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Donor–Recipient BSA Matching Is Prognostically Significant in Solitary and En Bloc Kidney Transplantation From Pediatric Circulatory Death Donors

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Background. As the rate of early postoperative complications decline after transplant with pediatric donation after circulatory death (DCD) kidneys, attention has shifted to the long-term consequences of donor–recipient (D-R) size disparity given the pernicious systemic effects of inadequate functional nephron mass. **Methods.** We conducted a retrospective cohort study using Organ Procurement and Transplantation Network data for all adult (aged ≥ 18 y) recipients of pediatric (aged 0–17 y) DCD kidneys in the United States from January 1, 2004 to March 10, 2020. **Results.** DCD pediatric allografts transplanted between D-R pairs with a body surface area (BSA) ratio of 0.10–0.70 carried an increased risk of all-cause graft failure (relative risk [RR], 1.36; 95% confidence interval [CI], 1.10–1.69) and patient death (RR, 1.32; 95% CI, 1.01–1.73) when compared with pairings with a ratio of >0.91 . Conversely, similar graft and patient survivals were demonstrated among the >0.70 –0.91 and >0.91 cohorts. Furthermore, we found no difference in death-censored graft survival between all groups. Survival analysis revealed improved 10-y patient survival in recipients of en bloc allografts ($P=0.02$) compared with recipients of single kidneys with D-R BSA ratios of 0.10–0.70. A similar survival advantage was demonstrated in recipients of solitary allografts with D-R BSA ratios >0.70 compared with the 0.10–0.70 cohort ($P=0.02$). **Conclusions.** Inferior patient survival is likely associated with systemic sequelae of insufficient renal functional capacity in size-disparate DCD kidney recipients, which can be overcome by appropriate BSA matching or en bloc transplantation. We therefore suggest that in DCD kidney transplantation, D-R BSA ratios of 0.10–0.70 serve as criteria for en bloc allocation or alternative recipient selection to optimize the D-R BSA ratio to >0.70 .

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INTRODUCTION

Kidney transplantation is an important therapeutic intervention in the management of end-stage renal disease. Unfortunately, there remains a considerable and highly detrimental gap between the number of patients in need of renal transplant and current organ availability.^{1–4} In an effort to offset this deficit, several strategies have been used to broaden the donor pool. Here we sought to explore the utilization of pediatric allografts from donation after circulatory death (DCD) donors as one such strategy.

Although donation after brain death (DBD) organs have long been the dominant source of deceased donor allografts, the dramatic organ shortage has evoked a renewed interest in DCD kidneys over the last several decades.^{4–6} Despite higher rates of delayed graft function (DGF) after transplantation of kidneys from DCD donors, it has been shown that DGF does not correlate to worse long-term graft function in these recipients.^{7–9} Furthermore, long-term patient and graft survival following transplant of well-selected DCD kidneys are similar to that of DBD organs.^{10,11} In accordance with these findings, the utilization of DCD kidneys in the United States has increased over recent decades to account for approximately 24% of deceased donation in 2019.⁴

While transplantation from deceased pediatric donors is not a novel experience for most transplant centers, there remains a general reluctance toward their widespread use.¹² This sentiment is in part due to concern for early postoperative graft loss secondary to size-related complications, an apprehension that is likely compounded in the DCD subpopulation where there are higher rates of early allograft dysfunction at baseline.¹² Despite the historically high rates of early complications, pediatric kidneys demonstrate excellent long-term graft survival in both DBD and DCD populations, necessitating further investigation into the downstream functional consequence of donor–recipient size disparities.^{12–15}

Inadequate donor kidney size remains an important consideration when using pediatric allografts, primarily due to the potential impacts of insufficient nephron mass characterized by hyperfiltration-associated injury, graft dysfunction, and chronic functional decline.^{16–20} As a strategy to mitigate these pernicious outcomes, en bloc kidney transplantation has been established as a viable alternative to solitary transplant of small DBD and DCD allografts.^{12,14,21,22} Although superior outcomes have been demonstrated when using en bloc kidneys as opposed to solitary allografts in small pediatric donors, consensus selection criteria for this technique has not yet been established in DCD transplantation.^{23,24}

The purpose of this study was to examine long-term outcomes of pediatric-derived DCD kidneys transplanted into adult recipients with a particular focus on donor–recipient size disparity. Body surface area (BSA) was chosen as the marker for allograft size based on prior studies implicating BSA as an accurate surrogate for renal parenchymal volume (RPV) and functional nephron mass.^{25–27} We hypothesized that donor–recipient BSA matching provides useful prognostic information when applied to DCD kidneys from pediatric donors. Furthermore, we theorized that donor–recipient BSA ratios can serve as an effective guide to clinical decision making when considering solitary versus en bloc kidney transplantation from the pediatric DCD donor population.

METHODS

Study Population and Data Source

We conducted a retrospective analysis of all adult (aged ≥ 18 y) kidney transplant recipients in the United States who underwent primary solitary or en bloc DCD kidney transplantation from 0- to 17-y-old donors between January 1, 2004 and March 10, 2020. The U.S. organ allocation policy during the study period had no standard criteria for solitary versus en bloc kidney allocation practices and was instead left to the discretion of the individual transplant programs. Recipients were excluded if they were aged < 18 y, if they received simultaneous organ transplants, or if they received a repeat kidney transplant. Donors were excluded if they were aged > 17 y. The Organ Procurement and Transplantation Network database is de-identified and publicly available; therefore, this study was exempt from human subjects review as approved by the University of Washington Human Subjects Division.

Variables

Using data reported on United Network for Organ Sharing (UNOS) transplant recipient forms, we determined donor age, sex, race, height, weight, cause of death (anoxia, cerebral vascular accident, head trauma, other), serum creatinine, and

history of medical comorbidities (diabetes mellitus [DM], hypertension). We determined recipient age, height, weight, sex, race, diagnosis of renal disease, hepatitis C virus serostatus, history of peripheral vascular disease, years on dialysis, and end-calculated panel reactive antibodies. We also determined the graft cold ischemia time (CIT) in hours, whether the graft was preserved by machine perfusion before transplantation, and whether the graft was transplanted en bloc. Between the donor and recipient, we ascertained the blood type ABO match (identical, compatible, incompatible), degree of HLA-DR and HLA-B antigen mismatch, and donor-to-recipient ratio of BSA (D-R BSA ratio). Donor and recipient BSA was calculated using the formula reported by Mosteller.²⁸ We collected data on the regional location of transplant centers, center code of transplant programs, and distance between the donor and recipient in miles to aid in data imputation of missing variables.

There were 6 missing values for donor serum creatinine; these were imputed with the median value for serum creatinine. There were 41 missing values for CIT, which were imputed with linear regression using region, center code, and distance. There were > 900 missing values for warm ischemia time; therefore, this variable was not collected. Sensitivity analysis determined that there were no changes in analytic results after imputation of data.

Statistical Analysis

Using UNOS donor data, we stratified cohort members into 2 groups based on whether they received an en bloc or solitary kidney transplantation. To describe and compare donor, recipient, and transplant logistics, as well as donor-to-recipient combination characteristics between cohorts of en bloc versus single-kidney transplants, we analyzed continuous variables using median and interquartile ranges (IQRs) with the Student *t* test or the Kruskal-Wallis test, as appropriate for each distribution. We used percentages and chi-square tests for categorical variables. Our primary outcomes of interest to determine optimal adult recipients for DCD kidneys from 0- to 17-y-old donors were death-censored graft loss, all-cause graft loss, and patient death. To determine the unadjusted and adjusted hazard ratio of associated variables for graft loss or patient death, we used univariable and multivariable Cox proportional hazards models. Associations between variables were determined for all variables. Variables with an association of > 0.80 were removed from the analysis to avoid problems with multicollinearity. We controlled for all donor variables. All results were considered significant with a *P* value < 0.05 . We performed all statistics using JMP-Pro Version 15.1.0 (SAS Institute, Inc, Cary, NC).

RESULTS

From January 1, 2004, to March 10, 2020, there were 2103 DCD kidneys transplanted from pediatric donors (aged 0–17 y) into adult (aged ≥ 18 y) recipients. Of these 2103 transplants, 340 were transplanted en bloc, while 1763 were transplanted as solitary kidneys. Uncontrolled DCD donors accounted for only 2.2% ($n=46$) of all cases. There was no difference in survival or recipient age compared with controlled donors, nor did the multivariable analyses change with exclusion of this group. As such, the 46 uncontrolled donor cases were included in all subsequent analyses.

TABLE 1.**Donor and recipient demographic data of single and en bloc pediatric DCD kidneys transplanted into adult recipients**

| Variables ^a | Type of kidney transplant | | P |
|------------------------------|---------------------------|--------------------------|--------|
| | En bloc (N = 340) | Single (N = 1763) | |
| Donor | | | |
| Age (y) | 1 (IQR, 0–2) | 14 (IQR, 10–16) | <0.001 |
| Donor age groups (y) | | | <0.001 |
| 0–5 | 328 (96.5%) | 204 (11.6%) | |
| 6–12 | 9 (2.7%) | 465 (26.4%) | |
| 13–17 | 3 (0.9%) | 1094 (61.1%) | |
| BSA (m ²) | 0.46 (IQR, 0.34–0.58) | 1.56 (IQR, 1.12–1.83) | <0.001 |
| Height (cm) | 75.0 (IQR, 61.9–91.0) | 160.0 (IQR, 135.0–173.0) | <0.001 |
| Weight (kg) | 10.0 (IQR, 6.8–14.0) | 54.2 (IQR, 33.5–70.0) | <0.001 |
| Female gender | 150 (44.1%) | 633 (35.9%) | 0.005 |
| Race | | | 0.003 |
| Asian | 15 (4.4%) | 33 (1.9%) | |
| Black | 51 (15.0%) | 187 (10.6%) | |
| Hispanic | 41 (12.1%) | 191 (10.8%) | |
| Other | 6 (1.8%) | 18 (1.0%) | |
| White | 227 (66.8%) | 1334 (75.7%) | |
| Hypertension | 3 (0.9%) | 16 (0.9%) | 1 |
| Diabetes mellitus (any type) | 0 | 30 (1.7%) | 0.01 |
| Cause of death | | | <0.001 |
| Anoxia | 235 (69.1%) | 877 (49.7%) | |
| CVA | 13 (3.8%) | 101 (5.7%) | |
| Other | 29 (8.5%) | 107 (6.1%) | |
| Trauma | 63 (18.5%) | 678 (38.5%) | |
| Serum creatinine (mg/dL) | 0.3 (IQR, 0.2–0.43) | 0.7 (IQR, 0.43–1.0) | <0.001 |
| Recipient | | | |
| Recipient age (y) | 51 (39–60) | 50 (40–60) | 0.52 |
| Recipient age groups (y) | | | 0.92 |
| 18–40 | 94 (27.7%) | 469 (26.6%) | |
| 41–60 | 165 (48.5%) | 869 (49.3%) | |
| ≥61 | 81 (23.8%) | 425 (24.1%) | |
| BSA (m ²) | 1.76 (IQR, 1.61–1.91) | 1.90 (IQR, 1.72–2.10) | <0.001 |
| Height (cm) | 165.1 (IQR, 157.5–172.7) | 167.6 (IQR, 160.0–175.3) | <0.001 |
| Weight (kg) | 66.7 (IQR, 58.1–76.4) | 77.6 (IQR, 65.4–91.7) | <0.001 |
| Female gender | 169 (49.7%) | 782 (44.4%) | 0.07 |
| Race | | | <0.001 |
| Asian | 78 (22.9%) | 161 (9.1%) | |
| Black | 78 (22.9%) | 584 (33.1%) | |
| Hispanic | 77 (22.7%) | 310 (17.6%) | |
| Other | 6 (1.8%) | 49 (2.8%) | |
| White | 101 (29.7%) | 659 (37.4%) | |
| Diagnosis | | | 0.001 |
| Alport's syndrome | 6 (1.8%) | 21 (1.2%) | |
| Malignancy | 3 (0.9%) | 11 (0.6%) | |
| Diabetes mellitus (any type) | 79 (23.2%) | 429 (24.3%) | |
| Glomerulonephritis | 14 (4.1%) | 115 (6.5%) | |
| Hypertension | 77 (22.7%) | 485 (27.5%) | |
| IgA nephropathy | 32 (9.4%) | 123 (7.0%) | |
| Obstructive | 11 (3.2%) | 37 (2.1%) | |
| Other | 61 (17.9%) | 185 (10.5%) | |
| Polycystic disease | 31 (9.1%) | 144 (8.2%) | |
| Systemic lupus erythematosus | 11 (3.2%) | 72 (4.1%) | |
| HCV serostatus positive | 12 (3.5%) | 36 (2.0%) | 0.11 |
| Peripheral vascular disease | 22 (6.5%) | 125 (7.1%) | 0.82 |
| Years on dialysis | 3.0 (IQR, 1.5–5.0) | 3.7 (IQR, 1.7–6.0) | 0.002 |
| End CPRA | 0 (IQR, 0–1.8) | 0 (IQR, 0–13) | <0.001 |

^aVariables selected per original KDRI article (Rao); however 0- to 17-y-old donors were excluded in that analysis.

BSA, body surface area; CPRA, calculated panel reactive antibody; CVA, cerebral vascular accident; DCD, donation after circulatory death; HCV, hepatitis C virus; IgA, immunoglobulin A; IQR, interquartile range.

An analysis comparing the descriptive statistics of en bloc and solitary pediatric DCD kidney donors is shown in Table 1. Among this population, the median age of an en bloc donor was 1 y (IQR, 0–2) compared with a median age of 14 y (IQR, 10–16) in the solitary donor cohort ($P < 0.001$). Similarly, the overall distribution of donor age differed significantly ($P < 0.001$) between the 2 groups with 96.5% of en bloc transplants coming from the 0- to 5-y-old age group, while 61.1% of the solitary transplants came from the 13- to 17-y-old age group. The median BSA of a solitary DCD kidney donor was 1.56 m² (IQR, 1.12–1.83), which is >3-fold increase from the 0.46 m² (IQR, 0.34–0.58) observed among en bloc DCD kidney donors ($P < 0.001$). The serum creatinine

was within normal limits in both populations but was correspondingly lower at a median of 0.3 mg/dL (IQR, 0.2–0.43) in the en bloc cohort compared with a median of 0.7 mg/dL (IQR, 0.43–1.0) in the solitary cohort ($P < 0.001$). Females represented 44.1% of en bloc donors and 35.9% of solitary donors ($P < 0.001$). The composition of race ($P = 0.003$) and cause of death ($P < 0.001$) differed significantly between en bloc and solitary pediatric DCD donors; however, White was the predominant race and anoxia the foremost cause of death in both groups.

An analysis comparing the descriptive statistics characterizing recipients of en bloc versus solitary pediatric DCD kidneys is also shown in Table 1. The age distribution of patients

TABLE 2.
Transplant descriptive data of single and en bloc pediatric DCD kidneys transplanted into adult recipients

| Variables ^a | Type of kidney transplant | | P |
|-----------------------------|------------------------------------|------------------------------------|--------|
| | En bloc (N = 340) | Single (N = 1763) | |
| Transplant logistics | | | |
| Cold ischemia time (h) | 19.2 (IQR, 13.8–25.6) | 18.6 (13.5–23.6) | 0.048 |
| Kidney placed on pump | 152 (44.7%) | 1145 (65.0%) | <0.001 |
| Donor–recipient combination | | | |
| D-R BSA ratio | 0.26 (IQR, 0.20–0.32/R, 0.01–0.80) | 0.77 (IQR, 0.59–0.95/R, 0.23–1.60) | <0.001 |
| D-R BSA ratio groups | | | <0.001 |
| 0.10–0.70 | 339 (99.7%) | 658 (37.3%) | |
| >0.70–0.91 | 1 (0.3%) | 562 (31.9%) | |
| >0.91 | 0 | 543 (30.8%) | |
| ABO match | | | 0.15 |
| Identical | 334 (98.2%) | 1695 (96.1%) | |
| Compatible | 4 (1.2%) | 51 (2.9%) | |
| Incompatible | 2 (0.6%) | 17 (1.0%) | |
| HLA-B locus mismatches | | | 0.01 |
| 0 | 8 (2.4%) | 116 (6.6%) | |
| 1 | 83 (24.4%) | 436 (24.7%) | |
| 2 | 249 (73.2%) | 1211 (68.7%) | |
| HLA-DR locus mismatches | | | <0.001 |
| 0 | 24 (7.1%) | 273 (15.5%) | |
| 1 | 160 (47.1%) | 869 (49.3%) | |
| 2 | 156 (45.8%) | 621 (35.2%) | |

^aVariables selected per original KDRI article (Rao); however 0- to 17-y-old donors were excluded in that analysis. DCD, donation after circulatory death; D-R BSA, donor to recipient ratio of body surface area; IQR, interquartile range.

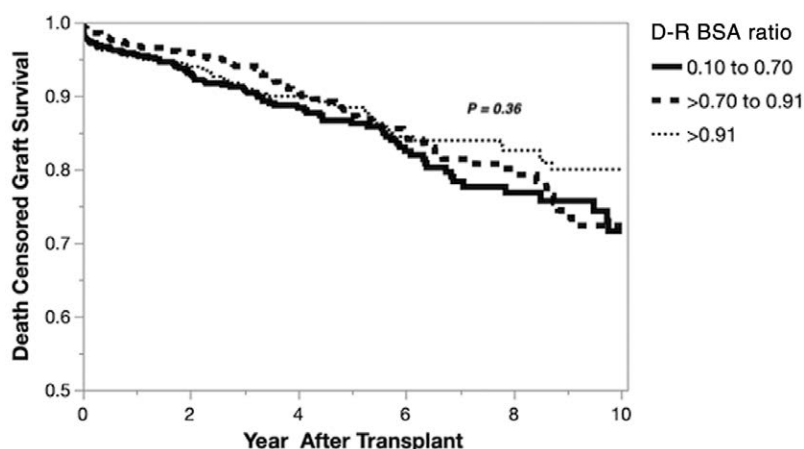


FIGURE 1. Kaplan-Meier curves for death-censored graft survival comparing D-R BSA ratio cohorts among solitary kidney recipients. D-R BSA, donor to recipient ratio of body surface area.

receiving pediatric DCD kidneys was similar between those who underwent en bloc and solitary kidney transplantation, with a median age of 51 y (IQR, 39–60) and 50 y (IQR, 40–60), respectively. However, the median BSA of those receiving en bloc kidneys was 1.76 m² (IQR, 1.61–1.91), which was significantly ($P<0.001$) lower than the median of 1.90 m² (IQR, 1.72–2.10) seen in those receiving solitary allografts. Recipients of pediatric DCD kidneys required dialysis before transplant for a median of 3.0 y (IQR, 1.5–5.0) and 3.7 y (IQR, 1.7–6.0) in the en bloc and solitary recipient cohorts, respectively ($P=0.002$). The composition of race differed

significantly ($P<0.001$) between recipients of en bloc and solitary pediatric DCD kidneys; however, White was the most common race in both cohorts. Recipient diagnoses also differed significantly ($P<0.001$) between groups, with the most common diagnosis of en bloc recipients being diabetic nephropathy (23.2%), while the predominant diagnosis of solitary recipients was hypertensive nephropathy (27.5%).

Donor–recipient pairing and transplantation analyses are shown in Table 2. Among pediatric DCD donor–recipient pairs, the median BSA ratio of an en bloc transplant was 0.26 (IQR, 0.20–0.32; range, 0.01–0.80) compared with a median

TABLE 3.**Cox proportional hazard model for death-censored graft loss in 10 y among solitary pediatric DCD kidneys transplanted into adult recipients**

| Variables | Univariable analysis | | | | Multivariable analysis | | | |
|------------------------------|----------------------|------|------|--------|------------------------|------|------|--------|
| | RR | LCI | UCI | P | RR | LCI | UCI | P |
| Recipient | | | | | | | | |
| Recipient age groups (y) | | | | | | | | |
| 18–40 | Ref | | | | | | | |
| 41–60 | 0.50 | 0.38 | 0.68 | <0.001 | 0.54 | 0.40 | 0.72 | <0.001 |
| ≥61 | 0.46 | 0.31 | 0.67 | <0.001 | 0.49 | 0.33 | 0.73 | <0.001 |
| Female gender | 0.86 | 0.66 | 1.13 | 0.28 | | | | |
| Diagnosis | | | | | | | | |
| Alport's syndrome | 0.62 | 0.15 | 2.67 | 0.52 | | | | |
| Malignancy | 1.99 | 0.46 | 8.54 | 0.36 | | | | |
| Diabetes mellitus (any type) | 0.69 | 0.40 | 1.18 | 0.18 | | | | |
| Glomerulonephritis | Ref | | | | | | | |
| Hypertension | 0.89 | 0.53 | 1.48 | 0.64 | | | | |
| IgA nephropathy | 0.84 | 0.41 | 1.69 | 0.62 | | | | |
| Obstructive | 0.65 | 0.22 | 1.90 | 0.43 | | | | |
| Other | 0.64 | 0.34 | 1.23 | 0.18 | | | | |
| Polycystic disease | 0.39 | 0.18 | 0.87 | 0.02 | | | | |
| Systemic lupus erythematosus | 2.08 | 1.10 | 3.92 | 0.02 | 2.30 | 1.41 | 3.73 | <0.001 |
| HCV serostatus positive | 1.36 | 0.60 | 3.07 | 0.46 | | | | |
| B21 | | | | | | | | |
| Peripheral vascular disease | 0.78 | 0.40 | 1.53 | 0.47 | | | | |
| Years on dialysis | 1.01 | 0.97 | 1.06 | 0.50 | | | | |
| End CPRA | 0.99 | 0.98 | 1.01 | 0.50 | | | | |
| Donor–recipient combination | | | | | | | | |
| D-R BSA ratio groups | | | | | | | | |
| 0.10–0.70 | 1.26 | 0.91 | 1.75 | 0.17 | | | | |
| >0.70–0.91 | 1.08 | 0.77 | 1.52 | 0.64 | | | | |
| >0.91 | Ref | | | | | | | |
| ABO match | | | | | | | | |
| Identical | Ref | | | | | | | |
| Compatible | 0.55 | 0.18 | 1.72 | 0.30 | | | | |
| Incompatible | 1.95 | 0.48 | 7.88 | 0.35 | | | | |
| HLA-B locus mismatches | | | | | | | | |
| 0 | Ref | | | | | | | |
| 1 | 0.92 | 0.50 | 1.71 | 0.79 | | | | |
| 2 | 1.24 | 0.71 | 2.17 | 0.46 | 1.39 | 1.02 | 1.88 | 0.04 |
| HLA-DR locus mismatches | | | | | | | | |
| 0 | Ref | | | | | | | |
| 1 | 0.91 | 0.61 | 1.34 | 0.63 | | | | |
| 2 | 1.03 | 0.68 | 1.54 | 0.90 | | | | |
| Transplant logistics | | | | | | | | |
| Cold ischemia time (h) | 1.02 | 1.01 | 1.04 | 0.002 | 1.02 | 1.01 | 1.04 | 0.001 |
| Kidney placed on pump | 1.02 | 0.89 | 1.35 | 0.89 | | | | |

Controlled for donor variables of history of hypertension, history of diabetes mellitus (any type), cause of death, and serum creatinine.

CPRA, calculated panel reactive antibody; DCD, donation after circulatory death; D-R BSA, donor to recipient ratio of body surface area; HCV, hepatitis C virus; IgA, immunoglobulin A; LCI, lower confidence interval; RR, relative risk; UCI, upper confidence interval.

of 0.77 (IQR, 0.59–0.95; range, 0.23–1.60) in solitary transplantation ($P < 0.001$). Accordingly, the overall distribution of D-R BSA ratios differed significantly ($P < 0.001$) between the 2 groups, with a BSA ratio of 0.10–0.70 comprising 99.7% of en bloc DCD kidney transplants. In contrast, a relatively even distribution was observed between D-R BSA ratios of 0.10–0.70 (37.3%), >0.70–0.91 (31.9%), and >0.91 (30.8%) in recipients of solitary pediatric DCD kidneys. The composition of HLA-B locus mismatch ($P = 0.01$) and HLA-DR locus mismatch ($P < 0.001$) differed significantly between en bloc and solitary pediatric DCD transplants; however, 2 HLA-B antigen mismatches and 1 HLA-DR antigen mismatch were predominant in both cohorts. There was no difference in ABO matching between en bloc and solitary groups, with the vast majority of transplants occurring between ABO identical pairs. The median CIT was 48 min longer ($P = 0.048$) during the en bloc technique (19.2 h; IQR, 13.8–25.6) versus solitary transplant (18.6 h; IQR, 13.5–23.6). Significantly ($P < 0.001$) more solitary pediatric DCD kidneys were placed on pump (65.0%) before transplantation than en bloc DCD kidneys (44.7%).

The unadjusted death-censored allograft survival in pediatric-derived solitary kidney transplantation was similar between all D-R BSA ratio cohorts (Figure 1). The Cox proportional hazard model for death-censored graft survival is given in Table 3, which redemonstrates a lack of correlation between donor–recipient BSA matching and allograft loss when censored for patient death. However, several factors were associated with death-censored graft loss in the multivariable analysis including 2-antigen mismatch at the HLA-B locus (relative risk [RR], 1.39; 95% confidence interval [CI], 1.02–1.88), increased CIT (RR, 1.02; 95% CI, 1.01–1.03), and recipient diagnosis of systemic lupus erythematosus (RR, 2.30; 95% CI, 1.41–3.73). Interestingly, increased recipient age was found to be protective against death-censored allograft loss with recipients aged 41–60 and ≥ 60 y having a decreased RR of 0.54 (95% CI, 0.40–0.72) and 0.49 (95% CI, 0.33–0.73), respectively compared with younger recipients.

The Kaplan-Meier-calculated all-cause graft survival in solitary kidney transplantation from pediatric donors was similar when the D-R BSA ratio resides between >0.70 and 0.91 or >0.91 (Figure 2). However, a significant ($P = 0.009$) all-cause graft survival benefit was demonstrated when using

donor–recipient pairs with a BSA ratio >0.91 compared to those with a ratio of 0.10–0.70 (Figure 2). The Cox proportional hazard model for all-cause graft failure is shown in Table 4. Similar to the unadjusted graft survival curves, there was no difference in the risk of graft failure between D-R BSA ratios of >0.70–0.91 and >0.91. Conversely, multivariable analysis revealed that ratios falling between 0.10 and 0.70 conferred a higher risk of graft failure when compared with those that were >0.91 (RR, 1.36; 95% CI, 1.10–1.69). Recipient factors associated with graft failure in the multivariable analysis include age ≥ 61 y versus an 18- to 40-y-old cohort (RR, 1.53; 95% CI, 1.23–1.91), as well as diagnoses of diabetic nephropathy (RR, 1.33; 95% CI, 1.06–1.67) and systemic lupus erythematosus (RR, 1.92; 95% CI, 1.20–3.06). Factors protective against graft failure included recipients of female gender (RR, 0.81; 95% CI, 0.66–0.99) and a diagnosis of polycystic kidney disease (RR, 0.60; 95% CI, 0.38–0.95).

Consistent with all-cause graft survival, the unadjusted patient survival was significantly ($P = 0.02$) improved when the D-R BSA ratio was >0.91 as opposed to 0.10–0.70 (Figure 3). Conversely, there was comparable patient survival between the >0.70–0.91 and >0.91 D-R BSA ratio cohorts (Figure 3). As demonstrated in the Cox proportional hazard model for patient death given in Table 5, multivariable analysis revealed a RR of 1.32 (95% CI, 1.01–1.73) for D-R BSA ratios of 0.10–0.70 when compared with ratios >0.91. Again, there was no significant difference in risk of patient death between the >0.70–0.91 and >0.91 cohorts. In contrast to death-censored graft outcomes, increased recipient age was strongly associated with worse patient death in both the 41- to 60-y-old (RR, 2.46; 95% CI, 1.5–3.98) and ≥ 61 -y-old (RR, 5.70; 95% CI, 3.51–9.26) cohorts versus recipients aged 18–40 y. Increased years on dialysis before transplant (RR, 1.07; 95% CI, 1.03–1.11) and hepatitis C virus seropositivity (RR, 2.27; 95% CI, 1.26–4.09) both conferred a high risk of patient death in the multivariable analysis. Additionally, diabetic nephropathy as an underlying diagnosis was associated with worse patient survival (RR, 1.86; 95% CI, 1.43–2.41).

Overall, an unadjusted analysis of the impact of en bloc versus solitary kidney transplantation from pediatric donors into adult recipients revealed improved ($P = 0.02$) 10-y patient survival when using the en bloc technique (Figure 4). This analysis was then repeated in the context of donor–recipient

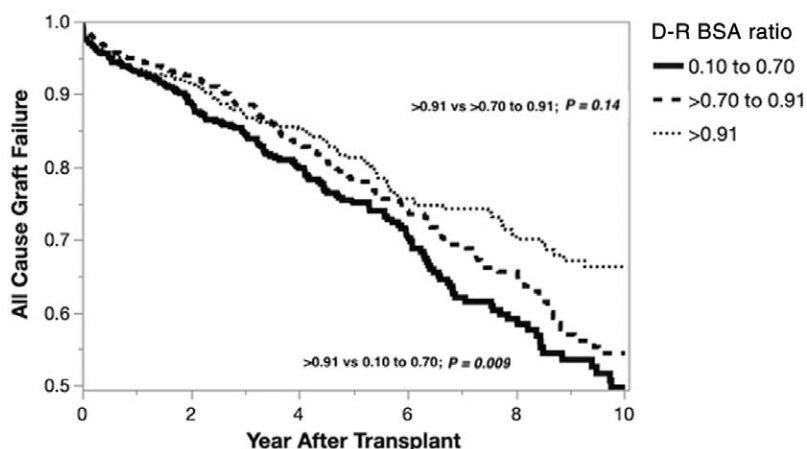


FIGURE 2. Kaplan-Meier curves for all-cause graft survival comparing D-R BSA ratio cohorts among solitary kidney recipients. D-R BSA, donor to recipient ratio of body surface area.

BSA matching (Figure 5), which demonstrated a significant ($P=0.002$) survival benefit when performing en bloc transplantation versus solitary kidney transplantation with a D-R BSA ratio falling between 0.10 and 0.70. Furthermore, donor–recipient pairs with a BSA ratio >0.70 had improved patient survival compared to the 0.10–0.70 cohort ($P=0.02$) in solitary transplantation. No difference in patient survival was observed when comparing en bloc to solitary transplantation with D-R BSA ratios >0.70 .

A Cox multivariable subanalysis (data not shown) was performed on a cohort consisting of en bloc recipients, as well as recipients of solitary kidneys with D-R BSA ratios of >0.70 .

Neither recipient diagnosis of DM nor age ≥ 61 y was associated with worse long-term graft survivals. However, recipient age ≥ 61 y did yield a RR for patient death of 5.35 (95% CI, 3.00–9.51). Similar to graft survival, DM inferred no greater risk for patient death in this cohort.

DISCUSSION

As DCD kidney transplantation becomes more widely adopted, attention must be given to the nuanced considerations underlying the allocation of certain allografts, notably those derived from small pediatric donors. We find that

TABLE 4.

Cox proportional hazard model for all-cause graft loss in 10 y among solitary pediatric DCD kidneys transplanted into adult recipients

| Variables | Univariable analysis | | | | Multivariable analysis | | | |
|------------------------------|----------------------|-------|------|-------|------------------------|------|------|----------|
| | RR | LCI | UCI | P | RR | LCI | UCI | P |
| Recipient | | | | | | | | |
| Recipient age groups (y) | | | | | | | | |
| 18–40 | Ref | | | | | | | |
| 41–60 | 0.86 | 0.67 | 1.11 | 0.25 | | | | |
| ≥ 61 | 1.42 | 1.10 | 1.86 | 0.01 | 1.53 | 1.23 | 1.91 | <0.001 |
| Female gender | 0.81 | 0.66 | 0.99 | 0.04 | 0.81 | 0.66 | 0.99 | 0.048 |
| Diagnosis | | | | | | | | |
| Alport's syndrome | 0.45 | 0.11 | 1.91 | 0.28 | | | | |
| Malignancy | 1.51 | 0.36 | 6.37 | 0.57 | | | | |
| Diabetes mellitus (any type) | 1.50 | 0.98 | 2.29 | 0.06 | 1.33 | 1.06 | 1.67 | 0.01 |
| Glomerulonephritis | Ref | | | | | | | |
| Hypertension | 1.12 | 0.07 | 1.71 | 0.62 | | | | |
| IgA nephropathy | 0.86 | 0.47 | 1.57 | 0.63 | | | | |
| Obstructive | 1.07 | 0.50 | 2.28 | 0.86 | | | | |
| Other | 0.76 | 0.45 | 1.30 | 0.32 | | | | |
| Polycystic disease | 0.64 | 0.36 | 1.15 | 0.14 | 0.60 | 0.38 | 0.95 | 0.03 |
| Systemic lupus erythematosus | 1.63 | 0.91 | 2.92 | 0.10 | 1.92 | 1.20 | 3.06 | 0.006 |
| HCV serostatus positive | 1.64 | 0.95 | 2.86 | 0.08 | | | | |
| Peripheral vascular disease | 1.54 | 0.06 | 2.24 | 0.02 | | | | |
| Years on dialysis | 1.03 | 0.99 | 1.06 | 0.07 | | | | |
| End CPRA | 0.99 | 0.98 | 1.01 | 0.24 | | | | |
| Donor–recipient combination | | | | | | | | |
| D-R BSA ratio groups | | | | | | | | |
| 0.10–0.70 | 1.47 | 1.15 | 1.88 | 0.002 | 1.36 | 1.10 | 1.69 | 0.004 |
| >0.70 –0.91 | 1.21 | 0.94 | 1.57 | 0.14 | | | | |
| >0.91 | Ref | | | | | | | |
| ABO match | | | | | | | | |
| Identical A31 | Ref | | | | | | | |
| Compatible | 0.82 | 0.41 | 1.65 | 0.58 | | | | |
| Incompatible | 2.37 | 0.88 | 6.35 | 0.09 | | | | |
| HLA-B locus mismatches | | | | | | | | |
| 0 | Ref | | | | | | | |
| 1 | 1.20 | 0.75 | 1.90 | 0.45 | | | | |
| 2 | 1.28 | 0.83 | 1.97 | 0.27 | | | | |
| HLA-DR locus mismatches | | | | | | | | |
| 0 | Ref | | | | | | | |
| 1 | 0.94 | 0.70 | 1.25 | 0.65 | | | | |
| 2 | 0.94 | 0.66 | 1.26 | 0.66 | | | | |
| Transplant logistics | | | | | | | | |
| Cold ischemia time (h) | 1.01 | 1.004 | 1.03 | 0.008 | | | | |
| Kidney placed on pump | 0.91 | 0.74 | 1.11 | 0.36 | | | | |

Controlled for donor variables of history of hypertension, history of diabetes mellitus (any type), cause of death, and serum creatinine.

CPRA, calculated panel reactive antibody; DCD, donation after circulatory death; D-R BSA, donor to recipient ratio of body surface area; HCV, hepatitis C virus; IgA, immunoglobulin A; LCI, lower confidence interval; RR, relative risk; UCI, upper confidence interval.

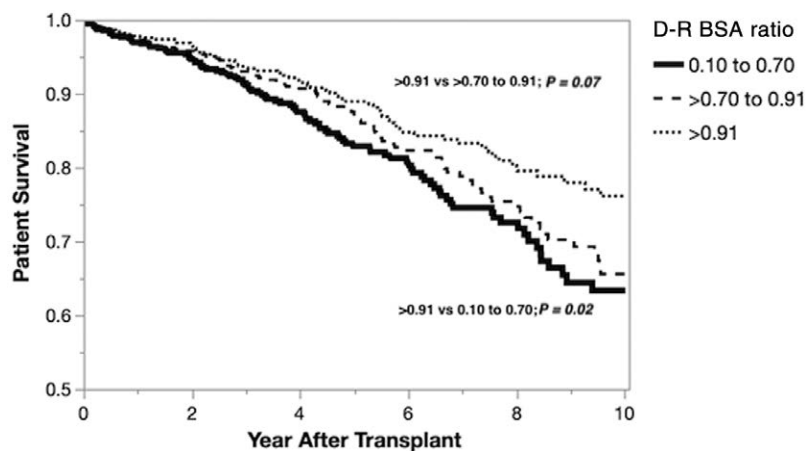


FIGURE 3. Kaplan-Meier curves for patient survival comparing D-R BSA ratio cohorts among solitary kidney recipients. D-R BSA, donor to recipient ratio of body surface area.

optimal utilization of pediatric DCD kidneys requires careful appraisal of donor-to-recipient size relation. Here, we report that solitary DCD pediatric allografts transplanted between donor–recipient pairs with a BSA ratio of 0.10–0.70 carry an increased risk of all-cause graft failure and patient death when compared to matched pairings with a ratio of >0.70. A similar analysis of en bloc versus solitary kidney transplantation revealed improved long-term patient survival among en bloc recipients compared with recipients of single kidneys with D-R BSA ratios of 0.10–0.70. Taken together, we found that in solitary DCD kidney transplantation, stratification of D-R BSA ratios revealed incongruent long-term outcomes between cohorts, which was alleviated by en bloc allocation in disparate pairs. In this context, we recommend solitary allocation for donor and recipient pairs with a BSA ratio of >0.70 and en bloc transplantation for those with BSA ratios of 0.10–0.70. To facilitate the utilization of this criterion, our group has developed an online tool to guide solitary versus en bloc decision making in the real-time clinical setting (https://cbatl.shinyapps.io/Peds_DCD_BSA_Matching/).

There has long been considerable apprehension about the utilization of pediatric DCD kidneys in adult recipients. These concerns have historically focused on allograft size as it relates to anatomic structure and functional nephron mass. With respect to vessel caliber, considerable progress has been made in the incidence of early size-related vascular complications such as graft thrombosis, which has recently been reported by some centers to have a rate as low as 0%–5%.^{24,29,30} This trend is likely related to improved institutional experience, advanced operative technique, and prophylactic antithrombotic therapy.^{12,29,31} Although DCD kidney transplantation can complicate the clinical picture given a higher baseline risk of early allograft dysfunction, DGF in this population does not herald worse long-term graft function.^{7–9} Furthermore, pediatric DCD kidneys have been shown to have similar long-term renal function and graft survival compared with age-matched DBD kidneys.^{13,22} Given the acceptable outcomes of pediatric DCD kidneys and a decline in early postoperative complications following transplantation from small donors, attention has shifted to the long-term functional consequence of inadequate allograft size. Fortunately, our analysis has shown that appropriate donor–recipient size matching can overcome these functional consternations.

To date, several comparative strategies have been explored to optimize kidney allocation from small donors; however, a consensus assessment of renal functional as it relates to donor and allograft size remains elusive. Glomerular number is a known correlate to renal function; however, this value is highly variable and fixed at birth.³² Therefore, age-, transplant-, or pathology-mediated kidney enlargement is influenced by compensatory nephritic hypertrophy as opposed to an expanded glomerular reserve, thus confounding our ability to accurately assess the functional capacity of an organ as it relates to its volume.^{32–34} Further complicating this assessment is the presence of nonfunctional structural components such as renal sinus fat, which is negatively correlated to glomerular filtration rate (GFR) and intimately associated with hypertension.^{35,36} Though likely to be minimal in small, otherwise healthy pediatric donors, these considerations underscore the inaccuracy of volume-based assessments of renal function as determined by imaging or gross examination. Alternatively, Johnson et al²⁵ report that RPV, composed of the cortex and medulla, is independently and directly correlated with GFR. Importantly, BSA, as opposed to volumetric measurement of the organ, consistently and accurately represents RPV and can therefore serve as a surrogate for functional nephron mass.^{25–27} In this context, we found that donor–recipient BSA matching is prognostically significant when considering solitary DCD kidney transplantation from pediatric donors.

We have demonstrated inferior all-cause graft and patient survival following solitary transplantation of DCD kidneys from small donors into disparately sized recipients despite preserved death-censored graft survival. These outcomes suggest that recipients of proportionally smaller DCD allografts tend to die with operational kidneys, though terminal GFR and systemic sequelae of inadequate renal function remain unknown due to limitations of the UNOS database. We postulate that the increased incidence of death observed in recipients of small solitary DCD kidneys is related to systemic sequelae of inadequate functional nephron mass, similar to the deleterious physiologic effects of nontransplant patients with declining renal function. Importantly, this mortality deficit is not observed among recipients of adequately size-matched solitary kidneys, defined by this study as D-R BSA ratios of >0.70. This conjecture is supported by the well-described impacts of inadequate kidney size on patient physiology and survival.

TABLE 5.**Cox proportional hazard model for patient death in 10 y among adult recipients of solitary pediatric DCD kidney allografts**

| Variables | Univariable analysis | | | | Multivariable analysis | | | |
|------------------------------|----------------------|------|-------|--------|------------------------|------|------|--------|
| | RR | LCI | UCI | P | RR | LCI | UCI | P |
| Recipient | | | | | | | | |
| Recipient age groups (y) | | | | | | | | |
| 18–40 | Ref | | | | | | | |
| 41–60 | 2.75 | 1.71 | 4.43 | <0.001 | 2.46 | 1.52 | 3.98 | <0.001 |
| ≥61 | 6.60 | 4.11 | 10.60 | <0.001 | 5.70 | 3.51 | 9.26 | <0.001 |
| Female gender | 0.76 | 0.59 | 0.98 | 0.04 | | | | |
| Diagnosis | | | | | | | | |
| Alport's syndrome | Unstable | | | 0.99 | | | | |
| Malignancy | 1.58 | 0.21 | 12.1 | 0.66 | | | | |
| Diabetes mellitus (any type) | 2.48 | 1.42 | 4.34 | 0.001 | 1.86 | 1.43 | 2.41 | <0.001 |
| Glomerulonephritis | Ref | | | | | | | |
| Hypertension | 1.33 | 0.75 | 2.36 | 0.33 | | | | |
| IgA nephropathy | 0.75 | 0.31 | 1.78 | 0.51 | | | | |
| Obstructive | 1.40 | 0.54 | 3.65 | 0.49 | | | | |
| Other | 0.72 | 0.34 | 1.50 | 0.38 | | | | |
| Polycystic disease | 0.81 | 0.38 | 1.72 | 0.58 | | | | |
| Systemic lupus erythematosus | 0.76 | 0.27 | 2.11 | 0.60 | | | | |
| HCV serostatus positive | 2.61 | 1.46 | 4.66 | 0.001 | 2.27 | 1.26 | 4.09 | 0.006 |
| Peripheral vascular disease | 2.25 | 1.49 | 3.41 | <0.001 | | | | |
| Years on dialysis | 1.05 | 1.01 | 1.09 | 0.02 | 1.07 | 1.03 | 1.11 | <0.001 |
| End CPRA | 0.99 | 0.98 | 1.01 | 0.63 | | | | |
| Donor–recipient combination | | | | | | | | |
| D:R BSA ratio groups | | | | | | | | |
| 0.10–0.70 | 1.57 | 1.15 | 2.15 | 0.005 | 1.32 | 1.01 | 1.73 | 0.04 |
| >0.70–0.91 | 1.34 | 0.98 | 1.86 | 0.07 | F28 | | | |
| >0.91 | Ref | | | | | | | |
| ABO match | | | | | | | | |
| Identical | Ref | | | | | | | |
| Compatible | 1.05 | 0.46 | 2.35 | 0.91 | | | | |
| Incompatible | 2.19 | 0.54 | 8.84 | 0.27 | | | | |
| HLA-B locus mismatches | | | | | | | | |
| 0 | Ref | | | | | | | |
| 1 | 1.42 | 0.82 | 2.48 | 0.21 | | | | |
| 2 | 1.09 | 0.64 | 1.86 | 0.74 | | | | |
| HLA-DR locus mismatches | | | | | | | | |
| 0 | Ref | | | | | | | |
| 1 | 1.01 | 0.70 | 1.47 | 0.94 | | | | |
| 2 | 1.004 | 0.68 | 1.48 | 0.99 | | | | |
| Transplant logistics | | | | | | | | |
| Cold ischemia time (h) | 1.008 | 0.99 | 1.02 | 0.21 | | | | |
| Kidney placed on pump | 0.83 | 0.65 | 1.07 | 0.16 | | | | |

Controlled for donor variables of history of hypertension, history of diabetes mellitus (any type), cause of death, and serum creatinine.

CPRA, calculated panel reactive antibody; DCD, donation after circulatory death; D:R BSA, donor to recipient ratio of body surface area; HCV, hepatitis C virus; IgA, immunoglobulin A; LCI, lower confidence interval; RR, relative risk; UCI, upper confidence interval.

There is evidence in kidney transplantation to implicate inadequate nephritic functional capacity in the development of hyperfiltration-associated injury manifested by hypertension, proteinuria, glomerulosclerosis, and an insidious decline in renal function.^{17–19,37} Additionally, worse patient and graft survivals have been reported between poorly size-matched donor–recipient pairs.^{38,39} Obscuring the impact of graft size is compensatory renal hypertrophy observed after transplantation from small donors.⁴⁰ However, renal hypertrophy is known to poorly compensate for proteinuria and may be associated with progressive chronic renal injury.^{20,25,41} These findings validate our claim that DCD allografts from small pediatric donors should be transplanted within the context of

relative recipient size, with a D-R BSA ratio of >0.7 representing the safe lower limit of equitable single-kidney allocation.

As an alternative to solitary kidney transplantation, the en bloc technique has emerged as an effective strategy to compensate for inadequate solitary renal size. Initially complicated by higher rates of surgical complications and early allograft loss secondary to global hypoperfusion and thrombosis, en bloc transplantation has more recently been shown to have exceptional long-term outcomes.^{14,24} National registry analysis by Bhayana et al²⁹ found that en bloc allografts have improved long-term graft survival compared with matched standard criteria deceased donor kidneys and demonstrated higher GFR compared with solitary pediatric grafts. These

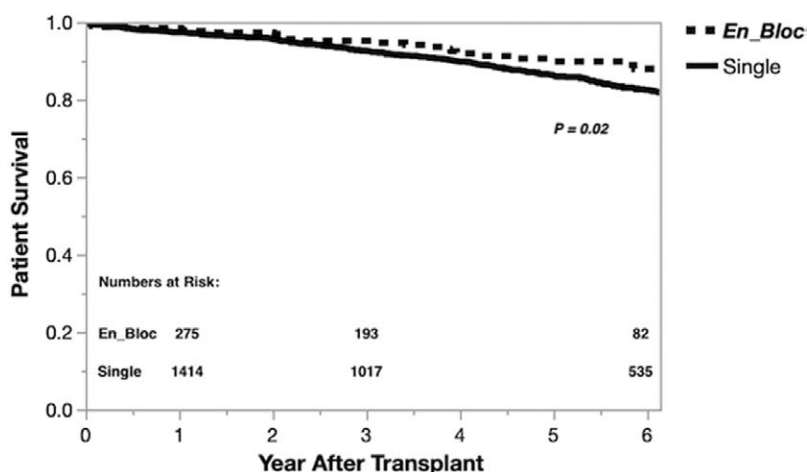


FIGURE 4. Kaplan-Meier curves for patient survival comparing en bloc and solitary kidney recipients.

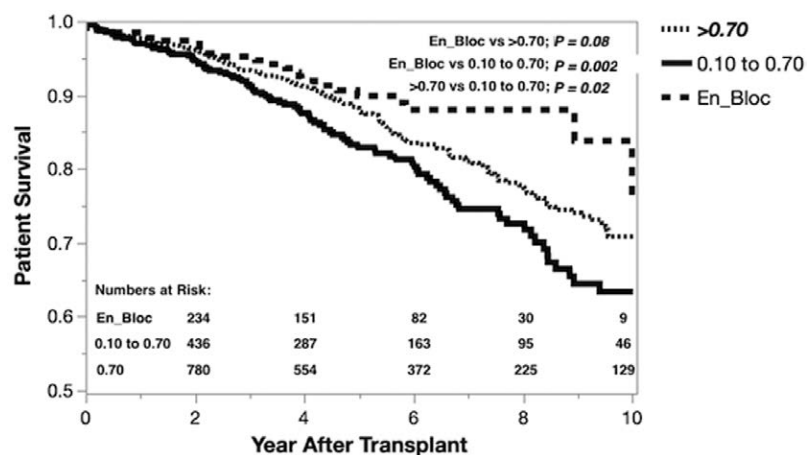


FIGURE 5. Kaplan-Meier curves for patient survival comparing en bloc vs D-R BSA ratio stratified solitary kidney recipients. D-R BSA, donor to recipient ratio of body surface area.

findings were supported by multiple single-center analyses demonstrating similar long-term outcomes between en bloc, solitary pediatric, and standard adult kidney transplant recipients.^{12,14,16,30} Furthermore, recent studies have revealed similarly low rates of graft thrombosis in en bloc and solitary transplantation.^{24,29,30} Additional analyses between DCD and DBD en bloc kidney transplants demonstrate high rates of DGF in DCD cohorts, but otherwise comparable outcomes characterized by low rates of graft thrombosis and primary nonfunction, as well as preserved long-term GFR and graft survival.^{22,42} Given acceptable early postoperative outcomes, long-term functional reserve has become germane to the development of consensus criteria for en bloc allocation in DCD transplantation.

We discovered a significant survival advantage when using en bloc kidneys as opposed to solitary allografts in DCD transplantation between donor and recipient pairs with a BSA ratio of 0.10–0.70, indicating that this technique can overcome the long-term consequences of inadequate single-kidney function. We therefore extend the prognostic utility of D-R BSA ratios to en bloc transplantation and propose that ratios of 0.10–0.70 serve as an indication for this allocation strategy. Through this lens, we found a surprisingly high rate of BSA-disparate solitary DCD kidney transplantation in the UNOS

database, with 37.3% of pairs having had a BSA ratio of 0.10–0.70, which we consider to be high risk for worse long-term outcomes. Based on our criteria, we suggest that these kidneys instead be transplanted en bloc or be alternatively allocated to smaller recipients to abate the effects of disparate BSA ratios. It is important to acknowledge that reallocation of solitary kidneys as en bloc grafts will decrease the number of recipients per donor; however, we propose that it is better to maximize recipient survival than to perform transplants yielding a known survival deficit.

Important factors when considering allocation strategies aimed at optimizing patient and graft survivals include recipient age, comorbidities, and transplant logistics. Among all solitary recipients, our analysis did reveal increased RR of patient death among recipients aged ≥ 61 y, as well as those diagnosed with diabetic nephropathy. To address this issue within the context of D-R BSA matching, we performed a subanalysis of appropriately allocated organs defined as en bloc recipients or recipients of solitary kidneys with D-R BSA ratios of >0.70 , which failed to implicate recipient age or DM as risk factors for graft failure. Further, DM was not found to portend worse patient survival within this size-matched cohort. Conversely, recipient age ≥ 61 y was associated with worse long-term patient survival; however, this is expected given that advanced age will always

be a risk factor for patient death. Regardless, we do believe that these candidates should be offered suitable size-matched organs, and therefore conclude that D-R BSA matching should not be avoided in older or diabetic recipients of pediatric DCD kidneys. Finally, we did observe a small RR for death-censored graft failure with prolonged CIT, consistent with the known effects of extended cold time on kidney survival. It is therefore important to minimize CIT while maintaining proper BSA matching to optimize graft and patient outcomes.

The primary limitations of this study include the retrospective design and the use of a large public database that does not delineate discrete reasons underlying graft failure and patient death, early postoperative complications, nor important long-term outcomes such as terminal GFR or comorbidities. Nevertheless, results of this analysis have revealed discrepant long-term outcomes in solitary DCD kidney transplants from pediatric donors as a function of donor–recipient BSA matching. In contrast to the deleterious outcomes observed after solitary transplantation between BSA-disparate pairs, we have demonstrated a survival benefit when these kidneys are instead transplanted en bloc. Given the well-described effects of insufficient parenchymal volume on renal dysfunction, we believe that the unfavorable long-term outcomes observed after BSA-mismatched transplants are related to the systemic and physiologic effects of inadequate allograft functional capacity. In this context, we encourage the use of D-R BSA ratios in the technical decision making underlying DCD kidney transplantation from pediatric donors. Specifically, we suggest that size-related criteria for en bloc DCD transplantation be defined by a D-R BSA ratio of 0.10–0.70.

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