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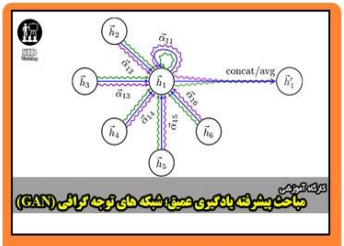

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Impact of Donor Source on the Outcome of Live Donor Kidney Transplantation: A Single Center Experience

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Abstract

Background: Renal transplantation is the ideal method for management of end-stage renal disease. The use of living donors for renal transplantation was critical for early development in the field and preceded the use of cadaveric donors. Most donors are related genetically to the recipients, like a parent, a child, or a sibling of the recipient, but there are an increasing percentage of cases where donors are genetically unrelated like spouses, friends, or altruistic individuals. Donor shortages constitute the major barrier for kidney transplantation, and much effort has been made to increase the supply of living donors. The impact of donor source on the outcome of renal transplantation is not adequately studied in our country.
Objectives: The aim of the study was to evaluate the impact of donor source on the outcome of live donor kidney transplantation.
Patients and Methods: From March 1976 to December 2013, the number of patients that underwent living renal transplantation sharing at least one HLA haplotype with their donors was 2,485. We divided these patients into two groups: (1) 2,075 kidney transplant recipients (1,554 or 74.9% male and 521 or 25.1% female) for whom the donors were living related, (2) 410 kidney transplant recipients (297 or 72.4% male and 113 or 27.6% female) for whom the donors were living unrelated. All patients received immunosuppressive therapy, consisting of a calcineurin inhibitor, mycophenolate mofetil, or azathioprine and prednisolone. We compared acute rejection and complication rates, as well as long-term graft and patient survival of both groups. Demographic characteristics were compared using the chi-square test. Graft survival and patient survival were calculated using the Kaplan-Meier method.
Results: The percentages of patients with acute vascular rejection were significantly higher in the unrelated group, while percentages of patients with no rejection were significantly higher in the related group, but there were no significant differences regarding patient and graft survivals between both groups.
Conclusions: Kidney transplant recipients who received their grafts either from live related donors or live unrelated donors had comparable patient and graft survival outcomes.

Keywords: Kidney Transplantation, Live-Donor, Consanguinity

1. Background

Renal transplantation is the best available renal replacement therapy for end-stage renal disease. Kidney transplant recipients have a better quality of life and consume fewer health care resources compared with patients on dialysis (1). The number of patients with end-stage renal disease is rising rapidly, while those who can undergo a kidney graft are limited because of the donor organ shortage. The organs supplied by living donors are superior to those from cadaveric sources (2). Therefore, much effort has been made to increase the supply of living donors. Improvements in the use of immunosuppression and advances in tissue typing have been associated with better patient and graft survivals in recent years (3). Despite studies that compared the outcome of related and unrelated living donation worldwide, an evaluation of the impact of live unrelated kidney donor (LURD) as a source for renal transplantation has not been adequately studied in Egypt (4). Thus, we conducted the present study.

2. Objectives

Concerning this hypothesis, we decided to study the donor-recipient relationship and its impact on both graft and patient survival among Egyptian patients. In Egypt, there are no cadaveric kidney transplantations and the

only source for renal transplantation is through living donation. So, we tried to encourage all types of living donation participants to answer the question whether unrelated donation is inferior to related donation.

3. Patients and Methods

This study was comprised of 2,485 kidney transplant recipients who received their grafts between March 1976 and December 2013 at our center. Out of this total, 2,075 received their grafts from living related donors (related group a parent, a child, or a sibling of the recipient), while 410 received their grafts from live unrelated kidney donors (unrelated group-spouses, friends, or altruistic individuals). The recipients shared at least one HLA haplotype with their donors. The mean follow-up time was 7.72 ± 6.15 years. We compared demographic characteristics, acute rejection episodes, chronic rejection, complication rates and long-term graft, and patient survivals among the groups. Rejection was diagnosed on the basis of an increase in serum creatinine, confirmed by examination of a graft biopsy sample. All donors and recipients were evaluated by standard biochemical, serological, and radiological evaluation and they received immunosuppressive therapy. Demographic characteristics were compared using the chi-square test. Graft and patient survivals were calculated using the Kaplan-Meier method. All analyses were performed using SPSS 16.0. P values, less than 0.05 were considered to be statistically significant. The study was approved by our ethics committee.

4. Results

A total of 2,075 living related donor (LRD) and 410 living unrelated donor (LURD) transplants were performed during the period. Demographic characteristics of the recipients and donors are shown in Table 1. Our results showed high statistical significance regarding both donor and recipient age (P < 0.001); the mean age of donors was higher in the related group (LRD 36.2 ± 10.5 years versus LURD 31.4 ± 6.4 years), while the mean age of recipients was higher in the unrelated group (LURD 34.8 ± 11.1 years versus LRD 28.8 ± 9.8 years). The percentage of male donors was significantly higher in the unrelated group (P < 0.001). Hematological workup showed that blood grouping had a high statistical significance (P = 0.002), however, no significant difference regarding blood transfusion could be observed between both groups (P = 0.71). The percentage of couples with one DR matched locus was higher in the unrelated group (LURD 94.9% versus LRD 85.5%), while the percentage of couples with two DR matched loci was higher in the related group (LRD 14.5% versus LURD 5.1%). The percentages of couples with zero, one, and two HLA matching were higher in the related group (8.8%, 12.8%, 64.5%), respectively, while the percentages of couples with three and four HLA matching were higher in the unrelated group (39.8% and 21.9%) (Table 1).

Table 1. Characteristics of Live Kidney Donors and Kidney Transplants at the Time of Transplantation[a]

Variable	Related Group (n = 2,075)	Unrelated Group (n = 410)	P Value
Recipient age, y	28.8 ± 9.8	34.8 ± 11.1	< 0.001
Recipient gender			< 0.001
Male	1,554 (74.9)	297 (72.4)	
Female	521 (25.1)	113 (27.6)	
Donor age, y	36.2 ± 10.5	31.4 ± 6.4	< 0.001
Donor gender			< 0.001
Male	906 (43.7)	297 (72.4)	
Female	1,169 (56.3)	113 (27.6)	
Hematological characteristics			
Blood groups			0.002
Same	1,689 (81.4)	299 (72.9)	
Different compatible	386 (18.6)	111 (27.1)	
Blood transfusion			0.71
No	1500 (72.3)	300 (73.2)	
Yes	575 (27.7)	110 (26.8)	
Immunological work up			
A) HLA class I matching			< 0.05
Zero	183 (8.8)	4 (0.9)	
One	264 (12.8)	15 (3.7)	
Two	1,339 (64.5)	138 (33.7)	
Three	189 (9.1)	163 (39.8)	
Four	100 (4.8)	90 (21.9)	
B) HLA class II (DR) matching			< 0.05
One	1,775 (85.5)	389 (94.9)	
Two	300 (14.5)	21 (5.1)	

[a]Values are expressed as No. (%) or mean ± SD.

The most common causes of end-stage kidney disease (ESKD) in the LURD group were glomerulonephritis and polycystic kidney disease (n = 66, 16.1% and n = 43, 10.5%), while in the LRD were due to unknown causes and obstructive uropathy (n = 1,406, 67.7% and n = 98, 4.7%) (Table 2).

Table 2. Pre-Transplant Medical Comorbidity[a]

Variable	Related Group (n = 2,075)	Unrelated Group (n = 410)	P Value
Hypertension			0.84
No	174 (42.4)	891 (42.9)	
Yes	236 (57.6)	1,184 (57.1)	
Schistosomiasis			< 0.001
No	315 (76.8)	1,430 (68.9)	
Yes	95 (23.2)	645 (31.1)	
Original kidney disease			
Glomerulonephritis	< 0.001	66 (16.1)	238 (11.4)
Chronic pyelonephritis	0.865	47 (11.5)	232 (11.3)
Hypoplasia	0.936	3 (0.7)	16 (0.8)
Polycystic kidney disease	< 0.001	43 (10.5)	36 (1.7)
Nephrosclerosis	0.841	9 (2.2)	49 (2.4)
Obstructive uropathy	0.005	7 (1.7)	98 (4.7)
Unknown	0.005	235 (57.3)	1,406 (67.7)

[a]Values are expressed as No. (%).

Table 3. Induction Immunosuppressive Protocols[a]

Induction Therapy	Related Group (n = 2,075)	Unrelated Group (n = 410)	P Value
Anti-thymocyte globulin (ATG)	144 (6.9)	67 (16.4)	< 0.001
Basiliximab (SIMULECT)	908 (43.8)	162 (39.5)	0.111
Others [Muromonab-CD3 (OKT3), Daclizumab (ZENAPAX), Alemtuzumab (CAMPATH)]	85 (4.1)	12 (2.9)	0.262
No induction	938 (45.2)	169 (41.2)	0.138

Table 4. Maintenance Immunosuppressive Protocols[a]

Immunosuppressive Protocols	Related Group, (n = 2,075)	Unrelated Group, (n = 410)	P Value
Steroid-Azathioprine or MMF[b]	280 (13.5)	29 (7.1)	< 0.001
Steroid-cyclosporine or Tac-Azathioprine[c] or MMF	1,296 (62.5)	306 (74.6)	< 0.001
Steroid-cyclosporine or Tac-mTOR[d] or MMF	145 (6.9)	28 (6.9)	0.904
Tac-MMF	354 (17.1)	47 (11.4)	0.004

[a]Values are expressed as No. (%).
[b]Mycophenolate mofteil (MMF).
[c]Tacrolimus (Tac).
[d]Mammalian target of rapamycin (mTOR).

In regards to induction and maintenance immunosuppressive protocols, ATG induction had the highest percentage in the unrelated group (LURD 16.4% versus LRD 6.9%) (Table 3). The percentages of recipients maintained on steroid-azathioprine or mycophenolate mofteil (MMF) and tacrolimus (Tac)-MMF were significantly higher in the related group (LRD 13.5% versus LURD 7.1%, and LRD 17.1% versus LURD 11.4%), respectively, while the percentages of recipients maintained on Steroid-cyclosporine Azathioprine or MMF were significantly higher in the unrelated group (LURD 61.2% versus LRD 52.2%) with comparable percentages in both groups regarding other protocols (Table 4).

Post-transplant medical complications were analyzed. There were no significant differences between both groups regarding hypertension, diabetes mellitus, hepatic problems, infections, or malignancy (Table 5). The rate of acute vascular rejection was significantly higher in the unrelated group (LURD n = 26, 6.3% versus LRD n = 71, 3.41%), while the rate of cases without acute rejection was significantly higher in the related group (LRD n = 960, 46.3% versus LURD n = 167, 40.7%) (Table 6).

There was no statistical significance between both groups in regards to creatinine clearance and serum creatinine for one, three, and five years post transplantation (P = 0.684, 0.579, 0.201, and 0.107), respectively (Table 7). The graft and patient survival of each group is shown in Tables 8 and 9.

Kaplan-Meier graft and patient survival curves for each group are shown in Figures 1 and 2. There were no significant differences regarding graft and patient survival between both groups (P = 0.071 and P = 0.386, respectively).

5. Discussion

Kidney donation by biologically unrelated persons has been attempted in different areas of the world, including the Middle and Far East (5). These donations have received adverse publicity because of multiple factors, including

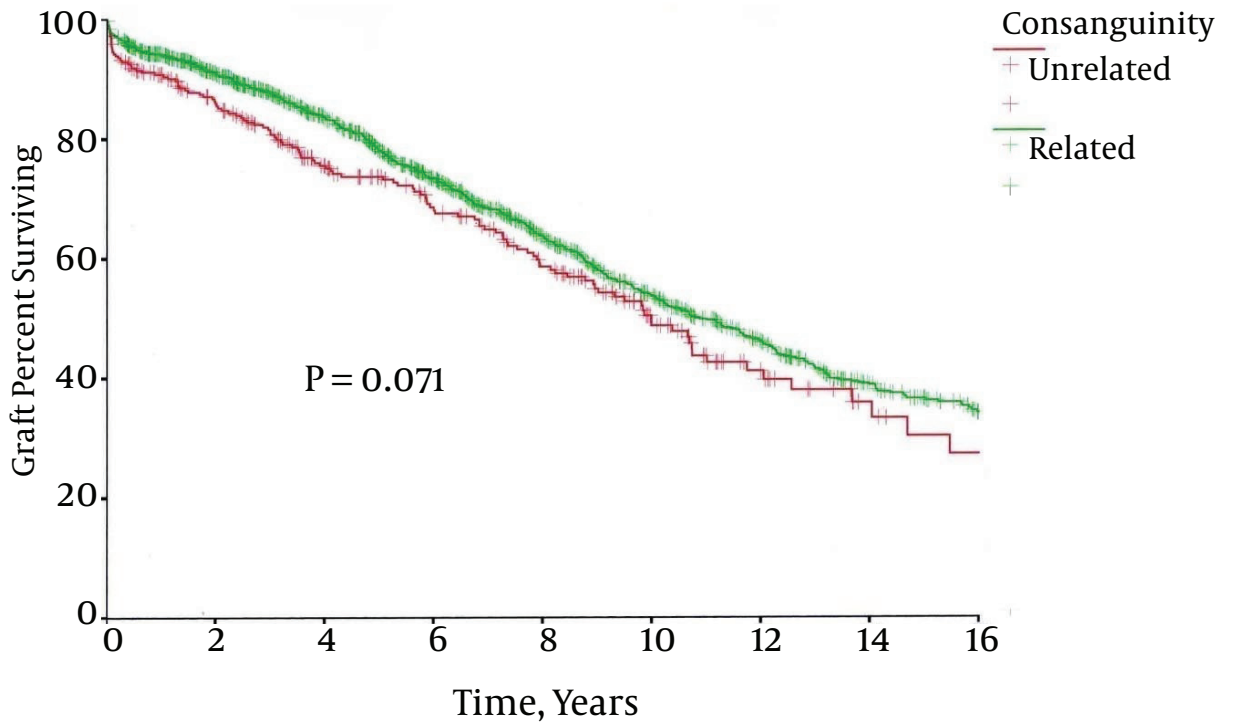

Figure 1. Graft Survival in LRD and LURD

the following: unresolved ethical issues like donor payment and possible coercion, unacceptably high donor and recipient morbidity and mortality, and poor allograft survival rates (6). With these points in mind, our center allows transplantation from living unrelated donors under certain circumstances, like hereditary nephritis, polycystic renal diseases and in the case of re-transplantation. Renal transplantation from living unrelated donors is successful, but has been met with some opposition due to poor tissue antigen compatibility and fear of commercialization.

In the present study, we note several important demographic differences between the two groups. Living unrelated recipients tend to be more elderly with younger donors, and a high percentage of male donors; however, in the living related group there are a high percentage of female donors, which was observed in live-donor programs in most countries, including the United States and Australia (7, 8). In Australia, female donors accounted for 53% and 62% of overall LRD and LURD donors, respectively; the latter likely reflects the growth in spousal donation (9). The reason for the greater proportion of female donors remains unclear, although some contributing factors could be medical (higher rates of cardiovascular disease in men) or psychosocial (financial issues and differing perception towards donation between genders) (10, 11). Our immunological work agrees with Fuller TF et al. and Humar A et al. (12, 13), since the number of live related transplants (LRT) with 3 & 4 HLA & 2DR matching are significantly higher than in the live unrelated transplants (LURT).

We started our transplantation program in the Mansoura urology and nephrology center (UNC) moving from one immunosuppressive protocol to another by starting with steroid and azathioprine and moving to the use of MMF, TAC, and sirolimus. Our study revealed no significant differences between LRT and LURT regarding immunosuppressive protocols, apart from the protocols Steroid-Azathioprine or MMF and Tac-MMF where a higher percentage of LRD group ($P < 0.001$) and ($P = 0.004$) respectively and this correlated with better HLA matching that encouraged less immunosuppressive drugs, like a steroid-free regimen (Tac and MMF protocol), while the protocols Steroid-cyclosporine Azathioprine or MMF were significantly higher in the unrelated group ($P < 0.001$). For induction immunosuppression, we considered the poorer HLA matching in the unrelated group and used anti-thymocyte globulin (ATG) and this correlated with the KDIGO guidelines that recommend the use of ATG, which is a potent immunosuppressive agent, rather than interleukin-2 recep-

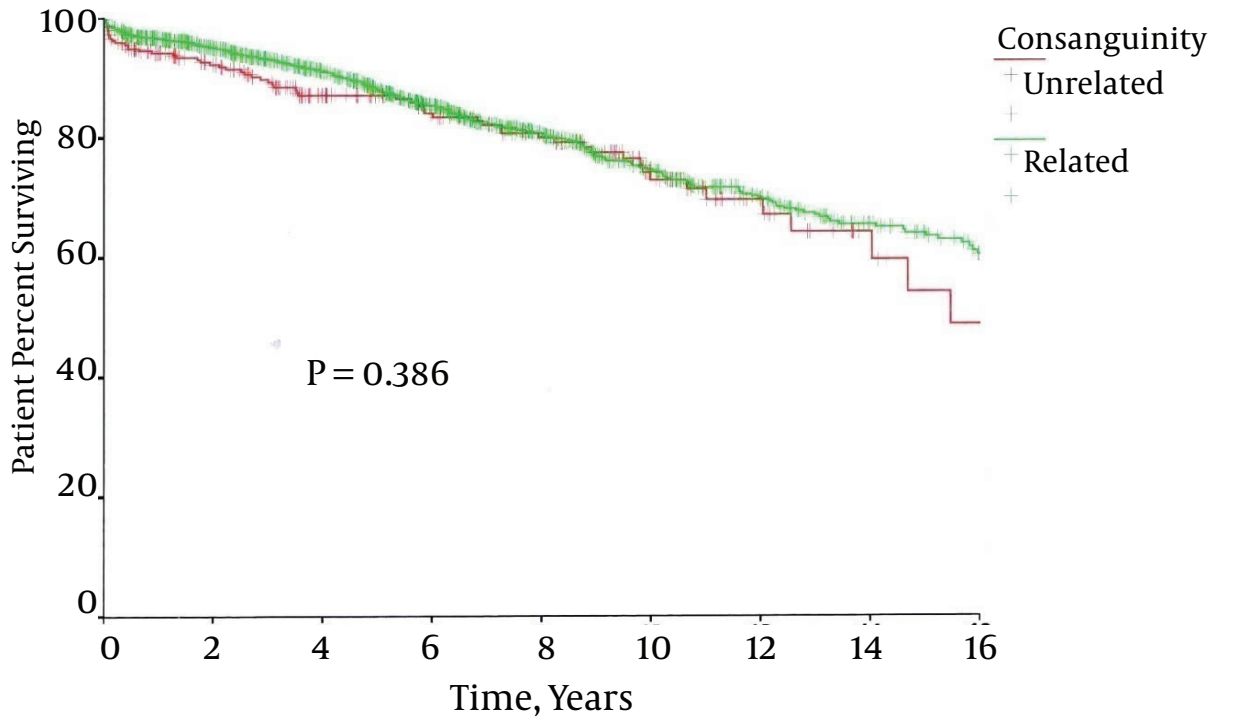

Figure 2. Patient Survival in LRD and LURD

tor antibodies principally for groups at high-risk for allograft rejection (14).

Although the incidence of early graft loss because of acute rejection has decreased steadily over the past decades, acute rejection is considered a major risk factor for chronic rejection and a strong predictor of long-term graft survival in both cadaveric and living donor kidney transplants (15, 16). In the present study, the percentages of patients with acute vascular rejection were significantly higher in the unrelated group (P = 0.005). This is not in agreement with Humar A et al. (13), who reported that the incidence of acute rejection was not higher for LURD recipients after comparing 595 LRDs with 116 LURDS; these mismatching results could be explained by the difference in immunosuppression protocols or the difference in HLA matching. Surprisingly in our study, there was no difference in the biopsy proved chronic rejection between both groups (P = 0.07), despite the higher incidence of acute vascular rejection in LURD. We found a higher incidence of early rejection in LURD compared to LRD and this agrees with Fuller et al. and Matas AJ et al. (12, 16), who reported higher percentages of early and severe rejections in LURT than LRT. There are some important factors that might impede the use of LURD sources, such as the elderly age of donors and the higher number of HLA mismatches compared with LRD (12). Our study is not in agreement with previous studies, since the LURD ages were significantly younger than LRD ages; this may be due to most LURD recipients in that study being friends and spouses, which is not the same as in our study. We reported no significant differences in regards to creatinine clearance and serum creatinine for one, three, and five years post transplantation between the two groups.

The one-, five-, and ten-year graft survival rates were 97%, 86.6%, and 67.9%, respectively, for recipients of LRD, while that for recipients of LURD were 95.4%, 83.6%, and 66.7%, respectively (Figure 1) (Tables 8 and 9). The one-, five-, and ten-year patient survival rates were 97.1%, 95.1%, and 80.8%, respectively, for recipients of LRD, while that for recipients of LURD were 95%, 88.8%, and 67%, respectively (Figure 2) (Tables 8 and 9). Worldwide, long-term graft survival of LURD kidneys is also encouraging. For example, in the 2008 annual report of the scientific registry of transplant recipients, the unadjusted five-year survival of LURD kidneys was the same as that of living related donor kidneys (approximately 80 %) (17). In Italy, graft survival rates of 172 LURT recipients were 87% in one year, 79% in five years, and 69% in nine years (18). On the other hand, D'Alessandro AM

Table 5. Post-Transplantation Medical Complications[a]

Variable	Related Group (n = 2,075)	Unrelated Group (n = 410)	P Value
Hypertension			0.84
Yes	1,228 (59.3)	245 (59.8)	
No	847 (40.7)	165 (40.2)	
Diabetes mellitus			0.07
Yes	343 (16.5)	106 (25.8)	
No	1,732 (83.5)	304 (74.2)	
Hepatic problems			0.82
Yes	129 (5.7)	23 (5.4)	
No	1,946 (94.3)	387 (94.6)	
Infections			0.88
Yes	378 (17.8)	75 (18.1)	
No	1,697 (82.2)	335 (81.9)	
Malignancy			0.15
Yes	97 (4.7)	26 (6.3)	
No	1,978 (95.3)	384 (93.7)	

[a]Values are expressed as No. (%).

Table 6. Number and Type of Rejection Episodes[a]

Variable	Related Group (n = 2,075)	Unrelated Group (n = 410)	P Value
Number of acute rejections			
No rejection	960 (46.3)	167 (40.7)	0.03
One episode	614 (29.6)	129 (31.5)	0.447
$\geq$ Two episodes	501 (24.1)	114 (27.8)	0.116
Type of rejection			
Acute cellular	728 (35.1)	156 (38.1)	0.25
Acute vascular	71 (3.41)	26 (6.3)	0.005
Chronic rejection	490 (23.6)	80 (19.5)	0.07
Rejection free	786 (37.9)	148 (36.1)	0.496

[a]Values are expressed as No. (%).

et al. (19), reported that patient survival in LURD recipients was worse than in LRD recipients; however, this study included a high percentage of diabetic patients.

Table 7. Serum Creatinine and Creatinine Clearance at Last Follow-up[a]

Variable	Related Group (n = 2,075)	Unrelated Group (n = 410)	P Value
Serum creatinine, mg/dL			
After one year	1.38 $\pm$ 0.69	1.35 $\pm$ 0.61	0.579
After three years	1.62 $\pm$ 0.95	1.54 $\pm$ 0.88	0.201
After five years	1.71 $\pm$ 1.04	1.59 $\pm$ 0.89	0.107
Creatinine clearance at last follow-up, mL/min			
Creatinine clearance	63.45 $\pm$ 33.75	61.61 $\pm$ 33.46	0.384

[a]Values are expressed as mean $\pm$ SD.

5.1. Limitations

There are potential limitations associated to our study. First, it is a retrospective single center study. Second, there were many changes in immunosuppressive protocols over the last few decades, but we should consider that the study was comprised of live matched donors and the majority were related donors with insignificant immunological risks in the unrelated group.

5.2. Conclusions

Graft survival is affected by factors like age of the donor, degree of HLA compatibility, original kidney disease, number and severity of acute rejection episodes, despite that kidney transplant recipients who received their grafts either from live related donors or live unrelated donors had a comparable patient and graft survival. Kidney donation by volunteers who are genetically unrelated to their recipients is medically successful, socially valuable, and ethically acceptable provided that donors are healthy, competent, and well-informed.

Table 8. Graft and Patient Survival of the Related Group

Years	Survival Rate	SE	Hazard Ratio	Confidence Interval (95% CI)
Graft survival				
1 year	0.97	0.004	0.03	(0.9622, 0.9778)
5 years	0.866	0.008	0.13	(0.8503, 0.8817)
10 years	0.679	0.013	0.32	(0.6535, 0.7045)
Patient survival				
1 year	0.971	0.004	0.03	(0.9622, 0.9778)
5 years	0.951	0.005	0.05	(0.9402, 0.9598)
10 years	0.808	0.011	0.192	(0.7864, 0.8296)

Table 9. Graft and Patient Survival of the Unrelated Group

Years	Survival Rate	SE	Hazard Ratio	Confidence Interval (95% CI)
Graft survival				
1 year	0.954	0.011	0.046	(0.9314, 0.9755)
5 years	0.836	0.02	0.164	(0.7968, 0.875)
10 years	0.667	0.029	0.333	(0.6101, 0.7238)
Patient survival				
1 year	0.95	0.011	0.05	(0.9284, 0.9716)
5 years	0.888	0.017	0.112	(0.8547, 0.9213)
10 years	0.76	0.027	0.24	(0.7071, 0.8129)

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Footnote

Authors' Contribution: All the authors contributed equally in this manuscript.

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کارگاه های آموزشی مرکز اطلاعات علمی جهاد دانشگاهی

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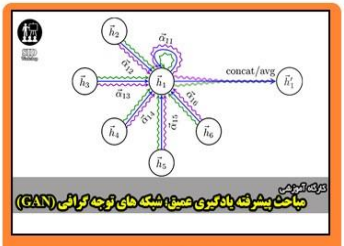
ترفند های جستجو



مباحث پیشرفته یادگیری عمیق؛
شبکه های توجه گرافی
(Graph Attention Networks)

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