ORIGINAL ARTICLE

Donor hepatitis C antibody positivity misclassifies kidney donor profile index in non-hepatitis C-infected donors: time to revise the kidney donor profile index – a retrospective cohort study

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SUMMARY

The kidney donor profile index (KDPI) defines an hepatitis C (HCV) positive donor based on HCV antibody (Ab) and/or nucleic acid amplification test (NAT) positivity, with donors who are not actively infected (Ab+/NAT−) also classified as HCV positive. From Scientific Registry of Transplant Recipients dataset, we identified HCV-negative recipients, who received a kidney transplant from HCV Ab+/NAT− (n = 116) and HCV Ab−/NAT− (n = 25 574) donor kidneys. We then compared recipients' estimated glomerular filtration rate (eGFR) at 6 months in matched cohorts, using combined exact matching (based on KDPI) and propensity score matching. We created two separate matched cohorts: for the first cohort, we used the allocation KDPI, while for the second cohort we used an optimal KDPI, where the HCV component of KDPI was considered negative in Ab+/NAT− patients. The mean ± SD age of the allocation KDPI-matched cohort at baseline was 59 ± 10 years, 69% were male, 61% were white. Recipients' eGFR at 6 months after transplantation was significantly higher in the HCV Ab+/NAT− group compared to the HCV Ab−/NAT− group (61.1 ± 17.9 vs. 55.6 ± 18.8 ml/min/1.73 m^2, P = 0.011) in the allocation KDPI-matched cohort, while it was similar (61.8 ± 19.5 vs. 62.1 ± 20.1 ml/min/1.73 m^2, P = 0.9) in the optimal KDPI-matched cohort. Recipients who received HCV Ab positive, but NAT-negative donor kidneys did not experience worse 6-month eGFR than correctly matched HCV Ab−/NAT− recipients.

Transplant International 2020; 33: 1732–1744

Key words
graft function, hepatitis C, kidney donor profile index, kidney transplantation

Received: 18 July 2020; Revision requested: 13 August 2020; Accepted: 7 September 2020;
Published online: 5 October 2020

doi:10.1111/tri.13743

Introduction

The kidney donor profile index (KDPI) is a numerical measure computed on the basis of ten donor factors including donor age, height, weight, ethnicity, history of hypertension and diabetes, cause of death, serum creatinine level, hepatitis C (HCV) status and donation after circulatory death status, and risk-stratifies a deceased donor kidney relative to other recovered kidneys [1]. Higher KDPI is associated with lower quality and expected longevity of a kidney. In this calculation, a HCV positive donor is defined as a donor with positive HCV antibody (Ab) and/or nucleic acid amplification test (NAT). As a result, even a donor who is not actively infected [HCV Ab positive and HCV NAT-negative], is considered HCV positive for KDPI calculation. Kidneys from HCV positive donors have higher KDPI than kidneys from otherwise similar HCV-negative donors and hence considered to be at risk for poorer graft outcome [2]. This leads to an increased organ discard rate and underutilization of kidneys from HCV positive donors [3]. Candidates, who are expected to live the longest (Estimated Post-Transplant Survival (EPTS) score of 20% or less) are prioritized to receive kidneys from donors with a KDPI ≤20% in the new Kidney Allocation System (KAS). Many of the kidneys from HCV positive donors (Ab positive and/or NAT positive) are not prioritized to recipients with EPTS score of 20% or less due to the perceived worse outcome reflected in their high KDPI [4], which might result in potentially losing "kidney life."

On the other hand, most recent studies have shown favorable patient and graft survival in recipients of HCV antibody and/or NAT+ donor kidneys in the direct-acting antiviral (DAAs) drug era [4–6]. In addition, Potluri *et al.* [6] showed that transplantation of HCV-viremic donors into HCV-seronegative recipients had similar 1-year estimated Glomerular Filtration Rate (eGFR), despite the worse KDPI assigned to the HCV-viremic donors, compared to matched (based on predictors of organ quality) HCV non-viremic donors. Moreover, it was also shown that eGFR at 6 and 12 months was similar in HCV-seronegative recipients who received an HCV-viremic donor compared to HCV-seronegative recipients who received similar quality HCV-negative kidneys using optimal KDPI [6,7]. The concept of optimal KDPI was introduced by Reese at al., who proposed to calculate KDPI by considering the HCV component to be negative in recipients who experienced HCV cure shortly after transplantation of a kidney from an HCV-viremic donor [6,7]. In addition, Sibulesky *et al.* showed that the kidney graft survival of the HCV non-viremic kidneys (HCV Ab+/NAT−) tended to be superior to HCV-negative kidneys when matched by KDRI and the EPTS score of the recipients [4]. If these kidneys were considered to be HCV-negative, their survival was comparable to the matched HCV non-infected kidneys [4,8]. However, it is still unknown whether short-term outcomes, such as eGFR at 6 months, would be comparable in HCV-negative recipients who received donor kidneys from HCV Ab positive and NAT-negative (HCV Ab+/NAT−) as compared to those who received kidneys from HCV Ab-negative and NAT-negative (HCV Ab−/NAT−) donors. The group from Vanderbilt University showed that kidney transplant recipients from HCV Ab+/NAT− donors will not become RNA positive after transplantation [9], so theoretically these kidneys should have better short-term graft function than HCV Ab−/NAT− donor kidneys as their KDPI is artificially higher only because of HCV Ab positivity.

The aim of our study was to compare eGFR at 6 months after transplantation of kidneys from HCV Ab+/NAT− vs. HCV Ab−/NAT− donors in HCV-negative recipients. We performed two different comparisons. First, we compared eGFR at 6 months after transplantation of HCV Ab+/NAT− and matched HCV Ab−/NAT− donors using allocation KDPI in the matching process, hypothesizing that eGFR will be higher in the HCV Ab+/NAT− group compared to the HCV Ab−/NAT− group. Then, we compared eGFR at 6 months after transplantation of HCV Ab+/NAT− and matched HCV Ab−/NAT− donors using optimal KDPI in the matching process. In this approach, we hypothesized that eGFR will be similar in the recipients receiving an organ from HCV Ab+/NAT− and HCV Ab−/NAT− donors.

Materials and methods

Cohort definition and data source

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors [10].

Our exposure of interest was the nucleic acid test (NAT) status of the donor, which was reported in the SRTR database only after April 1, 2015. Therefore, we used a cohort that was transplanted after April 1, 2015. The baseline cohorts contained 33 346 adult deceased-kidney-transplant HCV Ab-negative recipients transplanted between April 1, 2015 and March 2, 2018. Furthermore, we needed to calculate KDPI from the 10 variables (donor's age, height, weight, ethnicity/race, history of hypertension and diabetes, cause of death, serum creatinine, donation after cardiac death, and HCV Ab status) provided by UNOS/OPTN, and therefore, those without these variables were also excluded. We also excluded the recipients transplanted from HCV NAT positive donors. There was no clinically significant difference in the characteristics of the included and excluded patients (Table S1). The remaining 32 662 recipients were divided into two groups based on the result of donors' HCV antibody test (either positive or negative) and we further excluded those who did not have eGFR available at 6 months after kidney transplant, which was our outcome measure of interest (Fig. 1).

Definition of the exposure and control groups

The main exposure of interest was the donor HCV Ab status. The exposure group was defined as transplantation from an HCV Ab+/NAT− donor [HCV Ab+/NAT− group, $N = 116$] and the control group was defined as transplantation from an HCV Ab−/NAT− donor [HCV Ab−/NAT− group, $N = 25\ 574$] (Fig. 1).

The definition of outcome

The primary outcome of interest was estimated glomerular filtration rate (eGFR) at six months after transplantation. The eGFR was calculated using the CKD-EPI formula [11]. We accepted ±30 days as a window period of the date of measurement of serum creatinine for eGFR at six months after transplantation.

Covariates

The following information was extracted from the SRTR database about recipients: age, gender, race, body mass index (BMI), induction therapy including anti-thymocyte globulin (ATG), any calcineurin inhibitors (CNI) and mycophenolic acids (MPA) at discharge, history of organ transplantation, a history of delayed graft function (DGF) defined as a need for at least one dialysis session within 1 week after transplantation, history of diabetes and dialysis therapy before transplantation, and the number of human leukocyte antigen (HLA) mismatches.

The following information was extracted from the SRTR database about donors: for calculating UNOS allocation KDPI, age, ethnicity/race, height, weight, history of diabetes (DM) and hypertension (HTN), cause of death, donation after cardiac death (DCD), serum creatinine before donation, and HCV Ab serostatus. Gender was also extracted for the baseline characteristics.

Calculation of UNOS allocation KDPI and optimal KDPI

We strived to rigorously match the two groups based on UNOS allocation KDPI and optimal KDPI similar to the Transplanting Hepatitis C Kidneys into Negative KidnEy Recipients (THINKER) trial and clinical practice-based studies [7,12]. With regard to UNOS allocation KDPI, KDPI was calculated in accordance with "A Guide to Calculating and Interpreting the Kidney Donor Profile Index (KDPI), updated: May 15, 2019" using each year's KDRI to KDPI mapping table issued by OPTN [13]. With regard to optimal KDPI, we recalculated the original KDPI scores as if donors were HCV-uninfected (HCV Ab+/NAT−) (Fig. 2). Optimal KDPI values are typically 20–25% lower than the original score [6,12].

Two steps matching method

We implemented a two steps matching method to create comparable groups. First, we performed exact matching on allocation/optimal KDPI in the two recipient groups (HCV Ab+/NAT− and HCV Ab−/NAT− group), resulting in patient pairs with identical allocation/optimal KDPI. We then performed additional matching using propensity scores (PS) to account for the confounding effects arising from differences in the participants' baseline characteristics in the HCV Ab+/NAT− and the HCV Ab−/NAT− groups. First, covariates associated with receiving HCV Ab+/NAT− were identified using logistic regression analysis and were used for calculating PSs. We used the "psmatch2" command in STATA to generate 1:4 PS matched cohorts using nearest neighbor matching with replacement. The following variables were used for the logistic regression model to create the PS: recipients' age, gender, BMI,

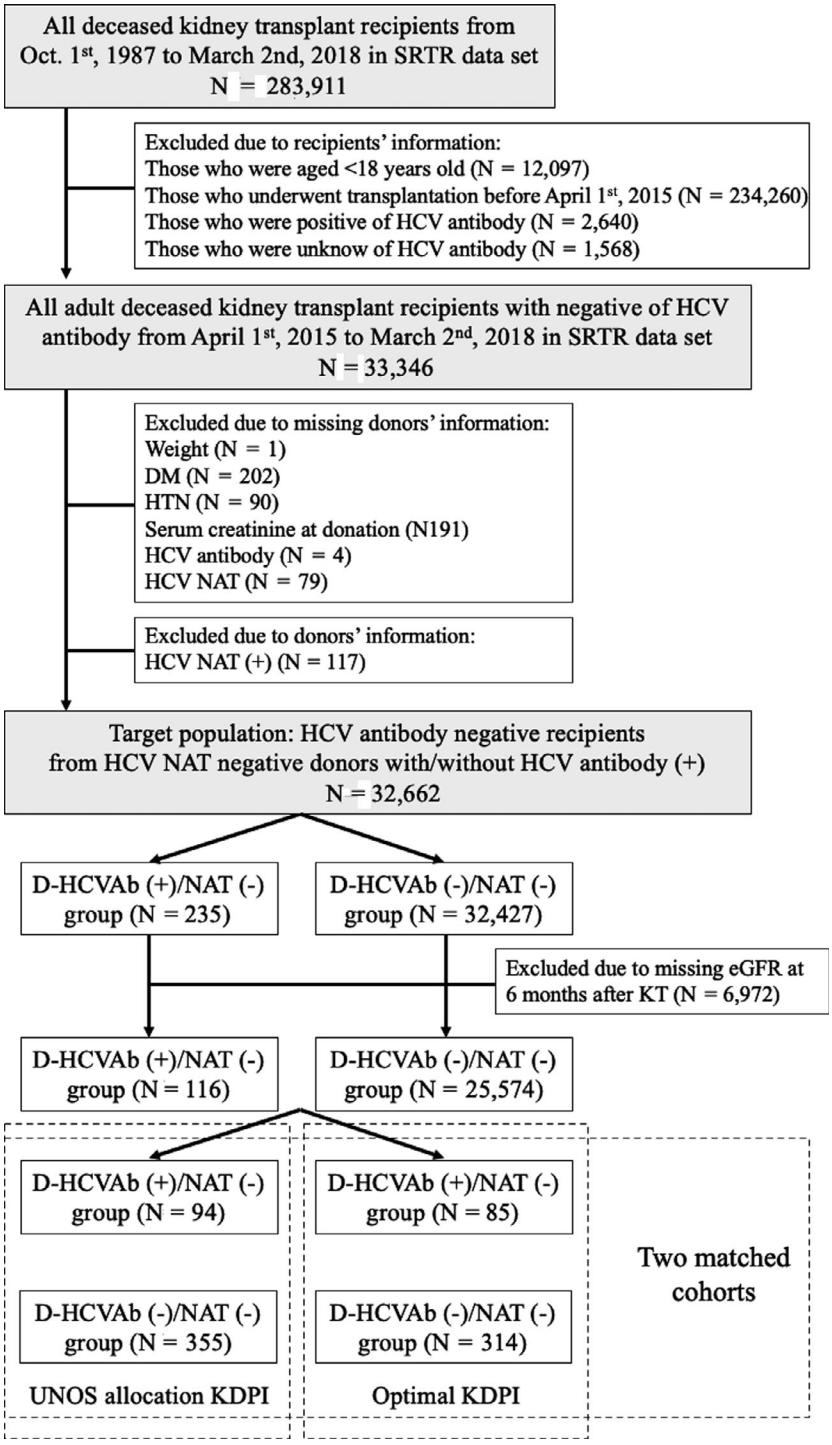

Figure 1 Flow chart of selection of the patients. Ab, antibody; DM, diabetes mellitus; HCV, hepatitis C virus; KDPI, Kidney donor profile index; KT, kidney transplant; NAT, nucleic acid test; SRTR, scientific registry of transplant recipients.

previous kidney transplant, induction treatment, HLA mismatches, DGF.

The distribution of recipients' PSs in both HCV Ab+/NAT− and HCV Ab−/NAT− groups after matching are shown in Fig. S1a for UNOS allocation KDPI and in Fig. S1b for optimal KDPI.

Statistical analysis

Baseline characteristics were presented as means ± standard deviation (SD) or medians and interquartile ranges (IQR) for continuous variables, and numbers and percentages (%) for categorical variables, as appropriate.

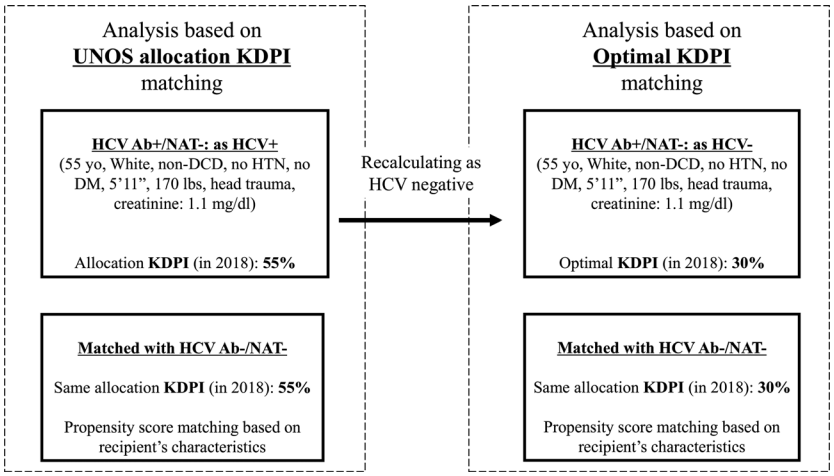

Figure 2 KDPI recalculation and matching process. Ab, antibody; DCD, donation after cardiac death; DM, diabetes mellitus; HCV, hepatitis C virus; HTN, hypertension; KDPI, kidney donor profile index; NAT, nucleic acid test; UNOS, United Network for Organ Sharing.

Differences between groups were analyzed by student *T*-tests or the Mann-Whitney test for continuous variables and the chi-square test for categorical variables. Standardized differences were calculated to compare characteristics between PS matched cohorts.

We used student *T*-tests for comparing the eGFR at 6 months after transplantation between HCV Ab+/NAT− and HCV Ab−/NAT− groups for both the UNOS allocation KDPI-matched cohort and for the optimal KDPI-matched cohort.

P values were two-sided and the significance level was set at less than 0.05 for all analyses. All analyses were conducted using STATA Version 13 (STATA Corporation, College Station, TX, USA). This study was approved by the Institutional Review Board of The University of Tennessee Health Science Center (18-05819-NHSR).

Results

Baseline characteristics

The baseline characteristics for the entire cohort before matching are shown in Table 1. The HCV Ab+/NAT− group was significantly older, had a higher proportion of males and a higher prevalence of diabetes, as well as higher HLA mismatches compared to the HCV Ab−/NAT− group. On the other hand, the HCV Ab+/NAT− group had a significantly higher rate of preemptive kidney transplantation and a lower prevalence of history of organ/kidney transplantation compared to HCV Ab−/NAT− group. As expected, UNOS allocation KDPI was significantly higher in the HCV Ab+/NAT− group compared to the HCV Ab−/NAT− group, while the optimal KDPI distribution was the opposite. The difference between UNOS allocation KDPI and optimal KDPI was approximately 20% in the HCV Ab+/NAT− group (Table 1).

Table 2 shows the baseline characteristics of the UNOS allocation-matched and optimal KDPI-matched cohorts. The UNOS allocation KDPI-matched cohort consisted of 94 HCV Ab+/NAT− recipients and 355 HCV Ab−/NAT− recipients. UNOS allocation KDPI was well matched between the two groups, as were most of the cohort baseline characteristics.

The optimal KDPI-matched cohort consisted of 85 HCV Ab+/NAT− recipients and 314 HCV Ab−/NAT− recipients. The optimal KDPI and most of the cohort characteristics itself were well matched between the two groups.

Estimated GFR at six months after kidney transplantation

The eGFR at 6 months after KT in the HCV Ab+/NAT− group was significantly higher compared to the HCV Ab−/NAT− group, with a mean difference of 5.5 ml/min/1.73 m^2 (95% CI: 1.3–9.7 ml/min/1.73 m^2) in the UNOS allocation-matched cohort (Table 3). On the other hand, the eGFR at 6 months after KT in the HCV Ab+/NAT− group was similar to the HCV Ab−/NAT− group [mean differences of 0.3 ml/min/1.73 m^2 (95% CI: −4.5 to 5.1 ml/min/1.73 m^2)] in the optimal KDPI-matched cohort (Table 3).

Discussion

In this national registry-based retrospective cohort study using the Scientific Registry of Transplant Recipients

Table 1. Baseline characteristics of HCV antibody-negative kidney transplant recipients who received a kidney allograft from an HCV NAT-negative deceased donor between April 1, 2015 and March, 2018.

	HCV Ab+/NAT− group (*N* = 116)	Missing no.	HCV Ab−/NAT− group (*N* = 25 574)	Missing no.	*P* value	Standardized differences
Recipient information						
Age, years, mean ± SD	58.4 ± 10.8	0	51.7 ± 13.5	0	<0.001	0.550
Sex, male, *n* (%)	80 (69.0)	0	15 032 (58.8)	0	0.026	−0.202
BMI, kg/m^2, mean ± SD	27.4 ± 5.3	1	28.1 ± 5.5	225	0.135	−0.141
Race, *n* (%)						
Caucasian	67 (57.8)	0	14 678 (57.4)	0	0.163	−0.022
African American	42 (36.2)		8476 (33.1)			
Asian	4 (3.5)		1848 (7.23)			
Native American	0		292 (1.1)			
Pacific Islander	2 (1.7)		120 (0.5)			
Multiracial	1 (0.9)		160 (0.6)			
Diabetes at transplantation, *n* (%)	51 (44.0)	0	8693 (34.1)	77	0.025	
Dialysis before transplantation, *n* (%)	95 (81.9)	0	23 310 (91.3)	29	<0.001	
Duration of dialysis, days, median (IQR)	1692 (1202, 2370)	8/95	1783 (1070, 2559)	1378/23 310	0.619	
Induction therapy, *n* (%)						
Non-induction	12 (10.4)	1	2304 (9.1)	123	0.550	0.030
ATG	64 (55.7)		15 476 (60.8)			
Alemtuzumab	16 (13.9)		3917 (15.4)			
IL-2 receptor blocker	23 (20.0)		3753 (14.8)			
OKT3	0		1 (<0.1)			
CNI use at discharge, *n* (%)	113 (98.3)	1	24 606 (96.6)	113	0.336	
MPA use at discharge, *n* (%)	114 (99.1)	1	24 641 (96.8)	113	0.154	
Previous any organ transplantation, *n* (%)	10 (8.6)	0	3979 (15.6)	0	0.040	
Previous kidney transplantation, *n* (%)	5 (4.3)	0	3697 (14.5)	0	0.002	−0.353
HLA mismatch, *n* (%)						
0 mismatch	0	0	1269 (5.0)	121	0.137	
1 mismatch	2 (1.7)		399 (1.6)			
2 mismatches	4 (3.5)		1375 (5.4)			
3 mismatches	13 (11.2)		3822 (15.0)			
4 mismatches	35 (30.2)		7087 (27.8)			
5 mismatches	42 (36.2)		7867 (30.9)			
6 mismatches	20 (17.2)		3634 (14.3)			
Total HLA mismatches, *n*, mean ± SD	4.5 ± 1.1	0	4.1 ± 1.5	121	0.005	0.312
Delayed graft function, *n* (%)	21 (18.1)	0	7040 (27.5)	2	0.023	−0.218
Donor information						
Age, years, mean ± SD	36.1 ± 12.2	0	37.4 ± 15.7	0	0.374	

Table 1. Continued.

	HCV Ab+/NAT− group (*N* = 116)	Missing no.	HCV Ab−/NAT− group (*N* = 25 574)	Missing no.	*P* value	Standardized differences
Sex, male, *n* (%)	50 (43.1)	0	15 744 (61.6)	0	<0.001	
BMI, kg/m^2, mean ± SD	26.7 ± 6.5	0	27.9 ± 7.2	0	0.071	
Race, *n* (%)						
Caucasian	114 (98.3)	0	20 831 (81.5)	0	<0.001	
African American	1 (0.9)		3808 (14.9)			
Asian	0		657 (2.6)			
Other	1 (0.9)		287 (1.1)			
Ethnicity of Hispanic/Latino, *n* (%)	7 (6.0)	0	3762 (14.7)	0	0.008	
Presence of diabetes, *n* (%)	2 (1.7)	0	1653 (6.5)	0	0.038	
Presence of hypertension, *n* (%)	20 (17.2)	0	6894 (27.0)	0	0.019	
Donation after cardiac death, *n* (%)	19 (16.4)	0	5188 (20.3)	0	0.296	
Cause of death, *n* (%)						
Anoxia	89 (76.7)	0	10 124 (39.6)	0	<0.001	
Cerebrovascular/stroke	8 (6.9)		6480 (25.3)			
Head trauma	15 (12.9)		8141 (31.8)			
Central nerve system tumor	0		92 (0.4)			
Other	4 (3.5)		737 (2.9)			
Serum creatinine before donation, mg/dl, mean ± SD	1.05 ± 0.61	0	1.23 ± 1.10	0	0.074	
Serum creatinine before donation, mg/dl, median (IQR)	0.96 (0.70, 1.23)	0	0.90 (0.70, 1.34)	0	0.671	
Serum creatinine >1.5 mg/dl before donation, *n* (%)	17 (14.7)	0	4987 (19.5)	0	0.189	
UNOS allocation KDPI, %	72.6 ± 16.0	0	59.8 ± 25.4	0	<0.001	0.625
Optimal KDPI, %	51.0 ± 20.7	0	59.8 ± 25.4	0	<0.001	

ATG, anti-thymocyte globulin; BMI, body mass index; CNI, calcineurin inhibitor; HCV, hepatitis C virus; HLA, human leukocyte antigen; IL-2, interleukin 2; IQR, interquartile range; KDPI, kidney donor profile index; MPA, mycophenolate acid; NAT, nucleic acid test; No, numbers; OKT3, anti-CD3 antibody; SD, standard deviation; UNOS, United Network for Organ Sharing.

The HCV Ab+/NAT− group is defined as HCV antibody-negative recipients who received transplantation from HCV antibody positive and NAT-negative donors. The HCV Ab−/NAT− group is defined as HCV antibody-negative recipients who received transplantation from HCV antibody-negative and NAT-negative donors. *P* values for continuous variables with mean ± SD are results of *t*-tests and with median (IQR) are result of the Mann-Whitney tests, and for categorical variables are results of chi-square tests.

Table 2. Baseline characteristics of HCV Ab+/NAT− and HCV Ab−/NAT− groups after matching based on UNOS allocation KDPI and optimal KDPI.

	UNOS allocation KDPI				Optimal KDPI			
	HCV Ab+/NAT− group (N = 94)	HCV Ab−/NAT− group (N = 355)	P value	Standardized differences	HCV Ab+/NAT− group (N = 85)	HCV Ab−/NAT− group (N = 314)	P value	Standardized differences
Recipient information								
Age, years, mean ± SD	58.6 ± 9.1	59.5 ± 10.8	0.471	−0.087	58.1 ± 9.9	57.7 ± 11.6	0.774	0.037
Sex, male, *n* (%)	65 (69.2)	245 (69.0)	0.980	−0.003	58 (68.2)	212 (67.5)	0.900	−0.015
BMI, kg/m^2, mean ± SD	27.4 ± 5.2	27.3 ± 5.6	0.857	0.021	27.6 ± 5.0	27.7 ± 5.5	0.873	−0.020
Race, *n* (%)								
Caucasian	57 (60.6)	215 (60.6)	0.396	−0.013	53 (62.4)	197 (62.7)	0.670	−0.026
African American	31 (33.0)	104 (29.3)			27 (31.8)	87 (27.7)		
Asian	4 (4.3)	30 (8.5)			3 (3.5)	22 (7.0)		
Native American	0	4 (1.1)			0	0		
Pacific Islander	1 (1.1)	1 (0.3)			1 (1.2)	5 (1.6)		
Multiracial	1 (1.1)	1 (0.3)			1 (1.2)	1 (0.3)		
Diabetes at transplantation, *n* (%)	41 (43.6)	144 (40.8)	0.621		35 (41.2)	122 (39.0)	0.713	
Dialysis before transplantation, *n* (%)	76 (80.9)	316 (89.5)	0.023		72 (84.7)	273 (87.2)	0.545	
Duration of dialysis, days, median (IQR)	1699 (1294, 2449)	1872 (1140, 2629)	0.614		1692 (1294, 2449)	1760 (1133, 2662)	0.770	
Induction therapy, *n* (%)								
Non-induction	8 (8.5)	41 (11.6)	0.748	0.054	8 (9.4)	43 (13.7)	0.156	−0.004
ATG	59 (62.8)	203 (57.2)			53 (62.4)	157 (50.0)		
Alemtuzumab	12 (12.8)	47 (13.2)			12 (14.1)	43 (13.7)		
IL-2 receptor blocker	15 (16.0)	64 (18.0)			12 (14.1)	71 (22.6)		
OKT3	0	0			0	0		
CNI use at discharge, *n* (%)	92 (97.8)	338 (95.2)	0.254		83 (97.7)	306 (97.5)	0.919	
MPA use at discharge, *n* (%)	93 (99.0)	340 (95.8)	0.141		84 (98.8)	306 (94.5)	0.450	
Previous any organ transplantation, *n* (%)	9 (9.6)	28 (7.9)	0.597		8 (9.4)	15 (4.8)	0.104	
Previous kidney transplantation, *n* (%)	5 (5.3)	20 (5.6)	0.906	−0.014	3 (3.5)	10 (3.2)	0.874	0.019
HLA mismatch, *n* (%)								
0	0	7 (2.0)	0.502		0	8 (2.6)	0.691	
1	1 (1.1)	3 (0.9)			1 (1.2)	3 (1.0)		
2	3 (3.2)	11 (3.1)			2 (2.4)	7 (2.2)		
3	12 (12.8)	47 (13.2)			11 (13.0)	31 (9.9)		
4	29 (30.9)	89 (25.1)			24 (28.2)	81 (25.8)		
5	36 (38.3)	122 (34.4)			33 (38.8)	116 (36.9)		
6	13 (13.8)	76 (21.4)			14 (16.5)	68 (21.7)		

Table 2. Continued.

	UNOS allocation KDPI				Optimal KDPI			
	HCV Ab+/NAT− group (N = 94)	HCV Ab−/NAT− group (N = 355)	P value	Standardized differences	HCV Ab+/NAT− group (N = 85)	HCV Ab−/NAT− group (N = 314)	P value	Standardized differences
Total HLA mismatches, n, mean ± SD	4.4 ± 1.1	4.5 ± 1.3	0.796	−0.032	4.5 ± 1.1	4.5 ± 1.3	0.881	−0.019
Delayed graft function, n (%)	17 (18.1)	67 (18.9)	0.862	−0.020	15 (17.7)	58 (18.5)	0.862	−0.021
Donor information								
Age, years, mean ± SD	37.3 ± 12.8	44.8 ± 14.5	<0.001		35.9 ± 12.4	35.0 ± 13.7	0.562	
Sex, male, n (%)	53 (56.4)	146 (41.1)	0.008		47 (55.3)	122 (38.9)	0.007	
BMI, kg/m^2, mean ± SD	27.3 ± 6.9	28.2 ± 7.5	0.297		27.0 ± 6.9	27.1 ± 7.0	0.926	
Race, n (%)								
Caucasian	92 (97.9)	279 (78.6)			83 (97.7)	264 (84.1)	0.009	
African American	1 (1.1)	65 (18.3)			1 (1.2)	36 (11.5)		
Asian	0	8 (2.3)			0	12 (3.8)		
Other	1 (1.1)	3 (0.8)			1 (1.2)	2 (0.6)		
Ethnicity of Hispanic/Latino, n (%)	7 (7.5)	45 (12.7)	0.159		6 (7.1)	44 (14.0)	0.086	
Presence of diabetes, n (%)	1 (1.1)	30 (8.5)	0.012		2 (2.4)	16 (5.1)	0.280	
Presence of hypertension, n (%)	18 (19.2)	153 (43.1)	<0.001		11 (12.9)	52 (16.6)	0.417	
Donation after cardiac death, n (%)	18 (19.2)	91 (25.6)	0.192		15 (17.7)	43 (13.7)	0.359	
Cause of death, n (%)								
Anoxia	73 (77.7)	140 (39.4)	<0.001		66 (77.7)	143 (45.5)	<0.001	
Cerebrovascular/stroke	8 (8.5)	129 (36.3)			7 (8.2)	60 (19.1)		
Head trauma	11 (11.7)	76 (21.4)			10 (11.8)	100 (32.9)		
Central nerve system tumor	0	1 (0.3)			0	2 (0.6)		
Other	2 (2.1)	9 (2.5)			2 (2.4)	9 (2.9)		
Serum creatinine before donation, mg/dl, mean ± SD	1.05 ± 0.64	1.11 ± 0.79	0.525		1.05 ± 0.49	1.41 ± 1.33	0.015	
Serum creatinine before donation, mg/dl, median (IQR)	0.98 (0.70, 1.20)	0.90 (0.65, 1.28)	0.645		0.99 (0.74, 1.23)	1.00 (0.70, 1.60)	0.480	
Serum creatinine >1.5 mg/dl before donation, n (%)	12 (12.8)	54 (15.2)	0.552		11 (12.9)	88 (28.0)	0.004	

Table 2. Continued.

	UNOS allocation KDPI				Optimal KDPI			
	HCV Ab+/NAT− group (N = 94)	HCV Ab−/NAT− group (N = 355)	P value	Standardized differences	HCV Ab+/NAT− group (N = 85)	HCV Ab−/NAT− group (N = 314)	P value	Standardized differences
UNOS Allocation KDPI, %	74.8 ± 15.1	74.9 ± 14.8	0.952	−0.007	73.6 ± 15.1	61.5 ± 21.4	<0.001	
Optimal KDPI, %	51.8 ± 20.0	74.6 ± 17.4	0.001		51.6 ± 19.3	52.1 ± 19.7	0.842	−0.024

ATG, anti-thymocyte globulin; BMI, body mass index; CNI, calcineurin inhibitor; HCV, hepatitis C virus; HLA, human leukocyte antigen; IL-2, interleukin 2; IQR, interquartile range; KDPI, kidney donor profile index; MPA, mycophenolate acid; NAT, nucleic acid test; No, numbers; OKT3, anti-CD3 antibody; SD, standard deviation; UNOS, United Network for Organ Sharing.

The HCV Ab+/NAT− group is defined as HCV antibody-negative recipients who received transplantation from HCV antibody positive and NAT-negative donors. The HCV Ab−/NAT− group is defined as HCV antibody-negative recipients who received transplantation from HCV antibody-negative and NAT-negative donors. P values for continuous variables with mean ± SD are results of t-tests and with median (IQR) are result of the Mann-Whitney tests, and for categorical variables are results of chi-square tests.

data set, we demonstrated that the eGFR at 6 months after KT in the HCV Ab+/NAT− group was significantly higher compared to the UNOS allocation KDPI-matched HCV Ab−/NAT− group. However, eGFR at 6 months after KT was almost identical when matched using the optimal KDPI. We calculated the optimal KDPI by considering the HCV component to be negative in HCV Ab+/NAT− donors as proposed by Reese *et al.* [7]. Our analysis indicates that HCV Ab+/NAT− donors perform better than expected based on UNOS allocation KDPI and might have been allocated differently based on the optimal KDPI. The UNOS allocation KDPI was approximately 20–25% higher than the optimal KDPI in the HCV Ab+/NAT− group, so many of them would have been allocated in different sequence based on optimal KDPI [12]. Our study results along with previous results [4–7] indicate that consideration should be given to revise KDPI and the HCV Ab component of KDPI should be removed.

While previous studies indicated that the long-term outcomes of HCV Ab+/NAT− versus HCV Ab−/NAT− kidneys are similar [4,5], none of these studies assessed the donor quality effect on short-term outcomes such as eGFR at 6 months after KT. While long-term outcomes might be affected by several recipients and post-transplantation factors, short-term eGFR correlates better with donor quality, which was the focus of our study. Previously Lee *et al.* [14] showed a strong linear relationship between KDPI and median eGFR. Additionally, the group from the University of Virginia showed that kidney graft function, as measured by GFR at 6 months post-kidney transplant, is a powerful predictor of long-term post-transplant outcomes [15]. Moreover, numerous studies have shown that early achieved eGFR is an important determinant of graft and patient survival [16–18], so eGFR at 6 months can also serve as a surrogate of long-term outcomes.

The eGFR at 6 months after KT was significantly higher in the HCV Ab+/NAT− group compared to HCV Ab−/NAT− group, with a mean difference of 5.5 ml/min/1.73 m^2, which is a clinically significant difference of graft function. This finding supports previous observations by Sibulesky *et al.* [4], who showed that the KDRI underestimates the superior quality and outcomes of the kidney grafts recovered from HCV non-viremic donors. La Hoz *et al.* [19] also showed similar serum creatinine at 6 months in the HCV Ab+/NAT− group compared to HCV Ab−/NAT− group, but did not perform match based on optimal KDPI. While one of the aims of the new kidney allocation system (KAS) is longevity matching, kidneys from HCV Ab+/NAT−

Table 3. Recipients' estimated glomerular filtration rate at 6 months after transplantation.

UNOS allocation KDPI matching	HCV Ab+/NAT− group *N* = 94	HCV Ab−/NAT− group *N* = 355	Mean difference (95% CI)	*P* value
eGFR (ml/min/1.73 m^2), mean ± SD	61.1 ± 17.9	55.6 ± 18.8	5.5 (1.3 to 9.7)	0.011
eGFR (ml/min/1.73 m^2), median (IQR)	60.5 (47.6, 72.2)	53.5 (42.3, 66.4)		0.008*
Optimal KDPI matching	***N* = 85**	***N* = 314**	**Mean difference (95% CI)**	***P* value**
eGFR (ml/min/1.73 m^2), mean ± SD	61.8 ± 19.5	62.1 ± 20.1	0.3 (−4.5 to 5.1)	0.904
eGFR (ml/min/1.73 m^2), median (IQR)	59.8 (46.7, 73.8)	60.1 (47.0, 75.8)		0.869*

95% CI, 95% confidence interval; D, donor's; GFR, glomerular filtration rate; HCV, hepatitis C virus; IQR, interquartile range; KDPI, kidney donor profile index; *N*, numbers; NAT, nucleic acid test; SD, standard deviation.

The HCV Ab+/NAT− group is defined as HCV antibody-negative recipients who received transplantation from HCV antibody positive and NAT-negative donors. The HCV Ab−/NAT− group is defined as HCV antibody-negative recipients who received transplantation from HCV antibody-negative and NAT-negative donors.

*Mann-Whitney *U* test was used for comparing the groups.

donors are being misclassified as having higher KDPI (20–25% more on an average) in the current KDPI calculation despite their superior quality and may not be prioritized to recipients with longer expectant survival. In a recent study, at least 122 more kidneys could have been prioritized to recipients with EPTS <20% if HCV Ab status had been considered negative [4].

Our results support and complement the results of previous studies showing no difference in patient and graft survival in patients receiving HCV positive, but non-infected compared to HCV-negative kidneys. While transmission risk of viremia from HCV NAT+ donors is universal [12], the transmission rate from HCV Ab+/NAT− donors is expected to be very low [9]. Sibulesky *et al.* [4] showed that the kidney graft survival of HCV positive kidneys tended to be superior to HCV-negative kidneys when matched by KDRI. One of the limitations of their study was that the majority of the recipients of non-viremic HCV kidneys were actually HCV seropositive, so the HCV status of the recipient might have had an effect on outcomes. In our study, we identified HCV seropositive recipients and also those who received kidneys from HCV-infected donors, and excluded them. Recently, Cannon et. al showed that recipients transplanted with kidneys from HCV Ab+ donors when compared to a propensity-matched group of recipients of kidneys from HCV Ab− donors had similar 1-year patient and graft survival [5]. However, prior to our result it was still unknown whether short-term outcomes, such as eGFR at 6 months, would be comparable in HCV-negative recipients who received kidneys from HCV Ab+/NAT− donors and from HCV Ab−/NAT− donors. Based on the results of these three studies [4,5] we can conclude that both short- and long-term outcomes are similar in recipients receiving HCV Ab+/NAT− versus HCV Ab−/NAT− kidneys.

As of recently, it was not known whether HCV-infected (HCV Ab+/Ab− and NAT+) kidney recipients who received early treatment for HCV infection, have similar outcomes as recipients who received non-infected kidneys. With the availability of highly effective, safe, and tolerable DAAs therapy, transplantation of kidneys from HCV-infected (NAT+) donors has become feasible with excellent graft function and 100% cure rate [7,12,20,21]. Additionally, Potluri *et al.* [6] showed that transplantation of HCV-viremic kidneys into HCV-seronegative recipients resulted in similar 1-year eGFR as matched HCV non-viremic kidneys despite the worse KDPI assigned to the HCV-viremic kidneys. Furthermore, in the THINKER trial, renal function at 6 and 12 months was similar among recipients of HCV-infected kidneys compared to matched recipients of HCV-negative kidneys [7].

Our study has several strengths. To the best of our knowledge, our study is the first one to examine if there is a difference in the short-term outcomes of HCV-seronegative recipients who received kidneys from HCV Ab+/NAT− donors compared to those who received kidneys from HCV Ab−/NAT− donors. We performed direct matching of recipients using allocation and optimal KDPI and we also used propensity score matching to balance recipient- and transplantation-related confounders between groups. Additionally, we used a national cohort, therefore our results are generalizable to the US transplant population. Finally, we were able to identify HCV Ab+ but non-infected donors using NAT data.

Our study also has limitation. Similarly to other retrospective observational study, the effect of residual

confounding cannot be excluded. We used a single eGFR to define 6-month graft function, which may limit accuracy due to fluctuations in serum creatinine. The number of HCV Ab+/NAT− patients in our cohort was relatively small which limited our statistical power and which made it difficult to achieve a perfect match with the HCV Ab−/NAT− group on all patients' characteristics. Moreover, we did not have reliable data on the timing of rejection and on panel reactive antibodies, so these important confounders were excluded from our analysis. Finally, a significant proportion of patients had missing values in the variables that were used to calculate the propensity score, therefore these patients have been excluded from our final cohort, which might limit the external validity of our results. Moreover, the outcomes of death and graft loss within 6 months were significantly more common in the HCV Ab−/NAT− group compared to the HCV Ab+/NAT− group among the excluded patients, suggesting that their inclusion in the analysis would have made the described associations even stronger.

Conclusion

Our results demonstrate that recipients who received HCV Ab+/NAT− donor kidneys had similar 6-month eGFR compared to HCV Ab−/NAT− recipients with similar optimal KDPI. We also confirmed that allocation KDPI underestimates the quality of these kidneys. Based on our results and those of previous studies [4,5,19] we propose that HCV Ab+/NAT− donor status should be considered as HCV-negative in the KDPI calculation.

Finally, our results along with those of previous studies [4–7,19] indicate that short- and long-term outcomes are similar in recipients who received HCV non-infected/HCV-infected kidneys versus those who received HCV-negative kidneys. These results raise questions about the need to revise the KDPI.

Authorship

MY: contributed to conception and design of the study, acquisition of data, performed the analysis and contributed to interpretation of data. Dr. Yazawa wrote the manuscript and approved the final approval of the version. VB: contributed to conception and design of the study and wrote the manuscript. MT: he contributed drafting the article or revising it critically for important intellectual content. AA: she contributed drafting the article or revising it critically for important intellectual content. MT: contributed to conception and design of the study. AB: contributed to conception and design of the study and contributed drafting the article. PKP: contributed to acquisition of data. JDE: contributed to conception and design of the study. CPK: he contributed drafting the article or revising it critically for important intellectual content. MZM: contributed to conception and design of the study, acquisition of data, performed the analysis and contributed to interpretation of data. Dr. Molnar wrote the manuscript and approved the final approval of the version. Dr. Molnar takes responsibility for the data and analysis accuracy and all other aspects of the work.

Funding

The authors have declared no funding.

Conflict of interest

The authors have declared no conflicts of interest.

Acknowledgements

The results of this paper have not been published previously in whole or part. The data reported here have been supplied by the Hennepin Healthcare Research Institute (HHRI) as the contractor for the Scientific Registry of Transplant Recipients (SRTR). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of or interpretation by the SRTR or the U.S. Government.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Histogram of propensity score in a matched population based on UNOS allocation KDPI (Panel a) and optimal KDPI (Panel b).

Table S1. Baseline characteristics of included and excluded HCV antibody negative kidney transplant recipients who received a kidney allograft from an HCV NAT negative deceased donor between April 1st, 2015 and March 2nd, 2018.

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