Received: 12 October 2019 | Accepted: 20 October 2019

DOI: 10.1111/tid.13204

ORIGINAL REPORT

WILEY

Trends in utilization of deceased donor kidneys based on hepatitis C virus status and impact of public health service labeling on discard

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Funding information
This research is partly supported by the University of Texas Southwestern The George M. O'Brien Kidney Research Core Center grant (NIH P30DK079328).

Abstract

Background: Kidneys from deceased donors infected with hepatitis C virus (HCV) are underutilized. Most HCV virus-infected donors are designated as Public Health Service increased donors (PHS-IR). Impact of PHS and HCV designations on discard is not well studied.

Methods: We queried the UNOS data set for all deceased donor kidneys between January 2015 and December 2018. The final study cohort donors (n = 38 702) were stratified into three groups based on HCV antibody (Ab) and NAT status: (a) Ab−/NAT− (n = 35 861); (b) Ab+/NAT− (n = 973); and (c) Ab±/NAT+ (n = 1868). We analyzed utilization/discard rates of these organs, the impact of PHS-IR and HCV designations on discard using multivariable two-level hierarchical logistic regression models, forecasted number of HCV viremic donors/kidneys by 2023.

Results: During the study period, (a) the number of viremic donor kidneys increased 2 folds; (b) the multilevel mixed-effects logistic regression models showed that, overall, the PHS labeling (OR 1.20, CI 95% CI 1.15-1.29) and HCV designation (OR 2.29; 95% CI 2.15-2.43) were independently associated with increased risk of discard; (c) contrary to the general perception, PHS-IR kidneys across all HCV groups, compared to PHS-IR kidneys were more likely to be discarded; (d) we forecasted that the number of kidneys from HCV viremic donor kidneys might increase from 1376 in 2019 to 2092 in 2023.

Conclusion: Hepatitis C virus viremic kidneys might represent 10%-15% of deceased donor organ pool soon with the current rate of the opioid epidemic. PHS labeling effect on discard requires further discussion of the utility of this classification.

KEYWORDS

discard, hepatitis C virus, nucleic acid testing, public health service - increased risk, utilization

Abbreviations: Ab, Antibody; DDRT, Deceased Donor Renal Transplant; HCV, Hepatitis C Virus; KDPI, Kidney Donor Profile Index; NAT, Nucleic Acid Test; PHS-IR, Public Health Service Increased Risk; UNOS, United Network for Organ Sharing.

Ariyamuthu and Sandikci contributed as a first author.

1 | INTRODUCTION

Renal transplantation (RT) is the treatment of choice for end-stage renal disease (ESRD).[1,2] Despite recent increases in the number of deceased donor (DD) RT,[3] there still exists a wide gap between supply and demand for RT. While there has been a concerted effort to maximize the utilization of kidneys from existing donors[4] and to increase the donor pool as well,[5] the proportion of kidneys discarded remains high. The last decade in the United States (US) has witnessed a significant change in the demographics of opioid users.[6] Opioid use is increasing among Caucasians with even higher rates in the Midwestern United States. Heroin use went up fivefold from 2002 to 2013,[7] coinciding with a surge in intravenous drug use (IVDU), hepatitis C virus (HCV) transmission, and opioid-related overdose deaths.[8-11] Donors dying due to overdose are more likely to be infected with HCV,[11] and organs from HCV-positive donors are underutilized.[12-15] Single-center studies have utilized HCV antibody positive[16,17] and viremic donors[18-20] for RT with good short-term outcomes. A recent national registry analysis by our group confirms excellent short-term outcomes for such transplants.[21]

Kidneys recovered from opioid overdose-death donors have predominantly been classified as the public health service increased risk (PHS-IR) donors, implying higher transmission risk of viral infection (mainly HCV, hepatitis B [HBV], and human immunodeficiency virus [HIV]) through organ donation (previously defined as Center for Disease Control and Prevention high-risk donors).[22-24] New guidelines obligated use of nucleic acid testing (NAT) supplementing serologic ones (mainly for HCV, HBV, and HIV) in 2013 for all PHS-IR donors and were officially implemented in 2015 in the US[24]

The purpose of our study was to analyze the trends in center specific, organ procurement organization (OPO) level, regional utilization of adult kidney donors based on donor HCV Ab and NAT status, study the impact of PHS labeling and HCV designation on discard of those kidneys, and forecast the number of HCV viremic donors by 2023.

2 | PATIENTS AND METHODS/MATERIALS AND METHODS

2.1 | Study population

This study used data from the OPTN STAR files administered by the United Network of Organ Sharing (UNOS), which includes data submitted by members on all donors, waitlisted candidates, and transplant recipients in the United States. The Health Resources and Services Administration (HRSA) of the US Department of Health and Human Services (DHHS) oversees the activities of the OPTN and the contractor. The University of Texas Southwestern Institutional Review Board approved the study.

This retrospective cohort study included all deceased donors registered in the OPTN STAR files from January 1st, 2015 through December 31st, 2018. Donors with incomplete HCV Ab and NAT information were excluded. Thus, we identified 38 702 deceased donors as a final cohort during the study period. For our analyses, HCV uninfected donor is defined as a donor with negative HCV Ab and negative NAT (HCV Ab−/NAT−); an HCV seropositive, non-viremic donor is defined as a donor with positive HCV Ab and negative NAT (HCV Ab+/NAT−); and an HCV viremic donor is identified as a subject with positive HCV NAT, regardless of the HCV Ab status (HCV Ab ±/NAT+). The term "HCV-positive donor" refers to donors with a positive HCV Ab and/or positive HCV NAT.

The study cohort donors (n = 38 702) were stratified into three groups based on HCV Ab and NAT status: (a) Ab−/NAT− (n = 35 861); (b) Ab+/NAT− (n = 973), and (c) Ab±/NAT+ (n = 1868). Under each HCV categories, the kidneys (N = 70 450) from above donors were further classified as "PHS-IR" or "PHS-IR" for the logistic regression analysis to predict discard: (a) HCV Ab−/NAT− (n = 66 224) category was composed of PHS-IR (n = 13 411, 20.3%) and PHS-IR (n = 52 787, 79.7%); (b) HCV Ab+/NAT− (n = 1459) category was composed of PHS-IR (n = 1030, 70.7%) and PHS-IR (n = 427, 29.3%); (c) HCV Ab±/NAT+ (n = 2767) category was composed of PHS-IR (n = 2298, 83.0%) and PHS-IR (n = 469, 17.0%).

2.2 | Primary outcomes

Primary outcome measures were transplantation and discard rates of deceased donors, utilization of NAT+ donors by transplant centers, Organ Procurement Organizations (OPO), UNOS Region, the impact of PHS-IR and HCV designation on discard, and forecasted number of HCV viremic kidneys by 2023.

2.3 | Statistical methods

Donor characteristics were summarized by mean and standard deviation for continuous variables, and count and percent of the total for categorical variables. Comparisons between groups were made using *t* test or Wilcoxon rank-sum test (non-parametric), one-way ANOVA or Kruskal-Wallis test by ranks (non-parametric) for continuous variables, and chi-squared test for categorical variables as appropriate. The Holm multiple comparison adjustments were used as a follow up to one-way ANOVA to calculate multiplicity adjusted *P*-values. The magnitude of missing data was minimal (<2%); thus, imputation was not used. A *P*-value < .05 was considered statistically significant. Statistical analyses were performed with Stata/MP14 (StataCorp LP) and R Free Software Foundation (version 3.5.1 version).

To account for variations in discard rates among the UNOS Regions (there are total of 11 regions in the US) and OPOs (there are total of 58 OPOs under eleven UNOS Regions), we utilized multilevel (two-level and three-level models) mixed-effect logistic regression models. For this analysis, we used the Stata command

of "melogit" which fits mixed-effects models for binary responses (https://www.stata.com/manuals14/melogit.pdf). Mixed-effects logistic regression contains both fixed and random effects. It is useful for modeling intracluster correlation because donors in the same cluster (the UNOS Region or OPO) are correlated and share common cluster-level random effects. We run three separate mixed-effects logistic regression analysis defining random effects for (a) the UNOS Regions (two-level models); (b) OPOs (two-level models); and (c) OPOs nested within the UNOS Regions (three-level models). For simplicity, we only reported results of the mixed-effects logistic regression models for the UNOS Regions (two-level models) because the results of other two models (for OPOs and OPOs nested within the UNOS Regions) did not show any major differences.

The mixed-effects logistic regression models were adjusted for previously identified donor factors in the literature,[25,26] including donor age > 50 or not, either kidney biopsied, glomerulosclerosis > 20% or not if biopsied, cytomegalovirus (CMV) status, KDPI, cause death due to cerebrovascular accident (CVA), donation after cardiac death (DCD) status, height, weight, history of tattoo, either kidney pumped, cold ischemica time, hepatitis B core antibody status, hepatitis B surface antigen status, history of diabetes, history of hypertension, history of cocaine use, history of IV drug use (IVDU), terminal creatinine >1.5 mg/dL or not, ABO blood type, transplant year, and race. We did not find multicollinearity between individual elements of KDPI (10 donor variables) and KDPI score; therefore, we decided to keep KDPI in the multivariable mixed-effects logistic regression models.

The potential number of deceased donors with HCV NAT positivity is forecasted into the year 2023 using time series analysis with trend adjusted exponential smoothing method; Excel's built-in FORECAST.ETS function was utilized for this purpose.

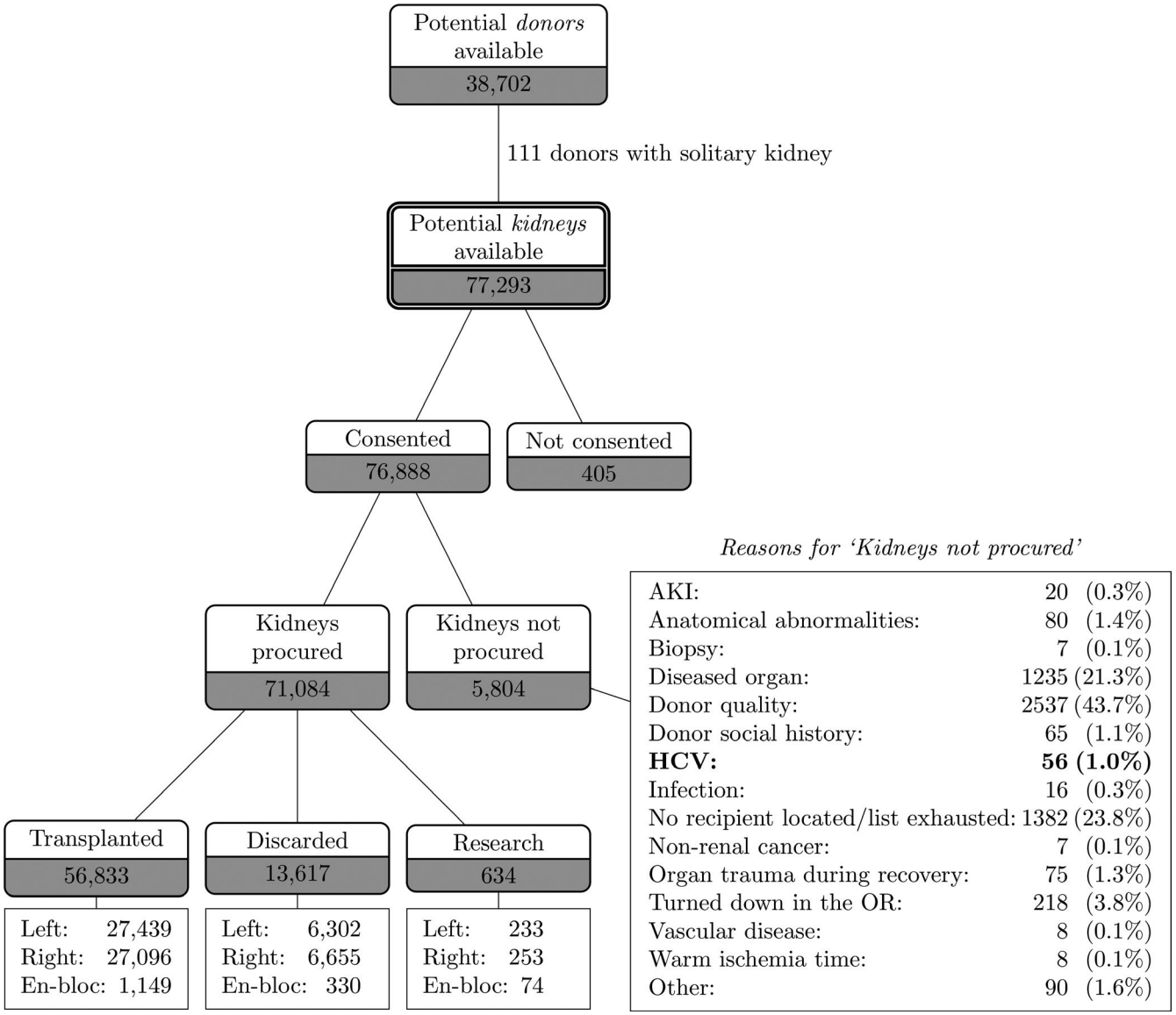

FIGURE 1 Flowchart of deceased donors registered in the UNOS database between January 1, 2015, and December 31, 2018, in the United States

TABLE 1 Characteristics of deceased donors by HCV status between January 1, 2015, and December 31, 2018, in the United States

					P-values[a]		
					Ab−, NAT− vs		Ab+, NAT− vs
	All groups	Ab−, NAT−	Ab+, NAT−	Ab±, NAT+	All ways	Ab+, NAT−	Ab±, NAT+	Ab±, NAT+
n[b]	38 702	35 861	973	1868				
Age (y), Mean ± SD	40.0 ± 17.3	40.0 ± 17.7	41.6 ± 12.8	37.3 ± 11.1	<.001 ***	.026*	<.001 ***	<.001 ***
Gender, n (%)					<.001 ***	<.001 ***	<.001 ***	<.001 ***
Female	15 366 (39.7)	14 243 (39.7)	463 (47.6)	660 (35.3)				
Male	23 336 (60.3)	21 618 (60.3)	510 (52.4)	1208 (64.7)				
Race, n (%)					<.001 ***	<.001 ***	<.001 ***	.863
White	25 543 (66.0)	23 266 (64.9)	788 (81.0)	1489 (79.7)				
Black	6143 (15.9)	5886 (16.4)	79 (8.1)	178 (9.5)				
Hispanic	5295 (13.7)	5047 (14.1)	87 (8.9)	161 (8.6)				
Other	1721 (4.4)	1662 (4.6)	19 (2.0)	40 (2.1)				
BMI (kg/m^2), Mean ± SD	28.0 ± 7.3	28.0 ± 7.4	28.2 ± 6.4	26.7 ± 5.4	<.001 ***	.067	<.001 ***	<.001 ***
Blood type, n (%)					<.001 ***	.022*	.038*	.761
O	18 579 (48.0)	17 152 (47.8)	499 (51.3)	928 (49.7)				
A	14 300 (37.0)	13 235 (36.9)	357 (36.7)	708 (37.9)				
B	4522 (11.7)	4224 (11.8)	99 (10.2)	199 (10.7)				
AB	1299 (3.4)	1248 (3.5)	18 (1.8)	33 (1.8)				
Region of recovery, n (%)					<.001 ***	<.001 ***	<.001 ***	.281
1	1393 (3.6)	1190 (3.3)	65 (6.7)	138 (7.4)				
2	4828 (12.5)	4238 (11.8)	217 (22.3)	373 (20.0)				
3	5965 (15.4)	5538 (15.4)	143 (14.7)	284 (15.2)				
4	4141 (10.7)	3961 (11.0)	62 (6.4)	118 (6.3)				
5	5817 (15.0)	5538 (15.4)	103 (10.6)	176 (9.4)				
6	1544 (4.0)	1480 (4.1)	26 (2.7)	38 (2.0)				
7	3103 (8.0)	2977 (8.3)	48 (4.9)	78 (4.2)				
8	2735 (7.1)	2597 (7.2)	37 (3.8)	101 (5.4)				
9	1700 (4.4)	1566 (4.4)	59 (6.1)	75 (4.0)				
10	3382 (8.7)	3030 (8.4)	111 (11.4)	241 (12.9)				
11	4094 (10.6)	3746 (10.4)	102 (10.5)	246 (13.2)				
DCD, n (%)					<.001 ***	<.001 ***	<.001 ***	.969
No	31 705 (81.9)	29 181 (81.4)	862 (88.6)	1662 (89.0)				
Yes	6997 (18.1)	6680 (18.6)	111 (11.4)	206 (11.0)				

(Continued)

TABLE 1 (Continued)

	All groups	Ab−, NAT−	Ab+, NAT−	Ab±, NAT+	*P*-values[a]			
					All ways	Ab−, NAT− vs Ab+, NAT−	Ab−, NAT− vs Ab±, NAT+	Ab+, NAT− vs Ab±, NAT+
ECD, n (%)					<.001 ***	.007**	<.001 ***	<.001 ***
No	30 263 (78.2)	27 774 (77.4)	795 (81.7)	1694 (90.7)				
Yes	8439 (21.8)	8087 (22.6)	178 (18.3)	174 (9.3)				
Diabetes (any type), n (%)					<.001 ***	.642	<.001 ***	.002**
No	33 862 (88.1)	31 282 (87.8)	855 (88.8)	1725 (93.4)				
Yes	4581 (11.9)	4351 (12.2)	108 (11.2)	122 (6.6)				
Hypertension, n (%)					<.001 ***	.843	<.001 ***	<.001 ***
No	25 087 (65.3)	23 026 (64.7)	631 (65.6)	1430 (77.7)				
Yes	13 313 (34.7)	12 572 (35.3)	331 (34.4)	410 (22.3)				
PHS increased risk, n (%)					<.001 ***	<.001 ***	<.001 ***	<.001 ***
No	28 879 (74.6)	28 225 (78.7)	294 (30.2)	360 (19.3)				
Yes	9815 (25.4)	7628 (21.3)	679 (69.8)	1508 (80.7)				
Cause of death, n (%)					<.001 ***	<.001 ***	<.001 ***	.624
Anoxia	15 937 (41.2)	14 068 (39.2)	643 (66.1)	1226 (65.6)				
Cerebrovascular	10 651 (27.5)	10 196 (28.4)	173 (17.8)	282 (15.1)				
Head Trauma	10 945 (28.3)	10 488 (29.2)	137 (14.1)	320 (17.1)				
Other	1169 (3.0)	1109 (3.1)	20 (2.1)	40 (2.1)				
KDPI (%), Mean ± SD	53.6 ± 29.6	52.9 ± 30.0	68.5 ± 21.9	60.7 ± 21.3	<.001 ***	<.001 ***	<.001 ***	<.001 ***

Note: Significance codes: 0 '***' 0.001 '**' 0.01 '*' 0.05.

Abbreviations: Ab, Antibody; BMI, Body Mass Index; DCD, Donation after Cardiac Death; ECD, Extended Criteria Donor; HCV, Hepatitis C Virus; KDPI, Kidney Donor Profile Index; NA, No data Available; NAT, Nucleic Acid Testing; PHS, Public Health Service; SD, Standard Deviation.

[a]ALL-ways comparisons *P*-value from chi-squared test for categorical variables and Kruskal-Wallis rank test for numerical variables; pairwise comparisons *P*-value from chi-squared test for categorical variables and Wilcoxon rank test for numerical variables, both adjusted by Holm's method for multiple pairwise testing.

[b]n: number of records in each group. Missing/unknown values in any particular variable are ignored when reporting summary statistics.

TABLE 2 Characteristics of transplanted deceased donor kidneys by HCV status between January 1, 2015, and December 31, 2018, in the United States

						P-values[a]		
						Ab−, NAT− vs.		Ab+, NAT− vs.
	All groups	Ab−, NAT−	Ab+, NAT−	Ab±, NAT+	All ways	Ab+, NAT−	Ab±, NAT+	Ab±, NAT+
n[b]	56 833	54 232	968	1633				
Age (y), Mean ± SD	36.3 ± 15.9	36.3 ± 16.2	37.2 ± 10.8	32.9 ± 8.4	<.001 ***	.163	<.001 ***	<.001 ***
Gender, n (%)					<.001 ***	<.001 ***	.199	<.001 ***
Female	21 664 (38.1)	20 617 (38.0)	462 (47.7)	585 (35.8)				
Male	35 169 (61.9)	33 615 (62.0)	506 (52.3)	1048 (64.2)				
Race, n (%)					<.001 ***	<.001 ***	<.001 ***	.470
White	38 147 (67.1)	35 927 (66.2)	842 (87.0)	1378 (84.4)				
Black	8020 (14.1)	7910 (14.6)	34 (3.5)	76 (4.7)				
Hispanic	8148 (14.3)	7930 (14.6)	68 (7.0)	150 (9.2)				
Other	2518 (4.4)	2465 (4.5)	24 (2.5)	29 (1.8)				
BMI (kg/m^2), Mean ± SD	27.5 ± 7.1	27.6 ± 7.1	28.1 ± 6.3	26.1 ± 5.1	<.001 ***	<.001 ***	<.001 ***	<.001 ***
Blood type, n (%)					<.001 ***	.010 **	.005 **	.919
O	27 269 (48.0)	25 915 (47.8)	503 (52.0)	851 (52.1)				
A	21 079 (37.1)	20 184 (37.2)	347 (35.8)	548 (33.6)				
B	6629 (11.7)	6308 (11.6)	105 (10.8)	216 (13.2)				
AB	1856 (3.3)	1825 (3.4)	13 (1.3)	18 (1.1)				
DCD, n (%)					<.001 ***	<.001 ***	<.001 ***	.207
No	45 931 (80.8)	43 590 (80.4)	854 (88.2)	1487 (91.1)				
Yes	10 902 (19.2)	10 642 (19.6)	114 (11.8)	146 (8.9)				
ECD, n (%)					<.001 ***	<.001 ***	<.001 ***	.001 **
No	49 968 (87.9)	47 446 (87.5)	909 (93.9)	1613 (98.8)				
Yes	6865 (12.1)	6786 (12.5)	59 (6.1)	20 (1.2)				
Diabetes (any type), n (%)					<.001 ***	.431	<.001 ***	<.001 ***
No	52 910 (93.6)	50 398 (93.5)	909 (94.5)	1603 (98.8)				
Yes	3600 (6.4)	3527 (6.5)	53 (5.5)	20 (1.2)				
Hypertension, n (%)					<.001 ***	.441	<.001 ***	<.001 ***
No	42 259 (74.9)	40 073 (74.4)	731 (76.2)	1455 (90.0)				
Yes	14 166 (25.1)	13 776 (25.6)	228 (23.8)	162 (10.0)				
PHS increased risk, n (%)					<.001 ***	<.001 ***	<.001 ***	<.001 ***
No	43 016 (75.7)	42 554 (78.5)	243 (25.1)	219 (13.4)				
Yes	13 809 (24.3)	11 670 (21.5)	725 (74.9)	1414 (86.6)				
Cause of death, n (%)					<.001 ***	<.001 ***	<.001 ***	.490
Anoxia	23 267 (40.9)	21 417 (39.5)	691 (71.4)	1159 (71.0)				
Cerebrovascular	12 864 (22.6)	12 622 (23.3)	113 (11.7)	129 (7.9)				
Head Trauma	18 908 (33.3)	18 446 (34.0)	147 (15.2)	315 (19.3)				
Other	1794 (3.2)	1747 (3.2)	17 (1.8)	30 (1.8)				
KDPI (%), Mean ± SD	44.8 ± 27.0	44.4 ± 27.3	58.7 ± 19.7	49.8 ± 16.8	<.001 ***	<.001 ***	<.001 ***	<.001 ***

Note: Significance codes: 0 '***' 0.001 '**' 0.01.

Abbreviations: Ab, Antibody; BMI, Body Mass Index; DCD, Donation after Cardiac Death; ECD, Extended Criteria Donor; HCV, Hepatitis C Virus; KDPI, Kidney Donor Profile Index; NA, No data Available; NAT, Nucleic Acid Testing; PHS, Public Health Service; SD, Standard Deviation.

[a]ALL-ways comparisons *P*-value from chi-squared test for categorical variables and Kruskal-Wallis rank test for numerical variables; pairwise comparisons *P*-value from chi-squared test for categorical variables and Wilcoxon rank test for numerical variables, both adjusted by Holm's method for multiple pairwise testing.

[b]n: number of records in each group. Missing/unknown values in any particular variable are ignored when reporting summary statistics.

3 | RESULTS

3.1 | The study cohort selection

During the study period, 38 702 potential kidney donors became available (Figure 1). Consent was obtained only for 76 888 kidneys, of which 5804 kidneys were not procured. Notably, HCV as the reported reason for a kidney not being procured was only 1%. Among the 71 084 kidneys that were procured, 56 833 (73.9%) kidneys were transplanted, 13 617 (17.7%) kidneys were discarded, and 634 (0.8%) were used for research.

3.2 | Characteristics of all deceased donors by HCV status and disposition

Characteristics of the deceased donors by HCV status are shown in Table 1. Ab−/NAT− donors comprised the majority of the study cohort (n = 35 861) and served as the reference group. There were 1868 donors in the Ab±/NAT+ (viremic) group and 973 donors in the Ab+/NAT− group. The highest number of HCV viremic donor kidneys was recovered in the UNOS region 2 (US States DE, DC, MD, NJ, PA, and WV; a total of 373 donors).

Among all deceased donors (Table 1) and recovered kidneys for transplantation (mainly transplanted and discarded ones, shown in Tables 2 and 3), compared to the reference group (HCV Ab−/NAT−), HCV viremic donors were younger more likely to be White, and male, less likely to be diagnosed with diabetes and hypertension, and had less donation after circulatory death (DCD) donors. As expected, HCV viremic donors also had higher KDPI and were also more likely to be labeled as PHS - IR donors.

3.3 | Disposition of deceased donor kidneys by HCV status

Trends in deceased donor kidney disposition by HCV status over time is shown in Figure 2. Number of Ab+/NAT− kidneys that were transplanted increased from 103 (35.9% of such kidneys) in 2015 to 444 (66%) in 2018. The discard rate in the same group decreased from 32.4% to 22.4%. The percentage of viremic donor kidneys transplanted (from 41% to 50%) and discarded (from 32% to 33%) slightly increased. Disposition categories for the reference group remained stable during the study period.

3.4 | Comparison of KDPI categories in transplanted and discarded deceased donors by HCV status

The KDPI distributions of transplanted and discarded kidneys for the reference group were widely separated (left-skewed in the discarded group) and stayed stable for four years period (see Figure 3). The similar distribution pattern was observed in HCV Ab+/NAT− group in 2018. On the other hand, the KDPI distributions of transplanted and discarded kidneys for the viremic group mostly overlapped, and the median KDPI percentage was persistently higher in the discarded group during the study period.

3.5 | Reasons for kidney discard by HCV status

Table 4 shows the reasons for kidney discard by HCV status. 'No recipient located/list exhausted' and biopsy findings uniformly appear to be two most common reasons for discard across all groups.

3.6 | Kidney discards by the HCV groups and PHS designations

Table 5 shows relevant characteristics discards by the HCV categories and PHS designations in recovered kidneys (excluding the ones used for research) for transplantation and demonstrates the effect of HCV and PHS designation on discard using multivariable mixed-effect logistic regression models. In all cohort (N = 70 450), 23.8% of the kidneys were designated as PHS-IR, had a mean (SD) KDPI of 51.0 ± 29.0%, and experienced a discard rate of 19.3%. PHS-IR (odds ratio [OR] 1.20, 95% confidence interval [CI] 1.15-1,29) and HCV designations (OR 2.29, 95% CI 2.15-2.43) were independently associated with increased risk of discard.

In HCV Ab−/NAT− group (n = 66 224), 20.3% of the kidneys were designated as PHS-IR, and the donor age, mean KDPIs, and discard rates were lower in PHS-IR group compared to PHS-IR group. The PHS designation was associated with a 17% increased risk of discard (OR 1.24, 95% CI 1.15-1.34) in PHS-IR group compared to the reference group (PHS-IR) in this category.

In HCV Ab+/NAT− group (n = 1459), 70.7% of the kidneys were designated as PHS-IR, and the donor age, mean KDPIs, and discard rates were lower in PHS-IR group compared to PHS-IR group. While the PHS designation was not associated with increased risk of discard (OR 1.24, 95% CI 0.84-1.83) in PHS-IR group compared to the reference group (PHS-IR in this category), HCV Ab+/NAT− status increased the odds of discard by approximately 2-fold (OR 2.07, 95% CI 1.78-2.40) compared to the reference group (HCV Ab−/NAT− group).

In HCV Ab±/NAT+ group (n = 2767), 83.0% of the kidneys were designated as PHS-IR, and similarly, the donor age, mean KDPIs, and discard rates were lower in PHS-IR group compared to PHS-IR group. While the PHS designation was not associated with increased risk of discard (OR 1.04, 95% CI 0.79-1.38) in PHS-IR group compared to the reference group (PHS-IR in this category), HCV Ab±/NAT+ status increased the odds of discard by approximately 5-fold (OR 5.21, 95% CI 4.62-5.89) compared to the reference group (HCV Ab−/NAT− group).

In the PHS-IR kidneys across all HCV groups, compared to the PHS-IR, more recovery biopsies were performed (slightly higher

TABLE 3 Characteristics of discarded deceased donor kidneys by HCV status between January 1, 2015, and December 31, 2018, in the United States

					P-values[a]			
					Ab−, NAT− vs.	Ab+, NAT− vs.		Ab−, NAT− vs. Ab±, NAT+
	All groups	Ab−, NAT−	Ab+, NAT−	Ab±, NAT+	All ways	Ab+, NAT−	Ab±, NAT+	
n[b]	13 617	11 992	491	1134				
Age (y), Mean ± SD	50.5 ± 16.0	51.9 ± 16.0	43.8 ± 12.9	38.6 ± 11.1	<.001 ***	<.001 ***	<.001 ***	<.001 ***
Gender, n (%)					<.001 ***	.328	<.001 ***	<.001 ***
Female	6208 (45.6)	5573 (46.5)	245 (49.9)	390 (34.4)				
Male	7409 (54.4)	6419 (53.5)	246 (50.1)	744 (65.6)				
Race, n (%)					<.001 ***	<.001 ***	<.001 ***	.832
White	9108 (66.9)	7786 (64.9)	394 (80.2)	928 (81.8)				
Black	2350 (17.3)	2221 (18.5)	40 (8.1)	89 (7.8)				
Hispanic	1565 (11.5)	1427 (11.9)	49 (10.0)	89 (7.8)				
Other	594 (4.4)	558 (4.7)	8 (1.6)	28 (2.5)				
BMI (kg/m^2), Mean ± SD	29.4 ± 7.6	29.6 ± 7.8	28.1 ± 6.3	27.2 ± 5.5	<.001 ***	<.001 ***	<.001 ***	.007**
Blood type, n (%)					<.001 ***	.181	.004 **	.938
O	6401 (47.0)	5595 (46.7)	242 (49.3)	564 (49.7)				
A	5069 (37.2)	4439 (37.0)	188 (38.3)	442 (39.0)				
B	1621 (11.9)	1452 (12.1)	53 (10.8)	116 (10.2)				
AB	522 (3.8)	502 (4.2)	8 (1.6)	12 (1.1)				
DCD, n (%)					.940	.999	.941	.974
No	10 802 (79.3)	9517 (79.4)	390 (79.4)	895 (78.9)				
Yes	2815 (20.7)	2475 (20.6)	101 (20.6)	239 (21.1)				
ECD, n (%)					<.001 ***	<.001 ***	<.001 ***	<.001 ***
No	7028 (51.6)	5596 (46.7)	385 (78.4)	1047 (92.3)				
Yes	6589 (48.4)	6396 (53.3)	106 (21.6)	87 (7.7)				
Diabetes (any type), n (%)					<.001 ***	<.001 ***	<.001 ***	.008**
No	10 293 (76.4)	8816 (74.2)	420 (87.3)	1057 (94.5)				
Yes	3182 (23.6)	3060 (25.8)	61 (12.7)	61 (5.5)				
Hypertension, n (%)					<.001 ***	<.001 ***	<.001 ***	<.001 ***
No	5519 (41.0)	4377 (36.8)	290 (60.2)	852 (76.9)				
Yes	7957 (59.0)	7509 (63.2)	192 (39.8)	256 (23.1)				
PHS increased risk, n (%)					<.001 ***	<.001 ***	<.001 ***	<.001 ***
No	10 675 (78.4)	10 241 (85.4)	184 (37.5)	250 (22.0)				
Yes	2936 (21.6)	1745 (14.6)	307 (62.5)	884 (78.0)				
Cause of death, n (%)					<.001 ***	<.001 ***	<.001 ***	.795
Anoxia	5231 (38.4)	4259 (35.5)	278 (56.6)	694 (61.2)				
Cerebrovascular	5850 (43.0)	5536 (46.2)	121 (24.6)	193 (17.0)				
Head Trauma	2162 (15.9)	1868 (15.6)	78 (15.9)	216 (19.0)				
Other	374 (2.7)	329 (2.7)	14 (2.9)	31 (2.7)				
KDPI (%), Mean ± SD	76.8 ± 21.6	78.1 ± 21.5	74.2 ± 20.0	64.1 ± 19.5	<.001 ***	<.001 ***	<.001 ***	<.001 ***

Note: Significance codes: 0 0.001 '**' 0.01 '***' <0.001.

Abbreviations: Ab, Antibody; BMI, Body Mass Index; DCD, Donation after Cardiac Death; ECD, Extended Criteria Donor; HCV, Hepatitis C Virus; KDPI, Kidney Donor Profile Index; NA, No data Available; NAT, Nucleic Acid Testing; PHS, Public Health Service; SD, Standard Deviation.

[a]ALL-ways comparisons *P*-value from chi-squared test for categorical variables and Kruskal-Wallis rank test for numerical variables; pairwise comparisons *P*-value from chi-squared test for categorical variables and Wilcoxon rank test for numerical variables, both adjusted by Holm's method for multiple pairwise testing.

[b]n: number of records in each group. Missing/unknown values in any particular variable are ignored when reporting summary statistics.

than 50%) that showed a higher percentage of glomerulosclerosis >20% and moderate-to-severe interstitial fibrosis.

3.7 | Kidney transplant center/OPO/UNOS region utilization of HCV viremic kidneys

Figure 4 shows the heat map geographic data (the number of kidneys) from viremic donors recovered (Figure 4A) and transplanted (Figure 4B) based on the UNOS Regions. The UNOS Regions 2 and 3 were more likely to procure, and transplant kidneys from viremic donors. Figures 5 and 6 show the geographic distribution of transplantation with viremic kidneys according to the OPOs and individual transplant centers, respectively. The number of OPOs that transplanted at least 25 kidneys from viremic donors increased from only one in 2015 to six in 2018. There were at least two centers that transplanted more than 60 viremic donor kidneys in 2018.

3.8 | Forecasting number of potential viremic kidneys by 2023

We forecasted a potential number of HCV NAT+ DD kidneys that may become available in 2023, based on actual numbers of such kidneys from 2015-2018, using time series trend adjusted exponential smoothing method. We predict about 2092 HCV-positive kidneys from deceased donors would be available by 2023 (Figure 7), the model assumes that the opioid epidemic and related overdose deaths continue to rise exponentially with the same trend.

4 | DISCUSSION

This study reveals some key insights about the recent trends in kidney transplant utilization in the United States: (a) an increasing number and utilization rates of Ab+/NAT− kidneys (annual transplant rate increased from 35.9% in 2015 to 66% in 2018) showing a

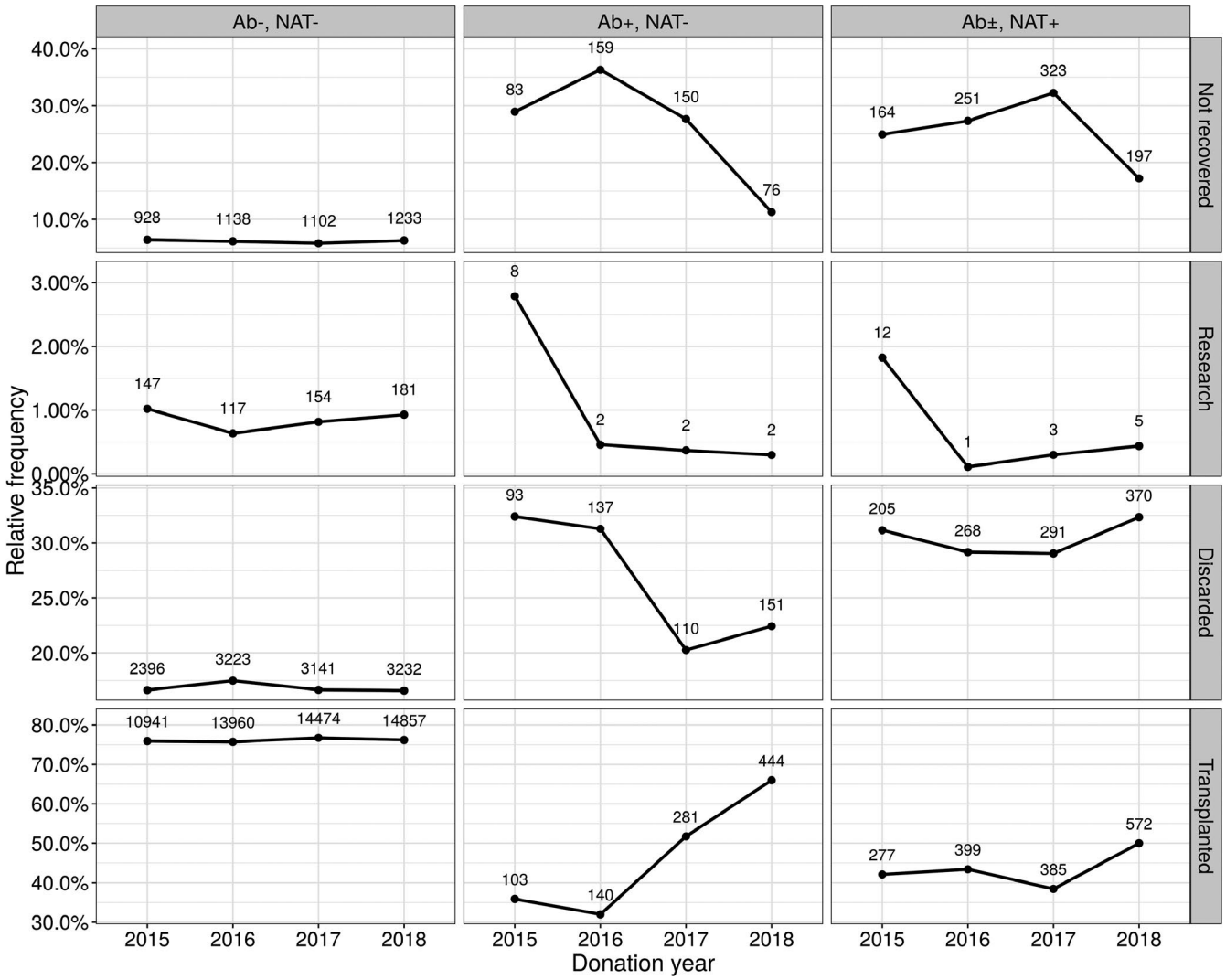

FIGURE 2 Disposition of deceased donor kidneys based on HCV Ab and NAT status between January 1, 2015, and Dec 31, 2018, in the United States

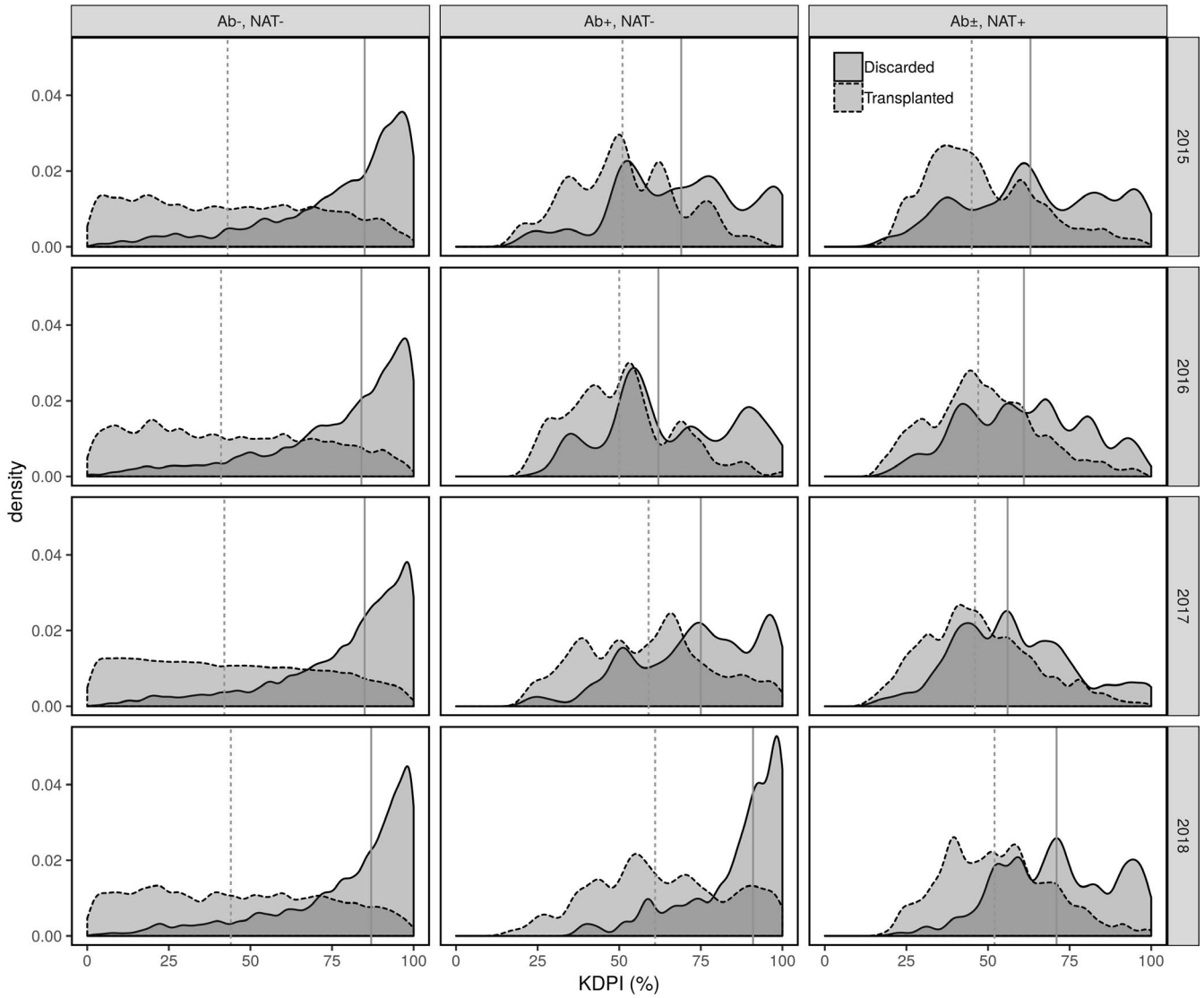

FIGURE 3 KDPI distribution by HCV status and disposition (transplant vs. discard) between January 1, 2015, and December 31, 2018, in the United States (dashed and solid vertical lines indicate median KDPI for transplanted and discarded kidneys, respectively)

positive change in transplant centers' behavior and patient acceptance of minimal infectious transmission risk organs; (b) the number of viremic donor kidneys increased from 658 in 2015 to 1144 in 2018, and the number of OPOs transplanting at least 25 viremic donor kidneys increased from one in 2015 to six in 2018; (c) no recipient located/list exhausted' was the most common reason for discard across all groups (40.4%), and even higher in the viremic donor group (65.4%); (d) PHS designation (OR 1.20, CI 95% CI 1.15-1.29) and HCV status (2.29; 95% CI 2.15-2.43) were independently associated with increased risk of discard; (e) PHS-IR kidneys across all HCV groups, compared to PHS-IR kidneys, were more likely to be discarded (contrary to common perception), had higher KDPI scores, and underwent more biopsies showing slightly higher percentage of glomerulosclerosis (GS) >20% and moderate-to-severe interstitial fibrosis (IF); (f) the reasons for high kidney discards are multifactorial, could partially be explained by KDPI score, the performance of procurement biopsy and its findings for HCV-infected kidneys; (g) We forecasted that the number of kidneys from HCV viremic donors would increase from 1376 in 2019 to 2092 in 2023 which might represent 10%-15% of deceased donor organ supply over the next few years with current rate of opioid epidemic.

Decision to discard a deceased donor kidney is influenced by several factors including variability in regional/OPO/center wait time and wait-list size, center transplant rates/aggressiveness, KDPI score, CIT, decision to biopsy and biopsy findings, pump parameters, regional and national share, living donation access, PHS designation, HCV status, perceived risk/benefit ratio, recipients socioeconomic status. Accepting a PHS-IR organ offers survival benefit to recipients compared to those who declined it and are waiting for a PHS-IR donor offer and staying on dialysis.[5,27-30] There exist a notion that a disproportionate number of discarded kidneys originate from PHS-IR donors.[31,32] In our study cohort (the kidneys recovered for transplantation), the PHS-IR kidneys accounted for 23.8% of total organ pool and 21.6% discarded kidneys, and, contrary to common perception,

TABLE 4 Characteristics of discarded deceased donor kidneys by HCV status between January 1, 2015, and December 31, 2018, in the United States

					P-values[a]			
					Ab−, NAT− vs			Ab−, NAT− vs Ab±, NAT+
	All groups	Ab−, NAT−	Ab+, NAT	Ab±, NAT+	All ways	Ab+, NAT−	Ab±, NAT+	
Disposition reason, n[b] (%)					<.001 ***	<.001 ***	<.001 ***	.079
AKI	784 (5.8)	722 (6.0)	26 (5.3)	36 (3.2)				
Anatomical abnormalities	772 (5.7)	723 (6.0)	23 (4.7)	26 (2.3)				
Biopsy	3943 (29.0)	3768 (31.4)	57 (11.6)	118 (10.4)				
CIT	294 (2.2)	262 (2.2)	5 (1.0)	27 (2.4)				
Diseased organ	400 (2.9)	385 (3.2)	1 (0.2)	14 (1.2)				
Donor quality	333 (2.4)	273 (2.3)	20 (4.1)	40 (3.5)				
Donor social history	19 (0.1)	4 (0.0)	3 (0.6)	12 (1.1)				
HCV	120 (0.9)	8(0.1)	40 (8.1)	72 (6.3)				
Infection	44 (0.3)	39 (0.3)	2 (0.4)	3 (0.3)				
No recipient located/list exhausted	5536 (40.7)	4496 (37.5)	298 (60.7)	742 (65.4)				
Non-renal cancer	102 (0.7)	101 (0.8)	7 (1.4)	1 (0.1)				
Organ trauma during recovery	521 (3.8)	499 (4.2)	2 (0.4)	15 (1.3)				
Pump	335 (2.5)	327 (2.7)	1 (0.2)	8 (0.7)				
Renal cancer	35 (0.3)	32 (0.3)	2 (0.4)	1 (0.1)				
Turned down in the OR	62 (0.5)	60 (0.5)	4 (0.8)	2 (0.2)				
Vascular disease	145 (1.1)	141 (1.2)	NA (NA)	3 (0.3)				
Warm ischemia time	66 (0.5)	62 (0.5)	NA (NA)	2 (0.2)				
Other	106 (0.8)	90 (0.8)	NA (NA)	12 (1.1)				

Note: Significance codes: 0 0.001 '***' <0.001.

Abbreviations: Ab, Antibody; BMI, Body Mass Index; DCD, Donation after Cardiac Death; ECD, Extended Criteria Donor; HCV, Hepatitis C Virus; KDPI, Kidney Donor Profile Index; NA, No data Available; NAT, Nucleic Acid Testing; PHS, Public Health Service; SD, Standard Deviation.

[a]ALL-ways comparisons *P*-value from chi-squared test for categorical variables and Kruskal-Wallis rank test for numerical variables; pairwise comparisons *P*-value from chi-squared test for categorical variables and Wilcoxon rank test for numerical variables, both adjusted by Holm's method for multiple pairwise testing.

[b]n: number of records in each group. Missing/unknown values in any particular variable are ignored when reporting summary statistics.

the PHS-IR kidneys experienced lower discard rates across all HCV groups compared to the PHS-IR kidneys under same HCV categories. Lower discard rates in PHS-IR designated groups could be explained by their donor's younger age, lower KDPI scores, and a lower likelihood of undergoing procurement biopsies. However, when adjusting for factors associated with discard (using regression analysis), we found that PHS-IR designation is independently associated with increased discard risk in HCV Ab−/NAT− group, but not in HCV Ab+ and/or HCV NAT+ groups. Hepatitis C virus Ab+ and NAT+ designations seem to negate PHS-IR's relatively small effect on discard.

The American Society of Transplantation Consensus Conference on HCV donors and organ transplantation recently recommended that HCV Ab+/NAT− donors (without other increased risk factors) not be considered at increased risk of HCV transmission.[33] A single-center study also demonstrated the safety of transplanting HCV Ab+/NAT− donor kidneys into HCV-negative recipients.[16] Accordingly, our study documents the increased nationwide utilization of HCV Ab+/NAT− donor kidneys in the last 3 years. This represents a pool of donors that is probably still underutilized, and so far has not resulted in a documented viral transmission and hence may not need antiviral therapy. Our study brings to light some challenging ethical dilemmas. Allocating HCV Ab or NAT+ organs to HCV Ab and NAT+ recipients while bypassing HCV-negative recipients is a thought-provoking concern when considering longer wait-list time

TABLE 5 Kidney discards by HCV groups and PHS designations and predicting discard in recovered kidneys for transplantation using multivariable mixed-effects logistic regression models

All cohort[a] (n = 70, 450)		HCV Ab−, NAT− (n = 66 224)			HCV Ab+, NAT− (n = 1459)			HCV Ab±, NAT+ (n = 2767)		
		PHS-IR	PHS-IR	*P*-value	PHS-IR	PHS-IR	*P*-value	PHS-IR	PHS-R	*P*-value
PHS[b], n (%)	16 739 (23.8)	13 411 (20.3)	52 787 (79.7)		1030 (7.7)	427 (29.3)		2298 (83.0)	469 (17.0)	
Age (y), Mean ± SD	39.0 ± 16.9	34.6 ± 13.3	40.3 ± 17.9	<.001	34.5 ± 11.3	48.9 ± 11.2	<.001	33.5 ± 8.8	43.8 ± 11.2	<.001
KDPI %, Mean ± SD	51.0 ± 29.0	38.9 ± 25.7	53.4 ± 29.5	<.001	57.8 ± 18.8	78.8 ± 19.1	<.001	52.8 ± 17.6	69.7 ± 2.8	<.001
Biopsy of either kidney, n (%)	37 863 (53.8)	6361 (47.4)	29 087 (55.1)	<.001	552 (53.9)	329 (77.1)	<.001	1215 (52.9)	313 (66.7)	<.001
GS > 20%, n (%)	5266 (13.9)	671 (10.6)	4423 (15.2)	<.001	38 (6.9)	46 (14)	<.001	62 (5.1)	26 (8.3)	.03
IF moderate or severe, n (%)	3326 (8.8)	423 (6.7)	2774 (9.5)	<.001	30 (5.4)	30 (9.1)	.04	44 (3.6)	25 (8.0)	.001
Discard rate, n (%)	13 617 (19.3)	1745 (13.0)	10 241 (19.4)	<.001	307 (29.8)	184 (43.1)	<.001	884 (38.5)	250 (53.3)	<.001
Estimated odds ratios for discard and 95% confidence intervals[c]										
PHS designation	1.20 (1.15-1.29)	1.24 (1.15-1.34)	Reference	<.001	1.24 (.84-1.83)	Reference	.28	1.04 (.79-1.38)	Reference	.78
HCV designation	2.29 (2.15-2.43)	Reference			2.07 (1.78-2.40)		<.001	5.21 (4.62-5.89)		<.001

Abbreviations: Ab, Antibody; GS, Glomerulosclerosis; HCV, Hepatitis C virus; IF, Interstitial fibrosis; KDPI, Kidney profile risk index; NAT, Nucleic acid testing; PHS-IR, Public health service increased risk; SD: Standard Deviation.

[a]All cohort includes the recovered kidneys, either transplanted or discarded, excludes the ones used for research.

[b]PHS status is missing for 26 patients in the HCV Ab−, NAT− group and two patients in the HCV Ab+, NAT− group.

[c]Multivariable two-level mixed-effects logistic regression models (the second level of the model defining different intercepts for each United Network for Organ Sharing (UNOS) Region in a random-intercept model to account for regional variations in discards) were estimated to predict discard. The models were adjusted f or previously identified donor factors in the literature, including donor age >50 or not, either kidney biopsied, if biopsied glomerulosclerosis >20% or not, cytomegalovirus (CMV) status, cause death due to cerebrovascular accident (CVA), donation after cardiac death (DCD) status, height, weight, history of tattoo, KDPI, either kidney pumped, cold ischemia time, hepatitis B core antibody status, hepatitis B surface antigen status, history of diabetes, history of hypertension, history of cocaine use, history of IV drug use (IVDU), terminal creatinine >1.5 mg/dL or not, ABO blood type, and race (White, African American, Hispanic, Asian, and others), and transplant year.

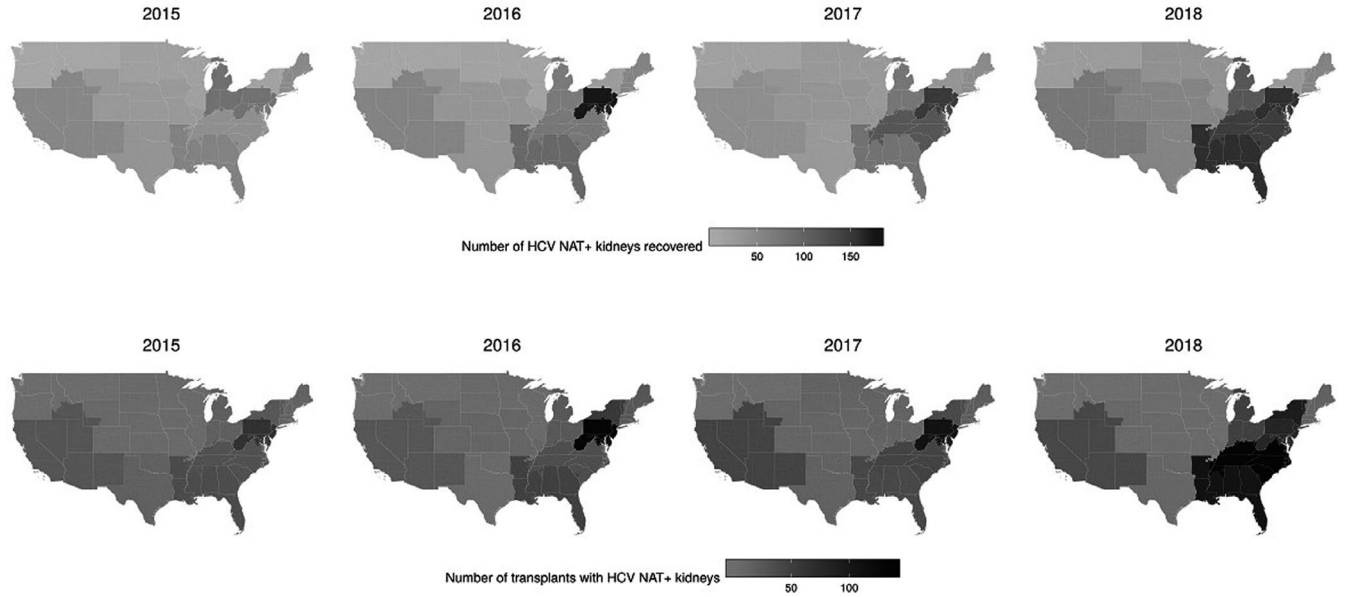

FIGURE 4 Geographic distribution by the UNOS Region for hepatitis C virus (HCV) infected donors and transplants with HCV-infected kidneys

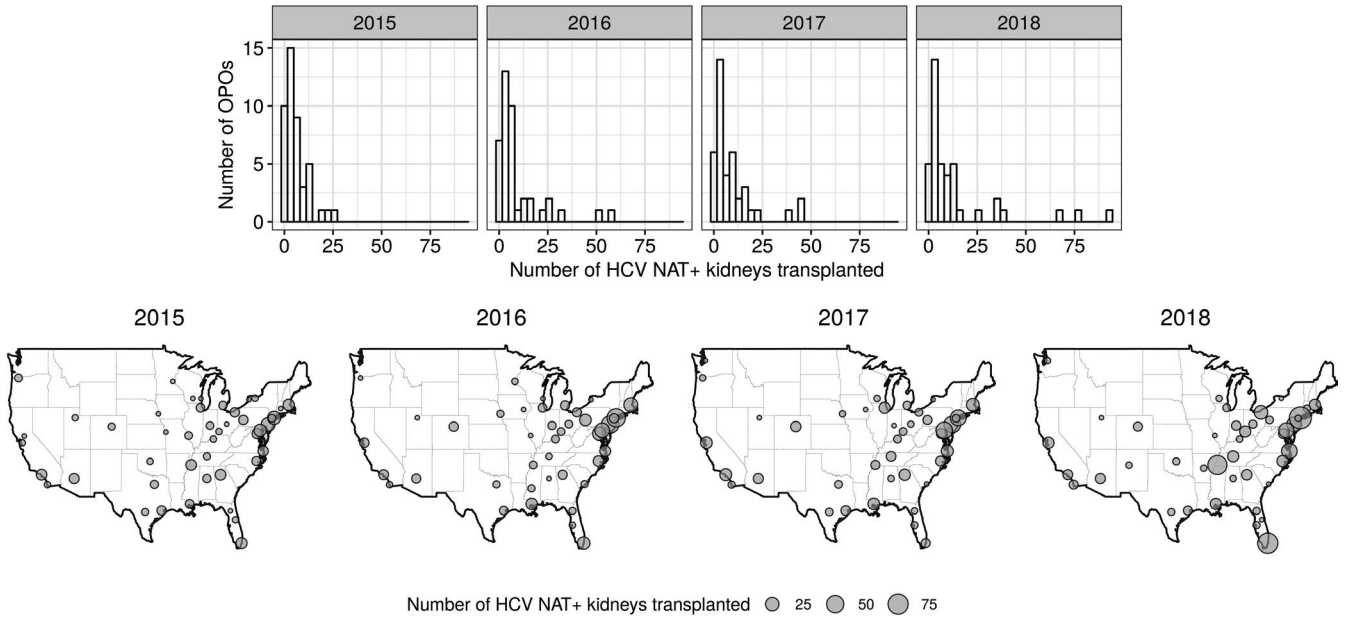

FIGURE 5 Geographic distribution of hepatitis C virus (HCV) infected (NAT+) kidney transplantation by the organ procurement organization (OPO) donation service area (DSA) between 2015 and 2018

for HCV-negative recipients not willing to accept PHS organs, primarily due to lack of access or education on disease transmission. Whether HCV Ab or NAT+ organ utilization for HCV Ab or NAT+ recipients is more beneficial than for HCV Ab or NAT– recipients, in terms of graft or patient survival and cost-effectiveness, remains to be seen. Education of public and private payers is crucial to help provide payment for initial HCV treatment and additional therapy, should resistance be a challenge post-transplant (<5%); thus, we propose that every transplant institution establish an individual or a group of HCV champion providers tasked with education and consenting of patients, being a facilitator in negotiations with insurance carriers, and in-depth analyzers of all outcomes of HCV Ab and/or NAT+ organs.

A recent analysis showed that transplanting viremic donor kidneys into negative recipients could be cost-effective with an incremental cost-effectiveness ratio of $56 018 per quality-adjusted life-year (QALY) from the payer's perspective, and $4647 per QALY from the societal perspective, compared to remaining on the waitlist for one additional year.[34] Also, Gupta et al[35] found that kidney transplants using HCV + donors for HCV- recipients was a less costly approach ($138 000 versus $329 000) and resulted in slightly more years of life (YOL) (4.7 versus 4.8) when compared to HCV- donors for HCV- recipients.

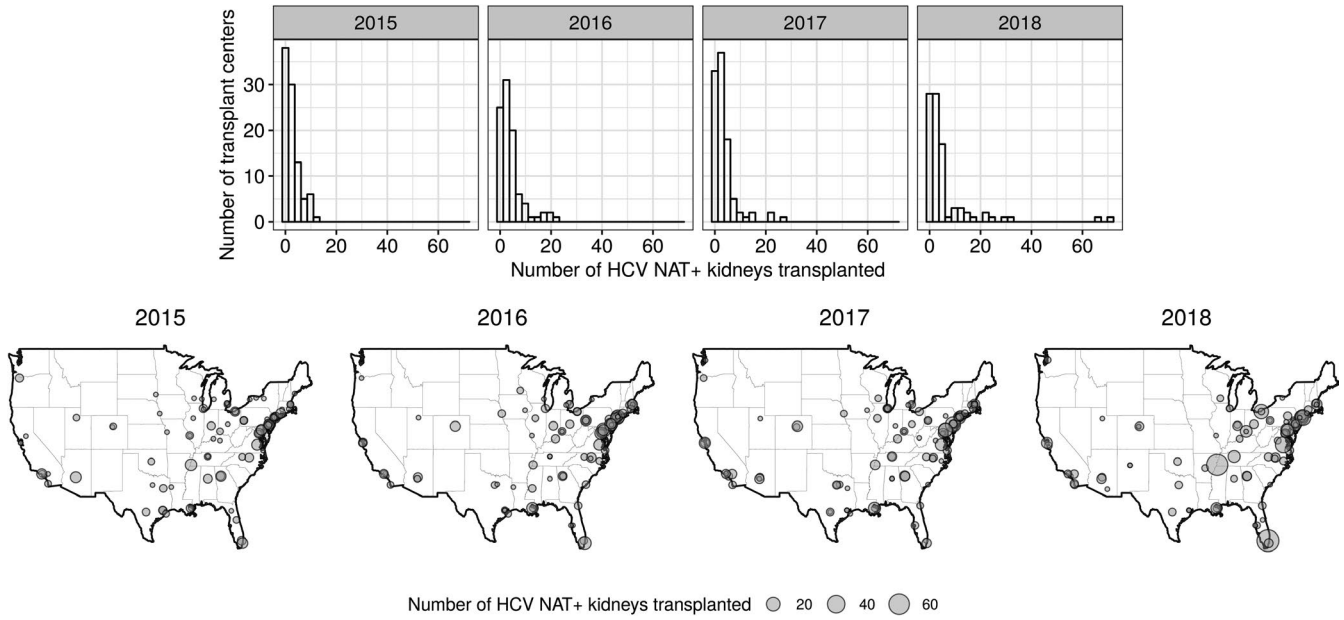

FIGURE 6 Geographic distribution of hepatitis C virus (HCV) infected (NAT+) kidney transplantation by transplant center between 2015 and 2018

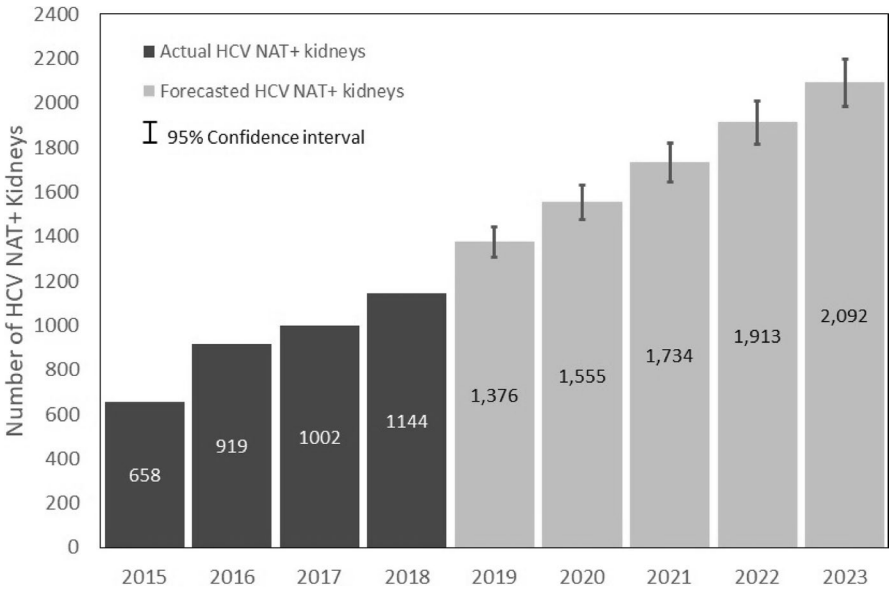

FIGURE 7 Forecasting number of potential HCV NAT+ kidneys by the year 2023 (computed using time series trend adjusted exponential smoothing method)

According to a recent OPTN data analysis, overdose deaths (N = 63 632 in 2016) and overdose-death donors (N = 1804 in 2016), although accounting to a meager 3% of such deaths, continued to increase exponentially last several (the study period ended in 2016).[31] Based on our analysis, the number of the HCV NAT+ kidneys doubled in 4 years during our study period (from 658 in 2015 to 1144 in 2018), and we would expect those kidneys to reach around 2000 in 2023 assuming current trends in opioid use and related death rates remain unchanged. The rising trend for available HCV NAT+ kidneys to transplant is supported by a recent publication (our estimation of 344 vs. actual number of 374 for the first quarter of 2019).[36]

Unfortunately, during the study period, the discards for HCV NAT+ kidneys were unacceptably high around 40%, and those kidneys carried a 10-fold higher risk of discard. In era of DAA therapy curing HCV with >95% success and expectation of 10%-15% of deceased donor pool originating from HCV NAT+ kidneys (based on our forecasting), an urgent policy changes are needed to tackle opioid epidemic, minimize discard with efficient allocation of those kidneys to the centers routinely using for HCV naive or infected recipients, mitigate PHS labeling effect, and disseminate evidence-based experience on this evolving topic.

Another issue with HCV viremic donors is that they are unlikely to be placed in younger recipients (longevity matched donor-recipient pairs, mainly allocation of KDPI < 20% kidneys to young recipients with the longest post-transplant survival expectancy) due to adverse impact of HCV Ab positivity on KDPI calculation,

even though they are otherwise good quality kidneys.[37] One UNOS study of Ab+/NAT− kidneys concludes that if such kidneys are considered to be HCV-, their survival would be comparable to the matched non-HCV-infected kidneys, less likely to be classified as KDPI > 85%, and the risk of DGF was significantly lower when compared to non-HCV kidneys.[38] A recent companion study also confirms similar or superior short-term outcomes from transplantation with HCV+ kidneys.[21] Hence, some authors even question the need for including HCV Ab result with donor offers and KDPI calculations and recommend uniform utilization of NAT status alone.[39-41]

Strengths of our study include a large sample size of a national data set. Limitations of our study include the following: (a) it is a retrospective registry data analysis without a control group; (b) the OPTN data set does not include information regarding potential donors in whom a donor consent was not obtained and not recovered for transplant; (c) missing data can introduce bias; (d) reporting delays and labeling errors might happen.

In conclusion, HCV-positive donors are likely to increase in near future years, unless there is a dramatic reduction in the current opioid crisis. Organs from HCV-positive donors could potentially expand the organ pool, especially given the effective antiviral therapy available against HCV, and increase access to transplant across all patients, including HCV-negative recipients. PHS labeling effect on discard requires rediscussion of purpose and utility of classification. We predict that as center level and patient comfort level spreads in accepting HCV viremic donors, HCV NAT+ organ utilization will increase significantly soon, similar to the increasing trend observed in HCV Ab+/NAT− organ utilization in the last 3 years.

ACKNOWLEDGEMENTS

The authors thank Dr John Friedewald for his critical review of the manuscript and Mehmet US Ayvaci, PhD for his technical support.

CONFLICT OF INTEREST

The authors declared no conflict of interest related to the topic.

AUTHOR CONTRIBUTIONS

VKA participated in study design and manuscript writing. BS and BT participated in study design, data analysis, and manuscript writing. NA, CH, MPM, RP, and AA participated in manuscript writing.

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How to cite this article: Ariyamuthu VK, Sandikci B, AbdulRahim N, et al. Trends in utilization of deceased donor kidneys based on hepatitis C virus status and impact of public health service labeling on discard. *Transpl Infect Dis*. 2020;22:e13204. https://doi.org/10.1111/tid.13204