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ORIGINAL ARTICLE

Poor outcomes for children on the wait list at low-volume kidney transplant centers in the United States

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Abstract
Background Low case volume has been associated with worse survival outcomes in solid organ transplantation. Our aim was to analyze wait-list outcomes in conjunction with posttransplant outcomes.
Methods We studied a cohort of 11,488 candidates waitlisted in the Organ Procurement and Transplantation Network (OPTN) for pediatric kidney transplant between 2002 and 2014, including both deceased- and living-donor transplants; 8757 (76 %) candidates received a transplant. Candidates were divided into four groups according to the average volume of yearly transplants performed in the listing center over a 12-year period: more than ten, six to nine, three to five, and fewer than three. We used multivariate Cox regression analysis to identify independent risk factors for wait list and posttransplant mortality.
Results Twenty-seven percent of candidates were listed at low-volume centers in which fewer than three transplants were performed annually. These candidates had a limited transplant rate; only 49 % received a transplant versus 88 % in high-volume centers (more than ten transplants annually) ($p < 0.001$). Being listed at a low-volume center showed a fourfold increased risk for death while on the wait list [hazard ratio (HR) 4.0 in multivariate Cox regression and 6.1 in multivariate competing risk regression]. It was not a significant risk factor for posttransplant death in multivariate Cox regression.
Conclusions Pediatric transplant candidates are listed at low-volume transplant centers are transplanted less frequently and have a much greater risk of dying while on the wait list. Further studies are needed to elucidate the reasons behind the significant outcome differences.

Keywords Posttransplant survival · Waitlist survival · Case volume · Transplant rate · Pediatric kidney transplant

Abbreviations

BMI	Body mass index
CI	Confidence interval
ESRD	End-stage renal disease
HLA	Human leukocyte antigen
HR	Hazard ratio
ICU	Intensive care unit
OPTN	Organ Procurement and Transplantation Network
UNOS	United Network for Organ Sharing

Introduction

Renal transplantation is the preferred modality to treat pediatric patients with end-stage renal disease (ESRD) because of good posttransplant survival [1] and the potential for better cognitive development, social adjustment, and quality of life

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(QoL) compared with chronic dialysis [2]. Factors such as geographic variation, race/ethnicity, and socioeconomic status are known to affect access of pediatric patients to kidney transplant [3, 4] and may affect outcomes. Additionally, center volume is known to affect outcomes for many procedures [5–16], including solid-organ transplantation [17–23]. None of these studies explored differences in wait-list outcomes.

A previous investigation uncovered modest differences in postrenal transplant outcomes in low-volume compared with higher-volume centers, but wait-list outcomes were not examined [20]. In a recent analysis of pediatric liver transplantation, poor wait-list outcomes were found in low-volume compared with higher-volume pediatric liver transplant centers [24]. The differences in wait-list mortality between high- and low-volume liver centers overshadowed the relatively minor posttransplant outcome differences.

Wait list and posttransplant outcomes are closely connected. By selectively choosing the best candidates for transplantation, a center can maximize its posttransplant outcomes at the expense of its transplantation rate and wait-list mortality. There is a selective pressure for this strategy, since both the United Network for Organ Sharing (UNOS) and insurance companies emphasize posttransplant outcomes as opposed to wait-list outcomes [25]. We therefore used this novel approach to analyze the national pediatric kidney wait-list and posttransplant experience. We hypothesized that low-volume pediatric kidney transplant centers will have inferior outcomes compared with higher-volume centers and that the most pronounced outcome differences will be in patients on the waiting list.

Methods

Study population We performed a retrospective analysis of the United Network of Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) deidentified patient-level data of all candidates listed for kidney transplant between 1 March 2002 and 31 December 2014. We analyzed renal registry data for all transplant candidates younger than 18 years (4 % were >18 at the time of transplant). Donor and recipient characteristics were reported at the time of transplant, and follow-up information was collected at 6 months and then yearly after transplantation for the period of study. Patients undergoing combined or multivisceral transplantations and candidates placed on the wait list for combined or multivisceral transplants were excluded from the study. A total of 11,488 patients were followed from the date of listing, and 8,757 candidates (76 %) received a transplant during the study period. All patients were followed to either death ($n = 709$) or the date of last known follow-up ($n = 10,779$).

Statistical analysis We analyzed data with Stata® 12 (Stata Corp, College Station, TX, USA). Continuous variables were reported as mean ± standard deviation (SD) and compared using Student's t test. Contingency table analysis was used to compare categorical variables. Results were considered significant at a p value of <0.05, and all reported p values were two sided.

For our wait-list analysis, candidates were followed from the time of listing to date of death on the transplant wait list, as established by the Social Security Death Masterfile and the UNOS death date. We used Kaplan-Meier analysis with log-rank test and Cox regression for time-to-event analysis. The primary outcome measure was death on the wait list. Time to death was assessed as the time from the date of listing to the date of death while on the wait list. Wait-list candidates who received a transplant were censored on the date of transplantation. We also performed a Fine-Gray competing risk regression analysis [26] where transplantation was the competing outcome. The primary outcome was death on the wait list. Candidates listed in programs that did not perform transplants in the study period were dropped from analysis. The transplant rate was calculated by including all candidates listed for transplantation during the study period. The outcome of interest for these candidates was transplantation, including both living- and deceased-donor transplants. Our approach does not account for short-term variations.

In our posttransplant patient survival analysis, we followed recipients from date of transplant to death. In our posttransplant graft survival analysis, we followed recipients from the date of transplant to the date of return to dialysis. We used Kaplan–Meier analysis with log-rank test and Cox regression for time-to-event analysis. The primary outcome measure was death after transplantation and time to death was assessed as the time from transplantation to the date of death. Recipients lost to follow-up or alive on 31 December 2014 were censored at the date of last known follow-up.

Patient survival, either on the wait list or posttransplant, was the dependent variable, and the risk factors were the independent variables in the regression analysis. Risk factors that were significant in univariate analysis ($p < 0.05$) were included in the multivariate analysis. Multivariate Cox regression was performed combining 100 bootstraps. We resampled observations with replacements from the data set 100 times in a method referred to as nonparametric bootstrapping.

Risk factors We considered multitude of donor and recipient risk factors as listed in Table 1.

Transplant centers Pediatric kidney transplant volume for each center was the average number of cases performed yearly from 2002 to 2014. Adult volume was not considered. Centers were categorized as low volume when their records showed fewer than three cases performed per year (Fig. 1). The slope

Table 1 Risk factors considered in univariate and multivariate analysis

Donor risk factors	Entry completion (%)	Recipient risk factors	Entry completion (%)	Center risk factors	Entry completion (%)
African American	100	Admitted to hospital	99.5	Center volume more than ten transplants per year	100
Age	100	ABO incompatible	100	Center volume six to ten transplants per year	100
Age >2 years	100	African American	100	Center volume three to five transplants per year	100
Cause of death		Age	100	Center volume fewer than three transplants per year	100
Anoxia	72.6	Age <2 years	100		
Cerebral vascular accident	72.6	BMI	98.9		
Cold ischemia time in hours	88.9	Diagnosis: lupus	100		
Creatinine	72.5	Dialysis	99.9		
Diabetes mellitus	96.7	HLA matching	99.6		
Donation after cardiac death	NA	Previous transplantation	100		
Donor BMI	98.6	Ventilator	100		
Donor weight (per kg)	99.1	Weight in kg	100		
Donor weight <6 kg	99.1	Weight <6 kg	98.6		
Female	100				
Liviing donor	NA				
National allocation	100				
Regional allocation	100				

BMI body mass index, *HLA* human leukocyte antigen, *NA* not applicable

of the curve was steepest between 0 and 3 cases per year. The other groups were categorized as rough multiples of three, with some concessions made to keep the number of centers comparable between groups. One hundred and ninety-five centers had listed children (<18 years) for kidney transplantation during the study period; 17 programs had greater than ten annual transplants, 23 had between six and ten, 32 had between three and five, and 123 had fewer than three.

To account for any geographic inequities in the supply and demand of kidney allografts for transplantation, we included the UNOS region of listing as a covariate.

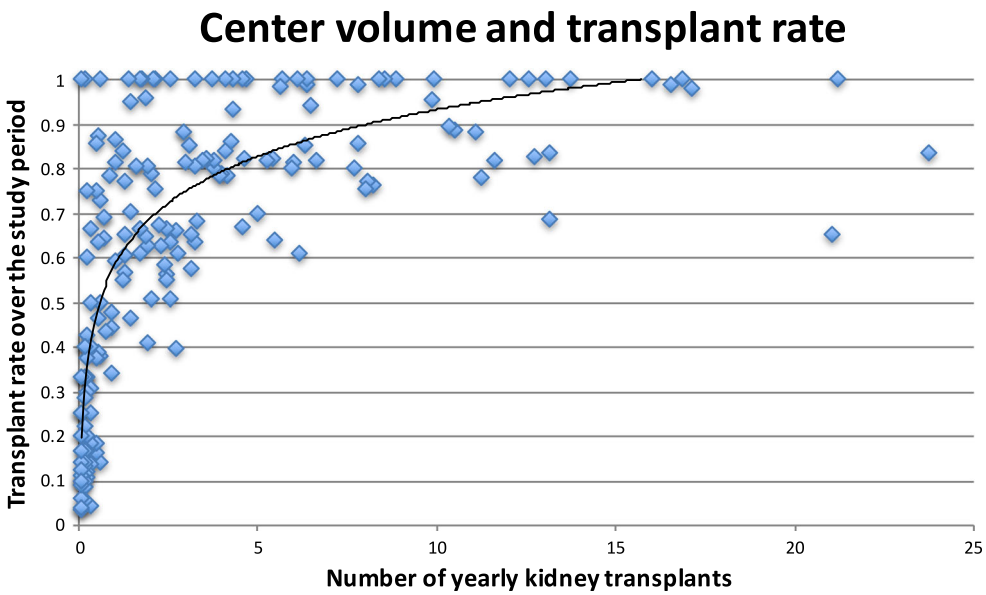

Fig. 1 Logarithmic trend line of transplant rate versus center volume in number of yearly transplants

Kidney allocation policy In the USA, cadaveric kidney grafts are allocated by geography, time on the wait list on dialysis, and recipient/donor age and expected survival. In brief, organs are first offered locally to one of 58 donor service areas, then to the larger region (comprising multiple states), then nationally. While time on the wait list is the main determinate for wait-list priority, pediatric recipients are given priority when the donor is younger than 35 years old. UNOS regions encompass several states and represent the next step in expanding the offer of an available organ. For instance, UNOS region 4 comprises Texas and Oklahoma, while region 10 comprises Indiana, Michigan, and Ohio [27]. Small-volume centers can meet the minimum requirements for accreditation for transplants performed yearly, and designation as a living-donor program is handled separately, e.g. a program can lose its living-donor status but maintain deceased donor privileges [28].

Inactive on the waiting list For patients listed but not transplanted during the study period, we analyzed the percentage of candidates who were inactive at the time of listing and at the most recent follow-up in order to investigate whether inactive candidates were affecting the transplant rate of the volume groups.

Missing variables Multiple imputation with predicted mean matching was performed for incomplete predictors in the UNOS/OPTN database (Table 1).

Results

Study population The study population for the wait-list survival analysis consisted of 11,488 candidates <18 years old. Wait-list analysis comprised 12,659 years-at-risk for the pediatric kidney transplant recipients. Mean wait-list follow-up was 1.2 years: 9 % of patients waited >3 years, for a mean wait time of 5.2 years; 41 % of candidates waiting >3 years had a previous transplant. The study population for the posttransplant patient survival analysis had 8,757 recipients; posttransplant patient survival analysis comprised 36,791 years-at-risk for kidney transplant recipients. Mean follow-up was 4.2 years. Demographic data are summarized in Table 2. Patient status at the end of follow-up is summarized in Table 3.

At the time of listing, candidates in low-volume centers were older compared with higher-volume centers (Table 2). At the time of transplant, recipients in low-volume centers were significantly older, taller, and weighed more than candidates listed in higher-volume centers (Table 2).

Data Entry Rate Data entry completion rates for variables are listed in Table 1. Most variables were well populated (>95 %). Multiple imputation with predicted mean values was performed for missing variables.

Transplant Rate Centers reporting more than ten transplants per year had a transplant rate of 88 %; those with six to ten per year, 89 %; three to five per year, 82 %; and fewer than three per year, 47 % (Fig. 2). Figure 1 shows the dot plot of the transplant rate for each center's transplant volume.

Wait-list survival analysis We considered recipient and center risk factors as listed in Table 1. Risk factors that were significant in univariate analysis were then subjected to multivariate analysis. Risk factors significant in multivariate analysis are presented in Table 4. The most significant risk factors were: listing in a center with transplant volume fewer than cases per year [hazard ratio (HR) 4.0, confidence interval (CI) 2.9–5.4] and recipient weight <10 kg (HR 2.5, CI 1.7–3.8). The Kaplan-Meier curve for wait-list survival is shown in Fig. 3.

Competing risk wait-list analysis We confirmed our Kaplan–Meier and Cox regression wait-list analysis with a competing risk analysis. The most significant risk factor in competing risk multivariate regression was also center volume <with fewer than three cases per year (HR 6.1, CI 4.4–8.5). Other significant risk factors were: recipient weight <10 kg (HR 2.8, CI 1.9–4.3), recipient age <2 years (HR 2.3, CI 1.6–3.4), UNOS region 2 (HR 1.4, CI 1.1–1.9), African American (HR 1.4, CI 1.1–1.8), male gender (HR 0.7, CI 0.6–0.9), and UNOS region 9 (HR 0.5, CI 0.2–0.8). Cumulative incidence of wait-list mortality from our competing risk analysis is shown in Fig. 4.

Posttransplant patient survival analysis In this analysis, center volume was not a significant risk factor for posttransplant patient survival. We considered the risk factors listed in Table 1, and those that with significant univariate analysis were then subjected to multivariate analysis. The risk factors significant in multivariate analysis are presented in Table 4. The most significant risk factor was the diagnosis of lupus (HR 2.4, CI 1.2–4.7): 48 % of the lupus recipients were African American and 88 % of all lupus patients were teenagers. In addition, lupus is a systemic disease with significant morbidity. Center volume was significant in univariate but not in multivariate analysis. The Kaplan–Meier analysis revealed no significant differences between volume groups: more than ten transplants per year 99 % 1-year survival, 98 % 3-year survival, and 97 % 5-year survival; six to ten transplants per year 99 % 1-year survival, 98 % 3-year survival, and 97 %

Table 2 Demographics

	More than ten transplants per year	Six to ten transplants per year	Three to five transplants per year	Fewer than three transplants per year
Number of centers	17	23	32	123
Listed candidates 2002–2014	3,785	2,600	2,003	3,100
Percent of total listed candidates	33.0 %	22.6 %	17.4 %	27.0 %
Transplanted recipients	3,334	2,312	1,646	1,465
Transplant rate	88.1 %	88.9 %	82.2 %	47.3 %*
% Living donor*	25.7 %	23.0 %	22.4 %*	12.3 %*
Waiting time in days, median (25–75th percentile)*	232 (9three to five01)	158 (61–366)*	132 (50–323)*	174 (66–403)*
Candidates at the time of listing				
African American*	19.9 %	23.6 %*	21.4 %	25.2 %*
Age (years)*	10.8 ± 5.5	11.0 ± 5.3	11.1 ± 5.4	11.8 ± 5.5*
Dialysis	58.4 %	63.1 %*	60.9 %	59.9 %
Male*	59.5 %	57.8 %	58.5 %	56.5 %*
Recipients at the time of transplantation				
African American*	19.0 %	23.5 %*	21.7 %*	24.2 %*
Age (years)*	12.0 ± 5.5	11.8 ± 5.3	12.0 ± 5.4	13.4 ± 4.8*
Under 2 year	9.2 %	7.9 %	8.6 %	4.1 %
Cold ischemia time (hours)	11.3 ± 10.5	10.8 ± 8.3	11.7 ± 8.7	11.1 ± 8.0
Diagnosis: dysgenesis*	10.9 %	12.8 %	8.7 %*	9.1 %
Diagnosis: FSGS	12.5 %	12.8 %	12.6 %	14.0 %
Diagnosis: obstruction	8.1 %	9.7 %	8.2 %	7.2 %
Dialysis	76.0 %	75.5 %	74.7 %	73.9 %
Donor age (years)	26.2 ± 11.0	26.1 ± 10.9	26.0 ± 11.7	26.2 ± 11.2
Height (cm)*	137.9 ± 30.1	137.3 ± 29.7	138.6 ± 30.0	147.5 ± 26.9*
Hospitalized	2.6 %	2.7 %	2.1 %	2.7 %
Peak PRA*	7.6 ± 20.5	9.8 ± 22.9*	9.6 ± 23.3*	9.9 ± 23.3*
Preemptive transplantation	24.0 %	24.5 %	25.3 %	26.1 %
Time from dialysis to listing (days)*	292.0 ± 597.7	402.8 ± 657.1*	362.2 ± 601.9*	349.3 ± 584.6*
Weight (kg)	42.4 ± 22.6	42.2 ± 23.0	42.9 ± 22.8	50.6 ± 23.6*
<10 kg	2.5 %	1.9 %	2.5 %	1.2 %*

FSGS focal segmental glomerulosclerosis, *PRA* panel-reactive antibody

* $P < .05$ compared with > 10 transplants per year

5-year survival; three to five transplants per year 99 % 1-year survival, 98 % 3-year survival, and 97 % 5-year survival; less than three transplants per year 99 % 1-year survival, 98 % 3-year survival, and 97 % 5-year survival.

Graft survival High-volume centers (more than ten transplants per year) had significantly better graft survival compared with centers with each of the other groups: six to ten transplants per year, three to five transplants per year, and fewer than three transplants per year ($p = 0.03$, $p = 0.06$, and $p = 0.002$; respectively, using the log rank test). In centers with more than ten transplants per year: 95 % 1-year survival, 88 % 3-year survival, and 80 % 5-year survival; six to ten transplants per year: 95 % 1-year survival, 85 % 3-year survival, and 76 % 5-year survival; three to five transplants per year: 95 % 1-year survival, 85 % 3-year survival, and 75 % 5-year survival; and fewer than three transplants per year: 94 % 1-year survival, 82 % 3-year survival, and 72 % 5-year survival.

Children younger than 2 years Although we found no differences in posttransplant survival, we determined that high-volume centers achieved the best wait-list survival for children <2 years when compared with all other groups (centers reporting six to ten, three to five, and fewer than three transplants per year with $p = 0.05$, $p = 0.001$, and $p < 0.001$; respectively using the log rank test). more than ten transplants per year: 95 % 1-year survival, 94 % 3-year survival, and 94 % 5-year survival; six to ten transplants per year: 92 % 1-year survival, 85 % 3-year survival, and 85 % 5-year survival; three

Table 3 Patient status at the end of follow-up (% all patients)

	More than ten transplants per year	Six to ten transplants per year	Three to five transplants per year	Fewer than three transplants per year
Alive after transplant*	86.1 %	86.6 %	80.1 %	46.0 %*
Dead after transplant*	2.0 %	2.4 %	2.0 %	1.2 %*
Alive without transplantation*	10.3 %	9.5 %	15.9 %*	45.0 %*
Transferred to another center	1.6 %	1.8 %	2.5 %*	9.2 %*
Condition improved	0.5 %	0.6 %	1.3 %	2.5 %*
Died on wait list*	1.7 %	1.5 %	1.9 %	7.8 %*

* $p < .05$ compared with > 10 transplants per year

to five transplants per year: 92 % 1-year survival, 90 % 3-year survival, and 90 % 5-year survival; and fewer than three transplants per year: 77 % 1-year survival, 74 % 3-year survival, and 69 % 5-year survival.

Inactive on the waiting list Among candidates who were listed but not transplanted during the study period, we found no significant differences in the percentage of candidates who were inactive at the time of listing or at their most recent follow-up: 41.2 % of candidates were inactive at the time of listing, and 52.9 % were inactive on most recent follow-up in centers reporting more than ten cases per year; 43.8 % at time of listing, 55.1 % at most recent follow-up for centers reporting six to ten cases per year; 38.7 % at time of listing, 54.9 % at most recent follow-up for centers reporting three to five cases; 41.8 % at time of listing, 53.5 % at most recent follow-up for centers reporting fewer than three cases.

Discussion

Investigators previously reported inferior posttransplant outcomes in low-volume kidney transplant programs [20]. Our analysis is unique in that it shows that the most pronounced outcomes differences are in patients on the wait list: 27 % of children waiting for a kidney transplant are listed in low-volume centers, which have a low transplant rate (49 % vs 88 % in higher-volume centers). Pediatric kidney candidates listed at these low-volume centers have a fourfold increased risk of dying while waiting for a kidney transplant (HR of 4.0, CI 2.9–5.4 in multivariate analysis). Our follow-up analysis of low-volume centers confirms that more patients actually die on the wait list in such centers. It is not clear from this registry-based data why the children are dying. The lack of granular data makes even speculation difficult. In addition, compared with high-volume centers, low-volume centers remove more patients from the list because of an improved medical condition (Table 3). Our analysis reports that low-volume centers have a significantly reduced proportion of living-donor

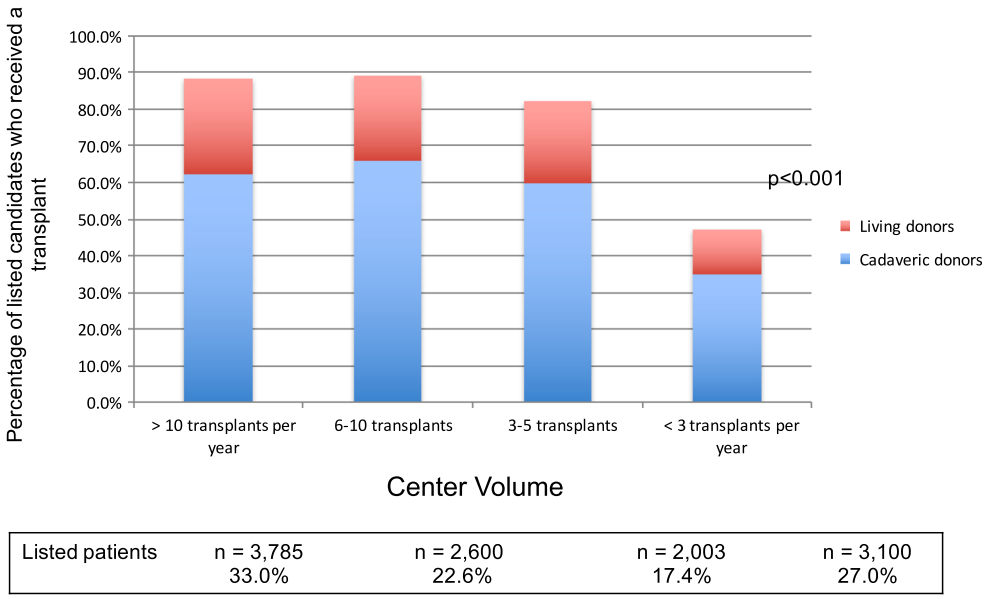

Fig. 2 Transplant rate by center volume. The transplant rates of centers with fewer than three transplants per year was significantly different from the transplant rates of the other centers ($p < 0.001$). The transplant rate is defined by the total number of people listed in the study period who went on to transplant

Table 4 Multivariate Analysis: Pediatric Kidney Transplant Waitlist Survival and posttransplant survival. Risk factors significant in univariate analysis are included. Univariate analysis is not shown

	HR	*P* value	CI
A. waitlist survival			
Risk factors (at the time of listing)			
Statistically significant			
Center volume: fewer than three transplants per year	3.95	0	2.91–5.36
<10 kg	2.54	0	1.69–3.82
<2 years old	2.31	0	1.57–3.40
Region 3	1.46	0.021	1.06–2.02
Male	0.65	0	0.52–0.80
Region 5	0.64	0.004	0.47–0.88
Region 9	0.42	0.006	0.23–0.78
Region 6	0.24	0.004	0.06–0.95
Not statistically significant			
African American	1.17	0.20	0.92–1.49
Region 2	1.13	0.38	0.85–1.51
Center volume: three to five transplants per year	1.13	0.10	0.98–1.30
Center volume: six to ten transplants per year	1.07	0.52	0.87–1.33
B. posttransplant survival			
Risk factors (at the time of transplant)			
Diagnosis: lupus	2.44	0.007	1.23–4.67
National share	1.73	0.041	1.02–2.94
<2 years	1.65	0.024	1.07–2.54
Dialysis dependent	1.51	0.026	1.05–2.18
Previous transplant	1.48	0.05	1.00–2.19
Region 3	1.43	0.05	1.01–2.04
Not statistically significant			
<6 kg	4.64	0.14	0.59–36.33
Live donation	1.66	0.49	0.40–6.95
1 HLA mismatch	1.32	0.49	0.60–2.92
African American	1.31	0.09	0.96–1.80
0 HLA mismatch	1.28	0.46	0.66–2.49
Center volume fewer than three transplants per year	1.15	0.52	0.76–1.73
Cold ischemia over 20 h	1.22	0.31	0.84–1.78
Center volume six to ten transplants per year	1.09	0.37	0.91–1.30
Center volume three to five transplants per year	1.03	0.64	0.90–1.18
Region 5	0.66	0.06	0.44–1.01
2 HLA mismatch	0.55	0.10	0.27–1.12
Donor creatinine > 2.0	0.54	0.39	0.13–2.19

HR hazard ratio, *CI* confidence interval, *HLA* human leukocyte antigen

transplants (Table 2). All of these factors contribute to the reduced transplant rate in low-volume centers. Paradoxically, we found longer waiting times in high-volume centers. This is difficult to explain and may represent regional variations.

The root causes behind these observed differences is difficult to identify given the currently available data in the OPTN database. It may be that the significant pressure to maintain posttransplant outcomes incentivizes low-volume centers with limited numbers to minimize risk by avoiding sicker candidates. Low-volume centers may have fewer nephrologists and facilities to manage the demanding needs of dialysis-dependent pediatric candidates. Additionally, low-volume centers may have fewer surgeons, resulting in limited availability for donor procurements and transplants [20]. On the other hand, poor access to pre-ESRD care may be a setup for poor wait-list outcomes in low-volume centers. Late treatment for chronic kidney disease in underserved areas may make children sicker when they present for

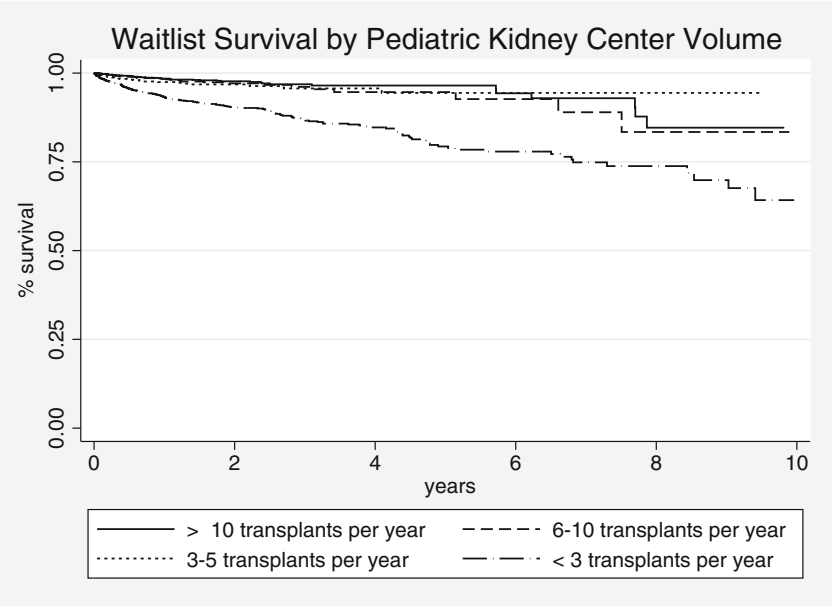

Fig. 3 Kaplan–Meier curve of wait-list survival versus pediatric kidney transplant center volume. *P* value < 0.01 for each group; log-rank test with reference to fewer than three transplants per year

transplant evaluation at low-volume centers [29]. We observed that candidates listed in low-volume centers had a higher degree of sensitization (peak panel-reactive antibody) compared with those in high-volume centers (Table 2).

The association between low-volume and poor outcomes has been established for a multitude of procedures across many fields [5–16], including the field of solid-organ transplantation [17–23]. The focus of this analysis on wait-list mortality frames an important consideration in volume studies: What patient outcomes lead to a particular procedure? Pre- and postprocedural outcomes in conjunction provide a more complete picture of the possible deficits in low-volume centers.

The significant difference between wait-list outcomes at low- versus higher-volume pediatric centers suggests that increased scrutiny should be paid to center transplant rates and wait-list mortality. Further studies are needed to substantiate these findings and explore the issues behind the discrepancies. This is not a trivial issue, since 27 % of all candidates are listed in low-volume centers, with an impaired transplant rate and a much greater chance of dying on the wait list. Access to transplantation should be incorporated in further analysis, since many low-volume centers are serving geographically isolated

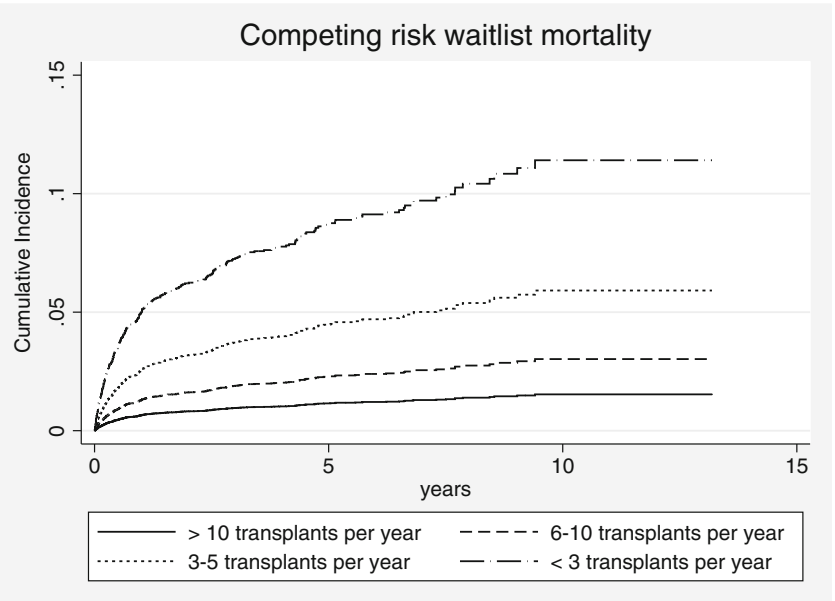

Fig. 4 Estimated cumulative incidence functions from competing risk analysis versus pediatric kidney transplant center volume. *P* value < 0.01 for each group, with reference to fewer than three transplants per year

populations. Many families simply do not have the resources to travel to be listed in high-volume centers.

Limitations

Since the passage of the National Transplantation Act of 1984, data entry has been mandatory for all US transplant centers. Nevertheless, all patient registries often suffer from variability in data entry. The findings from this study were based on large cohorts of patients and are unlikely to be significantly affected by small amounts of missing data. We attempted to account for missing data with multiple imputation analysis. A significant limitation was that candidates who were delisted in one center and relisted in another were given another patient identification number and were not linked to this analysis. We tried to account for this by using the waitlist removal code designating transfer to another center.

This data was generated from US transplant centers using the OPTN database and cannot be extrapolated to other countries.

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Compliance with ethical standards

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