Predictive Factors of Renal Graft Failure in Tunisian Children and young adults: A Retrospective Study

Facteurs prédictifs de l'échec de la transplantation rénale chez les enfants et les adultes jeunes Tunisiens : Une étude rétrospective.

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Abstract

Introduction: Pediatric end-stage renal disease is a rare but severe condition that causes numerous complications and impairs the quality of life of children. Kidney transplantation is the therapy of choice in pediatric end-stage renal disease.
Aim: Our study aimed to identify the predictive factors of renal graft failure after kidney transplantation in Tunisian children and young adults.
Methods: We conducted a retrospective bicentric study of children and young adults (age≤20 years) who had undergone renal transplantation between 1989 and 2019 in Tunisia. We analyzed long-term survival rates and complications after pediatric kidney transplantation and searched for predictive parameters for graft dysfunction. We used a univariate and a multivariate analysis to identify predictive factors of graft survival.
Results: A total of 112 patients underwent 115 kidney transplantations. Graft failure occurred in 30% of the cases. The overall 1-, 3-, 5- and 10-year graft survival rates were 92%, 89.1%, 85.9% and 74.5% respectively. The following parameters strongly influenced graft survival: immunosuppressive regimen including an association other than Mycophenolate mofetil- tacrolimus and corticosteroids (p=0.002), year of transplant (p<0.0001 for 1987–2000), deceased donor (p = 0.039), underlying etiology of end-stage renal disease (p=0.045), occurrence of acute or chronic rejection (p<0.001), a urine protein greater than 0.3 g/l per day (p=0.002), post-transplant urologic complications (p=0.002), five-year creatinine level>1.28 mg/dl (p<0.001). The overall 1-, 3-, 5- and 10-year patients survival rates were 97%, 95%, 90.2% and 84.4% respectively.
Conclusions: Our study identified several predictive factors of graft failure in Tunisian children and young adults undergoing renal transplantation.

Key words: Kidney transplantation, children, predictive factors, living donors, deceased donors, graft survival, graft failure

Résumé

Introduction: La transplantation rénale est la thérapie de choix au cours de l'insuffisance rénale terminale pédiatrique.
Objectif: Identifier les facteurs prédictifs d'échec de la transplantation rénale chez les enfants et les jeunes adultes Tunisiens.
Méthodes: Il s'agissait d'une étude rétrospective bi centrique portant sur des enfants et des adultes jeunes (âge ≤ 20 ans) ayant eu une transplantation rénale entre 1989 et 2019. Nous avons analysé les taux de survie à long terme et les complications après la transplantation rénale. Ont été étudié les facteurs prédictifs de la perte du greffon. Nous avons utilisé une analyse univariée et une analyse multivariée pour identifier les facteurs prédictifs de la survie du greffon.
Résultats: Au total de 112 patients ont eu 115 transplantations rénales. Une défaillance du greffon était survenue dans 30% des cas. Les taux de survie du greffon à 1, 3, 5 et 10 ans étaient respectivement de 92%, 89,1%, 85,9% et 74,5%. Les paramètres suivants ont fortement influencé la survie du greffon : le schéma immunosuppresseur reposant sur une association autre que mycophénolate mofétil - tacrolimus et corticostéroïdes (p=0,02), l'année de la transplantation (p<0,0001 pour 1987-2000), le donneur en état de mort encéphalique (p=0,039), l'étiologie sous-jacente de l'insuffisance rénale terminale (p=0,045), la survenue de rejet aigu ou chronique (p<0,001), une protéinurie supérieure à 0,3 g/l par jour (p=0,002), la survenue de complications urologiques en post-greffe (p=0.002), et une créatinine sérique à 5 ans>1.28 mg/dl (p<0.001). Les taux de survie des patients à 1, 3, 5 et 10 ans étaient respectivement de 97%, 95%, 90,2% et 84,4%.
Conclusions: Notre étude a identifié plusieurs facteurs prédictifs de la perte du greffon chez les enfants et les jeunes adultes Tunisiens ayant eu une transplantation rénale.

Mots clés: Transplantation rénale, enfant, facteurs prédictifs, donneurs vivants, donneurs décédés, survie du greffon, échec de la transplantation

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Introduction

End-stage kidney disease (ESKD) is rare in children, but has unique characteristics in this population. In Tunisia, the incidence of ESKD among children was estimated at 4.25 per million age-related population in 2015 (1), which is similar to other countries (2-5). The progression to ESKD in childhood can have devastating consequences, including increased mortality and cardiovascular morbidity, impaired growth, and psychosocial adjustment issues that significantly affect quality of life (6-10). Kidney transplantation (KTX) is the preferred treatment for pediatric ESKD and has numerous benefits, such as improved survival and quality of life (11-12). However, infectious complications remain common despite significant advancements in immunosuppression, immunology, and microsurgery.

Several factors can affect graft survival in children, including donor and recipient age, donor type, HLA mismatch, pre-transplant dialysis, previous transplant history, underlying cause of ESKD, number of acute rejections, and post-transplant infections (13). However, most of the available data come from developed countries, with little information on predictive factors of graft survival in low-income countries.

Therefore, the purpose of our study was to determine the predictive factors for renal graft failure after kidney transplantation in Tunisian children and young adults.

Methods

Study population

Children and young adults who underwent KTX before the age of 20 between January 1989 and December 2019 were included in our study. Patients with hyperacute rejection were excluded from our study. We collected data from medical charts and electronic records and followed patients at the two referral departments for KTX in Tunisia (Pediatric nephrology department and internal medicine A department in Charles Nicolle Hospital, Tunis, Tunisia)

Our study was a retrospective observational study that focused on children and young adults who underwent KTX before the age of 20. Demographic data collected included the patient's age at the time of KTX and gender. We also gathered clinical, biological, and radiological data, such as physical examination data, current treatments, functional complaints, and viral serological tests. Prior to the KTX, we obtained radiological data, which included kidney and bladder ultrasound, voiding cystourethrogram, and urodynamic assessment if there was suspicion of bladder dysfunction. Furthermore, we recorded the etiology of ESKD for all patients.

Immunosuppressive treatment

For induction therapy, polyclonal anti-thymocyte globulins (ATG), or IL-2 receptor antagonist monoclonal antibody were indicated based on the recipients' immunologic risk profile.

ATG were prescribed at a dose of 1.5 mg/kg/day in 112 cases, and this was administered for a duration of 5 to 10 days following KTX. Basiliximab, an (IL-2R) antagonist was prescribed in 15 cases for patients with low immunological risk at a dose of 20 mg, two hours before transplantation, followed by a second dose 4 days later, as the weight of the transplant recipients exceeded 35 kg in all three cases. Corticosteroids (CS) was then prescribed at a dose of 60 mg/m2 SBA subcutaneously and gradually reduced in steps of 5 mg/day until a dose of 10 mg/day.

CS therapy was combined with a calcineurin inhibitor (CNI) (Cyclosporine A (CsA) or Tacrolimus (Tac)) and/or an antimetabolite (Azathioprine or Mycophenolate Mofetil (MMF)). The inclusion of Azathioprine, CsA, MMF, and Tac in our immunosuppression protocol was respectively implemented in 1986, 1987, 1999, and 2001.

MMF was given at 1200 mg/BSA/day in two divided doses (max daily dose of 2000 mg). The therapeutic window considered effective for exposure to MPA (active metabolite of MMF) in our patients was an AUC of 30 to 60 mg•h/L (HPLC) or 37 to 70 mg•h/L. Criteria for conducting therapeutic MMF monitoring in children consist of the following: lower doses of CNIs, switching or discontinuing CNIs, a high risk of immunologic complications, alterations in gastrointestinal, hepatic, or renal function, potential drug interactions, and non-adherence.

The initial oral dose of tacrolimus was 0.2 mg/kg per day given in two divided doses, it was started when the serum creatinine fell below 2.5 mg/dl. Target whole-blood trough levels were 10–20 ng/mL between days 0 and 14, and 5-15 ng/mL thereafter.

The pharmacological monitoring of CNIs was initially performed every other day during the immediate postoperative period and until the desired levels were achieved. From 4 to 6 months post kidney transplantation, residual level testing was requested once every 15 days, then monthly between 7 and 12 months, and thereafter on a quarterly basis. Residual level monitoring was also requested whenever there was a change in prescription or when the patient's condition could affect blood levels. Additionally, it was done whenever there was a decrease in renal function, which could indicate toxicity or rejection, in accordance with the recommendations of KDIGO.

Rejection episodes

A graft biopsy was indicated in the presence of clinical signs of rejection (fever, prolonged oligo-anuria, a tender and painful graft, hypertension...) an unexplained increase in creatinine (Absence of dehydration, urinary obstruction, high CNI levels or other apparent cause), positive donor specific antibodies (DSA), and in all challenging diagnoses. Protocol biopsy was not a common practice.

Treatments used in Antibody-mediated rejection (AMR) was based on: daily plasmapheresis (PLEX) for three to five initial sessions associated with pulse CS. Polyclonal immunoglobulins (IVIG) were prescribed at a dose of 1 g/

kg after each PLEX session Rituximab was administered by intravenous infusion at a standard dose of 375 mg/m2 weekly for four consecutive weeks (on days 1, 8, 15 and 22 of the rejection episode). The effectiveness of the treatment protocol was evaluated by the DSA mean fluorescence intensity (MFI) reduction.

Before the advent of Rituximab, the protocol for managing AMR included increasing maintenance immunosuppression, IVIG. Often, it was accompanied by ATG or CS pulses with the assumption of associated T-cell mediated rejection (TCMR).

Treatment of TCMR was based on CS pulses, ATG in severe forms (1,5 mg/Kg/d for 7 days).

Antibiotic prophylaxis

All patients received antibiotic prophylaxis, which consisted of intravenous cefazolin during the surgery. For the postoperative period, they received Trimethoprim-Sulfamethoxazole for six months to prevent bacterial infections and pneumocystis jirovici pneumonia. In addition, all patients, except for those who received a CMV-negative kidney, were given daily prophylactic treatment against cytomegalovirus for six months.

Laboratory investigation

We obtained blood samples twice a week during the first month after the KTX, followed by once a week for the next three months, once a month for the subsequent four years, and then every three months. We calculated creatinine clearance (CrCl) using the Schwartz formula (14). Additionally, we performed a routine cytobacteriological examination of the urine during the first month and repeated it if there were signs suggestive of a urinary tract infection.

Sample size and statistical analysis

We obtained a sample of 115 KTX from two nephrology departments in Tunisia, and our primary outcome measure was renal graft survival after KTX. We used both univariate and multivariate analyses to evaluate baseline factors that could predict graft survival. We also used the Kaplan-Meier method to generate cumulative survival curves and compared differences between these curves using the log-rank test. We considered several factors as possible predictors of graft survival, including gender, age at KTX, presence of vesicoureteral reflux before KTX, pre-transplant surgical and urinary tract infection (UTI) history, donor type (deceased donor (DD) or living donor (LD)), transplanted kidney, occurrence of graft rejection, and post-KTX complications. We used $\chi 2$ tests to compare categorical variables between groups and t-tests to compare continuous variables between two groups when distributions were approximately normal and variances were approximately equal. Data are presented as mean and standard deviation. We considered a p value of less than 0.05 as statistically significant throughout our analysis. We conducted all statistical analyses using SPSS version 24 (IBM Corporation). It is important to note that kidney transplantations are fully funded by the national health insurance for insured patients, whereas the hospital assumes the financial responsibility for non-insured individuals. Lastly, our study was approved by the Charles Nicolle hospital review board.

Results

During the study period, 115 kidney transplants were carried out on 112 patients, with three patients undergoing two transplantations. The average age was 15.5 ± 3.5 years, and there was a male/female ratio of 1.5. The majority of recipients (n=77; 68.1%) received left donor kidney transplants, and most of the kidney transplants (71.3%) took place during the 2000s (Table 1)

Table 1. Patient's characteristics following RTX

Characteristic		n (%)
Age		
	Age≤10 Y	10 (8.84%)
	11<Age>15 Y	43 (38.05%)
	Age>15 Y	60 (53.09%)
Gender		
	Male	68 (60.2%)
	Female	45 (39.8%)
Average weight		40,4Kg ± 12,2
Period transplantation		
	1987-2000	33 (28.7%)
	2000-2019	82 (71.3%)
Primary renal disease		
	CAKUT	34 (30%)
	✓ Primary vesicoureteral reflux	15 (44%)
	✓ Bladder dysfunction	8 (23.5%)
	✓ Renal hypoplasia	5 (14.7%)
	✓ Posterior urethral valves	3 (8%)
	✓ Obstructive megaureter	3 (8%)
	Hereditary nephropathies	30 (26%)
	✓ Nephronophthisis	10 (33.3%)
	✓ Steroid resistant nephrotic syndrome	8 (26.6%)
		8 (26.6%)
	✓ Alport syndrome	3 (10%)
	✓ Autosomal Dominant Polycystic Kidney Disease	1 (3%)
	✓ Cystinosis	23 (20%)
	Glomerular nephropathies	10 (43.5%)
	✓ Steroid resistant nephrotic syndrome	5 (21.8%)
	✓ Focal segmental glomerulosclerosis	3 (13%)
	✓ Primary IgA nephropathy	3 (13%)
	✓ ANCA-associated vasculitis	2 (8.7%)
	✓ Membranoproliferative glomerulonephritis	28 (24%)
	Unknown etiology	
Dialysis modalities		
	HD	52 (45.2%)
	PD	37 (32.2%)
	HD+PD	25 (21.7%)
	Pre-emptive kidney transplantation	1 (0.9%)
Immunosuppression induction therapy		
	ATG	100 (90%)
	anti-*IL-2R* monoclonal antibodies	15 (10%)
Donor		
	LD	
	✓ Mean age (Years)	77 (68%)
	✓ F/M ratio	39.6±10.1(27-60)
	✓ Relationship	1.75 (49F, 28M)
	▪ Mothers	47(61%)
	▪ Fathers	20 (26%)
	▪ Brothers	7 (9%)
	▪ Sisters	2 (2.6%)
	▪ Aunts	1 (1.4%)
	DD	36 (32%)

Table 1. (Continued) Patient's characteristics following RTX

Characteristic	n (%)
Side of the kidney transplant	
Left kidney	68 (60.2%)
Right kidney	45 (39.1%)
Urological complications following KTX	
Vesicoureteral reflux	12 (10.43%)
Urinary fistula	5 (4.3%)
Lymphocele	4 (3.4%)
Ureteral stricture	1 (0.86%)
Urolithiasis	1 (0.86%)
Infectious complications following KTX	
Viral infections	66 (57.4%)
➢ CMV	20 (30.3%)
➢ VZV	20 (30.3%)
➢ HSV	12 (18.2%)
➢ BK	7 (10.6%)
➢ EBV	7 (10.6%)
Bacterial infections	66 (57.4%)
➢ Urinary tract infections	41 (62.1%)
➢ Sepsis	12 (18.2%)
➢ Skin infection	5 (7.5%)
➢ Pneumonia	4 (6%)
➢ Tuberculosis.	4 (6%)

CAKUT: congenital anomalies of the kidneys and urinary tracts, ANCA: Antineutrophil cytoplasmic antibody, HD: Hemodialysis, PD: Peritoneal dialysis, LD: Living Donor, DD: Deceased Donor, KTX: Kidney Transplantation, CMV: Cytomegalovirus, VZV: varicella zoster virus, HSV: herps simplex virus, EBV: Epstein-Barr virus

All the children underwent transplantation in the iliac fossa.

Prior to the kidney transplants, 9 patients who received a transplant from a deceased donor tested positive for anti-HLA antibodies. However, all patients who underwent a transplant had negative cross-match results. None of the transplants in our series were ABO-incompatible.

The total number of hospital admissions after the kidney transplants was 321, with an average of 2.84 admissions per patient. Twenty-nine children (25.7%) experienced at least one episode of acute rejection, which was diagnosed in cases of acute kidney injury (AKI) occurring within the first three months after transplantation. The median time for the first episode of rejection was 38.66 days (ranging from 6 to 128 days). Chronic rejection was observed in 20.4% of cases (n=23), characterized by the presence of proteinuria and a gradual decline in graft function.

The overall survival rates for patients at 1, 3, 5, and 10 years were 97%, 95%, 90.2%, and 84.4%, respectively (Figure 1).

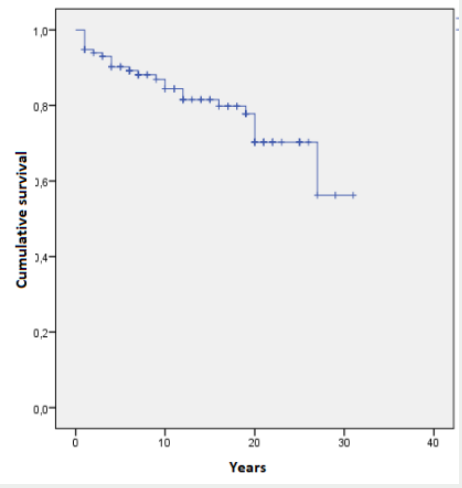

Figure 1. Overall survival of transplant recipients

As for graft survival rates, they were 92%, 89.1%, 85.9%, and 74.5% at 1, 3, 5, and 10 years, respectively (Figure 2).

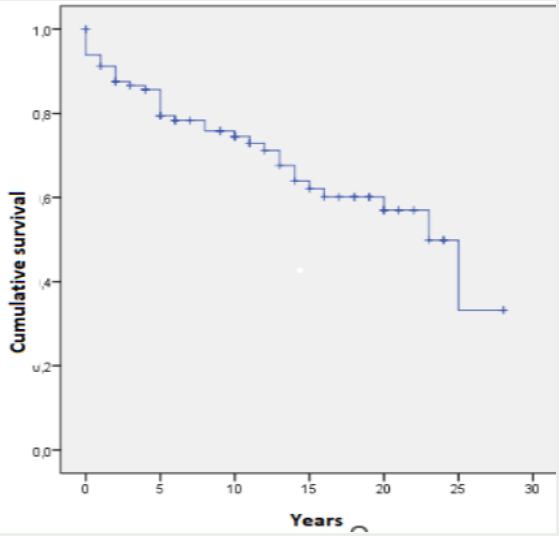

Figure 2. Renal graft survival

Multivariate analysis revealed that the most significant negative factors for graft function loss were hereditary kidney disease, post-transplant urologic complications, episodes of acute or chronic rejection, and a creatinine level greater than 1.28 mg/dL after 5 years (Table 2).

Table 2. Predictive factors of Renal Graft failure (Multivariate analysis)

Variable	OR	$CI_{95\%}$	p
Immunosuppression combination other than MMF-Tac-CS	0.383	[0.87; 0.168]	0,002
Acute rejection	6.5	[2.58 ; 16.32]	<0.001
Chronic rejection	45.08	[9.63 ; 211]	<0.001
DD	3.25	[1.51 ; 6.98]	0.039
Transplant year: 1987-2000	8.39	[3.60 ; 19.51]	<0.001
Etiology of ESKD: hereditary kidney disease	3.48	[4.16 ; 20.21]	0.045
Post-transplant urologic complications	0.428	[0.85 ; 0.223]	0.002
Five-year creatinine level > 1.28 mg/dL	7.2	[3.15 ; 17.23]	<0.001
Daily urine protein >0.3g/L	7.23	[2.12 ; 24.67]	<0.001

OR: Odds ratio, CI: Confidence Interval, MMF: Mycophenolate Mofetil, Tac: Tacrolimus, CS: Corticosteroids, DD: Deceased Donor, ESRD: End-stage renal disease,

Discussion

According to research, KTX is the most effective treatment for ESKD in children, improving life expectancy and quality of life (15,16). Improved graft survival rates have been reported in recent years, including the present study which found better survival rates in transplanted children in the 2000s compared to previous years, with satisfactory rates compared to other studies (17-19). Factors such as pre-transplant dialysis, surgical approach, ischemia time, acute rejection, lower urinary tract (LUT) dysfunction, postoperative urologic interventions, and infections did not have a significant prognostic influence on graft function over time in this study (20-25). LD was associated with better survival, which is consistent with the literature (26-27), according to the Organ Procurement and Transplantation Network and Scientific Registry of Transplant Recipients, the graft

survival rate is higher for living kidney donation when compared to deceased donation. The impact of HLA mismatches on graft survival is controversial, with some studies reporting a significant impact while others, including this study, found no association (28-32). It is possible that HLA matching may be less important over time due to improved immunosuppressive regimens or advancements in HLA typing technology.

In the pediatric population, urological disease as cause of ESKD is relatively common; thus, a detailed evaluation of the recipient before KT to avoid graft dysfunction is mandatory. In contrast to some studies, uropathies were not found to be predictive factors of graft failure in this study, with comparable graft survival reported for recipients with and without underlying structural kidney disease (33-36). However, correction of structural urogenital abnormalities, and optimization of emptying and storage function of the bladder have to be achieved before transplantation. The multi-center design and long follow-up time are strengths of this study, to our knowledge, this is the first study from an Arab or African country that has analyzed factors related to prolonged renal graft survival (37,38). Limitations include the retrospective design and small, heterogeneous cohort, which may affect the interpretation of the results. Factors such as medication adherence and variations in immunosuppressive medication levels were not documented.

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