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ORIGINAL ARTICLE

Liver allografts from hepatitis C positive donors can offer good outcomes in hepatitis C positive recipients: a US National Transplant Registry analysis

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Summary

Organ donors are screened for the hepatitis C antibody (anti-HCV) and those with positive tests can be used under extended criteria donation. However, there is still a question of long-term organ viability. The aim of this study was to assess the long-term outcomes of anti-HCV positive (HCV+) liver grafts. The US Organ Procurement and Transplantation Network Scientific Registry was reviewed for the period from April 1994 to February 6, 2008 and 56 275 liver transplantations were analyzed. In total, there were 19 496 HCV+ recipients and 934 HCV+ donors. Patient and graft survival were assessed accounting for both donor and recipient anti-HCV status. Multivariable proportional hazards survival models were developed to adjust for factors known to affect post-transplant survival. With anti-HCV negative (HCV−) recipient/HCV− donor as the reference, the adjusted hazard ratio for death was similar for HCV+ recipient/HCV− donor compared with HCV+ recipient/HCV+ donor (1.176 vs. 1.165, $P = 0.91$). Our results suggest that HCV+ liver donors do not subject the HCV+ recipient to an increased risk for death over the HCV− donor, keeping in mind that careful donor and recipient selection is critical for the proper use of these extended criteria donors.

Introduction

The prevalence of hepatitis C virus (HCV) infection in the United States is approximately 1.6% of the population, corresponding to about 4.1 million people [1]. HCV infection becomes chronic in approximately 80% of patients and eventually 20% of those affected chronically will go on to develop cirrhosis. In recent years, HCV cirrhosis has accounted for 25–50% of all liver transplants performed in the United States [1,2]. With an increased demand for liver transplantation, donor organ shortage has become the major limiting factor in the transplantation process. According to data obtained from the United Network for Organ Sharing (UNOS), more than 16 000 patients are waiting for a liver transplant as of March 2009 while less than 6700 successful liver donations occur each year [3]. One method for addressing the organ shortage is the use of extended criteria donation or marginal donor candidates.

An example of marginal donor expansion is the use of HCV positive (HCV+) grafts for HCV+ patients requiring liver transplantation. Whereas the notion of using HCV+ donors was initially rejected over concerns of allograft dysfunction and viral transmission, this trend has reversed in recent years based on a number of studies by single transplant centers adopting the practice. Early studies found little evidence that either short-term graft or patient survival was affected by transplanting HCV+

grafts instead of HCV negative (HCV−) grafts into HCV+ patients [4–10]. A 10-year follow-up from a single-center study found similar long-term (8 years) outcomes and severe HCV recurrence rates in HCV+ recipients of HCV+ and HCV− grafts [11], although there was a higher rate of HCV recurrence defined by histology in the HCV+ donor group and their numbers of long-term survivors were small. During the early years of liver transplantation in the USA, studies utilized the UNOS database to analyze the effect of HCV donor status on a larger scale. Marroquin *et al.* followed 2923 liver transplants in HCV+ recipients performed from April 1994 to June 1997, 96 of those involving HCV+ donors. It was concluded that similar graft survival and equivalent if not increased patient survival rates were evident in the HCV+ donor compared with the HCV− donor for HCV+ recipients [12]. Velidedeoglu, *et al.*, performed the largest study to date, following 5243 HCV+ recipients, 190 of which had an HCV+ donor, from January 1995 to December 1999. Three-year graft survival rates were similar among both patient populations [13]. Other more recent small trials have continued to support the notion of using HCV+ grafts in HCV+ recipients without major clinical detriment [14,15]. The purpose of this study is to investigate the long-term effect of liver transplantation using HCV+ donors including data from the modern era of organ allocation, transplantation and immunosuppression.

Materials and methods

The Organ Procurement and Transplantation Network (OPTN) liver transplant dataset was analyzed for all adult (age ≥ 18), non-status 1, liver transplantations occurring in the U.S from the initial time when hepatitis C status was reported to the OPTN in April 1994 through February 6, 2008. Recipients with more than 1 year of follow-up were included in the analysis. Recipient and donor factors known from the literature or clinical practice to influence mortality after liver transplantation were analyzed between those patients receiving HCV− allografts and compared with those receiving HCV+ allografts. Factors compared between groups included donor and recipient gender, age, and race. Recipient medical factors included hepatitis C status, pretransplant diabetes mellitus, presence of hepatocellular carcinoma (HCC), and retransplantation status. Donor and procedural medical factors included cause of death, organ sharing type (local, regional, national), and cold ischemia time. Because values for cold ischemia time were missing in 6500 records (11.55%), category mean was substituted for the missing values of this variable. All other variables were missing in <3% of records and no imputation was performed for any other variables. Severity of recipient illness was assessed using the serum total bilirubin and creatinine levels at the time of transplant in recipients. These were used in substitution of the MELD score because international normalized ratio was not reported to UNOS prior to 2002.

Univariate categorical comparisons were performed using the chi-square test. Continuous variables were compared using the Student's *t*-test. Univariate, unadjusted survival was estimated using the Kaplan–Meier technique. Adjusted multivariate survival models were constructed using Cox proportional hazards techniques. Risk stratification for donors in multivariate models was adjusted using the donor risk index (DRI) [16]. The level of statistical significance in type 1 error was set at ≤0.05 and all statistical tests were two-sided. All statistical analyses and dataset manipulations were performed with SAS, version 9.1 (Cary, NC, USA). No local institutional review board approval was required for use of the deidentified UNOS dataset.

Results

A total of 56 275 liver transplantations were analyzed; 934 (1.7%) of all successful liver donations involved an HCV+ donor. Figure 1 shows that the frequency of HCV+ donors used for liver transplants has increased steadily over recent years. Table 1 shows the characteristics of transplants involving HCV+ and HCV− donors. In total there were 19 496 HCV+ recipients and 934 HCV+ donors; 79.3% of HCV+ donor grafts went to HCV+ recipients compared to 33.9% of HCV− donors going to HCV+ recipients ($P < 0.0001$). As expected, there were significant differences between those transplants involving HCV+ donors and HCV− donors. Compared with HCV− grafts, patients receiving HCV+ grafts were slightly older (51.8 vs. 50.6 years, respectively,

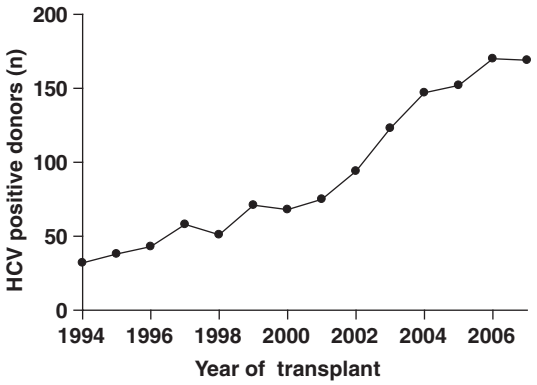


Figure 1 Number of successful HCV positive liver donors since 1994.

Table 1. Recipient and donor characteristics from liver transplants performed with donors positive for the HCV antibody at the time of transplantation.

	Anti-HCV negative donor (n = 55 341)	Anti-HCV positive donor (n = 934)	P-value
Recipient characteristics			
Male, n (%)	34 969 (63.2)	688 (73.7)	<0.0001
Age, mean years (95% CI)	50.6 (50.5–50.7)	51.8 (51.3–52.3)	<0.0001
Caucasian, n (%)	43 138 (78.0)	672 (72.0)	<0.0001
Diabetes mellitus, n (%)	8312 (15.0)	154 (16.5)	0.21
Recipient HCV infection, n (%)	18 755 (33.9)	741 (79.3)	<0.0001
Recipient with HCC, n (%)	3626 (6.5)	83 (8.9)	0.004
Retransplantation, n (%)	4103 (7.4)	45 (4.8)	0.003
Creatinine at transplant, mean mg/dl (95% CI)	1.39 (1.38–1.40)	1.31 (1.24–1.38)	0.05
Bilirubin at transplant, mean mg/dl (95% CI)	6.99 (6.91–7.07)	5.11 (4.59–5.63)	<0.0001
Days on waiting list, mean (95% CI)	235 (232–238)	286 (259–313)	<0.0001
Donor characteristics			
Male, n (%)	33 684 (60.9)	592 (63.4)	0.12
Age, mean years (95% CI)	37.0 (36.9–37.2)	41.4 (40.6–42.1)	<0.0001
Caucasian, n (%)	41 975 (75.9)	662 (70.9)	0.0004
Cause of death			
Cerebrovascular accident, n (%)	21 491 (38.8)	409 (43.8)	<0.0001
Head trauma, n (%)	22 728 (41.1)	371 (39.7)	
Anoxia, n (%)	4629 (8.4)	132 (14.1)	
Organ sharing			
Local, n (%)	39 434 (71.3)	482 (51.6)	<0.0001
Regional, n (%)	11 669 (21.1)	264 (28.3)	
National, n (%)	4144 (7.5)	188 (20.1)	
Cold ischemia time, mean hours (95% CI)	8.66 (8.63–8.70)	8.75 (8.52–8.99)	0.45
Donor risk index, mean (95% CI) [16]	1.78 (1.77–1.79)	1.82 (1.79–1.85)	0.005

$P < 0.0001$), more likely to be male (73.7% vs. 63.2%, $P < 0.0001$), less likely to be Caucasian (72.0% vs. 78.0%, $P < 0.0001$), and had a higher prevalence of pretransplant HCC (8.9% vs. 6.6%, $P = 0.004$). Fewer HCV+ donors were used for retransplantation (4.8% vs. 7.4%, $P < 0.003$). Recipient severity of illness, as measured by pretransplant creatinine (1.31 vs. 1.39 mg/dl, $P = 0.05$) was only slightly different between groups. However, recipients transplanted with HCV+ grafts had a mildly lower total bilirubin compared with those with HCV− grafts (5.11 vs. 6.99 mg/dl, $P < 0.0001$).

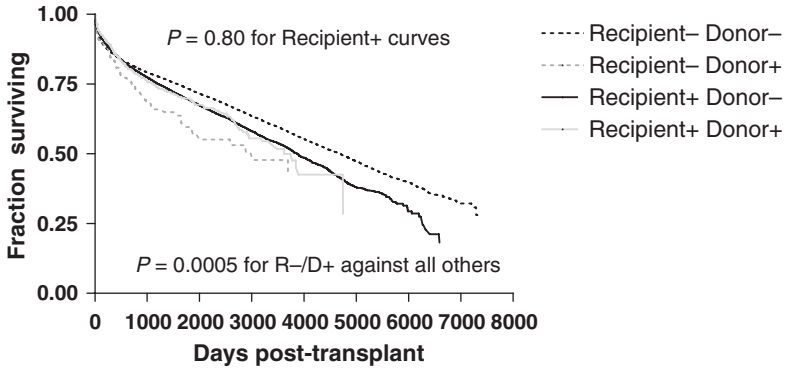
Table 1 also shows the donor characteristics with respect to HCV status. Moreover, there were many significant differences between HCV− and HCV+ donors. Compared with HCV− donors, HCV+ donors were older (41.4 vs. 37.0 years, $P < 0.0001$). Similarly, they were less likely to be Caucasian (70.9% vs. 75.9%, $P < 0.0004$). Cerebrovascular accident (43.8% vs. 38.8%) and anoxia (14.1% vs. 8.3%) were more frequent causes of death in the HCV+ donors ($P < 0.0001$). HCV+ organs were much more likely to exported to other UNOS regions compared with HCV− organs (20.1% vs. 7.5%, $P < 0.0001$); however, cold ischemia times were not different ($P = 0.45$). Recipients of HCV− donors had a shorter waiting time, 235 vs. 286 days in HCV+ donors, $P = 0.0002$. Despite these differences, overall donor risk between groups, as measured by the DRI, were statistically different but the absolute difference was negligible (1.82 in the HCV+ group vs. 1.78 in the HCV− group, $P = 0.005$).

Table 2 shows details of the special group of recipient negative, donor positive transplants compared with all other transplants with hepatitis C recipients or donors. Compared with all other transplants involving HCV, recipient negative, donor positive transplants involved more male recipients, older recipients and donors, longer graft cold ischemia times, and higher DRI organs. The most significant difference in this group compared with all other HCV-related transplants was the high prevalence of recipients with HCC (43.0% vs. 6.5%, $P < 0.0001$). Of the 83 recipient negative, donor positive transplantations, only 49 (59.0%) were performed under a formal MELD exception for HCC. Although details are lacking from the dataset, this would suggest that many of these high risk transplants were performed for liver malignancies outside accepted criteria for HCC MELD exceptions (Milan class T3 and above).

Figure 2 shows the unadjusted Kaplan–Meier survival estimates for the four patient groups based on recipient and donor HCV status. The best survival was achieved in

Table 2. Details of transplants occurring with HCV antibody positive donors and HCV negative recipients.

	Anti-HCV positive donor (*n* = 193)	All other transplants involving HCV (recipient or donor) (*n* = 56 082)	*P*-value
Recipient characteristics			
Male, *n* (%)	142 (73.6)	35 515 (63.3)	0.003
Age, mean years (95% CI)	52.8 (51.7–53.9)	50.6 (50.5–50.7)	0.0002
Caucasian, *n* (%)	143 (74.1)	43 667 (77.9)	0.21
Diabetes mellitus, *n* (%)	31 (16.1)	8435 (15.0)	0.69
Recipient with HCC, *n* (%)	83 (43.0)	3626 (6.5)	<0.0001
Retransplantation, *n* (%)	15 (7.8)	4133 (7.4)	0.83
Creatinine at transplant, mean mg/dl (95% CI)	1.22 (1.11–1.33)	1.39 (1.38–1.40)	0.002
Bilirubin at transplant, mean mg/dl (95% CI)	4.72 (3.64–5.80)	6.96 (6.88–7.05)	<0.0001
Days on waiting list, mean (95% CI)	204 (147–260)	236 (233–239)	0.26
Donor characteristics			
Male, *n* (%)	130 (67.4)	34 146 (60.9)	0.07
Age, mean years (95% CI)	41.3 (39.5–43.0)	37.1 (36.9–37.2)	<0.0001
Caucasian, *n* (%)	133 (68.9)	42 504 (75.8)	0.03
Cause of death			
Cerebrovascular accident, *n* (%)	83 (43.0)	21 817 (38.9)	<0.0001
Head trauma, *n* (%)	77 (39.9)	23 022 (41.1)	
Anoxia, *n* (%)	30 (15.5)	4731 (8.4)	
Organ sharing			
Local, *n* (%)	91 (47.2)	39 825 (71.0)	<0.0001
Regional, *n* (%)	47 (24.4)	11 886 (21.2)	
National, *n* (%)	55 (28.5)	4277 (7.6)	
Cold ischemia time, mean hours (95% CI)	9.27 (8.78–9.75)	8.66 (8.63–8.70)	0.01
Donor risk index, mean (95% CI)	1.87 (1.79–1.94)	1.78 (1.77–1.79)	0.02



Number at risk at various survival time points by Kaplan-Meier technique.

Time point (Days)	0	365	730	1 000	2 000	3 000	4 000	5 000	6 000	7 000
R–/D–	36 586	30 600	25 628	23 268	14 380	8 426	4 717	2 249	719	33
R–/D+	193	153	101	85	37	18	5	0	0	0
R+/D–	18 755	15 831	12 923	11 471	6 181	2 794	1 153	338	41	0
R+/D+	741	621	472	407	170	63	13	0	0	0

Figure 2 Unadjusted survival estimates based on recipient and donor HCV status.

Table 3. Multivariate proportional hazards survival model showing independent predictors of mortality after transplantation.

	Hazard ratio	*P*-value	95% CI
Recipient characteristics			
HCV positive	1.170	<0.0001	1.135–1.207
Age	1.021	<0.0001	1.019–1.022
Male gender	1.035	0.026	1.004–1.066
African American race	1.361	<0.0001	1.291–1.434
Pretransplant diabetes mellitus	1.241	<0.0001	1.192–1.291
Year of transplant procedure	0.995	0.004	0.991–0.998
Serum creatinine at transplantation	1.089	<0.0001	1.079–1.100
Serum total bilirubin at transplantation	1.007	<0.0001	1.005–1.008
Organ used for retransplantation	1.952	<0.0001	1.861–2.047
Donor characteristics			
HCV positive	1.071	0.236	0.956–1.199
Age	1.007	<0.0001	1.006–1.008
Male gender	0.982	0.231	0.952–1.012
African American race	1.047	0.045	1.001–1.096
Cause of death not CVA, head trauma, or anoxia	1.067	0.055	0.999–1.141
Regional organ sharing	1.207	<0.0001	1.148–1.269
National organ sharing	1.083	<0.0001	1.046–1.121
Cold ischemia time	1.006	0.0003	1.003–1.009

the transplants with neither the recipient nor donor being affected by HCV with 5-year survival of 71.3%. The worst survival was in the recipient negative, donor positive group (55.1%). Survival in the recipient negative, donor positive group was significantly worse than all other groups ($P = 0.0005$). There was no statistical difference in 5-year survival in recipients with HCV using HCV+ allografts (67.0%) or HCV− allografts (67.8%), $P = 0.80$. Table 3 shows the adjusted mortality model accounting for other risk factors for death after transplantation. After adjusting for multiple factors and recipient HCV status, donor HCV status was not an independent predictor of mortality after liver transplantation (HR = 1.07, $P = 0.24$, 95% CI: 0.96–1.20). In addition, considering recipient negative, donor positive transplants against all other HCV-related transplants, the increased risk of death in this group persisted in the adjusted multivariate analysis (HR = 1.34, $P = 0.01$, 95% CI: 1.07–1.69). Figure 3 represents the adjusted hazard ratios for death in each of the four patient groups based on recipient and donor HCV status. Compared with HCV− donor and recipient, all recipients or donors with HCV had a statistically significant increased risk for mortality after transplantation. There was no statistical difference in adjusted hazard of death in HCV+ recipients, regardless of donor HCV status (donor HCV− HR = 1.176, 95% CI: 1.140–1.212 vs. donor HCV+ HR = 1.165, 95% CI: 1.025–1.325, $P = 0.91$).

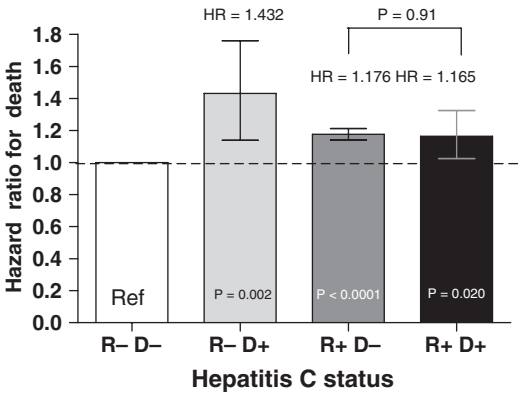


Figure 3 Adjusted hazard ratio for death based on recipient and donor HCV status.

Discussion

The aim of this study was to assess the outcome of HCV+ liver grafts using the largest dataset with the longest follow-up available in the USA. Over 56 000 liver transplantations were analyzed including more than 27 000 transplants since the initiation of the MELD allocation system in 2002, an era which has not been analyzed with regard to HCV+ donors. Not surprisingly, we found the best outcomes were observed when both recipient and donor were negative for HCV. After adjusting for known mortality risk factors in an HCV+ recipient, we found that a potential recipient with HCV cirrhosis is not subjected to excess mortality if an HCV+ liver allograft is used. As expected, HCV− recipients of HCV+ donors had the worst outcomes, but these events were understandably rare and were likely under extreme circumstances not borne out by a database analysis such as this.

Our study found that mean survival times in HCV+ recipient/HCV+ donor was 9.8 years compared to 10.6 years for HCV+ recipient/HCV− donor. However, once these figures were adjusted for factors known to affect post-transplant survival, the hazard ratio was equivalent for both groups. This indicates that the use of HCV+ grafts for HCV+ recipients is comparable in outcome even for long-term survival to using HCV− grafts. It is without question that successful donors with HCV antibodies are very carefully scrutinized in the time immediately prior to donation and are likely to be good candidates for donation with the exception of their HCV status. This argument is supported by the finding in this study that the DRIs were not clinically different between

those with and without HCV despite many other differences between these two populations. It is also understood (although the dataset has no information on this) that liver biopsies on the HCV+ donors prior to donation must have shown minimal to no fibrosis and likely minimal active inflammation.

Faced with the growing problem of organ shortage for liver transplantations, many institutions have resorted to using extended criteria or marginal donors to expand the donor pool and decrease the mortality on the waiting list. Examples of other methods which have been proven to be an effective way of expanding the number of eligible donors include using grafts recovered after cardiac death, reduced-size grafts from living-donor or split-liver transplantations, older donors, steatotic livers with appropriate selection, livers from hepatitis B core antibody positive donors, and using regional and national sharing for locally rejected organs [17]. While the percentage of Americans with HCV antibodies is small, the absolute denominator of potential donors is quite large, based on estimates from the NHANES study [1].

Any large database is subject to reporting bias, data entry errors, and inaccuracies. The UNOS/OPTN database is not immune to this problem and some have questioned the accuracy of many of the variables in this database. However, the use of multiple cross-validations (including the use of the social security master death registry) helps to ensure that mortality is well represented in this dataset. Similarly, the occurrence of a liver transplant and the objective laboratory assessments for recipients and donors are well documented and easily verifiable. Further study on the accuracy and validity of the UNOS dataset is ongoing and will be a valuable asset to the transplant research community.

The HCV+ donor pool that is transplanted into the HCV+ recipient is not a uniform population. It is estimated that approximately 20% of these donor organs come from people who have cleared an acute HCV infection and as such possess minimal risk of HCV transmission. Even those with HCV+ livers and detectable virus do not represent a homogeneous population. The virologic consequence is not uniform. In some instances, the recipient's strain will become dominant, and in others the donor strain remains dominant within the liver. The ability to predict which outcome will occur and whether there are differences between the two populations are not currently possible. The degree of underlying liver damage from pre-existing HCV is another variable that is not captured within the current reporting system. One would probably be safe in assuming that most of the HCV+ livers used within the initial experience had minimal to no fibrotic damage. As reports of successful transplantation of HCV+ donor livers becomes more commonplace, one would predict that the use of more fibrotic organs will occur. Whether these organs will have the same long-term function is not assured by the current analysis. Moreover, an unknown percentage of positive HCV ELISA tests will be false positives in people with no known exposure or risk factors for HCV infection. Although successful organ donors are not a representative sample of the US population, it must be assumed that some of the HCV+ donors in this study did not transmit the virus to the recipient. This is likely to be a small fraction of the population in this study but should be understood in interpreting this data. Assuming that these 'false positives' are distributed evenly throughout the HCV+ donor population in this study, the increase in mortality in the recipient negative, donor positive group argues that donor transmission is significant and that false positives are not heavily influencing the conclusions of this article.

In summary, using the largest dataset available for analysis and the longest follow-up available in the USA, there does not appear to be an increased risk of post-transplant mortality in HCV+ recipients when using well selected donors with the antibody to HCV at the time of donation. Further study of this population and viremia measurements at the time of donation will be important to definitively evaluating this practice. With careful implementation and informed consent from the recipients, a significant pool of extended criteria liver donors could be created with a potential for improving waitlist death rates and maintaining superior post-transplant outcomes.

Authorship

PGN and MAMB: research design and conceptualization, writing of the paper, and statistical analysis. CKA and SCK: research design and conceptualization. DTN: writing of the paper. TMS and TLP: research design and conceptualization and writing of the paper.

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