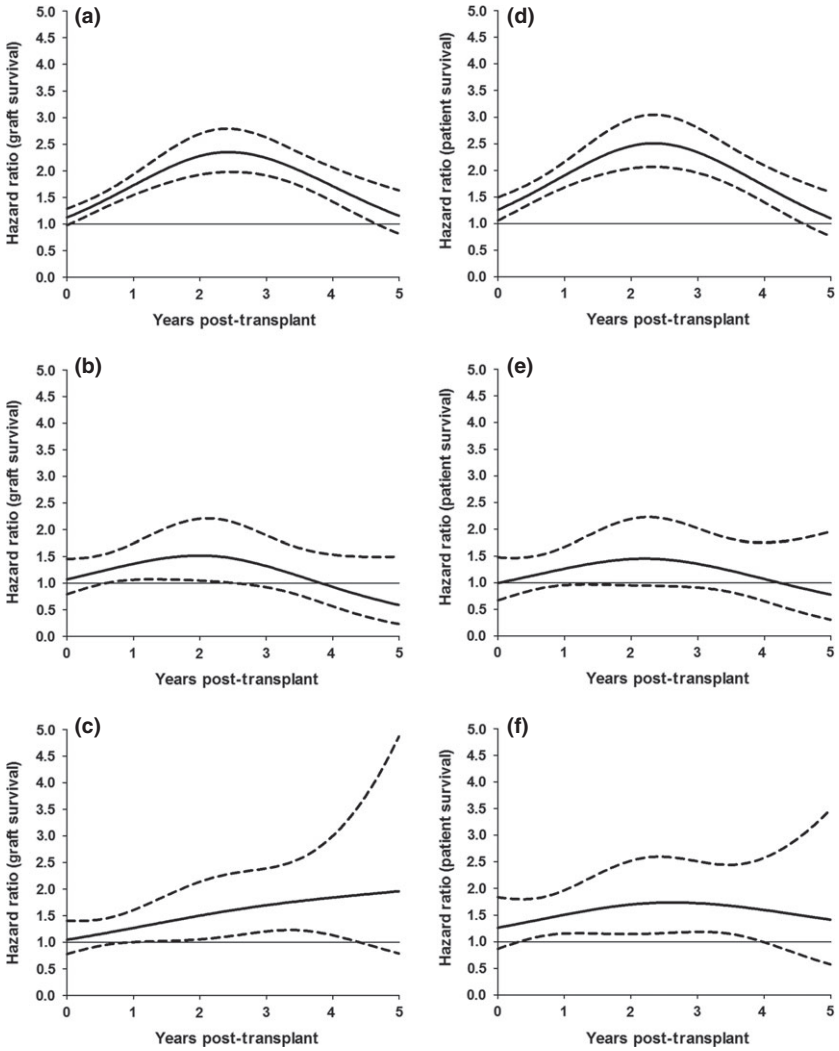

Figure 2 Plot of adjusted hazard ratios (HR) for the effect of hepatitis C virus (HCV) RNA status on graft failure using non-proportional hazards modeling over the first 5 years after liver transplantation using the full cohort 1993–2007: HCV RNA-positive cases vs. non-HCV controls (a), HCV RNA-negative cases vs. non-HCV controls (b), and HCV RNA-positive cases vs. HCV RNA-negative cases (c). Plot of adjusted HR for the effect of HCV RNA status on death using non-proportional hazards modeling over the first 5 years after liver transplantation: HCV RNA-positive cases vs. non-HCV controls (d), HCV RNA-negative cases vs. non-HCV controls (e), and HCV RNA-positive cases vs. HCV RNA-negative cases (f). Dotted lines represent the 95% confidence intervals.

There was an observed decline in the hazards for both graft loss and death among RNA-positive patients after the third year post-transplant, indicating a potential selective survival bias. Therefore, we performed a *post hoc* subgroup analysis of the RNA-positive cohort to further investigate factors that may predict early (i.e., within 3 years after transplant) graft loss. In univariable analysis, RNA-positive cases with early graft loss were more frequently African American or Hispanic ($P = 0.03$), female ($P < 0.01$), diabetic ($P < 0.01$), and required hemodialysis ($P < 0.01$) or mechanical ventilation ($P < 0.01$). Donors for cases with early graft loss were older ($P < 0.01$), and had higher BMI's ($P = 0.01$), and their surgery occurred more often during the MELD era ($P < 0.01$) with a trend toward longer cold ischemia times ($P = 0.06$).

Results of multivariable logistic regression to identify factors significantly associated with early graft loss among the RNA-positive cohort are displayed in Table 2 using the following recipient (age, gender, ethnicity, BMI, diabetes status, hemodialysis status, MELD score, and mechanical ventilation status) and donor (age, BMI, DCD status, cold ischemia time, and transplant era) variables. Among other findings, female recipients were strongly associated with early graft loss.

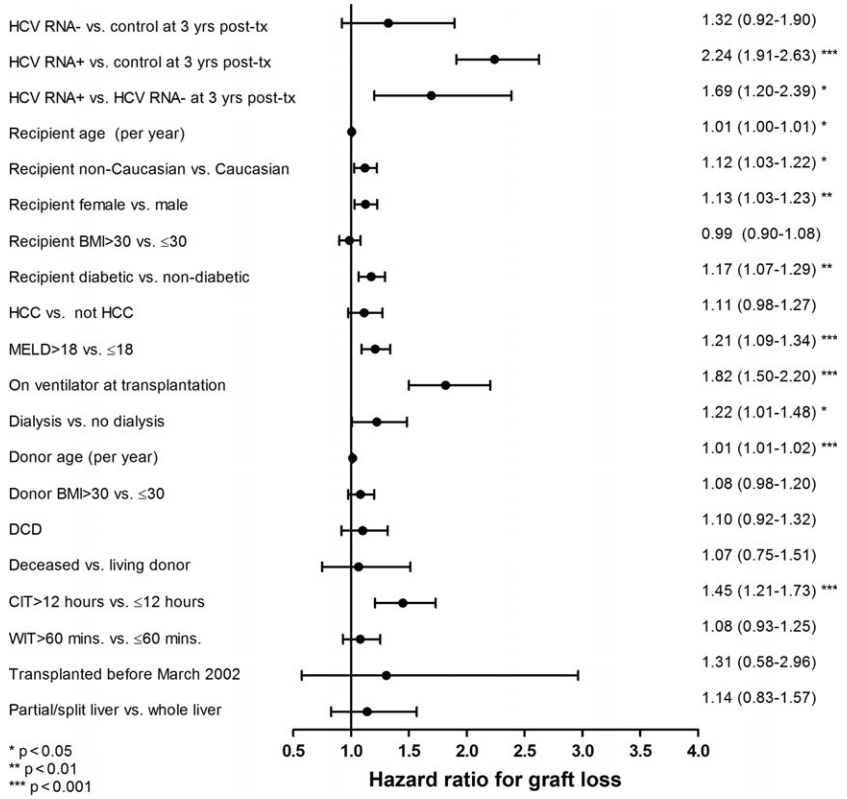

Figure 3 Forest plot of adjusted hazard ratios (HR) with 95% confidence intervals for variables included in the multivariable non-proportional analysis on graft survival using the full cohort 1993–2007. BMI, body mass interval (kg/cm^2); HCC, hepatocellular carcinoma; MELD, Model for End-stage Liver Disease score; DCD, death after cardiac death; CIT, cold ischemia time; WIT, warm ischemia time.

Discussion

Our study uncovered three novel findings. First, patients transplanted with a listing diagnosis of hepatitis C who are HCV RNA-negative at the time of transplantation have graft and patient survival similar to non-HCV patients. Second, the previously described poor survival of patients transplanted for hepatitis C appears to be restricted to HCV RNA-positive cases. Third, we identified and characterized a subgroup of HCV RNA-positive cases with more aggressive disease leading to early graft loss and death at 3 years post-transplant. All the patients included in this study required results recorded for both HCV antibody and HCV RNA status, and had a listing diagnosis including HCV (HCV cohort) or other (controls). However, a large portion of the SRTR dataset was excluded because data were missing from one or more of these key inclusion criteria. To address this concern, we compared the baseline characteristics between the included and excluded HCV patients and found them to be similar. Thus, it is likely that our findings are generalizable to all HCV cases undergoing liver transplantation in the US.

The findings of the current study support the accepted notion that rendering HCV patients RNA-negative prior to transplantation could improve post-transplant outcomes. Unfortunately, conventional therapy using interferon-based treatment is complex and poorly tolerated [16–18]. Rates of post-transplant clearance of HCV range from only 20% to 25% in highly selected patients treated pretransplant [19–24]. However, a new era in the treatment of HCV, using direct-acting antivirals, has arrived. Telaprevir and boceprevir in combination with pegylated interferon and ribavirin (i.e., triple therapy) increase rates of SVR in patients with compensated cirrhosis from 25% to 50% [25–28]. And, newer interferon-free therapies have demonstrated even higher rates of SVR in this same group. Hopefully, using treatments with interferon-free regimens will expand the options for pretransplant HCV therapy and have a positive impact on post-transplant outcomes. We believe that post-transplant HCV treatment would have only a minor impact on these findings due to the low rates of sustained response from interferon-based therapies that would be available in the era we analyzed.

The current study suggests that the previously described poor outcome of HCV liver recipients using the SRTR

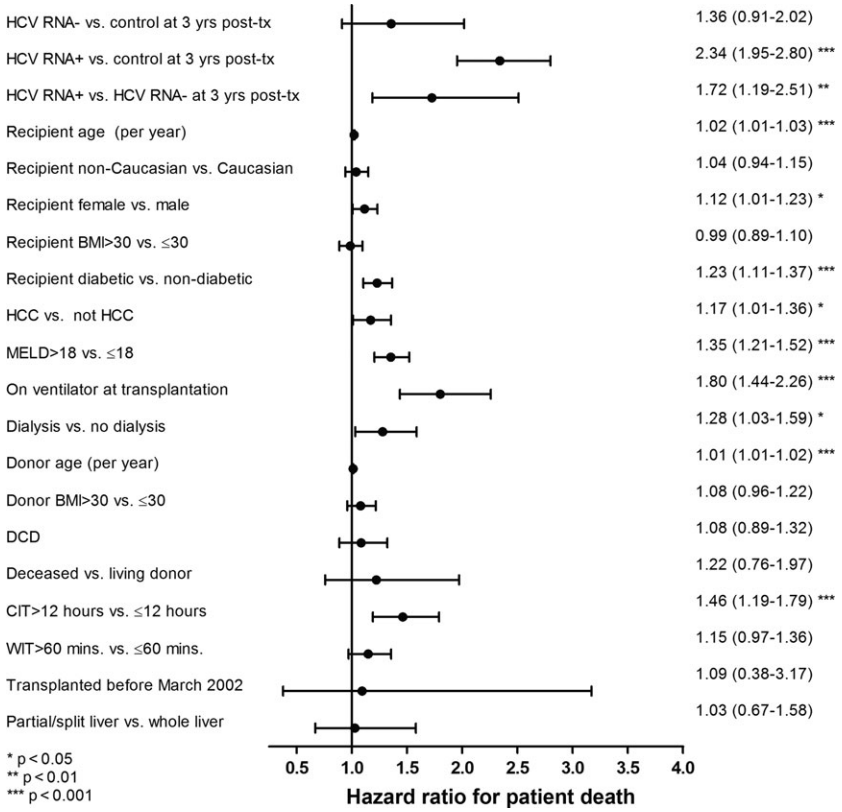

Figure 4 Forest plot of adjusted HR with 95% confidence intervals for variables included in the multivariable non-proportional analysis on patient survival using the full cohort 1993–2007. BMI, body mass interval (kg/cm^2); HCC, hepatocellular carcinoma; MELD, Model for End-stage Liver Disease score; DCD, death after cardiac death; CIT, cold ischemia time; WIT, warm ischemia time.

Table 2. Significant variables from our multivariable logistic regression analysis of the HCV RNA-positive cohort to determine factors associated with early graft loss (within 3 years post-transplant) during 1993–2007.

	OR	95% CI	*P*-value
Female recipient	1.50	1.25–1.80	<0.01
MELD score (per unit)	1.02	1.01–1.03	<0.01
Ventilator requirement	2.15	1.30–3.55	<0.01
Donor age (per year)	1.02	1.01–1.02	<0.01
Donor BMI (per unit)	1.02	1.00–1.03	0.047
Cold ischemia time (per hour)	1.04	1.01–1.06	<0.01

HCV, hepatitis C virus; OR, odds ratio; CI, confidence interval; MELD, Model for End-Stage Liver Disease score; BMI, body mass index (kg/cm^2).

database is restricted to the group who are HCV RNA-positive at the time of transplantation [11]. In the study by Dr. Forman and colleagues using the SRTR database, cases were defined by positive enzyme immunoassay, recombinant immunoblot assay (RIBA), or HCV RNA at the time of transplant. Using HCV antibody or RIBA status to define the HCV cohort without a confirmatory viral load allows inclusion of patients with past exposure or those on treatment for HCV, which could reduce the observed difference in survival. Nevertheless, the study demonstrated that HCV cases had a lower graft (56.8%) and patient (69.9%) survival after 5 years compared to non-HCV controls (67.7% and 76.6%, respectively; $P < 0.0001$). Our analysis confirmed and extended these results by analyzing the impact of pretransplant HCV RNA status, positive or negative. We found that the previously described lower survival for HCV recipients was limited to the RNA-positive cases, and a positive HCV RNA pretransplant was an independent predictor of graft loss and death on multivariable analysis. However, patients with HCV listing diagnosis that were HCV RNA-negative had similar graft and patient survival as the non-HCV control group. This finding is somewhat intuitive, yet, this is the first time a large national database was used to describe it.

Another novel finding of our study was the identification of a subgroup of HCV RNA-positive patients with early graft loss and death at 3 years post-transplant. In multivariable analyses, these cases were more likely to be female, African American, and have received a liver from older and

obese donors. Many explanations for this subgroup of patients with early graft loss are possible. In order to eliminate the potential of severe peri-transplant complications leading to graft loss, we performed a sensitivity analysis excluding patients with graft loss in the first 90 days of transplant as well as cases of graft nonfunction. Results of this sensitivity analysis were not significantly different from the overall cohort. We also note that a subanalysis of transplants occurring between 2005 and 2007, a more contemporary group, did not change the results of our survival analysis. Another explanation for this disparity of graft survival within the HCV RNA-positive group relates to a poor response to post-transplant HCV treatment. This hypothesis may explain why African Americans were more frequently associated with this group. Furthermore, we note this subgroup of patients with early graft loss was associated with increasing donor age, which has already been shown to have a negative impact on post-transplant outcomes for patients with HCV. Finally, female gender was associated with increased risk of early graft loss. Population level studies suggest that women infected with HCV typically have a lower risk of cirrhosis and liver-related death compared to men with HCV infection in the pretransplant setting. We note that the majority of transplant recipients in this cohort were male; however, the subgroup of recipients with early graft loss was associated with female gender. The atypical aggressive course of HCV infection in women post-transplant that we have noted was also demonstrated in a separate study of the UNOS dataset as well as a multicenter patient-level study [29,30]. The explanation for this aggressive course of HCV infection in women post-transplant is not known. However, there may be a selection bias in that a small subset of women with inherently more aggressive HCV infection that require transplantation may then continue to have an aggressive course post-transplant. Furthermore, concerns regarding disparity in metabolism of immunosuppressive medications, assessment of renal function based on serum creatinine, and episodes of acute rejection may also play a role in these women. Unfortunately, our dataset was insufficient to compare immunosuppressive regimens, surgical complications, or use of pretransplant or post-transplant antiviral therapy. Nonetheless, our analysis suggests that this subgroup of patients with increasing donor age, female gender, and African American race are at greatest risk of post-transplant graft loss and death, and should be targeted for treatment, either in the pretransplant or in the early post-transplant period.

An intriguing question that arises from the results of this study relates to the duration of undetectable HCV RNA as well as the means by which the virus became undetectable. We cannot describe the duration of undetectable HCV RNA or the means (i.e., treatment versus spontaneous) by which the virus was cleared from the UNOS dataset as this information is not collected from the transplant centers. This question is important in light of the new interferon-free treatment era we have entered. Defining the duration of treatment pretransplant or peri-transplant that ultimately improves post-transplant outcomes could have various benefits including better graft and patient survival, fewer post-transplant protocol liver biopsies, and lower healthcare costs.

This study has limitations that warrant further discussion. First and foremost is the concern regarding the ability to accurately categorize patients as HCV RNA-negative. We are limited in our ability to confirm the reported undetectable HCV RNA due to the national, multicenter de-identified dataset that was utilized. Therefore, we used a strict definition of HCV as the primary listing diagnosis and positivity for HCV antibody to define the HCV RNA-negative group so that we could be assured that these patients had at least a past infection with HCV. We assume that the majority of these patients had past treatment response or were currently on treatment at the time of transplant when the RNA data were collected. Patients with spontaneous clearance of infection may also be included in this definition. However, it would be unlikely that a patient with spontaneous clearance of HCV would progress to end-stage liver disease and require transplantation as a direct result of HCV. We note that only 8% of patients receiving liver transplant with HCV listing diagnosis had an undetectable HCV RNA. This finding is in keeping with prior studies that demonstrate that achieving sustained virologic response to treatment in patients with cirrhosis reduces, but does not eliminate, the risk of hepatic decompensation. Another concern relates to the lower limit of detection of older assays. It is possible that the cases included from the earlier portion of this study could have been misclassified as undetectable virus due to the lower sensitivity of the assay at that time. However, we would anticipate that if a sufficient number of patients were misclassified by the assay that our results would demonstrate no difference in graft or patient survival from those cases with detectable HCV RNA. Furthermore, a subanalysis of cases occurring between 2005 and 2007 when current highly sensitive viral assays were available continued to demonstrate a significant graft and patient survival benefit for patients that were HCV RNA-negative compared to those that were HCV RNA-positive. Conversely, we cannot entirely rule out that a secondary liver diagnosis led to transplantation in patients with undetectable HCV RNA and possibly a better post-transplant outcome. To evaluate this concern, we performed a sensitivity analysis of our RNA-negative patients separating out those with a secondary listing diagnosis of alcohol-related liver disease, and our overall findings did not change (data not included). Overall, we conclude that our strict adherence to the inclusion criteria enhanced the accurate

categorization of the HCV RNA-negative group at the time of transplant.

Another limitation that warrants mention regards the post-transplant recurrence of HCV infection as well post-transplant treatment for HCV. Data documenting post-transplant recurrence in the HCV RNA-negative group would be invaluable to determine the proper duration of antiviral treatment pretransplant that would be associated with a post-transplant sustained response. We cannot make accurate comments as to how many patients in the HCV RNA-negative group experienced recurrence. However, we presume that a substantial number of post-transplant recurrences would likely sway our results to no difference in survival between the HCV RNA-negative or RNA-positive group. We cannot comment on receipt of post-transplant antiviral treatment or sustained response in either HCV group. It should be noted that serial quantitative viral load results, pre- or post-transplant, are not available in the dataset. Finally, the accuracy of the SRTR database is dependent upon accuracy of data entry from each transplant center. A recent study comparing pre- and post-transplant data from the A2ALL database with the SRTR database showed discrepancies in entered data [31].

In conclusion, this study used a large national database to provide further support that undetectable HCV RNA at the time of transplant could improve graft and patient survival relative to cases that are HCV RNA-positive. Furthermore, HCV RNA-positive recipients characterized by female gender, African American race, co-existent diabetes mellitus, mechanical ventilation or dialysis at transplantation, and receipt of a liver graft from a donor with advanced age or high BMI are at increased risk for early graft loss and death within 3 years of transplant. Until prospective multicenter randomized studies can be performed to validate these findings, we suggest an attempt at pre-transplant antiviral treatment, preferably managed at a liver transplant center, to render patients HCV RNA-negative prior to liver transplantation be considered.

Authorship

BEF: collected and analyzed data and co-wrote manuscript. AM-C: collected data and co-wrote manuscript. SK: analyzed data. JG: analyzed data, reviewed and edited manuscript. GTE: reviewed and edited manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1 Unadjusted Kaplan–Meier curves comparing the 5-year graft survival (a) and patient survival (b) after liver transplantation between non-HCV controls, HCV RNA-positive cases, and HCV RNA-negative cases using a contemporary cohort of transplants occurring between 2005 and 2007.

Figure S2 Plot of adjusted hazard ratios for the effect of HCV RNA status on graft failure using non-proportional hazards modeling over the first 5 years after liver transplantation based on era of cohort (full cohort 1993–2007 vs. contemporary cohort 2005–2007): HCV RNA-positive cases vs. contemporary cohort 2005–2007): HCV RNA-positive cases vs. non-HCV controls (a), HCV RNA-negative cases vs. non-HCV controls (b), and HCV RNA-positive cases vs. HCV RNA-negative cases (c).

Figure S3 Forest plot of adjusted hazard ratios with 95% confidence intervals for variables included in the multivariable non-proportional analysis on graft survival based on era of cohort (full cohort 1993–2007 vs. contemporary cohort 2005–2007).

Table S1. Analysis of missing data from the baseline characteristics of the total dataset and included patients (both HCV and non-HCV cohorts).

Table S2. Baseline characteristics of the excluded and included non-HCV controls.

Table S3. Baseline characteristics of the excluded and included HCV cases.

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