

Repeat Kidney Transplantation with Living Donor is as Safe and Efficient as First Transplantation

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Abstract

Background: The number of patients relisted for repeat kidney transplantation is increasing due to prolonged survival after first transplantation. This study is designed to compare the outcomes of second living donor kidney transplantation (LDKT) with first LDKT.

Methods: Data were collected retrospectively for 1429 LDKT, performed from 1995 to 2020 at Samsung Medical Center. Demographic data of recipients and donors, immunologic factors, and outcomes of 2nd LDKT were compared to those of 1st LDKT.

Results: Among 1429 cases of LDKT, 1355 were 1st LDKT, and 74 were 2nd LDKT. Basic demographic data were comparable for these two groups of patients. The 5- and 10-year graft survival of 1st LDKT were 94% and 84%, respectively, while those of 2nd LDKT were 96% and 86%, showing no significant differences ($p = 0.399$). The 5-year patient survival of 1st LDKT was 98% and that of 2nd LDKT was 96%, while the respective 10-year survival was 94% and 93%, showing no significant differences ($p = 0.766$). Multivariate analysis confirmed that history of previous transplantation was not a risk factor of graft survival (HR 0.83, $p = 0.677$) or patient survival (HR 1.68, $p = 0.396$).

Conclusions: Therefore, repeat kidney transplantation with living donor is reasonable treatment of choice for patients experiencing graft loss.

Background

Since the introduction of kidney transplantation in South Korea in 1969, the number of kidney transplantation has been increasing remarkably. Specifically, 554 cases were performed in 2000, 1289 cases in 2010, and 2293 cases in 2019, doubling every 10 years, according to the KONOS (Korean Network for Organ Sharing). Over the last two decades, more than 70% of patients who received kidney transplantation were aged between 20 to 59 years. As life expectancy after transplantation is increasing, most cases are probable candidate for repeat kidney transplantation at some point in their lifetime [1]. This is due to the limited 10-year lifespan of allografts [2].

The number of patients rejoining the waitlist due to prior allograft loss is increasing and accounts for 9.2% of total transplant patients, according to Korean national data. Among 26,074 patients on the waitlist for kidney transplantation, 2,399 would be undergoing repeat surgery. This phenomenon is occurring not only in Korea, but worldwide, especially in the US [3]. Therefore, this study was designed to understand the outcomes of 2nd kidney transplantation as the needs for repeat transplantation is increasing.

The aim of the present study is to clarify the efficacy and safety of repeat renal transplantation compared to those of first transplant. Only living donor related kidney transplantation was included to reduce heterogeneity in donor-related factors. The study had the largest number of patients to date and could provide stronger evidence than previous studies.

Methods

Patients were collected from a single institution, Samsung Medical Center, Seoul, Korea, from February 1995 to May 2020. This study included only adult patients who underwent living donor kidney transplantation and excluded from cadaveric donors, history of more than three time of renal transplantation, and multiple organ transplantation. This study was reviewed and approved by the Institutional Review Boards of Samsung Medical Center (2020-03-214-002).

Clinical data of demographics (age, sex, BMI), underlying kidney disease, diabetes mellitus and hypertension were collected from both recipients and donors. Immunologic information such as panel-reactive antibody (PRA) identification, human leukocyte antigen (HLA) profile, donor specific antibody (DSA), and serum creatinine level were reviewed. Data associated with surgical technique (total operative time, cold ischemic time, anastomosis time) and in hospital postoperative complications also were collected.

The primary outcomes of this study were death-censored graft survival and patient survival between 1st and 2nd LDKT grafts. The secondary outcomes were changes of graft function according to time, postoperative complications, and risk factors associated with graft failure and patient mortality.

Continuous variables were described as mean and standard deviation and analyzed with independent t-test or Mann-Whitney U test. Categorical data were described as number and percentage and analyzed with Chi square or Fisher's exact test. A generalized estimating equation (GEE) was employed to compare the trends of creatinine according to time. For survival analysis, death-censored graft survival was employed using a graph generated by Kaplan-Meier method. The prognosis was compared by Cox's proportional hazards model and described as hazard ratio (HR) and 95% confidence interval (CI). For multivariable analysis, variables with $p < 0.05$ in univariable analysis were selected. Statistical significance was defined as $p < 0.05$. Statistical analysis was executed using SAS version 9.4 (SAS Institute, Cary, NC) and R 4.0.0 (Vienna, Austria; <http://www.R-project.org/>)

Results

Clinical characteristics

A total of 1429 patients met in the inclusion criteria, 1355 received first LDKT and 74 received second LDKT. There were no statistically significant differences in sex, age, prevalence of DM, and hypertension between the two groups of recipients. The BMI of recipients of 1st transplant was significantly higher than that of 2nd transplant ($p = 0.001$), and there were differences in cause of renal failure between the two groups. Demographic characteristics of donors between the groups did not show statistically significant differences.

From a perspective of immunologic risk, there was a significant difference in proportion of patients with DSA (+); 24% in the 2nd KT patient and 6.9% in the 1st KT patients ($p < 0.001$). As an inductive

immunosuppressive agent, the 81% of patients with 2nd KT were treated with ATG. On the other hand, in the 1st KT group, 32% of the patients required no inductive agent, 40% used basiliximab, and 29% used ATG, a significant differences of induction therapy compared to the 2nd KT group ($p < 0.001$). There were no differences in total operative time, cold ischemic time, and anastomosis time between the two groups (Table 1).

Table 1
Clinicopathologic characteristics according to history of KT

		1st LDKT (<i>n</i> = 1355)		2nd LDKT (<i>n</i> = 74)		<i>p</i> -value
		<i>n</i>	%	<i>n</i>	%	
Follow up period (year)		7.8 ± 5.5		5.9 ± 4.7		
Recipient factors						
Age (year)		45 ± 12		47 ± 9.8		0.315
Sex (male)		791	58	37	50	0.155
BMI		23 ± 3.4		22 ± 3.6		0.001
DM (%)		300	22	10	14	0.080
HTN (%)		1083	80	55	74	0.244
Cause of renal failure	DM nephropathy	266	20	4	5.4	<0.001
	GN	432	32	28	38	
	ADPCKD	55	4.1	7	9.5	
	HTN	179	13	3	4.1	
	Others	432	32	32	43	
Donor factors						
Age, y		42 ± 12		42 ± 11		0.442
Sex (%male)		669	49	45	61	0.055
BMI		24± 3.1		24±3.8		0.828
DM		12	0.89	1	1.4	0.501
HTN		70	5.2	7	9.5	0.113
serum Cr(mg/dL)		0.82±0.16		0.86±0.17		0.105
Immunologic factors						
ABO incompatible		148	11	6	8.1	0.565
Induction	No agent	430	32	6	8.1	<0.001
	Basiliximab	537	40	8	11	

KT kidney transplantation, *LDKT* living donor kidney transplantation, *DDKT* deceased donor kidney transplantation, *BMI* body mass index, *DM* diabetes mellitus, *HTN* hypertension, *GN* glomerular nephropathy, *ADPCKD* autosomal dominant polycystic kidney disease, *ATG* antithymocyte globulin, *CNI* calcinurin inhibitor, *HLA* human leukocyte antigen, *OP* operation

		1st LDKT (n = 1355)		2nd LDKT (n = 74)		p-value
		n	%	n	%	
	ATG	388	29	60	81	
Initial maintenance	CNI +antimetabolite	1341	99	74	100	>.999
	Sirolimus or everolimus	14	1.0	0	0	
# of mHLA I	0 ~ 2	950	70	50	68	0.642
	3 ~ 4	405	30	24	32	
# of mHLA II	0 ~ 1	1104	81	61	82	0.837
	2	251	19	13	18	
DSA	(-)	1261	93	56	76	<0.001
	(+)	94	7.0	18	24	
Op related factors(min)						
Total op time		269 ± 84		288 ± 75		0.102
Cold ischemic time		134 ± 123		146 ± 119		0.068
Anastomosis time		32 ± 16		33 ± 12		0.257
<i>KT</i> kidney transplantation, <i>LDKT</i> living donor kidney transplantation, <i>DDKT</i> deceased donor kidney transplantation, <i>BMI</i> body mass index, <i>DM</i> diabetes mellitus, <i>HTN</i> hypertension, <i>GN</i> glomerular nephropathy, <i>ADPKD</i> autosomal dominant polycystic kidney disease, <i>ATG</i> antithymocyte globulin, <i>CNI</i> calcinurin inhibitor, <i>HLA</i> human leukocyte antigen, <i>OP</i> operation						

Primary outcomes: graft and overall survival

The 5-year graft survival was 94% in 1st LDKT compared to 96% in 2nd LDKT, and 10-year graft survival rates were 84% and 86%, respectively, and the differences were not significant ($p = 0.399$) (Fig. 1). The 5-year patient survival of 1st LDKT was 98%, and that of 2nd LDKT was 96%; respective 10-year survival rates were 94% and 93%, which showed no significant difference ($p = 0.766$) (Fig. 2). Among 64 deaths from 1st LDKT, 44 recipients had functioning graft and all three deaths from 2nd LDKT had functioning graft.

Risk factors associated with graft failure and patient death

Univariate analysis revealed history of kidney transplantation, diabetes mellitus (DM) (recipient), BMI (recipient), age (donor), ABO incompatible transplantation, and number of HLA II mismatch to be associated with increased risk of graft failure. Subsequent multivariate analysis confirmed that age of

donor (HR 1.03, $p < 0.001$) and number of mismatched HLA II (HR 1.63, $p = 0.006$) increased the risk of graft failure of LDKT (Table 2). Furthermore, risk factors associated with patient overall survival were history of KT, age (recipient), underlying kidney disease, DM (recipient), age (donor), hypertension (donor), and number of HLA II mismatches according to univariate analysis. Multivariate analysis showed age of recipient (HR 1.07, $p < 0.001$), DM of recipient (HR 0.08, $p = 0.005$), hypertension of donor (HR 2.53, $p = 0.044$), and number of HLA II mismatches (HR 1.90, $p = 0.023$) to be associated with higher risk of mortality. History of previous transplantation was not a risk factor of neither graft and patient survival (Table 3).

Table 2
Risk factor analysis associated with graft failure

	Univariate analysis		Multivariate analysis	
	HazardRatio	p-value	HazardRatio	p-value
Recipient Age	0.99	0.054		
Recipient Sex	1.09	0.557		
Recipient BMI	1.05	0.021	1.04	0.074
Recipient DM	1.43	0.050	1.26	0.227
Recipient HTN	0.74	0.078		
Donor age	1.03	<0.001	1.03	<0.001
Donor sex	0.79	0.095		
Donor BMI	1.01	0.518		
Donor DM	1.01	0.991		
Donor HTN	0.66	0.471		
Donor serum Cr	0.66	0.341		
History of KT	0.68	0.402	0.83	0.677
ABO incompatible	2.16	0.013	1.64	0.118
Inductive agent	r-ATG vs. no agent	1.41	0.128	
	Basiliximab vs. no agent	1.16	0.429	
	r-ATG vs. Basiliximab	1.22	0.386	
No. of HLA I mismatch	1.28	0.100		
No. of HLA II mismatch	1.82	<0.001	1.63	0.006
DSA(+)	1.68	0.117		
Total OP time	1.0	0.961		
Cold ischemic time	1.0	0.090		
Anastomosis time	0.99	0.573		
<i>BMI</i> body mass index, <i>DM</i> diabetes mellitus, <i>HTN</i> hypertension, <i>KT</i> kidney transplantation, <i>r-ATG</i> rabbit anti thymocyte antigen, <i>HLA</i> human leukocyte antigen, <i>DSA</i> donor specific antibody, <i>OP</i> operation				

Table 3
Risk factor analysis associated with patient death

	Univariate analysis		Multivariate analysis	
	HazardRatio	P value	HazardRatio	P value
Recipient Age	1.08	<0.001	1.07	<0.001
Recipient Sex	1.05	0.841		
Recipient BMI	1.05	0.196		
Recipient DM	2.22	0.004	0.08	0.005
Recipient HTN	0.85	0.578		
Donor age	1.03	0.009	1.02	0.168
Donor sex	1.07	0.784		
Donor BMI	1.01	0.836		
Donor DM	1.68	0.689		
Donor HTN	3.81	0.002	2.53	0.044
Donor serum Cr	0.69	0.629		
History of KT	1.19	0.766	1.68	0.396
ABO incompatible	0.76	0.708		
Inductive agent	r-ATG vs. no agent	1.14	>0.999	
	Basiliximab vs. no agent	0.91	>0.999	
	r-ATG vs. Basiliximab	1.25	>0.999	
No. of HLA I mismatch	1.14	0.628		
No. of HLA II mismatch	2.46	<0.001	1.90	0.023
DSA(+)	0.80	0.763		
Total OP time	1.00	0.529		
Cold ischemic time	1.00	0.487		
Anastomosis time	1.00	0.219		
<i>BMI</i> body mass index, <i>DM</i> diabetes mellitus, <i>HTN</i> hypertension, <i>KT</i> kidney transplantation, <i>r-ATG</i> rabbit anti thymocyte antigen, <i>HLA</i> human leukocyte antigen, <i>DSA</i> donor specific antibody, <i>OP</i> operation				

Secondary outcomes: graft function and complications

This study analyzed changes of serum creatinine level for 10 years after transplantation to evaluate trends of graft function over time. With time, serum creatinine level of both groups tended to increase, though there was no significant difference in rate of change between the groups ($p = 0.238$). In other words, there was no difference in change in graft function between recipients of 1st and 2nd LDKT over time (Fig. 3).

Among postoperative complications, postoperative bleeding, defined as requiring transfusion after surgery, was most common in both groups (13% in 1st KT group and 12% in 2nd KT group). The next most common complications were lymphocele, wound complication, and ureteral leakage, in that order. But there were no differences in frequency and type of complications between the groups ($p = 0.340$) (Table 4).

Table 4
Post OP complications (n, %)

	1st LDKT (n = 1355)	2nd LDKT (n = 74)	p-value
Renal artery stenosis	3 (0.22)	0 (0)	0.340
Ureteral leakage	24 (1.8)	3 (4.1)	
Ureteral stenosis	8 (0.59)	1 (1.4)	
Post op bleeding	179 (13)	9 (12)	
Wound complication	33 (2.4)	0 (0)	
Renal vein thrombosis	1 (0.07)	0 (0)	
Lymphocele	73 (5.4)	7 (9.5)	
Others	9 (0.66)	0 (0)	

Discussion

We analyzed clinical data of 1429 patients who underwent living donor kidney transplantation. Graft and patient survival were not significantly different rate between 1st and 2nd transplant groups ($p = 0.399$ and 0.766 , respectively). The trends of graft function according to time were comparable in terms of levels of serum creatinine ($p = 0.238$). Furthermore, multivariate analysis revealed that repeat transplantation did not increase the risk of graft failure (HR 0.83, $p = 0.677$) or patient death (HR 1.68, $p = 0.396$). These results support the hypothesis that second renal transplantation with living donor kidney is as effective and safe as first transplantation.

These results are consistent with previous studies about repeat renal transplantation. Pour-Reza-Gholi et al. compared clinical outcomes of 103 cases of second renal transplantation with 2009 cases of first transplants, showing comparable five-year patient survival [4]. However, as this study included not only living but also deceased donor, there was a limitation of heterogeneity arisen from donor related factors. Another study from El-Agroudy et al. compared outcomes of 1352 cases of 1st transplants and 52 cases of 2nd renal transplantation from living related donors only and showed no significant differences in overall patient and graft survivals between the two groups. As this study included Egyptian patients only, there could be differences in demographic characteristics according to race [5].

The patients who consider repeat transplantation after graft loss has two options, either waiting for a deceased donor or looking for an appropriate living donor. Previous studies have reported that repeat transplantation clearly has a benefit on survival compared to remaining on dialysis. Ojo et al. analyzed 19208 patients with graft failure and found that retransplantation (RR 0.77 with $p < 0.01$) reduced the risk of long-term patient mortality compared to those who remained on waitlist (RR 1.0) [6]. Rao et al. revealed retransplantation to be associated with a covariate-adjusted 50% reduction in mortality relative to remaining on dialysis after graft loss [7]. However, repeat kidney transplantation can be challenging due to organ shortage [3]. The advantage of living donor kidney transplantation is reduction of waiting time before transplantation compared to deceased donor transplantation [8]. Thus, with an appropriate living donor for repeat transplantation, the risk of mortality can be reduced compared to that of those remaining on the waitlist. Furthermore, because repeat renal transplantation from living donor has comparable outcomes compared to 1st transplant, it could be reasonable treatment of choice for patients with allograft loss.

Recipients of repeat transplantation are exposed to higher immunologic risk than those of first transplantation [9, 10]. The presence of donor-specific antibodies was significantly higher in patients with prior transplantation (6.9% vs. 24%, $p < 0.001$) (Table 1). Although repeat transplantations involve immunological disadvantages, our result showed comparable graft survival of 1st and 2nd kidney transplants. The only difference in immunosuppressive strategy between the two groups was the use of inductive agent. More than 80% of patients with repeat transplantation were treated with anti-thymocyte globulin (ATG), while 40% of patients with 1st KT used basiliximab (monoclonal antibody against CD25, which is IL-2 receptor alpha chain) or ATG (11%), a significant difference ($p < 0.001$). As ATG blocks T cell membrane proteins globally, it depletes antibodies and produces profound and durable lymphopenia, while basiliximab specifically blocks IL-2 signal pathway [11].

The next analysis was to determine if these global immunosuppressive effects of ATG over basiliximab lead to comparable outcome between groups, even immunologic vulnerability. Among 74 patients in the repeat transplantation cohort, 1 out of 6 patients from no agent group, 1 out of 8 patients from basiliximab group, and 2 out of 60 patients from ATG group experienced graft failure within 10 years of follow up. Although the number of cases was not enough to acquire statistically significant results, use of ATG seemed to have protective effects on graft survival compared to no agent and basiliximab (Table 5). However, univariate analysis found no increased risk of graft failure according to type of inductive agent

(Table 2). Previous studies do not support the superiority of ATG over no agent and basiliximab as an inductive agent for repeat transplantation in perspective of graft and patient survival [12–14]. Therefore, there exist limitations to conclude that the use of ATG in repeat transplantation contributes to the comparable result although immunological disadvantages in patient with repeat transplantation in our study. Further investigation about the inductive agent in repeat transplantation is needed.

Table 5
Inductive agent in second transplantation and its 10-year graft failure

	2nd LDKT = 74		10yr graft failure	
	n	%	n	%
No agent	6	8.1	1	17%
Basiliximab	8	11	1	13%
ATG	60	81	2	3.4%
<i>ATG anti thymocyte globulin</i>				

This analysis enrolled 6 patients with ABO-incompatible living donor kidney transplantation among 74 cases of repeat transplantation (Supplementary Table 1). In addition to induction treatment with ATG, all patients were treated with desensitization therapy of plasmapheresis, IVIG, and rituximab to avoid the hyperacute rejection. Only one patient experienced delayed graft function and was treated with renal replacement therapy within a week of operation. Patient #1 and #2 were followed up for more than 2000 days and showed functioning graft without mortality. Although there was a limited number of patients with ABO- incompatible repeat transplantation, the absence of graft failure and death is very encouraging. Therefore, with appropriate preconditioning and considering risk and benefit, ABO-incompatible repeat kidney transplantation could be chosen in circumstances of organ shortage.

This study has limitations of the retrospective design, and its performance from single center. Those who received a 2nd kidney transplant are more likely to have selection bias as they are healthier or show better performance status than those who return to dialysis after allograft loss. Relatively small size of the repeat transplantation group might weaken its power of analysis. Nevertheless, this study is valuable since it provided more robust evidence of efficacy of repeat kidney transplantation specifically with living donor.

Conclusion

This study revealed that repeat renal transplantation with living donor kidney offers comparable graft and patient survival, and graft function to first transplantation, without any compromise in complications. Therefore, repeat kidney transplantation with living donor is a reasonable treatment of choice to reduce waiting time for transplantation.

Abbreviations

LDKT: living donor kidney transplantation; BMI: body mass index; DM: diabetes mellitus; HR: hazard ratio; RR: relative risk; PRA: panel-reactive antibody; HLA: human leukocyte antigen; DSA: donor specific antibody; ATG: anti thymocyte antigen

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the Institutional Review Boards of Samsung Medical Center (2020-03-214-002), who granted a waiver of patients' consent. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable

Availability of data and materials

The data analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare there are no competing interests.

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Authors' contributions

Dr. Namkee Oh and Prof Kyo Won Lee participated in research design, writing of the paper, performance of the research, participated in data analysis. Hyun Cho, M.Sc. and Sook Young Woo, M.Sc. participated in data analysis. Prof Jinsoo Rhu, Prof Seunghwan Lee, Prof Jong Man Kim, Prof Gyu-Seong Choi, Prof

Jae Berm Park, and Prof Jae-Won Joh participated in performance of the research. The authors read and approved the final manuscript.

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Figures

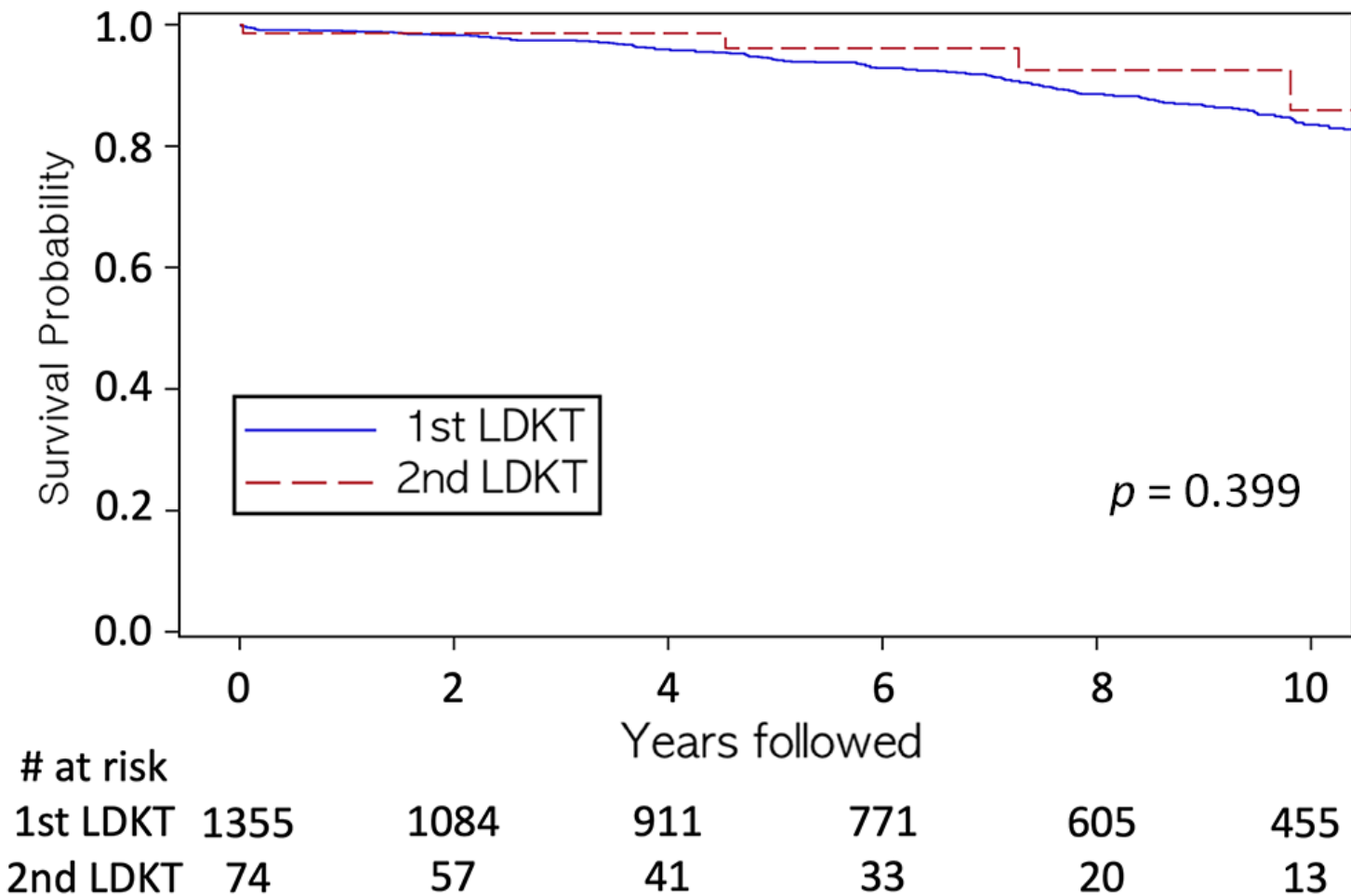
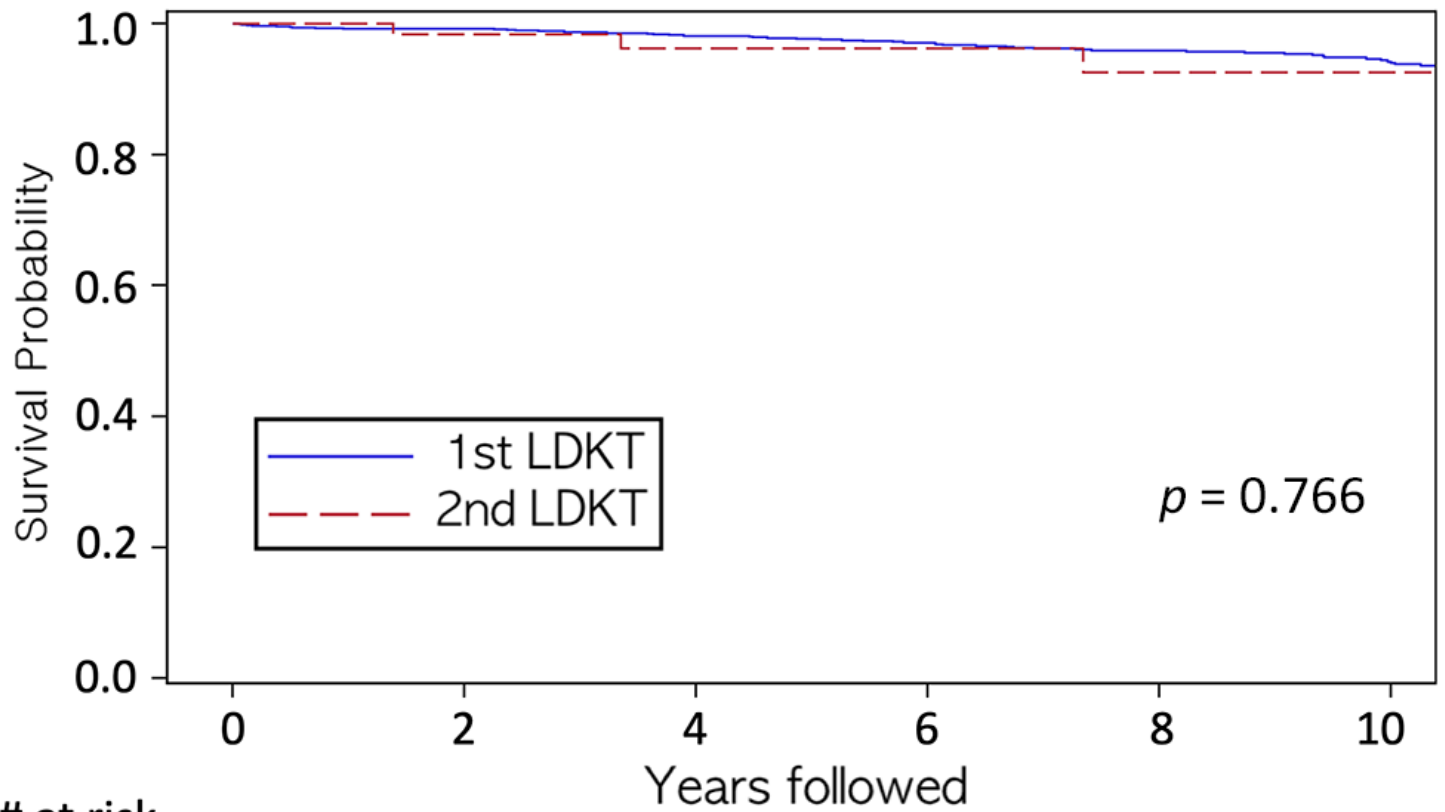


Figure 1

Kaplan-Meier plot for death censored graft survival for 10 years. The 5-year graft survival was 94% in 1st LDKT compared to 96% in 2nd LDKT, and 10-year graft survival rates were 84% and 86%, respectively, and the differences were not significant ($p = 0.399$).



at risk

1st LDKT	1355	1084	916	777	610	462
2nd LDKT	74	57	41	33	20	13

Figure 2

Kaplan-Meier plot for patient survival for 10 years. The 5-year patient survival of 1st LDKT was 98%, and that of 2nd LDKT was 96%; respective 10-year survival rates were 94% and 93%, which showed no significant difference ($p = 0.766$).

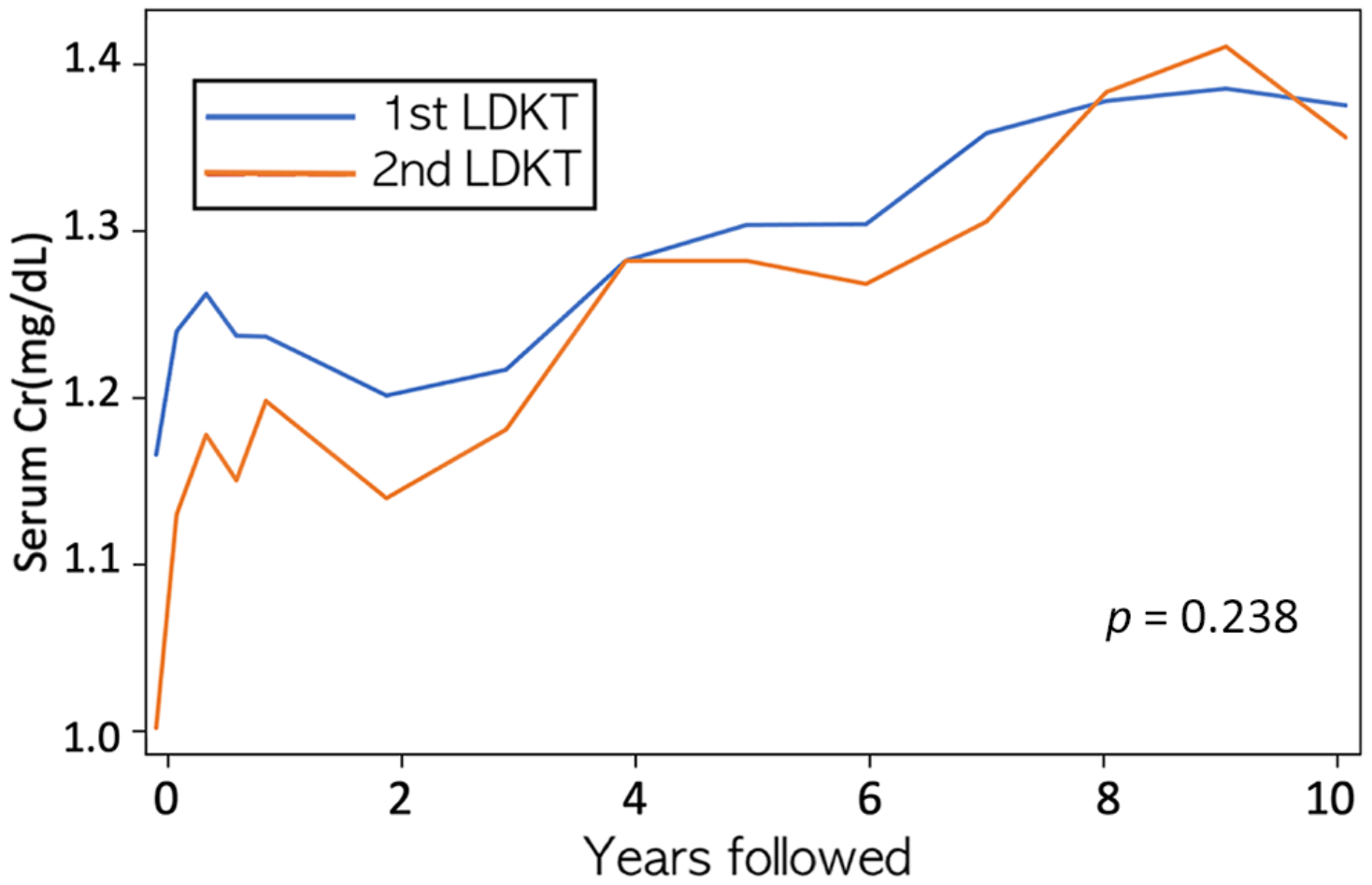


Figure 3

The changes of serum creatinine level for 10 years after transplantation. There was no significant difference in rate of change between the groups ($p = 0.238$).

Supplementary Files

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