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Brief Communication

Underutilization of Timely Kidney Transplants in Those With Living Donors

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Preemptive kidney transplant (PKTx) and kidney transplant (KTx) within 1 year of dialysis initiation have been associated with superior outcomes. Wait times should be minimal for transplants with living donors; however, there is lack of literature studying utilization of timely KTx in this population. We designed this retrospective study using data from United Network for Organ Sharing Standard Transplant Analysis and Research files from 2000 to 2012 to assess the trends in utilization of PKTx and Early KTx (combination of PKTx or transplant within 1 year of dialysis initiation) in recipients of living donor KTx. Only 32.6% transplants were PKTx, and 61.9% were Early KTx. A significant improvement in proportion of PKTx was seen from 27.5% in 2000 to 35.4% in 2006, with no change since. Similarly, the proportion of Early KTx increased from 61.4% in 2000 to 63.6% in 2006, with no increase since. Similar results were seen after adjusted analysis and were independent of living donor type. Although there was some improvement in utilization of timely transplants in the early part of the last decade, there has been no improvement since. Considering the benefits of timely kidney transplant, it is important to understand the reasons behind the same and to improve utilization.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; cPRA, calculated panel reactive antibodies; ESRD, end-stage renal disease; KTx, kidney transplant; PKTx, preemptive kidney transplant; USRDS, United States Renal Data System

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Introduction

More than 600 000 Americans suffer from end-stage renal disease (ESRD) (1). Dialysis and kidney transplantation are the mainstays of renal replacement therapy for these patients. Kidney transplantation is preferable to dialysis for several reasons. Patient survival is significantly greater with kidney transplantation (2). In addition, quality of life is better after a successful kidney transplant (KTx), and overall health care costs are lower (3–5). The majority of ESRD patients wait for many years for a KTx from the deceased donor pool. Living donor kidney transplantation is an alternative that is not only superior to deceased donor kidney transplantation, with less acute rejections and better long-term graft survival (6), but also has the potential to avoid long wait times associated with deceased donor waitlists. Living donors also provide an opportunity for transplantation before initiation of maintenance dialysis, that is, *preemptive* kidney transplantation (PKTx).

PKTx has been associated not only with superior patient survival (7–10) but also with better death-censored allograft survival (7,9), better quality of life (11), a higher rate of return to work (12,13), and overall lower medical expenditure (13) in comparison to transplants performed after starting dialysis. Although dialysis is a life-saving therapy, it is associated with significant morbidity and mortality, especially related to cardiovascular disease and infections (14,15). By avoiding chronic dialysis, PKTx can avoid such associated complications. Few studies, however, have shown that if transplantation can be performed within 1 year of initiating dialysis, outcomes may still be comparable to those of PKTx (7,9).

PKTx composes a small proportion of transplants in the United States (16). The reasons are varied and include delayed diagnosis of chronic kidney disease (CKD), delayed referral to nephrology or transplant, lack of education or knowledge, and delay in identifying and evaluating living donors (17,18). For those who are transplanted from living donors, wait times for transplants should be minimal, with the majority being transplanted preemptively. We designed this study to look at the utilization and trends of PKTx in

those undergoing living donor KTx. Because patients who receive a KTx within 1 year of initiation of dialysis may still have outcomes comparable to those with PKTx, we also looked at the proportion and trends of those receiving KTx as a combination of preemptive or within 1 year of dialysis initiation (Early KTx).

Materials and Methods

Study design

We designed a retrospective cohort study for adults undergoing living donor KTx, using data from the United Network for Organ Sharing Standard Transplant Analysis and Research files.

Study population

We included recipients of living donor KTx from January 2000 to December 2012 who were aged ≥18 years at the time of transplant. Recipients of multiorgan transplants were excluded. As kidney paired exchange and list exchange are used primarily to circumvent the issue of incompatible living donors and thus can experience delayed transplants in comparison to those with compatible living donors, they were excluded from the study. We included those on dialysis before transplant with available dialysis initiation date before the date of KTx and those with available living donor type (living related or unrelated) information.

Study variables

Those with PKTx were identified based on missing dialysis initiation date and ''no'' as the response to the question, ''Pretransplant Dialysis,'' on the transplant recipient registration form. Pretransplant dialysis time was calculated as the difference between transplant date and dialysis initiation date in those who responded ''yes'' to the same question.

Outcomes

The primary outcome of interest was the proportion of those with PKTx among recipients of living donor KTx. In addition, we calculated the proportion of those who received Early KTx, defined as receiving a KTx either preemptively or within 1 year of dialysis initiation. Trends for proportions of PKTx and Early KTx over time were also assessed. Finally, we calculated odds for receiving PKTx and Early KTx over time in models adjusted for both donor and recipient characteristics.

Statistical analysis

All statistical analyses were performed using Stata 13.1 (StataCorp, College Station, TX). The chi-square test was used to compare categorical variables, and the t-test was used to compare continuous variables. Linear regression was used to assess trends of PKTx and Early KTx over time. To allow for nonlinear relationship between proportions of PKTx or Early KTx and time period, time period was modeled by linear splines. The knot placement for splines was estimated based on the location that yielded the lowest residual sum of squares (19). The location was then rounded off to the nearest whole number for the year of transplant. The independent effect of year of transplant on proportions of PKTx and Early KTx was assessed using separate multivariable logistic regression models with PKTx and Early KTx as dependent variables. All clinically relevant variables including both donor and recipient characteristics were used in the final multivariable models. To assess whether the effect of year was different by living donor type (related vs. unrelated), an interaction between living donor type and year of transplant was checked. For most variables, missing data were <5% except for donor BMI (7.8%), recipient functional status at the time of listing (7.8%) and recipient education (13.8%). Casewise deletion was used to handle missing data. To confirm that this method of missing data handling did not affect our results, we did a sensitivity analysis using logistic regression models with missing values for each variable recoded as *missing categories*.

Because calculated panel reactive antibodies (cPRA) only began to be reported in December 2007, separate models with cPRA were fitted for those with available cPRA data and including all the other covariates included in the initial multivariable logistic regressions to assess the odds of PKTx and Early KTx over time. An interaction term between living donor type and year of transplant was checked to assess whether the effect of year was different by living donor type (related vs. unrelated). To assess whether odds for PKTx or Early KTx differed for different cPRA categories (0, 0–20, 21–80, >80), an interaction term between cPRA and year of transplant was looked for in both models.

Results

Patient characteristics

A total of 68 128 patients who received a living donor KTx were included in the study. Overall, 63.7% of living donor transplant recipients received transplants from a living related donor. Of the recipients, 32.2% (21 977) had available cPRA values at the time of transplant, of which 78.4% had zero cPRA.

As shown in Table 1, those who received PKTx were older (mean age 47.8 ± 13.5 vs. 46.3 ± 14.0 years for those without PKTx; $p < 0.001$), more often female and white in comparison to those who did not receive a preemptive transplant. Those with preemptive transplants also tended to have A blood group, have no history of diabetes, be first-time transplant recipients, have an education level of college or higher, have private insurance as the primary payer and polycystic kidney disease as the cause for ESRD in comparison to those who did not receive PKTx. Donors for those with preemptive transplants were older (mean age 42.1 ± 11.1 vs. 40.2 ± 11.3 years for those without PKTx; $p < 0.001$), white and A blood group in comparison to those who did not receive PKTx.

Similarly, recipients who received Early KTx (Table 2) were younger (mean age 46.6 ± 13.8 vs. 47.0 ± 14.0 years for those without Early KTx; $p < 0.001$), were white, had A blood group, had no history of diabetes, were first-time transplant recipients, had highest education of college or higher, had private insurance and had polycystic kidney disease as the cause for ESRD compared with those who did not receive Early KTx. Their donors tended to be older (mean age 41.5 ± 11.1 vs. 39.7 ± 11.4 years for those without Early KTx; $p < 0.001$), white and A blood group compared with those who did not receive Early KTx.

Incidence and trends of PKTx and Early KTx

Only 32.6% of recipients transplanted with a living donor had a PKTx. In total, 61.9% were transplanted either preemptively or within 1 year of dialysis initiation (Early KTx), and 38.1% were transplanted after ≥1 year on dialysis.

Table 1: Baseline characteristics of those who received and did not receive PKTx

Characteristics		Non-PKTx[1] n = 45 924 (%)	PKTx[1] n = 22 204 (%)	p-value
Recipient age group (years)	≤30	16.5	12.5	<0.001
	31–44	27.4	26.4	
	45–64	45.9	50.0	
	≥65	10.2	11.1	
Donor age group (years)	≤30	23.0	17.3	<0.001
	31–44	40.4	39.3	
	45–64	35.4	41.7	
	≥65	1.2	1.7	
Recipient sex	Female	38.9	41.5	<0.001
Donor sex	Female	59.9	59.7	0.69
Recipient race	White	62.1	79.2	<0.001
	Black	16.7	8.7	
	Hispanic	15.3	8.0	
	Others	5.9	4.1	
Donor race	White	64.4	79.9	<0.001
	Black	15.1	8.1	
	Hispanic	15.3	8.2	
	Others	5.2	3.8	
Recipient BMI	<18.5	3.1	2.6	<0.001
	18.5–24.9	35.8	34.7	
	25.0–29.9	31.7	33.8	
	30.0–34.4	18.7	19.4	
	≥35.0	9.4	7.7	
Donor BMI	<18.5	0.9	1.1	<0.001
	18.5–24.9	31.7	33.4	
	25.0–29.9	37.3	38.0	
	30.0–34.4	18.0	15.8	
	≥35.0	4.4	3.4	
Recipient ABO	A	37.1	41.0	<0.001
	B	13.2	11.9	
	O	3.5	4.3	
	AB	46.2	42.8	
Donor ABO	A	24.8	27.9	<0.001
	B	7.6	7.1	
	O	0.8	0.9	
	AB	66.8	64.1	
Recipient with diabetes		29.9	23.6	<0.001
Recipient with previous kidney transplant		9.4	7.5	<0.001
Recipient education	Grade school or less	4.2	1.9	<0.001
	High school	36.9	29.3	
	College or higher	45.0	55.3	
Recipient insurance	Public	48.2	22.7	<0.001
	Private	51.0	76.1	
	Others	0.8	1.2	
Recipient with malignancy history		4.7	5.1	0.03
Recipient functional status	Good	79.5	84.3	<0.001
	Impaired	12.8	7.7	
Recipient ESRD diagnosis	GN	27.4	27.4	<0.001
	Diabetes	23.5	17.8	
	HTN	18.6	13.2	
	PKD	7.2	17.0	
	Others	22.3	23.8	

ESRD, end-stage renal disease; GN, glomerulonephritis; HTN, hypertension; PKD, polycystic kidney disease; PKTx, preemptive kidney transplant.
[1]Column percentage total may not add to 100% for missing values.

A significant improvement in the proportion of PKTx was observed from 27.5% in 2000 to 35.4% in 2006; however, the proportion of PKTx has not changed significantly since then. Similarly, the proportion of Early KTx increased from 61.4% in 2000 to 63.6% in 2006, but there has been no significant change in that since (Figure 1). On adjusted analysis, the odds of PKTx increased until 2006, with no significant increase since (Figure 2A). Similarly, the adjusted odds of Early KTx increased until 2006, after which no significant increase

Table 2: Baseline characteristics of those who received and did not receive Early KTx

Characteristics		Nonearly KTx[1] n = 25 977 (%)	Early KTx[1] n = 42 151 (%)	p-value
Recipient age group (years)	≤30	15.6	14.9	<0.001
	31–44	26.3	27.6	
	45–64	47.0	47.4	
	≥65	11.1	10.1	
Donor age group (years)	≤30	24.4	19.0	<0.001
	31–44	40.6	39.8	
	45–64	33.8	39.7	
	≥65	1.2	1.5	
Recipient sex	Female	39.5	39.9	0.42
Donor sex	Female	60.2	59.7	0.17
Recipient race	White	55.5	75.2	<0.001
	Black	20.1	10.4	
	Hispanic	17.9	9.8	
	Others	6.5	4.6	
Donor race	White	58.2	76.4	<0.001
	Black	18.1	9.6	
	Hispanic	17.9	9.9	
	Others	5.8	4.1	
Recipient BMI	<18.5	2.9	2.9	<0.001
	18.5–24.9	35.3	35.6	
	25.0–29.9	31.0	33.3	
	30.0–34.4	19.3	18.7	
	≥35.0	10.3	7.9	
Donor BMI	<18.5	0.9	1.0	<0.001
	18.5–24.9	31.1	32.9	
	25.0–29.9	36.9	37.9	
	30.0–34.4	18.7	16.5	
	≥35.0	4.6	3.7	
Recipient ABO	A	35.0	40.4	<0.001
	B	14.0	12.1	
	O	3.2	4.1	
	AB	47.8	43.4	
Donor ABO	A	23.4	27.3	<0.001
	B	7.8	7.2	
	O	0.7	0.9	
	AB	68.1	64.6	
Recipient with diabetes		30.9	25.9	<0.001
Recipient with previous kidney transplant		9.1	8.5	0.005
Recipient education	Grade school or less	5.2	2.3	<0.001
	High school	38.9	31.6	
	College or higher	41.2	52.8	
Recipient insurance	Public	59.4	27.9	<0.001
	Private	39.9	71.0	
	Others	0.7	1.1	
Recipient with malignancy history		5.2	4.6	0.002
Recipient functional status	Good	77.8	83.1	<0.001
	Impaired	13.9	9.4	
Recipient ESRD diagnosis	GN	26.0	28.2	<0.001
	Diabetes	24.3	19.9	
	HTN	21.2	14.2	
	PKD	5.8	13.3	
	Others	21.7	23.5	

ESRD, end-stage renal disease; GN, glomerulonephritis; HTN, hypertension; KTx, kidney transplant; PKD, polycystic kidney disease.
[1]Column percentage total may not add to 100% for missing values.

was noted (Figure 2B). Similar results were seen when missing values of each variable were recoded as missing categories (Figures S1A and B). The interaction term between variables for living donor type and year of transplant was not significant in either regression model ($p = 0.9$ in the model with PKTx as a dependent variable and $p = 0.3$ in the model with Early KTx as a dependent variable).

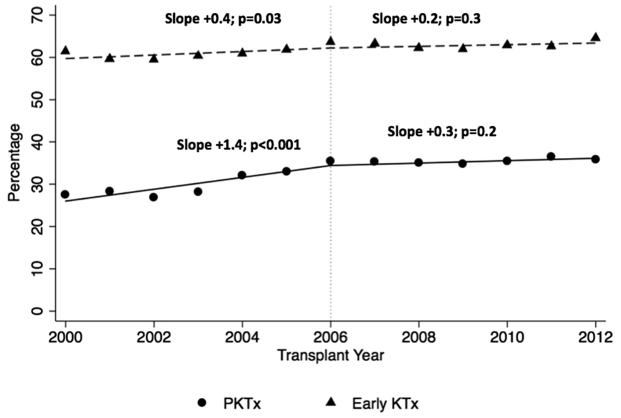

Figure 1: Trends for PKTx and Early KTx. Vertical dotted line at year 2006 shows the inflection point for linear splines. PKTx, preemptive kidney transplant; KTx, kidney transplant.

When cPRA was included in the multivariable model for regression, no significant difference was observed in the odds of receiving PKTx or Early KTx over time (Figures 2C and D). The interaction term between the variable for living donor type and year of transplant was not significant in either model ($p = 0.9$ in both models with the PKTx or Early KTx as dependent variable). Similarly, the interaction term between cPRA and year of transplant was not significant ($p = 0.5$ in the model with PKTx as a dependent variable and $p = 0.2$ in the model with Early KTx as a dependent variable), suggesting a similar effect of year regardless of cPRA.

Discussion

Using national data of living donor KTx recipients, we showed that only one-third have undergone PKTx and less

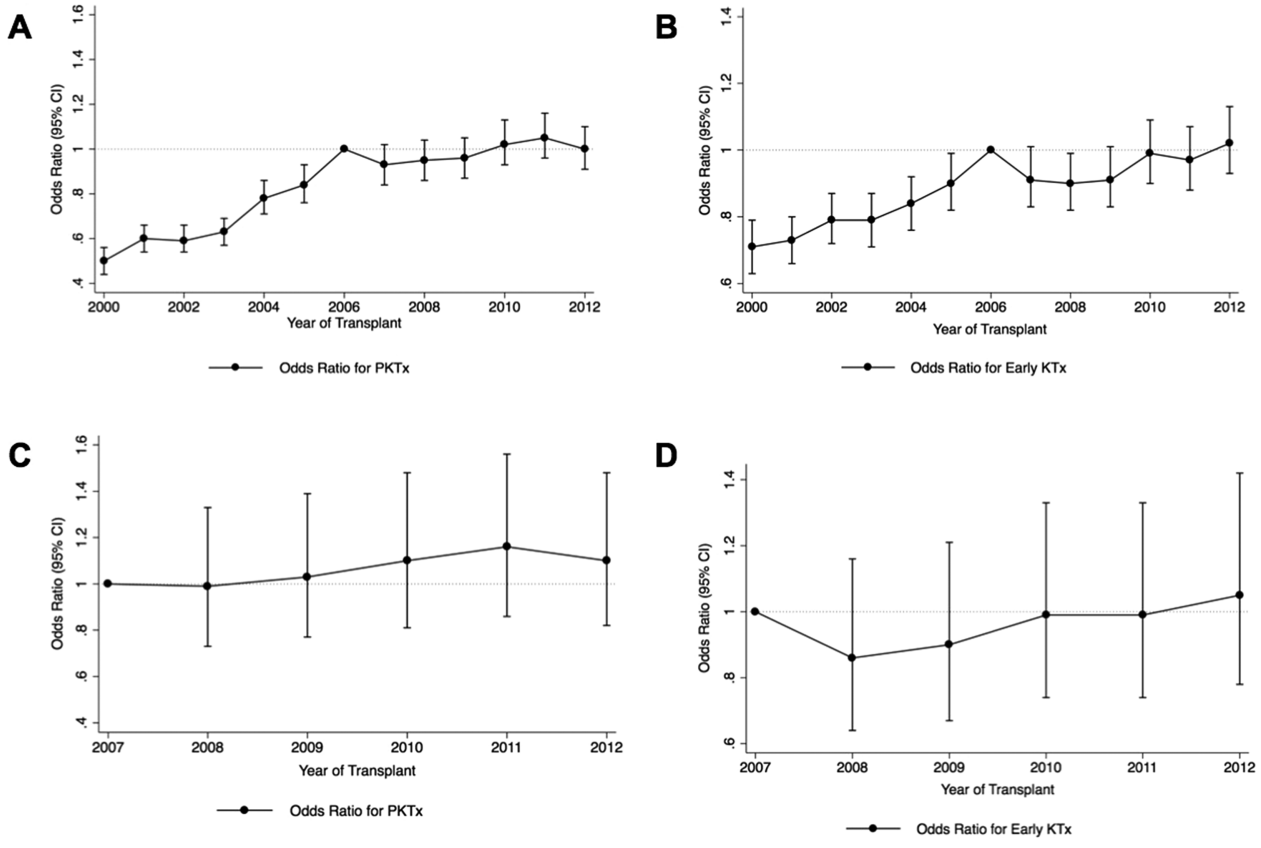

Figure 2: Adjusted odds ratios for receiving PKTx or Early KTx. (A, B) Odds ratios for receiving PKTx (A) or Early KTx (B) were adjusted for recipient age, sex, race, BMI, blood group, diabetes history, insurance, ESRD diagnosis, history of previous kidney transplants, history of any malignancy, functional status at the time of listing, highest education, donor age, sex, race, BMI, blood group, living donor type, and year of transplant. (C, D) Odds ratios for receiving PKTx (C) or Early KTx (D), with model adjusted for cPRA, were adjusted for recipient age, sex, race, BMI, blood group, diabetes history, insurance, ESRD diagnosis, history of previous kidney transplants, history of any malignancy, functional status at the time of listing, highest education, donor age, sex, race, BMI, blood group, living donor type, cPRA, and year of transplant. CI, confidence interval; cPRA, calculated panel reactive antibodies; ESRD, end-stage renal disease; KTx, kidney transplant; PKTx, preemptive kidney transplant.

than one-third were transplanted within 1 year of dialysis initiation. We also showed that the proportions of PKTx and overall Early KTx increased until 2006 but they have not seen any significant rise since then on both unadjusted and adjusted analysis. The effect appeared to be similar regardless of living related or unrelated donors and after adjustment for cPRA.

PKTx has been shown to be associated with improved patient survival compared with those staying on dialysis before transplant. Using national data from United States Renal Data System (USRDS), Meier-Kriesche et al (7) showed that being on dialysis before transplant negatively affected patient survival in a dose-dependent manner, especially for those on dialysis >6 mo. Similarly favorable effects of PKTx on patient survival have been shown in later studies by Goldfarb-Rumyantev et al using USRDS data (9) and by Milton et al using the Australian and New Zealand Dialysis and Transplantation Registry (10). However, Goldfarb-Rumyantev et al showed that the impact of pretransplant dialysis on posttransplant patient survival becomes significant only after 1 year of chronic dialysis. The literature though seems to support the finding that spending >1 year on dialysis before transplant adversely affects patients' posttransplant survival. Consequently, our results assume greater importance and cause for concern because there appears to have been no significant improvement in proportions of both PKTx and Early KTxs since 2006.

It is interesting to note that although there has been a trend to provide earlier PKTx (20), based on the results of our study, this does not seem to have translated into increasing proportions of PKTx. Some important reasons for lower numbers of preemptive transplants have been thought to be lack of availability of living donors, lack of insurance, lack of education or knowledge, delayed diagnosis of CKD, and delayed referral for transplant (17,18). We tried to mitigate the first issue by restricting our sample to only those transplanted using living donors outside of kidney paired exchange. There has been an overall decrease in living donors since 2004 (21), and that has been thought to contribute to a low proportion of PKTx (22); however, because we included only the recipients of living donor KTx, this should not have affected our results. We controlled for presence and type of health insurance held by recipients and attempted to control for overall education status of the recipient in our adjusted regression model; however, that may not be a true reflection of a patient's health literacy. Lack of education or knowledge about transplant is difficult to assess in the database used, as is to assess the impact of delayed diagnosis or CKD or delayed referral, but by including those who were transplanted after being on dialysis for almost 1 year, we expected that the effect of those factors would have been mitigated to some extent through education and referral provided by dialysis centers. Dialysis centers have a requirement to discuss transplants with all patients and to provide referral if the patient agrees.

Although timing of referral for KTx is not provided in the database, we found that the proportions of PKTx and Early KTx were highest among those who were not on dialysis at the time of listing and lowest among those who were on dialysis for ≥6 mo at the time of listing (Table S1). When dialysis status at the time of listing was added as a variable in regression analysis with Early KTx as the dependent variable, the odds of Early KTx were much lower among those on dialysis for <6 mo and lowest among those on dialysis for ≥6 mo at the time of listing in comparison to those who were not on dialysis at the time of listing (Table S2). This points to the fact that earlier listing is likely associated with earlier transplants in those with living kidney donors. Because earlier referrals could lead to earlier listings, we could extrapolate these findings to say that earlier referrals could potentially result in earlier transplants. This analysis, however, needs to be interpreted with caution because 25.3% of those transplanted were never listed, and listing time may not necessarily correlate with referral time. Other factors such as accommodation of donor schedule can also lead to transplant not being done preemptively.

The implications of lack of improvement in preemptive transplants are concerning. In addition to survival benefit, preemptive transplants have been associated with improved death censored allograft survival (7,9), better quality of life (11) and overall lower overall medical expenses (13). These benefits further highlight the importance of directing attention toward attempts to increase preemptive transplants. Given the fact that these are the patients who have willing living donors from whom they would be transplanted, every effort should be made to increase the chances of a preemptive transplant or at least transplant as soon as possible after initiating chronic dialysis. It is important to note that maintaining a fine balance between how long to wait for a transplant and not waiting for too long is important because earlier transplant may not necessarily mean better (20) and could result in premature exposure to immunosuppression.

Even though we used a national database, our study has some limitations. This is a retrospective study and thus is prone to selection bias. Even though we attempted to adjust for confounding variables that could affect the chances of PKTx or Early KTx, many unreported or, in some cases, unidentifiable characteristics could have affected our results. As discussed, patients' transplant literacy, delayed diagnosis of CKD or delayed referral for transplant could not be accounted for in the study; however, we would have expected these characteristics to improve over the study period, leading to an increasing proportion of PKTx and Early KTx. Patients with incompatible living donors are increasing being enrolled in kidney paired exchange programs (23). We excluded these recipients because they may need to wait to find a compatible living donor, and that could lead to understandably increased wait times and potential loss of the opportunity for PKTx or Early KTx that

may bias our results. Only a few centers enroll compatible recipient donor pairs in kidney paired exchange programs. We were not able to identify patients undergoing desensitization that could lead to similarly longer wait times and potential loss of opportunities for PKTx or Early KTx; however, desensitization is practiced by only selected centers and thus should not have affected our results significantly. In addition, there seemed to be similar lack of increase in adjusted odds for PKTx and Early KTx for all levels of cPRA over time, further confirming our results. Because center-level data are not available in the database studied, we were not able to account for the clustering due to individual center practices in our analysis.

In summary, we have shown that PKTx accounts for only about one-third of total living donor KTxs, and less than two-thirds of living donor transplants are performed preemptively or within 1 year of chronic dialysis initiation. The proportion of both PKTx and Early KTx increased in the earlier part of last decade but has been stagnant since. Further studies are needed to understand the reasons behind the same and to improve the utilization of PKTx and Early KTx, especially in those who are ultimately transplanted using living donors.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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Supporting Information

Additional Supporting Information may be found in the online version of this article.

Table S1: Proportion of preemptive and early kidney transplants by dialysis status at the time of listing.

Table S2: Independent effect of dialysis status at the time of listing on odds of getting an early kidney transplant.

Figure S1: Adjusted odds ratios for receiving PKTx (A) or Early KTx (B) while including missing values of each variable recoded as ''missing'' categories. Odds ratios were adjusted for recipient age, sex, race, BMI, blood group, diabetes history, insurance, ESRD diagnosis, history of previous kidney transplants, history of any malignancy, functional status at the time of listing, highest education, donor age, sex, race, BMI, blood group, living donor type, and year of transplant. ESRD, end-stage renal disease; KTx, kidney transplant; PKTx, preemptive kidney transplant.