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Authors

Sageshima, Junichiro
Troppmann, Christoph
McVicar, John P
et al.

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Impact of Willingness to Accept Hepatitis C Seropositive Kidneys Among Hepatitis C RNA-Positive Waitlisted Patients

Junichiro Sageshima, MD,[1] Christoph Troppmann, MD,[1] John P. McVicar, MD,[1] Chandrasekar Santhanakrishnan, MD, MPH,[1] Angelo M. de Mattos, MD, MPH,[2] and Richard V. Perez, MD[1]

Background. Kidney transplantation from hepatitis C seropositive (HCV+) donors may benefit hepatitis C RNA-positive (RNA+) candidates, but it is unclear how the willingness to be listed for and accept such kidneys affects waitlist and transplant outcomes. **Methods.** In a single-center retrospective analysis, HCV+ transplant candidates (N = 169) listed from March 2004 to February 2015 were evaluated. All RNA+ candidates were offered the option to be listed for HCV+ donors. RNA– candidates were listed only for HCV– donors. **Results.** Fifty-seven patients (51% of all RNA+ transplant candidates) willing to accept HCV+ donors were listed for both HCV+ and HCV– donor kidneys. During 6-year follow up, 43 (75%) of 57 patients accepting HCV+ versus 19 (35%) of 55 patients not accepting HCV+ received a deceased donor kidney transplant ($P < 0.0001$). Multivariable analysis demonstrated that willingness to be listed for and accept HCV+ kidneys was associated with receiving deceased donor kidney transplant ($P = 0.0016$). Fewer patients accepting HCV+ donors (7 [12%] vs 16 [29%]) were removed from the list due to death or deteriorated medical condition ($P = 0.0117$). Posttransplant patient and graft survival rates were not significantly different. Overall patient survival since the listing (combined waitlist and posttransplant survival) was similar among the groups. **Conclusions.** HCV RNA+ candidates had better access to transplantation and similar overall survival before the era of widespread use of direct-acting anti-HCV agents.

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Kidney transplantation is the treatment of choice with quality and life benefits in many of end-stage kidney disease (ESKD) patients. In transplant candidates with hepatitis C virus (HCV) infection, where the immunosuppressive medications can adversely affect HCV-associated complications and increase mortality,[1-3] kidney transplantation still provides more life years to ESKD patients than staying on maintenance dialysis therapy.[4-6] In response to a growing demand for transplantable kidney grafts, more potential donors with extended acceptance criteria are being explored as additional sources of organs, HCV-infected donors being one of them. Although increased posttransplant mortality has been observed in the era before widespread use of direct-acting antivirals (DAA) when kidney grafts recovered from HCV-positive donors (HCVD+) are transplanted into HCV-negative candidates,[7-10] utilization of such grafts may be a valuable option for transplant candidates who are already infected with HCV.[11,12] To directly and indirectly increase the number of kidney transplants in HCV-positive and -negative ESKD patients, respectively, exploring this option is tempting because of a relatively high prevalence of HCV infection in dialysis patients (3-23%) and potential donors (3-4%) along with a high discard rate (>50%) of HCVD+ kidneys.[13,14]

The outcomes of deceased donor kidney transplantation (DDKT) from HCVD+ to HCV-positive recipients are mixed. Shorter waiting time, which is a potential advantage of HCVD+ transplantation,[15-18] does not necessarily lead to survival benefit. In fact, large-scale studies using registry data showed inferior patient survival when HCV-positive patients received kidney grafts from HCVD+ as compared with transplants from HCV-negative donors (HCVD–).[7,8,17] Contrary to those reports, early single-center studies with short follow-up demonstrated comparable, but not superior, transplant outcomes.[15,16,19,20] More recent studies with longer follow-up also supported these findings.[18,21] Because these studies compared only transplanted patients (HCVD+ vs HCVD–), it is unclear how HCVD+ acceptance status

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[1] *Department of Surgery, University of California Davis, Sacramento, CA.*

[2] *Department of Internal Medicine, University of California Davis, Sacramento, CA.*

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Correspondence: Junichiro Sageshima, MD, University of California Davis Medical Center, 2315 Stockton Boulevard HSF 2011, Sacramento, CA 95817. (jsageshima@ucdavis.edu).

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(willing vs not willing to accept HCVD+ kidneys) affects overall (pretransplant and posttransplant) outcome. Thus, in the present study, we sought to assess whether listing for HCVD+, in addition to listing for HCVD–, increases access to transplantation and improves outcome.

MATERIALS AND METHODS

Study Design and Patients

In a single-center retrospective analysis, we identified HCV seropositive (anti-HCV antibody positive by the third generation enzyme immunoassay) kidney alone transplant candidates who were placed on the kidney transplant waitlist at our center from March 2004 to February 2015. We further tested them for viremia by HCV RNA assay. We explained the risks and benefits of HCVD+ transplantation in the pretransplant education session and offered a potential listing option for HCVD+ transplantation if they were positive for HCV RNA. The patients who were willing to accept kidneys recovered from HCVD+ were listed for both HCVD– and HCVD+ (group Y). The patients who declined HCVD+ listing were listed for only HCVD– (group N). All HCV RNA-negative patients were listed only for HCVD– (group C). United Network for Organ Sharing used donor seropositivity to define HCVD+ and nucleic acid testing results were not routinely reported during the study period. The study was approved by Institutional Review Board of the University of California, Davis Health (IRB ID: 945771).

Patient Evaluation, Management, and Follow-up

Besides routine pretransplant evaluation, liver biopsy or transient elastography[22] was obtained to assess the degree of liver fibrosis. Patients with advanced liver disease (≥ stage 3) were referred for combined liver and kidney transplantation and are not included in this study. Antiviral treatment (pretransplant or posttransplant) for HCV occurred at the discretion of the treating physician; no specific strategy was pursued by our center. Standard immunosuppression consisted of rabbit antithymocyte globulin induction and tacrolimus and mycophenolate maintenance. Immunologically high-risk recipients also received corticosteroids for maintenance.

The follow-up data, while patients were followed up at our center, were obtained from center's clinical transplant database and hospital's electronic health records. The Organ Procurement and Transplantation Network data supplemented the follow-up data, especially for patients who were not followed by our center, delisted before transplantation, or transplanted at another center (multiple listing). Patients were followed until death, lost to follow-up, or April 2016.

Outcome Measures and Statistical Analyses

Data are shown as median and interquartile range (IQR) or count and percentage. We compared continuous variables by the Kruskal-Wallis test and categorical variables by the Pearson χ^2 test. For waitlisted patients, the transplant event rates were calculated in each group from the listing date; transplants at another center were counted as events, but living donor transplants were censored from this DDKT analysis. Similarly, the waitlist mortality and the removal rate by death or medical deterioration were calculated from the listing date. The impact of HCVD+ acceptance status on receiving DDKT was evaluated with a Cox regression model after adjusting for dialysis duration, calculated panel-reactive antibody level (cPRA), and ABO blood type. Unadjusted posttransplant patient and graft survival (censoring and not censoring for death with a functioning graft) estimates were expressed as Kaplan-Meier survival curves and compared by the log-rank test. Adjusted survival rates were compared by the Cox proportional hazards model. In addition to raw demographic data, we calculated the Estimated Posttransplant Survival (EPTS) scores to adjust for recipient factors.[23] Likewise, we calculated the Kidney Donor Risk Indices (KDRIs) and Kidney Donor Profile Indices to adjust for donor factors.[24,25] KDRIs were not scaled to the median donor of any particular year. To separately assess the impact of donor HCV status and known non-HCV variables of donors, we also calculated modified KDRIs by removing the donor HCV factor from the equation. Given the small numbers of sample and event (death and graft loss) data, we used these aggregated risk scores (ie, EPTS and KDRI) to evaluate risk ratios, instead of using raw demographic variables to avoid overfitting of the model. Finally, overall patient survival rates from the listing date (regardless of transplant status) in each group were calculated. JMP 12.0.1 for Mac (SAS Institute Inc., Cary, NC) was used at a 2-sided significance level (type I error) of 0.05.

RESULTS

Patient Demographics

We identified 169 HCV seropositive patients; 112 of them were HCV RNA-positive (Figure 1). Over half of HCV RNA-positive patients were willing to accept kidneys from HCVD+ and listed to accept both HCVD+ and HCVD– (group Y, N = 57). The remaining patients were listed not to accept HCVD+ (ie, accepting only HCVD–, group N, N = 55). HCV RNA-negative patients were also listed to be offered only HCVD– (group C, N = 57). The patient demographics at listing are detailed in Table 1. There were no overall significant differences in baseline demographics among groups except that diabetes was less common in group C (HCV RNA-negative) patients (P = 0.0404). Although the proportions of candidates with diabetes as original disease were similar between group Y and group N (45.6% vs 47.3%, P = 0.8603), more candidates with HCV-RNA had diabetes (46.4% in group Y and N combined vs 26.3% in group C, P = 0.0115). Of note, more male HCV-RNA–positive patients (56.8%) were willing to accept HCVD+ than female patients (35.5%, P = 0.0436).

Patient Disposition and Access to Transplantation

Median (IQR) follow-up duration was 45.3 (23.8-78.1), 29.7 (19.1-56.6) and 38.5 (18.3-67.3) months in group Y, group N, and group C, respectively (P = 0.1598). A slightly higher percentage of HCV RNA-positive candidates were willing to accept HCVD+ during the first half of the study period (60% vs 40% during the second half of the study period), leading numerically longer follow-up duration in group Y and more end-of-study censoring in group N. We found no other clear reasons (eg, baseline comorbidities, delisting reasons, or inactive duration) to explain the difference. As shown in Table 2, a larger proportion of patients received DDKT in group Y (P < 0.0001). This was due to a significantly larger number of kidneys transplanted from HCVD+, whereas the number of kidneys transplanted from

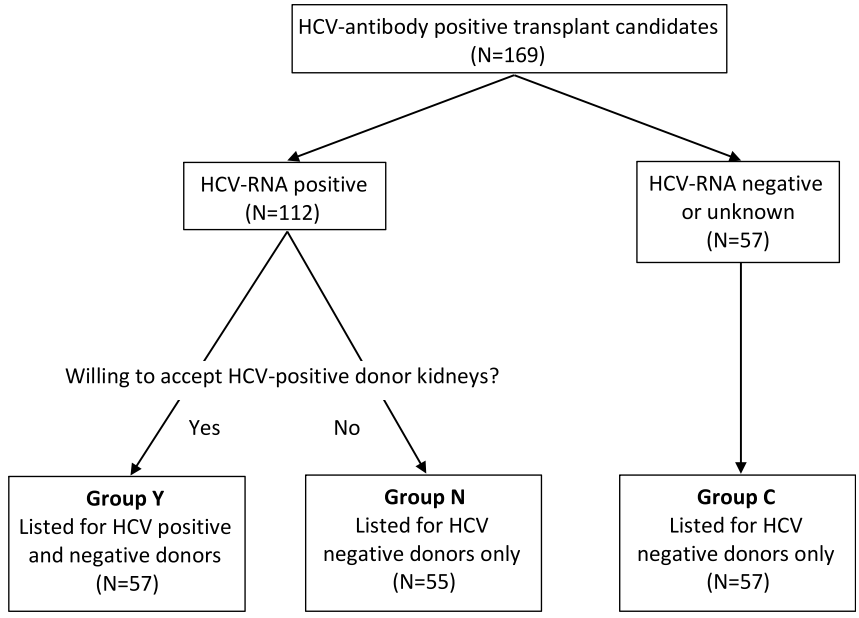

FIGURE 1. Flow chart of study group allocation. HCV antibody-positive candidates were tested for HCV RNA. Candidates who were HCV RNA-positive and willing to accept a kidney graft from a HCV-positive donor were listed for both HCV-positive and HCV-negative donor kidneys; the remaining candidates were listed only for HCV-negative donor kidneys.

HCVD– was smaller ($P = 0.0013$). The difference remained statistically significant when the cumulative incidence of transplant events, including transplants at another center, was compared in a time-dependent manner (Figure 2A, $P < 0.0001$ comparing the 3 groups and $P < 0.0001$ comparing between group Y and group N). In a multivariate model,

TABLE 1.

Patient demographics

	Group Y (n = 57)	Group N (n = 55)	Group C (n = 57)	*P*
Listing age, y	58.1 (51.1-62.4)	55.5 (51.3-64.2)	56.1 (47.3-61.1)	0.5950
Sex				0.1201
Female	11 (19.3%)	20 (36.4%)	18 (31.6%)	
Race/Ethnicity				0.1493
Black	24 (42.1%)	25 (45.5%)	13 (23.2%)	
Hispanic	14 (24.6%)	10 (18.2%)	11 (19.6%)	
White	15 (26.3%)	16 (29.1%)	26 (46.4%)	
Other	4 (7.0%)	4 (7.3%)	6 (10.7%)	
Blood Type				0.3431
A	20 (35.1%)	17 (30.9%)	21 (36.8%)	
B	11 (19.3%)	6 (10.9%)	15 (26.3%)	
AB	1 (1.8%)	2 (3.6%)	1 (1.8%)	
O	25 (43.9%)	30 (54.6%)	20 (35.1%)	
BMI, kg/m^2	27.2 (23.9-31.8)	26.8 (23.7-30.6)	29.2 (23.9-32.3)	0.3218
cPRA > 40%	12 (21.1%)	16 (29.1%)	18 (31.6%)	0.4193
Original disease				0.0404*
Diabetes	26 (45.6%)	26 (47.3%)	15 (26.3%)	
Previous transplant				0.5435
Liver	2 (3.5%)	4 (7.3%)	4 (7.0%)	
Kidney	4 (7.0%)	8 (14.6%)	8 (14.0%)	
Prelisting dialysis (yes)	53 (93.0%)	48 (87.3%)	50 (87.7%)	0.5491
Prelisting dialysis, d	671 (190-1389)	527 (174-865)	539 (175-1120)	0.3185
HCV antibody (positive)	57 (100%)	55 (100%)	57 (100%)	1.0000
HCV RNA				<0.0001*
Positive	57 (100%)	55 (100%)	0 (0%)	
Unknown			6 (10.5%)	

* indicates significant *P* value.

Group Y, HCV RNA-positive candidates who were listed for both HCV-positive and -negative donor kidneys. Group N, HCV RNA-positive candidates who were listed for only HCV-negative donor kidneys. Group C, HCV RNA-negative or unknown candidates who were listed for only HCV-negative donor kidneys. Data are shown as median (IQR) or count (percentage).

BMI, body mass index; HCV, hepatitis C virus; RNA, ribonucleic acid.

TABLE 2.

Postlisting outcomes

	Group Y (n = 57)	Group N (n = 55)	Group C (n = 57)	*P*
Received a DDKT	42 (73.7%)	17 (30.9%)	23 (40.4%)	<0.0001*
Received a DDKT from a HCV– donor	6 (10.5%)	17 (30.9%)	23 (40.4%)	0.0013*
Received a DDKT from a HCV+ donor	36 (63.2%)	0 (0.0%)	0 (0.0%)	<0.0001*
Received a LDKT	2 (3.5%)	2 (3.6%)	6 (10.5%)	0.1937
Transplanted at another center	1 (1.8%)	2 (3.6%)	5 (8.8%)	0.1892
Died on WL	2 (3.5%)	7 (12.7%)	4 (7.0%)	0.1822
Removed from WL due to deteriorated medical condition	5 (8.8%)	9 (16.4%)	5 (8.8%)	0.3425
Removed from WL due to other reasons[a]	4 (7.0%)	4 (7.3%)	5 (8.8%)	0.9306
Remaining on WL	1 (1.8%)	14 (25.5%)	9 (15.8%)	0.0014*

[a] For example, relocation, refusal, or psychosocial candidate issues.

* indicates significant *P* value.

Group Y: HCV RNA-positive candidates who were listed for both HCV-positive and -negative donor kidneys. Group N: HCV RNA-positive candidates who were listed for only HCV-negative donor kidneys. Group C: HCV RNA-negative or unknown candidates who were listed for only HCV-negative donor kidneys. Data are shown as count (percentage within the groups).

LDKT, live-donor kidney transplantation; WL, waitlist.

willingness to accept HCVD+ was associated with more DDKT events after adjusting for dialysis duration, cPRA and ABO blood type ($P = 0.0016$). Of note, these findings were not affected by the listing era. Although 7 (12.3%) patients were removed from the waitlist due to death or deteriorated medical condition in group Y, 16 (29.1%) patients were removed from the list by the same reasons in group N ($P = 0.0277$). As shown in Figure 2B, the cumulative incidence of removal by death or medical deterioration was significantly higher in group N ($P = 0.0286$ comparing the 3 groups and $P = 0.0117$ comparing between group Y and group N). More patients were still waiting for a kidney transplant in group N (25.5% vs 1.8% in group Y) at the end of the study.

Posttransplant Patient and Graft Survival

The recipient and donor characteristics were similar except for recipient sex, donation after circulatory death (DCD) status and hypothermic perfusion pump use (Table 3). The proportions of recipients with diabetes as original disease were similar between group Y and group N (52.4% vs 47.1%, $P = 0.7111$), whereas more recipients with HCV-RNA had diabetes (50.9% in groups Y and N combined vs 21.7% in group C, $P = 0.0167$). The posttransplant patient survival (Figure 3A, 67.4%, 85.7% and 95.7% at 6 years in group Y, group N and group C, respectively) and graft survival (Figure 3B, 54.4%, 76.2% and 84.3%, ditto) rates were numerically different, but the difference did not reach statistical significance ($P = 0.2863$ for patient survival and $P = 0.1375$ for graft survival comparing between group Y and group N). Death-censored graft survival rates were not significantly different among the groups either (Figure 3C, 75.4%, 88.9% and 88.2%, $P = 0.2487$ comparing between group Y and group N). Multivariate analyses demonstrated that neither recipient HCV RNA status nor donor HCV status were associated with patient or death-censored graft survival rates. The listing status among HCV RNA-positive patients (ie, group Y vs group N) did not affect posttransplant patient ($P = 0.2108$) or death-censored graft ($P = 0.1246$) survival after adjusting EPTS and KDRI.

Overall Patient Survival

When the estimated patient survival rates were compared since the time of listing (Figure 4, combined waitlist and

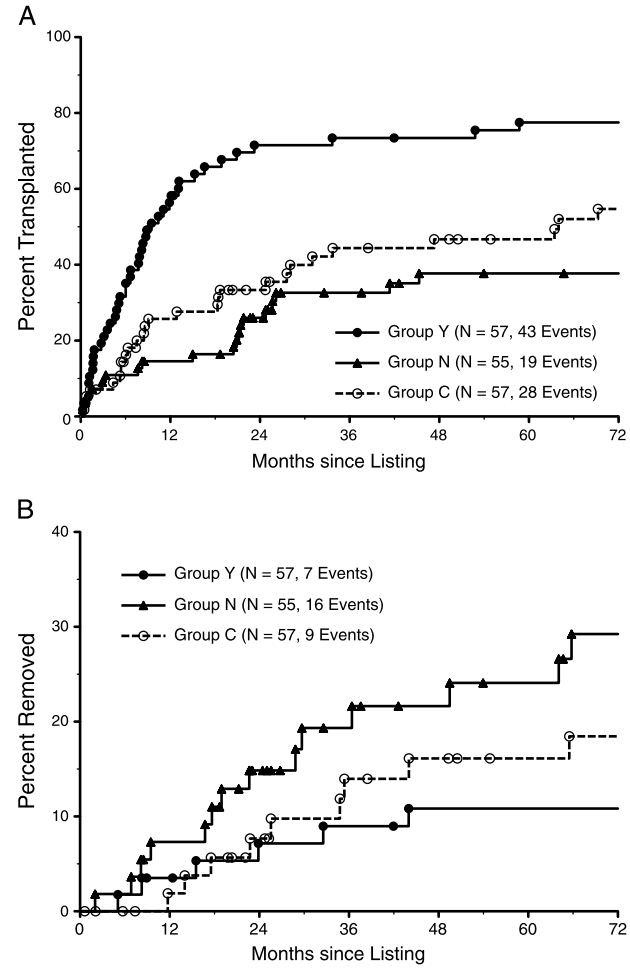

FIGURE 2. DDKT and waitlist removal rates among waitlisted patients. Group Y: HCV RNA-positive candidates who were listed for both HCV-positive and -negative donor kidneys. Group N: HCV RNA-positive candidates who were listed for only HCV-negative donor kidneys. Group C: HCV RNA-negative or unknown candidates who were listed for only HCV-negative donor kidneys. A, Cumulative incidence of transplant events ($P < 0.0001$ comparing the 3 groups and $P < 0.0001$ comparing group Y vs group N). B, Cumulative incidence of removal due to death or medical deterioration ($P = 0.0286$ comparing the 3 groups and $P = 0.0117$ comparing group Y vs group N).

TABLE 3.

Recipient and donor demographics

	Group Y (n = 42)	Group N (n = 17)	Group C (n = 23)	*P*
Recipient				
Transplant age, y	59.3 (54.3-63.6)	55.9 (54.3-65.0)	57.8 (50.5-61.3)	0.6119
Sex	4 (9.5%)	7 (41.2%)	4 (17.4%)	0.0172*
Female				
Race/ethnicity				0.5235
Black	19 (45.2%)	8 (47.1%)	5 (21.7%)	
Hispanic	10 (23.8%)	4 (23.5%)	6 (26.1%)	
White	10 (23.8%)	3 (17.7%)	8 (34.8%)	
Other	3 (7.1%)	2 (11.8%)	4 (17.4%)	
Blood type				0.9933
A	15 (35.7%)	6 (35.3%)	9 (39.1%)	
B	9 (21.4%)	3 (17.7%)	5 (21.7%)	
AB	1 (2.4%)	1 (5.9%)	1 (4.4%)	
O	17 (40.5%)	7 (41.2%)	8 (34.8%)	
BMI, kg/m^2	26.8 (24.4-31.1)	27.4 (24.9-31.0)	26.9 (23.3-30.3)	0.9463
cPRA > 40%	9 (21.4%)	4 (23.5%)	5 (21.7%)	0.9841
Original disease				0.0531
Diabetes	22 (52.4%)	8 (47.1%)	5 (21.7%)	
Previous transplant				0.8819
Liver	2 (4.8%)	1 (5.9%)	2 (8.7%)	
Kidney	3 (7.1%)	2 (11.8%)	3 (13.0%)	
Pretransplant dialysis	40 (95.2%)	17 (100%)	22 (95.7%)	0.6631
Pretransplant dialysis, d	1027 (465-1623)	1201 (229-1523)	1338 (740-2095)	0.3819
EPTS, %	70.5 (38.8-80.3)	67.0 (35.0-76.5)	50.0 (31.0-60.0)	0.1774
Donor				
Age, y	42.5 (24.8-50.3)	35.0 (21.5-50.0)	40.0 (18.0-55.0)	0.7719
Sex				0.0739
Female	9 (21.4%)	8 (47.1%)	10 (43.5%)	
Race/ethnicity				0.6797
Black	4 (9.5%)	3 (17.7%)	4 (17.4%)	(Overall)
Hispanic	6 (14.3%)	4 (23.5%)	3 (13.0%)	0.5704
White	30 (71.4%)	10 (58.8%)	16 (69.6%)	(black vs non-black)
Other	2 (4.8%)	0 (0.0%)	0 (0.0%)	
BMI, kg/m^2	25.5 (22.1-29.7)	23.0 (21.4-28.5)	23.6 (19.9-29.5)	0.3846
Cause of death				0.8081
Cerebrovascular accident	12 (28.6%)	5 (29.4%)	5 (21.7%)	
Medical history				
Hypertension	8 (19.1%)	4 (23.5%)	4 (17.4%)	0.8841
Diabetes	2 (4.8%)	1 (5.9%)	0 (0.0%)	0.5334
Serum creatinine, mg/dL	0.90 (0.60-1.33)	1.06 (0.65-1.75)	0.90 (0.50-1.20)	0.3733
Cold ischemia time, h	20.0 (12.3-28.3)	17.4 (12.4-33.4)	23.5 (18.1-30.3)	0.3263
Perfusion pump use	24 (57.1%)	17 (94.1%)	23 (87.0%)	0.0031*
DCD	5 (11.9%)	7 (41.2%)	9 (39.1%)	0.0142*
Donor warm ischemia time, min	22 (16-28)	16 (14-24)	20 (11-61)	0.7551
HCV status (positive)	36 (85.7%)	0 (0%)	0 (0%)	<0.0001*
KDPI, %	61 (40-81)	65 (31-86)	65 (37-86)	0.9225
KDRI[a]	1.34 (1.10-1.67)	1.42 (1.01-1.79)	1.41 (1.07-1.81)	0.9134
KDRI without HCV[a]	1.06 (0.92-1.40)	1.42 (1.01-1.79)	1.41 (1.07-1.81)	0.0250*

[a] KDRI is calculated as the relative risk compared with a healthy 40-year-old reference donor (RAO) and is not scaled to the median donor. KDRI without a HCV status component was also calculated to compare donor factors other than the HCV status.

Group Y, HCV RNA-positive candidates who were listed for both HCV-positive and -negative donor kidneys. Group N, HCV RNA-positive candidates who were listed for only HCV-negative donor kidneys. Group C, HCV RNA-negative or unknown candidates who were listed for only HCV-negative donor kidneys.

KDPI, kidney donor profile index.

posttransplant mortality), there was no difference among 3 groups (75.0%, 72.9% and 75.0% at 6 years in group Y, group N, and group C, respectively, $P = 0.9037$) and between group Y and group N ($P = 0.6632$). A multivariate analysis showed no impact of recipient HCV RNA status ($P = 0.33908$) or the listing groups ($P = 0.41145$) on the overall patient survival. To identify which patient population would benefit most from HCVD+ listing, we analyzed

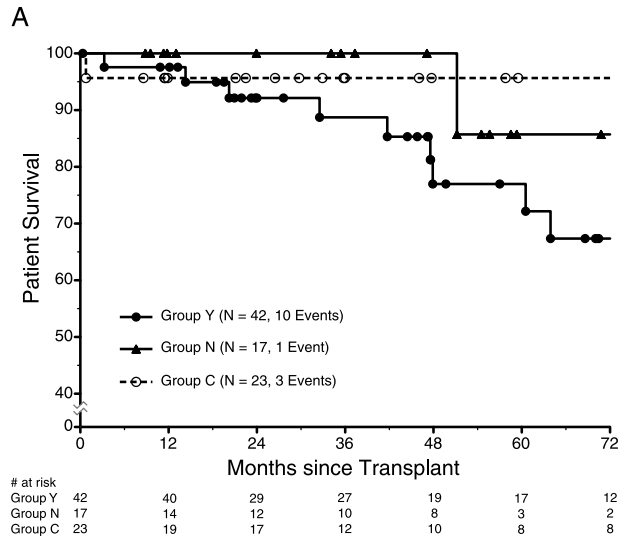

FIGURE 3. Posttransplant patient and graft survival. A, Posttransplant patient survival ($P = 0.2863$ comparing group Y vs group N). B, Graft survival (without censoring death with functioning graft, $P = 0.1375$ comparing group Y vs group N). C, Death-censored graft survival ($P = 0.2487$ comparing group Y vs group N).

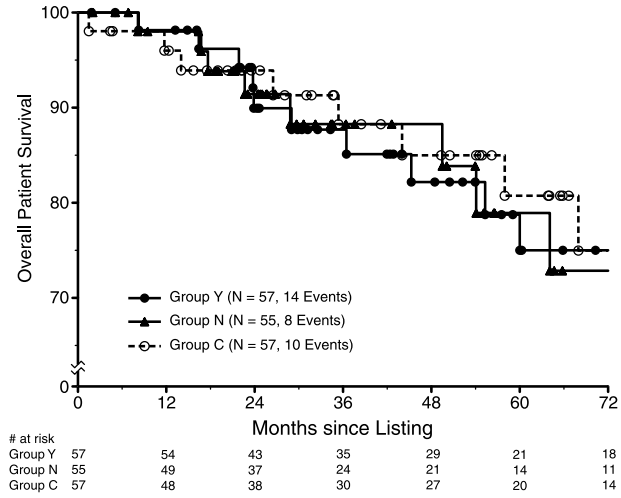

FIGURE 4. Overall patient survival. The patients were followed throughout pretransplant (waitlist) and posttransplant since listing ($P = 0.9037$ comparing the 3 groups and $P = 0.6632$ comparing group Y vs group N).

survival in the different strata (eg, patients with long vs short dialysis) but did not find significant differences in any particular cohort.

DISCUSSION

In this single-center study, we have demonstrated greater access to DDKT and enhanced waitlist outcomes in transplant candidates who were willing to accept kidneys from an additional pool of deceased donors (ie, HCVD+). Among HCV RNA-positive candidates, the transplant rate doubled by adding HCVD+ listing, whereas the removal rate by death or deteriorated medical conditions doubled by declining HCVD+ listing. Although previous studies had already shown decreased waiting time in HCVD+ DDKT as compared with HCVD– transplants, such studies included only transplanted recipients, instead of including all waitlisted candidates.[15-18] Thus, the impact of additional HCVD+ listing on waitlist outcomes has remained unclear. Because registry data do not include HCV antibody status of waitlisted candidates and HCV RNA status of waitlisted candidates or transplant recipients,[14] a study such as ours using registry data could not have been performed. Furthermore, the listing status (eg, acceptance of HCVD+) may not reflect actual individual patients' preference—some centers may use the centers' default organ acceptance criteria to evaluate and discuss each case with candidates at the time of organ offer. The present study of HCV-positive candidates with center-level granular data is therefore unique and provides important insights into waitlist and transplant outcomes of patients with HCV infection.

Although posttransplant patient and graft survival rates were not significantly different, we observed a trend toward lower patient and graft survival in recipients accepting HCVD+ (group Y). Because only a small number of patients were transplanted and few events (ie, death or graft loss) were observed in group N, the power of our posttransplant survival analysis was low (lower than 40%). It is thus possible that the lack of statistical significance was a type II error.

The trend observed in our study is in accordance with previous studies that used the Scientific Registry of Transplant Recipients (SRTR) data and showed significantly lower patient and graft survival in HCVD+[8,17,26] as the majority of our group Y patients received a graft from HCVD+. The marked disparity in outcomes observed among single-center studies may in part be explained by different donor and recipient characteristics.[9,10,18,21] The recipient demographics in our study were overall well balanced including for EPTS. Of note, the only significant difference between the groups was a higher percentage of male candidates were willing to accept HCVD+. Although we are unable to specify why a difference in acceptance rates existed based on sex, it would be interesting to explore what factors actually affect candidates' decision to accept HCVD+ in future studies including socioeconomic status, place of residence (urban vs rural), waiting time or factors related to the education and consent process. Overall donor quality was also comparable indicated by similar KDRI; however, when HCV was removed as a factor from the KDRI equation, the score was significantly better for group Y patients, suggesting that the aggregate of other factors (ie, age, height/weight, ethnicity, hypertension/diabetes history, cause of death, serum creatinine, and DCD status) was more favorable in group Y. In fact, significantly fewer DCD donor kidneys were transplanted into group Y patients with less perfusion pump use for preservation. Although these factors did not have significant impact on survival (data not shown), it is possible that surgeons intentionally or unintentionally used stricter donor selection criteria for patients in group Y. If even more stringent donor selection criteria would have been used for HCVD+, posttransplant outcome would likely have improved but waitlist outcome would have worsened due to prolongation of waiting time and poorer access to transplantation. In their subgroup analysis, Kucirka et al had demonstrated similar hazard of death and graft loss of HCVD+ transplants in African-American, older patients (>60 years), diabetics, and those with high PRA (>80%), highlighting the impact of recipient characteristics on posttransplant outcome also for HCV+ recipients. Nonetheless, our study has for the first time demonstrated similar postlisting patient survival in HCV-RNA–positive transplant candidates—irrespective of their willingness to accept HCVD +, suggesting that the potential survival benefit of early transplant[4,6] in patients who were willing to accept HCVD+ was offset by inferior posttransplant outcome of HCVD+.

Among several limitations of the current study, the most prominent one is a lack of information about HCV genotype, viral load and antiviral treatment. Our study's period included mainly the era before the availability and more widespread use of DAA; but irrespective of the HCV treatment era, we were unable to obtain detailed information on antiviral treatment (eg, interferon, ribavirin, DAAs) because the majority of the patients were followed outside of our transplant center before and after listing for, and after, transplantation. Interferon- or ribavirin-based anti-HCV therapy is not well tolerated in ESKD patients and its efficacy is limited.[27-29] Although the number of patients who received the pertinent therapy was likely very small, it is still possible that some patients did indeed receive such therapy or even more recent and effective DAA therapy, which could have altered patient and graft survival. We were also unable to obtain histopathological information about baseline and subsequent (pretransplant and posttransplant) evolution of the candidates' and recipients' liver disease. Although the progression of the liver disease was shown to be similar or even slowed down after kidney transplantation,[5] it is possible that our patients had some degree of baseline differences in liver fibrosis at listing or at transplant, specifically in the patients who had been on dialysis for a long time because disease progression may occur more rapidly while on dialysis.[5] Because of the limitation of United Network for Organ Sharing/Organ Procurement and Transplantation Network data collection, we used donor HCV serology to define HCVD+ and were unable to evaluate the impact of donor HCV viremia on posttransplant outcome. Other limitations of the study include the retrospective nature of the analysis, the limited number of patients and low generalizability. First, although donor and recipient characteristics were adjusted by multivariate analysis, factors not collected or included in the analysis could have affected the outcome. It would be unpractical and unethical to conduct a randomized study against a candidate's will, but prospective data collection could have increased data accuracy and enabled more detailed analyses. Second, the study was conducted in a single center with a relatively small number of patients. As outlined in the previous paragraph, the event rates were low especially in posttransplant outcomes, and the possibility of a type II error was not excluded. Finally, the study was conducted in a busy urban transplant center in a region with a large waiting list and long waiting times, thus the findings may not apply to regions with a short list and waiting time or regions with different donor (eg, age) and recipient (eg, time on dialysis) characteristics.

Extrahepatic involvement of HCV is known to affect pretransplant and posttransplant outcome, including kidney function,[30,31] diabetes mellitus[26,32,33] and cardiovascular disease.[34] The proportions of diabetes between group Y and group N were nearly identical and should not have affected the main outcome of the study; however, diabetes was more prevalent in these 2 groups than HCV-RNA-negative group C and this difference could have affected the outcomes, including more delisting events observed in group N and numerically lower posttransplant patient survival in groups Y and N than group C. Although the long-term impact of anti-HCV treatment, specifically DAA, on hepatic and extrahepatic morbidity awaits further studies, different combinations of anti-HCV agents for virtually all genotypes have been reported in ESKD and posttransplant patients with dramatic improvement of response rates and tolerability over historical cohorts.[28,35–41] With universal use of DAA in transplant candidates and recipients, the survival rates of HCV+ patients will likely increase and the negative impact of HCVD+ will likely decrease, and the small numerical differences of posttransplant survival we observed in the current study may be diminished by DAA. This strategy has been successfully extended to HCVD+ kidney transplantation into HCV-positive[42,43] and HCV-negative recipients.[44] Therefore, with increasing availability of modern HCV treatment modalities for dialysis and posttransplant patients, a similar study could result in a markedly different outcome. At the same time, as DAA use spreads to the general HCV+ population, the advantage of HCVD+ listing (ie, short waiting time) may decrease as the proportion of HCVD+ drops over time.

Our study still has several important clinical implications, even in the current era of modern HCV treatment with DAA. First, it demonstrates that HCVD+ can be safely used to expand the current very limited deceased donor pool. Although in our study overall survival and posttransplant outcomes for those willing (vs not willing) to accept a HCVD+ DDKT were similar, the transplantation of HCVD+ kidneys still had the net effect of offloading the DDKT waitlist. Second, even though in the future many more HCV+ transplant candidates will likely receive anti-HCV treatment, there will be a certain number of patients who have lack of insurance and access to the typically very expensive modern HCV treatments. Finally, our study demonstrates again that kidneys from HCVD+ are not associated with intrinsically worse outcomes. This is an important finding as more recently proposed approaches would entail transplantation of HCVD+ kidneys into HCV- recipients followed by HCV treatment.[44] Our study outcomes also support that approach in that HCVD+ serostatus was not an independent risk factor for graft loss — even in recipients that were still positive for HCV. Thus, it may be important to educate community providers that pretransplant anti-HCV treatment may not be the best choice for some patients, especially for those with earlier stage hepatic disease.

In conclusion, the current study demonstrates the benefits of accepting HCVD+ in HCV-positive transplant candidates, including shorter waiting time, higher transplant rate and lower removal rate by death or deteriorated medical conditions. Overall survival from the transplant listing appeared to be similar among HCV-positive candidates regardless of their willingness to accept HCVD+. Further studies are required to determine if these findings persist in the era of new anti-HCV treatment.

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