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Balancing competing needs in kidney transplantation: Does an allocation system prioritising children affect the renal transplant function?

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Running title

Prioritising children in kidney transplant allocation

Keywords

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Abbreviations

BP	blood pressure
CIT	cold ischemia time
CNI	calcineurin-inhibitor
eGFR	estimated glomerular filtration rate
HLA	human leukocyte antigen
KTX	kidney transplantation
MMF	mycophenolate mofetil
PRA	panel reactive antibodies
RRT	renal replacement therapy
SOAS	Swiss Organ Allocation System
UPC	urine protein-creatinine
yrs	years

ABSTRACT

Introduction

Children often merit priority in access to deceased donor kidneys by organ-sharing organizations. We report the impact of the new Swiss Organ Allocation System

(SOAS) introduced in 2007, offering all kidney allografts from deceased donors<60 years preferentially to children.

Methods

The retrospective cohort study included all paediatric transplant patients (< 20 years of age) before (n=19) and after (n=32) the new SOAS (from 2001-2014). Estimated glomerular filtration rate (eGFR), urine protein to creatinine ratio (UPC), need for antihypertensive medication, waiting times to kidney transplantation (KTX), number of pre-emptive transplantations and rejections, and the proportion of living donor transplants were considered as outcome parameters.

Results

Patients after the new SOAS had significantly better eGFRs 2 years after KTX (Mean Difference, MD=25.7 ml/min/1.73m^2, P=0.025), lower UPC ratios (Median Difference, MeD=-14.5 g/mol, P=0.004), decreased waiting times to KTX (MeD=-97 days, P=0.021) and a higher proportion of pre-emptive transplantations (Odds Ratio=9.4, 95%CI=1.1-80.3, P=0.018), while the need for antihypertensive medication, number of rejections and living donor transplantations remained stable.

Conclusion

The new SOAS is associated with improved short-term clinical outcomes and more rapid access to KTX. Despite lacking long-term research the study results should encourage other policy makers to adopt the SOAS approach.

INTRODUCTION

Kidney transplantation (KTX) is considered as the best treatment option for children and adults with end-stage renal disease [1]. The steadily increasing number of renal transplant candidates challenges the relatively unchanged kidney donor pool [2-4].

Children with end-stage renal disease represent a numerical minority and can suffer from long-term effects on growth, and physical and cognitive development [5-8]. To address these issues, most organ-sharing organizations have developed specific allocation strategies for children [9-11]. Prior to the new Swiss Organ Allocation System (SOAS), kidney allograft allocation was based only on the factor time spent on the waiting list. The new SOAS was established to offer all renal allografts from deceased donors < 60 years preferentially to AB0-compatible children and young adults (< 20 yrs) aiming to reduce waiting time on the list for paediatric patients. Only patients in need of urgent KTX due to imminent lack of access to any mode of dialysis are preferred over children and young adults. Furthermore, the new SOAS provides the opportunity to place children on the waiting list without prior dialysis if the estimated glomerular filtration rate (eGFR) is < 15 ml/min per 1.73m^2.

We carried out a retrospective multicentre cohort study in all patients undergoing deceased donor KTX from 2001 to 2014 at Swiss paediatric nephrology transplant centres. The study objective was the assessment of the short-term clinical outcome of kidney transplants in children determined by eGFR, urine protein to creatinine (UPC) ratio, need for hypertensive medication, time spent on the transplant list, number of pre-emptive transplantations and rejections, and the proportion of living donor transplants.

METHODS

A retrospective multicentre cohort study was conducted by reviewing data from the Swiss Paediatric Renal Registry (SPRR) [12]. The registry contains demographic and clinical data for each patient dialysed and/or transplanted during childhood and adolescence in Switzerland since the introduction of renal replacement therapy

(RRT) in 1970. This study includes the SPRR data for all patients undergoing primary deceased donor KTX from 2001 to 2014 at paediatric nephrology transplant centres. Informed consent was obtained from the parents and/or from adolescent patients.

Inclusion criteria for patients were defined as follows: < 20 years of age at time of deceased donor KTX. The study cohort was separated into two groups: patients transplanted from January 2001 – June 2007 were compared with those after the implementation of the new SOAS (July 2007 – June 2014). Patients placed on the transplant list before the new SOAS but transplanted afterwards were excluded due to the possible bias on patient characteristics such as waiting time. All patients received only transplants from ABO-compatible and heart-beating donors.

Demographic and clinical characteristics were collected for both groups, such as sex, age, ethnic group, blood group, primary diagnosis, duration and modality of dialysis (haemodialysis or peritoneal dialysis), and time on dialysis. The primary diagnosis was classified according to one of the three specified categories: Congenital anomalies of the kidney and urinary tract, hereditary or acquired renal disorder [12]. Also, donor-related demographic and clinical characteristics were obtained such as age, body mass index, duration of cardiopulmonary reanimation, catecholamine administration, hypertension history, diabetes mellitus, cause of death, and data on last available creatinine, C-reactive protein and UPC ratio in the first morning spot urine.

Quality characteristics of the transplant included data on ethnicity match, number of HLA mismatches, cold ischemia time (CIT), peak panel reactive antibodies (PRA) and immunosuppressive treatment regimen. This maintenance regimen consisted of

calcineurin-inhibitor (CNI; cyclosporine A or tacrolimus) combined with either mycophenolate mofetil (MMF) or azathioprine with or without induction therapy but corticosteroid administration for at least 12 months.

The following clinical and laboratory data were collected for each patient on the first out-patient clinic appointment and one and two years after KTX: plasma creatinine (µmol/l), body weight (kg) and height (cm), antihypertensive medication (aiming for a 24-hour blood pressure target < 95^{th} percentile or < 50^{th} percentile if proteinuria is present), and measurement of UPC ratio in the first morning spot-urine at last follow-up. Estimated GFR was calculated using the Schwartz-formula method [13]. Diagnosis of rejection was made by a kidney biopsy either routinely performed (6 months after KTX) or following clinical indication based on the available Banff classification or previously used classification systems [14, 15].

The primary outcome measure was the eGFR (ml/min per 1.73m^2 body surface) one and two years after KTX. Amount of proteinuria, number of patients with hypertension medication, time on waiting list (days), number of pre-emptive transplantations and rejections, and the proportion of living donor transplants were considered as secondary outcome measures.

Demographic, disease-related and transplant-related variables were described using frequencies and percentages for categorical variables and mean ± standard deviation (normally distributed) or median and range (not normally distributed) for continuous variables. Group differences were assessed with Pearson's chi-squared test for categorical variables and with independent sample *t*-test or Mann-Whitney test for continuous variables. The effect of the new SOAS on eGFR was analysed in a linear mixed effects model with random intercepts per subject and the following

baseline adjustment variables: follow-up time point, age at KTX, donor age, immunosuppressive treatment therapy, pre-transplant dialysis time, waiting time in the transplant list, UPC ratio at last follow-up, number of HLA mismatches and rejection. Comparison of the model with and without the effect in question was carried out by likelihood ratio tests, thereby obtaining a P-value for the effect. All data analyses were conducted using R 3.1.2 with the additional packages lmer4 1.1-10 and rms 4.5-0 [16-18].

RESULTS

In total, 51 patients fulfilled the inclusion criteria, with 19 receiving KTX before and 32 after the new SOAS. Basic demographic and clinical characteristics were similar for patients undergoing deceased donor KTX before and after the new SOAS, as shown in Table 1. Significant differences between groups were only found in the pre-transplant dialysis time, which was significantly decreased after the new SOAS, from a median 555 days to 148 days (median difference MeD=-407days, P=0.006). Corresponding donor characteristics were comparable for both groups (Table 2) and revealed no significant differences except for an increase in donor age (mean difference MD=9.3years, P=0.040). The only difference regarding transplant characteristics was the type of combination immunosuppression therapy, with a significant shift towards CIN/MMF (odds ratio OR=14.3, 95%CI=1.7-121.8, P=0.013). We excluded 9 patients (4 before and 5 after the new SOAS) for the following reasons: graft loss as a consequence of hyperacute rejection and vascular thrombosis (n=2), loss of follow-up (n=3), recurrence of primary underlying disease (n=1) and death due to sepsis (n=3) < 1 year after KTX. Two additional patients were excluded due to listing before, but transplantation after the new SOAS. Excluded

patients did not show differences in recipient characteristics compared to those included for analysis regarding sex (p=0.212), mode of dialysis (p=0.055), blood group (p=0.559), age at KTX (p=0.378), ethnicity (p=0.105) and etiology of renal disease (p=0.217). They were not included in the analysis due to missing data for the primary outcome and the majority of secondary outcomes.

Detailed results for the comparison of primary and secondary outcome measures between patients before and after the new SOAS are presented in Table 3. Estimated GFR showed significant differences at 1 year (MD=24.1ml/min per 1.73m^3, P=0.013) and 2 years (MD=25.7ml/min per 1.73m^3, P=0.025) after KTX, with increased mean values after the policy change. Also, patients after the new SOAS had lower UPC ratio levels (MeD=-14.5g/mol, P=0.004), a shorter median time spent on the KTX waiting list (MeD=-97days, P=0.021, see Figure 1), and a higher proportion of preemptive transplantations (5% vs. 34%, OR=9.4, 95%CI=1.1-80.3, P=0.018). More than half of the patients needed antihypertensive medication after KTX, but this did not differ between groups. The number of rejections was not significantly different between both groups. Patients with routinely performed kidney biopsy 6 months after KTX did not necessarily have clinical signs of rejection or underwent therapy for rejection.

The comparison of living donor proportions among all transplantations carried out in the study period revealed a non-significant trend towards a lower number of living donor transplants after the new SOAS (OR=0.5, 95%CI=0.2-1.0, P=0.052). Linear mixed effect modelling was applied to detect the influence of the new SOAS on eGFR, given a set of baseline covariates. We found a significant effect of the new

law ($\chi^2(1)=15.129$, P=0.0001), increasing the eGFR by 45.4 ml/min per 1.73m^2 (95%CI=24.5-66.3 ml/min per 1.73m^2).

DISCUSSION

Current allocation policies often link the priority of paediatric patients to additional requirements (see Table 4) [10, 11, 19-23]. The new SOAS limits these requirements only to a blood group compatible donor aged < 60 years, resulting in an increased donor pool. Even if available organs are rejected, this permissive policy results in further offers within a short period of time, since physicians are free to decline transplants without further consequences. Moreover, the paediatric age limit for recipients after the new SOAS is < 20 years, independently of previous KTXs and therefore lies in the upper range compared to the majority of other countries, in which children are defined as being < 18 years old [21].

Estimated GFR is considered as the best indicator for renal function in children and adolescents [24]. Our data revealed significantly better eGFRs in children after the new SOAS for the 1 and 2 year outcome. With similar demographic and clinical characteristics for patients before and after the new SOAS, linear mixed model analysis showed that the new SOAS has a significant effect on renal function, even when baseline variables, which are possibly associated with graft failure or decreased graft function were adjusted for, such as HLA-mismatch, rejections and immunosuppressive treatment medication. Interestingly, only donor age was significantly different between both groups, with older kidney donors after the new SOAS, contrary to the widespread recommendation to prefer size-matched kidneys from younger patients [19, 25-27].

We found a significant decrease in time on dialysis for patients after the new SOAS, which seems to be mainly driven by the marked increase in pre-emptive KTX from 5 to 34%. This increase can be traced back to the new SOAS, allowing unrestricted listing of patients with eGFRs < 15 ml/min per 1.73m^2. The effectiveness of a priority policy for children should be mainly evaluated by changes in waiting time. This time span is highly variable for children throughout European countries, ranging from approximately 4 to 36 months, with a median of 11 months spent on the transplant list in 2008 [21]. Our data showed that the median time on the waiting list for children in Switzerland dropped from approximately 6 months to less than 3 months after the SOAS introduction. The new SOAS has decreased the time on dialysis to a point where about 97% of all children receive an organ within 4 years of RRT, as compared to only 76.9% in European countries in 2008 [28].

Improved graft outcomes can be achieved with pre-emptive KTX and it is therefore recommended, particularly in paediatric patients [29, 30]. The median prevalence of pre-emptive KTX among 29 European countries, however, was only around 17% in 2008, which is comparable to the United States [21, 28, 31-33]. The increased rate after the new SOAS should result in overall improved long-term graft survival [34-36].

There has been an ongoing debate concerning the impact of HLA matching on the outcome of a renal transplant [37-42]. We have to acknowledge that we were not able to detect an effect on HLA-matching strategy after the policy change. The number of mismatches seen in our study is congruent with a current trend, which shows that about 90% of all deceased donor kidney-only transplantations have HLA mismatches to some extent [39, 43, 44] . However, HLA mismatch leads to a higher risk for a sensitised state in the presence of re-transplantation, which is associated with longer waiting times [41, 45, 46]. An optimized approach with less

histocompatibility mismatches should consequentially be preferred in future organ selection processes.

While the proportion of our patients treated for high BP with at least one antihypertensive drug was unchanged in both groups, the UPC ratio was significantly decreased. Systolic hypertensive blood pressure (BP) as well as proteinuria are strong and independent predictive factors for graft survival in paediatric patients [47-50]. CIT represents an independent risk factor for delayed graft function [51, 52]. As the kidney organs are retrieved and transplanted within a relatively small geographical area, resulting CITs were shown to be similar for the kidneys allocated before and after the new SOAS (median CIT between 8.25 and 8.0 hours) [53].

Prioritising children in kidney allocation policies may raise concerns regarding medical and ethical issues leading to political discussions, because arguments in favour of adults may also be used [20]. This fact gains even more weight given the decreased living donor transplant rates in countries with a priority policy for children, as a direct consequence of more readily available deceased donor organs [33, 54, 55]. Although the proportion of living donor grafts is still markedly higher in Switzerland compared to the median proportion (43%) among a total of 29 European countries, this trend is also visible in our data (65% vs. 48% living donor grafts) and will simultaneously aggravate the existing organ shortage [21, 22]. Then again, since children only encompass about 1-3% of all waitlisted patients, a shift in the graft source from living to deceased donors will not have an extensive effect on waiting times on the list for adult patients [2, 3]. Notwithstanding, an approach that involves encouraging living donations should still be pursued.

The main limitation of the current study is the retrospective design that clearly does not have the advantages of a prospective study, the small sample size limiting the evaluation of potential confounders for the observed eGFR improvement and the absence of long-term outcome data. Our findings, however, should be viewed as a preliminary assessment of the new SOAS and long-term effects of this policy will be reported. Although the working procedures and guidelines within Switzerland tend to be very uniform due to the relatively small geographic area, we cannot exclude that there was a change in the work-up process over time. In addition, there may be a selection bias of patients due to advances in treatment strategies in paediatric KTX [56].

CONCLUSION

In conclusion, the findings of our study highlight the significant effects of the new SOAS, leading to an improved short-term clinical outcome of kidney transplants in children, increased number of pre-emptive deceased donor transplantations and reduced waiting times on list. Although the current study strengthens the arguments for prioritising children in renal transplantation, we still require further research to accumulate more evidence for these findings by assessing the effects of long-term graft survival.

Figure Legend

Figure 1. Kaplan-Meier plot of waiting time on the transplant list for children receiving a deceased donor allograft before and after the new SOAS. The log-rank comparison test showed a significantly decreased rate for children after the new SOAS (P=0.007).

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Table 1. Recipient characteristics. Values are given as mean ± SD, median (min;max), or as absolute counts (percentage).

	Before SOAS (n=19)	After SOAS (n=32)	P-value
Demographics			
Sex (female)	10 (53)	11 (34)	0.235
Age at KTX – yrs	11.1 ± 4.7	10.7 ± 5.1	0.907
Ethnicity			0.829
Caucasian	16 (84)	29 (91)	
Middle East	1 (5)	1 (3)	
Hispanic	2 (11)	1 (3)	
Asian	0 (0)	1 (3)	
Clinical characteristics			
Blood group			0.467
0	12 (63)	20 (65)	
A	7 (37)	10 (29)	
B	0	2 (6)	
AB	0	0	
Etiology of renal disease			0.384
CAKUT	6 (32)	5 (16)	
hereditary	8 (42)	12 (37)	
acquired	5 (26)	15 (47)	
Mode of dialysis			**0.060**
HD	11 (58)	13 (41)	
PD	7 (37)	8 (25)	
Pre-transplant dialysis – days	555 (0;1715)	148 (0;3859)	**0.006**

CAKUT, congenital anomalies of the kidney and urinary tract; HD, haemodialysis; PD, peritoneal dialysis; SOAS, Swiss Organ Allocation System; SD, standard deviation; KTX, kidney transplantation

Table 2. Donor and transplant characteristics. Values are given as mean ± SD, median (min;max), or as absolute counts (percentage).

	Before SOAS (n=19)	After SOAS (n=32)	P-value
Donor			
Age – yrs	23.0 ± 15.0	32.3 ± 15.4	**0.040**
Body Mass Index – kg/m^2	24.7 (15.3;27.8)	24.2 (12.6;40.1)	0.961
Cardiopulmonary reanimation duration – min	0 (0;60)	0 (0;50)	0.980
Support with catecholamines	13 (68)	22 (69)	0.980
History of hypertension	2 (11)	0 (0)	0.061
at KTX			
Creatinine – µmol/l	76 (26; 148)	67 (38; 276)	0.316
Protein/creatinine>20 g/mol	5 (26)	7 (22)	0.560
C-reactive protein-mg/l	85.5 (5; 238)	99 (4; 534)	0.444
Diabetes mellitus	0 (0)	0 (0)	–
Death – cerebrovascular accident	13 (68)	18 (56)	0.389
Transplant			
Ethnicity match[1]	16 (84)	29 (91)	0.492
HLA mismatches	5 (2;6)	5 (3;6)	0.970
Cold ischemia time – min	495 (261; 1050)	476 (294; 971)	0.802
Peak Panel Reactive Antibodies > 4%	1 (5)	2 (6)	0.842
Immunosuppressive treatment			
Induction therapy	7 (37)	14 (44)	0.716
Maintenance therapy			**0.013**
CIN/AZA	3 (16)	0 (0)	
CIN/MMF	13 (68)	31 (97)	

[1] all donors were of Caucasian ethnicity

AZA, azathioprine; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; SOAS, Swiss Organ Allocation System; SD, standard deviation; KTX, kidney transplantation

Table 3. Outcome measures. Values are given as mean ± SD, median (min;max), or as absolute counts (percentage).

	Before SOAS (n=19)	After SOAS (n=32)	P-value
Primary outcomes			
Renal function – ml/min per 1,73m^2			
eGFR 1 yr after KTX	67.8 ± 28.3	91.9 ± 33.2	**0.013**
eGFR 2 yrs after KTX	65.3 ± 33.2	91.0 ± 38.0	**0.025**
Secondary outcomes			
Protein/creatinine – g/mol	14.5 (0;477)	0 (0;94)	**0.004**
Hypertension medication	12 (63)	21 (66)	0.675
Waiting time on list – days	173 (9;1433)	76 (6;591)	**0.021**
Pre-emptive KTX	1 (5)	11 (34)	**0.018**
Rejection[1]	6 (32)	9 (28)	0.804
Living donor transplants – living / total (%)	36/55 (65)	29/61 (48)	0.052

[1] based on kidney biopsy either performed routinely or following clinical indication
KTX, kidney transplantation; SOAS, Swiss Organ Allocation System; eGFR, estimated glomerular filtration rate; SD, standard deviation

Table 4. Major characteristics of the Swiss Organ Allocation System (SOAS) in comparison to Eurotransplant and the Organ Procurement Transplantation Network (OPTN) USA for the allocation of deceased kidneys.

	SOAS	Eurotransplant	OPTN
Paediatric status	< 20 yrs.	< 16 yrs.	< 18 yrs.
Extended paediatric status	—	• start of dialysis < 16 yrs. • registration on waiting list < 16 yrs. (if dialysis started < 17 yrs.) • proof to be in maturation	• listing regardless clinical criteria • start of dialysis < 18 yrs.
Paediatric bonus system	• not applicable	• extra 100 points • points for HLA mismatch doubled	• age at match

Pre-emptive KTX	• yes (eGFR < 15)	• yes, for high urgent cases only • no points for waiting time are accrued	• possible
Allocation algorithm criteria[1]	child ↓ adult	AM[2] ↓ HLA match ↓ status paediatric ↓ adult	• combination of EPTS[3] and KDPI-scoring[4]

[1]restricted to ABO-compatible recipients only
[2]Acceptable mismatch program (adult/paediatric) to privilege highly sensitised transplant recipients
[3]Estimated post-transplant survival (EPTS): Combining various recipient factors to summarise the need of a functioning kidney transplant based on a calculated score
[4]Kidney donor profile index (KDPI): Combining various donor factors to summarise the risk of graft failure after kidney transplant based on a calculated score
KTX, kidney transplantation; eGFR, estimated glomerular filtration rate in ml/min per 1.73m^2; HLA, human leucocyte antigen;