EFFECT OF HEPATITIS C VIRUS INFECTION ON OUTCOMES AFTER KIDNEY TRANSPLANTATION

by

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A Dissertation Submitted to the Faculty of Harvard Medical School

in Partial Fulfillment of

the Requirements for the Degree of Master of Medical Sciences in

Clinical Investigation (MMSCI)

Harvard University

Boston, Massachusetts

April 2020

Area of Concentration: Kidney Transplantation/Infection/Organ Allocation

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I have reviewed this thesis. It represents work done by the author under my guidance/supervision.

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Acknowledgements

Foremost, I would like to express my sincere gratitude to my primary mentors Prof. Nahel Elias and Prof. Joren C. Madsen. Prof. Elias's dynamism, vision, and meticulosity have deeply inspired me. His immense knowledge of transplantation and patient guidance helped me in all the time of this project. I would like to recognize the invaluable support and instruction from Prof. Joren C Madsen during the development of this research work and his brilliant comments on our papers. Without their persistent help, this dissertation would not have been possible.

I wish to express my hearty appreciation to Prof. Brian C. Healy, Prof. Julie Buring, Prof. Miguel Hernán, and all other teachers in this program, for leading me to the Veritas.

I would like to thank Dr. Andric Perez-Ortiz, Dr. Gregory A. Leya, and Dr. Eve Roth for their excellent collaboration. I would also like to thank Dr. Enid Martinez as the program representative, Professor Winfred Williams and Prof. David C Chang as the project advisors, and Professor Eliot C. Heher as a member of my thesis committee, for their advice and assistance in keeping my progress on schedule. Many thanks to Prof. Alessandro Alessandrini, Prof. Robert B. Colvin, and Prof. Paul S. Russell for their support and inspiration. It was a great privilege and honor to study in the Center for Transplantation Sciences at Massachusetts General Hospital.

I am incredibly grateful to Dr. Ajay Singh and Dr. Finnian McCausland, faculty directors of the MMSCI program, who offered me this great opportunity. I would also like to acknowledge Katie Cacioppo and Claire O'Connor for arranging courses and activities.

I am indebted to Chinese PLA General Hospital for funding me to study at Harvard, and in particular, to president Ren, who translated his vision into reality.

Finally, my deepest gratitude to my family for their continuous and unparalleled love, help, and support.

Thank you!

Qing Yuan

Overview of the Thesis Papers

Kidney transplantation (KT) is the best therapy for ESRD patients, including Hepatitis C virus (HCV) infected patients on dialysis(1). HCV+ donor kidneys have been a vital resource to alleviate the organ shortage. HCV has an estimated national prevalence of 0.84% (95% CI, 0.75%-0.96%) among adults in the United States(2), and a prevalence of 9.9 % among adult patients with end-stage renal disease(ESRD) (3). The opioid crisis increased the overdose-death donors by 17% per year and accounted for 13.4% of all deceased donors in 2017. These organs are of improved quality, given the donor's age, but within which 18% had HCV infection(4). Beginning in December 2013, direct-acting antivirals (DAAs) markedly changed the landscape of HCV treatment, with over 95% sustained virologic response rates(5-7). The superior quality of HCV+ kidneys, the increased prevalence of HCV in donors, along with the breakthrough in HCV treatment, have contributed to the rapid rise of transplants where the donor and/or recipient had HCV infection (8).

A better understanding of the effects of HCV infection on transplant outcomes could help to make the right decision regarding transplantation of HCV infected organs and/or recipients. Despite various studies evaluated the effect of HCV infection in donor or recipient, most of them were performed in the pre-DAA era(9-12). Moreover, when analyzing the effect of HCV infection in the recipient, most studies did not differentiate the donor's HCV status. Similarly, when addressing the effect of HCV infection in the donor, the recipient's HCV status was not differentiated. The assumption that the effect of HCV

infection in recipients (or donors) remains the same across HCV positive and negative donors (or recipients) may not be valid. The potential effect modification by donor or recipient's HCV status is critical in providing the correct information for clinical practice but remains largely unknown. Furthermore, the HCV effect observed in the donor and/ or recipient in the pre-DAA era may be completely changed in the post-DAA era.

National registries with large sample size allow for sophisticated analyses and enhanced study power. It also contains the data from small or nonacademic centers, which provides a much broader perspective than most cohort studies, for the findings to be generalized across the United States. The HCV-antibody status has been recorded in the national registry, Organ Procurement and Transplantation Network (OPTN), since 1994. To date, no previous study has systematically evaluated the effect of HCV infection in the pre and post-DAA eras.

Paper 1

Effect of Recipient Hepatitis C Status on the Outcome of Deceased Donor Kidney Transplantation.

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Presented at the 100th Annual Meeting of the New England Surgical Society, Montreal, Quebec, September 2019.

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Abstract

Background: Hepatitis C virus (HCV) infection has been deemed detrimental to kidney transplantation (KT) outcome. Breakthrough HCV treatment with direct-acting antiviral (DAA) medications improved the probability of HCV+ utilization for KT even in non-infected (HCV-) recipients. We hypothesized that recipient HCV infection influences deceased donor KT outcome; and this effect could be modified by donor HCV status, and DAAs use.

Study Design: We conducted a retrospective cohort study based on data from the Organ Procurement and Transplantation Network (OPTN) as of September 2018. A mate kidneys analysis was performed with HCV+ and HCV- recipients of solitary adult KT from ABO-compatible deceased donor between Jan 1994, and Jun 2018. We selected donors where one KT recipient was HCV+, and the mate kidney recipient was HCV-. Both HCV- and HCV+ donors were identified and analyzed as separate. Outcomes including survival of patients, grafts and death-censored grafts (DCGS) were compared between the groups.

Results: 425 HCV+ and 5,575 HCV- donor's mate kidneys were transplanted in HCV discrepant recipient. HCV+ recipients of HCV- donor had worse patient and graft survival (aHR: $_{1.19}1.28_{1.37}$, $_{1.18}1.26_{1.34}$, respectively) and DCGS (aHR: $_{1.15}1.24_{1.34}$) compared to HCV- recipients. Comparable patient and graft survival, and DCGS were found in recipients of HCV+ donors, regardless of recipient HCV status. The risk associated with HCV positivity in donors or recipients in the pre-DAA era (before Dec 2013) was no longer statistically significant in the post-DAA era.

Conclusion: Given comparable outcomes between HCV+ and HCV- recipients in post DAA era or when receiving HCV+ donor kidneys, broader utilization of HCV+ kidneys regardless of the recipient's HCV status should be advocated, and allocation algorithm for HCV+ kidneys should be revised.

Abbreviations and Acronyms:

CIT = cold ischemia time

DAA = direct-acting antiviral

DCGS = death-censored graft survival

DGF = delayed graft function

ESRD = end stage renal disease

GS = graft survival

HCV = hepatitis C virus

OPTN = Organ Procurement and Transplantation Network

PRA = panel reactive antibody

PS = patient survival

Introduction

Utilization of hepatitis C virus positive (HCV+) donor kidneys is a strategy for combating organ shortage. Given concern for transmission of the virus, the majority of HCV+ kidneys were transplanted into HCV infected recipients. However, only about 25% of HCV+ recipients received an HCV+ kidney (4,952 of 16,534) according to the data from OPTN between 1994 and 2018. This was not caused by insufficient HCV+ donors, as the discard rate in HCV+ kidney was 52.3% from 2005 to 2013 as compared to 16.7% in HCV- kidney(1); but due to an unwillingness to accept HCV+ kidney and concern for the virus related post-transplant impaired outcomes. HCV infection was associated with proteinuria, chronic rejection, transplant glomerulopathy, post-transplant diabetes, and HCV-associated glomerulonephritis in kidney recipients(2). The treatment for HCV used to be mainly interferon-based, with low cure rate and high adverse effects, including graft rejection(3-5). Indeed, several epidemiological studies found that HCV infection in either donor or recipient was associated with a higher risk of mortality and graft loss(3, 5).

The Kidney Allocation System (KAS) included the HCV status in donor as a risk factor for post-transplant outcome, based on a prediction model built with data before 2009(6). However, the state of kidney transplantation (KT) with HCV+ kidney and recipient are gradually changing recently. The opioid crisis increased the overdose-death donors by 17% per year and accounted for 13.4% of all deceased donors in 2017. These organs are of improved quality, given the donor's age, but with an increased prevalence of HCV infection(7). The breakthrough in HCV treatment with direct-acting antiviral (DAA) medications further improved the probability of HCV+ kidney utilization(8). More than

eight distinct DAA regimens have been FDA-approved and made available for use since December 2013. In the post DAA era, over 95% of HCV can be cured without additional risk for rejection(9-11). HCV positivity almost became a blessing for candidates to get better priority for receiving an HCV + donor kidney(12). Currently, many trials for using HCV+ kidney in HCV- recipients are indeed ongoing(13).

Notably, no previous studies investigated the effect modification by donor HCV status. An assumption that the effect of HCV infection in recipients remained the same across HCV+ and HCV- donors was made inadvertently, which may not be valid. We here elucidate the effect of recipient HCV infection on the outcome of deceased donor KT especially in the era of DAA therapy. We hypothesize that the effect of recipient HCV infection on KT outcome could be modified by the HCV status in the donor, and by DAAs use. We analyzed the national registry data to characterize these modifications with a design of mate kidneys from the same donor to address the influence of the recipient status and eliminate the predominant effects of donor characteristics.

Methods

Data source

We utilized data from the Organ Procurement and Transplantation Network (OPTN). Analysis and Research file released in September 2018 based on data collected through June 2018. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

Study design and participants

We conducted a retrospective cohort study of mate kidney recipients. We identified all adult (≥18 years old) solitary kidney alone transplants from ABO-compatible deceased donor performed between January 1, 1994, and June 30, 2018. Exclusions were multi-organ transplants, pediatric recipients, ABO-incompatible, and en-bloc KT. Two donor datasets were created within the first all donors were HCV+ (seropositive or nucleic acid test positive as defined by OPTN), and the second HCV- (seronegative and nucleic acid test not positive). In each dataset, a donor has one kidney transplanted into an HCV+ recipient while the other transplanted into an HCV- recipient.

Exposure and outcome classification and assessment

HCV status is reported in the registry but not necessarily confirmed or assessed at the time of transplant for recipients. The outcomes were death-censored graft survival (DCGS), patient survival, and graft survival, following transplantation defined as the earliest of re-transplantation or return to dialysis.

Potential confounders

Providing the mate kidney analysis design, we did not adjust for donor-derived variables. The following recipient factors were included in the Cox proportional hazard model: age (continuous), gender, transplant year, ethnicity (African-American, other) , body mass index (BMI, calculated as weight (kg)/height $(m)^2$; ≤30, >30 kg/m^2, missing), duration of maintenance dialysis prior to transplantation (<3, ≥3 years, missing), diabetes, end-stage renal disease (ESRD) etiology (diabetic, hypertension, other), previous transplant history, delayed graft function (DGF), comorbidity (defined as history of at least one of the following conditions: malignancy, drug-treated chronic obstructive pulmonary disease, or peripheral vascular disease), current panel reactive antibody (PRA) level (≤30%, >30%, missing), cold ischemia time (CIT; ≤24, >24 h, missing), number of HLA-A, B and DR mismatches (HLA MM; ≤3, >3, missing),and insurance status (private, nonprivate, missing). The appropriate functional form of model covariates was determined by perceived impact on clinical meaningfulness.

Statistical analysis

Demographics and clinical characteristics were compared using chi-square test for categorical variables and student's t-tests for continuous variables whose distributions approximated normality. Survival rates were presented in Kaplan-Meier curves and analyzed by log-rank tests. Cox proportional hazards models were fit to estimate hazard ratios and 95% confidence intervals (CIs) for patient survival, graft survival, and DCGS after adjusting for all potential confounders. Time to outcome was defined as the time from the date of transplant until the date of outcome (death or graft failure), censored for

loss to follow-up or end of the study period (June 30, 2018). We defined two eras (pre-DAA era: January 1, 1994, to December 5, 2013, vs. post-DAA era: December 5, 2013, to June 30, 2018) and used three-year survival to address the difference before and after the introduction of DAAs. The paired characteristics within the mate kidneys was accounted for in Cox models with adjustment of the standard error of the hazard ratio (sandwich estimator). The final Cox model excluded cases with missing insurance, PRA, BMI, CIT, DGF, and HLA MM because of low sample sizes within missing categories. All of the covariates included in the Cox model were examined for adherence to the proportional hazard assumption. All analyses were performed using RStudio software, version 1.1.456 (RStudio Team (2015). RStudio: Integrated Development for R. RStudio, Inc., Boston, MA). A p-value of less than 0.05 identified statistical significance, and all confidence intervals also used a 95% threshold.

Results

Recipient characteristics

During the period of 1994 to 2018, there were 258,522 adult solitary kidney alone transplantation from ABO-compatible deceased donors performed, of which, 185,802 were from HCV- donor to HCV- recipient (D-R-), 8,176 were from HCV- donor to HCV+ recipient (D-R+), 1,235 were from HCV+ donor to HCV- recipient (D+R-), and 4,492 were from HCV+ donor to HCV+ recipient (D+R+). The HCV- and HCV+ mate donor cohorts consisted of 5,775 and 425 donors, respectively (Figure 1). The distribution of transplants was not evenly spread out over the time-period of study, but increased as time went by, especially in the HCV+ donors (eFigure 1).

In the HCV- donor cohorts, HCV+ recipients were less female (30.6% vs 39.3%), more African American (47% vs. 33%), less obese (23.8% vs. 30%), and less privately insured (18% vs. 24.8%) compared to the HCV- recipients (Table 1). They were less diabetic (29.4% vs. 30.8%), more hypertension caused kidney failure (30.2% vs. 24.3%), longer dialysis duration (62.9% vs. 52.1% >3 years) compared to the HCV- recipients (Table 2). They were also more with previous transplantation history (26.9% vs. 15.8%), more sensitized (23.6% vs. 19.2% with current PRA >30%), with shorter cold ischemia time (21% vs. 22.5% >24h), more DGF (32.9% vs. 28.2%) compared to the HCV- recipients (Table 3).

In the HCV+ donor cohorts, the HCV+ recipients were younger (53.7 vs. 55.5), less female (18.4% vs 27.5%), more African American (62.1% vs. 50.8%) compared to the HCV-

recipients (Table 1). They were also more HLA mismatch (89.6% vs. 83.5% >3) compared to the HCV- recipients (Table 3). The HCV+ and HCV- recipient groups in each donor cohorts were similar in terms of the other characteristics evaluated.

Crude survival for the entire period:

Compared with the D-R- cohorts, the D-R+ cohorts had significantly impaired crude DCGS, with 92.6% vs. 93.8%, 84.2% vs. 87.6%, 75.4% vs. 81.2%, 51.8% vs. 63.6% at 1, 3, 5, and 10-year ($p<0.001$), respectively (Figure 2A). The D-R+ cohorts also showed worse crude patient and graft survival than those in the D-R- cohorts ($p<0.001$ for both) (eFigure 1A, eFigure 1C)

However, the D+R- and D+R+ cohorts showed comparable post-transplant outcomes. The crude 1, 3, 5, 10-year DCGS were 94.1% vs. 94.6%, 83.3% vs. 83.9%, 66.4% vs. 72.4%, 45.5% vs. 48.5%($p=0.17$) (Figure 2B). The crude patient and graft survival were also comparable between two cohorts ($p=0.31$, $p=0.61$, respectively) (eFigure 1B, eFigure 1D)

Crude survival in pre and post DAA eras:

We identified 4,495 HCV- donors, 294 HCV+ donors in the pre-DAA era, and 1,280 HCV- donors and 131 HCV+ donors in the post-DAA era. The post-transplant outcomes in the pre DAA era were consistent with the results of the entire period. The D-R+ cohort showed significantly worse crude DCGS as compared to the D-R- cohort ($p<0.001$, Figure 3A), while the D+R+ and D+R- had comparable DCGS ($p=0.56$, Figure3B). During the post-DAA era, no statistically significant difference in DCGS were detected between the D-R-

and D-R+ cohorts (p=0.43, Figure 3C), neither between the D+R- and D+R+ cohorts (p=0.57, Figure 3D).

The crude patient and graft survival were varied in parallel with DCGS between cohorts during pre and post DAA eras, except that D+R+ showed even better patient survival than D+R- recipients in the pre-DAA era (p=0.028, eFigure 3C).

Adjusted Survival

After adjustment for recipient and transplant confounders, we found that the recipient's HCV infection when receiving an HCV- kidney was associated with 1.24-fold higher death censored graft failure, 1.28-fold higher mortality, and 1.26-fold higher graft failure as compared to HCV- recipients (aHR: $_{1.15}1.24_{1.34}$, $_{1.19}1.28_{1.37}$, and $_{1.18}1.26_{1.34}$, respectively). However, when receiving an HCV+ kidney, the HCV+ and HCV- recipients showed comparable DCGS, patient and graft survival (aHR: $_{0.77}1.04_{1.42}$, $_{0.74}0.94_{1.21}$, and $_{0.83}1.04_{1.3}$) (Figure 4).

In the pre-DAA era, the adjusted DCGS were comparable between D-R+ and D-R- (aHR: $_{0.97}1.11_{1.25}$), while the D-R+ cohort had 1.17-fold higher mortality (aHR: $_{1.02}1.17_{1.34}$) and 1.13-fold higher graft failure (aHR: $_{1.03}1.13_{1.25}$) than the D-R- cohort.

In contrast, when receiving an HCV+ kidney in the pre-DAA era, or receiving either type of kidney in the post-DAA era, the adjusted DCGS, patient and graft survival were comparable between HCV+ and HCV- recipients (Figure 4).

Sensitivity analyses

Limited impact was found on the magnitude of the hazard ratio or the significance of the findings of DCGS, patient and graft survival, after exclusion of cases with missing data. We also found consistent results when using October 1, 2014 (the start of FDA-approved DAA therapy) as a cut point for pre and post DAA eras.

Discussion

This study demonstrates that HCV infection in deceased donor KT recipients was a prognostic indicator for poorer DCGS (aHR 1.24), patient and graft survival (aHR 1.28, 1.26, respectively). Notably, this detrimental effect was only observed when receiving kidneys from HCV- donor. We found different trends of the HCV effect between HCV- and HCV+ donors, as well as between pre-DAA and post-DAA eras. When receiving HCV+ donor kidneys in pre-DAA era, comparable graft survival and DCGS were observed between HCV+ and HCV- recipients, with even better unadjusted patient survival in HCV+ recipients (3-year risk difference 7.5%, overall p=0.028). During post-DAA era, no significant difference in post-transplant outcomes was detected between HCV+ and HCV- recipients, regardless of donor HCV status.

Our results in HCV- donor's kidneys were similar to those of several previous studies that found recipient HCV infection be a risk factor for patient survival, graft survival and/or acute rejection relative to HCV- recipients(14). A meta-analysis in 2014 systemically evaluated the effect of HCV infection among recipients from 18 observational studies and reported a combined 1.85 times higher mortality and 1.76 times higher graft loss in HCV+ recipients as compared to the HCV- population (15). Also using a mate kidney analysis, although without differentiating donor HCV status, Xia et al. used OPTN data from 2000 to 2013, and reported that the HCV infection in the recipient significantly impaired patient and graft survival (aHR 1.24 for both)(16). Heo used propensity score matching to balance both donor and recipient's characteristics and focused on a relatively closed

cohort for long term outcome. The authors found that HCV infection in recipients was associated with decreased long-term patient and graft survival(17). None of them distinguished HCV+ donors from HCV- donors when assessing the HCV effect in recipients. A more recent study from Bowring et al. reported HCV+ donor was associated with increased post-transplant mortality in HCV+ recipients as compared with HCV- donor kidneys(1). They also found among those who received HCV- donor kidneys, HCV+ recipients had higher mortality (aHR, 1.281.361.46) relative to HCV- recipients. However, the authors did not assess these effects in HCV+ donors. They also reported that the risk associated with being an HCV+ recipient or with receiving an HCV+ kidney was not statistically significantly different in the post DAA era as compared to the pre DAA era.

There were 198,104 HCV- deceased donors where both kidneys were transplanted into adult ABO-compatible recipients since April 1st, 1994, when the donor hepatitis C serostatus data was added into the OPTN database. During the same time period, there were only 4,776 HCV+ deceased kidney donors, which is about 1/40th of HCV- donors. This explains why the specific effect of recipient's HCV infection with HCV+ donors could be easily undermined. Since HCV+ donors are increasing due to the HCV epidemic and opioid crisis, the different effect in HCV+ donors illustrated in our study might add knowledge to guide future clinical decision making. In the perspective of maximizing donor organ longevity, allocation of HCV- kidneys into HCV+ recipients indicate loss of potential graft longevity based on previous studies as well as our study in pre DAA era; whereas our updated results suggest not to consider this loss when allocating HCV+ kidneys in pre DAA era, or both types of kidneys in the post DAA era.

Donor HCV status and DAA use can alter the detrimental effect of recipient HCV status on post-transplant survival for reasons including: 1) Donor anti-virus immune response might establish some local kidney protection, therefore contributing to improved graft and patient survival(18). On the other hand, DAA utilization fundamentally altered the landscape of HCV treatment, without additional side effects in transplant recipients. This could significantly improve the HCV+ recipients' outcome, whether they received HCV+ or HCV- kidneys. 2) The unmeasured confounders in the HCV+ donor dataset may bias the estimated effect by impairing the outcome of HCV- recipients and hence narrow the effect size between HCV+ and HCV- recipients. 3) Statistically， there was smaller sample size in post DAA era as compared to pre DAA era, same was that of the HCV+ donor dataset relative to HCV- donor dataset. We detected significant interaction term for donor HCV status with recipient HCV status ($p=0.175$ for DCGS, $p<0.001$ for both patient and graft survival) when we pooled HCV+ and HCV- donor datasets together. No significant interaction term for DAA era with recipient HCV status was detected. Nonetheless, the insufficient sample size may also be the cause of statistical nonsignificance in interaction terms. Therefore, we also reported the separated analysis of pre and post DAA era based on the clinical meaningfulness. Consistently, Mary G. Bowring et al. also reported that the risk associated with being an HCV+ recipient was not statistically significantly different in the post DAA era(1). The DAA therapy was introduced into clinical practice since late 2013. The abrogation of detrimental effects of HCV in recipient remain to be investigated with larger-scale observational studies.

Our results are subject to the limitations inherent in the design of mate kidney analysis. The effect of HCV infection in the donor was not able to be assessed directly. Previous studies had shown detrimental effects on patient and graft survival when compare HCV+ donors with HCV- donors(19). Consistently, the unadjusted DCGS, patient and graft survival, were decreased in HCV+ donors in comparison to HCV- donors in our study. The mate kidney design also restricted our sample size as it excluded those donors with only one kidney transplanted, as well as those two kidneys transplanted into recipients of same HCV status, which could potentially affect the generalizability of our findings in this study. We utilized Cox proportional hazards model to adjust for recipient and transplant-related confounders. The estimation could, therefore, be biased by residual confounding caused by the recipient, or transplant factors not included in the data recorded by OPTN, such as HCV genotype, viral load, duration and severity of HCV infection, and intensity of immunosuppression. As another limitation of this study, the treatment for HCV in recipients was also not recorded. It was possible that recipients in pre DAA era got DAA therapy several years post-transplantation and had an improved outcome, which may bias our results also.

In conclusion, recipient HCV infection is only associated with an impaired post-transplant outcome when receiving an HCV- kidney. Given comparable outcomes when receiving HCV+ donor kidneys, broader utilization of HCV+ kidneys in either HCV+ or HCV- recipients should be advocated. In the post-DAA era, the recipient's HCV status is even less relevant in the outcome, regardless of the donor's HCV status, hence the current influence of the HCV + donor status on the allocation policy should be reconsidered.

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Tables

Table 1 Recipient Demographics at Kidney Transplantation

Variable	D-R+, n = 5775	D-R-, n = 5775	p Value	D+R+, n = 425	D+R-, n = 425	p Value
Age, y, mean (SD)	51.2 (11.1)	50.7 (13.2)	0.073	53.7 (10.7)	55.5 (11.1)	0.018
Female sex, n (%)	1769 (30.6)	2272 (39.3)	< 0.001	78 (18.4)	117 (27.5)	0.002
Recipient ethnicity, African American, n (%)	2716 (47.0)	1903 (33.0)	< 0.001	264 (62.1)	216 (50.8)	0.001
BMI, kg/m^2, mean (SD)	26.6 (5.2)	27.5 (5.5)	< 0.001	27.0 (4.9)	27.3 (4.9)	0.345
BMI Category (%)			< 0.001			0.218
≤ 30	4316 (74.7)	3948 (68.4)		319 (75.1)	314 (73.9)	
> 30	1376 (23.8)	1730 (30.0)		103 (24.2)	102 (24.0)	
Unknown	83 (1.4)	97 (1.7)		3 (0.7)	9 (2.1)	
Insurance (%)			< 0.001			0.189
Private	1042 (18.0)	1433 (24.8)		93 (21.9)	109 (25.6)	
Nonprivate	4726 (81.8)	4338 (75.1)		328 (77.2)	315 (74.1)	
Unknown	7 (0.1)	4 (0.1)		4 (0.9)	1 (0.2)	

Table 2 Recipient Kidney Related Disease and Dialysis Information at Kidney Transplantation

Variable	D-R+, n =5775	D-R-, n = 5775	p Value	D+R+, n = 425	D+R-, n = 425	p Value
Diabetes, n (%)			0.002			0.632
No	3580 (62.0)	3574 (61.9)		217 (51.1)	225 (52.9)	
Yes	1771 (30.7)	1865 (32.3)		189 (44.5)	177 (41.6)	
Unknown	424 (7.3)	336 (5.8)		19 (4.5)	23 (5.4)	
ESRD, n (%)			< 0.001			0.838
Other	2753 (47.7)	2888 (50.0)		145 (34.1)	142 (33.4)	
Diabetes	1278 (22.1)	1486 (25.7)		131 (30.8)	139 (32.7)	
Hypertension	1744 (30.2)	1401 (24.3)		149 (35.1)	144 (33.9)	
DIAL_DAY, mean (SD)	1997.1 (1624.1)	1536.0 (1190.9)	< 0.001	1229.0 (1023.3)	1175.3 (937.9)	0.449
DIAL Category, n (%)			< 0.001			0.333
≤ 3y	1697 (29.4)	2174 (37.6)		213 (50.1)	226 (53.2)	
> 3y	3633 (62.9)	3006 (52.1)		175 (41.2)	155 (36.5)	
U	445 (7.7)	595 (10.3)		37 (8.7)	44 (10.4)	
Comorbidity, n (%)			0.12			0.348
No	3390 (58.7)	3459 (59.9)		174 (40.9)	195 (45.9)	
Yes	668 (11.6)	601 (10.4)		60 (14.1)	55 (12.9)	
Unknown	1717 (29.7)	1715 (29.7)		191 (44.9)	175 (41.2)	

DIAL_DAY, recipient's dialysis days; ESRD, end stage renal disease

Table 3 Recipient Transplant Information

Variable	D-R+, n = 5775	D-R-, n 5775	p Value	D+R+, n = 425	D+R-, n = 425	p Value
TX_YearCat, n (%)			1			1
1994-1999	1302 (22.5)	1302 (22.5)		113 (26.6)	113 (26.6)	
2000-2009	2245 (38.9)	2245 (38.9)		131 (30.8)	131 (30.8)	
2010-2018	2228 (38.6)	2228 (38.6)		181 (42.6)	181 (42.6)	
Prev_TX, yes, n (%)	1554 (26.9)	910 (15.8)	< 0.001	66 (15.5)	61 (14.4)	0.7
CPRA, mean (SD)	19.9 (33.4)	16.4 (31.1)	< 0.001	8.4 (20.6)	9.6 (22.4)	0.413
CPRA Category, n (%)			< 0.001			0.767
0	3355 (58.1)	3671 (63.6)		294 (69.2)	291 (68.5)	
0-30	922 (16.0)	870 (15.1)		74 (17.4)	68 (16.0)	
> 30	1362 (23.6)	1106 (19.2)		42 (9.9)	51 (12.0)	
Unknown	136 (2.4)	128 (2.2)		15 (3.5)	15 (3.5)	
CIT, mean (SD)	18.6 (8.9)	19.0 (9.0)	0.043	20.3 (9.0)	21.0 (8.9)	0.278
CIT Category, n (%)			0.043			0.914
≤ 24	4254 (73.7)	4209 (72.9)		281 (66.1)	280 (65.9)	
> 24	1212 (21.0)	1299 (22.5)		129 (30.4)	132 (31.1)	
Unknown	309 (5.4)	267 (4.6)		15 (3.5)	13 (3.1)	
DGF, n (%)			< 0.001			0.53
No	3873 (67.1)	4141 (71.7)		329 (77.4)	336 (79.1)	
Yes	1899 (32.9)	1629 (28.2)		95 (22.4)	89 (20.9)	
Unknown	3 (0.1)	5 (0.1)		1 (0.2)	0 (0.0)	
HLA_MM, n (%)			0.296			0.012
≤ 3	1878 (32.5)	1957 (33.9)		44 (10.4)	70 (16.5)	
> 3	3892 (67.4)	3813 (66.0)		381 (89.6)	355 (83.5)	
Unknown	5 (0.1)	5 (0.1)		0 (0.0)	0 (0.0)	

CIT, cold ischemia time; CPRA, recipient's current panel reaction antibody; DGF, delayed graft function; HLA_MM, HLA mismatch; Prev_TX, recipient have previous transplantation history; TX_YearCat, category of transplant year;

Figures

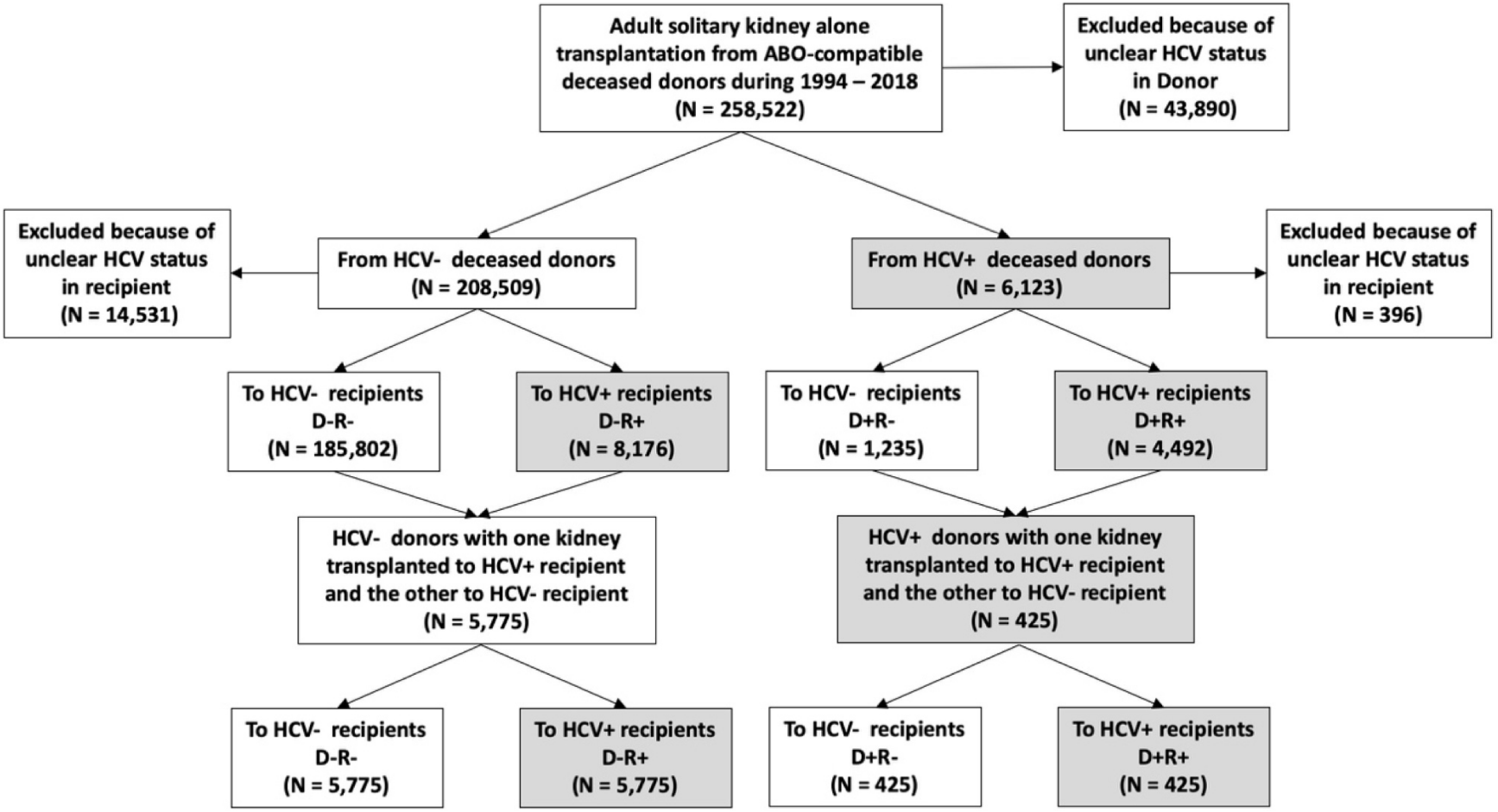


Figure 1 The flowchart of study cohorts identification

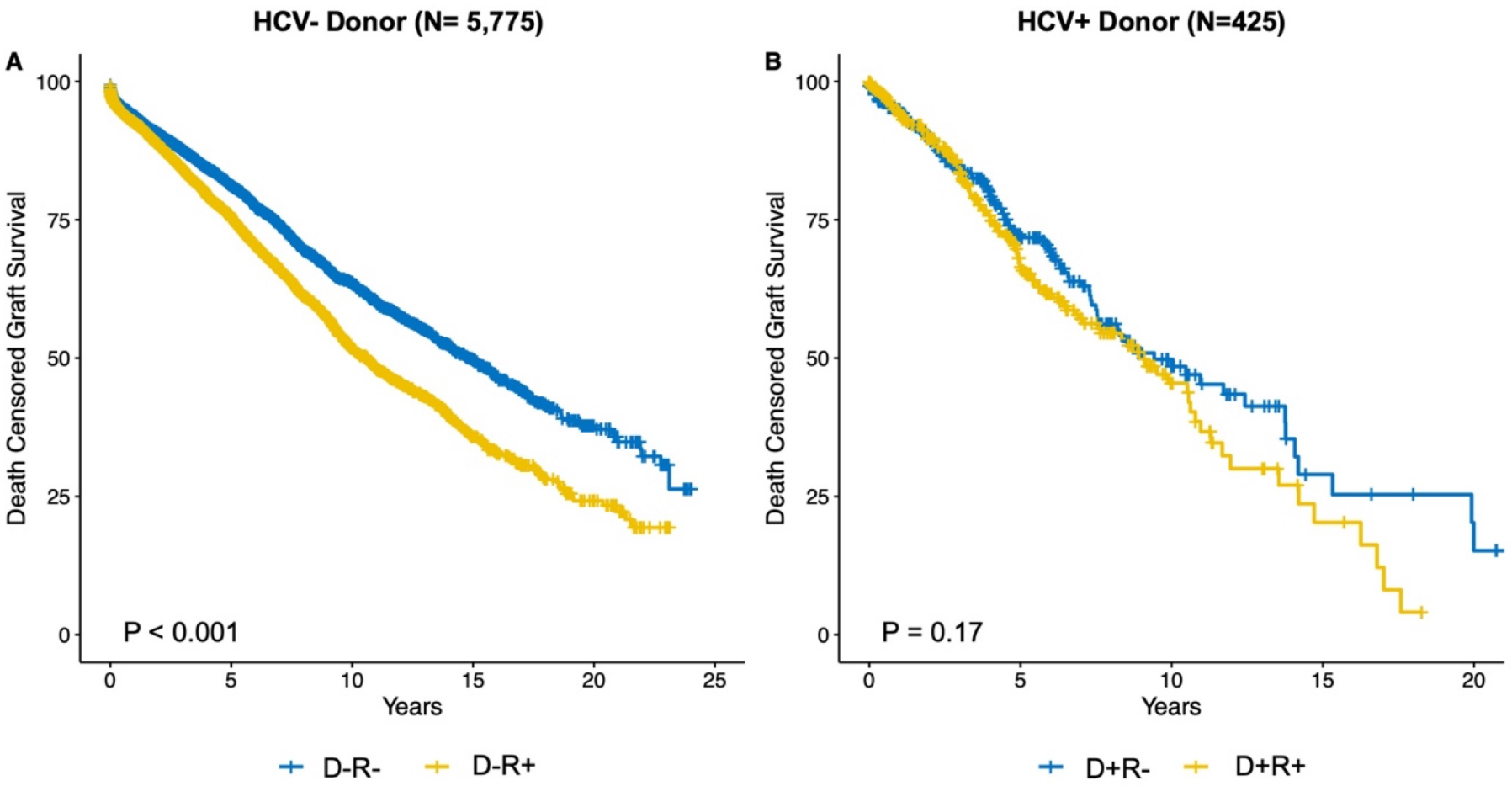


Figure 2 Crude death-censored graft survival in (A) HCV- (hepatitis C virus) donor cohorts and (B) HCV+ donor cohorts in the entire time period

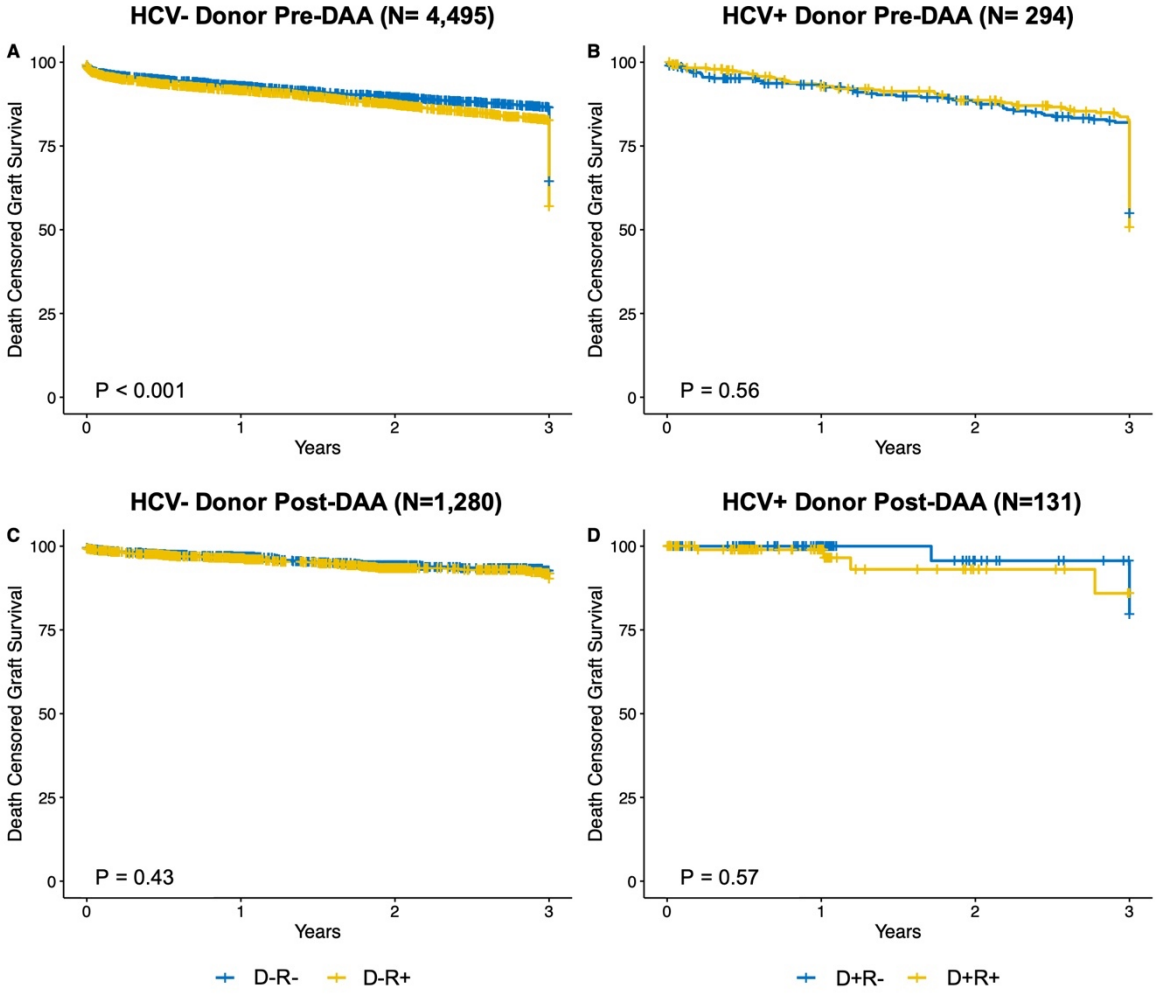


Figure 3 Crude death-censored graft survival in HCV- (hepatitis C virus) and HCV+ donor cohorts in the pre- and post-DAA (direct-acting antiviral) (A) HCV- Donor Pre-DAA (N = 4,495) (B) HCV+ Donor Pre-DAA (N = 294) (C) HCV- Donor Post-DAA (N = 1,280) (D) HCV+ Donor Post-DAA (N=131)

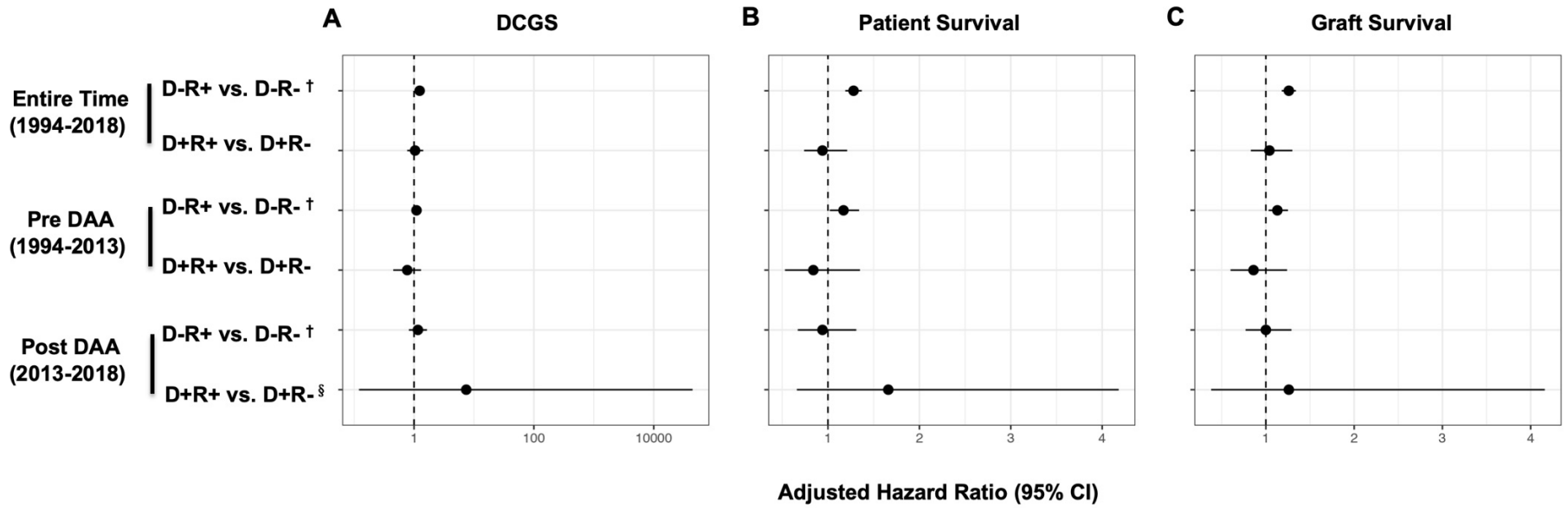
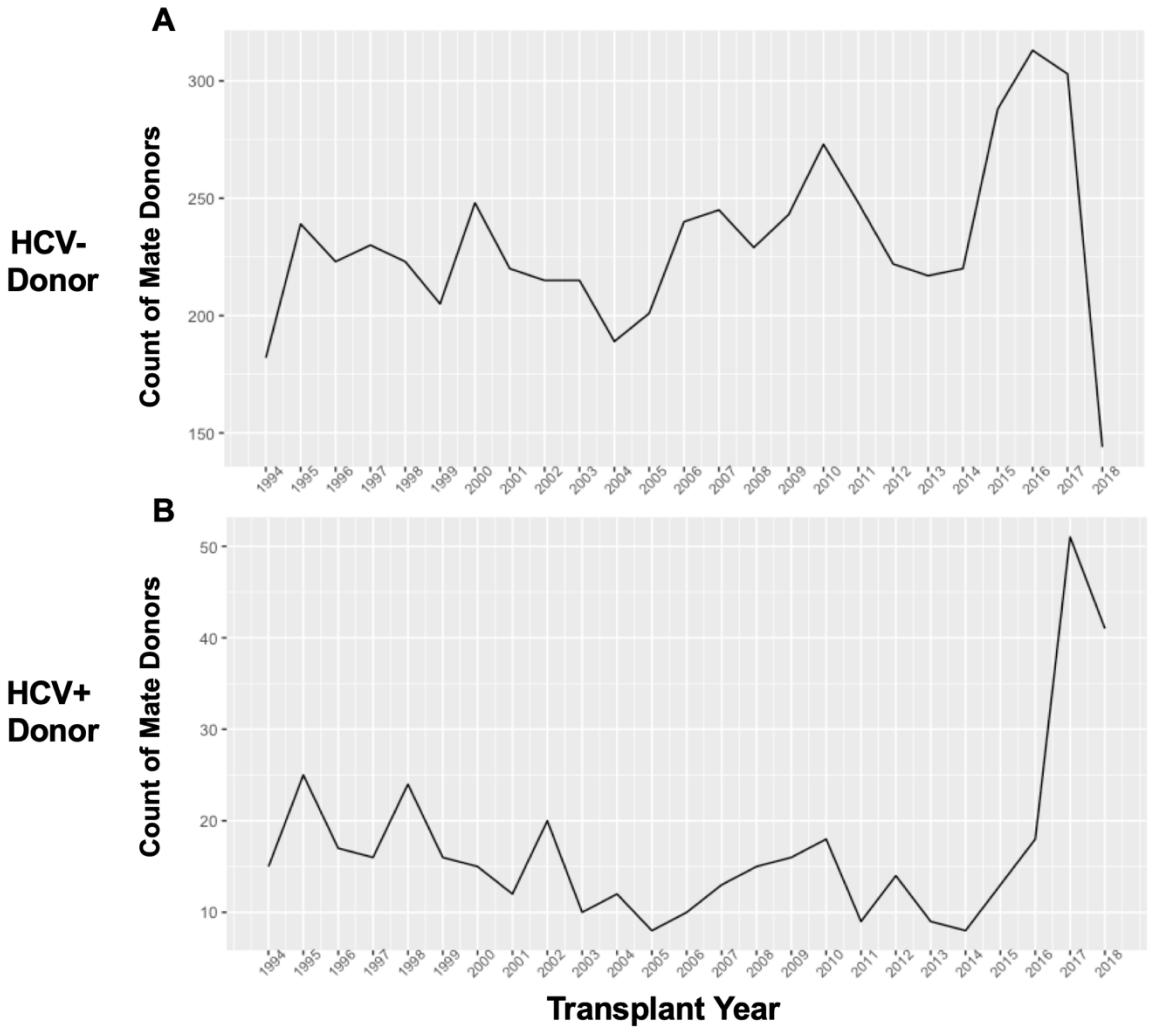


Figure 4 Adjusted hazard ratio of hepatitis C virus infection in recipient for (A) death-censored graft survival, (B) patient survival, and (C) graft survival.

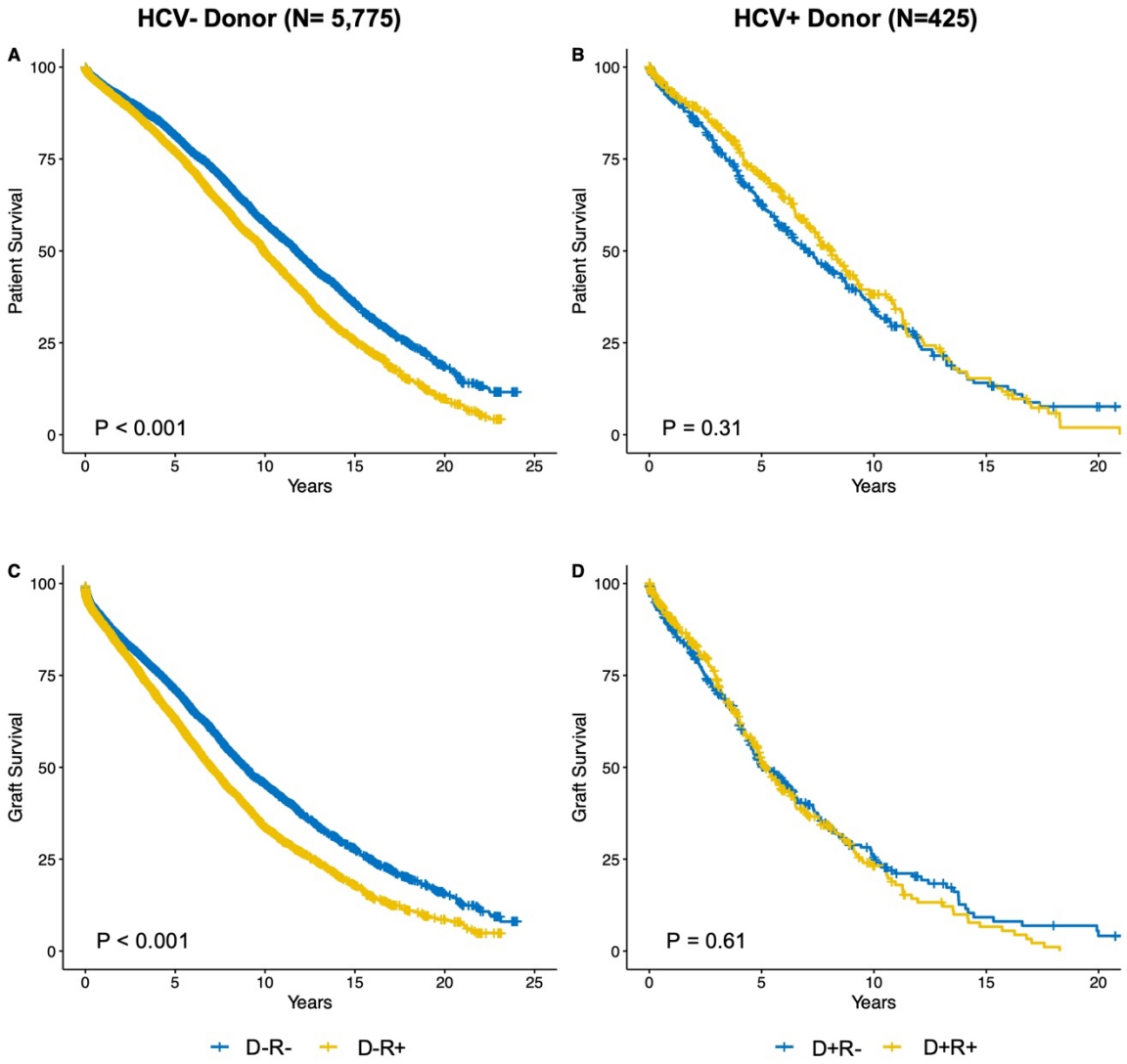
Adjusted for confounders including recipients' age, sex, transplant year, ethnicity, BMI, dialysis time, diabetes, end stage renal disease, previous transplant history, comorbidity, current panel reactive antibody, cold ischemia time, human leukocyte antigen mismatches, and insurance status; and stratified on DGF (delayed graft function) groups (DGF=Y, DGF=N). DAA, direct-acting antiviral

* Examination of the proportionality of death-censored graft survival, patient and graft survival between the D-R+ and D-R- suggested nonproportionality. To simplify the model for interpretation and keep one model across analyses, we accepted this small departure from the proportional hazards assumption.

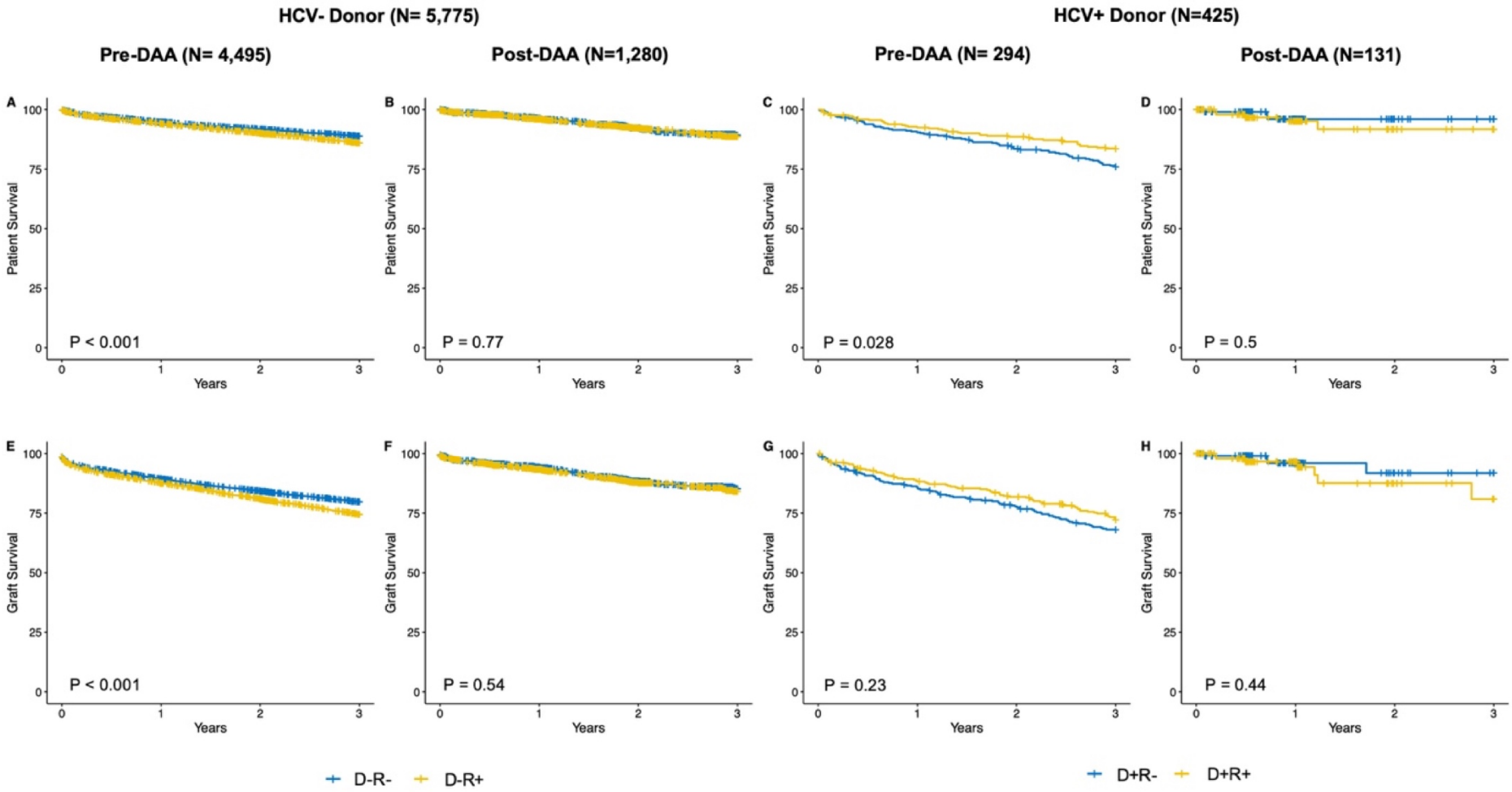
† When applying the same COX model in estimating the death-censored graft survival between D+R+ and D+R- in the post-DAA (direct-acting antiviral) cohort, we ran out of iterations and did not converge. Results demonstrated were from a modified model excluded dialysis time, current panel reactive antibody and cold ischemia time.



eFigure 1 Yearly distribution of the mate kidney transplantation



eFigure 2 Crude patient and graft survival in HCV- (hepatitis C virus) and HCV+ donor cohorts in the entire time period (A) HCV- Donor (N = 5,775) (B) HCV+ Donor (N = 425) (C) HCV- Donor (N = 5,775) (D) HCV+ Donor (N = 425)



eFigure 3 Crude patient and graft survival in HCV- (hepatitis C virus) and HCV+ donor cohorts in the pre- and post-DAA (direct-acting antiviral) eras (A) Pre-DAA (N = 4,495) (B) Post-DAA (N = 1,280) (C) Pre-DAA (N = 294) (D) Post-DAA (N = 131) (E) Pre-DAA (N = 4,495) (F) Post-DAA (N = 1,280) (G) Pre-DAA (N = 294) (H) Post-DAA (N = 131)

Paper 2

Influence of Donor and Recipient Hepatitis C Virus Infection on Outcomes after Kidney Transplantation, a Propensity Score Matched National Study across 25 years

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Presented at the 15th Annual Academic Surgical Congress, Orlando, FL, February 2020.

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Abstract

Hepatitis C Virus (HCV) infection in a donor, recipient, or both affects deceased-donor kidney transplantation outcomes. Direct-acting antivirals (DAA) may influence those outcomes. The Organ Procurement and Transplantation Network (OPTN) data of adult first-time solitary deceased-donor kidney transplant recipients 1994-2019 were allocated into four groups by donor or recipient HCV infection. We performed patient survival (PS) and death-censored graft survival (DCGS) pairwise comparisons after propensity score matching to assess donors and/or recipients HCV infection effect. We stratified our study by DAA era to evaluate for potential effect modification.

In the pre-DAA era, donor HCV infection decreased PS and DCGS in all recipients. However, recipient HCV infection impaired PS and DCGS only with uninfected donors. HCV dual-infection (donor plus recipient) group had worse PS and DCGS than the dual-uninfected. Donor HCV infection derived worse post-transplant outcomes than recipient HCV infection. The risk associated with HCV infection in donors and/or recipients was no longer statistically significant in the post-DAA era, except for impaired PS in dual-infected versus dual-uninfected.

Kidney donor HCV infection negatively affected transplant outcomes in all recipients, while recipient HCV infection impaired outcomes only with uninfected donors. Early post-DAA era analysis showed no effect of donor or recipient HCV infection.

Keywords:

Hepatitis C Virus, Kidney Transplantation, Direct-Acting Antiviral Therapy, Propensity Score Matching.

Abbreviations and Acronyms:

HCV = hepatitis C virus

DAA = direct-acting antiviral

OPTN = Organ Procurement and Transplantation Network

PS = patient survival

DCGS = death-censored graft survival

ESRD = end-stage renal disease

DGF = delayed graft function

PRA = panel reactive antibody

CIT = cold ischemia time

Introduction

Hepatitis C virus (HCV) is prevalent among potential kidney transplant donors and recipients, with important implications for patient survival and graft outcomes. More than two million people in the United States (US) are infected with HCV with an estimated national prevalence of 0.84% (95% CI, 0.75%-0.96%) among adults [1], and 9.9 % among adult patients with end-stage renal disease(ESRD) [2]. HCV prevalence was shown to be 3.45% among normal-risk potential organ donors and 18.2% among high-risk potential organ donors [3]. Furthermore, as the number of overdose death (ODD) donors rises, roughly 18% of ODD donors are HCV+[4]. Among kidney transplant recipients, between 1.8 to 8 percent are HCV+, most of whom were infected pretransplant[5,6].

Kidney transplantation (KT) is the best therapy for ESRD patients, including HCV infected patients on dialysis; quality of life is enhanced by limiting the multiple morbidity and life-constraining schedules associated with chronic dialytic modalities and, most importantly, patient survival is increased[7]. HCV+ donor kidneys are potentially an important resource to alleviate the shortage of available kidneys for transplantation in the U.S.[4]. Despite a significantly higher risk of HCV transmission and decreased survival compared to patients who receive kidneys from HCV- donors, recipients of kidneys from HCV+ donors still have improved survival compared to individuals who remain on the waiting list (adjusted hazard ratio [HR] 0.76)[8]. When given the option, a majority of patients on the kidney waitlist opt to accept an HCV+ kidney at an earlier point in time rather than wait for a standard criteria HCV- kidney, which generally entails several years of wait time [9]. Nonetheless, HCV+ donor to HCV- recipient kidney transplants have not traditionally been recommended, hence a large number of high-quality kidneys from HCV+ deceased donors have been discarded each year [10].

Beginning in December 2013, direct-acting antivirals (DAAs) markedly changed the landscape of HCV treatment with over 95% sustained virologic response rates[11]. Meanwhile, the number of ODD donors in the U.S. increased from 66 donors in 2000 to 1,263 donors in 2016, with a median HCV+ donor age of 31 years[4]. The superior quality of HCV+ kidneys, the increased prevalence of HCV in donors and recipients, and the breakthrough in HCV treatment have contributed to the rapid rise of transplants where the donor and/or recipient had HCV infection. In the post-DAA era, waitlisted kidney candidates were 2.2 times more likely to list as willing to accept an HCV+ kidney and HCV+ recipients were 1.95 times more likely to have received an HCV+ kidney when compared to the pre-DAA era [10].

Despite advances in antiviral therapy for HCV infection, the Kidney Donor Risk Index (KDRI) algorithm, which factors in the donor HCV infection status, is still being used by the OPTN in the US to evaluate the quality of deceased donor kidneys. The KDRI was derived from an outcome prediction model based on ten donor and four transplant characteristics initially using transplants between 1995 and 2005. Positive HCV infection in the donor was assigned the largest coefficient amongst the dichotomous donor factors [12]. This might result in an overestimation of the risk of HCV+ donor kidneys and, therefore, is outdated in the post-DAA era. It also operates to deprive candidates of high-quality HCV+ kidneys if they, or their accepting center, decline kidney offers with a KDRI beyond a certain threshold; and contributes to the aforementioned high discard rate of these kidneys.

Previous studies have suggested that HCV infection in the donor or recipient is associated with impaired post kidney transplant outcomes [13-16]. However, studies analyzing the effect of HCV infection in the recipient often did not differentiate the donor's HCV status [13]. Similarly, when addressing the effect of HCV infection in the donor, the recipient's

HCV status was not differentiated [14]. The assumption that the effect of HCV infection in recipients and donors remains the same across all donor-recipient combinations may not be valid. Therefore, a better, more comprehensive understanding of the effects of HCV infection on transplant outcomes could facilitate appropriate decision-making with respect to HCV infected organs and/or recipients.

In this study, we sought to understand the effect of HCV infection in donors and recipients on deceased donor kidney transplantation (DDKT) recipient and graft survival, and to discern if those effects differed among various combinations of HCV+ donors and recipients. We hypothesized that the effect of HCV in donors or recipients could be modified by recipient or donor HCV status. Additionally, these effects may be influenced by the DAA use. We used national registry data with propensity score matching to systematically characterize the HCV effect on post kidney transplant outcome and further address this question in the post DAA era.

Methods

Data Sources

This study used data from the Organ Procurement and Transplantation Network (OPTN). Analysis and Research file released in June 2019 based on data collected through March 2019. The content in this paper is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

Study Population

We identified all adult (age ≥18) first-time solitary kidney transplant recipients from an ABO-compatible deceased donor between January 1994 and March 2019 in the U.S. Patients with missing or uncertain HCV-antibody status in the donor or recipient were excluded. Patients were allocated into four groups according to HCV infection in the donor(D+) or recipient(R+): D-R-, D+R-, D-R+, and D+R+.

Outcome and Exposure Classification

The outcomes of interest were patient survival (PS) and death-censored graft survival (DCGS) following kidney transplantation. DCGS was defined as time to re-transplantation or return to dialysis, whichever came first. Recipient HCV status is reported in the registry but not necessarily confirmed or assessed at the time of transplant. We used an antibody(Ab) test for donor and recipient, as indicated in the OPTN STAR file. HCV+ status was defined as HCV Ab+ or HCV nucleic acid test (NAT) positive, while HCV- was defined as HCV Ab- without HCV NAT+.

Propensity Score Matching

We performed pairwise comparisons of patient survival (PS) and death-censored graft survival (DCGS) after propensity score matching to assess the effect of HCV infection in

donors and/or recipients. Briefly, a cohort of the D+R- patients were compared to a cohort of D-R- patients to address the effect of a HCV donor infection in HCV- recipients, while D+R+ patients were compared with D-R+ patients to assess for the effect of HCV donor infection in HCV+ recipients. Similarly, D+R+ vs. D+R- patients were compared to assess for the effect of recipient HCV infection on outcomes of HCV+ donor kidneys. D-R+ vs. D-R- pairings were compared to assess for the effect of recipient HCV infection on outcomes in HCV- donor kidneys. Finally, we compared D+R+ vs. D-R- pairings to assess for the effect of HCV infection in both donors and recipient on outcomes, and compared D+R- vs. D-R+ pairings to assess for whether HCV infection in donors or recipients alone was more detrimental on outcomes.

Pairs of subjects were matched by the probability of positive HCV exposure based on a multivariable logistic regression model with 40 potential predictors from the donor, recipient, and transplant procedure. Model variables and missingness are shown in Supplement Table 1. Variables were chosen based on SRTR risk adjustment models[17]. We used complete-case analysis for categorical variables missing fewer than 1% of values and included a missing indicator in the initial step for those missing more than 1%. For continuous variables, the missing values were imputed with the median, and a missing indicator was also included for those missing percentage > 1% （Suppl.Table 1）. The potential outliers of continuous variables were winsorized at 1 and 99 percentiles. By focusing on the effect of HCV exposure in a sample of subjects that resemble the exposed subjects, we estimated the average treatment effect in the treated (ATT). We used the nearest neighbor matching with 1:1 ratio, without replacement, and with a caliper of width equal to 0.2 of the standard deviation (SD) of the logit of the propensity score. A balance diagnosis was performed by comparing the characteristics between matched

groups. An SD greater than 0.1 was considered as a sign of imbalance, and the propensity score prediction model was refitted to ensure the balance between matched groups (Supp.Figure 1). We further stratified our study by DAA era (before or after December 2013) to evaluate potential effect modification.

Statistical analysis

Survival rates were presented in Kaplan-Meier curves and analyzed by log-rank tests. Time to the outcome was defined as the time from the date of transplant until the date of outcome (death or graft failure) and censored for loss to follow-up or end of the study period. Absolute and relative risk difference in mortality and death-censored graft failure (DCGF) were estimated using Austin's methods[18]. All analyses were performed using RStudio software, version 1.1.456 (R. RStudio, Inc., Boston, MA). A p-value of less than 0.05 identified statistical significance, and all confidence intervals also used a 95% threshold.

Results

1. Changing characteristics of kidney transplantation relative to HCV in donors and recipients

We identified 166,160 D-R-, 6,251 D-R+, 3,854 D+R+, and 1,672 D+R- patients during the study (Figure1). D+R+ transplants increased at a similar rate to D-R- transplants in the pre-DAA era (before December 2013), while the number of D+R- and D-R+ transplants remained stable for two decades. However, the utilization of HCV+ kidneys surged in the post-DAA era, starting initially with the traditional operating paradigm (D+ to R+), which peaked in 2016 and soon shifted to more aggressive utilization of HCV+ kidneys (D+ to R-). The number of D+R- transplants was 583 in 2018 compared to fewer than 50 per year in all years before 2016 (Figure 2).

The characteristics of donor, recipient and transplant factors in the four cohorts are detailed in Tables 1, 2, Supp. 2, 3. The D+R- donors in the pre-DAA era were predominantly male, white or African American, with low BMIs, and who succumbed to head trauma. Their terminal renal indices showed low SCR and BUN, and the rate of DCD in this cohort was low. Low rates of diabetes and hypertension were also observed. (Table 1a, Supp. 2a). In contrast, recipients in the D+R- cohort tended to be the oldest (57 [IQR, 47, 65]), and had been on dialysis for a short period of time. Thirty-seven percent D+R- and 38%D+R+ were shared nationally and D+R- had the longest cold ischemia time (CIT) at 20 hours [IQR, 16.0, 26.0]. D+R- and D+R+ cohorts also had higher HLA mismatch than that of D-R- and D-R+. However, the incidence of delayed graft function (DGF) in D+R- was 25.3% which was lower than that in the D-R+ or D+R+ cohorts and similar to the rate observed in the D-R- (Table 1c, Supp. 2c).

In the post-DAA era, HCV+ donors were younger than the HCV- donors and had lower rates of diabetes and hypertension. Donors in the D+R- cohort were predominantly white

(85.2%), died primarily of anoxic brain injury (72%) and had the highest terminal BUN levels and HBV infection rates (Table 2a, Supp. 3a). The recipients of D+R- kidneys tended to be white (45.7%), highly educated (30.6% with post high school degree), least likely to have hypertension as a cause of renal failure, and most likely to have a comorbid diagnosis of malignancy(12.8%). Consistent with observations from the pre-DAA era, D+R- transplants had the lowest rate of DGF (20.5%) despite the longest CIT (18.4[IQR, 13.1, 23.8])(Table 2c).

2. The association between HCV infection in donor and post-transplant outcome

The D-R- patients had the best crude PS and DCGS, while the D+R- patients had the worst crude PS and DCGS in the pre-DAA era. Donor HCV infection was associated with worse crude PS and DCGS regardless of the HCV status of the recipient (D-R- vs. D+R-, adjusted $p < 0.001$, D-R+ vs. D+R+, adjusted $p < 0.001$)(Figure 3A, 3B). The crude 3-year PS was 89.6%, 73.1%, 86.7% and 84.8% for D-R-, D+R-, D-R+ and D+R+, respectively. The crude 3-year DCGS was 88.8%, 80.1%, 84.2% and 82% for D-R-, D+R-, D-R+ and D+R+, respectively (Table 3).

After matching, 1272 pairs of HCV+ and 528 pairs of HCV- recipients were generated. Among the HCV+ recipients, receiving an HCV+ deceased donor kidney was associated with 1.28-fold higher mortality (HR $_{1.15}1.28_{1.42}$) and 1.22-fold higher death-censored graft failure (DCGF) (HR $_{1.08}1.22_{1.39}$) when compared to receiving an HCV- kidney (Figure 4A). These increased risks translated to a 3-year PS of 86.3% vs. 84.8%, and 3-year of DCGS of 83.6% vs. 81.6% for D-R+ vs. D+R+ recipients, respectively. The absolute risk difference (aRD) was 3.3% (95%CI, 1.8%, 4.7%) for PS and 3.1% (95%CI, 1.2%, 5%) for DCGS at 3 years (Table 3).

Among HCV- recipients, receiving an HCV+ kidney was associated with 1.55-fold higher mortality (HR $_{1.33}1.55_{1.80}$) and 1.64-fold higher DCGF (HR $_{1.33}1.64_{2.02}$) compared to

receiving an HCV- kidney(Figure 4A). These increased risks translated to 3-year PS of 85.3% vs. 73.5%, and 3-year of DCGS of 86.9% vs. 80.4% for D-R- vs. D+R- recipients, respectively. The aRD was 8% (95%CI, 5.2%, 10.9%) for PS and 7.4% (95%CI, 4.3%, 10.5%) for DCGS at 3 years (Table 3).

In the post-DAA era, comparable crude PS and DCGS were observed among all four cohorts (Figure 3C, 3D). The crude 3-year PS was 91%, 86.1%, 88.1% and 89.8% for D-R-, D+R-, D-R+ and D+R+, respectively. The crude 3-year DCGS was 92.5%, 92.6%, 92.4% and 94.2% for D-R-, D+R-, D-R+ and D+R+, respectively (Table 3). After matching, there were 290 pairs of HCV+ and 791 pairs of HCV- recipients. In contrast with the trends in the pre-DAA era, the risks associated with receiving an HCV+ kidney in either HCV+ or HCV- recipients were not statistically significantly different in PS or DCGS in the post-DAA era (Figure 4B, Supp.Figure 3).

3. The association between HCV infection in recipient and post-transplant outcome

In the pre-DAA era, HCV infection in recipients of HCV- donor kidneys significantly impaired both crude PS and DCGS (D-R- vs. D-R+, adjusted $p < 0.001$ for log-Rank test). However, HCV infection in recipients of HCV+ donors demonstrated a protective 22% lesser rate of mortality (D+R- vs. D+R+, adjusted $p < 0.001$ for log-Rank test, $HR_{0.69}0.78_{0.87}$), despite the DCGS remaining comparable between two groups (D+R- vs. D+R+, adjusted $p = 0.998$) (Figure 3A, 3B).

After matching, we generated 461 pairs of HCV+ and 4646 pairs of HCV- deceased donors. We found that HCV infection in the recipient was associated with 1.25-fold higher mortality ($HR_{1.18}1.25_{1.33}$) and 1.31-fold higher DCGF ($HR_{1.22}1.31_{1.41}$) in HCV- donor. These increased risks translated to 3-year PS of 88.7% vs. 86.7%, and 3-year of DCGS of 86.5% vs. 84.2% for D-R- vs. D-R+ recipients, respectively. The aRD between D-R- and D-

R+ was 2.6% (95%CI, 1.9%, 3.2%) for PS and 3.5% (95%CI, 2.6%, 4.4%) for DCGS at 3 years (Table 3). In contrast, comparable outcomes were found between HCV+ and HCV- recipients of HCV+ donors (HR $_{0.86}1_{1.18}$ for mortality, $_{0.87}1.01_{1.31}$ for DCGS) (Figure 4A, Supp.Figure 4).

In the post-DAA era, we generated 508 pairs of HCV+ and 1440 pairs of HCV- recipients after matching. The risk associated with recipient's HCV infection when receiving either HCV+ or HCV- kidney was not statistically significantly different in PS or DCGS (Figure 4B).

4. The association between HCV infection in donor plus recipient and post-transplant outcome

In the pre-DAA era, HCV infection in the donor and recipient significantly impaired both crude PS and DCGS (D-R- vs. D+R+, adjusted $p < 0.001$ for log-Rank test) (Figure 3A, 3B). There were 2150 pairs of D-R- and D+R+ transplants after matching. HCV infection in donor and recipient was associated with 1.56-fold higher mortality (HR $_{1.43}1.56_{1.7}$) and 1.71-fold higher DCGF (HR $_{1.54}1.71_{1.9}$) compared to the D-R- transplants. These increased risks translated to 3-year PS of 89% vs. 85%, and 3-year of DCGS of 87.8% vs. 82.7%, for D-R- vs. D+R+ recipients, respectively. The aRD between D-R- and D+R+ were 5.3% (95%CI, 4.3%, 6.4%) for PS and 7.1% (95%CI, 5.7%, 8.5%) for DCGS at 3 years (Figure 4A, Table 3).

In the post-DAA era, 803 pairs of D-R- and D+R+ transplants were generated after matching. HCV infection in donor and recipient marginally significantly increased the mortality (p =0.049 for log-rank test, Supp. Figure 5E). The cox proportional hazard model also showed that the hazard of mortality was increased by 1.43-fold (HR $_{1.0}1.43_{2.04}$) as compared to the D-R- transplants, with an aRD of 3.3% (95%CI, 0, 6.7%) at 3 years. The 3-year PS were 91.8% and 88.4% for D-R- and D+R+ recipients, respectively. The risk

associated with HCV infection in donor and recipient was not statistically significantly different in DCGS (Figure 4B, Table 3).

5. The association between HCV infection in donor or recipient and post-transplant outcome

In the pre-DAA era, HCV infection in the donor had more impact on crude patient survival than in the recipient (D+R- vs. D-R+, adjusted $p < 0.001$ for log-Rank test) (Figure 3A, 3B). After matching, there were 444 pairs of D+R- and D-R+ transplants. Compared with infection in recipients, donor HCV infection was associated with 1.36-fold higher mortality (HR $_{1.16}1.36_{1.61}$) and 1.34-fold higher DCGF (HR $_{1.08}1.34_{1.67}$). These increased risks translated to 3-year PS of 75.6% vs. 85.4%, and 3-year of DCGS of 81.1% vs. 84.5%,for D+R- vs. D-R+ recipients, respectively. The aRD between D+R- and D-R+ were 5.4% (95%CI, 2.6%, 8.6%) for PS and 4.8% (95%CI, 1.4%, 8.2%) for DCGS at 3 years (Figure 4A, Table 3).

In the post-DAA era, 253 pairs of D-R+ and D+R- transplants were identified after matching. Both of the PS and DCGS in the matched patients were comparable between D-R+ and D+R- cohorts (Figure 4B, Table 3).

Discussion

In our national study of 177,937 deceased kidney transplant recipients across 25 years, we found a marked increase in the utilization of HCV+ kidneys in the post-DAA era. This started initially with HCV+ kidney transplants to HCV+ recipients in 2014, followed by a dramatic shift towards transplants of HCV+ kidneys into HCV- recipients in the next two years. The annual number of D+R- kidney transplants increased by tenfold in 2018 compared to 2016. In the pre-DAA era, despite generally being older, with less time undergoing dialysis and higher prevalence of malignancy, D+R- recipients received kidneys from younger donors. In the post-DAA era, the majority of HCV+ donors were deceased after drug overdose[4]. Interestingly, education level was highest in the D+R- cohort, which suggests that a higher level of health literacy may help potential recipients better understand and execute informed consent and appreciate the true benefits of late generation DAA in fully ameliorating the risks of an HCV+ kidney[19]. This education effort should be expanded into the candidate population at large to minimize the disadvantage of the lower socio-economic status groups. The short-term outcome as far as DGF was indeed favorable in D+R- transplants, despite the longest CIT and higher HLA mismatch as compared with other cohorts in both pre and post DAA eras. HCV infection was always associated with poorer PS and DCGS, when it was in the donor or in recipients who received HCV- kidneys. Donor HCV infection impacted PS and DCGS to a greater extent than did recipient HCV infection. We also found that donor plus recipient HCV infection (D+R+ vs. D-R-) and donor infection in HCV- recipient(D+R- vs. D-R-) displayed the largest absolute risk difference of mortality and DCGF. Importantly, the risk associated with HCV infection in donors and/or recipients was no longer statistically significant in the post-DAA era, except for a marginally significantly impaired PS in D+R+ vs. D-R-, which possessed the largest extent of risk difference in the pre-DAA era.

Despite debate over the transmission of HCV infection through transplantation[20-22], the presumed risk of such transplants led to rarely performing them in the pre-DAA era. The absolute number of annual HCV+ donor to HCV-recipient transplants always remained below 50 prior to 2016. The introduction of DAA encouraged broader acceptance of HCV+ candidates as well as more aggressive utilization of HCV+ kidneys. Two pilot trials evaluating the efficacy and safety of transplanting kidneys from HCV+ donors into HCV- recipients found that despite the inevitable transmission of HCV infection, if followed by DAA therapy, these transplants could provide well-functioning allografts and HCV cure in a cost-effective manner[23,24]. Similarly, our observational study showed that in the post-DAA era, the D+R- cohorts had equivalent outcomes as D-R- patients.

A number of studies evaluated the effect of donor HCV infection on kidney transplant outcomes in the pre-DAA era[15,25,26]. Compared with staying on the waiting list, receiving an HCV+ kidney was associated with improved survival among all patients[8]. A single-center analysis summarizing data from 1990 to 2007 compared the long-term outcome of D+R+ with D-R+. Their result showed donor HCV infection in HCV+ recipients was not a significant risk factor for mortality, graft failure, or liver disease[25]. However, national registry data from 1995 to 2008 showed that D+R+ patients had a 2.6-fold higher hazard of joining the liver list ($P<0.001$). Nevertheless, the absolute risk difference in subsequently listing for liver transplant was <2% between recipients of HCV+ and HCV- kidneys. [26]. A recent study using data from 2005 to 2017 reported that among HCV+ recipients, receiving an HCV+ kidney was associated with 19% higher mortality(aHR, $_{1.07}1.19_{1.32}$), while it was not statistically significantly different in the post-DAA era[10]. Our study evaluated the HCV effect of donor separately in HCV+ recipients and in HCV- recipients and found similar trends of donor HCV associated impairment of PS and DCGS

in both groups of recipients. However, the absolute risk difference of mortality and DCGF was much larger in the HCV- recipients than in those HCV recipients who were positive(Table 3a, 3b).

There have been two meta-analyses evaluating the effect of recipients' HCV infection status on kidney transplant outcome[16,27]. Both found that HCV infection was associated with increased mortality (aHR: $_{1.49}1.85_{2.31}$, $_{1.33}1.69_{1.97}$) and graft loss (aHR: $_{1.46}1.76_{2.11}$, $_{1.22}1.56_{2.00}$). However, both studies did not distinguish donor HCV status. In our study, we found that the effect of recipient's HCV infection was dramatically modified by the HCV status in donor. HCV infection in recipients only impaired transplant outcomes when receiving an HCV-, but not HCV+ kidney. This finding was consistent with our previous study using mate kidney analysis, which examined the outcomes of transplanting a pair of kidneys from the same donor, one to an HCV+ recipient, the other to a recipient who was HCV negative [28].

There are several limitations to our study. First, the majority of D+R- patients were transplanted in the post-DAA era with relatively short follow up. This necessitated dividing the dataset into pre- and post-DAA eras, resulting in smaller sample sizes for analysis. This reduction in sample size may limit the power of the study. Second, we used propensity score matching to eliminate the confounders between comparator groups. The estimation could be biased by unmeasured potential confounders, which are not recorded in the registry data, such as HCV genotype, viral load, duration and severity of HCV infection, and intensity of immunosuppression. Third, we lack viremia data throughout the study period. While most viremic patients are antibody positive, there is a portion of antibody positive patients that are aviremic. The HCV infection was defined in our study as it is in the OPTN data by antibody status prior to 2015, and both antibody and nucleic acid test(NAT) result since 2015. Antibody positive aviremic donors or

recipients were included as HCV+ in both eras' analyses. There is a miniscule fraction of viremic patients who are antibody negative. This population would have been included in the HCV- cohort in the pre-DAA analysis . Including these cohorts of donors or recipients would render worse outcomes in the uninfected population and hence underestimate the difference observed between groups. Fourth, the registry data does not verify whether HCV+ recipients subsequently received DAA treatment; though in most clinical scenarios, anti-HCV treatment would be indicated. Fifth, we used a pair matching method to estimate the "average treatment effect in the treated". Some exposed subjects were excluded from the matched sample because of no available unexposed subjects within the specified caliper distance of the exposed subjects. There might be potential bias generated when unmatched exposed subjects differ systematically from the matched exposed subjects[29]. However, other statistical methods, including full matching or inverse probability weighting, with the aim to include all the samples in both groups in comparison could also result in biased estimation due to increased heterogenicity within each group. Lastly, we used single imputation for those variables with missingness over 1 percent. Limited impact was found on the magnitude of the hazard ratio or the significance of the findings of DCGS and patient survival, with multiple imputation method.

In conclusion, although HCV infection in either donors or recipients of kidney transplants had negative impacts on PS and DCGS in the pre-DAA era, in the post-DAA era neither HCV infection in the donor nor recipient appears to portend worse outcomes. Thus, HCV+ kidneys should be used more frequently to increase the opportunities for waitlisted kidney recipient candidates to first, receive a kidney transplant and second, a kidney transplant with superior outcome potential. This study is another supportive tool

towards future utilization of HCV+ kidneys as standard of care. Given the comparable outcomes across all four patient cohorts in the post-DAA era, a new allocation algorithm incorporating HCV+ kidneys, and eliminating their negative influence on the KDRI, is urgently needed to improve the utilization and allocation of this under-utilized resource.

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Tables

Table 1a Characteristics of Donors the pre DAA era

	D-R-	D-R+	D+R-	D+R+	*P* Value
n	116108	4646	550	2455	
Age (median [IQR])	40.0 [23.0, 51.0]	40.0 [24.0, 51.0]	41.0 [34.0, 46.0]	42.0 [33.0, 49.0]	<0.001
Gender = M (%)	69042 (59.5)	2762 (59.4)	380 (69.1)	1574 (64.1)	<0.001
BMI (median [IQR])	25.6 [22.4, 29.7]	25.6 [22.3, 29.4]	24.8 [22.1, 28.0]	25.1 [22.3, 28.6]	<0.001
Race (%)					<0.001
White	83490 (71.9)	3209 (69.1)	409 (74.4)	1824 (74.3)	
African American	14085 (12.1)	698 (15.0)	91 (16.5)	341 (13.9)	
Hispanic	14482 (12.5)	574 (12.4)	45 (8.2)	260 (10.6)	
Other	4051 (3.5)	165 (3.6)	5 (0.9)	30 (1.2)	
Cause of Death (%)					<0.001
Anoxia	19852 (17.1)	750 (16.1)	67 (12.2)	470 (19.1)	
Cerebrovascular/Stroke	44318 (38.2)	1800 (38.7)	196 (35.6)	985 (40.1)	
Head Trauma	48450 (41.7)	1926 (41.5)	281 (51.1)	960 (39.1)	
Other	3488 (3.0)	170 (3.7)	6 (1.1)	40 (1.6)	
DCD = Yes(%)	10101 (8.7)	368 (7.9)	11 (2.0)	105 (4.3)	<0.001
SCR (median [IQR])	1.0 [0.7, 1.3]	1.0 [0.7, 1.3]	0.9 [0.7, 1.2]	0.9 [0.7, 1.1]	<0.001
History of Diabetes = Yes (%)	6712 (5.8)	254 (5.5)	14 (2.5)	95 (3.9)	<0.001
History of Hypertension = Yes (%)	28967 (24.9)	1137 (24.5)	114 (20.7)	576 (23.5)	0.038
Smoking History = No (%)	78484 (67.6)	3039 (65.4)	234 (42.5)	1068 (43.5)	<0.001

BMI, body mass index; DCD, donation after cardiac death; SCR, serum creatinine

Table 1b Characteristics of Recipients in the pre DAA era

	D-R-	D-R+	D+R-	D+R+	*P* Value
n	116108	4646	550	2455	
Age (Median [IQR])	53.0 [42.0, 61.0]	51.0 [44.0, 58.0]	57.0 [47.0, 65.0]	53.0 [47.0, 59.0]	<0.001
Gender = M (%)	69448 (59.8)	3251 (70.0)	406 (73.8)	1995 (81.3)	<0.001
BMI (Median [IQR])	26.8 [23.6, 30.9]	26.1 [23.0, 29.9]	26.5 [23.6, 29.4]	26.4 [23.3, 29.8]	<0.001
Race (%)					<0.001
White	56376 (48.6)	1383 (29.8)	211 (38.4)	404 (16.5)	
African American	34683 (29.9)	2447 (52.7)	290 (52.7)	1789 (72.9)	
Hispanic	15940 (13.7)	517 (11.1)	27 (4.9)	201 (8.2)	
Other	9109 (7.8)	299 (6.4)	22 (4.0)	61 (2.5)	
Insurance = Nonprivate (%)	83051 (71.5)	3733 (80.3)	418 (76.0)	1831 (74.6)	<0.001
Education Level (%)					<0.001
High School	44906 (38.7)	1923 (41.4)	222 (40.4)	1195 (48.7)	
Technical	22531 (19.4)	931 (20.0)	86 (15.6)	450 (18.3)	
Post High School Degree	18972 (16.3)	494 (10.6)	59 (10.7)	254 (10.3)	
ESRD (%)					<0.001
Diabetes	32208 (27.7)	1193 (25.7)	178 (32.4)	783 (31.9)	
Hypertension	30368 (26.2)	1745 (37.6)	221 (40.2)	1108 (45.1)	
Other	53532 (46.1)	1708 (36.8)	151 (27.5)	564 (23.0)	
DIAL_DAY (Median [IQR])	1143 [708, 1691]	1344 [889, 2164]	976 [580, 1388]	1118 [603, 1596]	<0.001
CPRA (Median [IQR])	0.0 [0.0, 2.0]	0.0 [0.0, 2.0]	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	<0.001
PVD = Yes(%)	5374 (4.6)	210 (4.5)	26 (4.7)	111 (4.5)	<0.001
Diabetes = Yes (%)	38827 (33.4)	1491 (32.1)	225 (40.9)	1014 (41.3)	<0.001

BMI, body mass index; ESRD, end stage renal disease; DIAL_DAY, dialysis days; CPRA, current panel reaction antibody; PVD, peripheral vascular disease.

Table 1c Characteristics of Transplantation in the pre DAA era

	D-R-	D-R+	D+R-	D+R+	*P* Value
n	116108	4646	550	2455	
TX_Year (median [IQR])	2005 [2000, 2010]	2004 [1999, 2009]	2001 [1997, 2007]	2006[2001, 2010]	<0.001
Region (%)					<0.001
1	4694 (4.0)	167 (3.6)	11 (2.0)	74 (3.0)	
2	14123 (12.2)	661 (14.2)	112 (20.4)	823 (33.5)	
3	17507 (15.1)	704 (15.2)	64 (11.6)	235 (9.6)	
4	10816 (9.3)	414 (8.9)	29 (5.3)	136 (5.5)	
5	17680 (15.2)	655 (14.1)	63 (11.5)	260 (10.6)	
6	4356 (3.8)	156 (3.4)	6 (1.1)	7 (0.3)	
7	9360 (8.1)	403 (8.7)	54 (9.8)	137 (5.6)	
8	7738 (6.7)	252 (5.4)	23 (4.2)	55 (2.2)	
9	7150 (6.2)	355 (7.6)	29 (5.3)	222 (9.0)	
10	10186 (8.8)	457 (9.8)	104 (18.9)	192 (7.8)	
11	12498 (10.8)	422 (9.1)	55 (10.0)	314 (12.8)	
Shared (%)					<0.001
Local	85197 (73.4)	3464 (74.6)	223 (40.5)	931 (37.9)	
Regional	9559 (8.2)	377 (8.1)	124 (22.5)	591 (24.1)	
National	21352 (18.4)	805 (17.3)	203 (36.9)	933 (38.0)	
CIT (median [IQR])	18.0 [13.0, 23.1]	18.0 [13.0, 23.5]	20.0 [16.0, 26.0]	19.0 [15.0, 25.0]	<0.001
HLA Mismatch = 4-6 (%)	76253 (65.7)	3238 (69.7)	452 (82.2)	2151 (87.6)	<0.001
DGF = Yes (%)	28919 (24.9)	1440 (31.0)	139 (25.3)	756 (30.8)	<0.001

TX_Year, transplant year; CIT, cold ischemia time; HLA, human leucocyte antigen; DGF, delayed graft function

Table 2a Characteristics of Donors in the post DAA era

	D-R-	D-R+	D+R-	D+R+	*P* Value
n	46099	1443	1082	1303	
Age (median [IQR])	40.0 [27.0, 52.0]	42.0 [29.0, 52.0]	35.0 [29.0, 44.0]	32.0 [26.0, 39.0]	<0.001
Gender = M (%)	28136 (61.0)	853 (59.1)	617 (57.0)	818 (62.8)	0.012
BMI (median [IQR])	27.1 [23.4, 31.9]	27.5 [23.7, 32.2]	26.3 [23.3, 30.5]	25.6 [22.8, 29.4]	<0.001
Race (%)					<0.001
White	31238 (67.8)	929 (64.4)	922 (85.2)	1103 (84.7)	
African American	6325 (13.7)	273 (18.9)	44 (4.1)	58 (4.5)	
Hispanic	6421 (13.9)	187 (13.0)	94 (8.7)	116 (8.9)	
Other	2115 (4.6)	54 (3.7)	22 (2.0)	26 (2.0)	
Cause of Death (%)					<0.001
Anoxia	18056 (39.2)	574 (39.8)	779 (72.0)	882 (67.7)	
Cerebrovascular/Stroke	12337 (26.8)	397 (27.5)	109 (10.1)	127 (9.7)	
Head Trauma	14151 (30.7)	430 (29.8)	176 (16.3)	272 (20.9)	
Other	1555 (3.4)	42 (2.9)	18 (1.7)	22 (1.7)	
DCD = Yes (%)	10519 (22.8)	329 (22.8)	151 (14.0)	128 (9.8)	<0.001
SCR (median [IQR])	0.9 [0.7, 1.4]	1.0 [0.7, 1.4]	0.9 [0.7, 1.3]	0.9 [0.7, 1.1]	<0.001
History of Diabetes = Yes (%)	3616 (7.8)	123 (8.5)	41 (3.8)	30 (2.3)	<0.001
History of Hypertension = Yes (%)	13638 (29.6)	453 (31.4)	226 (20.9)	173 (13.3)	<0.001
Smoking History = No (%)	36564 (79.3)	1154 (80.0)	723 (66.8)	953 (73.1)	<0.001

BMI, body mass index; DCD, donation after cardiac death; SCR, serum creatinine

Table 2b Characteristics of Recipients in the post DAA era

	D-R-	D-R+	D+R-	D+R+	*P* Value
n	46099	1443	1082	1303	
Age (median [IQR])	55.0 [44.0, 64.0]	59.0 [52.0, 64.0]	60.0 [52.0, 67.0]	60.0 [55.5, 65.0]	<0.001
Gender = M (%)	27135 (58.9)	994 (68.9)	739 (68.3)	1017 (78.1)	<0.001
BMI (median [IQR])	28.6 [24.9, 32.8]	27.8 [24.4, 31.6]	29.1 [25.7, 33.3]	27.8 [24.5, 31.5]	<0.001
Race (%)					<0.001
White	16501 (35.8)	334 (23.1)	494 (45.7)	267 (20.5)	
African American	15762 (34.2)	784 (54.3)	392 (36.2)	855 (65.6)	
Hispanic	9079 (19.7)	226 (15.7)	117 (10.8)	137 (10.5)	
Other	4757 (10.3)	99 (6.9)	79 (7.3)	44 (3.4)	
Insurance = Nonprivate (%)	37085 (80.4)	1265 (87.7)	831 (76.8)	993 (76.2)	<0.001
Education Level (%)					<0.001
High School	19085 (41.4)	741 (51.4)	403 (37.2)	680 (52.2)	
Technical	11577 (25.1)	369 (25.6)	280 (25.9)	318 (24.4)	
Post High School Degree	10687 (23.2)	230 (15.9)	331 (30.6)	214 (16.4)	
ESRD (%)					<0.001
Diabetes	14439 (31.3)	477 (33.1)	438 (40.5)	601 (46.1)	
Hypertension	12513 (27.1)	543 (37.6)	270 (25.0)	444 (34.1)	
Other	19147 (41.5)	423 (29.3)	374 (34.6)	258 (19.8)	
DIAL_DAY (median [IQR])	1661 [1043, 2373]	1999 [1364, 2988]	1257 [637, 1674]	1065 [593, 1661]	<0.001
CPRA (mean (SD))	19.3 (32.8)	20.5 (33.5)	9.4 (21.9)	9.3 (21.3)	<0.001
PVD = Yes (%)	4590 (10.0)	186 (12.9)	118 (10.9)	148 (11.4)	0.001
Diabetes = Yes (%)	17213 (37.3)	583 (40.4)	521 (48.2)	714 (54.8)	<0.001

BMI, body mass index; ESRD, end stage renal disease; DIAL_DAY, dialysis days; CPRA, calculated panel reaction antibody; PVD, peripheral vascular disease.

Table 2c Characteristics of Transplantation in the post DAA era

	D-R-	D-R+	D+R-	D+R+	*P* Value
n	46099	1443	1082	1303	
TX_Year (median [IQR])	2016 [2015, 2018]	2016 [2015, 2018]	2018 [2017, 2018]	2016 [2015, 2017]	<0.001
Region (%)					<0.001
1	1601 (3.5)	62 (4.3)	35 (3.2)	65 (5.0)	
2	5404 (11.7)	182 (12.6)	151 (14.0)	349 (26.8)	
3	6590 (14.3)	221 (15.3)	181 (16.7)	150 (11.5)	
4	4526 (9.8)	173 (12.0)	45 (4.2)	67 (5.1)	
5	8107 (17.6)	238 (16.5)	101 (9.3)	144 (11.1)	
6	1911 (4.1)	55 (3.8)	13 (1.2)	6 (0.5)	
7	3192 (6.9)	110 (7.6)	37 (3.4)	45 (3.5)	
8	3130 (6.8)	86 (6.0)	5 (0.5)	44 (3.4)	
9	3057 (6.6)	85 (5.9)	125 (11.6)	174 (13.4)	
10	3507 (7.6)	79 (5.5)	195 (18.0)	84 (6.4)	
11	5074 (11.0)	152 (10.5)	194 (17.9)	175 (13.4)	
Shared (%)					<0.001
Local	35095 (76.1)	1115 (77.3)	337 (31.1)	379 (29.1)	
Regional	5349 (11.6)	157 (10.9)	345 (31.9)	348 (26.7)	
National	5655 (12.3)	171 (11.9)	400 (37.0)	576 (44.2)	
CIT (median [IQR])	16.7 [11.4, 22.6]	16.5 [11.0, 22.0]	18.4 [13.1, 23.8]	18.0 [12.3, 23.5]	<0.001
HLA Mismatch = 4-6 (%)	35126 (76.2)	1170 (81.1)	894 (82.6)	1154 (88.6)	<0.001
DGF = Yes (%)	13468 (29.2)	496 (34.4)	222 (20.5)	284 (21.8)	<0.001

TX_Year, transplant year; CIT, cold ischemia time; HLA, human leucocyte antigen; DGF, delayed graft function

Table3a Patient Survival at 3 Years

Cohorts in Comparison	D-R+	D+R+	D-R-	D+R-	Absolute risk difference
Patient Survival in the preDAA era (%)					
Crude	86.7 (85.8, 87.7)	84.8 (83.4, 86.3)	89.6 (89.5, 89.8)	73.1 (69.4, 76.9)	-
D+ vs. D- in R+	86.3 (84.4, 88.2)	84.8 (82.8, 86.8)	-	-	3.3 (1.8, 4.7)
D+ vs. D- in R-	-	-	85.3 (82.3, 88.4)	73.5 (69.8, 77.4)	8 (5.2, 10.9)
R+ vs. R- in D+	-	80.9 (77.3, 84.6)	-	76.7 (72.8, 80.7)	0.1 (-2.9, 3.1)
R+ vs. R- in D-	86.7 (85.8, 87.7)	-	88.7 (87.8, 89.6)	-	2.6 (1.9, 3.2)
D+R+ vs. D-R-	-	85 (83.4, 86.5)	89 (87.7, 90.4)	-	5.3 (4.3, 6.4)
D+R- vs. D-R+	85.4 (82.1, 88.8)	-	-	75.6 (71.6, 79.7)	5.4 (2.6, 8.6)
Patient Survival in the postDAA era (%)					
Crude	88.1 (85.7, 90.5)	89.8(87.7, 92)	91 (90.6, 91.3)	86.1 (77.6, 95.6)	-
D+ vs. D- in R+	90.2 (85.5, 95)	88.7 (84, 93.7)	-	-	2.7 (-2.9, 8.1)
D+ vs. D- in R-	-	-	89.1 (83.6, 94.9)	88.6 (81.6, 96.2)	-0.3 (-5.9, 6.1)
R+ vs. R- in D+	-	88.4 (84.3, 92.8)	-	85.1 (75.4, 96)	1.1 (-6.1, 7)
R+ vs. R- in D-	88.1 (85.7, 90.5)	-	89.5 (87.3, 91.8)	-	-0.5 (-3.3, 2.2)
D+R+ vs. D-R-	-	88.4 (85.5, 91.4)	91.8 (89.2, 94.4)	-	3.3 (0, 6.7)
D+R- vs. D-R+	88.7 (81.8, 96.3)	-	-	91.5 (85, 98.6)	3.2 (-5.9, 11.6)

Table3b Death-censored Graft Survival at 3 Years

Cohorts in Comparison	D-R+	D+R+	D-R-	D+R-	Absolute risk difference
Death-censored Graft Survival in the preDAA era (%)					
Crude	84.2 (83.1, 85.3)	82 (80.4, 83.6)	88.8(88.6, 89)	80.1 (76.6, 83.7)	-
D+ vs. D- in R+	83.6 (81.5, 85.8)	81.6 (79.4, 83.9)	-	-	3.1 (1.2, 5)
D+ vs. D- in R-	-	-	86.9 (83.9, 89.9)	80.4 (76.8, 84.1)	7.4 (4.3, 10.5)
R+ vs. R- in D+	-	79.4 (75.5, 83.5)	-	80.6 (76.9, 84.6)	1.2 (-2.5, 4.9)
R+ vs. R- in D-	84.2 (83.1, 85.3)	-	86.5 (85.5, 87.5)	-	3.5 (2.6, 4.4)
D+R+ vs. D-R-	-	82.7 (81, 84.4)	87.8 (86.4, 89.2)	-	7.1 (5.7, 8.5)
D+R- vs. D-R+	84.5 (81.1, 88.1)	-	-	81.1 (77.3, 85.1)	4.8 (1.4, 8.2)
Death-censored Graft Survival in the post DAA era (%)					
Crude	92.4(90.6, 94.2)	94.2 (92.5, 96)	92.5 (92.2, 92.8)	92.6 (87.3, 98.3)	-
D+ vs. D- in R+	90.1 (85.5, 94.9)	92 (87.9, 96.3)	-	-	0.4 (-5, 6.1)
D+ vs. D- in R-	-	-	92.2 (87.8, 96.8)	93.8 (88.5, 99.4)	-2.3 (-7.4, 2.1)
R+ vs. R- in D+	-	93 (89.6, 96.5)	-	92.3 (86.2, 98.8)	0.7 (-5, 5.4)
R+ vs. R- in D-	92.4 (90.6, 94.2)	-	92.1 (90.2, 94.1)	-	-0.2 (-2.4, 2)
D+R+ vs. D-R-	-	93.3 (90.9, 95.8)	93.3 (90.9, 95.8)	-	1.7 (-1.4, 4.5)
D+R- vs. D-R+	94.4 (89.3, 99.7)	-	-	93.3 (87.4, 99.5)	2.5 (-3.6, 10)

Supp.Table1 Variables Included in the Propensity Score Prediction Model and Respective Missingness & Disposal

Variable Name	Variable Type	Missing Number	Missing Percent	Disposal of Missingness
Donor factor				
Age	Continuous	0	0.00	-
Biological Sex	Categorical	0	0.00	-
BMI	Continuous	1085	0.61	Impute with Median
Race	Categorical	0	0.00	-
Blood Type	Categorical	0	0.00	-
Cause of Death	Categorical	11	0.01	Complete Case Analysis
Donation after Cardiac Death	Categorical	26	0.01	Complete Case Analysis
Terminal SCR	Continuous	272	0.15	Impute with Median
Terminal BUN	Continuous	307	0.17	Impute with Median
HBV Core Antibody	Categorical	0	0.00	-
Prerecovery Diuretics	Categorical	5695	3.20	Missing Indicator
Prerecovery Medications: T4	Categorical	5653	3.18	Missing Indicator
Received Vasodilators	Categorical	16	0.01	Complete Case Analysis
Lung Infection	Categorical	0	0.00	-
History of Diabetes	Categorical	29	0.02	Complete Case Analysis
History of Hypertension	Categorical	12	0.01	Complete Case Analysis
History of Smoking	Categorical	12	0.01	Complete Case Analysis
Recipient factor				
Age	Continuous	0	0.00	-
Biological Sex	Categorical	0	0.00	-
BMI	Continuous	1594	0.90	Impute with Median
Race	Categorical	0	0.00	-
Blood Type	Categorical	0	0.00	-
Insurance	Categorical	137	0.08	Complete Case Analysis
Education Level	Categorical	7048	3.96	Missing Indicator
ESRD	Categorical	2188	1.23	Missing Indicator
Dialysis Days	Continuous	18886	10.61	Missing Indicator & Impute with Median
Calculated PRA	Continuous	4125	2.32	Missing Indicator & Impute with Median
PVD	Categorical	7281	4.09	Missing Indicator
Diabetes	Categorical	6918	3.89	Missing Indicator
Previous Malignancy	Categorical	0	0.00	-

HIV Status*	Categorical	12130	6.82	Missing Indicator
Transplant factor				
Calendar Year of Transplant	Continuous	0	0.00	-
Region	Categorical	0	0.00	-
Shared	Categorical	0	0.00	-
Cold Ischemia Time	Continuous	7002	3.94	Missing Indicator & Impute with Median
HLA Mismatch	Categorical	124	0.07	Complete Case Analysis
HLA A Mismatch	Categorical	48	0.03	Complete Case Analysis
HLA DR Mismatch	Categorical	105	0.06	Complete Case Analysis
DGF	Categorical	10	0.01	Complete Case Analysis

BMI, body mass index; SCR, serum creatinine; BUN, blood urea nitrogen; HBV, hepatitis b virus; T4, tetraiodothyronine; ESRD, end stage renal disease; PRA, panel reaction antibody; PVD, peripheral vascular disease; HLA, human leucocyte antigen; DGF, delayed graft function; HIV, human immunodeficiency virus.
*HIV Status in recipient was not included in the post DAA era analysis because of small positive proportion

Supp.Table 2a Characteristics of Donors and Donation Procedure in the pre DAA era

	D-R-	D-R+	D+R-	D+R+	*P* Value
n	116108	4646	550	2455	
Blood Type (%)					<0.001
A	43102 (37.1)	1603 (34.5)	174 (31.6)	731 (29.8)	
B	13699 (11.8)	699 (15.0)	67 (12.2)	301 (12.3)	
AB	4348 (3.7)	191 (4.1)	8 (1.5)	14 (0.6)	
O	54959 (47.3)	2153 (46.3)	301 (54.7)	1409 (57.4)	
BUN (median [IQR])	13.0 [9.0, 19.0]	13.0 [8.0, 18.0]	11.0 [8.0, 16.0]	12.0 [8.0, 17.0]	<0.001
HBV (%)					<0.001
No	108786 (93.7)	4262 (91.7)	433 (78.7)	1982 (80.7)	
Yes	4789 (4.1)	270 (5.8)	87 (15.8)	423 (17.2)	
Unknown	2533 (2.2)	114 (2.5)	30 (5.5)	50 (2.0)	
Prerecovery Diuretics (%)					<0.001
No	51805 (44.6)	2087 (44.9)	251 (45.6)	1148 (46.8)	
Yes	58700 (50.6)	2295 (49.4)	261 (47.5)	1219 (49.7)	
Unknown	5603 (4.8)	264 (5.7)	38 (6.9)	88 (3.6)	
Prerecovery Medications: T4 (%)					<0.001
No	61790 (53.2)	2535 (54.6)	318 (57.8)	1175 (47.9)	
Yes	48457 (41.7)	1833 (39.5)	194 (35.3)	1185 (48.3)	
Unknown	5861 (5.0)	278 (6.0)	38 (6.9)	95 (3.9)	
Received Vasodilators = Y (%)	13332 (11.5)	518 (11.1)	66 (12.0)	315 (12.8)	0.171
Lung Infection = Confirmed (%)	32561 (28.0)	1237 (26.6)	110 (20.0)	761 (31.0)	<0.001
History of Smoking (%)					<0.001
No Smoking History	78484 (67.6)	3039 (65.4)	234 (42.5)	1068 (43.5)	
Smoking but Not Continued	6228 (5.4)	270 (5.8)	27 (4.9)	141 (5.7)	

Continued Smoking	30303 (26.1)	1282 (27.6)	280 (50.9)	1195 (48.7)
Unknown	1093 (0.9)	55 (1.2)	9 (1.6)	51 (2.1)

BUN, blood urea nitrogen; HBV, hepatitis b virus; T4, tetraiodothyronine

Supp.Table 2b Characteristics of Recipients in the pre DAA era

	D-R-	D-R+	D+R-	D+R+	*P* Value
n	116108	4646	550	2455	
BMI Missing = Y (%)	1378 (1.2)	73 (1.6)	17 (3.1)	38 (1.5)	<0.001
Blood Type (%)					<0.001
A	43299 (37.3)	1580 (34.0)	175 (31.8)	686 (27.9)	
B	14558 (12.5)	744 (16.0)	77 (14.0)	354 (14.4)	
Ab	6332 (5.5)	289 (6.2)	13 (2.4)	89 (3.6)	
O	51919 (44.7)	2033 (43.8)	285 (51.8)	1326 (54.0)	
Education Level (%)					<0.001
Grade School/None	7824 (6.7)	255 (5.5)	27 (4.9)	112 (4.6)	
High School	44906 (38.7)	1923 (41.4)	222 (40.4)	1195 (48.7)	
Technical	22531 (19.4)	931 (20.0)	86 (15.6)	450 (18.3)	
Post High School Degree	18972 (16.3)	494 (10.6)	59 (10.7)	254 (10.3)	
Unknown	21875 (18.8)	1043 (22.4)	156 (28.4)	444 (18.1)	
DIAL_DAY Missing = Y (%)	13290 (11.4)	369 (7.9)	51 (9.3)	220 (9.0)	<0.001
CPRA Missing = Y (%)	3702 (3.2)	144 (3.1)	33 (6.0)	117 (4.8)	<0.001
PVD(%)					<0.001
No	100105 (86.2)	3900 (83.9)	455 (82.7)	2153 (87.7)	
Yes	5374 (4.6)	210 (4.5)	26 (4.7)	111 (4.5)	
Unknown	10629 (9.2)	536 (11.5)	69 (12.5)	191 (7.8)	
Diabetes (%)					<0.001
No	71807 (61.8)	2818 (60.7)	291 (52.9)	1356 (55.2)	
Yes	38827 (33.4)	1491 (32.1)	225 (40.9)	1014 (41.3)	
Unknown	5474 (4.7)	337 (7.3)	34 (6.2)	85 (3.5)	
Malignancy (%)					<0.001

No	82232 (70.8)	3143 (67.6)	307 (55.8)	1853 (75.5)
Yes	4623 (4.0)	166 (3.6)	25 (4.5)	100 (4.1)
Unknown	29253 (25.2)	1337 (28.8)	218 (39.6)	502 (20.4)

BMI, body mass index; DIAL_DAY, dialysis days; CPRA, calculated panel reaction antibody; PVD, peripheral vascular disease.

Supp.Table 2c Characteristics of Transplantation in the pre DAA era

	D-R-	D-R+	D+R-	D+R+	*P* Value
n	116108	4646	550	2455	
CIT Missing = Y (%)	6191 (5.3)	324 (7.0)	36 (6.5)	129 (5.3)	<0.001
HLA-A Mismatch (%)					<0.001
0	20936 (18.0)	740 (15.9)	50 (9.1)	152 (6.2)	
1	42224 (36.4)	1665 (35.8)	212 (38.5)	911 (37.1)	
2	52948 (45.6)	2241 (48.2)	288 (52.4)	1392 (56.7)	
HLA_DR Mismatch (%)					<0.001
0	25225 (21.7)	888 (19.1)	46 (8.4)	136 (5.5)	
1	51434 (44.3)	2010 (43.3)	198 (36.0)	978 (39.8)	
2	39449 (34.0)	1748 (37.6)	306 (55.6)	1341 (54.6)	

CIT, cold ischemia time; HLA, human leucocyte antigen.

Supp.Table 3a Characteristics of Donors and Donation Procedure in the post DAA era

	D-R-	D-R+	D+R-	D+R+	*P* Value
n	46099	1443	1082	1303	
Blood Type (%)					<0.001
A	16891 (36.6)	520 (36.0)	420 (38.8)	408 (31.3)	
B	5617 (12.2)	187 (13.0)	98 (9.1)	167 (12.8)	
AB	1705 (3.7)	45 (3.1)	18 (1.7)	11 (0.8)	
O	21886 (47.5)	691 (47.9)	546 (50.5)	717 (55.0)	
BUN (median [IQR])	17.0 [12.0, 26.0]	17.0 [12.0, 25.0]	18.0 [13.0, 27.0]	16.0 [11.0, 22.0]	<0.001
HBV = Y (%)	1616 (3.5)	42 (2.9)	169 (15.6)	105 (8.1)	<0.001
Prerecovery Diuretics = Y (%)	26511 (57.5)	809 (56.1)	616 (56.9)	773 (59.3)	0.371
Prerecovery Medications: T4 = Y (%)	24839 (53.9)	763 (52.9)	647 (59.8)	808 (62.0)	<0.001
Received Vasodilators = Y (%)	5494 (11.9)	173 (12.0)	135 (12.5)	167 (12.8)	0.738
Lung Infection (%)					<0.001
N	16658 (36.1)	543 (37.6)	358 (33.1)	478 (36.7)	
Reported but not confirmed	23530 (51.0)	751 (52.0)	705 (65.2)	704 (54.0)	
Confirmed	5911 (12.8)	149 (10.3)	19 (1.8)	121 (9.3)	
History of Smoking (%)					<0.001
No Smoking History	36564 (79.3)	1154 (80.0)	723 (66.8)	953 (73.1)	
Smoking but Not Continued	1306 (2.8)	39 (2.7)	30 (2.8)	15 (1.2)	
Continued Smoking	7706 (16.7)	237 (16.4)	300 (27.7)	307 (23.6)	
Unknown	523 (1.1)	13 (0.9)	29 (2.7)	28 (2.1)	

BUN, blood urea nitrogen; HBV, hepatitis b virus; T4, tetraiodothyronine.

Supp.Table 3b Characteristics of Recipients in the post DAA era

	D-R-	D-R+	D+R-	D+R+	*P* Value
n	46099	1443	1082	1303	
Blood Type (%)					<0.001
A	16567 (35.9)	509 (35.3)	398 (36.8)	375 (28.8)	
B	5866 (12.7)	195 (13.5)	103 (9.5)	184 (14.1)	
AB	2547 (5.5)	67 (4.6)	44 (4.1)	49 (3.8)	
O	21119 (45.8)	672 (46.6)	537 (49.6)	695 (53.3)	
Education Level (%)					<0.001
Grade School/None	3871 (8.4)	90 (6.2)	47 (4.3)	69 (5.3)	
High School	19085 (41.4)	741 (51.4)	403 (37.2)	680 (52.2)	
Technical	11577 (25.1)	369 (25.6)	280 (25.9)	318 (24.4)	
Post High School Degree	10687 (23.2)	230 (15.9)	331 (30.6)	214 (16.4)	
Unknown	879 (1.9)	13 (0.9)	21 (1.9)	22 (1.7)	
DIAL_DAY Missing = Yes (%)	4227 (9.2)	79 (5.5)	125 (11.6)	112 (8.6)	<0.001
Malignancy = Yes (%)	3740 (8.1)	138 (9.6)	139 (12.8)	109 (8.4)	<0.001
HIV (%)					<0.001
No	11770 (25.5)	368 (25.5)	753 (69.6)	252 (19.3)	
Positive	662 (1.4)	73 (5.1)	11 (1.0)	70 (5.4)	
Unknown	33667 (73.0)	1002 (69.4)	318 (29.4)	981 (75.3)	

DIAL_DAY, dialysis days; HIV, human immunodeficiency virus.

Supp.Table 3c Characteristics of Transplantation in the post DAA era

	D-R-	D-R+	D+R-	D+R+	*P* Value
n	46099	1443	1082	1303	
HLA-A Mismatch (%)					<0.001
0	5236 (11.4)	124 (8.6)	77 (7.1)	57 (4.4)	
1	17710 (38.4)	533 (36.9)	416 (38.4)	497 (38.1)	
2	23153 (50.2)	786 (54.5)	589 (54.4)	749 (57.5)	
HLA-DR Mismatch (%)					<0.001
0	7493 (16.3)	180 (12.5)	103 (9.5)	66 (5.1)	
1	22331 (48.4)	689 (47.7)	535 (49.4)	534 (41.0)	
2	16275 (35.3)	574 (39.8)	444 (41.0)	703 (54.0)	

HLA, human leucocyte antigen.

Figures

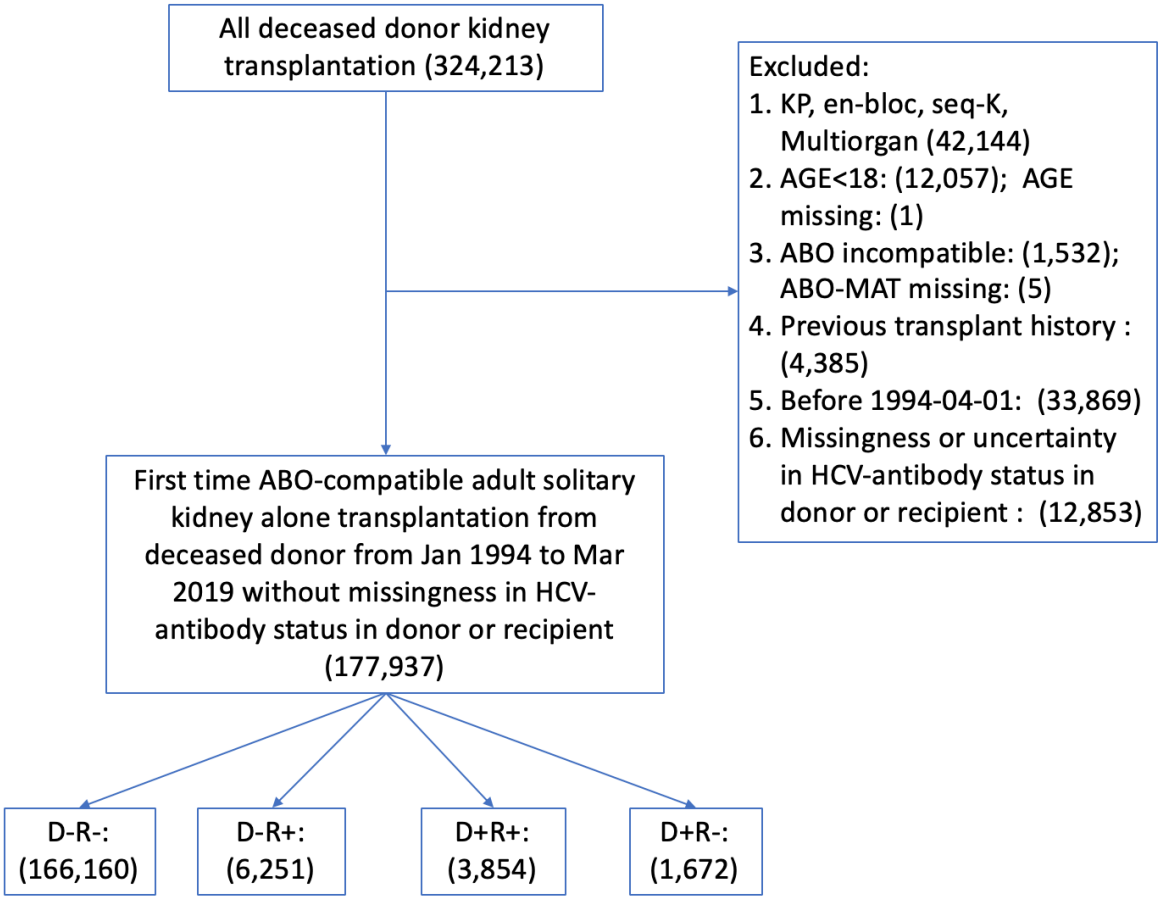


Figure 1. The Flowchart of Study Cohorts Identification

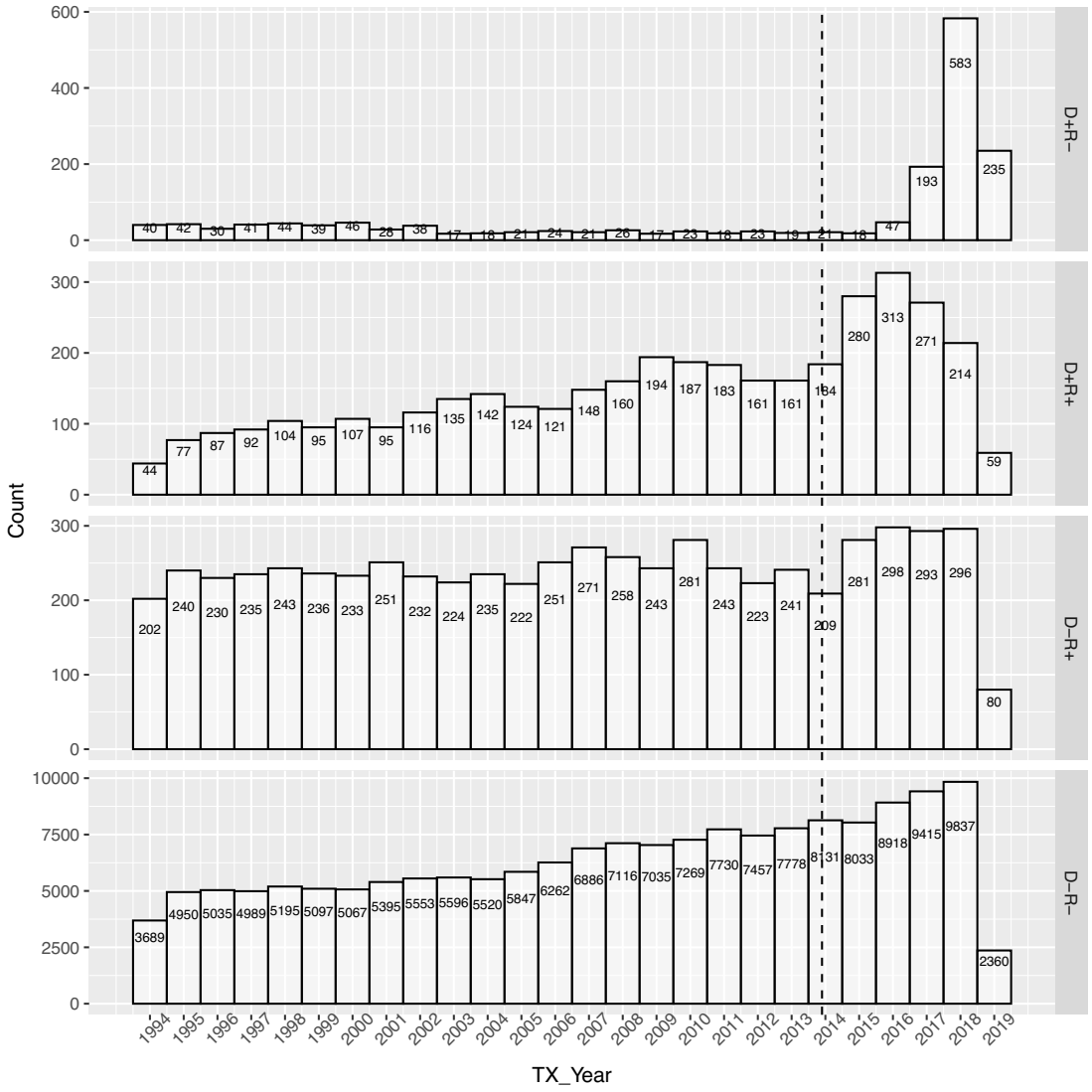


Figure 2 Yearly Distribution of the Kidney Transplantation Stratified by HCV Status in Donor and/or Recipient

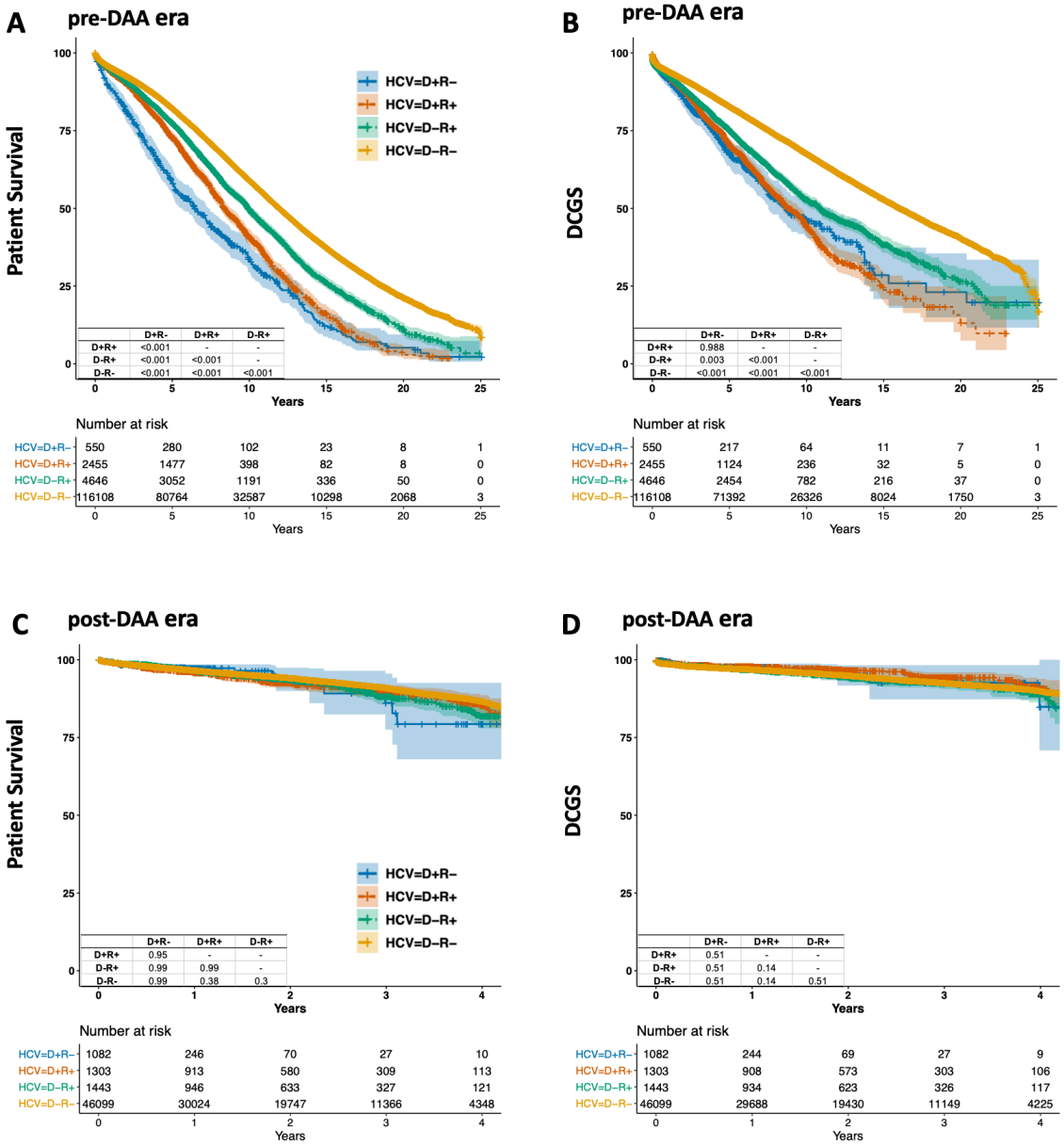


Figure 3 Crude Survival

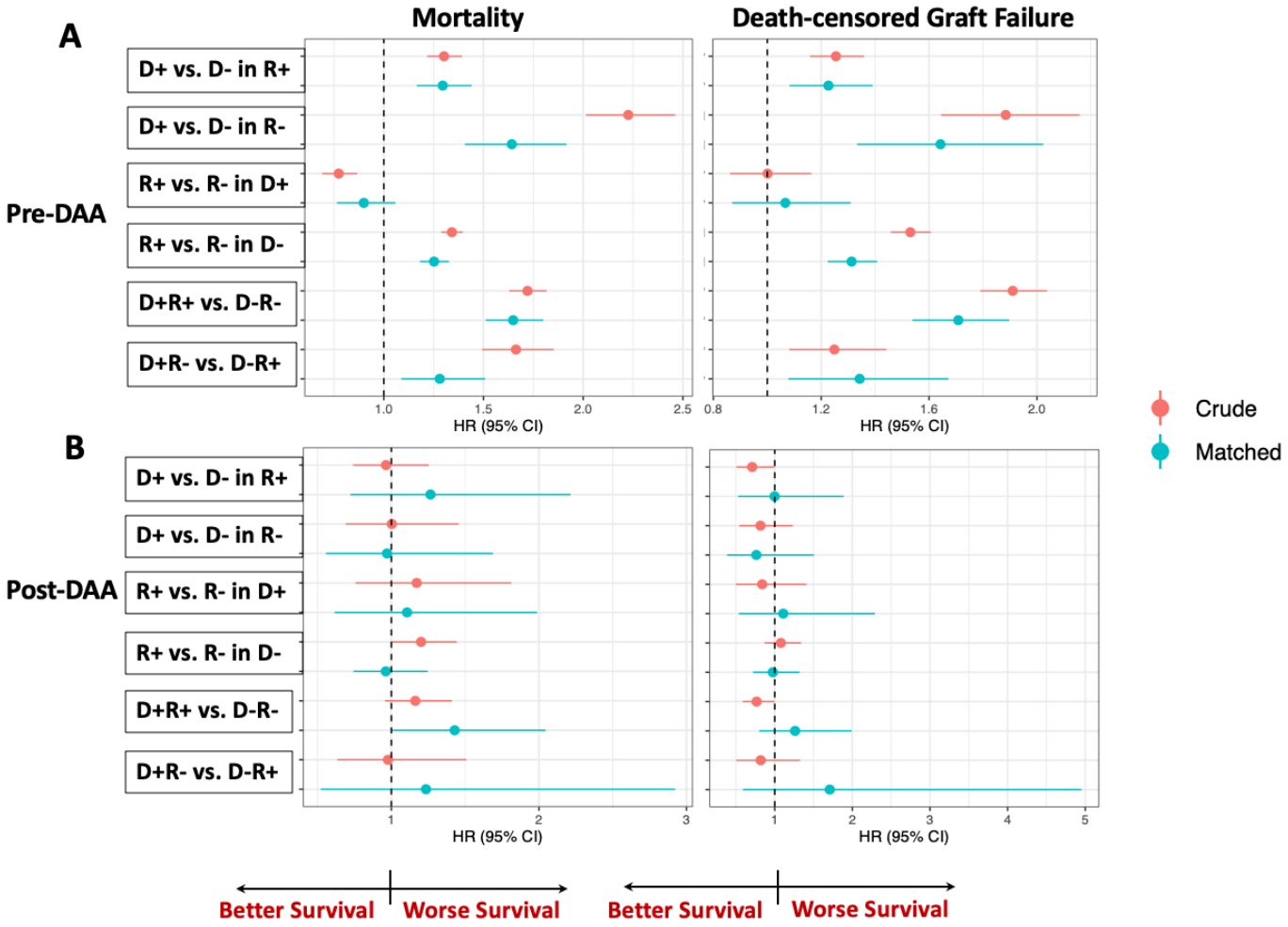
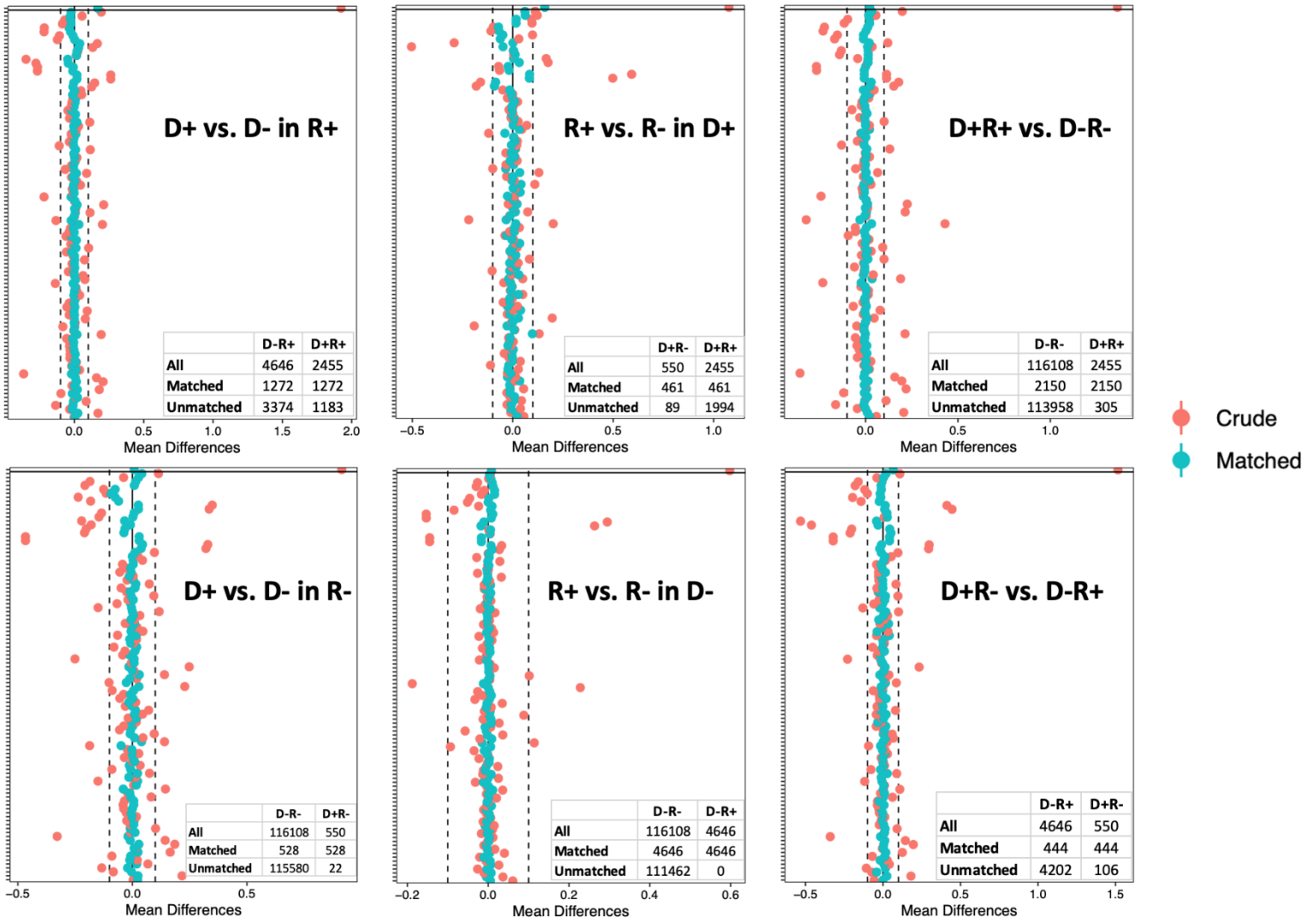
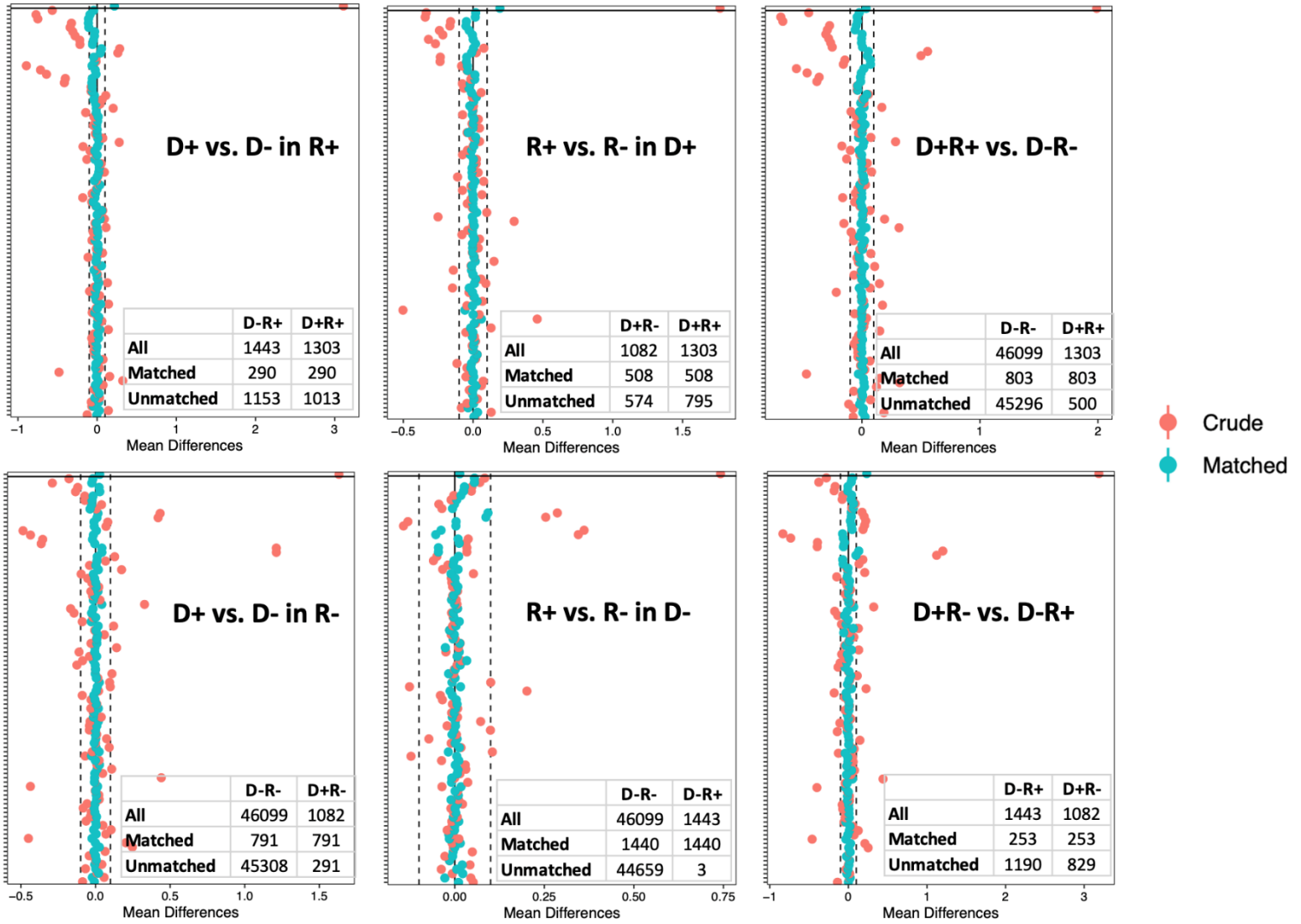


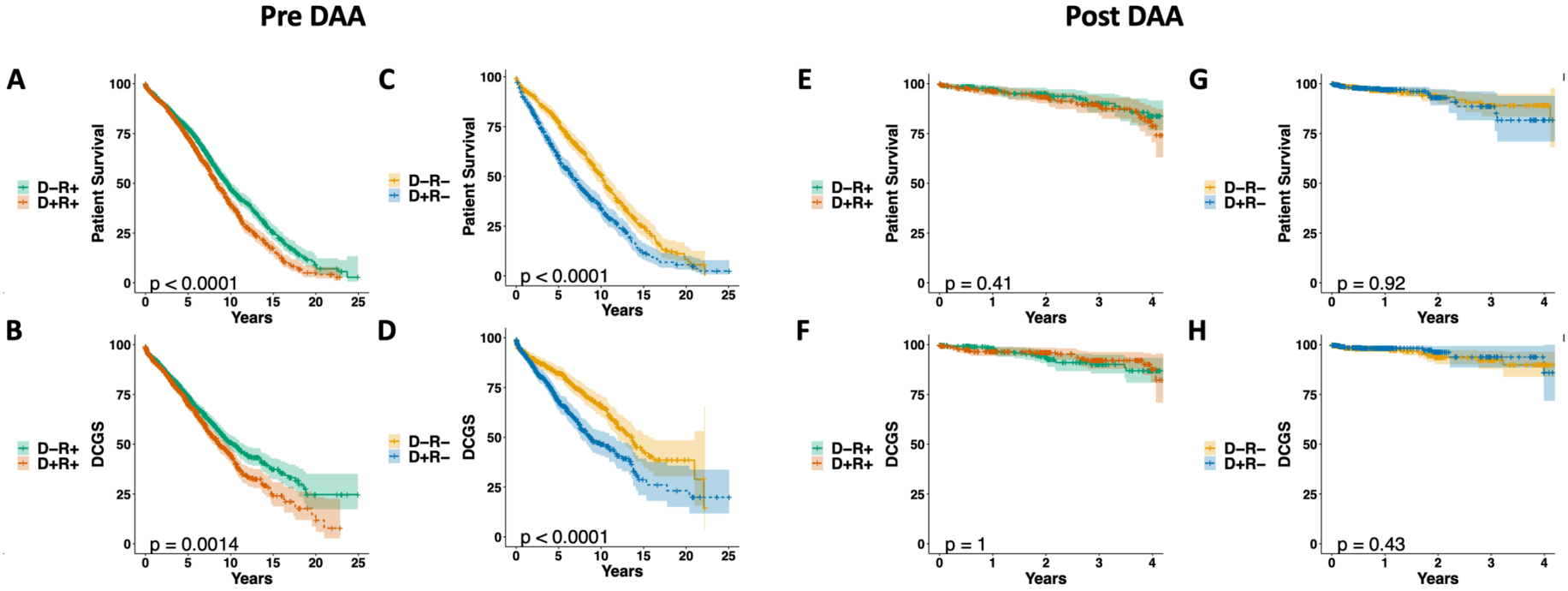
Figure 4 Relative Risk of Mortality and Graft Failure



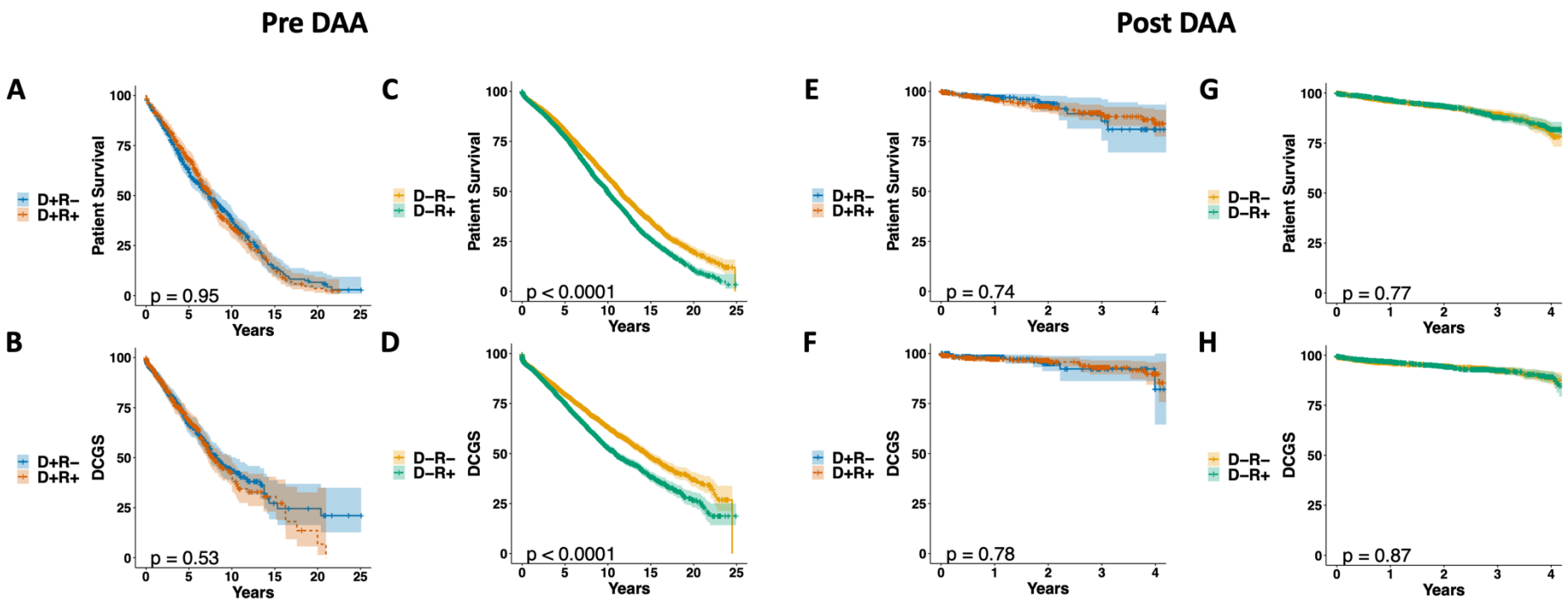
Supp.Figure 1 Balance diagnosis in the pre-DAA era



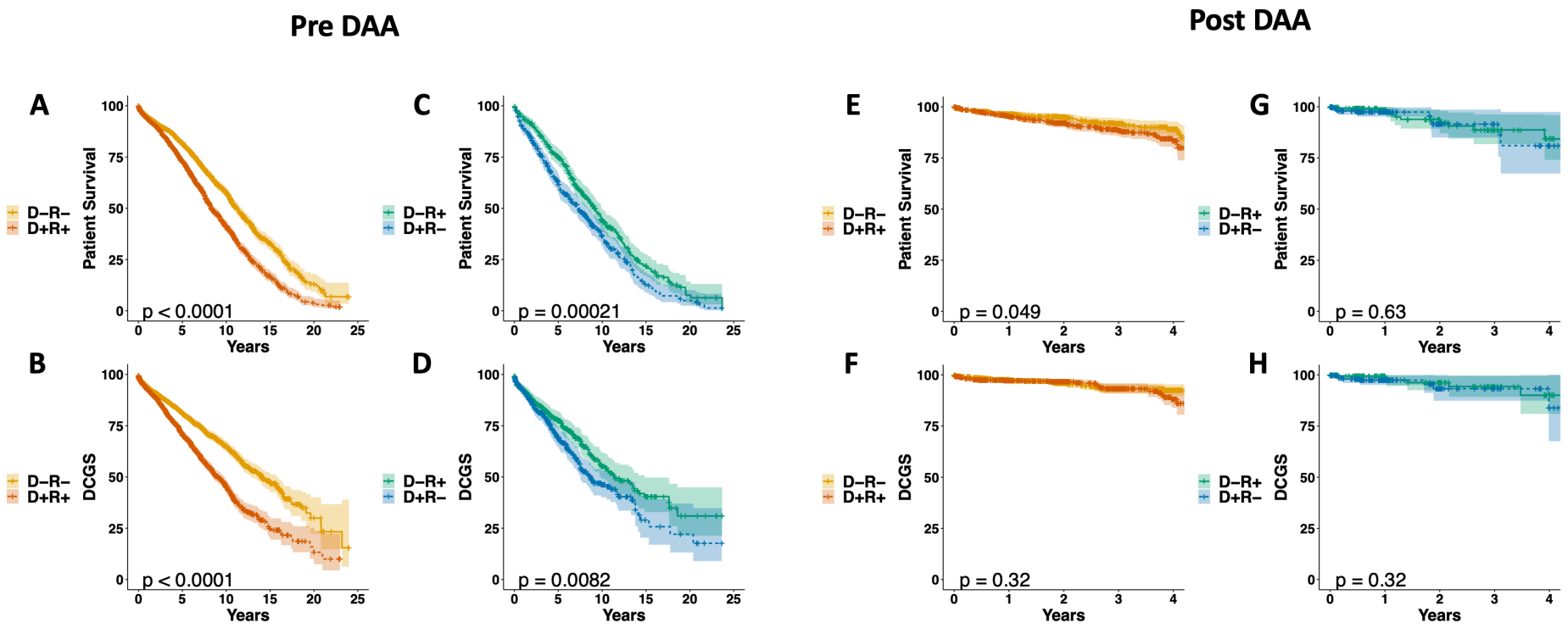
Supp.Figure 2 Balance diagnosis in the post-DAA era



Supp.Figure 3 Effect of HCV infection in Donor



Supp.Figure 4 Effect of HCV infection in Recipient



Supp.Figure 5 Effect of HCV infection in Donor and/or Recipient

Summary of Paper 1 and Paper 2 Conclusions

In the first paper, we found that HCV infection in deceased donor KT recipients was a prognostic indicator for poorer DCGS (aHR 1.24), patient and graft survival (aHR 1.28, 1.26, respectively). Notably, this detrimental effect was only observed when receiving kidneys from HCV- donor. We found different trends of the HCV effect between HCV- and HCV+ donors, as well as between pre-DAA and post-DAA eras. When receiving HCV+ donor kidneys in the pre-DAA era, comparable graft survival and DCGS were observed between HCV+ and HCV- recipients, with even better unadjusted patient survival in HCV+ recipients (3-year risk difference 7.5%, overall p=0.028). During the post-DAA era, no significant difference in post-transplant outcomes was detected between HCV+ and HCV- recipients, regardless of the donor HCV status.

In the second paper, we found HCV+ infection was always associated with poorer PS and DCGS, when it was in the donor, or in the recipients who received HCV- kidney. Donor HCV infection impacted PS and DCGS to a greater extent than did recipient HCV infection. We also found that donor plus recipient HCV infection(D+R+ vs. D-R-) and donor infection in HCV- recipient(D+R- vs. D-R-) displayed the largest absolute risk difference of mortality and DCGF. Importantly, the risk associated with HCV infection in donors and/or recipients was no longer statistically significant in the post-DAA era, except for impaired PS in dual-infected versus dual-uninfected.

Together, these results suggest that although HCV infection in either donors or recipients of kidney transplants had negative impacts on PS and DCGS in the pre-DAA era, in the

post-DAA era neither HCV infection in the donor nor recipient appears to portend worse outcomes. Thus, HCV+ kidneys should be used more frequently to increase the opportunities for waitlisted kidney recipient candidates to first, receive a kidney transplant and second, a kidney transplant with superior outcome potential. Given the comparable outcomes between D+R- and D+R+ patients, a new allocation algorithm incorporating HCV+ kidneys is urgently needed to improve the utilization and allocation of this under-utilized resource.

Discussion and Perspectives

The strength of the whole study includes: 1) both mate kidney analysis and propensity score matching strategy were applied, and a robust finding in the effect of recipient's HCV infection was detected in both approaches; 2) the effect modification by donor's HCV status when addressing the effect of recipient's HCV infection was first demonstrated; 3) with propensity score matching strategy, we systemically evaluated the effect of HCV infection in the donor, in the recipient, in donor plus recipient, and in donor vs. recipient; 4) we also specifically addressed the effect of HCV in the post-DAA era to provide timely support for clinical transplantation decision making in regard to HCV infected organs and/or recipients. According to a recent cost-effectiveness analysis, transplanting an HCV+ kidney to an HCV- candidate with concomitant DAA therapy was slightly more effective and substantially less expensive than continuing dialysis and waiting for an HCV-negative kidney(13). Therefore, our findings in this study provide a supportive tool towards future utilization of HCV+ kidneys as standard of care.

Major limitations in this study include: 1) the majority of D+R- patients were transplanted in the post-DAA era with relatively short follow up; 2) unmeasured potential confounders, which are not recorded in the registry data, including whether HCV+ recipients subsequently received DAA treatment; also, HCV status was defined by antibody test but not NAT test until 2015. 3) The mate kidney design in the first study excluded those donors with only one kidney transplanted, as well as those with two kidneys transplanted into recipients of same HCV status. The propensity score matching used in the second study also excluded those unmatched transplants in either group during pair matching procedure because of no available unexposed subjects within the specified caliper

distance of the exposed subjects. These excluded subjects may differ systematically from the matched subjects, which may bias our estimation and restrict the generalizability of the findings(14).

Future studies may focus on several directions: 1) evaluating the HCV effect in the post-DAA era with longer follow-up; 2) using virus nucleic acid result to include the viremic donor and recipient ; 3) fitting a model with transplant data in the post-DAA era to predict the quality of deceased donor kidney and guide the allocation of HCV+ kidney from a deceased donor.

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