Living Unrelated Versus Related Kidney Transplantation: A 25-Year Experience with 3716 Cases

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Purpose: To evaluate the results of transplantation from living unrelated donors (LURD) versus living related donors (LRD) with a long term follow-up of 25-30 years.

Materials and Methods: From 1984 to 2015, a total of3716 kidney transplantations (411 LRDs and 3305 LURDs) were enrolled to the study. Long-term survival of grafts and patients as well as the association between relation state and patients or grafts surveillance were the outcomes.

Results: A total of 3716 live donor kidney transplants (LRD, n = 411; LURD, n = 3305) were carried out over this period. The mean age of donors was 28 ± 54 years in the LURD group and 34.4 ± 11.7 years in LRD ($P < .001$), while the mean age of the recipients was 35.6 ± 15.6 years and 27.6 ± 10.1 years for the two groups, respectively. Donor age was the only statistically significant predictor of graft survival rate (hazard ratio = 1.021, 95% confidence interval: 1.012-1.031). Between 1984 and 2015, patient survival and graft survival improved significantly also patient survival and graft survival was similar in LURDs compared with LRDs.

Conclusion: It seems that the outcome of LURD and LRD is comparable in terms of patient and graft survival. Therefore, transplants from LURDs may be proposed as an acceptable management for patients with end stage renal disease.

Keywords: donor selection; humans; kidney transplantation; living donors; organ transplantation; risk assessment; risk factors.

INTRODUCTION

Renal transplantation is still an excellent treatment for patients with end stage renal disease (ESRD).[1,2] Considering the growing number of ESRD patients, the widening gap between the demand and supply of donor kidneys has led to a call for an expansion in the potential donor pool such as using unrelated living kidney donors.[3-7] Therefore, living unrelated donors (LURD) transplantation faced a revival and experienced 100% increase between 1994 and 1996, similarly the proportion of transplantation from LURDs is still growing worldwide.[8]

Although Human leukocyte antigen (HLA) matching of unrelated donors might not be expected to be opium, previous studies showed comparable results between LURDs and living related donors (LRDs).[1,7,9-13] However, short term follow-up, the patients' fall during the study and low sample sizes are the major limitations of these literatures. We believe that Iran has the largest experience with LURD transplantation. The first planned unrelated renal transplantation was performed on a spouse.[13] In Iran, donation from LURDs is strictly supervised by governmental agencies. Kidney transplantation has recently been restricted to university hospitals and donation is only possible to Iranian natives. Using the Iranian model by combining LRDs, LURDs, and cadaveric donors to form a donation pool, the waiting list for kidney transplantation has been shortened despite the growing number of patients waiting for transplantation. Therefore, there is currently a shorter waiting time for kidney transplantation in Iran compared to many other countries.

We had previously published medium term follow-up of LURDs versus LRDs in 2006.[2] Here, we provide longer term follow-up together with inclusion of newer transplantations from 2006 to 2014, including 3739 living donor transplantations.

MATERIALS AND METHODS

Patients and Setting

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Table 1. Characteristics of transplantations from living related donors versus living unrelated donors.

Variables	LURDs	LRDs	*P* Value
Donor age, years, mean ± SD	28.0 ± 5.4	34.4 ± 11.7	< .001
Recipient age, years, mean ± SD	35.6 ± 15.6	27.6 ± 10.1	< .001
Donor gender, no (%)			
Male	2736 (93)	208 (7)	< .001
Female	516 (72)	198 (28)	
Recipient gender, no (%)			
Male	2164 (89)	270 (11)	.81
Female	1136 (89)	138 (11)	
Transplantation years, no (%)			
1984-1999	849 (74)	302 (26)	< .001
2000-2015	2456 (96)	109 (4)	

Abbreviations: LRD, transplantation from living related donors; LURD, transplantation from living unrelated donors; SD, standard deviation.

This study was conducted from June 1984 to November 2015 in the Department of Urology at Labbafinejad university hospital (Referral Center, Shahid Beheshti University of Medical Sciences) in Tehran, Iran. With the collaboration of the Collaborative Transplant Study (CTS), data of 3716 transplant patients, donors and annual follow-ups was used for this study.

The study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, and each patient was given an informed consent prior to the study, which was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki as revised in 2000.

As part of the adopted LURD renal transplant program, during the evaluation of a renal transplant candidate, the transplant physician emphasized on the advantages of an LRD compared with LURD transplantation, such as longer graft survival rates and fewer acute rejection episodes, and recommended transplantation from an LRD. If the patient had no LRD or the potential donor is not willing to donate a kidney, the patient is referred to the Dialysis and Transplant Patients Association (DATPA) to find a suitable LURD. The DATPA is the site where those who wish to volunteer sign up as LURDs. The volunteers registered at DATPA underwent an evaluation in the foundation clinics. Permission from the parents in younger and single adults or the spouse to register was mandatory. The potential donors were required to be in complete health and a consent was obtained from each donor prior to the introduction to the potential recipients.

Most of the members of DATPA are ESRD patients. They receive no financial incentives to find an LURD or to refer the patient and donor to a transplant team. There was no role for a middleman or agency in this program. All transplant teams were affiliated with university hospitals and the government is responsible for all hospital expenses of transplantation. After transplantation, the LURD received an award from the government and a majority of the LURDs also received a rewarding gift from the recipient (or were arranged a reward by DATPA). Transplant teams received no in-

Table 2. Distribution of graft and patient survival rate during follow-ups.*

Variables	1 year	3-year	5-year	10-year	15-year	20-year	25-year
Graft survival rate							
LRD	89.0	77.4	70.2	54.9	40.0	31.5	31.5
LURD	90.0	85.6	81.6	71.1	55.6	38.6	38.6
Patient survival rate							
LRD	94.5	88.5	84.0	80.2	74.2	72.4	67.9
LURD	95.2	93.9	92.5	88.5	83.1	65.9	65.9

* Data are presented as percent.

Abbreviations: LURD, living unrelated renal donor; LRD, living related donor.

centives from the rewarding gifts or the governmental awards. The rewarding gifts has been limited to a range that enables the majority of patients of a poor socioeconomic class to afford with the help of charity foundations. This program was under the close observation of the Iranian Ministry of Health and Medical Education. According to a recent rule for transplantation in Iran, kidney transplantation to a foreign citizen is forbidden except neighbor countries that do not have transplantation programs (e.g. Afghanistan). In these cases, the donors have to be a native from the recipient country.[14]

Surgical and Laboratory Interventions

Our technique was standard retroperitoneal flank approach for open donor nephrectomy until 1997. Since 1997, the standard approach in our department has been laparoscopic donor nephrectomy including right side nephrectomy and inverted kidney transplantation.[15-17]

To evaluate the recipient, we limited our donor laboratory tests to ABO compatibility and preliminary cross-matching. These patients underwent: renal ultrasound, voiding cystourethrography (if needed), chest X-ray, ear-nose-throat examination, dental examination, complete blood count, blood coagulation tests, stool examination, venereal disease research laboratory, human immune deficiency antibody, human T-lymphotropic virus-1 antibody, hepatitis B surface antigen, hepatitis C virus antibody, urinalysis, urine culture, and sometimes renal biopsy. Other tests like gastrointestinal endoscopy were done when necessary.

Immunosuppression was similar for the two groups, and patients received cyclosporine-based immunosuppression. The allograft transplant was performed by anastomosis of the renal artery to the internal iliac artery or to the external or common iliac arteries when the internal was not suitable. The renal vein in almost all patients was anastomosed to the external iliac vein, and in some cases, to the common iliac vein. Aorta and inferior vena cava were the sites of vascular anastomosis in small pediatric recipients. Suture material was prolene 6-0 and 5-0 for vascular anastomosis. Ureteral anastomosis was done within modified Lich technique using ureteral stent. All transplantations were performed by the team led by three transplantation urologists (N.S., A.B. and A.T.).

Graft and patient surveillances were our primary outcomes. Secondary outcomes included the association of baseline characteristics, transplant year and the type of relation as well.

Statistical Analysis

Data entry and statistical analysis was performed employing STATA software version 11.0 (StataCorp, Texas, USA). Chi-square test was used to compare nominal baseline variables in the two groups (LRD and LURD). Independent samples t-test was used to compare numeric baseline variables between LURD and LRD recipients. Graft and patient survival were estimated by the Kaplan–Meier method and compared across levels of nominal variables by the log-rank test. Bonferroni correction was used for the number of testing for each predictor variable (6 testing correcting *P* value for statistical significance at .008). Statistically significant variables were introduced into a Cox regression model. The Cox proportional regression model was used to examine the influence of relation status on graft and patient survival adjusting for the effects of donor age, recipient age and stratified on transplantation year categories (1984-1999 and 2000-2015). Stratification of transplantation year categories was based on the different distribution of donor types (related, unrelated and cadaveric) in 1984-1999 compared to after 2000.

RESULTS

From 1984 to 2015, 3716 living transplantations were performed in our center consisting of 3305 LURD and 411 LRD transplants. Baseline characteristics of the patients are shown in **Table 1**. Graft and patient survivals rates during the follow-ups are shown in **Table 2**.

In Univariate log rank tests, graft or patient survival were not distinctive across different genders of donors or recipients (all *P* values > .05) but graft or patient sur-

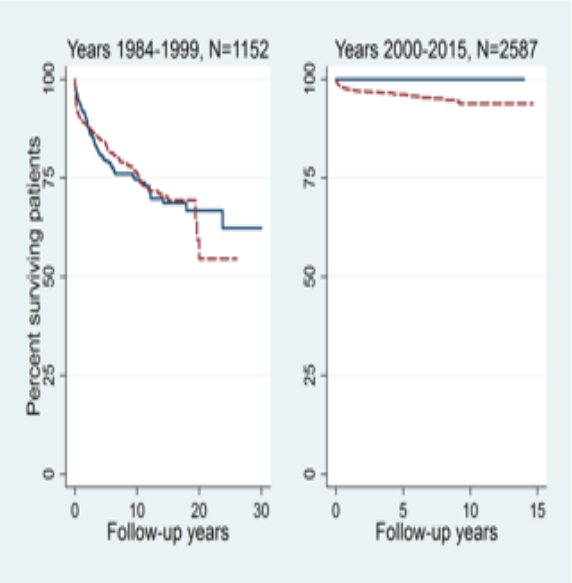

Figure 1. Kaplan-Meier curve for patient survival in transplantation from living related and unrelated donors. Solid line indicates transplantation from related donor, dashed line indicates transplantation from unrelated donor.

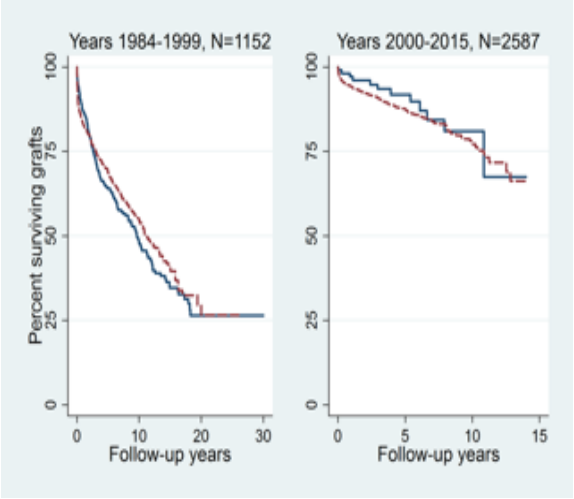

Figure 2. Kaplan-Meier curve for graft survival in transplantation from living related and unrelated donors. Solid line indicates transplantation from related donor, dashed line indicates transplantation from unrelated donor.

vival were dissimilar across different age groups of donors and recipients, different transplantation years and donor relationship status (LRD versus LURD).

In the Cox proportional hazard model, donor age, recipient age and relation status (related versus unrelated) were introduced into the model and the model was stratified based on transplantation year categories (1984-1999 and 2000-2015). Stratification was employed to remove the confounding effect of transplantation time as LRDs were performed more often prior to 1999, while after 2000 there was a relatively constant proportion of LRDs to LURDs. Donor age was the only statistically significant predictor of graft survival in the Cox model (hazard ratio [HR] = 1.021, 95% confidence interval [CI]:1.012-1.031). The same modeling was used to investigate the variables influencing the patient survival. In the latter model, donor age (HR = 1.020, 95% CI: 1.006-1.034) and recipient age (HR = 1.029, 95% CI: 1.021-1.037) were statistically significant predictors of the patient survival. In neither models the relation status (LRD versus LURD) was a significant predictor of graft (HR = 1.046, 95% CI: 0.862-1.268) or patient (HR = 0.991, 95% CI: 0.737-1.334) survival (**Figures 1 and 2**).

DISCUSSION

The most important finding of this study was comparable patient or graft survival rates for LURDs compared with LRDs. Donor and recipient gender was not associated with graft or patient survival rates (all *P* values > .05) but donor age, recipient age, transplantation year and relationship (LRD versus LURD) were statistically significant predictors of graft and/or patient survival rates.

Transplantation from living donors is increasingly becoming popular because of its excellent outcomes compared with cadaveric transplantations.[3,6] Previous studies showed acceptable results for LURD kidneys. We recently published the largest series reported from a single center including 2155 cases with excellent results.[13] Gjertson and Cecka reported a 5-year graft survival of 72% based on the analysis of United Network for Organ Sharing (UNOS) registry from 1987 to 1998.[6] Ahmad and colleagues reported an excellent 3-year graft survival of 93.7% in their series of LURDs from St. Mary Hospital of London during 2001 to 2004.[1] Furthermore, a 5-year survival of 82% has been reported from the University of Wisconsin series.[18] In Korea, the 5-year survival rate of LURTs was 86.9% similar to one-haplotype disparate living transplants.[19] The 5-year graft survival in the current study for 3305 LURDs was 81.6%.

The introduction of laparoscopic donor nephrectomy (LDN) has also resulted in a better motivation for potential donors.[3] We reported that LDN improved donor satisfaction without impairing graft outcome when compared to open donor nephrectomy.[15] Currently, almost all donor nephrectomies in our center are performed through laparoscopy. Since the adoption of this policy, we have had an increasing number of living donor transplantations in the past decade.

In this study, a great proportion of donors in the LRD group were parents who volunteered for kidney donation to their offspring. Hence, the average age for donors in the LRD group is higher than the LURD group. Older age is regarded as a risk factor for a higher rejection rate[3,10] observed in the LRD group. Employing multivariate analysis and adjusting for the effect of age, graft and patient survival in the LURD group is seen to be closely similar to the LRD group (**Figures 1 and 2**). Analysis of transplantation data by Opelz on The Cardio Thoracic Systems registries revealed that HLA mismatches have an important role in the outcome of transplantation.[20] Nevertheless, many single center studies have reported equal or even better short, medium and long term outcomes of transplantation in LURD series compared with LRDs.[1,2,7,9,11] It seems that the extremes of HLA mismatch influence the outcomes of transplantation as the best survivals have been reported with HLA-identical grafts. The 5-year graft survival reported for patients with moderate degrees of mismatch (1-4 antigen mismatch) is roughly equal in the range of 69% to 71.2%.[3] In this study, the crude outcome

of transplantation in terms of graft and patient survival was better in the LURD group; however, when analysis was performed this difference was no longer statistically significant in terms of transplantation year categories (**Figures 1 and 2**).

Regarding the best survival figures reported with HLA-identical transplantations or relatives with less HLA-mismatches,[3,6] the first choice for a living donor is still the patient's sibling or a HLA identical donor. If such a donor is not available, LURDs represent an alternative source of donation. Results of the current study with a long term follow-up moves in parallel with the results reported before. Interestingly, graft and patient survival was not worse in LURDs compared with LRDs. This observation has previously been reported,[1,2,7,9] while the reasons have not been fully defined. Motivation and induction medication for LURDs have been proposed as some of the possible reasons.

When long term follow-up of LURDs provide acceptable and consistent results in terms of graft function, survival and patient survival, ethical issues are still an impediment for full employment of LURDs as a potential source of kidney donation in many countries. In Iran, donation from LURDs is strictly supervised by governmental agencies. Kidney transplantation has recently been restricted to university hospitals and donation is only possible to Iranian natives. Using the Iranian model by combining LRDs, LURDs, and cadaveric donors to form a donation pool, the waiting list for kidney transplantation has been shortened despite the growing number of patients waiting for transplantation. By this strategy, the mortality of patients who are in kidney waiting list decreased, whereas, in the USA, 4,270 patients died while waiting for a kidney transplant in 2014. Another 3,617 people became too sick to receive a kidney transplant.[4]

Spouses constitute a potential population of motivated LURDs. Previous reports point to the excellent long term results of graft survival from spouses. Mittal and colleagues compared the graft survival from spouses relative to LRDs. No inferior functions of grafts from spouses were observed in comparison with relatives.[9] In another study Yoon and colleagues reported equal graft survival from spouses versus LURDs in spite of higher donor age and greater HLA mismatches in the spouse group.[12] UNOS registry data reveals that during 1987 to 1997, 62% of LURDs were spouses.[8] Chung and colleagues reported increasing frequency of donation from spouses from 5.1% in 1990s to 8.1% after 2000[23] and spouses constitute 15-20% of all kidney donations in India.[24]

In conclusion, the results of living unrelated kidney transplantation in our long-term follow-up with a large number of cases show that living unrelated kidney transplantation is as good as living related kidney transplantation. The organ shortage can be alleviated by using living unrelated kidney transplantation with successful results similar to living related kidney transplantation. Furthermore, by using living unrelated kidney transplantation the waiting time for patients was decreased, hence, the mortality of some patient in the waiting period is prevented.

CONCLUSIONS

It seems that outcome of LURD and LRD is comparable in terms of patient and graft survival. Therefore, transplants from LURDs may be proposed as a good therapeutic alternative for management of patients with ESRD.

CONFLICT OF INTEREST

None declared.

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