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RESEARCH ARTICLE

Long-Term Outcomes in 831 Kidney Transplant Recipients with 20 Years of Graft Function

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ABSTRACT
An understanding of long-term outcomes for kidney transplant (KTx) recipients who survive with graft function beyond a specific time posttransplant is the first step in creating protocols to optimize care for current and improve outcomes for future recipients. We studied 831KTx recipients-580 living donor (LD); 251 deceased donor (DD)—with graft survival (GS) >20 years. For primary LD recipients, 25-year patient survival (PS) was 83%; 35-year, 59%. Their 25-year death-censored graft survival (DCGS) was 89%; 35-year, 72%. DD recipients had lower PS (P<0.01), DCGS (P<0.01). After 20 years, two major causes of graft loss (GL) were death with function (DwF)(58%, LD; 58%, DD) and interstitial fibrosis and tubular atrophy (IFTA)(22%, LD; 23%, DD). Two major causes of DwF were cancer (31%, LD; 31%, DD) and cardiovascular disease(CVD)(19%, LD;17%, DD). Per multivariate analysis (MVA), risk factors for GL after 20 years in pre–calcineurin inhibitor(CNI) era were human leukocyte antigen (HLA) mismatches >3 antigens, pretransplant type 1 diabetes mellitus (DM1); in CNI era, a history of rejection, female gender. New comorbidities after 20 years were common: CVD (13%, non-DM1;18%, DM1), infections (27%, non-DM1;37%, DM1), 20-29 years posttransplant. Cancer after 20 years included: nonmelanotic skin cancer,22%; solid organ,7%; post-transplant lymphoproliferative disease(PTLD),2%. To improve long-term outcomes, clinical trials on prevention, recognition, and treatment of new comorbidities are needed.

KEYWORDS: Kidney Transplantation, Long-term outcomes, Infection, Cardiovascular Disease, Cancer.

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INTRODUCTION

Early in the history of clinical transplantation (i.e., through the mid-1970s), the rates of 1-year PS and GS were low. In the 1960s, for DD kidney transplant recipients in the United States, 1-year PS was 55%; GS, 35% [1]. Currently, with advances in immunosuppression, antimicrobial management, pretransplant histocompatibility testing, and pre- and posttransplant care, both short- and intermediate-term outcomes (1 to 10 years posttransplant) have improved, and more recipients are surviving long-term (i.e., with GS>10 years) [2, 3].
Numerous factors—e.g., end-stage renal disease (ESRD) or morbidity pretransplant, prolonged exposure to immunosuppression posttransplant—affect long-term PS, GS, and development of comorbidities. Moreover, as long-term recipients age, they can develop age-related morbidities that are not necessarily related to pretransplant conditions or to immunosuppression. Chapman et al. recently noted that the mortality rate of long-term recipients equaled that of individuals in the nontransplant population who were 30 years older [4].

A number of studies have looked at long-term survival and morbidity for an entire transplant population. However, only a few studies have looked at outcomes for a subgroup beyond a specific time posttransplant [2, 5-8]. In 2008, we described long-term outcomes for 2,202 recipients with GS of at least 10 years [2]. Herein, we describe 831 recipients with GS of at least 20 years, including their subsequent actuarial PS and GS, causes of death and graft loss, and development of new comorbidities. A better understanding of outcomes for long-term recipients is paramount. In fact, it is the first step in creating protocols to optimize care for current recipients and improve outcomes for future recipients. Specifically, surveillance and preventive strategies are needed to minimize development of comorbidities and to prolong both PS and GS.

MATERIALS AND METHODS

From June 7, 1963, through September 15, 1993, a total of 3,802 kidney transplants were performed at the University of Minnesota and had a potential GS of at least 20 years.

Of those 3,802 recipients, 1,937 had a living donor (LD); 1,865, a DD. Our immunosuppressive protocols have previously been described in detail [9]. After 1967, all recipients (except for those participating in a few clinical trials) underwent induction with a polyclonal antibody. Through the end of 1983 (Era1), prednisone and azathioprine were used as maintenance immunosuppression; from 1984 on (Era2), maintenance immunosuppression was calcineurin inhibitor (CNI)–based.

At our center, all donor and recipient information is kept in a database approved by our institutional review board. For all recipients in this study, we entered basic demographic characteristics, donor information, histocompatibility, cause of ESRD, cause and date of graft loss, and cause and date of death. Starting in 1984, with the introduction of cyclosporine (CSA) (Era2), we also recorded AR episodes, pre- and posttransplant comorbidities, and posttransplant hospitalizations.

Our follow-up protocols have previously been described [2]. Briefly, we enter data from predetermined times posttransplant (e.g., monthly for the first 6 months; then at 9, 12, and 18 months; thereafter, annually) into our database. In addition, we collect data from our center's clinical records, from our review of outpatient charts and information sent by other institutions, and from an annual survey that we send to all recipients. To document cause of death, we review medical records from outside institutions, obtain a copy of the death certificate, and/or contact the recipient's family. Similarly, we review medical records from outside institutions regarding graft loss, graft biopsy, and transplant nephrectomy. For recipients with chronic graft deterioration, we enter the cause of graft loss according to the last biopsy, if recent (or, alternatively, according to the biopsy plus subsequent clinical events). For recipients with infections or rejection diagnosed at outside institutions, we attempt to obtain reports of cultures and biopsies. For recipients with new comorbidities (e.g., cancer), we obtain the medical records and pathology reports.

To achieve consistency among data personnel, we have established "choice field" definitions for cause of death, cause of graft loss, rejection, biopsies, histocompatibility, donor information, comorbidities, and readmissions. Over time, the choice fields for cause of death have remained unchanged. However, the choice fields for cause of graft loss have evolved, as follows: "CNI-related nephrotoxicity" was added as a possible cause, "chronic rejection/chronic allograft nephropathy" was changed to "IFTA", and fields were added for "antibody-mediated rejection." The choice fields for CVD continue to include angina, cardiac arrest requiring defibrillation, arrhythmia, documented coronary artery disease, cardiomyopathy, congestive heart failure, myocardial infarct, or valve dysfunction. The choice fields for cerebrovascular disease continue to include stroke, intracerebral bleed, or transient ischemic attack. The definition of "sudden death" continues to be death at home with no obvious cause and no postmortem autopsy done.

For our current study, we compared the characteristics of recipients with GS of at least 20 years vs. all recipients transplanted in the same interval. For recipients with GS of at least 20 years, we determined the subsequent actuarial PS, GS, and DCGS; the primary cause of death and of graft loss; and the development of new comorbidities. We studied outcomes for subgroups based on donor source (LD vs. DD), transplant number (primary vs. retransplant), immunosuppressive era (Era1 vs. Era2), and pretransplant diagnosis of DM1(yes vs. no). Recipients with no follow-up data for 2 years and with no documentation of death were considered "lost to follow-up." All survival information was censored at the date of last follow-up. We defined graft loss by return to chronic dialysis, graft nephrectomy, retransplant, or death. For all comparisons between eras and subgroups, we used the generalized Wilcoxon test.

Using MVA, we studied risk factors for graft loss after 20 years posttransplant. Variables in our analysis for all recipients included donor source (LD vs. DD), number of HLA mismatches (0 to 2 vs. 3 to 6), ethnicity (Caucasian vs. non-Caucasian), age at transplant (< 18 vs. 18 to 49 vs. >50 years), transplant number (primary vs. retransplant), recipient gender (male vs. female), and pretransplant diagnosis of DM1 (yes vs. no). Given that more information was collected for Era 2 recipients, we included additional variables in our analyses of risk factors for that era (Table 7a, 7b).

For Era2 recipients, we also studied the development of posttransplant comorbidities, including infections, cancer, CVD, and cerebrovascular disease.

Results

Recipient and donor characteristics

Of the 3,802 transplants (1,937 LD, 1,865 DD) from June 7, 1963 through September 15, 1993, a total of 836(22%) (583 LD, 253 DD) grafts (in 831 recipients) had GS of at least 20 years (as of September 15, 2013). (Of those 831 recipients, 5 had undergone 2 transplants, each lasting ≥20 years.) Only 65(8%) of the 831 recipients were subsequently lost to follow-up: of these, 38 of them lost their graft with the date and cause entered into the database); the other 27 are presumed to still have graft function.

Characteristics for all 3,802 transplants and for the 831 recipients with GS of at least 20 years are summarized (Table 1). As compared with the entire cohort, those 831 recipients were more likely to have undergone a primary transplant (89%) with a LD graft (70%); to have had a 0% peak panel-reactive antibody (PRA) level (75%); and to have had a 0% PRA level at transplant (84%). We found no statistically significant differences between the entire cohort and the 831 recipients in ethnicity, age at transplant, gender, or DM status. Among the 831 recipients, the donor age was younger (25$\pm$13 years) for those with a DD graft than for those with an LD graft (34$\pm$11 years) ($P\leq 0.05$). Donors (LD and DD) were primarily Caucasian (97%); 51% were male.

The primary diseases associated with the highest rates of both GS and DCGS of at least 20 years were immunoglobulin A(IgA) nephropathy, Alport syndrome, congenital nephrotic syndrome, congenital anatomic disease, and pyelonephritis. In contrast, the primary diseases associated with the lowest rates of both GS and DCGS of at least 20 years were DM1, type 2 diabetes (DM2), hypertension, and focal segmental glomerulosclerosis (FSGS) (Table S1a, S1b).

Table 1: Recipient characteristics 20-year transplant survivors (n=831) vs. all transplants performed (n=3,802)

	20-year Tx survivors	All Tx performed		20-year Tx survivors	All Tx performed
Donor source			**Pretransplant diabetes**		
DD	30% *	49%	**Total**	22%	22%
LRD	68% *	50%	**DD**	25%	24%
LURD	<2%	1%	**LD**	20%	20%
Transplant number			**PRA at transplant**		
First	89% *	84%	0%	84% *	80%
Second	9%	13%	1-10%	4%	5%
Third	1%	2%	11-50%	7%	8%
Fourth	<1%	0.4%	>50%	5%	7%
Ethnicity			**Peak PRA**		
White	97%	96%	0%	75% *	70%
Black	1.3%	2%	1-10%	8%	7%
Asian	<1%	0.4%	11-50%	8% *	11%
American Indian	<1%	2%	>50%	9% *	12%
Mean recipient age at transplant (±SD)			**Type of transplant**		
DD	33±12	37±14	**KTA**	95%	94%
LD	27±13	30±15	**SPK**	4%	5%
			SLK	<1%	<1%
Gender			**KAOther**	<1%	<1%
Female	42%	40%			
Male	58%	60%			

* P≤0.05 comparing 20 Tx survivors with all Tx performed

Outcomes after 20 years

Patient survival

For primary LD recipients with GS of at least 20 years(n=540), actuarial PS at 25 years was 83%; at 35 years, 59%. For primary DD recipients with GS of at least 20 years(n=203), actuarial PS at 25 years was 74%; at 35 years, 35%($P< 0.03$). Similarly, for retransplant recipients with GS of at least 20 years (n = 88), actuarial PS was better for LD recipients than for DD recipients ($P< 0.03$) (Figure 1; Table S2).

Primary and retransplant recipients *with* pretransplant DM1 had worse PS after 20 years than those with other primary diseases. However, PS at 25 years did not significantly differ between the 2 immunosuppressive eras: *Era 1*, 83% for LD recipients (n= 309) and 74% for DD recipients (n=105); *Era 2*, 84% for LD recipients(n=271) and 72% for DD recipients(n=146).

The 3 most common causes of death with function (DwF) after 20 years for recipients *without* pretransplant DM1 were cancer (34%), CVD (18%), and sudden death (10%) (Table 2a). The rates were similar for LD vs. DD recipients, for primary vs. retransplant recipients, for both immunosuppressive eras (Era 1 vs. Era 1), and for the various intervals posttransplant (20 to 24 years, 25 to 29 years, 30 to 34 years, >34 years) (Table 2b; Table S3a, S3b, S3c).

In contrast, for primary and retransplant recipients *with* pretransplant DM1, the most common causes of DwF after 20 years were CVD (22%), sudden death (21%), and infections (14%). Recipients with DM1 died 6 years earlier, on average, from CVD and sudden death than those without DM1(Table 2a).

The most common causes of cancer deaths after 20 years for recipients *without* pretransplant DM1 were solid-tumor cancer (65%), skin cancer (19%), and PTLD (15%); for those *with* pretransplant DM1, solid-tumor cancer (67%) and skin cancer (33%). For both of these subgroups, the age of death secondary to cancer was similar.

Graft survival

For primary LD recipients with GS of at least 20 years(n=540), actuarial 25-year GS was 75%; 35-year, 45%. For primary DD recipients with GS of at least 20 years(n=203), actuarial 25-year GS was 67%; 35-year, 24% ($P\leq 0.01$) (Figure 2a). For retransplant recipients, we noted a trend toward improved GS for LD (vs. DD) recipients (Table S4).

Death-censored graft survival

For primary LD recipients with GS of at least 20 years(n=543), actuarial 25-year DCGS was 89%; 35-year, 72%. For primary DD recipients with GS of at least 20 years (n = 204), actuarial 25-year DCGS was 86%; 35-year, 54%($P\leq 0.01$) (Figure 2b). For retransplant recipients, we noted a trend toward improved DCGS for LD (vs. DD) recipients (Table S4).

Within subgroups, at 35 years posttransplant, 35% of recipients *without* (vs. 28% *with*) pretransplant DM1 still had a functioning graft ($P\leq 0.03$). But we found no significant differences in DCGS between those 2 subgroups.

At 25 years posttransplant, GS did not significantly differ for Era 1 vs. Era 2 recipients with GS of at least 20 years (Table S5).

Causes of graft loss

For recipients with GS of at least 20 years, most common subsequent causes of graft loss were DwF (58% LD; 58% DD) and "chronic rejection"/chronic allograft nephropathy/IFTA (22%, LD; 23%, DD). We found no significant differences between any subgroups in causes of

graft loss (Table 3a, 3b; Table S6a, S6b, S6c). The mean age for DwF was 61(±12) years for LD recipients and 64(±11) years for DD recipients; the mean age for graft loss secondary to IFTA was 48(± 12) years for LD recipients and 50(±14) years for DD recipients (Table 3a, 3b).

Risk factors for graft failure

For *Era 1* recipients with GS of at least 20 years, the risk factors for subsequent graft loss were HLA mismatches of ≥3 antigens and pretransplant DM1($P \leq 0.05$). For *Era 2* recipients with of at least 20 years, the risk factors for subsequent graft loss were a history of rejection and female gender($P \leq 0.05$). (OF note, information on acute rejection was not entered into the database in Era 1.)

Renal function

For recipients with GS of at least 20 years, renal function was similar for LD vs. DD recipients. The mean serum creatinine level(mg/dl) at *20 years* was 1.5(±0.7) for LD recipients and 1.5(±0.8) for DD recipients; at *25 years*, 1.5(±0.9) for LD recipients and 1.5(±0.9) for DD recipients; at *30 years*, 1.4(±0.9) for LD recipients and 1.5(±1.3) for DD recipients; at *35 years*, 2.0(±2.6) for LD recipients and 1.4(±0.8) for DD recipients; and at *40 years*, 1.4(±0.6) for LD recipients.

Renal function was also similar for CNI-free vs. CNI (≥6 months) recipients with GS of at least 20 years. The mean serum creatinine level at *25 years* was 1.4(±0.8) for CNI-free recipients and 1.7(±1) for CNI recipients; at *30 years*, 1.4(±1) for CNI-free recipients and 1.3(±0.6) for CNI recipients.

Long-term comorbidities (Era 2)

For Era 2 recipients with GS of at least 20 years, new diagnoses of infections were made *10 to 19 years* posttransplant for 56% of recipients *without* vs. 61% *with* pretransplant DM1; *20 to 29 years* posttransplant, for 27% *without* vs. 37% *with* pretransplant DM1 ($P \leq 0.05$) (Table 4a).

New diagnoses of CVD were made *10 to 19 years* posttransplant for 16% of recipients *without* vs. 35% *with* pretransplant DM1; *20 to 29 years* posttransplant, for 13% *without* vs. 18% *with* pretransplant DM1(Table 4a).

Similarly, the frequency of new diagnoses of peripheral vascular disease (PVD) was higher for recipients *with* (vs. *without*) pretransplant DM1: *10 to 19 years* posttransplant, 10% vs. 1%; *20 to 29 years* posttransplant, 5% vs. 1%. The frequency of new diagnoses of stroke was also higher for recipients *with* (vs. *without*) pretransplant DM1: *10 to 19 years* posttransplant, 9% vs. 4%; *20 to 29 years* posttransplant, 5% vs. 1% (Table 4a).

Of all Era 2 recipients, 6% had a new diagnosis of non-skin cancer before 20 years posttransplant; 7%, after 20 years (Table 4b). The mean age at the time of cancer diagnosis was the same for both of those time intervals. The frequency of specific types of non-skin cancer are highlighted in Table 5. The same percentage, 2%, had a new diagnosis of PTLD before vs. after 20 years posttransplant. A large percentage, 42%, had a new diagnosis of NMSC before 20 years, with an additional 22% after 20 years.

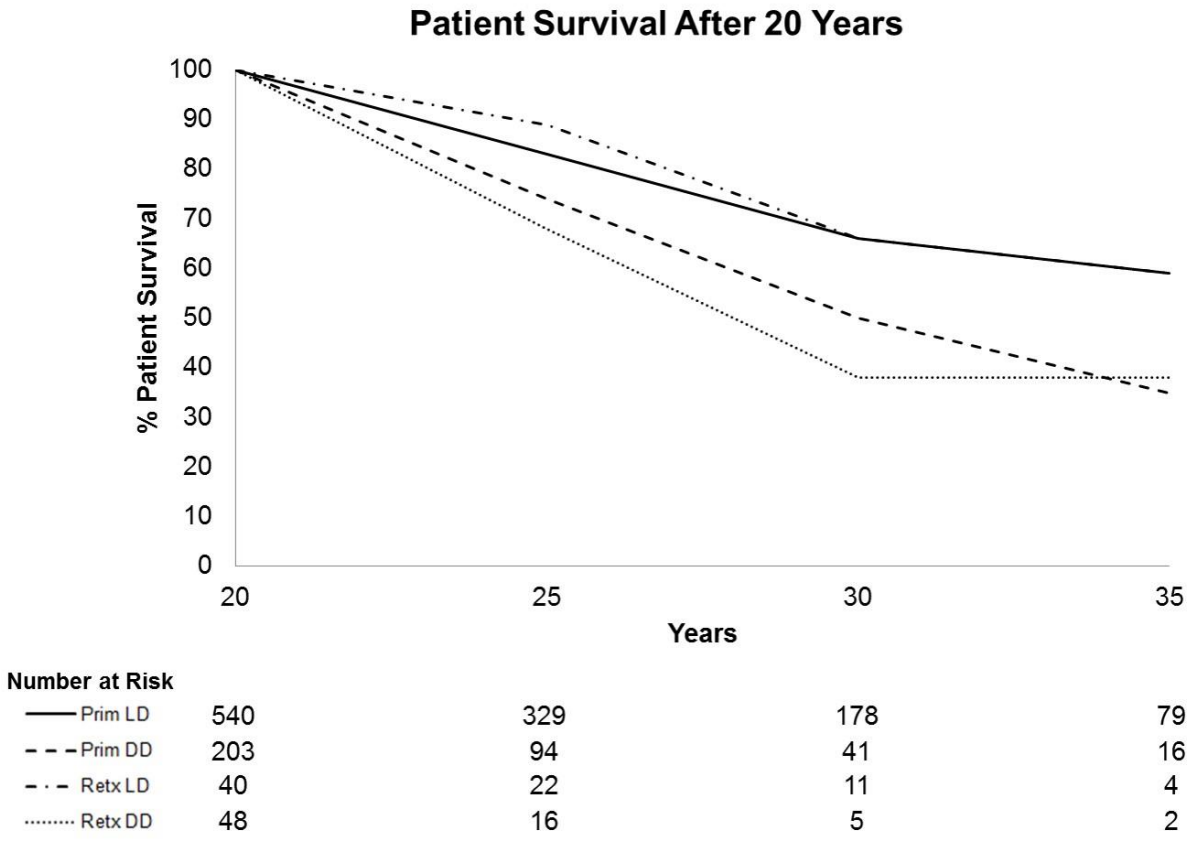

Figure 1: Patient survival with graft function >20 years, by donor source and primary versus retransplant. Note: *X-axis* represents number of years post-transplant; *Y-axis* represents % patient survival.

Table 2a: Primary cause of death with function after 20 years, by pre-Tx diabetic status.

	Nondiabetic (n = 209)	Mean age at death (± SD)	Pre-Tx DM (n = 63)	Mean age at death (± SD)
Malignancy	72 (34%)	59 ± 12	6 (10%)	60 ± 9
Cardiovascular	37 (18%)	64 ± 12	14 (22%)	58 ± 6
Sudden Death	21 (10%)	64 ± 9	13 (21%)	58 ± 9
Infection	18 (9%)	68 ± 13	9 (14%)	59 ± 8
Unknown	12 (6%)	58 ± 15	5 (2%)	61 ± 9
Diabetic Complications	2 (1%)	64 ± 18	5 (2%)	61 ± 7
Declined Med. Tx	4 (2%)	55 ± 20	4 (6%)	58 ± 4
Other	18 (9%)	61 ± 16	5 (8%)	57 ± 6
Pulmonary	10 (5%)	57 ± 15	1 (2%)	74
GI	6 (3%)	55 ± 18	1 (2%)	58
Trauma	5 (2%)	53 ± 18	--	--
Liver Failure	4 (2%)	56 ± 5	--	--

Table 2b: Primary cause of death with function after 20 years, by donor source.

	LD (n=135)	Mean age at death (±SD)	DD (n=70)	Mean age at death (±SD)
Malignancy	42 (31%)	59 ± 12	22 (31%)	61 ± 12
Cardiovascular	25 (19%)	63 ± 12	12 (17%)	66 ± 11
Sudden death	20 (15%)	60 ± 8	9 (13%)	66 ± 12
Infection	13 (10%)	68 ± 12	8 (11%)	69 ± 10
Unknown	3 (2%)	57 ± 2	5 (7%)	71 ± 8
Other	10 (7%)	67 ± 10	4 (6%)	66 ± 7
Pulmonary	4 (3%)	70 ± 18	2 (3%)	52 ± 3
Diabetic complications	7 (5%)	62 ± 10	--	--
Declined Tx medications	3 (2%)	51 ± 17	1 (1%)	54
GI	4 (3%)	54 ± 23	3 (4%)	57 ± 5
Trauma	3 (2%)	43 ± 16	2 (3%)	68 ± 6
Liver failure	1 (<1%)	57	2 (3%)	55 ± 8

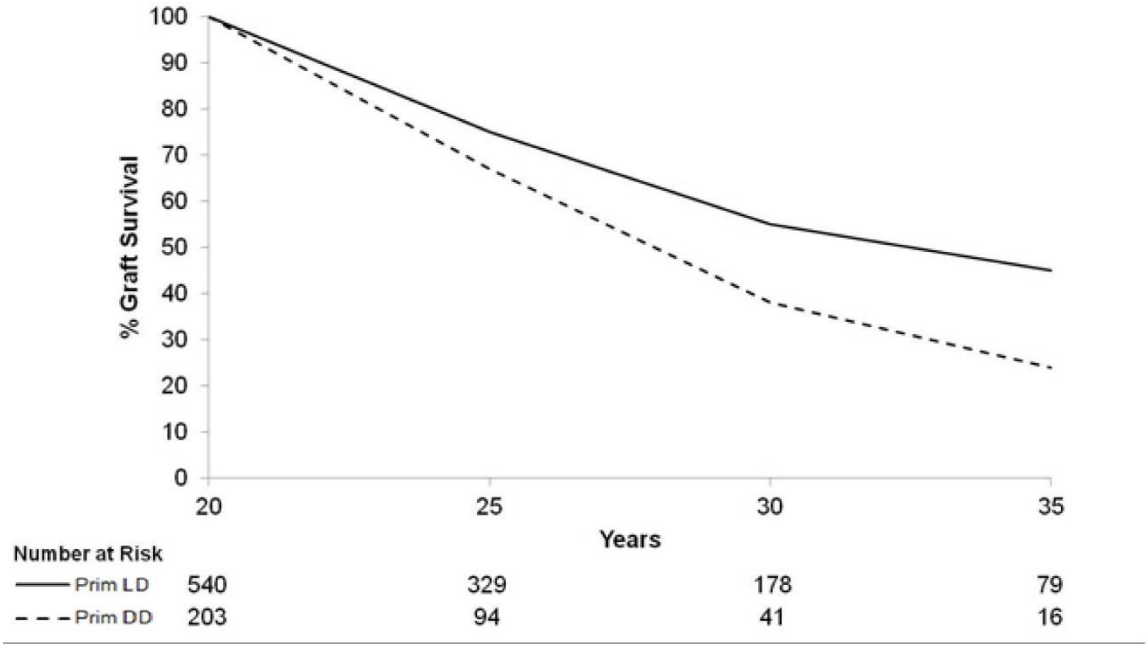

Figure 2a: Graft survival for patients with graft function >20 years, by donor source. Note: *X-axis* represents number of years post-transplant; *Y-axis* represents % graft survival.

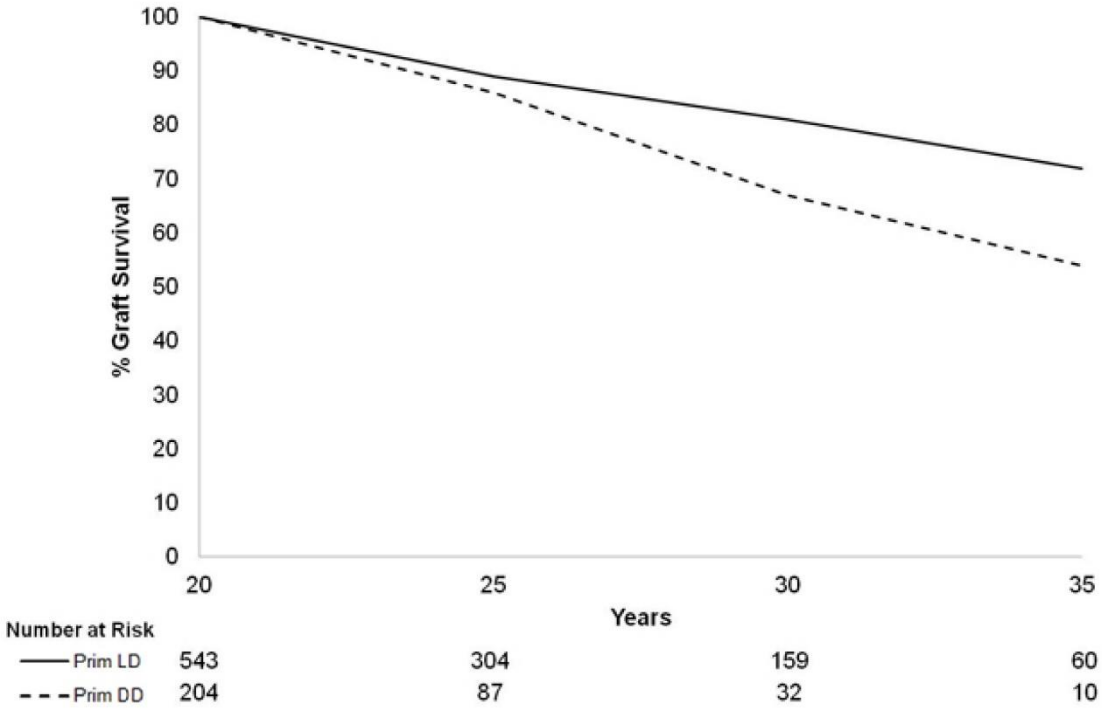

Figure 2b: Death censored graft survival for patients with graft function >20 years, by donor source. Note: *X-axis* represents number of years post-transplant; *Y-axis* represents % graft survival.

Table 3a: Primary causes of graft loss after 20 years, by donor source.

	LD		**DD**	
	(n=234)	**Mean age at death (± SD)**	**(n=121)**	**Mean age at death (± SD)**
Death with function	135 (58%)	61 ± 12	70 (58%)	64 ± 11
IFTA	52 (22%)	48 ± 12	28 (23%)	50 ± 14
Noncompliance	7 (3%)	44 ± 6	5 (4%)	45 ± 14
Recurrent disease	6 (3%)	51 ± 14	1 (1%)	54
***De novo* disease**	1 (<1%)	51	1 (1%)	53
Malignancy	2 (1%)	57 ± 24	1 (1%)	60
Acute rejection	1 (<1%)	28	1 (1%)	55
Infection	2 (1%)	36 ± 7	--	--
Glomerulopathy	6 (3%)	52 ± 6	--	--
Other	8 (3%)	50 ± 11	4 (3%)	52 ± 3
Unknown	14 (6%)	47 ± 14	10 (8%)	54 ± 10

Table 3b: Primary causes of graft loss after 20 years, by pre-Tx diabetic status.

	Nondiabetic		**Pre-Tx DM**	
	(n=278)	**Mean age at death (± SD)**	**(n=77)**	**Mean age at death (± SD)**
Death with function	155 (56%)	63 ± 13	50 (65%)	59 ± 8
IFTA	67 (24%)	47 ± 13	10 (17%)	57 ± 1
Noncompliance	12 (4%)	4 5± 10	--	--
Recurrent disease	5 (2%)	48 ± 11	2 (3%)	59 ± 12
***De novo* disease**	--	--	2 (3%)	52 ± 1
Malignancy	2 (0.7%)	57 ± 24	1 (1%)	60
Acute rejection	2 (0.7%)	41 ± 19	--	--
Infection	2 (0.7%)	36 ± 7	--	--
Glomerulopathy	4 (1%)	54 ± 7	2 (3%)	50 ± 5
Other	22 (8%)	51 ± 8	7 (9%)	54 ± 5
Unknown	19 (7%)	50 ± 14	--	--

Table 4a: New comorbidities in recipients with GS > 20 years, by time period and pre-transplant diabetic status.

	10 - 19 years		20 - 29 years	
	Non-diabetic (n=299)	**Diabetic (n=133)**	**Non-diabetic (n=299)**	**Diabetic (n=133)**
Infection	56%	61%	27%*	37%
CVD	16%*	35%	13%	18%
PVD	1%*	10%	1%	5%
Stroke	4%*	9%	1%	5%

*P ≤ 0.05 comparing non-diabetic to diabetic recipients

Table 4b: *De novo* diagnosis of malignancy in recipients with GS > 20 years for Era 2, by period post-transplant.

	Before 20 years %(n)	**Mean age at Dz (±SD)**	**After 20 years %(n)**	**Mean age at Dz (±SD)**
Non-skin cancer	6% (24)	54 (± 9)	7% (29)	53 (± 8)
NMSC	42% (180)	53 (± 9)	22% (53)	58 (± 10)
PTLD	2% (7)	45 (± 7)	2% (8)	52 (± 12)

Table 5: Non-skin malignancies in recipients with ≥20 years graft survival.

Type malignancy	**Before 20 years**	**≥20 years**
Urogenital	28%	26%
Gynecologic	13%	--
Breast	13%	--
Colon	10%	22%
ENT	8%	13%
Non-colon G.I.	--	13%
Other	13%	26%

DISCUSSION

In a series of analyses in the 1990s, Braun et al. reported on outcomes for a small group of recipients reaching 20 years posttransplant; all had received prednisone and azathioprine for maintenance immunosuppression. For those recipients, early delayed graft function(DGF) or acute rejection(AR) did not preclude GS of at least 20 years; however, by 20 years, a number had developed comorbidities (cardiovascular, neoplastic, infectious, and metabolic disorders; vasculopathy and acceleration of cardiac disease; and aggressive recurrent skin cancer) [10, 11]. In more recent cohorts of recipients with GS of at least 20 years, some previously identified problems are now less common: chronic viral hepatitis (markedly reduced since recognition that reuse of dialyzers were associated with hepatitis transmission); osteopenia, osteoporosis, and avascular necrosis (markedly reduced with steroid minimization protocols); and gout (reduced with the use of mycophenolic acid rather than azathioprine) [12, 13].

Several additional studies, each with relatively small numbers, of recipients on prednisone and azathioprine have found that LD recipients and younger recipients were more likely to have GS of at least 20 years, and that DwF was the most common cause of graft loss after 20 years. In those studies, CVD was the main cause of DwF [14-16].

Recent studies have reported outcomes after 20 years for populations that included some recipients on CNI-based maintenance immunosuppression. Of 1,174 recipients reported by Traynor et al., 255 (22%) had GS of at least 20 years. Factors associated with reaching that mark were younger recipient age, female gender, LD transplant, and no AR episodes. Notably, only 7% were LD recipients; of those recipients, 69% had an HLA-identical LD. CNI-based maintenance immunosuppression was associated with increased GS early posttransplant; but at 20 years, GS did not significantly differ for CNI vs. CNI-free recipients. Of those 255 recipients, 74% survived at least 25 years; the 2 major causes of graft loss were DwF and IFTA. The 2 major causes of death were CVD (32%) and cancer (29%) [7].

Of 706 recipients (7% LD) reported on by McCaughan and Courtney, 177(25%) had GS of at least 20 years. Similar to the findings of Traynor et al., younger recipient age and LD transplant were associated with reaching that mark. Of those 177 recipients, 83% survived at least 25 years; 48%, at least 35 years. The major cause of graft loss was DwF. The 3 major causes of death were cancer (29%), CVD (25%), and infections (12.5%). Comorbidities developing in the first 20 years included cancer (30%, most commonly NMSC) and CVD (16%). After 20 years, 59% developed new comorbidities, most notably cancer (37%(n=58)). Of the 58(37%) with cancer, 42 had NMSC and 16 had other types. In addition, 42(27%) developed CVD; 11(8%), DM1 [8].

Berehi et al. described a small group(n=56) with GS of at least 30 years. Of those recipients, 70% survived at least 35 years. More than 50% developed cancer: 46%, skin cancer; 28%, other types. The most frequent cause of death was cancer (40%), followed by CVD (20%) [6].

Our findings are compared with those of Traynor et al. and of McCaughan and Courtney in Table 6. However, our study differed from those 2 studies in 4 important ways. First, the vast majority of our recipients were treated with polyclonal induction therapy, which was rarely used in the other 2 studies. Second, more than 50% of our recipients were LD recipients, as compared with <10% in the other 2 studies. Third, we documented comorbidities only in the CNI era, whereas the other 2 studies provided that information for their entire population. Fourth, our much

larger number of recipients with GS of ≥20 years allowed us to look at outcomes in subgroups (LD vs. DD recipients; primary vs. retransplant; recipients with vs. without pretransplant DM1; and Era1, maintenance immunosuppression with prednisone and azathioprine, vs. Era2, CNI-based maintenance immunosuppression), as well as risk factors for decreased graft survival after 20 years.

All 3 studies found a similar percentage of recipients with GS of ≥20 years (Table 6). And all 3 found that DD transplant was a risk factor for graft loss before 20 years. Both of the other 2 studies (but not ours) found that older recipient age was also a risk factor for graft loss before 20 years; in addition, Traynor et al. found that male gender and a history of AR were also risk factors. Unlike the other 2 studies, ours found that retransplant, high peak or transplant PRA level, and certain primary diseases resulting in ESRD were also risk factors for graft loss before 20 years (Table 2, 3). Moreover, we also found the following risk factors for subsequent graft loss after 20 years: for Era1 recipients, HLA mismatches of ≥3 antigens and pretransplant DM1; for Era2 recipients, a history of rejection and female gender.

Table 6: Comparative Review of Current Data on Outcomes in Kidney Recipients with GS ≥20 Years.

Data analyzed	Traynor et al, 2012	McCaughan, 2015	U of Minnesota
# Transplants with potential GS ≥ 20 years	1174	706	3802
# LD	82 (7%)	49 (7%)	1937 (51%)
# Tx with GS ≥ 20 years			
Total	255 (22%)	177 (25%)	836 (22%)
LD	67 (26%)	26 (15%)	583 (70%)
Subgroup analysis			
LD vs DD	+	--	+
Pre-CNI vs CNI	+	--	+
Primary vs re-tx	--	--	+
Pre Tx DM vs none	--	--	+
Results			
Factors associated with GS ≥ 20 years	Younger recipient age, female gender, living donor, absence of rejection	Younger recipient age, living donor	When death is censored: Pre-CNI: <3 antigen HLA mismatch, absence of pre-transplant DM CNI era: absence of rejection, male gender
PS for GS ≥ 20 years	(LD/DD)	Overall	(LD/DD)
25 year			Primary: 83%/74%;
35 year	87%/72%	83%	re-tx: 89%/68%
	73%/42%	48%	Primary: 59%/35%;
			rere-tx: 59%/38%
DCGS for GS ≥ 20 years	(LD/DD)	Overall	(LD/DD)
25 year			Primary: 89%/86%;
35 year	80%/66%	92%	re-tx: 92%/68%
	66%/45%	78%	Primary: 72%/67%;
			re-tx: 65%/62%
Major causes of death	Malignancy (29%), CVD (32%), infection (2.6%)	Malignancy (29%), CVD (25%), infection (12.5%)	(No DM/pre-tx DM): malignancy (34%/10%), CVD (18%/22%), infection (9%/14%)
Major causes of GL	DwF (45%), IFTA (39%)	DwF (69%)	DwF (58%), IFTA (22%)
***De novo* co-morbidities after 20 years**	*(Overall including first 20 yrs post-transplant: CVD (17%), NMSC 36%, other CA 15%)*	20 yrs post-tx: hospitalization for infection 13%, CVD 27%, NMSC 24%, other CA 7%, PTLD 2%	20-29 yrs post-tx (no DM/DM): Infection 27%/37%, CVD 13%/18% 20 yrs post-tx: NMSC 22%, other CA 7%, PTLD 2%

For recipients with GS of ≥20 years, all 3 studies showed comparable 25-year PS; Traynor et al. reported better 35-year PS, although their numbers were small. All 3 studies found cancer and CVD to be the primary causes of DwF after 20 years; Traynor et al. found CVD to be the most common, as compared with cancer in both the study by McCaughan and Courtney and ours. We showed that the main causes of death were similar for LD vs. DD recipients, for primary vs. retransplant recipients, for both immunosuppressive eras, and for each of the 5-year

intervals (20 to 24 years, 25 to 29 years, 30 to 34 years, >34 years). However, we found that for recipients with pretransplant DM1, the most common causes of subsequent DwF after 20 years were CVD (22%), sudden death (21%), and infections (14%).

All 3 studies demonstrated similar DCGS at 25 years and at 35 years (although we also showed data for subgroups). In addition, all 3 studies found that the major causes of graft loss after 20 years were DwF and IFTA. In our subgroup analyses, we showed that the major causes of graft loss after 20 years were similar for LD vs. DD recipients, for primary vs. retransplant recipients, for both immunosuppressive eras, and for each of the 5-year intervals (20 to 24 years, 25 to 29 years, 30 to 34 years, >34 years).

Development of CVD after 20 years was common in all 3 studies. We showed that new diagnoses of CVD and PVD were not only more common for recipients with (vs. without) DM1 but also more common, interestingly, 10 to 19 (vs. 20 to 29) years posttransplant. Larger studies will be necessary to determine to what extent CVD is associated with aging, as compared with history of ESRD plus decades of immunosuppression.

The incidence of new diagnoses of cancer after 20 years was similar in all 3 studies. Although 42% of our recipients had NMSC within 20 years of transplant, an additional 22% developed it after 20 years; clearly, ongoing close surveillance must be a priority. We further showed differences in cancer profiles before and after 20 years (Table 5; Table 6), suggesting the need to tailor surveillance protocols. Aggressive targeted surveillance and prevention could help avoid a significant number of morbidities and decrease mortality [4].

There are limitations to our study. First, although 831 recipients had 20-year graft survival, there were smaller numbers in our subgroups. Second, our population is predominantly white; similar studies need to be done in non-white cohorts. Third, we did not collect detailed information on rejection and comorbidities in the pre-CNI era. This may be why we found that HLA mismatch, but not an acute rejection episode, was a risk factor for graft loss for patients transplanted in that era.

recipients. The screening methods that are currently the standard of care for the general population may not be sufficient for transplant recipients [18-21]. In addition, clinicians need to recognize that the risk of developing cancer and/or CVD is not uniformly distributed among transplant recipients, as seen in our and others' data [21, 22].

In summary, as survival with a functioning graft improves, protocols need to be developed to fine-tune longer-term immunosuppression and to screen for, prevent, and treat comorbidities. Addressing these challenges would improve the life expectancy of transplant recipients, bringing it closer to that of the general population.

CONCLUSIONS

Our findings suggest that, in the modern era of CNI-based maintenance immunosuppression, a history of rejection carries an impact on GS even after 20 years of function, thus emphasizing the need for immunologic surveillance. Furthermore, immunosuppressive protocols must continue to be tailored to long-term survivors, with the goal of avoiding rejection. Recent data from the prospective cohort of DeKAF (a national study of factors that affect long-term kidney transplant function) shows that late (> 3 months) immune-mediated events, as compared with early events, are a much greater risk factor for late graft loss [17].

At the same time, new and robust methods to screen for and prevent CVD and cancer are needed for transplant

ABBREVIATIONS

AR – acute rejection, CA – cancer, CNI – calcineurin inhibitor, COD – cause of death, CVD – cardiovascular disease, DC GS – death-censored graft survival, DGF – delayed graft function, DD – deceased donor, DM1 – type 1 diabetes mellitus, DM2 – type 2 diabetes mellitus, DwF – death with function, ESRD –end-stage renal disease, FSGS – focal segmental glomerulosclerosis, GF – graft function, GL – graft loss, GS – graft survival, HLA – human leukocyte antigen, IFTA – interstitial fibrosis and tubular atrophy, LD – living donor, MVA – multivariate analysis, NMSC – nonmelanomatous skin cancer, PRA – panel-reactive antibody, PS – patient survival, PTLD –posttransplant lymphoproliferative disease, PVD – peripheral vascular disease, Tx – transplant, UVA – univariate analysis

SUPPORTING INFORMATION

Supplementary tables S1-S6 are included below, following table for the original article.

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AUTHORS' CONTRIBUTIONS

The participation of each author corresponds to the criteria of authorship and contributorship emphasized in the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals of the International Committee of Medical Journal Editors. Indeed, all the authors have actively participated in the redaction, the revision of the manuscript, and provided approval for this final revised version.

COMPETING INTERESTS

The authors declare no competing interests with this case.

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SUPPLEMENTARY TABLES

Table S1a: Percent of all survivors ≥20 years, by primary disease.

	GF >20 years (n = 836)	GF <20 years (n = 2965)	% of Primary Dz survival with GF > 20 years
DM I	192 (23%)	1153 (39%)	14%
DM II	2 (0.2%)	73 (2%)	3%
Cystic, hereditary and congenital Dz			
Congenital anatomic Dz	67 (8%)	133 (4%)	34%
PKD	37 (4.4%)	170 (5.7%)	18%
Alport's syndrome	35 (4.2%)	47 (1.6%)	43%
Congenital nephrotic syndrome	21 (3%)	37 (1%)	36%
Other	19 (2%)	79 (3%)	19%
Glomerulonephritis (GN)			
Chronic GN	164 (20%)	421 (14%)	28%
IgA nephropathy	26 (3%)	24 (0.8%)	52%
MPGN	17 (2%)	60 (2%)	22%
FSGS	18 (2%)	100 (3%)	15%
Other	13 (2%)	41 (1%)	24%
Pyelonephritis, interstitial nephritis			
Pyelonephritis	56 (7%)	113 (4%)	33%
Other	21 (3%)	31 (1%)	41%
Miscellaneous conditions			
Acquired obstructive Nephropathy	55 (7%)	144 (5%)	28%
Malignancy	—	9 (0.3%)	—
Other	8 (1%)	21 (0.7%)	28%
Secondary GN, vasculitis, other immunologic Dz	42 (5%)	142 (5%)	23%
Hypertension	11 (1%)	84 (3%)	12%
Unknown	32 (4%)	80 (3%)	29%

Table S1b: Percent survivors >20 years death with function excluded, by primary disease.

	GF >20 years (n = 631)	GF <20 years (n = 1629)	% of Primary Dz survival with GF > 20 years
DM I	130 (21%)	507 (31%)	20%
DM II	2 (0.3%)	25 (1.5%)	7%
Cystic, hereditary and congenital Dz			
Congenital anatomic Dz	32 (10%)	103 (6%)	24%
PKD	21 (3%)	77 (5%)	21%
Alport's syndrome	30 (5%)	36 (2%)	45%
Congenital nephrotic syndrome	20 (3%)	34 (2%)	37%
Other	17 (3%)	63 (4%)	21%
Glomerulonephritis (GN)			
Chronic GN	114 (18%)	224 (8%)	34%
IgA nephropathy	23 (4%)	21 (1%)	52%
MPGN	17 (3%)	47 (3%)	27%
FSGS	13 (2%)	84 (5%)	13%
Other	12 (2%)	30 (2%)	29%
Pyelonephritis, interstitial nephritis			
Pyelonephritis	39 (6%)	60 (4%)	39%
Other	15 (2%)	18 (1%)	45%
Miscellaneous Conditions			
Acquired obstructive nephropathy	47 (7%)	102 (6%)	32%
Malignancy	—	2 (0.1%)	—
Other	9 (1%)	18 (1%)	33%
Secondary GN, Vasculitis, Other Immunologic Dz	30 (5%)	102 (6%)	23%
Hypertension	7 (1%)	37 (2%)	16%
Unknown	23 (4%)	39 (2%)	37%

Table S2: Patient survival after 20 years

	25 yrs	30 yrs	35 yrs	40 yrs	45 yrs
LD					
Primary					
# of Pts at risk (n)	329	178	79	32	10
	83%	66%	59%	52%	52%
Retx					
# of Pts at risk (n)	22	11	4	1	0
	89%	66%	59%	22%	0%
DD					
Primary					
# of Pts at risk (n)	94	41	16	2	1
	74%	50%	35%	22%	22%
Retx					
# of Pts at Risk (n)	16	5	2	1	1
	68%	38%	38%	38%	38%

Table S3a: Primary causes of death with function after 20 years, by transplant number and donor source

	Primary DD (n = 61)	Primary LD (n = 95)	Retransplant DD (n = 9)	Retransplant LD (n = 8)
Malignancy	18 (30%)	38 (40%)	4 (44%)	4 (50%)
CVD	10 (16%)	25 (25%)	2 (22%)	1 (12.5%)
Sudden Death	9 (15%)	19 (20%)	--	1 (12.5%)
Infection	7 (11%)	13 (14%)	1 (11%)	--
Other	4 (7%)	9 (9%)	--	1 (12.5%)
Unknown	5 (8%)	3 (3%)	--	--
Respiratory Disease	2 (3%)	4 (4%)	--	--
GI	2 (3%)	4 (4%)	1 (11%)	--
Declined Med. Tx.	--	3 (3%)	1 (11%)	--
Liver Failure	2 (3%)	1 (1%)	--	--
Trauma	2 (3%)	3 (3%)	--	--
DM Complications	--	6 (6%)	--	1 (12.5%)

Table S3b: Primary Causes of Death with Function after 20 Years, by Era and Donor Source

	Era 1 (through 1963)		Era 2 (1984 - present)	
	LD (n=103)	DD (n=43)	LD (n=32)	DD (n=27)
Malignancy	31%	30%	31%	30%
Cardiovascular	19%	16%	16%	19%
Sudden Death	13%	14%	22%	11%
Infection	11%	14%	6%	7%
Unknown	2%	7%	3%	7%
Other	9%	7%	3%	4%
Pulmonary	3%	2%	3%	4%
Diabetic Complications	7%	--	--	--
Declined Med. Tx	1%	--	6%	4%
GI	2%	5%	6%	4%
Trauma	2%	--	3%	7%
Liver Failure	1%	5%	--	--

Table S3c: Primary causes of death with function >20 years, by interval post-transplant and donor source

	20-24 years		25-29 years		30-34 years		35-39 years		40-44 years	
	DD (n=45)	**LD (n=68)**	**DD (n=17)**	**LD (n=51)**	**DD (n=5)**	**LD (n=9)**	**DD (n=3)**	**LD (n=4)**	**DD (n=0)**	**LD (n=2)**
Malignancy	16 (36%)	24 (35%)	2 (12%)	15 (29%)	2 (40%)	1 (11%)	2 (67%)	--	--	1 (50%)
Cardiovascular	8 (18%)	12 (18%)	4 (24%)	8 (16%)	--	1 (11%)	--	3 (75%)	--	1 (50%)
Infection	5 (11%)	5 (7%)	2 (12%)	6 (12%)	1 (20%)	2 (22%)	--	--	--	--
Sudden Death	6 (11%)	11 (16%)	2 (12%)	7 (14%)	--	1 (11%)	1 (33%)	1 (25%)	--	--
Unknown	2 (4%)	1 (1.5%)	1 (6%)	2 (4%)	--	1 (11%)	--	--	--	--
Other	2 (2%)	5 (7%)	2 (12%)	5 (10%)	1 (20%)	--	--	--	--	--
Pulmonary	1 (2%)	1 (1.5%)	1 (6%)	2 (4%)	--	1 (11%)	--	--	--	--
Diabetic	--	3 (4%)	--	4 (8%)	--	--	--	--	--	--
Declined Med. Tx	1 (2%)	2 (3%)	--	1 (2%)	--	--	--	--	--	--
GI	2 (4%)	2 (3%)	--	1 (2%)	1 (20%)	1 (11%)	--	--	--	--
Trauma	2 (4%)	2 (3%)	--	1 (2%)	--	--	--	--	--	--
Liver Failure	1 (2%)	--	1 (6%)	--	--	1 (11%)	--	--	--	--

Table S4: Graft survival and death censored graft survival after 20 years.

	25 yrs	30 yrs	35 yrs	40 yrs	45 yrs
LD					
Primary					
# of Pts at risk (n)	304	159	60	21	6
GS	75%	55%	45%	35%	30%
DCGS	89%	81%	72%	60%	57%
Retx					
# of Pts at risk (n)	22	7	3	1	0
GS	82%	44%	44%	30%	0%
DCGS	92%	65%	65%	65%	0%
DD					
Primary					
# of Pts at risk (n)	87	32	10	0	0
GS	67%	38%	24%	0%	0%
DCGS	86%	67%	54%	0%	0%
Retx					
# of Pts at risk (n)	11	4	1	0	0
GS	47%	43%	43%	0%	0%
DCGS	68%	62%	62%	0%	0%

Table S5: 25 year graft and death censored graft survival in recipients with >20 year graft function, by era and donor source

	Era 1 (through 1983)		**Era 2 (1984 – present)**	
	LD (n=309)	**DD (n=105)**	**LD (n=274)**	**DD (n=148)**
Graft Survival	77%	64%	75%	64%
D-C Graft Survival	91%	81%	86%	86%

Table S6a: Primary causes of graft loss after 20 years, by transplant number and donor source

	Primary DD (n = 101)	Primary LD (n = 218)	Retransplant DD (n = 20)	Retransplant LD (n = 16)
Death with Function	61 (60%)	127 (58%)	9 (45%)	8 (50%)
Chronic Rejection/IFTA	23 (23%)	47 (22%)	5 (25%)	5 (31%)
Noncompliance	3 (3%)	7 (3%)	2 (10%)	--
Recurrent Disease	1 (1%)	6 (3%)	--	--
De Novo Disease	1 (1%)	1 (0.5%)	--	--
Malignancy	1 (1%)	2 (1%)	--	--
Acute Rejection	1 (1%)	--	--	1 (6%)
Renal Artery Stenosis	1 (1%)	1 (0.5%)	--	--
Infection	--	2 (1%)	--	--
Cardiac Failure	1 (1%)	1 (0.5%)	--	--
CNI Toxicity	--	1 (0.5%)	--	--
Urologic Complications	--	1 (0.5%)	--	--
BK Virus	--	1 (0.5%)	--	--
Other	1 (1%)	2 (1%)	1 (5%)	1 (6%)
Unknown	7 (7%)	13 (6%)	3 (15%)	1 (6%)
Glomerulopathy	--	6 (3%)	--	--

Table S6b: Primary causes of graft loss after 20 years, by era and donor source.

	Era 1 (through 1963)		Era 2 (1984-present)	
	LD (n=167)	**DD (n=76)**	**LD (n=67)**	**DD (n=45)**
Death with function	62%	57%	48%	60%
Chronic rejection/IFTA	20%	24%	28%	22%
Noncompliance	4%	5%	1.5%	2%
Recurrent disease	2%	1.3%	3%	--
De novo disease	0.6%	1.3%	--	--
Malignancy	0.6%	1.3%	1.5%	--
Acute rejection	0.6%	--	--	2%
Renal artery stenosis	--	1.3%	1.5%	--
Infection	1%	--	--	--
Cardiac failure	0.6%	1.3%	--	--
CNI toxicity	--	--	1.5%	--
Urologic complications	0.6%	--	--	--
BK virus	--	--	1.5%	--
Other	1.2%	--	1.5%	4%
Unknown	7%	8%	4.5%	9%
Glomerulopathy	0.6%	--	8%	--

Table S6c: Primary causes of graft loss after 20 years by interval transplant and donor source

	20-24 years		25-29 years		30-34 years		35-39 years		40-44 years		45-49 years	
	DD (n=76)	LD (n=121)	DD (n=32)	LD (n=78)	DD (n=9)	LD (n=20)	DD (n=4)	LD (n=11)	DD (n=0)	LD (n=3)	DD (n=0)	LD (n=1)
Death with function	45 (59%)	68 (56%)	17 (53%)	51 (65%)	5 (56%)	9 (45%)	3 (75%)	4 (36%)	na	2 (67%)	na	1 (100%)
Chronic rejection	20 (26%)	30 (25%)	6 (19%)	9 (12%)	2 (22%)	7 (35%)	--	6 (55%)	na	--	na	--
Noncompliance	2 (3%)	5 (7%)	2 (12%)	6 (12%)	1 (20%)	2 (22%)	--	--	na	--	na	--
Recurrent disease	--	3 (2%)	1 (3%)	3 (4%)	--	--	--	--	na	--	na	--
De novo disease	1 (1%)	--	--	1 (1%)	--	--	--	--	na	--	na	--
Malignancy	--	1 (1%)	1 (3%)	1 (1%)	--	--	--	--	na	--	na	--
Acute rejection	1 (1%)	--	--	1 (1%)	--	--	--	--	na	--	na	--
Renal artery stenosis	1 (1%)	--	--	1 (1%)	--	--	--	--	na	--	na	--
Infection	1 (1%)	--	--	--	--	--	--	--	na	--	na	--
Cardiac failure	--	--	--	--	--	1 (5%)	1 (25%)	--	na	--	na	--
CNI toxicity	--	--	--	1 (1%)	--	--	--	--	na	--	na	--
Urologic complications	--	1 (1%)	--	--	--	--	--	--	na	--	na	--
BK virus	--	1 (1%)	--	--	--	--	--	--	na	--	na	--
Other	1 (1%)	2 (2%)	1 (3%)	1 (1%)	--	--	--	--	na	--	na	--
Unknown	5 (7%)	6 (5%)	3 (9%)	4 (5%)	2 (22%)	3 (15%)	--	--	na	1 (33%)	na	--
Glomerulopathy	--	3 (2%)	--	2 (3%)	--	--	--	1 (1%)	na	----	na	--