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Increasing Incidence of New-onset Diabetes after Transplant among Pediatric Renal Transplant Patients ¹

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Abstract

Background—Risk of new-onset diabetes after transplant (NODAT) is well characterized for adults but much less understood in pediatric transplant. This study examines the incidence and risk factors of NODAT in pediatric renal transplant patients.

Methods—The incidence of NODAT over the first three years following transplant were examined with United States Renal Data System data for primary renal transplant recipients (ages 0–21 years, transplanted between 1995 and 2004) with Medicare primary. Patients had no evidence of diabetes prior to transplant. We estimated the cumulative incidence rate and used Cox proportional hazards regression to identify risk factors for NODAT. Propensity scores were calculated for immunosuppression choice to adjust for potential confounding factors.

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Results—2168 recipients with valid immunosuppression records and without pretransplant evidence of diabetes were included. Unadjusted, cumulative NODAT incidence at three years posttransplant was 7.1%. Significant factors for increased risk of NODAT included Cytomegalovirus D+/R− serostatus (adjusted hazard ratio (aHR)=1.60), age 13–18 years (aHR=2.18), age 19–21 years (aHR=2.60), body mass index ≥ 30 (aHR=2.17) and use of tacrolimus (aHR=1.51). We failed to find any significant relationships between NODAT and graft failure/death.

Conclusions—While the incidence of NODAT among patients 0–21 years of age is lower than that for adult patients, it is higher than suggested by earlier research and may represent an increase over time. The lack of association between NODAT and graft/failure death has important implications for post-transplant care. A clearer understanding of risk factors can help guide posttransplant monitoring and clinical decision making.

Keywords

renal transplantation; pediatric transplantation; immunosuppression; posttransplant diabetes

Introduction

The development of new-onset diabetes after transplant (NODAT) is a major clinical concern following kidney transplantation and has been shown to be strongly associated with reduced graft function, increased cardiovascular morbidity and lower patient survival among adult recipients (1–6). The incidence of NODAT is estimated to be 15–20% within the first year of transplantation and as high as 25% within the first three years (1,2,7–10). The rate of diabetic complications is also considerably higher for patients developing diabetes mellitus (DM) after transplant than it is for the general population of persons with DM (7).

Although there has been much investigation of the development and consequences of NODAT among adults, relatively few studies have examined NODAT among pediatric patients (11–17) and these studies have yielded inconsistent results. Early work suggested that pediatric recipients were at a significantly lower risk of NODAT compared to their adult counterparts (1). Data from the North American Pediatric Renal Transplant Cooperative Study suggested an overall incidence rate of 2.6% among 1365 children transplanted between 1992 and 1997 (11) which is considerably lower than the 15–20% reported for adults (1,2,7–10). The strict definition of NODAT used in this pediatric study (i.e., requiring at least 2 weeks of insulin following transplant) may have led however to an underestimation of the true incidence of NODAT in children. A number of smaller studies have been conducted, but the results have been inconsistent, with rates of NODAT ranging from 2–20% (12–16). Further, research by Greenspan and colleagues suggests that there has been significantly increasing trend in the incidence of pediatric NODAT during the 13 years ending in 1999 (17). Their retrospective analysis of 229 pediatric transplants found incident rates of 2.1% in 1986–1990, 3.7% in 1991–1995 and 20% in 1996–1999. There are a number of factors that may have contributed to these inconsistencies including differences in patient populations, study design and definition of NODAT.

The current study sought examine the development and consequences of NODAT among pediatric renal transplant patients with Medicare primary in a large, recent national sample described in the United States Renal Data System (USRDS). More specifically, our objectives were to: 1) determine the incidence of NODAT in children after renal transplantation in 1995–2004 and whether this has changed over time; 2) identify risk factors associated with the development of NODAT and 3) to determine the impact of NODAT on graft failure and patient survival in children.

Materials and Methods

Data Sources

Data were obtained from the USRDS registry which includes data from the United Network for Organ Sharing (UNOS) and from Medicare billing claims records. Immunosuppressive regimens at discharge were identified using prescription payments in Medicare billing records supplied by USRDS.

Inclusion/Exclusion Criteria

All recipients of a first renal transplant between 1995 and 2004, who were younger than 22 years on the date of transplant and who had Medicare Parts A and B primary at the time of transplant were included. This time period was selected because in 1995 UNOS expanded the quantity of data elements collected, allowing inclusion of more predictive factors in the model. The year 2004 was selected as the final year for inclusion because it was the last year for which Medicare data were available. Patients were excluded if they had any evidence of DM prior to transplant, received a multi-organ transplant, or had received a prior transplant

As developed and validated previously (1,2,9,32), diagnosis of NODAT required that a patient have a minimum of one Medicare inpatient claim or two outpatient claims separated by no more than one year (ICD-9-CM codes 250, 250.0–250.93) with the first code for DM occurring after the point of transplant. The date of onset of NODAT was specified as the date of the first claim. Data were censored at the date of graft failure, death or at three years of follow-up, since this was the maximum follow-up period available for this cohort of transplant patients

Statistical Analysis

Kaplan-Meier analyses were used to identify the recipient factors (e.g., age, body mass index (BMI), race) and immunosuppression factors (calcineurin inhibitor (CNI), azathioprine, basiliximab/daclizumab, mycophenolate mofetil, murine anti-CD3 monoclonal antibody (OKT3), sirolimus and thymoglobulin) associated with the development of DM. Cox proportional hazards regression analyses were used to examine the multivariate relationships between these risk factors and the development of NODAT. Time-series analyses were censored for end of eligible coverage, 3-year follow-up, and (where appropriate) graft failure and death. The unadjusted accumulated incidence of each complication was calculated for each day posttransplant using the product-limit (Kaplan-Meier) method (18). The incidence levels at each day reflected the accumulated incidence level of the previous day plus the new incidence (e.g. number of new diagnoses divided by the numbers of subjects without an ICD-9-CM report of NODAT on that day).

Since assignment of patients to CNI was not randomized, propensity scores were generated in order to adjust for underlying characteristics that might have biased assignment of patients to tacrolimus (TAC) or cyclosporine A (CsA) at discharge. Chi-square tests to determine whether choice of CNI was associated with any recipient factor (age, gender, race, cadaveric donor status, hypertension, human leukocyte antigen matching, Cytomegalovirus seropairing and cold ischemia time). The propensity score (propensity for choice of TAC compared to CsA) was then calculated using logistic regression with stepwise selection (19) and then categorized into quintiles and used along the year of transplant to stratify the final Cox analysis. This approach was designed to adjust for any selection biases related to the choice of CNI (18). Adjusted hazard ratios (aHRs) were calculated to evaluate risk in Cox regression models. Forced entry of CNI was used in all Cox regression models, and was also used with a time-varying variable of NODAT diagnosis in outcome models that included graft failure, death and death-censored graft failure. All Cox regression models were stratified by year.

All analyses were performed using SAS for Windows software, version 9.1 (SAS Institute Inc., Cary, NC, USA). Differences were considered statistically significant at a 2-sided $P < 0.05$ level.

Results

Population Characteristics

A total of 2168 pediatric renal transplant recipients (age 0–21 years) without DM pretransplant and with Medicare A&B primary were included in this study (Table 1). Of the 2452 pediatric transplant patients in the USRDS, 88.4% ($n=2168$) had Medicare A&B primary were included in this analysis. The mean age at transplant was 14.7 years. 26.9% were black, and males and females were nearly equally represented (46.0% female). The mean BMI at the point of transplant was 21.5 and did not change over the 10 years under observation ($P=0.511$). Donors were an average age of 31.7 years and 50.7% were male. 54.8% of transplants were performed with kidneys from cadaveric donors. Use of induction agents among patients included 70.9% for basiliximab/daclizumab, 9.2% for OKT3 and 18.0% for thymoglobulin. At the point of discharge 1136 patients received CsA, 827 TAC, and 177 received neither. Assignment of CNI at discharge varied significantly based on multiple recipient factors, BMI ($P=0.003$), gender ($P=0.009$), percent reactive antibody (PRA) ($P < 0.001$) and pretransplant dialysis ($P=0.026$).

Factors Associated with Development of Diabetes Mellitus

Censored at three years following transplantation, NODAT was newly diagnosed in 7.1% (154 of 2168) of children. Mean length of follow-up was 736.5 days (Median=940.0). Although DM incidence rates appeared to rise by year, this result did not reach statistical significance ($P=0.093$, Figure 1). Univariate analysis (Table 2) found that the incidence of NODAT increased with the age of the child at transplant ($P < 0.001$) and was higher for children with BMI ≥ 30 ($P < 0.001$) and those of black race ($P=0.006$). In comparing TAC and CsA, we found that children receiving CsA had lower rates of NODAT than those patients who received TAC ($P=0.020$ (Figure 2)). NODAT was also associated with the use of azathioprine ($P=0.014$). When all of the patient, donor and transplant factors were combined in a single multivariate analysis (with propensity adjustment for CNI assignment), a subset of variables was found to be statistically associated with the development of DM (Table 3). These included increased age (13–18 years, aHR=2.18; 19–21 years, aHR=2.60), BMI ≥ 30 (aHR=2.17), discharge on TAC (aHR=1.51) and Cytomegalovirus D+/R– (aHR=1.60).

Relationship among NODAT, Graft Loss and Death

There were a total of 430 (19.8%) grafts that failed within three years of transplant in this population. Multivariate analysis surprisingly failed to find a significant relationship between NODAT and graft failure ($P=0.774$) (Table 3). NODAT and graft failure did share many of the same risk factors, however. The incidence of 3-year graft failure increased with age ($P < 0.001$), was higher for patients with BMI ≥ 30 ($P < 0.001$) and for those of female gender ($P=0.042$) and black race ($P < 0.001$). Graft failure was also higher for patients who did not receive any CNI ($P < 0.001$), those who received OKT3 as an induction agent ($P=0.003$) and for patients who did not receive mycophenolate mofetil ($P < 0.001$). Multivariate analysis found that graft loss increased with age (13–18 years, aHR=1.87; 19–21 years, aHR=2.10) and was higher for female recipients (aHR=1.32) and those with BMI ≥ 30 (aHR=1.54).

The 3-year mortality rate was 3.6% ($n=78$) in this pediatric transplant population. Similar to our analysis for graft failure, neither univariate nor multivariate analysis identified a significant relationship between NODAT and death ($P=0.774$) (Table 3). Death was more likely for patients with peak PRA 11–79% ($P=0.033$) and was less likely for those who received TAC or CsA ($P=0.001$).

Discussion

The number of pediatric renal transplants has risen significantly across the past decade with overall success rates that equal or exceed those of adults (20–22). Our understanding of pediatric transplantation, however, is gleaned largely from research on adult patients whose clinical situation and experience may be quite different. This issue is particularly salient for the development of NODAT which has been shown to significantly increase the risk of graft failure and death among adult transplant patients (1–6).

The current study is the largest to date to examine the development and consequences of NODAT among pediatric renal transplant recipients. We found that the overall rate of NODAT for these 2168 patients was 7.1% which is notably higher than the 2.6% rate previously observed in the North American Pediatric Renal Transplant Cooperative Study, the only other large-scale study conducted to date (11). Smaller studies have yielded inconsistent results with rates of NODAT ranging from 2–20% (12–14,17,23). Direct comparison of these studies is challenging due to notable differences in methodology, variables examined, sample size, patient age, and perhaps most importantly the criteria used to indicate NODAT.

Consistent with earlier research (11–16,17), we found that NODAT is much less common in children (7.1%) than in their adult counterparts (as high as 25% by year 3) (1,2,7–10), although these differences narrowed as the age of the child at transplant increased. For children younger than 13 years at transplant, only 4.4% developed NODAT compared to 10.1% of children ages 13–18 years. This increased risk may be a result of differences in body mass, immunosuppression/steroid dosing and primary cause of end-stage renal disease (ESRD).

Not surprisingly, we found that the rate of NODAT (7.1%) is considerably higher than the rate of diabetes among non-transplant children in the general population (0.18%) (24). Given the reports of escalating rates of Type 2 diabetes in the general pediatric population (25–26), we tested to see whether there have been similar increases in NODAT. Between 1995 and 2002 we found numerical increases in these rates annually, but they failed to reach statistical significance. This was at the same time, however, that there were concerted efforts to reduce the maintenance dose of immunosuppression and steroids in part to lower the rate of NODAT (8).

Previous research of adult transplantation has paid considerable attention to identifying the risk factors of NODAT which have included older recipient age, black race, deceased donor type, hepatitis C antibody status, use of TAC (vs. CsA), acute rejection episodes, and recipient body weight (1,2,5–9,27–28). Similar to these findings, we found that children are at increased risk of NODAT if they were of older age, obese (BMI ≥ 30) and had Cytomegalovirus D+/R–. As was mentioned earlier, comparison to prior adult research is challenging because of differences in criteria and methodology. To date, no two studies have examined the same set of potential risk factors. For example, the single center study by Greenspan et al. found that NODAT was associated with family history of diabetes and peri-transplant hyperglycemia, neither of which were available in the USRDS data we analyzed (17). The retrospective analysis of the North American Pediatric Renal Transplant Cooperative Study identified race, steroid dose and use of TAC as risk factors for NODAT (11). Other previous pediatric research (12–14,16) had smaller sample sizes which limited statistical power to identify risk factors. Nonetheless, the consistency of risk factors suggests that the same physiological mechanisms may be at play in children and adults.

Although the impact of NODAT on graft and death is well recognized in the adult population (1–6), we failed to find any such association among pediatric transplant patients. These null results, consistent with earlier research, have important implications for clinical decision-making after transplant. Although minimizing the risk of NODAT is certainly a goal of post-

transplant care, the primary objective has always been to prevent graft failure and death. The results of this study suggest that even if NODAT does develop, it does not have the impact on these ultimate patient outcomes that exists for adult patients. The large sample (i.e., 430 cases of graft failure and 78 deaths among our 2168 pediatric transplant patients) in this study provides confidence these null results are not due to low statistical power as had been suggested for prior research. It is possible, however, that the lack of association between NODAT and graft failure and death may be due to the fact that pediatric patients have overall lower mortality rates, fewer co-morbid conditions and better overall health state than their adult counterparts. It is also possible that the 3-year follow-up period is inadequate for identifying the development of NODAT in children.

A number of studies have previously examined the accuracy of administrative data such as Medicare for analyses of this type, and have found strong concordance between the codes in these data and the information present in patient medical records (29–31). Nonetheless, it is important to recognize that the data were collected for payment purposes, not for research. Consequently, there are certain limitations that should be taken into account when considering these results.

First, the absence of blood glucose levels and patient symptoms in the USRDS makes it impossible to use the gold standard definitions of diabetes established by the American Diabetes Association and the World Health Organization. The definition that was used in this study had been developed and shown accurate in several validation studies (32–34), but this definition still does not provide the definitive diagnosis possible with laboratory results. Second, there are a number of important factors (e.g., use of insulin, regimen adherence, glycemic control, family history) that are unavailable in these data. Third, it is quite possible that some patients had undiagnosed diabetes prior to transplantation, although this risk is lower in a pediatric population than in an adult population due to the relatively low incidence of non-insulin requiring diabetes. Fourth, children with primary Medicare coverage are a unique group and their results may not reflect that of the full population of pediatric transplant recipients. Fifth, as an observational study, causality cannot be established. Despite these limitations, registry analyses, with large national samples, provide a unique mechanism for examining complicated relationships among treatments and outcomes which would be impractical or unethical to examine in randomized clinical trials.

The results of this study suggest an increasing incidence of NODAT for children and adolescents following kidney transplantation. Although the rate of NODAT is lower than for adults, it is not insignificant. The existence of NODAT complicates the care delivery for these patients, places additional physiological stress on the body and provides already-worried parents and children with yet another health issue to worry about. At the same time, however, our study failed to find any significant association between NODAT, graft failure and death. This information is critical in guiding clinical decisions that must balance risk of all these outcomes. Choice of immunosuppressant and BMI were the only modifiable risk factors reaching significance. It is important to note that the choice of immunosuppression regimen, however, is often a balancing act between multiple factors that may be associated with risk of graft failure (e.g., risk of acute rejection, patient's prior success, side-effects and the protocol for a particular transplant center) (35–41). The risk of NODAT may be overshadowed by other risks in making this choice. Additional research, particularly as additional years of data are added to the USRDS, is needed to more fully understand these relationships.

Abbreviations

aHR

Adjusted Hazard Ratio

BMI	Body Mass Index
CI	Confidence Interval
CNI	Calcineurin Inhibitor
CsA	Cyclosporine A
DM	Diabetes Mellitus
ESRD	End-Stage Renal Disease
NODAT	New-Onset Diabetes after Transplant
OKT3	Murine Anti-CD3 Monoclonal Antibody
PRA	Percent Reactive Antibody
sd	Standard Deviation
TAC	Tacrolimus
UNOS	United Network for Organ Sharing
USRDS	United States Renal Data System

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Fig. 1.
3-year Incidence of NODAT by Year of Transplant, 1995–2002 (N = 1714).

Fig. 2.
3-year Incidence of NODAT by CNI at Discharge, 1995–2004 (N = 1963).

Table 1
Patient Characteristics, Pediatric Kidney Transplant Recipients for January 1995-December 2004 (N = 2168)

Variables	No. (%) of Transplants	TAC	CNI Assignment		P Value [*]
			CsA	Neither	
Age, years					
0-12	709 (32.7)	37.2	54.2	8.6	0.019
13-18	777 (35.8)	40.3	48.1	11.6	
19-21	682 (31.5)	36.7	55.4	7.9	
BMI					
< 30	1465 (67.6)	40.6	51.0	8.4	0.003
≥ 30	128 (5.9)	35.9	50.0	14.1	
Unknown	575 (26.5)	32.3	56.5	11.1	
Gender					
Male	1171 (54.0)	35.3	54.5	10.2	0.009
Female	997 (46.0)	41.5	49.9	8.5	
Race					
Black	584 (26.9)	42.0	50.5	7.5	0.035
Other/Unknown ^{***}	1584 (73.1)	36.7	53.1	10.2	
Diagnosed Hepatitis C					
Yes	38 (1.8)	42.1	50.0	7.9	0.860
No	2130 (98.2)	38.1	52.4	9.5	
Peak PRA, %					
0-10	1641 (75.7)	37.9	53.1	9.0	<.001
11-79	280 (12.9)	28.6	60.4	11.1	
≥ 80	65 (3.0)	40.0	49.2	10.8	
Unknown	182 (8.4)	54.4	35.2	10.4	
Pretransplant dialysis					
Yes	2103 (97.0)	38.1	52.7	9.2	0.026
No/Unknown ^{*3}	65 (3.0)	40.0	41.5	18.5	
Pretransplant transfusions					
Yes	739 (34.1)	31.3	59.5	9.2	<.001
No	1053 (48.6)	40.1	50.8	9.1	
Unknown	376 (17.3)	46.3	42.8	10.9	

Variables	No. (%) of Transplants	TAC	CNI Assignment		P Value*
			CsA	Neither	
Cause of ESRD					
Renal complications	743 (34.3)	39.0	52.1	8.9	0.726
Hypertension	85 (3.9)	36.5	57.6	5.9	
Other	813 (37.5)	36.7	53.1	10.2	
Unknown	527 (24.3)	39.5	50.9	9.7	

Abbreviations: BMI, body mass index; CNI, calcineurin inhibitor; PRA, percent reactive antibody; ESRD, end-stage renal disease

* Chi-Square test
** n=36 unknown
*3 n=17 unknown

Table 2
3-year Estimated Incidence Rates for Diabetes Mellitus, Graft Failure and Death (N = 2168)

Variables	NODAT		Graft Failure		Death	
	% (sd)	P Value	% (sd)	P Value	% (sd)	P Value
Age, years						
0-12	4.41 (0.86)	<.001	14.99 (1.46)	<.001	3.79 (0.81)	0.195
13-18	10.08 (1.28)		26.33 (1.79)		3.96 (0.81)	
19-21	11.37 (1.32)		28.71 (1.90)		5.45 (0.96)	
BMI						
< 30	8.49 (0.81)	<.001	20.99 (1.19)	<.001	4.25 (0.60)	0.892
≥ 30	20.58 (4.35)		45.67 (5.06)		5.90 (2.58)	
Unknown	5.31 (1.16)		24.51 (1.92)		4.44 (0.94)	
Gender						
Male	0.00 (0.00)					
	8.81 (0.93)	0.672	21.51 (1.34)	0.042	4.03 (0.63)	0.592
Female	8.30 (0.99)		25.60 (1.53)		4.80 (0.78)	
Race						
Black	11.11 (1.45)	0.006	32.72 (2.19)	<.001	4.50 (0.98)	0.891
Other/Unknown	7.62 (0.75)		20.01 (1.11)		4.33 (0.57)	
Diagnosed Hepatitis C						
Yes	16.09 (6.79)	0.098	33.59 (8.37)	0.152	8.05 (4.46)	0.137
No	8.45 (0.68)		23.21 (1.02)		4.31 (0.50)	
Peak PRA, %						
0-10	9.16 (0.76)	0.459	21.80 (1.11)	0.002	3.77 (0.51)	0.033
11-79	5.85 (1.53)		32.59 (3.06)		6.54 (1.75)	
≥ 80	6.70 (3.84)		23.60 (5.83)		3.51 (2.44)	
Unknown	5.68 (2.06)		21.85 (4.63)		8.36 (3.00)	
Pretransplant dialysis						
Yes	8.68 (0.69)	0.404	23.59 (1.03)	0.339	4.52 (0.51)	0.115
No/Unknown	5.34 (3.02)		17.22 (5.02)		0.00 (0.00)	
Pretransplant transfusions						
Yes	8.69 (1.13)	0.126	23.07 (1.68)	0.649	5.19 (0.90)	0.373
No	9.50 (1.04)		23.02 (1.47)		3.65 (0.66)	
Unknown	5.88 (1.38)		25.04 (2.45)		4.66 (1.19)	

Variables	NODAT		Graft Failure		Death	
	% (sd) *	P Value **	% (sd) *	P Value **	% (sd) *	P Value **
Cause of ESRD						
Renal complications	8.72 (1.16)	0.774	25.86 (1.80)	0.611	3.19 (0.73)	0.196
Hypertension	6.23 (2.70)		24.21 (5.19)		2.56 (1.79)	
Other	9.11 (1.13)		21.68 (1.59)		4.88 (0.86)	
Unknown	7.85 (1.35)		22.46 (2.01)		5.52 (1.09)	

Abbreviations: BMI, body mass index; PRA, percent reactive antibody; ESRD, end-stage renal disease; sd, standard deviation

* Kaplan-Meier analysis of 3-year incidence

** Log-Rank Chi-Square test of equality over strata

Table 3
Stepwise Cox Proportional Hazards Regression Results Modeling

Variables	aHR (95% CI)	P Value
3-year NODAT Incidence (N = 1963)		
Recipient Factors		
Age, years		
13–18 (vs. 0–12)	2.18 (1.33–3.57)	0.002
19–21 (vs. 0–12)	2.60 (1.58–4.28)	<.001
BMI		
≥ 30 (vs. < 30)	2.17 (1.26–3.75)	0.005
Transplant Factors		
Cytomegalovirus D+/R– vs. all others	1.60 (1.11–2.30)	0.011
CNI at discharge		
TAC (vs. CsA) *	1.51 (1.02–2.25)	0.040
3-year Graft Failure (N = 1963)		
Recipient Factors		
Age, years		
13–18 (vs. 0–12)	1.87 (1.38–2.54)	<.001
19–21 (vs. 0–12)	2.10 (1.55–2.85)	<.001
Body mass index		
≥ 30 (vs. < 30)	1.54 (1.06–2.22)	0.022
Gender		
Female (vs. male)	1.32 (1.05–1.67)	0.018
CNI at discharge		
TAC alone (vs. CsA) *	0.92 (0.70–1.20)	0.515
Diagnosis of diabetes before event *	0.93 (0.58–1.50)	0.774
3-year Death (N = 1963)		
Recipient Factors		
Age, years		
19–21 (vs. 0–12)	1.94 (1.14–3.33)	0.015
Cause of ESRD		
Renal complications (vs. Other)	0.55 (0.31–0.99)	0.049
Transplant Factors		
Cold ischemia time, hrs		
≥ 30 (vs. < 30)	2.62 (1.09–6.30)	0.032
CNI at discharge		
TAC (vs. CsA) *	0.81 (0.44–1.49)	0.495
Diagnosis of diabetes before event *	1.51 (0.57–3.99)	0.411

Abbreviations: BMI, body mass index; CNI, calcineurin inhibitor; ESRD, end-stage renal disease; TAC, tacrolimus; CsA, cyclosporine A; CI, confidence interval; aHR, adjusted hazard ratio

*
Forced entry