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Characteristics and Outcomes of Kidney Transplant Recipients with a Functioning Graft for More than 25 Years

Sandesh Parajuli[a] Didier A. Mandelbrot[a] Fahad Aziz[a] Neetika Garg[a] Brenda Muth[a] Maha Mohamed[a] Michael J. Armbrust[a] Brad C. Astor[a, b] Arjang Djamali[a, c]

[a]Division of Nephrology, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA; [b]Department of Population Health Sciences, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA; [c]Division of Transplant Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Keywords
Kidney transplant · Survival · Complications · Cardiovascular disease · Infections · Malignancy

Abstract
Background: Information regarding the clinical characteristics and outcomes of kidney transplant recipients (KTRs) with >25 years of graft survival is limited. ***Methods:*** In this single-center observational study, we characterized KTRs transplanted between 1973 and 1992 with active follow-up as of July 31, 2017. ***Results:*** We identified 112 patients with >25 years of allograft function. The mean posttransplantation follow-up was 29.8 ± 4.0 years. Glomerulonephritis was the most common cause of end-stage renal disease (ESRD) (52%). The majority received live donor transplants (66%), including 25 patients (22%) with human leukocyte antigen-matched kidneys. The incidence of biopsy-confirmed acute rejection was 21%, ranging from 0 to 26 years post transplantation. Donor-specific antibodies (DSA) were checked in 80% of patients at a mean of 28.4 ± 0.11 years post transplantation. Of these, only 15% were positive. The incidence of malignancy was 44%, with nonmelanoma skin cancers being most common. The incidence of infectious complications was 77%, mostly represented by urinary tract infections. At the time of last follow-up, 63% were on a calcineurin inhibitor (CNI)-free regimen, mean serum creatinine was 1.4 ± 0.6 mg/dL, and the prevalence of hypertension and dyslipidemia was 89 and 88%, respectively. ***Conclusion:*** The majority of patients with a long-term functioning graft had glomerulonephritis as cause of ESRD, had received a live donor kidney, were on a CNI-free regimen, and had a low incidence of DSA and opportunistic infections. These characteristics define a unique group of patients requiring specific post-transplantation monitoring and management.

Introduction

Kidney transplantation is the best form of treatment for patients with end-stage renal disease (ESRD) of any cause. Kidney transplant recipients (KTRs) experience survival benefits in all age groups [1], have better health-

E-Mail karger@karger.com
www.karger.com/kdd

Sandesh Parajuli, MBBS
4175 UW Medical Foundation Centennial Building
1685 Highland Avenue
Madison, WI 53705 (USA)
E-Mail sparajuli@medicine.wisc.edu

Table 1. Study population

Number of patients	112
Year of transplantation	1973–1992
Mean age at transplantation, years	34.0±8.9
Male	60 (54%)
Race	
Caucasian	107 (96%)
African American	2 (2%)
Other	3 (2%)
Cause of ESRD	
Glomerulonephritis	58 (52%)
Diabetes	10 (9%)
Hypertension	4 (3%)
Other	40 (36%)
Living donor transplant	74 (66%)
Living related, biological	68 (61%)
HLA-matched	25 (22%)
Previous KTRs	18 (16%)
Second transplant recipients	15 (13%)
Third transplant recipients	3 (3%)
Preemptive KTRs	45 (40%)
HLA 0 mismatch	28 (25%)
Deceased donor with HLA 0 mismatch	3 (3%)
Induction immunosuppressive medication	
Depleting antibody (MALG, ATG, OKT3)	55 (48%)
Unknown (depleting therapy or no induction)	58 (52%)
Maintenance immunosuppression on discharge	
Steroids	111 (99%)
CsA/Neoral	82 (73%)
Azathioprine	101 (90%)
Mycophenolate	5 (4%)
Mean hospital stay, days	21.3±5.3 (8–44)

ATG, antithymocyte globulin; CsA, cyclosporine; ESRD, end-stage renal disease; KTRs, kidney transplant recipients; MALG, Minnesota antilymphocyte globulin.

related quality of life [2], and kidney transplantation is cost-effective compared to being on dialysis [3]. Death-censored graft failure in kidney transplantation has improved significantly in the last 25–40 years. The half-life of a standard criteria, deceased donor kidney in the United States has increased by almost 50% from 10.6 years in 1989 to 15.5 years in 2005, and a similar pattern was seen with living donor transplants, mainly due to significant improvement in first-year graft survival [4]. Despite these advances, there has not been much improvement in long-term graft survival, and it is unlikely that a single kidney transplant will meet the need of lifelong renal replacement therapy, especially in younger KTRs [5]. The number of dialysis patients with a failed kidney transplant is increasing, and allograft failure among previous recipients of a kidney transplant is now the fourth leading cause of ESRD in the United States [6]. KTRs returning to dialysis have a significantly reduced survival rate compared to both the transplant-naïve dialysis population and those with functioning renal grafts [7–9]. Various factors, including age, disease recurrence, human leukocyte antigen (HLA) matching, delayed graft function, and various other donor-related factors that also influence graft survival influence the long-term outcome of kidney transplantation [10].

Despite these obstacles, there is a small group of patients with prolonged graft survival and good kidney function decades after transplantation. In this single-center observational study, we share our experience working with KTRs with a functional allograft for >25 years.

Methods

Study Population and Design

We analyzed data from KTRs in the Wisconsin Allograft Recipient Database. This single-center, retrospective observational study included KTRs at the University of Wisconsin, Madison who were actively followed at the University Hospital and Clinics and had a functional allograft for >25 years as of July 31, 2017. Patients transplanted at a different center but followed at our center, patients transplanted at our center but lost to follow-up, or those whose care was transferred to a different center were excluded from the study.

The Kidney Transplantation Program of the University of Wisconsin

The University of Wisconsin has a history of kidney transplantation dating back >50 years [11]. More than 13,000 kidney transplantations have been performed here to date. The University of Wisconsin, Madison also has a high-volume outpatient clinic with >1,000 outpatient visits per month [12].

Clinical Follow-Up and Monitoring

We follow our KTRs at either the University Hospital or various outreach regional clinics at least once a year until graft failure or until the patient decides to transfer their care to a different transplantation center.

Induction and Maintenance Immunosuppression

Our induction and maintenance immunosuppression regimens have evolved with time. In the past, we used depleting agents in all KTRs unless they were receiving an HLA 0 mismatch kidney. In the early 1980s, our primary induction immunosuppressive

Table 2. Posttransplantation complications

Patients with a kidney biopsy	50 (45%)
Mean interval from transplantation to biopsy, months	108.2±132.5 (0–356)
Biopsy findings (mean interval from transplantation to biopsy findings in months)	
Acute rejection	24 (21%) (65.6±117.7)
Calcineurin inhibitor toxicity	14 (13%) (52.0±88.3)
Disease recurrence	3 (3%) (57.3±49.9)
Patients with malignancy	49 (44%)
Malignancies	123
Mean interval from transplantation to malignancy, months	254.7±103.9 (12–509)
Type of primary malignancy (mean interval from transplantation to malignancy in months)	
Squamous cell carcinoma skin	18 (16%) (277.2±112.3)
Basal cell carcinoma skin	19 (17%) (214.9±86.2)
Melanoma skin	2 (2%) (249±124.5)
Skin cancer of unknown cell type	9 (8%) (211.4±70.7)
Kidney/prostate/uroepithelium cancer	10 (9%) (272.8±78.9)
Patients with infection	86 (77%)
Infections	388
Mean interval from transplantation to infection, months	155.8±97.7 (0.1–435)
Type of infection (mean interval from transplantation to infections in months)	
Urinary tract infection	38 (34%) (172.1±98.3)
Cytomegalovirus	11 (10%) (22.8±66.4)
Pneumonia	18 (16%) (137.8±78.2)
Gastrointestinal	9 (8%) (178.1±122.8)

medication was Minnesota antilymphocyte globulin (MALG); in the late 1980s and early 1990s, we began using OKT3, and later switched to antithymocyte globulin (ATG). Maintenance immunosuppression was similar in that we used cyclosporine, azathioprine, and steroids until the early 1990s and then switched to tacrolimus, mycophenolic acid, and prednisone. Most of our patients were maintained on triple immunosuppressive medications with tacrolimus or cyclosporine, mycophenolate mofetil or azathioprine, and prednisone as the standard of care. We did not routinely convert from cyclosporine to tacrolimus or mycophenolate to azathioprine unless there were any complications. Our long-term standard tacrolimus trough goal was 5–7 ng/mL and that of cyclosporine 50–100 ng/mL. Maintenance immunosuppression was adjusted, and some were discontinued based on transplantation provider discretion considering various factors, including immunological risk and complications.

Results

Study Population (Table 1)

A total of 2,749 KTRs were actively followed at our transplantation center as of July 31, 2017. Of that number, 112 (4%) had had the same kidney allograft for >25 years. Patients were transplanted between 1973 and 1992, the mean age at the time of transplantation was 34.0 ± 8.9 years, 54% were male, and the majority were Caucasian. Glomerulonephritis was the most common cause of ESRD (52%), and only 9% had diabetes as a cause of ESRD. The majority were living KTRs and 40% were preemptive KTRs; 18 (16%) had had previous kidney transplants, including 3 (3%) recipients who had received their third transplant; 23 patients had been transplanted in or prior to 1983 (pre-cyclosporine era) and the rest after 1983.

Transplantation-Specific Baseline Characteristics (Table 1)

A total of 28 patients (25%) received HLA 0 mismatch kidneys, including 3 from deceased donors. MALG was used for induction immunosuppression in 33% of the recipients, OKT3 in 11%, and ATG in 4%. We were not able to identify the induction immunosuppression in 52% of the patients, as it was not documented in the electronic medical records. However, based on our practice, we assume that the majority received a depleting agent with MALG or OKT3 unless they received an HLA 0 mismatch kidney. Ninety-nine percent of our patients were discharged home on steroids and 90% on azathioprine. The mean hospital stay post transplantation was 21.3 ± 5.3 days.

Table 3. Findings at last follow-up

Mean posttransplantation follow-up, years	29.8±4.0
Hypertension	100 (89%)
Diabetes	22 (20%)
Hyperlipidemia	98 (88%)
Coronary artery disease	20 (18%)
DSA findings at last follow-up	
Mean last DSA check interval post transplantation, years	28.4±0.11
Never tested	22 (20%)
Negative at last check	73 (65%)
Positive at last check	17 (15%)
DSA types/characteristics	
Class I DSA positive	3
Mean MFI	2,035±2,855
Types	A1 + B44 in 1 patient and B7 and A2 in 1 each
Class II DSA positive	12
Mean MFI	14,634±11,227
Types	10 patients had DSA against DQ and 3 had DSA against DR; 1 had DSA against both DQ and DR
Both class I and II DSA positive	2
Mean MFI	11,421±12,644
Types	both had DSA against B and DQ
Immunosuppressive medications	
Not on calcineurin inhibitor	70 (63%)
MPA + steroid	34 (30%)
Azathioprine + steroid	25 (22%)
CsA + MPA + steroid	13 (12%)
Tacrolimus + MPA + steroid	3 (3%)
Mean serum creatinine, mg/dL	1.4±0.6
Mean estimated glomerular filtration rate, mL/min/1.73 m^2	53.2±14
Mean urine protein-to-creatinine ratio, g/g	0.7±2.7

CsA, cyclosporine; DSA, donor-specific antibodies; MPA, mycophenolic acid.

Posttransplantation Complications (Table 2)

We examined three major posttransplantation complications: biopsy-proven rejection, malignancy, and infections. A total of 45% of the patients had 89 kidney biopsies, and 21% had features of acute rejection ranging from 0 to 312 months post transplantation. Similarly, 44% of the patients had 123 malignancies, with skin cancer being the most common. Other, less common, malignancies were lymphoma, breast cancer, and thyroid cancer. Seventy-seven percent had 388 infections, with urinary tract infections being the most common ones. Other less common infections were cellulitis, infective endocarditis, and sinusitis.

Findings at Last Follow-Up (Table 3)

At a mean posttransplantation follow-up of 29.8 ± 4.0 years, mean serum creatinine was 1.4 ± 0.6 mg/dL. The majority of patients had hypertension (89%) and hyperlipidemia (88%). At the last follow-up, 71 (63%) were on a calcineurin inhibitor (CNI)-free regimen, 22% had diabetes, and 20% had coronary artery disease. Only 20% were never tested for donor-specific antibodies (DSA), and of those tested, 15% were DSA positive, predominantly against DQ and DR. Out of the 71 patients on a CNI-free regimen, only 8 (11%) had DSA at last follow-up. Anecdotally, 1 patient with a kidney from an identical twin was not on any immunosuppressive medication. Of

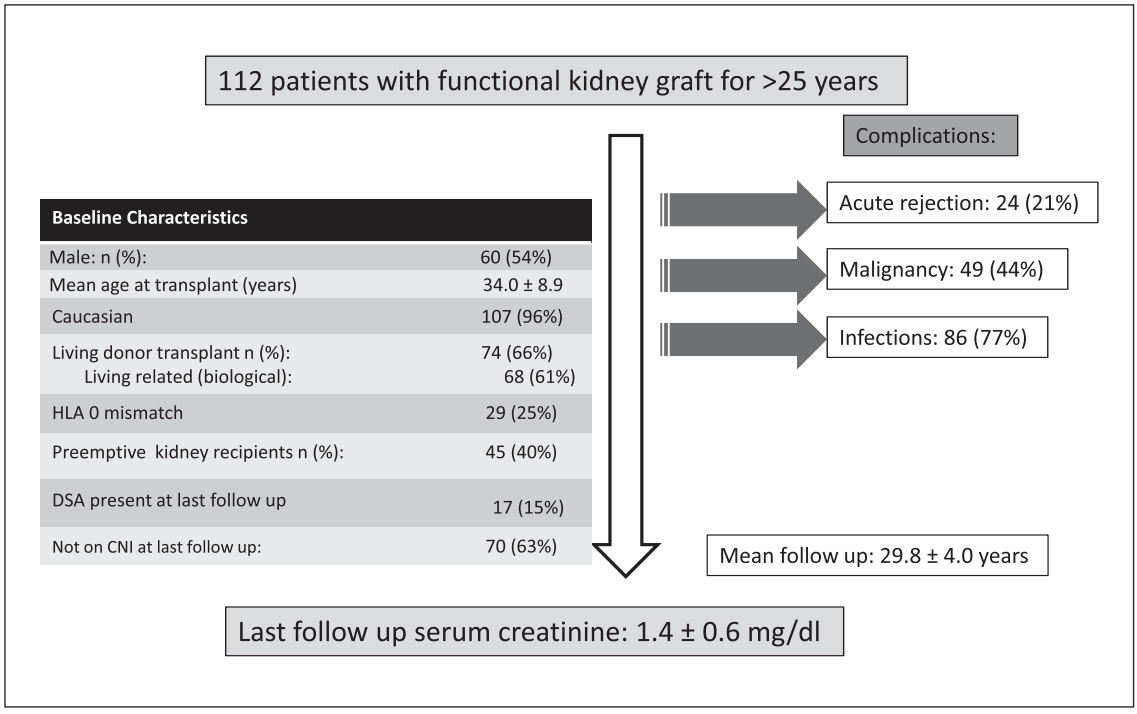

Fig. 1. Summary of patients with functional allografts for >25 years.

the 71 patients with a CNI-free regimen, the CNI was discontinued in 42 patients at an interval ranging from 1–24 years post transplantation due to complications or low immunological risk for rejection.

Discussion

In this large cohort of 112 KTRs with functional allograft for >25 years, we report some interesting findings as summarized in Figure 1. Twenty-one percent of the recipients had complications of rejection, 44% malignancy, and 77% infections, but patients maintained excellent graft function over this time. Hypertension and hyperlipidemia were prevalent, while diabetes and coronary artery disease were not, despite the fact that the patients had been KTRs for almost three decades.

There has been a significant improvement in the prevention of kidney rejection. Death with functional graft is the most common cause of graft failure, and cardiovascular disease (CVD), infections, and malignancies are the leading causes of death among KTRs [13]. CVD and mortality decrease after kidney transplantation compared to being on dialysis, but still remain more prevalent than in the general population. The risk of mortality is initially worse with kidney transplantation compared to dialysis, with a relative risk of 2.84; however, the risks are equal by 3–4 months post transplantation, and subsequently there are long-term survival benefits to the transplantation group [14]. Overall cardiovascular mortality is approximately two times higher in KTRs compared to the general population [15, 16]. After CVD, infections are the second most common cause of death in KTRs. The risk of infection is significantly higher after kidney transplantation than in the general population and is a common cause of morbidity and mortality. Urinary tract infection is the most common bacterial infection requiring hospitalization in KTRs [17]. Another common complication in our KTRs is malignancy. The overall incidence of malignancy in KTRs is three to five times higher compared to the general population, with skin cancer being the most common cancer [3].

Kidney transplantation is not a cure for patients with ESRD, but it is a better form of treatment for ESRD than dialysis. Rejection, and predominately antibody-mediated rejection, is the most common cause of death-censored graft failure. Other common causes of graft failure include recurrence of the original diseases and BK virus nephropathy [6]. The majority of KTRs revert back to chronic kidney disease stage 2 or 3 after transplantation

[18, 19]. KTRs are a unique subgroup of patients with chronic kidney disease due to the presence of a single functioning kidney, the use of immunosuppressive medications, and the duration of disease [3].

In a study from Northern Ireland, of the 706 KTRs transplanted between 1968 and 1993, 117 (16%) were still alive with a functional graft 20 years post transplantation [20]. The authors concluded that in these long-term kidney graft survivals, the focus of management should be on the prevention of cancers and CVD, as the prevalence was very high in these patients. In another study, the most common causes of death among KTRs 20 years after transplantation were CVD and malignancy [21]. As with our study, a higher incidence of cancer and CVD was found among 2,202 KTRs even 10 years after transplantation [22].

Despite these obstacles, some of the KTRs maintain excellent graft function. Kidney transplantation with functional graft for >25 years is a great success. As the prevalence of hypertension and dyslipidemia is significantly higher in our patient population, strategies for the optimum management of these cardiovascular risk factors may prevent cardiovascular events and prolong graft survival [23]. CVD is the most common cause of death in KTRs, despite recent efforts to increase the awareness of CVD in this patient population [24]. Hypertension with a blood pressure of >140/90 is prevalent in >70% of transplant recipients [25]. There are no randomized controlled trials of antihypertensive drugs or optimal blood pressure goals in transplant recipients. However, pharmacological therapy along with nonpharmacological interventions, including weight reduction, exercise, and dietary sodium restriction, are recommended [24]. Similarly, dyslipidemia is also strongly associated with CVD. Dyslipidemia is linked with some immunosuppressive medications, including corticosteroids, CNIs, and sirolimus [24]. The Kidney Disease Outcomes Quality Initiative recommends that all adults and adolescents be tested for dyslipidemia on a regular basis and after the adjustment of immunosuppressive medications [26]. Attention to dyslipidemia is required as interventions for dyslipidemia have an impact on reducing cardiac events in clinical trials specific to the transplantation population [27].

Other common complications seen in our patient population were infections, particularly urinary tract infections. All urinary tract infections in KTRs are considered complicated, and thus standard treatment typically involves 7–14 days of antibiotic therapy [17]. It is recommended that KTRs should receive routine vaccines as per national and local guidelines, except for live attenuated vaccines [28]. Proper screening as well as early diagnosis and treatment may prolong patient survival as some of the clinical presentations may not be typical in immunosuppressed recipients.

Our observations have the limitations inherent to this type of study. As this was a single-center study, it may not be possible to generalize our results to other centers. There was not much diversity in the patients' race. Due to the nature of the study with historical data, among the recipients transplanted before 1992, some transplant-related information was missing. However, to our best knowledge, our study is the largest cohort of this type of study from a single center. Not only do our data provide some of the important aspects of patients with prolonged graft survival and associated complications to the providers, they also provide some encouragement and positive reinforcement to newly transplanted recipients and to patients on waiting lists.

In summary, the majority of patients with a long-term functioning graft had glomerulonephritis as cause of ESRD, received a live donor kidney, were on a CNI-free regimen, and had a low incidence of DSA and opportunistic infections. These characteristics define a unique group of patients requiring specific posttransplantation monitoring and management. As the number of KTRs with prolonged graft survival may be rising, health care providers should be aware of the management of complications associated with prolonged graft survival in this unique group of patients.

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Statement of Ethics

All clinical and research activities were consistent with the principles of the Declaration of Helsinki. This study was approved by the Health Sciences Institutional Review Board at the University of Wisconsin. The study was of very minimal risk to the subjects, without any physical risk. The only potential risk was breach of confidentiality. We carefully reviewed our study procedures to ensure that the risk of breach of confidentiality was minimized as much as possible. For that reason, the research was conducted with waiver of informed consent per university policy.

Disclosure Statement

The authors have no financial disclosures or conflicts of interest. There were no funding sources.

Author Contributions

S. Parajuli: concept, design, data collection, analysis, manuscript preparation. D.A. Mandelbrot: design, analysis, manuscript preparation, editing. F. Aziz: analysis, editing. N. Garg: analysis, editing. B. Muth: analysis, editing. M. Mohamed: analysis, editing. M.J. Armbrust: analysis, editing. B.C. Astor: analysis, editing. A. Djamali: original idea, concept, design, analysis, manuscript preparation, editing.

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