Effect of kidney donor hepatitis C virus serostatus on renal transplant recipient and allograft outcomes

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Abstract

Background: Hepatitis C virus (HCV) infection is common in dialysis patients and renal transplant recipients and has been associated with diminished patient and allograft survival. HCV-positive (HCV+) kidneys have been used in HCV-positive (HCV+) recipients as a means of facilitating transplantation and expanding the organ donor pool; however, the effect of donor HCV serostatus in the modern era is unknown.

Methods: Using national transplant registry data, we created a propensity score–matched cohort of HCV+ recipients who received HCV-positive donor kidneys compared to those transplanted with HCV-negative kidneys.

Results: Transplantation with an HCV+ kidney was associated with an increased risk of death [hazard ratio (HR) 1.43 [95% confidence interval (CI) 1.18–1.76]; P < 0.001] and allograft loss [HR 1.39 (95% CI 1.16–1.67); P < 0.001] compared with their propensity score–matched counterparts. However, HCV+ kidneys were not associated with an increased risk of acute rejection [odds ratio 1.16 (95% CI 0.84–1.61); P = 0.35].

Conclusions: While use of HCV+ donor kidneys can shorten the wait for renal transplantation and maximize organ utility for all candidates on the waiting list, potential recipients should be counseled about the increased risks associated with HCV+ kidney.

Key words: hepatitis C, hepatitis C-positive donors, kidney transplantation
Introduction

Hepatitis C virus (HCV) infection is more prevalent in ESRD and renal transplant populations compared with the general US population; 4–10% of dialysis patients are HCV-positive (HCV+) [1, 2]. Direct-acting antivirals (DAAs) were introduced for the treatment of HCV infection in 2013, but despite this advance in HCV therapy, the majority of patients remain untreated [3].

Using national transplant registry data [4], we have previously demonstrated that HCV infection is associated with poor outcomes after renal transplantation, with a hazard ratio (HR) for death of 1.44 [95% confidence interval (CI) 1.33–1.56; P < 0.001] and for allograft loss of 1.43 (95% CI 1.31–1.56; P < 0.001). In our study, 28% of HCV+ recipients were transplanted with an HCV+ donor (HCV+D) kidney, but the specific contribution of donor HCV serostatus to patient outcomes was not examined.

Despite these considerations, transplantation of HCV+ organs will likely increase in response to the growing waitlist demand and the existence of effective HCV therapies. Use of HCV+D kidneys for HCV+ recipients has been associated with decreased waiting times for transplantation [5]. Patients accepting HCV+ kidneys waited on average 395 days fewer than those at the same center who declined such offers and increased organ utilization; from 2005 to 2014, 3273 HCV+D contributed 2402 kidneys to the donor pool [6]. While DAAs are effective in clearing HCV viremia after kidney transplant [7–9], it is too early to assess the impact of viral clearance on posttransplant outcomes.

Single-center reports [10, 11] and registry analyses [12–14] have examined the effect of donor HCV serostatus on outcomes, with conflicting results. Older analyses [12–14] employing data from the Organ Procurement and Transplantation Network (OPTN) database and the United States Renal Data System (USRDS) have demonstrated worse patient and allograft outcomes (~1.4-fold) associated with the use of HCV+D kidneys. However, a more contemporary series from Spain [10] that included 162 recipients of HCV+ kidneys failed to detect any differences in patient survival (PS) but noted diminished 5- and 10-year allograft survival in recipients from HCV+D kidneys. A series from the University of Maryland [11] compared outcomes for 195 HCV+ recipients of HCV+D kidneys to 66 HCV+ recipients of HCV−D kidneys; neither PS nor all-cause graft loss was significantly different on the basis of donor HCV serostatus. Thus the available data regarding outcomes for recipients of HCV+ organs are limited, either by the era in which the studies were conducted or by performance at a single transplant center.

Using national transplant registry data, we created a matched cohort of HCV+ recipients who received HCV+D kidneys compared with those transplanted with HCV−D kidneys in order to assess the impact of donor HCV serostatus on patient and allograft survival in the modern era.

Materials and methods

Study design

We performed a retrospective cohort analysis using registry data collected by the United Network for Organ Sharing (UNOS); this study is based on OPTN data as of 4 March 2016. The database includes information on all transplant recipients and donors in the USA submitted by the members of the OPTN. The Health Resources and Services Administration, US Department of Health and Human Services provides oversight of the activities of the OPTN contractor. The study met eligibility criteria for exempt review authorized by 45 Code of Federal Regulations (CFR) §46.101, category 4, as confirmed by the Institutional Review Board at the University of Pennsylvania.

Subjects

In our primary analysis, we studied patients transplanted between 1 January 2001 and 31 December 2015; this time point was selected to reflect advances in HCV therapy (US Food and Drug Administration approval of pegylated interferon with ribavirin to treat HCV) and modern immunosuppression practices [predominance of tacrolimus as the calcineurin inhibitor (CNI) at discharge from the index hospitalization]. In a secondary analysis, we included all patients who were transplanted between 19 February 1995 (the first HCV+D in the dataset after our exclusion criteria were applied) and 31 December 2015. Patient follow-up was through 4 March 2016. The cohort was restricted to adult transplant recipients (>18-years of age) reported to have a positive HCV serostatus and receiving their first renal transplant (Figure 1); recipients of multiorgan transplants and HIV/HCV coinfected recipients were excluded.

Exposures and outcome measures

The primary exposure was transplantation with an HCV+D kidney. The primary outcome was all-cause mortality. Secondary outcomes examined included all-cause allograft failure and treated rejection within the first year. For mortality, patients were censored at the time of death or the end of follow-up. For the composite outcome of all-cause allograft failure, patients were censored at the time of allograft failure, death or at the end of follow-up, whichever was first. Sensitivity analyses were also performed in which we assessed for allograft failure as a competing risk for death and death as a competing risk for allograft failure; in these analyses, allograft loss does not preclude death but may modify the risk of mortality.

Covariates

Covariates were selected a priori that were known risk factors for mortality or allograft loss based on clinical judgment and published literature [15–18] (see Tables 1 and 2). As HCV serostatus is part of the kidney donor profile index (KDPI), all components of the KDPI [15] were incorporated into models as individual covariates rather than using KDPI as a composite measure. We restricted our analysis to recipients of deceased donor organs. Recipient-associated covariates included age, gender, race/ethnicity, diabetes mellitus, etiology of ESRD, pretransplant time on dialysis, days on the waitlist, percent panel reactive antibody (PRA) and median household income. Median household income was estimated using recipient zip codes and 2010 US census data adjusted for 2014 dollars. Transplant-associated covariates included degree of human leukocyte antigen (HLA) matching, cytomegalovirus (CMV) antibody status and induction and maintenance immunosuppression regimen at discharge from the index hospitalization. All covariates included in the final models were <5% incomplete.

Statistical analysis

Statistical analyses were performed using STATA version 14.0 (StataCorp, College Station, TX, USA) with two-sided hypothesis testing and P < 0.05 as the criteria for statistical significance. Descriptive statistics (means, medians and proportions) were
used to describe baseline donor and recipient clinical and demographic characteristics comparing patients exposed to a HCV+D versus HCV−D kidney. Continuous variables were compared using Student’s t-test, or rank sum test for nonnormally distributed variables. Categorical variables were compared using chi-square test.

We used propensity score matching in order to balance important baseline characteristics between the exposure groups. We generated the propensity scores using logistic regression with key covariates that were determined a priori (Tables 1 and 2). We applied a nearest neighbor matching algorithm using a caliper of 0.01 with common support and no replacement to create 1:1 matches [20, 21]. Sensitivity analyses were performed including all patients from 19 February 1995 onwards, stratifying by patient age, adjusting for region and liver center status, as well as by adjusting the overall cohort by propensity score instead of matching. We assessed for balance and bias using t-testing for equality of the means in the two groups, standardized difference between the two groups, the variance ratio between the two groups (for continuous covariates) [19], visual examination of histograms of propensity scores between the two exposure groups (Supplementary Figure S1) and evaluation of Rubin’s B and R [22]. After performing the propensity score matching, Cox proportional hazards regression was used to estimate HRs and 95% CIs for mortality and all-cause allograft failure. Robust sandwich estimation of the variance of the regression coefficient was used to account for clustering within the matched groups [23, 24]. The proportional hazards assumption was assessed via weighted versions of Kaplan–Meier curves using log-log plots [25]. Competing risk analysis was performed using subdistribution hazards modeling [26]. Logistic regression was used to estimate the odds of acute rejection at 1 year.

**Results**

After applying our exclusion criteria, we identified 4531 HCV+ recipients transplanted from 1 January 2001 through 31 December 2015; of these, 1814 received a HCV+D kidney and 2717 received a HCV−D kidney (Figure 1). The median follow-up time was 3.1 years.

Recipients of an HCV+D kidney were older (median age 57 years; P < 0.001), more often male (83.5% versus 69.6%; P < 0.001) and Caucasian (68.2% versus 50.7%; P < 0.001; Table 3). They had a shorter median dialysis duration (2.7 years versus 4.7 years; P < 0.001) and spent fewer days on the waiting list (median days 231 versus 771; P < 0.001). Diabetes mellitus was more common in recipients of HCV+D kidneys (51.2% versus 39.7%; P < 0.001) and spent fewer days on the waiting list (median days 231 versus 771; P < 0.001). Diabetes mellitus was more common in recipients of HCV+D kidneys (51.2% versus 39.7%; P < 0.001). Lymphodepleting induction was frequently used in both groups, but less often in HCV+D recipients (63% versus 68.1%; P < 0.001), and tacrolimus was the predominant CNI utilized during the study period regardless of donor HCV serostatus.

**Propensity score matching**

We assembled a propensity score–matched cohort using 1:1 matching. There were no statistically significant differences noted (Tables 1 and 2).
Table 1. Balance table presenting the baseline characteristics after propensity score matching for patient death in the 2001–15 cohort

| Variable                        | HCV+ donor (n = 782) | HCV− donor (n = 782) | Percent bias | t-Test | P-value<sup>a</sup> |
|---------------------------------|----------------------|----------------------|--------------|--------|---------------------|
| Mean age (years)                | 55.6                 | 55.2                 | 3.7          | 0.44   |                     |
| Male (%)                        | 80.1                 | 78.5                 | 3.7          | 0.45   |                     |
| Race (%)                        |                      |                      |              |        |                     |
| African American                | 25.1                 | 22                   | NR           | NR     |                     |
| Caucasian                       | 60.7                 | 64.5                 | −7.9         | 0.12   |                     |
| Latino                          | 10.6                 | 10.5                 | 0.4          | 0.93   |                     |
| Asian                           | 2.4                  | 1.8                  | 3.8          | 0.38   |                     |
| Other                           | 1.2                  | 1.2                  | 0.0          | 1.00   |                     |
| Mean years on dialysis          | 4.1                  | 4.2                  | −3.1         | 0.51   |                     |
| Mean total days on waitlist     | 520                  | 533                  | −2.1         | 0.59   |                     |
| Pretransplant diabetes (%)      | 46.5                 | 47.8                 | −2.6         | 0.61   |                     |
| Cause of ESRD (%)               |                      |                      |              |        |                     |
| Diabetes                        | 35.9                 | 36.8                 | NR           | NR     |                     |
| Hypertension                    | 42.9                 | 43.1                 | −0.3         | 0.96   |                     |
| Other                           | 21.2                 | 20.1                 | 2.7          | 0.57   |                     |
| Median annual income by zip code ($) | 49 141       | 46 882               | 2.1          | 0.66   |                     |
| Mean donor age (years)          | 39.7                 | 38.9                 | 5.6          | 0.27   |                     |
| African American donor (%)      | 14.3                 | 14.7                 | −1.1         | 0.83   |                     |
| Diabetic donor (%)              | 7.5                  | 7.3                  | 0.4          | 0.91   |                     |
| Donor HTN (%)                   | 28.5                 | 26.5                 | 4.6          | 0.36   |                     |
| DCD donor (%)                   | 8.3                  | 8.2                  | 0.4          | 0.93   |                     |
| Donor creatinine > 1.5 mg/dL (%)| 11.7                 | 11.4                 | 1.1          | 0.81   |                     |
| Mean donor height (cm)          | 171.6                | 171.9                | −2.7         | 0.54   |                     |
| Mean donor weight (kg)          | 78.6                 | 78.9                 | −1.6         | 0.73   |                     |
| Mean CIT (h)                    | 18.4                 | 18.6                 | −3.6         | 0.51   |                     |
| Induction type (%)              |                      |                      |              |        |                     |
| Lymphodepleting                 | 70.5                 | 71.2                 | NR           | NR     |                     |
| Nonlymphodepleting             | 29.5                 | 28.8                 | 1.7          | 0.74   |                     |

CIT, cold ischemia time; DCD, donor after cardiac death; HTN, hypertension; NR, not reported.

<sup>a</sup>Additional statistical measures demonstrating sufficient balance for the overall match: Rubin’s B = 14.4% (reference range < 25%), Rubin’s R = 0.86 (reference range 0.5–2) [22].

### Patient and allograft survival

In our primary cohort, the use of an HCV+D kidney was associated with an increased risk of death compared with receipt of an HCV−D kidney [HR 1.43 (95% CI 1.18–1.76); P < 0.001; Table 4 and Figures 2 and 3]. The risk of allograft loss was also increased in recipients of HCV+D kidneys [HR 1.39 (95% CI 1.16–1.67); P < 0.001]. This difference in graft survival (GS) could not be attributed to an increased risk of acute rejection in recipients of HCV+D kidneys [OR 1.16 (95% CI 0.84–1.61); P = 0.35], but may be due to patient mortality; when death was treated as a competing risk for allograft failure, GS was not statistically different [GS subhazard ratio (SHR) 1.10 (95% CI 0.86–1.40); P = 0.44]. When graft loss was treated as a competing risk for death, outcomes were unchanged compared with the primary models [SHR 1.46 (95% CI 1.19–1.80)]. This negative effect on patient and allograft survival persisted in sensitivity analyses in which we adjusted for the propensity score in the overall cohort as an alternative approach (Table 4).

We also examined the effect of region, presumed center-level expertise in transplantation of patients with HIV (using performance of liver transplants as a surrogate) and recipient age category. Models including region yielded similar outcomes for PS [HR 1.42 (95% CI 1.17–1.74); P = 0.001] and allografts [GS HR 1.28 (95% CI 1.08–1.53); P = 0.005], as did models including liver transplant center [PS HR 1.49 (95% CI 1.20–1.85); P < 0.001; GS HR 1.31 (95% CI 1.08–1.58); P = 0.005] or stratification by age [PS age < 60 years: HR 1.47 (95% CI 1.14–1.88); P = 0.003; PS age ≥ 60 years: HR 1.66 (95% CI 1.18–2.34); P = 0.004; GS age < 60 years: HR 1.40 (95% CI 1.13–1.73); P = 0.002; GS age ≥60 years: HR 1.48 (95% CI 1.05–2.11); P = 0.026].

We observed similar results in our sensitivity analysis that included all HCV+ recipients transplanted since 19 February 1995, with 2086 recipients of HCV+D kidneys and 3349 recipients of HCV−D kidneys. Demographics (Supplementary Tables S1–S3) were comparable to the 2001–15 cohort. In a propensity score–matched analysis, the risk of patient death was increased in the HCV+D cohort [HR 1.52 (95% CI 1.24–1.88); P < 0.001], as was the risk of allograft loss [HR 1.40 (95% CI 1.17–1.68); P < 0.001] (Supplementary Table S4 and Supplementary Figure S2). We again failed to observe an increased risk of acute rejection [OR 1.19 (95% CI 0.86–1.64); P = 0.29].

An etiology of death was only available for 54% of patients; the most commonly reported causes of death were cardiovascular disease (HCV+D 23% versus HCV−D 25%) and infection (HCV+D 16% versus HCV−D 23%; P = 0.39). Cause of allograft loss was only reported in 51% of patients. The most common causes of graft loss did not differ on the basis of donor HCV serostatus (chronic rejection, HCV+D 34% versus HCV−D 32%; acute rejection, HCV+D 19% versus HCV−D 14%; P = 0.61), nor was there a significant difference in recurrent glomerular disease (HCV+D 5.4% versus HCV−D 6.1%).
In this study we present the results of our retrospective, propensity score–matched cohort analysis comparing outcomes for contemporary recipients of HCV\(^+\)D kidneys to recipients of HCV\(^/-\)C0D kidneys. Use of an HCV\(^+\)D kidney was associated with an increased risk of mortality and allograft loss, despite matching on the basis of important clinical predictors. Our findings were reproducible in an older cohort of patients and supported by our sensitivity analyses accounting for propensity score, region or transplant center effects in the model.

Our results are consistent with older registry analyses employing UNOS or USRDS data [12–14], despite limiting our cohort to HCV\(^+\) recipients. Bucci et al. [12] demonstrated an increased risk of death for recipients of HCV\(^+\)D kidneys [HR 1.46 (95% CI 1.04–2.05)] transplanted between 1994 and 1998. In contrast to current practice, 34% of recipients of HCV\(^+\)D kidneys were HCV\(^-\); HCV\(^-\) recipients had a greater burden of comorbidities, which may have biased these results. An analysis from Abbott et al. [13] found similar outcomes for patients transplanted from 1996 through 2001. Maluf et al. [14] examined outcomes for HCV\(^+\) recipients transplanted from 2001 to 2006 in the UNOS dataset; use of HCV\(^+\)D kidneys was associated with an increased risk of death [HR 1.43 (95% CI 1.28–1.59)] and allograft loss [HR 1.48 (95% CI 1.36–1.60)] but follow-up was short and the effect of immunosuppression was not accounted for.

The difference between single-center series results and ours is not surprising. While single-center studies are important and provide granular clinical data, the numbers of patients in the two largest single-center series [10, 11] are significantly smaller than those captured in our registry analysis, and generalizability to the greater US transplant population is limited.

Also consistent with prior studies [10, 12, 14] was a lack of association between HCV\(^+\)D kidneys and acute rejection. While recipient HCV serostatus is a risk factor for acute rejection [27, 28], with contributions from candidate PRA, dialysis vintage and

### Table 2. Balance table presenting the baseline characteristics after propensity score matching for allograft loss in the 2001–15 cohort

| Variable                              | HCV\(^+\) donor (n = 623) | HCV\(^-\) donor (n = 623) | Percent bias | t-Test | P-value*a |
|---------------------------------------|----------------------------|---------------------------|--------------|--------|-----------|
| Mean age (years)                      | 55.1                       | 55.1                      | −0.4         | 0.94   | 0.51      |
| Male (%)                              | 81.8                       | 80.4                      | 3.5          | 0.51   |           |
| Race (%)                              |                            |                           |              |        |           |
| African American                      | 23.4                       | 23.1                      | NR           | NR     |           |
| Caucasian                             | 62.6                       | 64.8                      | −4.6         | 0.41   |           |
| Latino                                | 10.6                       | 9.6                       | 3.1          | 0.57   |           |
| Asian                                 | 2.1                        | 1.4                       | 3.8          | 0.39   |           |
| Other                                 | 1.3                        | 1.1                       | 1.4          | 0.79   |           |
| Mean years on dialysis                | 4.1                        | 4.1                       | 1.7          | 0.74   |           |
| Mean total days on waitlist           | 534                        | 534                       | −0.1         | 0.98   |           |
| Pretransplant diabetes (%)            | 47.9                       | 46.3                      | 3.2          | 0.57   |           |
| Cause of ESRD (%)                     |                            |                           |              |        |           |
| Diabetes                              | 36.4                       | 34.2                      | NR           | NR     |           |
| Hypertension                          | 43.9                       | 43.5                      | 1.0          | 0.86   |           |
| Other                                 | 19.7                       | 22.3                      | −6.1         | 0.27   |           |
| Median annual income by zip code ($)  | 48 506                     | 48 513                     | −0.0         | 0.99   |           |
| Mean maximum PRA                      | 9.8                        | 10.9                      | −4.4         | 0.38   |           |
| Mean donor age (years)                | 40.3                       | 40.4                      | −1.5         | 0.92   |           |
| African American donor (%)            | 16.1                       | 14                        | 6.0          | 0.29   |           |
| Diabetic donor (%)                    | 8.3                        | 7.8                       | 0.7          | 0.88   |           |
| Donor HTN (%)                         | 29.8                       | 27.1                      | 6.2          | 0.29   |           |
| DCD donor (%)                         | 9.1                        | 8.2                       | 3.2          | 0.55   |           |
| Donor creatinine > 1.5 mg/dL (%)      | 11.5                       | 11.5                      | 0.0          | 1.00   |           |
| Mean donor height (cm)                | 171.6                      | 172.2                     | −4.2         | 0.37   |           |
| Mean donor weight (kg)                | 78.6                       | 79.8                      | −6.0         | 0.26   |           |
| Mean CIT (h)                          | 18.4                       | 18.8                      | −4.2         | 0.50   |           |
| Discharge CNI (%)                     |                            |                           |              |        |           |
| Tacrolimus                            | 89.1                       | 89.9                      | −2.3         | 0.65   |           |
| Cyclosporine                          | 7.2                        | 6.4                       | 3.2          | 0.57   |           |
| Both tacrolimus and cyclosporine      | 3.4                        | 3.3                       | NR           | NR     |           |
| Non-CNI-based immunosuppression       | 0.3                        | 0.4                       | −3.1         | 0.65   |           |
| Induction type (%)                    |                            |                           |              |        |           |
| Lymphodepleting                       | 71.6                       | 71.6                      | NR           | NR     |           |
| Nonlymphodepleting                    | 28.4                       | 28.4                      | 0.0          | 1.00   |           |
| ≥Zero HLA mismatch (%)                | 99.0                       | 98.6                      | 2.4          | 0.44   |           |
| CMV risk category (%)                 |                            |                           |              |        |           |
| Donor and recipient negative          | 8.9                        | 8.4                       | NR           | NR     |           |
| Recipient positive                    | 75.4                       | 78.2                      | −6.4         | 0.25   |           |
| Recipient negative, donor positive    | 15.7                       | 13.4                      | 6.2          | 0.26   |           |

GIT, cold ischemia time; CNI, calcineurin inhibitor; DCD, donor after cardiac death; HTN, hypertension; NR, not reported.

*aAdditional statistical measures demonstrating sufficient balance for the overall match: Rubin’s R = 19.9% (reference range < 25%), Rubin’s B = 0.88 (reference range 0.5–2) [22].

### Discussion

In this study we present the results of our retrospective, propensity score–matched cohort analysis comparing outcomes for contemporary recipients of HCV\(^+\)D kidneys to recipients of HCV\(^-\)D kidneys. Use of an HCV\(^+\)D kidney was associated with an increased risk of mortality and allograft loss, despite matching on the basis of important clinical predictors. Our findings were reproducible in an older cohort of patients and supported by our sensitivity analyses accounting for propensity score, region or transplant center effects in the model.

Our results are consistent with older registry analyses employing UNOS or USRDS data [12–14], despite limiting our cohort to HCV\(^+\) recipients. Bucci et al. [12] demonstrated an increased risk of death for recipients of HCV\(^+\)D kidneys [HR 1.46 (95% CI 1.04–2.05)] transplanted between 1994 and 1998. In contrast to current practice, 34% of recipients of HCV\(^+\)D kidneys were HCV\(^-\); HCV\(^-\) recipients had a greater burden of comorbidities, which may have biased these results. An analysis from Abbott et al. [13] found similar outcomes for patients transplanted from 1996 through 2001. Maluf et al. [14] examined outcomes for HCV\(^+\) recipients transplanted from 2001 to 2006 in the UNOS dataset; use of HCV\(^+\)D kidneys was associated with an increased risk of death [HR 1.43 (95% CI 1.28–1.59)] and allograft loss [HR 1.48 (95% CI 1.36–1.60)] but follow-up was short and the effect of immunosuppression was not accounted for.

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Also consistent with prior studies [10, 12, 14] was a lack of association between HCV\(^+\)D kidneys and acute rejection. While recipient HCV serostatus is a risk factor for acute rejection [27, 28], with contributions from candidate PRA, dialysis vintage and
The cautious use of immunosuppression due to concerns for progression of underlying liver disease, donor HCV serostatus is not known to be, and it should not impact these factors; therefore the lack of association is unsurprising.

The association of HCV+D kidneys with inferior clinical outcomes is not unexpected. HCV causes glomerular disease in native kidneys and is a risk factor for diabetes [29]. HCV infection has been implicated in the development of de novo glomerulonephritis, including renal transplant glomerulopathy [30, 31]. The association between HCV and glomerular disease may overwhelm any protective effect offered by conservative donor selection; in general these kidneys are from donors less likely to be labeled as expanded criteria or have a terminal creatinine >1.5 mg/dL [5]. As HCV donor genotype is not available pretransplant, there exists the possibility of superinfection with a second HCV genotype [32] and more rapid progression to cirrhosis. Outcomes may also be affected by recipient selection—these organs are offered at a higher rate to diabetic patients and those in longer wait areas who are at greater risk of dying while on dialysis [5].

While we cannot directly assess how many recipients in our cohort were treated for HCV, it was likely only a small proportion given the novelty of these agents and complexity of the insurance-approval process [33]. Despite the inferior patient and allograft outcomes demonstrated with the use of HCV+D kidneys, there is a subset of patients, if not all patients, who might benefit from expedited transplantation with an HCV+D kidney followed by immediate posttransplant eradication of HCV using DAAs.

Our study has several strengths. It is the largest registry study to date to address the effect of donor HCV serostatus on outcomes. It was limited to HCV+ donors and recipients, unlike prior studies, in order to reflect current practice and provide a more accurate assessment of the magnitude of risk associated with use of HCV+D kidneys. With registry data, center-level variation is less prominent, allowing us to examine larger trends in

Table 3. Clinical and demographic characteristics of the cohort transplanted from 2001 to 2015

| Variable                                | HCV+ donor (n = 1814) | HCV− donor (n = 2717) | P-value  |
|-----------------------------------------|-----------------------|-----------------------|----------|
| Patient characteristics                 |                       |                       |          |
| Age (years), median (IQR)               | 57.0 (52.0–61.0)      | 56.0 (49.0–61.0)      | <0.001   |
| Male, n (%)                             | 1517 (83.5)           | 1894 (69.6)           | <0.001   |
| Race, n (%)                             |                       |                       | <0.001   |
| African American                        | 366 (20.2)            | 813 (29.9)            |          |
| Caucasian                               | 1238 (68.2)           | 1381 (50.7)           |          |
| Latino                                  | 165 (9.1)             | 360 (13.2)            |          |
| Asian                                   | 29 (1.6)              | 118 (4.3)             |          |
| Other                                   | 18 (1.0)              | 51 (1.9)              |          |
| Cause of ESRD, n (%)                    |                       |                       | <0.001   |
| Diabetes                                | 586 (37.8)            | 806 (29.6)            |          |
| Hypertension                            | 759 (41.8)            | 1049 (38.5)           |          |
| Glomerular disease                      | 114 (6.3)             | 287 (10.5)            |          |
| Cystic disease                          | 39 (2.2)              | 136 (5.0)             |          |
| Other                                   | 160 (8.8)             | 320 (11.8)            |          |
| Missing data                            | 58 (3.2)              | 124 (4.6)             |          |
| Time on dialysis (years), median (IQR)  | 2.7 (1.5–4.5)         | 4.7 (2.8–7.0)         | <0.001   |
| Total days on waitlist, median (IQR)    | 231 (77–556)          | 771 (331–1327)        | <0.001   |
| Pretransplant diabetes, n (%)           | 924 (51.2)            | 1073 (39.7)           | <0.001   |
| Maximum PRA, median (IQR)               | 0 (0–1)               | 0 (0–24)              | <0.001   |
| PRA >30%, n (%)                         | 186 (10.2)            | 607 (22.3)            | <0.001   |
| Donor characteristics                   |                       |                       |          |
| Age (years), median (IQR)               | 41.0 (29.0–49.0)      | 42.0 (26.0–52.0)      | 0.24     |
| African American donor, n (%)           | 213 (11.7)            | 438 (16.1)            | <0.001   |
| Diabetic donor, n (%)                   | 71 (3.9)              | 223 (8.2)             | <0.001   |
| Donor HTN, n (%)                        | 429 (23.9)            | 786 (29.1)            | <0.001   |
| Donor height (cm), median (IQR)         | 173 (167, 180)        | 172 (165, 180)        | <0.001   |
| Donor weight (kg), median (IQR)         | 77 (68, 90)           | 79 (67, 93)           | 0.012    |
| Donor after cardiac death, n (%)        | 110 (6.1)             | 383 (14.1)            | <0.001   |
| Terminal serum creatinine (mg/dL), median (IQR) | 0.9 (0.7–1.1)       | 1.0 (0.7–1.3)         | <0.001   |
| CIT (h), median (IQR)                   | 19.0 (13.5–24.4)      | 16.8 (11.5–22.9)      | <0.001   |
| Imunosuppression                        |                       |                       |          |
| Discharge CNI, n (%)                    |                       |                       | 0.008    |
| Tacrolimus                              | 1578 (86.9)           | 2323 (85.3)           |          |
| Cyclosporine                            | 101 (5.6)             | 221 (8.1)             |          |
| Both tacrolimus and cyclosporine        | 5 (0.3)               | 7 (0.3)               |          |
| Non-CNI-based immunosuppression         | 132 (7.3)             | 172 (6.3)             |          |
| Induction type, n (%)                   |                       |                       | <0.001   |
| Lymphodepleting                         | 887 (63.0)            | 1529 (68.1)           |          |
| Nonlymphodepleting                      | 445 (31.6)            | 579 (25.8)            |          |

CIT, cold ischemia time; CNI, calcineurin inhibitor; HTN, hypertension; IQR, interquartile range.
patient and allograft outcomes. Outcomes were similar in patients transplanted in the modern era, reflecting contemporary transplant practice with regards to donor/recipient selection and immunosuppression management, as well as in a larger, older cohort, demonstrating the stability of our findings over time. However, as transplant practice has evolved over time, results from the cohort dating back to 1995 may not be generalizable to current patients and practice. As the use of DAAs after transplantation becomes more widespread, clearly understanding historic outcomes for HCV\textsuperscript{þ} recipients is important, as this is the benchmark against which any improvement in patient or allograft survival associated with these expensive therapies will be judged.

Furthermore, this study informs recipients about the potential hazards associated with acceptance of HCV\textsuperscript{þ} offers, which may (or may not) be mitigated by posttransplant treatment for HCV infection, especially since DAA therapy is often delayed \[8\].

Our statistical methodology is another strength of our study; unlike traditional regression models, the use of propensity score matching facilitates rigorous estimation of the effect of donor HCV status on posttransplant outcomes by directly addressing the issues of selection bias and confounding by indication. Our propensity score matching was robust, with well-balanced groups that did not differ significantly from each other. Additionally, multiple sensitivity analyses confirmed our original results.

Our study has several weaknesses. We are limited by the completeness and detail of the data collected by UNOS, which is true of any study utilizing registry data. UNOS only collects HCV serological data; viral loads for both donors and recipients were not available and we could not distinguish between donors or recipients with active viremia and those who spontaneously cleared the virus or received HCV treatment with a sustained virologic response. However, given the low HCV treatment rates among dialysis patients \[3\], it is reasonable to assume that most

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**Table 4. Cox regression models for patient death and allograft loss in the 2001–15 cohort**

| Method                                      | Outcome | n      | Model adjustments | HR    | 95% CI | P-value |
|---------------------------------------------|---------|--------|-------------------|-------|--------|---------|
| 1:1 matching                                | PS\textsuperscript{a} | 1564   |                   | 1.43  | 1.18–1.76 | <0.001  |
| No matching                                 | PS\textsuperscript{a} | 3121   | P-score           | 1.42  | 1.19–1.68 | <0.001  |
| 1:1 matching                                | PS\textsuperscript{a} | 1564   | Region            | 1.43  | 1.17–1.76 | <0.001  |
| 1:1 matching                                | PS\textsuperscript{a} | 1564   | Liver center      | 1.49  | 1.20–1.85 | <0.001  |
| 1:1 matching, restricted to patients <60 years of age | PS\textsuperscript{a} | 1085   |                   | 1.47  | 1.14–1.88 | 0.003   |
| 1:1 matching, restricted to patients ≥60 years of age | PS\textsuperscript{a} | 479    |                   | 1.66  | 1.18–2.34 | <0.001  |
| 1:1 matching                                | GS\textsuperscript{b} | 1246   |                   | 1.39  | 1.16–1.67 | <0.001  |
| No matching                                 | GS\textsuperscript{b} | 2670   | P-score           | 1.35  | 1.16–1.58 | <0.001  |
| 1:1 matching, restricted to patients <60 years of age | GS\textsuperscript{b} | 1246   | Region            | 1.39  | 1.16–1.67 | <0.001  |
| 1:1 matching                                | GS\textsuperscript{b} | 1246   | Liver center      | 1.44  | 1.19–1.76 | <0.001  |
| 1:1 matching                                | GS\textsuperscript{b} | 884    |                   | 1.40  | 1.13–1.73 | 0.002   |
| 1:1 matching, restricted to patients ≥60 years of age | GS\textsuperscript{b} | 362    |                   | 1.48  | 1.05–2.11 | 0.026   |

\textsuperscript{a}Propensity scores incorporated recipient age, recipient race, male sex, dialysis vintage, recipient diabetes, cause of ESRD, donor age, donor weight, donor race, donor hypertension, donor diabetes, donor after cardiac death, donor creatinine, induction, cold ischemia time, days on the waitlist and median household income by zip code.

\textsuperscript{b}Propensity scores incorporated recipient age, recipient race, male sex, dialysis vintage, recipient diabetes, donor age, donor weight, donor race, donor hypertension, donor diabetes, donor after cardiac death, donor creatinine, induction, cold ischemia time, PRA, discharge maintenance immunosuppression, days on the waitlist, any HLA mismatches and CMV risk status.

**Fig. 2.** Patient survival stratified by HCV donor serostatus in the 2001–15 cohort.
HCV seropositive recipients have active HCV viremia. HCV genotype information was also not available, making it impossible to identify those with HCV superinfection. Additionally, UNOS data do not contain information regarding liver histology or permit assessment of liver disease progression. As UNOS does not capture information regarding treatment of HCV after transplantation, we cannot comment on the effect, if any, of HCV therapy with DAAs on outcomes for recipients of HCV+D kidneys. Furthermore, the UNOS dataset lacks complete and granular data regarding the etiologies of death and allograft loss, limiting the identification of mitigating factors. Although propensity score matching has a number of important benefits, it may reduce generalizability by restricting an analysis to only matched patients and cannot mitigate against unmeasured confounding.

In our retrospective propensity score–matched analysis, receipt of an HCV+D kidney was associated with an ∼40% increased risk of death and allograft loss in HCV+ recipients. However, this approach, coupled with prompt initiation of anti-HCV therapy, can shorten the wait for renal transplantation and maximize organ utility for all candidates on the waiting list. Recipients should be counseled about the increased risks associated with these organ offers, but not necessarily decline them.

**Supplementary data**

Supplementary data are available online at http://ckj.oxfordjournals.org.

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**Authors’ contributions**

K.C.E.: data analysis/interpretation, drafting article; K.A.F.: study design, statistics, critical revision of article; J.B.C.: study design, statistics, drafting article; B.S.: data analysis, critical revision of article; J.E.L.: study design, critical revision of article; D.S.: study design, data analysis/interpretation, drafting article.

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**Conflict of interest statement**

None declared.

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