Clinical Outcomes in Living Donor Kidney Transplantation: A Single Center Experience in Latin America

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ABSTRACT

Background. In Latin America, few reports are available about the clinical outcomes of living donor kidney transplants (LDKT). We aim to evaluate the main clinical outcomes for LDKT patients in a single center's experience.

Methods. We retrospectively evaluated 530 LDKT patients who underwent transplantation from August 2008 to December 2020 at Colombiana de Trasplantes. Graft survival censored for death and patient survival were determined up to 5 years post-transplantation by the Kaplan-Meier method. Vascular and urinary complications, readmission, and reintervention rates were documented.

Results. A total of 530 LDKT patients were analyzed. Most of the recipients were men (56%). There were 123 patients (23.2%) with a preemptive transplant. Panel reactive antibody type I and II had higher immunologic risk (>20%) in 15.9% of the patients. The donor mean age was 37.8 ± 11.5 years. Most of the donors were women (52.6%) and related to the recipient (69.1%). Multivariate analysis identified panel reactive antibody type II ($P = 0.003$), female donor ($P = 0.001$), surgical reintervention at 30 days post-transplantation ($P < .01$), and delayed graft function ($P < .01$) as risk factors for graft loss. The graft survival death-censored rates were 93.7% and 89% at 1 and 5 years, respectively. Patient survival rates were 97.0% and 94.1% at 1 and 5 years after transplantation, respectively.

Conclusions. The long-term graft and patient survival rates in our center are comparable to previous reports from other leading centers. The clinical outcomes from a medium-sized center can be noteworthy, although not entirely new.

LIVING donor kidney transplant (LDKT) is the best therapeutic option for chronic kidney disease (CKD) and has become an important tool in transplant groups worldwide. Living kidney donation had relevant advantages in graft and patient survival, and it contributes to reduce the gap in organ supply for transplantation. The graft and patient survival rates are significantly higher in LDKT compared with deceased donor kidney transplantation. However, there is a lack of information on Latin American population.

In 2019, there were 3038 patients on the waiting list for an organ transplant in Colombia. A total of 92.8% of those patients were waiting for a kidney transplant. Moreover, the annual report of 2019 registered a total of 175 LDKT. From those, our transplant group performed 44% of the LDKT, making it Colombia's leading transplant center for LDKT [1]. However, there is still an imbalance between kidney donors and the waiting list. To reduce this demand, transplant groups have developed strategies such as living donor kidney transplantation, presenting a real option for the patient [2], as it has been observed worldwide [3].

Currently, there is no publication in Colombia that exclusively evaluates clinical outcomes after kidney transplantation in living donors. The measurement of the clinical outcomes in our population is essential to generate knowledge that allows for strengthening the exercise of this practice throughout the country and optimizes the long-term follow-up of patients. Furthermore,

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despite the efforts made by government entities under the direction of the National Institute of Health, there is little information about indicators that reflect the clinical outcomes of kidney transplant patients in general and even more about LDKT patients. Therefore, we aim to evaluate our LKDT patients in the main clinical outcomes, graft, and patient survival.

MATERIALS AND METHODS

Study design and population

This is a retrospective observational cohort of all LDKT recipients who were operated on in Colombiana de Trasplantes (including a network of 2 centers: Bogotá and Barranquilla) from August 2008 to December 2020. During the study period, 611 consecutive patients were transplanted. Exclusion criteria included pediatric recipients (n = 67) and retransplantation (n = 14). Thus, 530 out of 611 LDKT patients were analyzed in the final cohort for the study. The electronic medical records of the total recipients were reviewed. Recipient, donor, clinical, and surgical variables were collected from institutional medical records for our database.

Recipient Selection

A detailed evaluation of transplant candidates was performed; the major goals are to ensure that the recipient will tolerate surgery, has vasculature that will enable anastomoses, and has no disease (eg, malignancy, infection) that would acutely be worsened by immunosuppression.

Donor Evaluation

The medical evaluation of all living donors was made by a multidisciplinary team. All living kidney donors (LKD) are evaluated by the ethics committee. The LKD glomerular filtration rate is measured by 24-hour urinary creatinine clearance. Computed tomography angiography was performed to identify the renal vascular anatomy and recognize renal vascular variants. Our transplant team does not accept LKD with clinical history of hypertension or diabetes mellitus.

IMMUNOSUPPRESSIVE PROTOCOLS

All patients received standard induction therapy with alemtuzumab, basiliximab, or antihuman thymocyte immunoglobulin according to the immunologic risk or transplant clinical guidelines. The duration of steroids is up to 7 days and then they are withdrawn. The maintenance immunosuppressive therapy is dual therapy with calcineurin inhibitors and antimetabolites, and it is steroid-free.

Prophylaxis is given with preventive therapy for C*ytomegalovirus* with valganciclovir t, trimethoprim sulfamethoxazole for the treatment of *Pneumocystis jirovecii* and albendazole as *Strongyloides stercoralis* prophylaxis. The patients are discharged on day 2 postoperatively and closely followed as outpatients by a multidisciplinary team.

Rejection episodes

Acute rejection was classified according to the parameters described by Banff (2015) [4]. A biopsy was performed in those patients with an increase in serum creatinine >20% from baseline. Our center does not perform protocol biopsies. Treatment with steroids was started once the histologic diagnosis was confirmed. Acute rejection treatment is using initially 500 mg of methylprednisolone intravenously on the first day, 250 mg intravenous on the second day, and 125 mg on the third day of treatment. Subsequently, oral prednisolone is used from day 4 at 0.5 mg/kg/day for 2 weeks and afterward a gradual withdrawal [5].

Statistical analysis

Descriptive analyses were used to report the population's characteristics according to the nature of the variable and the data distribution. Frequencies and percentages were used to describe the categorical variables. Central tendency and dispersion measures were used to describe the quantitative variables.

Survival analysis was performed using the Kaplan-Meier survival probability method. Patient survival was calculated in years from the time of transplantation to the date of mortality. Death-censored graft survival was calculated in years from the time of transplantation to the date of graft loss; deceased patients were censored. Patients were censored at 5 years of follow-up whether they changed transplant group or were lost since the last follow-up date. Prespecified variables based on published literature and those available in our data were collected as potential risk factors for graft loss. To build the complete model, variables with P value < .25 in univariable analysis and those with clinical importance were selected to perform further analysis. The multivariate Cox regression model was used to identify independent risk factors for graft survival. *P* values, hazard ratio, and respective 95% CIs were obtained. Variable selection was performed to build the final model for graft loss using backward selection based on the Akaike information criterion. A *P* value of < .05 was accepted as statistically significant. Analysis was performed using Software R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

ETHICAL CONSIDERATIONS

The study was approved by the ethical committee. This retrospective research does not present any major risk according to the ethical considerations that were established in the national [6] and international regulations. We confirmed that all kidneys were voluntarily donated with written informed consent.

RESULTS

Patient demographics and clinical characteristics

A total of 530 LDKT patients were analyzed during the study period. In general, the male proportion was higher (56%) than the female proportion. The most common CKD etiology was the unknown cause. The proportion of preemptive transplants was 23.2%. Clinical history of hypertension (76.4%), diabetes (14.2%), and smoking (23.2%) were documented. Pretransplant obesity was present in 43 recipients (8.2%). The 55.9% of the LDKT patients had ≤3 HLA mismatches, and 43.9% had HLA

mismatches ≥4. The immunosuppressive induction therapy was selected depending on the immunologic risk of the LDKT patient. Panel reactive antibody (PRA) type I and II had higher immunologic risk (>20%) in 15.9% of the LDKT patients. The low immunologic risk was identified as PRA <20% with a proportion >90% in both subtypes. Table 1 summarizes the baseline characteristics of the LDKT recipient.

The use of immunosuppressive drugs for induction over time in this cohort was dependent on the immunologic risk in the LDKT patients. At 2012, ATG was the induction therapy of election and became exclusive since 2016. Before 2015, basiliximab was used in LDKT patients with low immunologic risk (Fig 1).

Donor characteristics

A total of 530 living donors were included in the study period. Most of the living donors were women (n = 279, 52.6%). The mean age of the donor was 37.8 ± 11.5 years. Obesity was present in 7.2% (n = 38) of donors with a majority of the LKD with a body mass index (BMI) between 30 kg/m^2 and 31 kg/m^2. Most of the patients were related donors and sibling was the main donor-recipient relationship (n = 213, 40.2%). Table 2 shows the baseline characteristics of the donor.

Table 1. LDKT Recipient Baseline Characteristics

Recipient Characteristics	Total (N = 530)
Sex, n (%)	
Male	297 (56.0)
Female	233 (44.0)
Underlying cause of CKD, n (%)	
Unknown	209 (39.4)
Glomerular	163 (30.8)
Diabetic	44 (8.3)
Hypertensive	43 (8.1)
Congenital	37 (7.0)
Other	19 (3.6)
Obstructive	15 (2.8)
Dialysis type, n (%)	
Peritoneal	204 (38.5)
Hemodialysis	203 (38.3)
Predialysis (pre-emptive transplant)	123 (23.2)
Duration of the dialysis (mo), mean (SD)	22.1 (33.5)
BMI (kg/m^2), n (%)	
<18	40 (7.5)
18-25	324 (61.1)
25-30	123 (23.2)
>30	43 (8.1)
Type of induction, n (%)	
Antithymocyte globulin	376 (70.9)
Alemtuzumab	103 (19.4)
Basiliximab	50 (9.4)
Daclizumab	1 (0.2)
PRA I, n (%)	
<20%	486 (91.7)
>20%*	39 (7.4)
Missing	5 (0.9)
PRA II, n (%)	
<20%	480 (90.6)
>20%*	45 (8.5)
Missing	5 (0.9)

BMI, body mass index; CKD, chronic kidney disease; LDKT, living donor kidney transplant; PRA, panel reactive antibody.

* Recipients with PRA type I or II >20% were considered to have high immunologic risk.

Clinical outcomes in LDKT recipients

Graft loss was present in 9.6% of the LDKT recipients. The 1.9% cases of arterial thrombosis were registered. Urinary leakage was the main postoperative complication. Morover, acute rejection immunologic episodes and hospital readmission were more frequent in the first 3 months after LDKT. Surgical reintervention at 30 days was 18.5%. Delayed graft function (DGF) had an incidence of 5.1%. Table 3 shows clinical outcomes and complications after LDKT.

Risk factors associated with graft loss in LDKT

We used a binary logistic regression to identify factors associated with graft loss within 5 years of follow-up after transplantation. In the regression analysis, the risk factors associated with graft loss in LDKT were PRA type II >20% (high immunologic risk), female donor, surgical reintervention, and DGF (Table 4).

Graft function after LDKT

The mean post-transplant glomerular filtration rate was estimated by the Cockcroft-Gault equation. The glomerular filtration rate in LDKT patients at different follow-up time points were 64 mL/min (SD = 21.6) at 3 months, 68 mL/min (SD = 22.3) at 12 months, 66.3 mL/min (SD = 21.9) at 3 years, and 64.7 mL/min (SD = 22.7) at 5 years, respectively (Fig 2).

Long-term graft and recipient survival

During the study period, 28 (5.3%) deaths were reported. We performed a Kaplan-Meier survival analysis to determine patient and graft survival in LDKT recipients. The patient and graft survival were 94.1% and 89% at 5 years of follow-up, respectively (Fig 3).

DISCUSSION

An LDKT is the best treatment for CKD patients. Worldwide, living kidney donation represents the 31.7% of total kidney transplants [3]. In Latin America, 19% of the kidney transplants were from living donors [7]. The increase in living kidney transplantation requires evaluating the clinical outcomes of LKDT recipients. Locally, there are no publications available with an exclusive analysis of clinical outcomes for LKDT patients. This study described the clinical outcomes of LKDT after 5 years of follow-up from a single center in Colombia.

In the literature, patient and graft survival in kidney transplant recipients has been widely documented worldwide

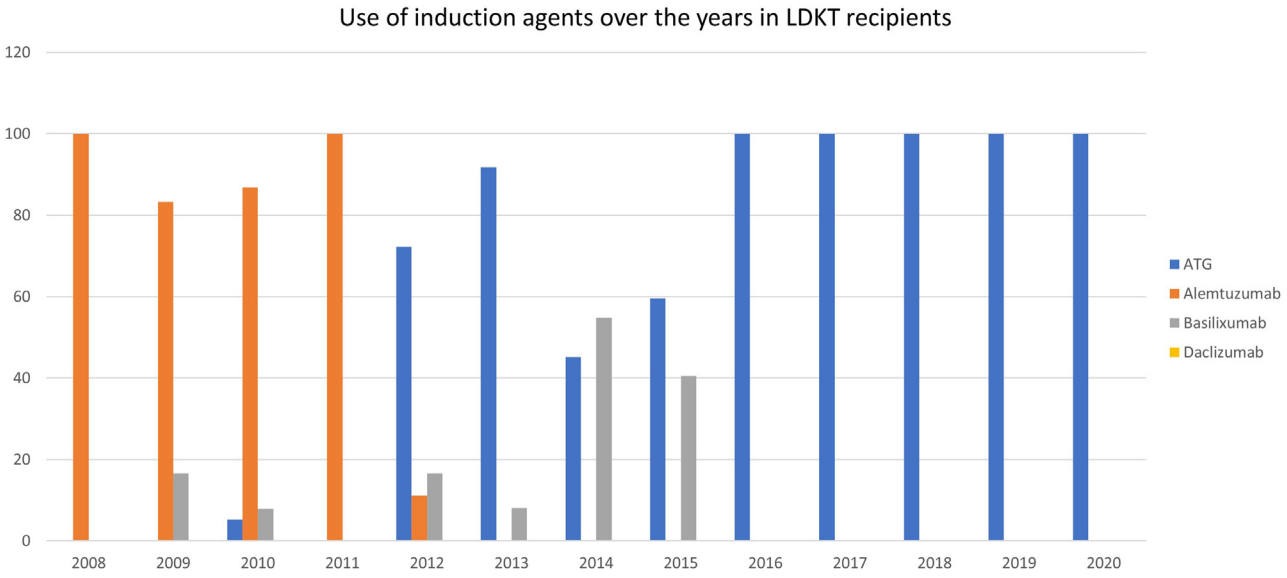

Fig 1. Immunosupresive agents in LDKT recipients. Use of induction agents over the years in living donor kidney transplant recipients. ATG, Anti-thymocyte globulin; LDKT, living donor kidney transplant.

Table 2. Baseline Characteristics of the Donor

Donor Characteristics	Total (N = 530)
Donor sex, n (%)	
Female	279 (52.6)
Male	251 (47.4)
Donor age, media (SD)	37.8 (11.5)
Donor BMI (kg/m^2) groups, n (%)	
<18	5 (0.9)
18-25	282 (53.2)
25-30	204 (38.5)
>30	38 (7.2)
Missing	1 (0.2)
Donor type, n (%)	
Related	366 (69.1)
Not related	164 (30.9)
Donor-recipient relationship, n (%)	
Sibling	213 (40.2)
Other	91 (17.2)
Espouse	73 (13.8)
Offspring	67 (12.6)
Mother	59 (11.1)
Father	27 (5.1)

BMI, body mass index.

Table 3. Clinical Outcomes and Complications in LDKT Recipients

Complications and Outcomes	Total (N = 530)
Main outcomes, n (%)	
Graft loss	51 (9.6)
Mortality	28 (5.3)
Vascular complications, n (%)	
Arterial thrombosis	10 (1.9)
Venous thrombosis	3 (0.6)
Postoperative complications, n (%)	
Urinary leakage	48 (9.1)
Hematoma	18 (3.4)
Acute rejection, n (%)	
0-3 mo	60 (11.3)
3-6 mo	19 (3.6)
6-12 mo	13 (2.5)
Hospital readmission, n (%)	
0-3 mo	184 (34.7)
3-6 mo	26 (4.9)
6-12 mo	21 (4.0)
Surgical reintervention at 30 d, n (%)	98 (18.5)
DGF, n (%)	27 (5.1)
Missing	1 (0.2)

DGF, delayed graft function; LDKT, living donor kidney transplant.

[8−12]. The graft and patient survival in LDKT patients at our study were comparable to findings from a cohort with 2500 LDKT patients at 5 years of follow-up [8]. Our results have shown that long-term patient survival rates in our center resemble prior reports from other leading transplant centers (from 94% to 97%) [13−15]. In Latin America, some publications from Chile, Brazil, and Mexico reported the graft survival in LDKT patients from 76.2% to 94%, at 5 years of follow-up [16−20]. These studies also found LDKT patient survival from 91.5% to 98% [16,17,20].

Some studies have published similar results on demographic characteristics. Most of our recipients were men as shown in the literature [8,11,16,21]. In our data, the main CKD etiology was unknown cause due to LDKT patients in the pretransplant phase came with a late stage of CKD and without clinical indication of kidney biopsy. The second most frequent CKD etiology in our study was glomerular pathology. Englum et al [12] found similar results in CKD etiology.

Table 4. Risk Factors Associated With Graft Loss in LDKT

Parameters	HR (CI 95%)	*P* Value
PRA type II >20%	3.02 (1.46−6.24)	.003
Female donor	3.33 (0.15−0.63)	.001
Surgical reintervention	5.98 (3.11−11.4)	< .01
DGF	4.46 (2.00−9.97)	< .01

DGF, delayed graft function; HR, hazard ratio; LDKT, living donor kidney transplant.

On the other hand, Matas et al [8] have published better patient and graft survival in LKDT patients with preemptive transplant (predialysis) compared with LKDT patients with more than 1 year of dialysis. Our cohort had an important percentage of LKDT recipients with preemptive transplants, which is comparable to the literature (23.2% vs 20%-24%) [21−23].

Moreover, obesity in LKDT recipients has been described as a risk factor for post-transplant complications. In a meta-analysis with 241,381 kidney transplant patients from living and cadaveric donors, obesity in recipients was a risk factor for acute rejection, recipient death, graft loss, and DGF [24]. Other research found that obesity decreases LKDT recipient survival [6]. Buggs et al [6] reported obesity in LKDT was associated with an increase in the incidence of DGF (25% vs 10%). Conversely, we did not find a significant relationship between obese recipients and graft loss in the multivariate model.

In our analysis, the female living donor was predominant. Worthy of comparison, previous studies have found that most of the living donors were women [10,21]. Publications have shown variable results in the donor-recipient relationship. Most of our living donors were related. Our center found that the most common donor-recipient relationship was a sibling as previously reported [25]. According to the literature, LDKT recipients with a related living donor had lower rates of DGF, graft loss, and acute rejection episodes compared with unrelated living donors [11,15]. We did not find a significant difference between the donor-recipient relationship and graft loss. Otherwise, different transplant centers have found that the main donor-recipient relationship was spouses [21] and not related living donors [26].

Additionally, recently obese living donors were considered in LDKT to expand the donor pool [27]. Our living donor kidney transplant program individualizes the decision to approve donor candidates with obesity and BMI between 30 and 35 kg/m^2 based on demographic and health profiles following KDIGO recommendations [28]. Most of our LKDs with obesity had a BMI of 30 to 31 kg/m^2. Living donors with BMI >35 kg/m^2 are not suitable for living kidney donation [29]. Despite the strategy to expand the living donor pool, obese living donors have been related to graft loss [14]. Our multivariate model did not show any significant association between the obese LKD and graft loss.

On multivariate analysis, we identified 4 risk factors related to graft loss with a moderate to strong magnitude of association: PRA type II >20%, female donor, surgical reintervention at 30 days after transplantation, and DGF.

Our first risk factor for graft loss was PRA type II >20%. The degree of sensitization represented by PRA is highly variable and inconsistent. The value of PRA depends both upon the panel composition and the technique used for antibody detection. Because of these variables, there is not a standard definition of immunological risk based on stratification of PRA type I or type II [10,17,23,30]. Some of them showed that immunologic high risk is a PRA type I or II higher to 10% [17,23] or higher to 20% [30] as our study. Rates of PRA with immunologic high risk (15.2%-21.4%) [17,23,30] are compatible with our findings.

Second, the risk factor of female donor has been evaluated for other cohorts. For example, using the large database of the Collaborative Transplant Study, Zeier et al [31] found a significant association between lower 5-year graft survival and receiving grafts from female donors as our results. This could theoretically be related to the fact that grafts from female donors are smaller with fewer nephrons and more susceptible to immunosuppressive-induced nephrotoxicity than grafts from male donors [32].

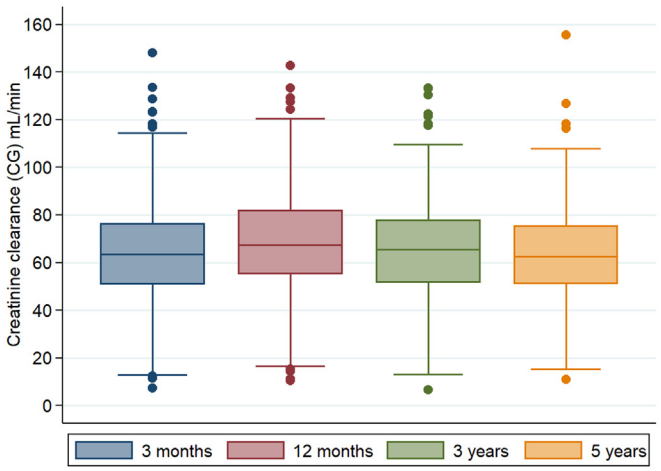

Fig 2. Graft function in LDKT recipients. Glomerular filtration rate estimated by the Cockcroft-Gault equation at different follow-up time points.

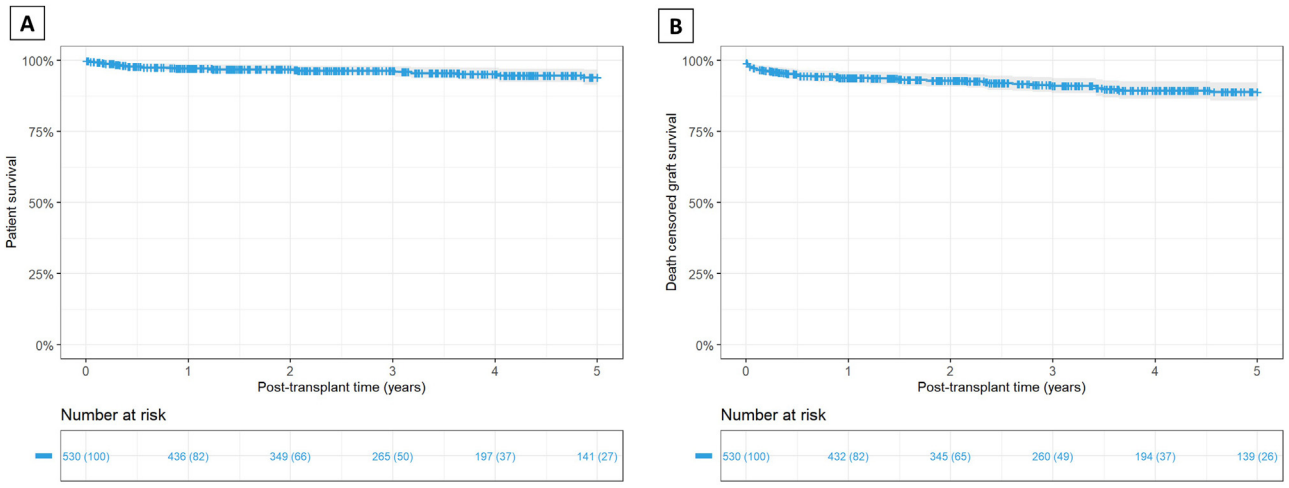

Fig 3. Patient and graft survival probability in LDKT recipients. Panel A. Patient survival at 5 years post-transplantation, Panel B. Death censured graft survival at 5 years post-transplantation.

Then, our third risk factor for graft loss was surgical reintervention within the 30 days after LDKT. Our surgical reintervention rate was 17.5% at 30 days after transplantation in comparison with another research with 40 LDKT patients showing 18.5% of incidence [21]. Surgical reintervention remained statistically significant when it was adjusted in a multivariate analysis ($P \leq 0.01$). The causes of reintervention were not included in the multivariate model.

Our last risk factor associated with graft loss was DGF, similar to the literature [8,17,33]. Matas et al [8] and Ferreira et al [17] showed a significant association between DGF and graft loss ($P < .0001$ and $P < .001$, respectively).

Otherwise, some of the variables described from now on are not significant in our multivariate model. Therefore, despite that the readmission rate was not a significant risk factor for graft loss in our study, a similar proportion to our findings was found in a cohort of 140 LDKT patients in the first month of follow-up [34]. For the first year post transplantation, we had a slightly lower rate of readmissions compared with the literature (43.6% vs 45%-52.2%) [16].

Besides, we also analyzed surgical complications in LDKT recipients. A total of 13 cases (2.5%) of vascular complications (arterial thrombosis and venous thrombosis) were recorded in our cohort. These results had a lower incidence than previous reports (4% to 18.5%) [8,35] and similar results in the venous thrombosis rate [36]. Urinary leakage was present in similar proportion to some publications [37−39].

The literature has reported that immunologic activity and neutrophil infiltration are reduced in LDKT recipients compared with the use of deceased donors in KT [32]. Our acute rejection rate was like the findings in a study of 2500 LDKT recipients [8]. In terms of graft loss, acute rejection was not significant in our multivariate model.

Finally, this study has some limitations. First, intrinsic information bias in the retrospective design is possible. Besides, due to its retrospective single center design, there may be residual confounding and it may have limited generalizability.

In conclusion, we found that long-term graft and patient survival rates at our center are comparable to previous reports from other leading center; risk factors for graft loss at 5 years of follow-up were PRA >20%, female donor, surgical reintervention at 30 days after transplantation, and DGF. Living kidney donation is an important opportunity to increase kidney transplantation with exceptional clinical outcomes. The expansion of living kidney donor programs should grow to improve the prognosis of kidney recipients.

DISCLOSURE

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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