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High Volume Center Experience for Recurrent Primary Disease in Kidney-transplanted Pediatrics

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Azadeh Afshin,^{1*}
Mostafa Sharifian,¹
Naser Simfroosh,²
Abbas Basiri,²
Saran Lotfollahzadeh,³
Nasrin Esfandiari¹

1 Pediatric Nephrology Research Center, Research Institute for Children Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

2 Urology and Nephrology Research Center, Shahid Labbafi Nejad Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

3 Pediatric Surgery Research Center, Pediatric Research Institute for Children Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

*** Corresponding Author**

Azadeh Afshin, Pediatric Nephrology Research Center, Department of Nephrology, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
 Tel: +982122226941
 E-mail: azi.afshin@gmail.com

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Introduction

Over the past 3 decades, kidney transplantation has been recognized as the treatment of choice for children with ESRD and stage 5 of Chronic Kidney Disease (CKD), since this treatment improves the overall survival of patients [1]. One of the most important drawbacks to this treatment is the recurrence of the primary disease in the transplanted kidney, a subgroup of chronic kidney

Introduction: Over the past 3 decades, kidney transplantation has been recognized as the treatment of choice for children with End Stage Renal Disease (ESRD) and stage 5 of chronic kidney disease (CKD). One of the most important drawbacks to this treatment is the recurrence of the primary disease in the transplanted kidney, which is considered the third most common leading cause of graft failure.

Materials & Methods: In this study, the data of 550 patients below 18 years who underwent kidney transplantation during a 33-year period from 1985 to 2017 due to kidney failure or ESRD were included to fill out a standard questionnaire. Those who suffered from primary disease relapse according to clinical or paraclinical criteria were included in the study to investigate the association of relapse with factors such as gender, age, and donor type, time to relapse with type of disease, and post-transplant immunosuppressive drugs with severity of pre-transplant kidney injury.

Results: Of 31 pediatric patients with primary disease recurrence (out of 550 transplanted kidney), 62.5% were male (n=20) and the remaining were female (n=11) with a mean age of 10.55 (± 0.665) years. The primary diseases in the transplanted kidney were focal segmental glomerulosclerosis (FSGS) (80.5%), systemic lupus erythematosus (12.5%), hemolytic uremic syndrome (6%), and primary hyperoxaluria in 1 patient. Totally, 10 cases (30%) showed recurrence of the primary disease 18 (± 22.95) months after transplantation on average. The final status of these 10 patients was significantly undesirable compared with that of other 21 patients without recurrence (p= 0.002). Of these 10 patients, 8 had graft failure and needed renal replacement therapy.

Conclusion: The results of this report confirm the necessity of follow-up considering the importance of the recurrence of the primary disease, especially FSGS, in children after kidney transplantation.

Keywords: Renal Transplantation; Recurrence; Focal Segmental Glomerulosclerosis; Hemolytic Uremic Syndrome; Systemic Lupus Erythematosus; Membranoproliferative Glomerulonephritis.

Running Title: Recurrent Primary Disease in Kidney-Transplanted Pediatrics

disease, which is considered the third most common leading cause of graft failure [2]. Novel generations of immunosuppressive agents accompanied by adequate pre and post-operative care have significantly decreased the risk of rejection in the transplanted kidneys [3].

Instead, recurrence of the primary disease in the transplanted kidney has become a major concern, which is unfortunately more common in children

to the extent that graft loss in children due to acute rejection and recurrence of the primary disease is about 8-9% and 8-7%, respectively. [4,5] In Iran, a few studies have focused on the recurrence of the primary disease in pediatric patients as an implicating factor of graft failure in transplanted kidneys.

The latest annual reports of North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) have suggested that recurrence of the primary disease includes approximately 7% of all and 9.6% of subsequent graft failures [6].

Increased risk of graft loss mostly results from the recurrence of focal segmental glomerulosclerosis (FSGS), atypical hemolytic uremic syndrome (aHUS), membranoproliferative glomerulonephritis (MPGN), and membranous nephritis [5, 7]. IgA nephropathy, lupus nephritis (a complication of systemic lupus erythematosus: SLE), glomerulonephritis associated with anti-neutrophil cytoplasmic antibody, and anti-glomerular membrane disease are amongst the low risk primary diseases in terms of recurrence [8].

So far, no effective strategy has been developed to improve the overall survival of these patients, indicating the need for long-term multi-center studies. However, recent studies suggest a new perspective for the treatment of these patients with recurrent FSGS using monoclonal antibodies (*e.g.* Rituximab).

According to these studies, treatment with monoclonal antibodies and/or plasmapheresis and gene therapy has presented new protocols for these patients [7-9].

Studies have shown that the treatment protocol, especially those containing a balanced immunosuppressive regimen, type of the primary disease, presence of other disorders (such as mutation in complement system factor H, cardiovascular disease, etc.), type of pre-transplant dialysis, and type of donor play crucial roles in the survival of transplanted tissue [2, 10-17].

In Iran, few studies have focused on the recurrence of primary disease in kidney-transplanted children.

In this regard, the present study was conducted to determine the rate of primary disease recurrence and its implications in kidney-transplanted children. Therefore, the results can show whether appropriate treatment measures before and after transplantation can prevent the recurrence of the primary disease.

Materials and Methods

A 32-year retrospective cohort study was done in kidney-transplanted pediatric patients at Mofid and Labbafinejad hospitals, Tehran, Iran between 1985 and 2017. This study was approved by the Medical Ethics Committee of Mofid Children's Hospital (IR.SBMU.MSP.REC.1397.41). Written informed consent was obtained from patients. The information was anonymous and confidential and no costs were imposed on patients.

Pediatric patients aged below 18 years at the time of transplantation (n=550) were included. The classic open extra-peritoneal technique was used for graft insertion.

Routine immunosuppression regimen consisted of prednisolone, cyclosporine/ tacrolimus/ sirolimus, and mycophenolate mofetil/azathioprine. In a few cases, treatment included anti-thymocyte globulin (ATG), rituximab, Intravenous immunoglobulin (IVIG), and plasmapheresis. Patient with a recurrent primary disease were isolated and their data, including age, sex, cause of ESRD, type of dialysis, family history of renal disorders, type and cause of graft loss, graft survival, immunosuppressive regimens, blood pressure before and after transplantation, age and type of donor, serum BUN and creatinine levels, and random urine protein, were collected using a standard questionnaire.

It should be mentioned that the graft survival time was defined as the interval between the time of transplantation and either last date of follow-up with a functioning graft, graft loss, or death. Meanwhile, regarding the RIFLE criteria, graft loss was defined as the absence of a functional graft resulting from patient's death, damaged graft, or need for chronic dialysis and a secondary transplantation.

IBM SPSS Statistics v.23 software (SPSS Inc., Chicago, USA) was used to analyze the data. The results of the continuous variables are presented as mean \pm SD, median, and range, and the results of discrete variables are presented as numbers and percentages.

The Kaplan-Meier survival analysis was used to estimate graft survival and patient survival, and Log-Rank test was applied to compare graft survival. Comparison of variables was performed using Student's t-test, Mann-Whitney U, one-way ANOVA, and Kruskal-Wallis analyses. The level of significance (*p*. value) was set at 0.05.

Results

Of 550 pediatric patients who underwent kidney transplantation in Shahid Labafi-Nejad Hospital, Tehran, Iran, 31 experienced the recurrence of the primary disease. Two of these patients died. One of them was a patient with FSGS who died due to thromboembolic events following transplant and the other one suffered from primary hyperoxaluria and only underwent kidney transplantation without liver transplantation.

Of 31 kidney transplanted patients with primary disease recurrence, 37.5% were female (n=11) and 62.5% were male (n=20) with a mean age of 10.5 (± 65.6) years old. The primary disease recurrence before kidney transplantation was reported to be SLE in 3 patients (12.5%), FSGS in 25 patients (87.5%), hemolytic uremic syndrome in 2 patients (6%), and primary hyperoxaluria in 1 patient (Figure 1).

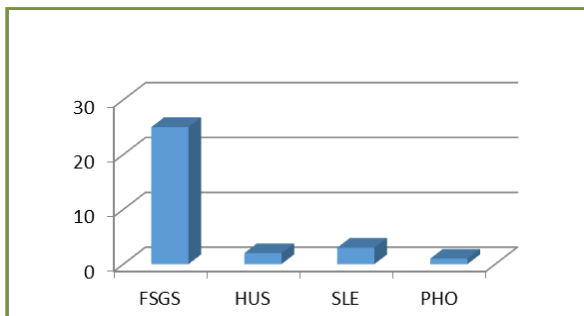


Figure 1. Primary diseases in study group (PHO: Primary Hyper Oxalluria)

The type of the primary disease did not have a significant effect on the patients’ survival rate (p=0.687). Prior to transplantation, hemodialysis and CAPD were performed in 16 (58.3%) and 9 (16.7%) patients respectively that were preemptive in 6 cases (25%). The difference in pre-transplant dialysis status did not affect the survival rate of the transplanted tissue significantly, either (p=0.947).

The mean age of the transplant recipients was 26.26 (± 42.1) years, and the difference in the age range of the donors did not affect the survival of the transplanted kidneys significantly (p = 0.749). There were 28 unrelated living, 1 related living (patient’s mother) and 2 deceased donors (Figure 2). The primary disease recurred in 10 patients [70% female (7) and 30% male (3)] with a mean age of 10 years within 18 (± 22.95) months after the transplantation. The final status of these 10 patients was significantly undesirable compared to the 21 patients without recurrence (p= 0.002). In 6 out of 10 patients, disease recurrence was

confirmed by biopsy from the transplanted kidney. The remaining 21 patients had a favorable status.

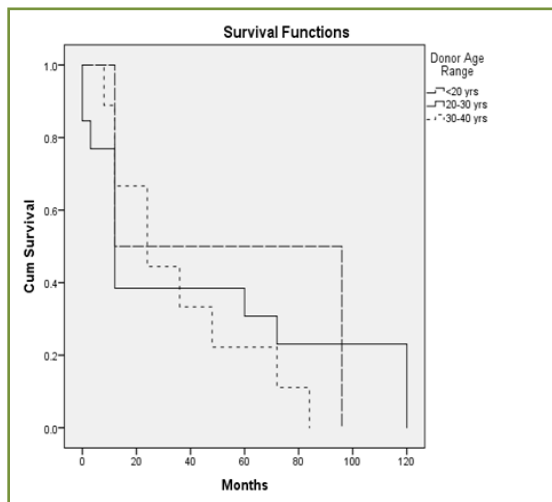


Figure 2. Graft survival based on donor age

The median serum creatinine level was 1.35 mg/dL. The median serum creatinine level was 4.4 (3.07-5.2) and 1.3 (0.975-1.8) mg/dL in patients with and without transplant rejection, respectively. This increase in the serum creatinine level in patients with rejection was statistically significant (p=0.011). In 3 cases, recurrence occurred within less than 2 weeks after transplantation while chronic rejection was detected in the remaining 7 cases.

FSGS and SLE recurred in 22.5% (n=7) and 3% (n=1) and primary hyperoxaluria and atypical HUS each recurred in 3% of the patients (n=1) (Table 1).

Table 1. Summary of patients outcome in study group

Primary disease	Transplanted No	Recurrent primary dis	Graft loss	Death
FSGS	25	7	5	1
SLE	2	1	1	-
HUS	2	1	1	-
PHO	1	1	1	1
Total	31	10	7	2

In these patients, the mean systolic and diastolic blood pressure was 133.75 (\pm 10.61) and 81.25 (\pm 13.56) mmHg before and 147.00 (\pm 25.48) and 84.38 (\pm 8.21) mmHg after transplantation, respectively. A statistically significant difference was observed in pre-transplantation systolic blood pressure between patients with and without recurrence ($p=0.026$), while there was no significant difference in the systolic blood pressure between the two groups after transplantation ($p=0.064$) (figure 3).

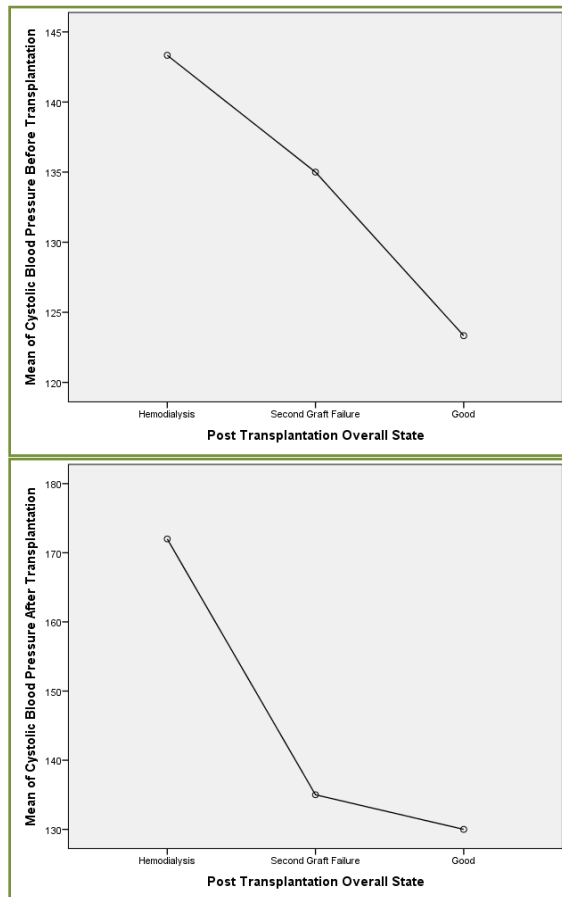


Figure 3. Blood pressure before and after transplantation.

- Lower systolic blood pressure before transplantation was observed in those with the better final status.
- The pattern of systolic blood pressure after transplantation also indicated a lower level of this variable in subjects with a desirable final status.

Of the 10 patients with recurrence, there was no statistical difference in the diastolic blood pressure before and after transplantation based on the final status of the patients ($p=0.227$ and $p=0.172$, respectively).

Discussion

Although kidney transplantation is the treatment of choice for patients with ESRD, a study in 2012 by Qaisari et al in Iran showed that only less than half of these children had a chance of having kidney transplants [18]. In addition, despite improvements in kidney transplantation in Iran similar to developed countries, the long-term survival of transplant is still not favorable [19, 20]. Therefore, it is necessary to identify factors that may affect the transplant outcomes in order to improve the life span of the transplanted tissue in pediatric transplantation. One of these effective factors affecting the transplant success is the recurrence of the primary disease after transplantation. In Iran, few studies have focused on the recurrence of the primary disease in kidney-transplanted pediatric patients.

In the present study, a total of 550 kidney transplantations were performed in Shahid Labafi-Nejad Hospital, Tehran, Iran between 1985 and 2017. Thirty-one patients with a chance of recurrent renal disease were examined. Among them, 37.5% were female ($n=11$) and 62.5% were male ($n=20$) with a mean age of 10.5 (\pm 65.6) years. Ten patients experienced the recurrence of the primary disease.

Similar to a study by Naderi *et al.* in 2017, the most common primary disease that recurred was FSGS (28%) in our study [15]. Thus, it seems that attention should be paid to the follow-up of the patients' clinical condition for recurrence of the primary disease in children suffering from FSGS and SLE.

There is no doubt that the probability of acute vascular rejection is higher in unrelated donors and living donors provide a better long-term patient and graft survival [21-23]. The majority of the donors in this study were unrelated and living. Since the number of dead or related donors was negligible in our study and groups could not be compared at these levels, there was not enough evidence to establish a link between the type of donor and the type of recurrent disease. Interestingly, in a recent study conducted by Walters et al, a significant increase was observed in the risk of recurrence of glomerulonephritis resulting from FSGS and IgA-nephropathy in those receiving grafts from living related donors as compared to deceased or unrelated donors [24]. Only one patient received a graft from a deceased donor in the current study; this patient had an acceptable good final status.

Table 2. Comparison of therapeutic approaches in patients with transplanted organ failure based on outcome

		Patients with transplanted organ failure receiving this treatment (n)	Final Condition of Patients with Failure (n)		p.value
			Rejection	Favorable	
Treatment after transplantation	ATG	3	1	2	1.000
	Plasma pheresis	4	3	1	1.000
	Rituximab	5	2	3	1.000
Status of dialysis before transplantation	HD	4	3	1	0.311
	CAPD	1	-	1	
	Preemptive	3	1	2	
Kidney biopsies after recurrence		7	6	1	-
ATG: Anti-thymocyte globulin, HD: Hemodialysis, CAPD: Continuous Ambulatory Peritoneal Dialysis. p.value ≤0.05 was considered statistically significant.					

According to Canadian registry reports, the most important risk factor in patients undergoing dialysis or kidney transplant is cardiovascular diseases, especially hypertension [25, 26]. In 80-90% of the CKD patients, chronic hypertension eventually results in ESRD over time; therefore, renal transplantation should be performed in these patients when blood pressure is reduced to below 130/80 mmHg [27].

The correlation coefficient did not show any significant relationship between systolic blood pressure before and after transplantation and diastolic blood pressure before and after transplantation.

However, systolic blood pressure before transplantation was significantly higher in patients with failure and those with more unfavorable outcomes.

In this regard, Pourmand *et al.* showed high rates of hypertension in kidney transplanted patients and claimed that early screening of blood pressure could reduce and even prevent complications leading to damage to the transplanted kidney [28]. All subjects with primary disease recurrence were treated with immunosuppressive drugs and received cyclosporine, prednisolone and CellCept. Of these, 13% (n=3) received ATG, 16.7% (n=4) received rituximab, and finally 16.7% (n=4) and 12.5% (n=3) underwent plasmapheresis and IVIG therapy, respectively. Differences in the treatment

regimen did not cause a significant improvement in the patients' condition. However, LaTonya *et al.* reported that the patients who received plasmapheresis and rituximab showed improvement in proteinuria [17]. This difference can be due to the lower number of patients with failure under treatment with plasmapheresis and rituximab in the present study.

In total, 8 patients (approximately 25%) experienced rejection of the transplanted kidney after primary disease recurrence which occurred within an average of 18 (± 22.95) months after the transplantation but did not result in the death of any of the subjects. There were no significant differences in the rate of transplant rejection based on the type of recurrence between the patients (p=1.000). Of the 8 patients in whom transplant rejection was reported, there were two cases of primary disease recurrence in less than a week after kidney transplantation while chronic rejection of the transplanted kidney occurred after recurrence of the primary disease in 6 other cases. As with previous reports, chronic rejection was the most common cause of graft rejection in our patients. It can be claimed that along with advances in transplantation, Iran has also successfully achieved international standards of post-transplant palliative care and treatments [19, 29]. Meanwhile, the increase in serum creatinine and urine protein in patients with rejection was

statistically significant ($p=0.011$, $p=0.001$, respectively); an imbalanced creatinine/ protein ratio is reported to be an accurate diagnostic indicator of transplanted kidney dysfunction [30, 31].

At the end of the study, of 31 patients with failure due to primary disease recurrence, 6 underwent hemodialysis, one experienced a second transplant rejection, 21 (67.2%) had favorable conditions after transplantation, and 2 died. This condition was due to the optimum balance of immunosuppressive treatments prescribed in this center in such a way that no serious infections or malignancies were reported in any of the subjects [32].

Conclusions

In conclusion, the results of this report confirmed the need for follow-up of the recurrence of the primary disease in children after kidney transplantation. However, there is still a need for more accurate studies to examine the effect of optimizing the transplantation strategy, characteristics of the preferred donor, linkage with liver transplantation, and plasmapheresis and specific immunosuppressive protocols in these patients compared to patients with other complications following kidney transplantation. Therefore, fewer patients may experience rejection of transplanted kidney as a result of primary disease recurrence and also rejection of a second transplanted kidney. The use of national and international registries and databases is also of great importance in the preparation of such reports and even conducting other types of interventions as clinical trials.

Conflict of Interest

The authors declare no conflict of interest.

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