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ORIGINAL ARTICLE

Donation after circulatory death is associated with increased fibrosis on 1-year post-transplant kidney allograft surveillance biopsy

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Abstract

Aim: The use of kidneys donated after circulatory death (DCD) provides an invaluable expansion of the organ supply for transplantation. Here, we investigated the effect of DCD on fibrotic changes on 1 1-year post 1-transplant surveillance kidney allograft biopsy.

Methods: Recipients of a deceased donor kidney transplant between 2013 and 2017 at a single institution, who survived 1 year and underwent surveillance biopsy, were included in the analysis (n = 333: 87 DCD kidneys, 246 kidneys donated after brain death [DBD]). Banff scores for interstitial fibrosis and tubular atrophy were summed as IFTA and compared between the groups.

Results: DCD and DBD groups were comparable for baseline characteristics. Delayed graft function was 39% in DCD versus 19% in DBD, P = .0002. Patient and graft survival were comparable for DCD and DBD cohorts. IFTA scores were higher in DCD compared to DBD (2.43±..13 vs. 2.01±..08, P = .0054). On multivariate analysis, the odds of IFTA > 2 in the DCD group was 2.5× higher (95%CI: 1.354.63) than in the DBD group. Within the DCD group, kidneys with IFTA > 2 had inferior 5-year graft survival (P = .037).

Conclusion: Compared to DBD kidneys, DCD kidneys developed a greater degree of fibrotic changes on 1-year post-transplant surveillance biopsy, which affected graft longevity within the DCD cohort.

KEYWORDS
donation after circulatory death, fibrosis, kidney transplantation, surveillance biopsy

1 | INTRODUCTION

There is a growing discrepancy between the number of patients that can benefit from kidney transplantation to the number of available kidneys for transplantation. In the United States, 41 000 patients with end-stage renal disease (ESRD) were added to the existing waitlist of 95 000 patients in the year 2019. In the same year 16 500 deceased donor kidneys were transplanted.[1] Deceased donor kidney transplantation can, therefore, only relieve a small proportion of the disease burden from ESRD, leading to thousands of patients who will die while waiting for a kidney transplant. Attempts to increase the donor pool for organ transplantation have included the use of organs from older

donors with comorbidities,[2] donation after circulatory death (DCD),[3] and machine perfusion as a method to salvage marginal organs that would, otherwise, get discarded.[4] The transplantation of these kidneys, in recent years defined as donors with high kidney donor profile index (KDPI), can still offer a significant improvement in life expectancy and quality of life to the recipient, in comparison to the poor survival and quality of life on the transplant waiting list.[5]

Nevertheless, it is warranted to carefully monitor the outcomes of marginal kidneys. With the use of DCD kidneys, the unavoidable period of warm ischemia between cessation of circulation and kidney perfusion with cold preservation fluid may potentially have detrimental effects on transplant outcomes. Although results have been acceptable,[6,7] variation in the use of DCD kidneys across transplant programs suggests that increased knowledge of their expected performance will assist in donor and recipient matching, and can improve population-based outcomes in ESRD overall.[8] In addition, the effect of DCD on post-transplant graft histology has been incompletely studied. A histologic analysis may be insightful as fibrosis and inflammation seen on kidney biopsies taken 1 year after transplantation correlate with long-term outcomes.[9]

Therefore, the aim of this study was to investigate the effect of kidney transplantation from DCD donors on the presence of fibrotic changes on surveillance biopsies obtained 1-year post-transplantation. The correlation of biopsy findings with long-term clinical outcomes was also studied.

2 | PATIENTS AND METHODS

2.1 | Patient cohort

The Institutional Review Board of the University of Pittsburgh approved this study (IRB PRO13060220). Candidacy for kidney transplantation was according to our institution's programmatic guidelines. Patients with ESRD were matched to deceased donor organs according to the United Network for Organ Sharing (UNOS) organ allocation system. All consecutive adult patients who received a deceased donor kidney between January 2013 and April 2017 were considered. Recipients who survived 1 year post-transplant and underwent surveillance biopsy were included in the analysis. Clinical and pathological data were reviewed.

2.2 | Protocol and acceptance criteria for organs donated after circulatory death

10 000–30 000 IU of heparin were administered while the donor patient was still fully supported. Withdrawal of mechanical, ventilated, or organ-perfusion support occurred in the operating room in nearly all cases. Circulatory death was determined by the local treating physician. A 5-min no touch period after the onset of cardiac arrest was observed. Donor warm ischemia was defined according to the revised Maastricht criteria for DCD.[10] For the analyses, we used functional warm ischemia time (fWIT), defined as the time between onset of hypoperfusion (systolic blood pressure < 60 mm Hg) and in situ perfusion of the kidneys with cold flush. Acceptance criteria of fWIT for DCD kidney retrieval was up to 60 min . Additional clinical data from organ donors included demographics, comorbidities, vasopressor needs, cause of death, KDPI at the time of organ allocation, and pump parameters with systolic pressure set at 30 mm Hg in case machine perfusion was used. These data were obtained using UNet (UNOS).

2.3 | Immunosuppression

The immunosuppression protocol for all kidney transplant recipients con of induction therapy with anti-thymocyte globulin (Thymoglobulin, 6 mg/kg IV divided over four daily doses) and a 5-day steroid taper, tacrolimus (aiming for trough levels 6–10 μg/ml), and mycophenolate mofetil (CellCept, 1000 mg twice a day). Standard prophylactic medication included valganciclovir (Valcyte) to prevent CMV infection, sulfamethoxazole-trimethoprim for PJP prophylaxis, and nystatin to prevent oral fungal overgrowth for a duration of 3 months.

2.4 | Clinical outcomes

Post-transplantation, recipient serum was collected to measure creatinine and estimate glomerular filtration rate (eGFR, calculated by CKD-EPI creatinine formula). Delayed graft function (DGF) was defined as the need for hemodialysis during the first week after kidney transplantation. Number of rejection episodes, and time until graft loss or patient death were recorded.

2.5 | Kidney graft pathology

Surveillance kidney allograft core needle biopsy was obtained 12 months post-transplant. The risks and benefits of biopsy were carefully weighed in each individual patient. Antiplatelet therapy was interrupted for 5 days prior to the biopsy. The cases in which a systemic anticoagulant was clinically indicated, surveillance biopsies were in general avoided. In those patients, indication biopsies were performed after temporarily withholding anticoagulation. An intraabdominal position of the kidney graft, or a very ill recipient per the discretion of the transplant team were other relative contraindications to performing a surveillance biopsy. All patients with 1-year post-transplant biopsy data were included in the analyses. All graft biopsies were scored according to the most recent Banff grading system by experienced transplant pathologists as part of our clinical protocol.[11] Scores for interstitial fibrosis and tubular atrophy (IFTA) ranged from 0 to 6. Interstitial fibrosis was graded as ci = 0, 1, 2, or 3, based on whether 0–5%, 6–25%, 26–50%, or > 50% of the cortical area was involved, respectively. Tubular atrophy was graded ct = 0, 1, 2, or 3 based on whether 0%, 0–25%, 26–50%, or > 50% of the cortical area had tubules with a thickened basement membrane, or tubules with a > 50% reduction in diameter.

TABLE 1 Baseline characteristics of recipients of DCD and DBD kidneys

	DCD ($n = 87$)	DBD ($n = 246$)	*P*-value
Recipient			
Age (years), mean ± std	53.9 ± 14	53.5 ± 14	.81
Male (*n* (%))	59 (67.8)	148 (60.2)	.25
Race (*n* (%))			.22
White	58 (66.7)	163 (66.3)	
African American	27 (31.0)	68 (27.6)	
Other	2 (2.3)	15 (6.1)	
BMI, mean ± std	30.4 ± 5.8	29.2 ± 6.2	.13
Diabetes (*n* (%))	17 (19.5)	66 (26.8)	.18
Days on wait list, median (IQR)	1427 (1022–1987)	1431 (741–1921)	.28
Pre-transplant dialysis (*n* (%))	79 (90.8)	223 (90.7)	.97
Days on dialysis, median (IQR)	1610 (1028–2251)	1603 (855–2245)	.56
Previous kidney transplant (*n* (%))	19 (21.8)	48 (19.5)	.64

Abbreviations: IQR, interquartile range; DCD, donated after circulatory death; DBD, donated after brain death.

2.6 | Statistical analysis

Continuous variables were reported by estimates of central tendency (mean or median) and spread (standard deviation or interquartile range). Categorical data were expressed as frequency and percentages. The outcomes of recipients of kidney grafts from DCD and DBD donors were compared using T-Tests, χ^2, and Kruskal-Wallis tests. Patient and graft survival were compared with Kaplan-Meier analysis and log-rank test. Multivariate logistic regression was used to compare the odds of an IFTA > 2, while adjusting for possible confounding variables that were derived from Tables 1 and 2 or identified in the literature.[12] IFTA > 2 was chosen as cut off so that high IFTA biopsies had at least a score of one (mild) for both IFTA, with a score of two (moderate) for at least one component. Backward stepwise selection was applied with elimination of covariates with *P*-value > .2 from the full model while retaining DCD in the model. Two-tailed *P*-values < .05 were considered statistically significant. All statistical analyses were performed using SAS, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

Between January 2013 and April 2017, 531 patients were the recipient of a deceased donor renal transplant. One-hundred thirty-six kidneys (26% of the cohort) were recovered after circulatory death (DCD group), and 395 (74%) after brain death (DBD group) (**Figure 1**). One-year graft survival was comparable between the DCD and DBD groups (94.1% in DCD vs. 94.4% in DBD, $P = .45$). There was also no difference in 1-year patient survival (97.1 vs. 96.7% respectively, $P = .96$). Rates of one-year post-transplant kidney allograft biopsy were 87/128 (68%) for DCD and 246/373 (66%) for DBD ($P = .85$).

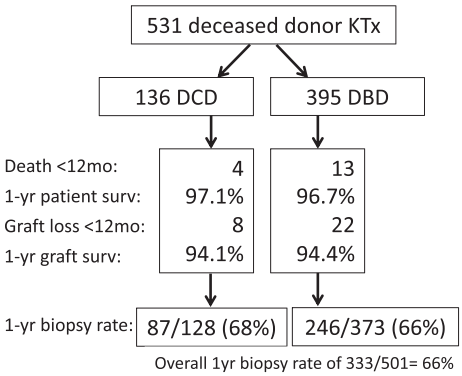

FIGURE 1 Cohort of 531 patients undergoing deceased donor kidney transplantation, stratified by circulatory versus brain death, with 1-year graft and patient survival, and 1-year biopsy rates. KTx – kidney transplantation

Among all patients with available 1-year biopsy data, we compared recipients of DCD kidneys with recipients of DBD kidneys. DCD and DBD groups were comparable for recipient baseline characteristics including age, gender, race, BMI, and diagnosis of diabetes (Table 1). DCD and DBD donors were comparable for demographics including age, gender, race, BMI, and comorbidities including diabetes and hypertension (Table 2). More donors in the DCD group died from anoxia. Vasopressor use was nearly absent in the DCD group and was significantly lower than in the DBD group. On average, DCD kidneys had a higher KDPI than DBD kidneys (51±18 in DCD vs. 44±27 in DBD, $P = .01$). However, a lower proportion of kidneys with KDPI > 85% was present in the DCD group (KDPI > 85% in 4% of DCD vs. 19% of DBD group, $P = .0003$). There were no differences in transplant-related variables such as time of cold ischemia, warm ischemia time at kidney implantation, panel reactive antibody levels, and number

TABLE 2 Donor and transplant characteristics

	DCD ($n = 87$)	DBD ($n = 246$)	*P*-value
Donor			
Age (years), mean ± std	41.5 ± 12	41.3 ± 14	.91
Male (*n* (%))	56 (64.4)	152 (61.8)	.67
Race (*n* (%))			.12
White	85 (97.7)	220 (89.4)	
African American	2 (2.3)	17 (6.9)	
Other	0	9 (3.7)	
BMI, mean ± std	29.5 ± 7.7	28.5 ± 7.0	.29
Vasopressor (*n* (%))	1 (1.2)	95 (38.6)	<.0001
History of Hypertension (*n* (%))	29 (33.3)	69 (28.1)	.35
History of Diabetes (*n* (%))	7 (8.1)	18 (7.3)	.82
Acute kidney injury – AKIN grade (*n* (%))			.23
0	78 (89.7)	202 (82.1)	
1	9 (10.3)	33 (13.4)	
2	0	8 (3.3)	
3	0	3 (1.2)	
Cause of death (*n* (%))			<.0001
Anoxia	51 (58.6)	82 (33.3)	
Cerebrovascular accident	12 (13.8)	82 (33.3)	
Head trauma	23 (26.4)	81 (32.93)	
Other	1 (1.2)	1 (.4)	
KDPI, mean ± std	50.7 ± 18.3	44.0 ± 26.5	.01
KDPI > 85 (*n* (%))	3 (3.5)	46 (18.7)	.0003
Transplant			
fWIT (min), mean ± std	17 ± 8	N/A	
CIT (min), median (IQR)	639 (413–885)	644 (451–928)	.74
PRA1≥20% (*n* (%))	13 (14.9)	50 (20.3)	.27
median # of HLA mismatches, median (IQR)	4 (4–5)	5 (3–5)	.67
Pump use (*n* (%))	33 (37.9)	21 (8.5)	<.0001

Abbreviations: AKIN, Acute Kidney Injury Network; fWIT, functional warm ischemia time; CIT, cold ischemia time; PRA1, panel reactive; IQR, interquartile range; DCD, donated after circulatory death; DBD, donated after brain death.

of HLA mismatches. In the DCD group, significantly more kidneys were preserved using machine perfusion (38% in DCD vs. 9% in DBD, $P < .0001$).

In the immediate post-transplantation phase, the rate of DGF was significantly higher in recipients of DCD kidneys compared to recipients of DBD grafts (39% vs. 19%, $P = .0001$) (**Table 3**). Serum creatinine levels at 1 year follow up were higher in DCD than in DBD kidney recipients (Creatinine: 1.95±.97 mg/dl in DCD vs. 1.57±.63 mg/dl in DBD, $P = .0008$). Estimated GFR was lower in DCD than in DBD recipients (eGFR: 40.4±16 mg/dl in DCD vs. 48.3±19 mg/dl in DBD, $P = .0005$). On comparison of the degree of allograft fibrosis on 1-year kidney graft surveillance biopsy, on average performed 378±56 days after transplant, we found significantly higher IFTA scores in the DCD compared to the DBD group (2.42±1.26 vs. 1.98±1.19, $P = .004$) (**Table 3**, **Figure 2A**). In the DCD group, there was also a significantly higher proportion of patients with IFTA scores greater than 2 (IFTA > 2) (**Figure 2B**). On multivariate analysis, DCD was found to be an independent variable determining the odds of having increased IFTA scores on graft biopsy performed 1-year post-transplant (**Table 4**). As the recipients of DCD kidneys had a significantly higher chance of DGF, and our group as well as others have previously associated DGF with IFTA,[13,14] we explored whether increased IFTA in DCD is mediated by DGF. Adjusting the relation between DCD and IFTA for DGF did not affect the odds ratio (which remained highly significant at 2.5), suggesting increased IFTA in DCD kidney grafts develops independently of DGF (**Table 4**). Hypothermic machine perfusion was more often used in DCD kidneys

TABLE 3 Clinical outcomes after deceased donor kidney transplantation

	DCD ($n = 87$)	DBD ($n = 246$)	*P*-value
Delayed graft function (*n* (%))	34 (39.1)	46 (18.7)	.0001
Creatinine at 12 months (mg/dl), mean ± std	1.95 ± .97	1.57 ± .63	.0008
eGFR at 12 months (ml/min/1.73 m^2), mean ± std	40.4 ± 16	48.3 ± 19	.0005
Rejection in the first 12 months (*n* (%))	35 (40.2)	88 (35.8)	.52
T cell-mediated rejection, by Banff criteria 1A 1B 2A 2B 3Antibody-mediated rejection	22 (25.3) 6 (6.9) 0 1 (1.1) 1 (1.1)5 (5.7)	48 (19.5) 31 (12.6) 3 (1.2) 0 06 (2.4)	
BK polyomaviremia > 1,000 copies/ml (*n* (%))	22 (25.3)	61 (24.8)	.99
IFTA, mean ± std	2.42 ± 1.26	1.98 ± 1.19	.004
IFTA > 2 (*n* (%))	33 (37.9)	49 (19.9)	.0008

Abbreviations: DCD, donated after circulatory death; DBD, donated after brain death.

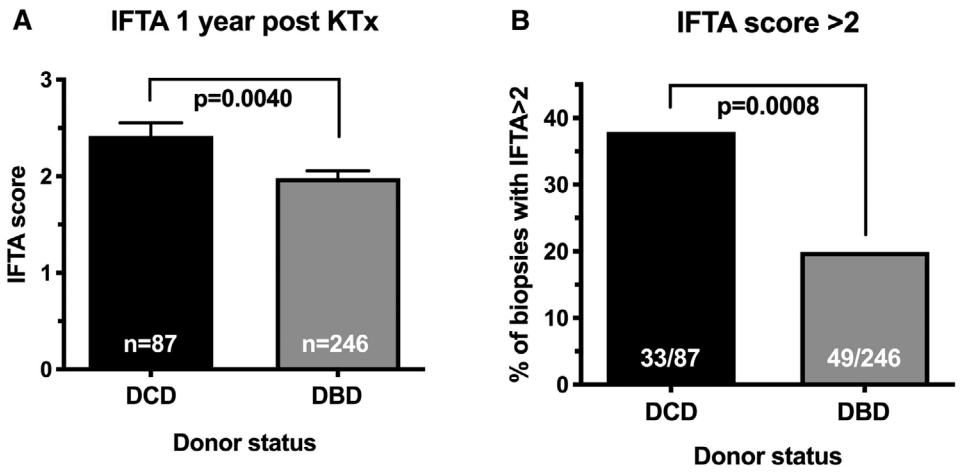

FIGURE 2 Comparison of (A) mean histological scores for interstitial fibrosis and tubular atrophy (IFTA) on surveillance biopsy, and (B) proportion of patients with IFTA > 2, between kidneys obtained after circulatory versus brain death. KTx – kidney transplantation

TABLE 4 Multivariate analysis of the effect of DCD versus DBD on IFTA score > 2

Effect of DCD compared to DBD, with DBD set as reference of 1.0	Odds ratio for IFTA > 2		
	OR	95% CI	*P*-value
DCD, unadjusted	2.5	1.4–4.2	.001
DCD, adjusted for donor variables[a]	2.476	1.29–4.76	.0065
DCD, adjusted for donor variables[a], CIT, rejection, and DGF	2.055	1.021–4.136	.0437
DCD, adjusted for donor variables[a], CIT, rejection, DGF, and recipient variables[b]	2.346	1.096–5.02	.028
Backward adjusted model[c]	2.496	1.345–4.634	.0324

[a]Donor variables included age, gender, race, BMI, hypertension, diabetes, vasopressor use, cause of death, and hypothermic perfusion pump use.
[b]Recipient variables included age, gender, race, BMI, and diabetes.
[c]In the backward adjusted model, covariates with $P > .2$ were eliminated from the full model.
Abbreviations: CIT, cold ischemia time; DGF, delayed graft function; DCD, donated after circulatory death; DBD, donated after brain death.

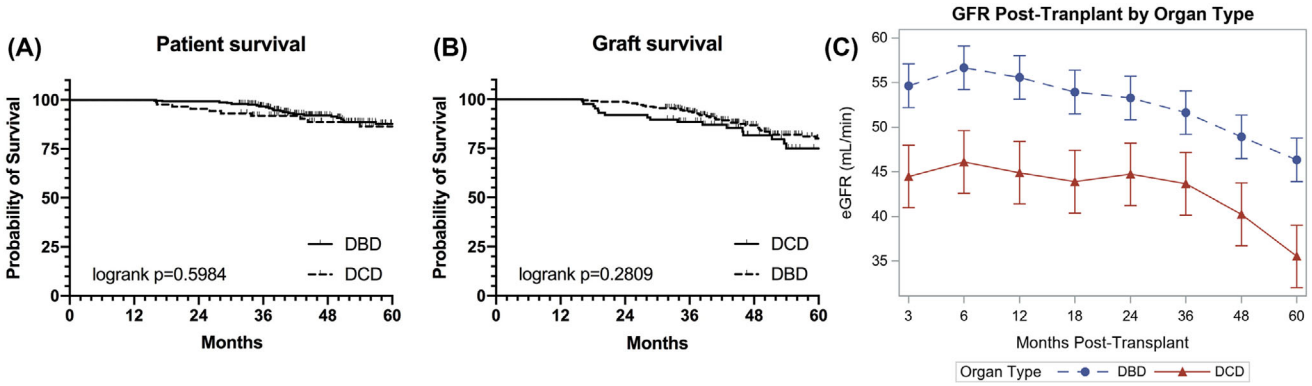

FIGURE 3 Five-year Kaplan Meier curves of patient (A) and graft survival (B) of kidneys donated after circulatory versus brain death. C) Kidney allograft function by estimated glomerular filtration rate (eGFR), comparing kidneys donated after circulatory versus brain death

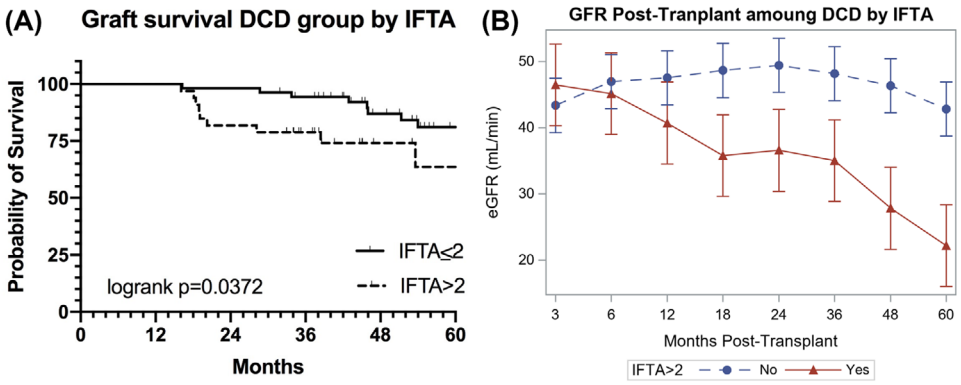

FIGURE 4 (A) Five-year Kaplan Meier curves showing inferior graft survival of DCD kidneys with IFTA > 2, compared to DCD kidneys with IFTA ≤ 2 on 1-year biopsy. (B) Kidney allograft function by estimated glomerular filtration rate (eGFR), showing a 5-year progressive decline in graft function of DCD kidneys with 1-year post-transplant IFTA > 2, compared to DCD kidneys with IFTA ≤ 2. *Note*: DCD, donated after circulatory death; DBD, donated after brain death

(**Table 2**), but pump use itself was not associated with increased fibrosis (IFTA > 2 in 31% of pumped DCD kidneys vs. 42% of non-pumped DCD kidneys, $P = .33$). Likewise, in the multivariate analysis pump use was not independently associated with increased IFTA. In contrast, the occurrence of any rejection episodes during the first year was associated with an increased odds of IFTA > 2 ($P < .0001$). After correction for rejection, the association between DCD and increased IFTA remained significant, indicating that DCD is associated with increased IFTA in an independent manner (**Table 4**).

Next, we aimed to examine the effect of DCD and IFTA on graft function and survival beyond 1 year (**Figure 3**). Although graft survival was lower for DCD kidneys compared to DBD kidneys at all time points, in the time-to-event analysis the differences were not statistically significant (log-rank $P = .28$, **Figure 3B**). Using a mixed model, we assessed long-term graft function by analysing post-transplant eGFR among the DCD and DBD groups. On average, those who received a DCD organ had a significantly lower GFR over the post-transplant time period (difference from unadjusted model: -9.6 ml/min, $P = .0001$) (**Figure 3C**). This difference persisted after adjustment for DGF (estimate for DCD: -8.2 ml/min, $P = .0011$). As there was a significantly greater proportion of DCD kidneys with IFTA > 2, we compared high IFTA to low IFTA kidneys in the DCD group. Indeed, IFTA > 2 was associated with inferior graft survival (5-year graft survival 63.6% for IFTA > 2 vs. 81.1% for IFTA ≤ 2, **Figure 4A**). We also found that the IFTA > 2 group had a significantly lower eGFR for all time points (all $P < .05$) (**Figure 4B**). In addition, there was a significant difference in the change in GFR overtime, where those with IFTA > 2 had a faster decline in kidney function compared to those with an IFTA score ≤2 ($P < .0001$).

To investigate whether recipients who underwent surveillance biopsy were representative of the total cohort of deceased donor kidney recipients, a sensitivity analysis was performed. Major recipient demographics were comparable between biopsied and non-biopsied groups (**Table S1**). Regarding donor characteristics, biopsied grafts were from slightly older, and more often obese and hypertensive donors. When graft and patient survival were compared, no significant differences were found (**Figure S1**). Therefore, we conclude that the

recipients who underwent 1-year surveillance biopsy were representative of the total cohort.

4 | DISCUSSION

The use of marginal kidneys for kidney transplantation can provide survival benefit when compared to remaining on the transplant waiting list.[5] Nevertheless, the outcomes of such kidneys should continue to be investigated in order to identify specific donor or transplant characteristics associated with inferior graft survival. This knowledge can inform transplant physicians and recipients about expected outcomes, and open new areas of research to improve transplant outcomes. We previously reported that mild donor acute kidney injury did not affect graft fibrosis (IFTA), but donation after circulatory death (DCD) seemed to be associated with increased IFTA in the multivariate analysis.[15] In this study, we investigated in detail the effect of DCD on IFTA on surveillance graft biopsy 1 year after kidney transplantation. We found that DCD kidneys had increased IFTA scores. Although the overall survival of DCD kidneys was comparable to kidneys donated after brain death, high IFTA scores were predictive of significantly inferior long-term graft survival within the DCD group.

When legislation around declaration of brain death was adopted in 1968, transplantation after DCD was abandoned by the majority of organ procurement organizations in the United States. However, as the demand for kidney transplantation continued to increase, new efforts to use DCD donors sparked in Europe in the 1990s. Currently, DCD is a well-accepted and indispensable source of kidneys for expansion of the donor pool. In the United States, in 2019 24% of deceased donor kidneys were retrieved after circulatory death[1]; in certain European countries this percentage is greater than 40%.[16,17] Nevertheless, the effect of DCD on kidney graft surveillance biopsies in relation to clinical outcomes has not been investigated before. According to the Banff criteria for kidney transplant pathology, IFTA is the histological evidence of chronic renal allograft injury. Although chronic renal allograft injury is a long-term process, histologic changes have been shown to occur as soon as 3 months after transplantation, and IFTA often progresses and eventually results in chronic renal dysfunction.[18–20] IFTA is an independent predictor of graft survival.[9] Indeed we found that high IFTA on 1 year biopsy was corresponding with decreased graft survival in DCD kidneys. We believe this analysis is an important evaluation of outcomes of DCD kidney transplantation as histological abnormalities such as IFTA occur before clinically apparent functional decline of the kidney.[21]

DCD kidneys can be expected to have a higher risk of delayed graft function (DGF), as we observed in our cohort. Our group and others previously reported increased IFTA in kidneys with DGF.[13,14,22] We therefore adjusted the relation between DCD and IFTA for DGF and found that this only minimally affected the estimate, which remained highly significant. We conclude that IFTA in DCD kidney grafts develops predominantly independently of DGF. Along these same lines, the occurrence of DGF itself has been repeatedly shown to be of no impact on long-term graft function of DCD kidneys.[23,24]

We do not routinely perform time of implantation biopsies to assess if IFTA is present at time of transplantation, but this question has been investigated by others. Truong et al. compared implantation with surveillance biopsies of kidneys from diabetic donors and found that, although diabetic nephropathy and IFTA were minimal at implantation, eight of 17 kidneys developed significant IFTA on follow up.[25] Development of IFTA, therefore, seems to occur predominantly post-transplant even in kidneys from diabetic donors. Warm ischemia time during organ retrieval should be kept as short as possible. A fWIT (time between onset of hypoperfusion and cold flush – fWIT) less than 20 min has been considered beneficial for optimum outcomes.[26] We did not find an association between fWIT and increased IFTA, likely because, fWIT was on average well below 20 min for our total DCD cohort. Other risk factors for inferior outcomes after transplantation of DCD kidneys are prolonged cold ischemia time, and donor hypertension.[3,27,28]

Our analyses demonstrate a significant difference in IFTA between DCD and DBD kidneys with a decreased graft survival in high IFTA DCD kidneys. We acknowledge that our retrospective study design of comparing DCD to DBD kidneys poses a limitation to an optimum comparison. Despite minimal differences in donor characteristics on average, our study does not analyze the clinical decision-making that accepting transplant surgeons and nephrologists perform on a case by case level. For example, kidneys in our DCD group had higher average KDPI (likely in part driven by DCD status), however, fewer DCD kidneys had a KDPI > 85% compared to kidneys from brain death donors. The latter likely reflects decision-making by transplant surgeons and nephrologists who are willing to accept a DCD kidney, but are less inclined to accept DCD kidneys with additional risk factors that drive a high KDPI. In order to accept a DCD (presumed higher risk) kidney for transplantation, other variables included in KDPI will have to be in the low or medium range. This decision-making is difficult to capture in research protocols and makes observational data more difficult to interpret.[29] Another limitation of our study is that 1-year biopsy rates were below 100% in both DCD and DBD cohorts. Several clinical circumstances can preclude a biopsy, and the benefits versus the risks of biopsy need to be weighed in each individual patient. The most common reason for exclusion was the need for uninterrupted anticoagulant therapy. Our sensitivity analyses indicate that there were no significant differences between biopsied and non-biopsied groups, suggesting evident bias was not introduced. We acknowledge that the observed difference in eGFR between DCD and DBD kidneys in our cohort was greater than reported in other, larger cohorts.[3,6] We cannot exclude that, this is indicative of an unmeasured difference in kidney graft quality that may account for the higher degree of fibrosis in DCD kidneys. Replication of the results in a larger, possibly multicenter cohort would be necessary to more definitively establish the association of DCD and kidney allograft fibrosis.

Although the relationship between DCD and IFTA has not been clearly established before, some insight in the pathogenesis by which a single ischemic insult during DCD leads to increased fibrogenesis and IFTA can be extrapolated from other investigations. IFTA is generally a prominent but non-specific manifestation of structural

allograft deterioration.[30] Any insult to the kidney graft resulting in injury and inflammation leads to dedifferentiation of epithelial cells, increased formation and activity of myofibroblasts with increased deposition of extracellular matrix as a common final pathway.[31] It is often hypothesized that an elevated level of inflammation can subsequently be a fruitful soil for further inflammatory and immunologic processes including subclinical rejection with more IFTA as final histologic endpoint.[31] Further discovery of molecular pathogenic pathways and associated therapeutic opportunities are the subject of current investigations.[32,33]

In conclusion, our analyses demonstrate that DCD is associated with increased fibrosis on kidney allograft surveillance biopsies and that increased IFTA is predictive of graft survival of DCD kidneys.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions.

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SUPPORTING INFORMATION

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

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