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The impact of recipient and donor characteristics on kidney transplant graft survival

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Abstract

Introduction

Many factors determine the outcomes of renal transplant, including characteristics of both donors and recipients. Antihuman leukocyte antigen donor-specific antibodies are strongly linked to antibody-mediated rejection and late allograft loss.

Aim

The aim was to determine the effect of recipient and donor characteristics on kidney transplant graft survival, with special stress on panel-reactive antibodies.

Participants and methods

This study included 168 adult recipient and donor couples. The authors analyzed data of kidney transplants performed between the years of 2008 and 2018 at National Institute of Urology and Nephrology.

Results

The authors found a significant increase in renal failure in recipients transplanted with unrelated donor kidney and in positive hepatitis C virus antibodies (HCV Abs) recipients ($P = 0.002$ and 0.001, respectively) and renal complications ($P \leq 0.001$). There was also a significant increase in panel-reactive antibody-positive recipients to get renal complications ($P = 0.03$). There was a significant increase in renal failure with old-aged recipients ($P = 0.008$) and with increased duration of transplant ($P = 0.003$). By multivariate regression, the authors deduced that young age decreases graft loss risk (hazard ratio (HR): 0.88; 95% confidence interval (95% CI): 0.79–0.97; $P = 0.017$). Recipients of unrelated donor graft and HCV infection were associated with higher hazard ratio graft loss (HR: 13.56; 95% CI: 2.58–71.22; $P = 0.002$, and HR: 7.96; 95% CI: 1.04–60.44; $P = 0.45$). Unrelated donors graft were associated with 4 times higher hazard ratio renal complication (HR: 4.18; 95% CI: 2.01–8.72; $P = 0.003$). HCV infection increases risk three times (HR: 3.24; 95% CI: 1.31–7.99; $P = 0.010$). Unrelated donor was a significant independent predictor for recipient graft loss risk in a period of more than 5 years after transplantation.

Conclusion

The authors concluded that recipient and donor characteristics have important roles on kidney transplant graft survival and also on renal complications.

Keywords: A recipient and donor characteristics, kidney transplant and graft survival, renal complications

Introduction

End-stage renal disease develops from a variety of causes, mainly type 2 diabetes mellitus, hypertension, and glomerulonephritis. Therefore, kidney transplant is an important lifesaving intervention, with a 1-year post-transplant mortality risk reduction of greater than 80% [1]. Related living donor kidney transplant supply a closely matched organ for the

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recipient. However, unrelated living kidney donations help in supplying patient needs [2].

Many factors determine the outcomes of renal transplants and graft survival, including characteristics of both donors and recipients, such as age, sex, body size, hepatitis C infection (HCV), and glomerular filtration rate (GFR); perfect matching of donor with recipient [human leukocyte antigen (HLA) match]; proper interventional techniques; and new immunosuppressant drugs [3,4]. Most recipients of living donor kidneys are males, whereas females are most of the living kidney donors [5].

HLA system is composed of two major histocompatibility complex (MHC) molecules: MHC class I and II. Typing of HLA with polymerase chain reaction allows higher resolution and more precision than the serology method through a DNA-based technique, resulting in increased knowledge of amino acid sequences of HLA alleles to identify its polymorphic positions [6].

Previous organ transplant, multiple pregnancies, and multiple transfusions of blood products are risk factors for the development of anti-HLA antibodies [7], which are strongly linked to antibody-mediated rejection and late allograft loss and present a major problem for recipients of second renal transplant.

The number of calculated panel-reactive antibodies (PRA) based on the specificity of a potential recipient's anti-HLA antibody profile is determined. This number represents the percentage of the donor pool with whom the recipient is predicted to have a positive cross-match [8].

Many renal failure patients could not receive a living donor kidney transplant owing to blood group or cross-match incompatibility with their intended living donor. By desensitization, they can successfully overcome the previous problems [9]. However, incompatibility outcomes are inferior to compatible live donor kidney transplant [10].

Anti-HLA donor-specific antibodies (DSAs) can be detected using complement-dependent lympho-cytotoxicity test (CDC), which is nonspecific, or solid-phase assays, which are more accurate and specific [11].

The aim of this study was to determine the effect of recipient and donor characteristics on kidney transplant graft survival with special stress on PRAs.

Participants and methods

This single-center study included 335 living related (LR) and unrelated (LUR) kidney transplants. Many were excluded from the study for different reasons, including infection (e.g. CMV and hepatitis B), malignancy, and death. On the contrary, some shifted their follow-up to another centers. Finally, the study included only 168 recipient and donor couples. Recipients were 120 males and 48 females, with age ranging from 18 years to 51 years on transplant. They were transplanted greater than or equal to 10 years ago ($N = 27$), greater than or equal to 5 years ($N = 49$), greater than 2 years ($N = 70$), and 2 years ($N = 22$) at National Institute of Urology and Nephrology between the year of 2008 and 2018 at Matareya in Cairo, Egypt.

All procedures were approved by the Institutional Ethics Committee. We performed analyses for recipients' and their donors' data, including age, sex, relatedness, previous transplant HLA MM, ABO compatibility, panel-reactive antibody at time of transplant, single antigen, and hepatitis C antibodies (Abs).

HLA typing is done by PCR technique [12]. The genomic DNA was extracted by using rapid nucleic acid extraction kit: QIA amp Blood Kit (QIAGEN GmbH, Hilden, Germany). The genomic DNA was amplified using the INNO-LiPA Amplification Kit (Innogenetics Belux NV, Belgium). The amplification procedure was carried out on thermal cycler apparatus (Bio-Rad, Hercules, California, USA). After amplification, a large number of biotinylated DNA copies of the target sequence were obtained.

INNO-LiPA line probe assay (Innogenetics N.V.) was used for typing HLA-A, HLA-B, and HLA-DRB1 at the allele level. The INNO-LiPA HLA typing tests are based on the reverse hybridization principle [13]. The amplified biotinylated DNA material was chemically denatured, and the separated strands were hybridized with specific oligonucleotide probes immobilized as parallel lines on the membrane-based strips. On each strip, there are 37 sequence-specific DNA probes and two control probes. This was followed by the stringent wash step and the addition of the streptavidin conjugated with alkaline phosphatase. The conjugate would bind to any biotinylated hybrid previously formed. Then, the strips were incubated with a substrate solution containing chromogen resulting in a purple/brown precipitate indicating the biotinylated DNA. The reaction was stopped by washing, and the reactivity pattern of the probes was recorded.

DSA and single-antigen (SA) tests were performed in the central laboratories of the armed forces by solid phase (Luminex, Austin, Texas, USA), where purified HLA molecules either a single HLA type or a combination of types are attached to beads. These molecules will bind to anti-HLA antibodies in the patient's serum. Using single-antigen technology, the Luminex technology can predict a patient's sensitization to particular HLA types before transplantation without performing a CDC or flow cytometric cross-match (termed a 'virtual cross-match') [14]. Luminex is rapid, sensitive, and specific and can detect anti-HLA antibodies below the threshold for a positive CDC cross-match. We use DSA assays for pre-transplant rejection risk prediction and post-transplant monitoring for development of de novo DSA in renal transplant recipients.

Close maintenance monitoring after transplant is very important. At our center, patients without complications were

discharged after about 1 week after transplant and were seen every week for 1 month in the outpatient clinics and then every 2 weeks for next 2 months and then every month for the first year. Then patients were monitored at least two to four times a year to facilitate tailoring immunosuppression regimens, especially in the elderly and high-risk patients.

Statistical analysis

Analysis was performed by statistical package software IBM SPSS version 24 version 24 (IBM corp: Armank, Newyork,USA) using means ± SD, proportions, χ2-test, Fisher's exact test, unpaired t-test, and Cox regression. All tests were bilateral, and a *P* value of 5% was the limit of statistical significance.

Results

We classified our 168 kidney transplant recipients according to presence or absence of renal failure into two groups:

(1) Group I (gp I): estimated glomerular filtration rate (eGFR) greater than or equal to 15 ml/min/1.73 m^2 (no renal failure).
(2) Group II (gp II): eGFR less than 15 (renal failure) (Table 1).

eGFR was calculated using the CKD-EPI equation [15].

GFR = 141*min (Scr/κ,1)α * max (Scr/κ, 1)$^{-1.209}$ * 0.993^{Age} *1.018 [if female] *1.159 [if black]. Scr is serum creatinine (mg/dl), κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

We further classified the patients into two groups according to the presence or absence of complications:

(1) Group A: patients with eGFR greater than or equal to 60 ml/min/1.73 m^2.
(2) Group B: patients with renal complications eGFR less than 60 ml/min/1.73 m^2(Table 2).

There was a significant increase of renal failure in transplant recipients with LUR donor kidney and in positive HCV antibodies (Abs) (*P* = 0.002 and 0.001, respectively) (Table 3 and Fig. 1) and with renal complications (*P* ≤ 0.001 and ≤0.001, respectively) on comparing with transplant recipients with LR donors and negative ELISA HCV Abs (Table 4 and Fig. 1c).

Moreover, there was a significant increase in PRA-positive recipients for renal complications than PRA-negative ones (*P* = 0.03, Fig 2c) and in transplant recipients from donors with dissimilar ABO blood group as compared with recipients with the same ABO group (*P* = 0.002) (Table 4). On the contrary, there was an insignificant increase in PRA-positive recipients for renal failure (*P* = 0.24) and in transplant recipients from donors with dissimilar ABO blood group (*P* = 0.065) (Table 3, Fig. 2).

Presence of positive single antigen or primary transplant would insignificantly increase graft loss and renal complication

Table 1: Mean±SD of groups I and II recipients' data (creatinine, urea, and eGFR) (according to presence or absence of kidney failure)

Kidney failure		Creatinine	Urea	eGFR
Group I	*n*	158	158	158
	Mean±SD	1.44±0.67	44.64±18.47	71.51±29.23
Group II	*n*	10	10	10
	Mean±SD	7.46±1.53	141.88±44.26	8.9±2.23
Total	*n*	168	168	168
	Mean±SD	1.8±1.61	50.43±30.96	67.79±32.01

eGFR, estimated glomerular filtration rate.

Table 2: Mean±SD of groups A and B recipients' data (according to presence or absence of complications)

Complications		Creatinine	Urea	eGFR
Group A	*n*	104	104	104
	Mean±SD	1.07±0.24	35.14±7.93	88.10±20.14
Group B	*n*	64	64	64
	Mean±SD	2.98±2.11	75.28±37.76	34.78±16.26
Total	*n*	168	168	168
	Mean±SD	1.80±1.61	50.43±30.96	67.79±30

eGFR, estimated glomerular filtration rate.

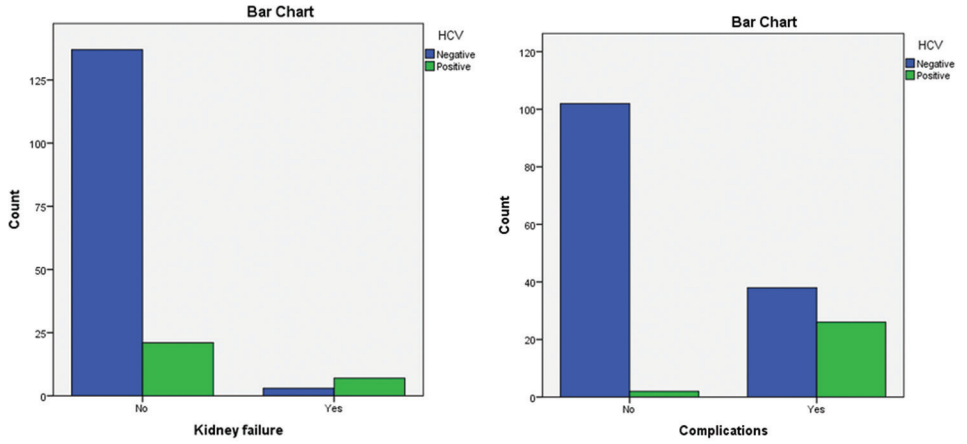

Figure 1: HCV in group I and II. No = group I, yes = group II. 1c: HCV in groups A and B. No = group A, yes = group B.

incidence (P = 0.33 and 0.31, and P = 0.72 and 0.67, respectively) (Table 3 and Figs. 3) (Table 4 and Fig. 3c).

Regarding sex, the combination of female donors and female recipients shows no graft failure nor renal complications (Tables 5a and 6a).

It was found that most of the recipients with renal failure or renal complications have had 3–5 mismatch (MM) with or without DR MM (Table 5a, Fig. 4) (Table 6a, Fig. 4c).

Table 7 shows significant increase in renal failure with old-aged recipients (P = 0.008) and with time elapsed after transplant (P = 0.003), whereas insignificant increase regarding donors age. However, there was a significant increase in renal complications with increased duration of transplant (P = 0.019) and insignificant increase of renal complications with old age of recipients or donors (Table 8).

By multivariate regression, we deduced that age, relation, and HCV variables significantly predict renal failure (P < 0.001), whereas relation, HCV infection, and PRA significantly predict renal complications (P < 0.001). Each of the variables was tested if they were independent predictors or not. Table 9 shows that younger age decreased graft loss risk [hazard ratio (HR) = 0.88, 95% confidence interval (95% CI): 0.79–0.97; P = 0.017]. Recipients of LUR donors graft were associated with 13 times higher hazard ratio graft loss than LR donors (HR: 13.56; 95% CI: 2.58–71.22; P = 0.002) (Fig. 5). HCV infection increases risk 8 times (HR: 7.96; 95% CI: 1.04–60.44; P = 0.045) (Fig. 6). Table 10 shows that LUR donor grafts are associated with 4 times higher hazard ratio renal complications (HR: 4.18; 95% CI: 2.01–8.72, P < 0.003) (Fig. 5c). HCV infection increases risk 3 times (HR: 3.24; 95% CI: 1.31–7.99; P = 0.010 (Fig. 6c), whereas PRA insignificantly predict renal complication (HR: 3.05; 95% CI: 0.97–9.57; P = 0.055).

By multivariate analysis, we also tested the variables if they independently predicted graft failure at a time less or more than 5 years after renal transplantation. Table 11 shows that LUR donor was a significant independent predictor for recipient graft loss risk in a period more than 5 years of transplant. Moreover, recipients were associated with increase renal failure risk 10 times as of LR donors (HR = 10.47; 95% CI: 1.31–83.62), but this association was not found at a time less than 5 years (HR = 17.42; 95% CI: 0.98–307.03).

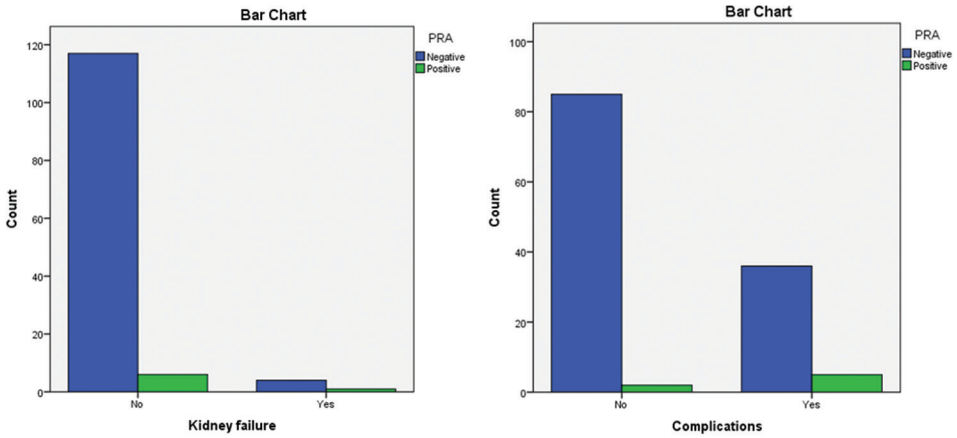

Figure 2: PRA in group I and II. No = group I, yes = group II. 2c: PRA in groups A and B. No = group A, yes = group B.

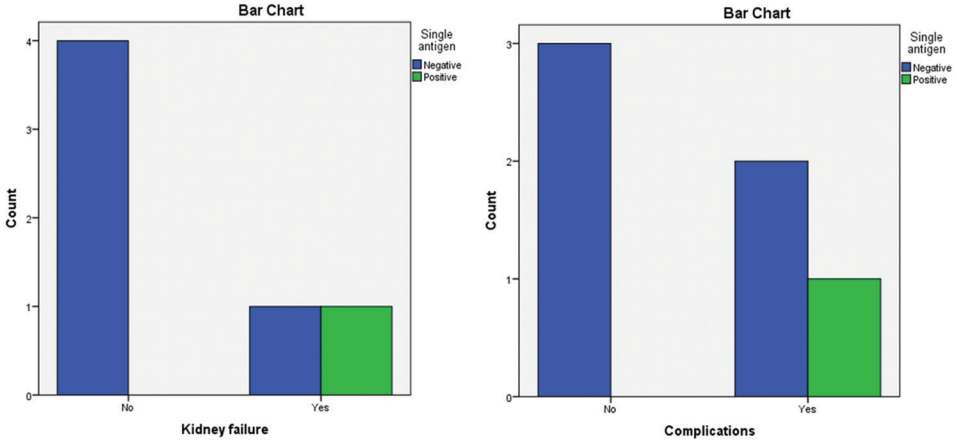

Figure 3: Single antigen in group I and II. No = group I, yes = group II. 3c: Single antigen in groups A and B. No = group A, yes = group B.

Table 3: Group I and group II recipients' demographics (according to renal failure)

	Relation binomial		Total	*P*
	Related	Nonrelated		
Group I				
Count	143	15	158	
%	96.6	75.0	94.0	
Group II				
Count	5	5	10	0.002
%	3.4	25.0	6.0	
Total				
Count	148	20	168	
%	100.0	100.0	100.0	
	Recipient sex			
	Male	Female		
Group I				
Count	113	45	158	
%	94.2	93.8	94.0	0.91
Group II				
Count	7	3	10	
%	5.8	6.3	6.0	
Total				
Count	120	48	168	
%	100.0	100.0	100.0	
	PRA			
	Negative	Positive		
Group I				
Count	117	6	123	
%	96.7	85.7	96.1	0.249
Group II				
Count	4	1	5	
%	3.3	14.3	3.9	
Total				
Count	121	7	128	
%	100.0	100.0	100.0	
	HCV			
	Negative	Positive		
Group I				
Count	137	21	158	<0.001
%	97.9	75.0	94.0	
Group II				
Count	3	7	10	
%	2.1	25.0	6.0	
Total				
Count	140	28	168	
%	100.0	100.0	100.0	
	ABO similarity			
	Similar	Dissimilar		
Group I				
Count	122	36	158	0.065
%	96.1	87.8	94.0	
Group II				
Count	5	5	10	
%	3.9	12.2	6.0	
Total				
Count	127	41	168	
%	100.0	100.0	100.0	
	Single antigen			
	Negative	Positive		
Group I				
Count	8	0	8	
%	80.0	0.0	66.7	
Group II				
Count	2	2	4	0.333
%	20.0	100.0	33.3	
Total				
Count	10	2	12	
%	100.0	100.0	100.0	
	Transplant before			
	No	Yes		
Group I				
Count	153	5	158	
%	94.4	83.3	94.0	
Group II				
Count	9	1	10	0.31
%	5.6	16.7	6.0	
Total				
Count	162	6	168	
%	100.0	100.0	100.0	

eGFR, estimated glomerular filtration rate; HCV, hepatitis C virus.

However, recipients' age and HCV infection were not associated with graft loss risk either before or after 5 years of transplant.

For renal complication, it was found that recipients with positive PRA increase its risk 6 times and both unrelated donor and HCV infection increase the risk 3 times in the period less than 5 years of transplant. (HR = 6.44, 95% CI: 2.02–20.52; HR = 3.11, 95% CI: 1.44–6.71; and HR = 3.42, 95% CI: 1.26–9.28, respectively) (Table 12).

When our patients were further subdivided according to related and unrelated donor transplants, no associated graft survival appears neither in young age nor in HCV negative patients in the 2 groups (HR = 0.92, 95% CI: 0.79–1.06; and HR = 4.99, 95% CI: 0.48–51.85, respectively, in related group and HR = 0.66, 95% CI: 0.37–1.17 and HR = 9.28, 95% CI: 0.18–475.78, respectively, in unrelated donors) (Table 13). Regarding renal complications, PRA and HCV were not risk factors in the 2 groups (HR = 1.33, 95% CI: 0.24–7.34 and HR = 0.98, 95% CI: 0.29–3.3, respectively, in related group and HR = 2.28, 95% CI: 0.28–18.66, and HR = 8.28, 95% CI: 0.98–69.7, respectively, in unrelated donors) (Table 14).

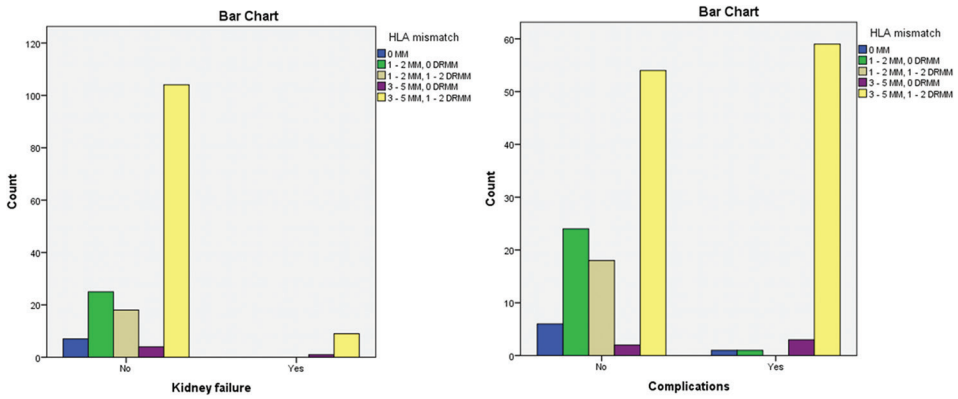

Figure 4: HLA MM in group I and II. No = group I, yes = group II. 4c: HLA MM in group A and B. No = group A, yes = group B.

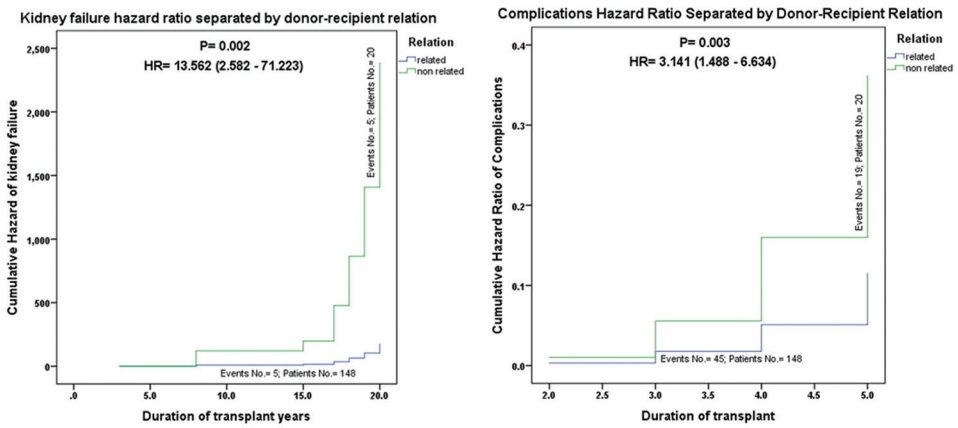

Figure 5: HR of unrelated donor to renal failure HR = hazard ratio. 5c: HR: of unrelated donor to renal complications HR = hazard ratio.

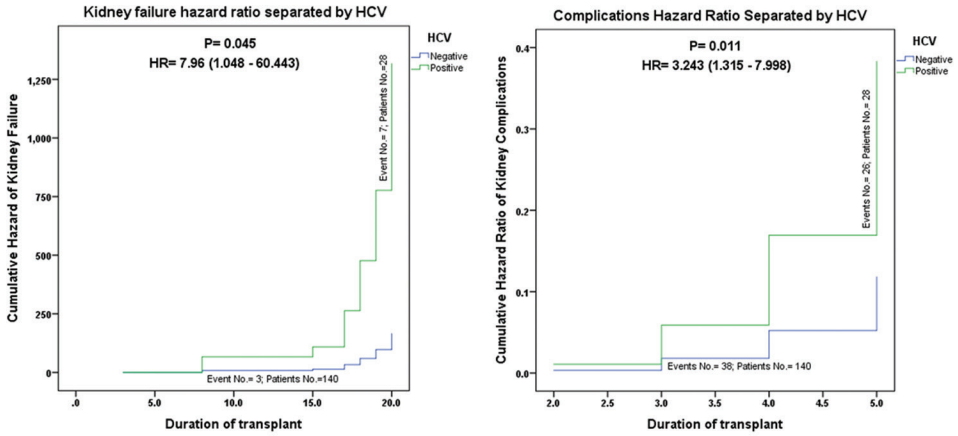

Figure 6: HR of HCV infection to renal failure HR = hazard ratio. 6c: HR: of HCV infection to renal complications HR = hazard ratio.

We found recipients of LUR donors kidney with negative HCV Abs but not HCV positive recipients had a significant increase in the risk of graft failure about 13 times more than recipients of LR donors and of renal complication about 3 times more (HR = 12.95, 95% CI: 1.01–164.7 and HR = 6.27, 95% CI: 0.81–48.34, respectively) (Table 15) and (HR = 2.75, 95% CI: 1.18–6.42 and HR = 0.34, 95% CI: 0.03–4.97, respectively) (Table 16). However, older recipients were not associated with poor graft survival in both HCV-negative and HCV-positive recipients (HR = 0.88, 95% CI: 0.72–1.07 and HR = 0.92, 95% CI: 0.82–1.03, respectively) (Table 15). PRA was associated with increase in the risk of renal complications about 7 times more than PRA-negative recipients in HCV-negative group but not positive one (HR = 2.75, 95% CI: 1.84–25.61 and HR = 0.29, 95% CI: 0.02–3.87, respectively).

Table 4: Group A and group B recipients' demographics (according to renal complication)

	Relation binomial		Total	*P*
	Related	Nonrelated		
Group A				
Count	103	1	104	
%	69.6	5.0	61.9	
Group B				
Count	45	19	64	<0.001
%	30.4	95.0	38.1	
Total				
Count	148	20	168	
%	100.0	100.0	100.0	
	Recipient sex			
	Male	Female		
Group A				
Count	79	25	104	0.097
%	65.8	52.1	61.9	
Group B				
Count	41	23	64	
%	34.2	47.9	38.1	
Total				
Count	120	48	168	
%	100.0	100.0	100.0	
	PRA			
	Negative	Positive		
Group A				
Count	85	2	87	
%	70.2	28.6	68.0	0.03
Group B				
Count	36	5	41	
%	29.8	71.4	32.0	
Total				
Count	121	7	128	
%	100.0	100.0	100.0	
	HCV			
	Negative	Positive		
Group A				
Count	102	2	104	<0.001
%	72.9	7.1	61.9	
Group B				
Count	38	26	64	
%	27.1	92.9	38.1	
Total				
Count	140	28	168	
%	100.0	100.0	100.0	
	ABO similarity			
	Similar	Not similar		
Group A				
Count	87	17	104	0.002
%	68.5	41.5	61.9	
Group B				
Count	40	24	64	
%	31.5	58.5	38.1	
Total				
Count	127	41	168	
%	100.0	100.0	100.0	
	Single antigen			
	Negative	Positive		
Group A				
Count	6	0	6	
%	60.0	0.0	50.0	0.72
Group B				
Count	4	2	6	
%	40.0	100.0	50.0	
Total				
Count	10	2	12	
%	100.0	100.0	100.0	
	Transplant before			
	No	Yes		
Group A				
Count	101	3	104	
%	62.3	50.0	61.9	
Group B				
Count	61	3	64	0.67
%	37.7	50.0	38.1	
Total				
Count	162	6	168	
%	100.0	100.0	100.0	

HCV, hepatitis C virus; PRA, panel-reactive antibody.

Discussion

Renal transplant is the first life-saving option for end-stage renal disease treatment. The outcomes have greatly improved with progress in immunologic workup, immunosuppressive therapy, and surgical techniques [16]. However, recipient and donor characteristics are important factors that need analysis and interpretation for better outcomes. We have analyzed the effects of donor and recipient age, sex, HLA MM, and HCV infection on both graft survival (renal failure outcome) and renal complications. Age and sex are important risk factors for graft failure incidence in living donor transplant [3].

The association between recipient and donor age and graft failure is already known [17]. We found that young age recipients significantly lead to 12% decrease of graft loss but insignificantly associated with 5-year survival and more than 5-year survival. Srithongkul *et al.* [18] performed a multivariate analysis on data from 211 kidney transplant patients and found that age significantly predicted recipient GFR after transplant. Consistent with our results is the study by Lepeytre *et al.* [19], which showed higher numerical rate of graft failure in recipients aged more than

Table 5: Group I and group II recipients and donors' characteristics (according to renal failure)

	Recipient-donor sex				Total
	Male *t*-female	Male *t*-male	Female *t*-female	Female *t*-male	
Group I					
Count	20	49	25	64	158
%	87.0	94.2	100.0	94.1	94.0
Group II					
Count	3	3	0	4	10
%	13.0	5.8	0.0	5.9	6.0
Total					
Count	23	52	25	68	168
%	100.0	100.0	100.0	100.0	100.0

	HLA mismatch					
	0 MM	1-2 MM, 0 DRMM	1-2 MM, 1.2 DMM	3-5 MM, 0 DRMM	3 MM, 1.2 DRMM	
Group I						
Count	7	25	18	4	104	158
%	100.0	100.0	100.0	80.0	92.0	94.0
Group II						
Count	0	0	0	1	9	10
%	0.0	0.0	0.0	20.0	8.0	6.0
Total						
Count	7	25	18	5	113	168
%	100.0	100.0	100.0	100.0	100.0	100.0

	Relation										Total
	Father	Mother	Brother	Sister	Cousin	Uncle	Aunt	Son	Daughter	Unrelated	
Group I											
Count	13	38	40	35	7	5	2	2	1	15	158
%	81.3	97.4	100.0	97.2	100.0	100.0	100.0	100.0	100.0	75.0	94.0
Group II											
Count	3	1	0	1	0	0	0	0	0	5	10
%	18.8	2.6	0.0	2.8	0.0	0.0	0.0	0.0	0.0	25.0	6.0
Total											
Count	16	39	40	36	7	5	2	2	1	20	168
%	100.0	100.0	100.0	100	100.0	100.0	100.0	100.0	100.0	100.0	100.0

	Recipient ABO					Total
	A1+	B+	A1B+	O+	O−	
Group I						
Count	62	31	23	38	4	158
%	91.2	96.9	95.8	95.0	100.0	94.0
Group II						
Count	6	1	1	2	0	10
%	8.8	3.1	4.2	5.0	0.0	6.0
Total						
Count	68	32	24	40	4	168
%	100.0	100.0	100.0	100.0	100.0	100.0

	Donor ABO							Total
	A1+	B+	A1B+	O+	O−	A1−	B−	
Group I								
Count	48	28	12	60	6	3	1	158
%	96.0	100.0	92.3	90.9	85.7	100.0	100.0	94.0
Group II								
Count	2	0	1	6	1	0	0	10
%	4.0	0.0	7.7	9.1	14.3	0.0	0.0	6.0

Contd...

Table 5: Contd...

	Donor ABO							Total
	A1+	B+	A1B+	O+	O−	A1−	B−	
Total								
Count	50	28	13	66	7	3	1	168
%	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

HLA, human leukocyte antigen.

Table 6: Group A and group B recipients and donors' characteristics (according to renal complications)

	Recipient-donor sex				Total
	Male-female	Male-male	Female-female	Female-male	
Group A					
Count	11	33	14	46	104
%	47.8	63.5	56.0	67.6	61.9
Group B					
Count	12	19	11	22	64
%	52.2	36.5	44.0	32.4	38.1
Total					
Count	23	52	25	68	168
%	100.0	100.0	100.0	100.0	100.0

	HLA mismatch					
	0 MM	1-2 MM, 0 DRMM	1-2 MM, 1.2 DMM	3-5 MM, 0 DRMM	3 MM, 1.2 DRMM	
Group A						
Count	6	24	18	2	54	104
%	85.7	96.0	100.0	40.0	47.8	61.9
Group B						
Count	1	1	0	3	59	64
%	14.3	4.0	0.0	60.0	52.2	38.1
Total						
Count	7	25	18	5	113	168
%	100.0	100.0	100.0	100.0	100.0	100.0

	Relation										
	Father	Mother	Brother	Sister	Cousin	Uncle	Aunt	Son	Daughter	Unrelated	
Group A											
Count	8	28	28	28	5	5	0	1	0	1	104
%	50.0	71.8	70.0	77.8	71.4	100	0.0	50.0	0.0	5.0	61.9
Group B											
Count	8	11	12	8	2	0	2	1	1	19	64
%	50.0	28.2	30.0	22.2	28.6	0.0	100.0	50.0	100.0	95.0	38.1
Total											
Count	16	39	40	36	7	5	2	2	1	20	168
%	100.0	100.0	100.0	100.	100.0	100.0	100.0	100.0	100.0	100.0	100.0

	Recipient ABO					Total
	A1+	B+	A1B+	O+	O−	
Group A						
Count	39	17	15	30	3	104
%	57.4	53.1	62.5	75.0	75.0	61.9
Group B						
Count	29	15	9	10	1	64
%	42.6	46.9	37.5	25.0	25.0	38.1
Total						
Count	68	32	24	40	4	168

Contd...

Table 6: Contd...

	Recipient ABO							Total
	A1+	B+	A1B+	O+	O−			
%	100.0	100.0	100.0	100.0	100.0			100.0
	Donor ABO							Total
	A1+	B+	A1B+	O+	O−	A1−	B−	
Group I								
Count	34	17	9	37	5	1	1	104
%	68.0	60.7	69.2	56.1	71.4	33.3	100.0	61.9
Group II								
Count	16	11	4	29	2	2	0	64
%	32.0	39.3	30.8	43.9	28.6	66.7	0.0	38.1
Total								
Count	50	28	13	66	7	3	1	168
%	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

HLA, human leukocyte antigen.

Table 7: Age and duration of transplantation of groups I and II patients

	Kidney failure	*n*	Mean±SD	*P*	Significance
Recipient age	Group I	158	31.399±8.77	0.008	S
	Group II	10	23.800±7.25		
Donor age	Group I	158	38.443±10.33	0.828	NS
	Group II	10	37.700±12.23		
Duration of transplant	Group I	158	6.342±5.28	0.003	S
	Group II	10	11.700±6.73		

S, significant.

Table 8: Age and duration of transplantation of groups A and B patients

	Complications	*n*	Mean±SD	*P*	Significance
Recipient age	Group A	104	31.49±8.89	0.31	NS
	Group B	64	30.063±8.78		
Donor age	Group A	104	39.000±10.12	0.35	NS
	Group B	64	37.422±10.89		
Duration of transplant	Group A	104	5.856±5.15	0,019	S
	Group B	64	7.969±5.84		

S, significant.

45 years. The study by Ashby *et al.* [4] disagrees ours. It stated that young adult recipients' transplant is associated with higher rate of graft failure. Regarding donor age, we deduced insignificant association with graft loss. This contradicts the results of Massie *et al.* [20], which found worse graft survival accompanying older donor age. Berger *et al*.[21] also reported that recipients of living donors aged 70 years and older had 62% higher risk of graft failure compared with recipients of living donors aged 50–59 years [21]. However, the study by Young *et al.* [22] reported no association between donor age and graft loss when age was treated as a continuous predictor, as our results, but they stated that 56% increase in risk from donors age greater than or equal to 60 years compared with donors age less than 60, which disagrees ours. Matter and his colleagues reported that differences between recipient and donor age cause an adverse effect on graft outcomes. They, [16] found no significant effect by multivariate analysis.

Donor and recipient sex is an important factor in evaluating kidney transplant outcome [23]. Many studies have examined the effect of donor and recipient sex on renal graft survival [24–26]. However, the results are controversial. This study revealed increased graft failure in female recipients transplanted with male kidneys. This is consistent with the results of Gratwohl *et al*. [27] and Tan *et al.* [28]. This may be owing to the effect of histocompatibility H-Y antibodies [27].

It is known that graft survival for female kidneys is poor when compared with male kidneys, mostly if inserted in a male recipient [29]. Zeier *et al.* [29] and Lepeytre *et al.* [19] reported an increase of graft loss when female kidneys are transplanted into male recipients or female recipients when compared with male kidneys. Immunologic, hormonal, anatomic (e.g. size mismatch and nephron mass), and pharmacologic factors may explain the effects of sex on renal transplant. It was found that an increased risk of proteinuria and worse outcome may be owing to low donor kidney/recipient weight ratio. More smaller female kidney size may lead to ischemic injury, immunologic reaction, or nephrotoxicity [30]. Moreover, sex hormones take part in renal release of cytokines, and growth factors, which may cause poor outcome. Verzola *et al.* [31] reported that testosterone causes renal damage, whereas estrogen has renal protective effect. Recipient pregnancy or urinary tract infection may be a cause of poor outcome in female aged 15–24 years, regardless of donor sex.

The study by Ashby *et al.*[4] revealed that the combination of a male donor and male recipient had the best graft outcome. However, Matter *et al.* [16] concluded that donor and recipient sex had no effect on graft survival. This may be owing to good HLA matching and relation.

Table 9: HR of variables to renal failure

	P	Significance	HR	95.0% CI	
				Lower	Upper
Recipient age	0.017	S	0.881	0.794	0.978
Relation binomial	0.002	S	13.562	2.582	71.223
HCV	0.045	S	7.960	1.048	60.443

Cl, confidence interval; HCV, hepatitis C virus; HR, hazard ratio; S, significant.

Table 10: HR of variables to renal complications

	P	Significance	HR	95.0% CI	
				Lower	Upper
Relation binomial	0.003	S	4.189	2.011	8.728
HCV	0.011	S	3.243	1.315	7.998
PRA	0.055	NS	3.056	0.975	9.576

Cl, confidence interval; HR, hazard ratio; S, significant.

Table 11: HR of variables of renal failure in relation to time

Strata	Significance	HR	95.0% CI	
			Lower	Upper
<5 years				
Recipient age	NS	0.785	0.610	1.011
Relation binomial	NS	17.422	0.989	307.035
HCV	NS	20.087	0.154	201.660
>5 years				
Recipient age	NS	0.915	0.821	1.020
Relation binomial	S	10.474	1.312	83.624
HCV	NS	5.481	0.608	49.414

Cl, confidence interval; HR, hazard ratio; S, significant.

Table 12: HR of variables of renal complications in relation to time

Strata	Significance	HR	95.0% CI	
			Lower	Upper
<5 years				
Relation binomial	S	3.118	1.448	6.718
HCV	S	3.429	1.266	9.289
PRA	S	6.444	2.023	20.522
>5 years				
Relation binomial	NS	2.876	0.213	65.983
HCV	NS	7.966	0.665	95.366
PRA	NS	5.562	0.521	88.64

Cl, confidence interval; HCV, hepatitis C virus; HR, hazard ratio; PRA, panel-reactive antibody; S, significant.

Table 13: HR of age and HCV to renal failure in related and unrelated groups

Relation binomial	Significance	HR	95.0% CI	
			Lower	Upper
Related				
Recipient age	NS	0.921	0.799	1.062
HCV	NS	4.991	0.481	51.851
Non related				
Recipient age	NS	0.666	0.378	1.171
HCV	NS	9.288	0.181	475.788

Cl, confidence interval; HCV, hepatitis C virus; HR, hazard ratio; S, significant.

Table 14: HR of HCV and PRA to renal complication in related and unrelated groups

Relation binomial		Significance	HR	95.0% CI	
				Lower	Upper
Related	HCV	NS	0.980	0.290	3.306
	PRA	NS	1.334	0.242	7.340
Non related	HCV	NS	8.285	0.985	69.703
	PRA	NS	2.284	0.280	18.663

Cl, confidence interval; HCV, hepatitis C virus; HR, hazard ratio; PRA, panel-reactive antibody; S, significant.

Table 15: HR of age and relation in HCV groups

HCV	Significance	HR	95.0% CI	
			Lower	Upper
Negative				
Recipient age	NS	0.884	0.726	1.076
Relation binomial	S	12.955	1.019	164.700
Positive				
Recipient age	NS	0.922	0.822	1.034
Relation binomial	NS	6.272	0.814	48.343

Cl, confidence interval; HCV, hepatitis C virus; HR, hazard ratio; S, significant.

Table 16: HR of PRA and relation to renal complication in HCV groups

HCV	Significance	HR	95.0% CI	
			Lower	Upper
Negative				
PRA	S	6.882	1.849	25.615
Relation binomial	S	2.753	1.180	6.422
Positive				
PRA	NS	0.293	0.022	3.876
Relation binomial	NS	0.345	0.034	4.976

Cl, confidence interval; HCV, hepatitis C virus; HR, hazard ratio; S, significant.

The degree of relationship between donor and recipient has been proven to have a role in the graft survival. Our study showed that unrelated donor was associated with both increased graft loss risk 13 times especially in a duration more than 5 years after transplantation and in HCV-negative recipients and renal impairment 4 times risk in less than 5-year duration. Our results are consistent with the study by Lee *et al.* [32], which demonstrated that LR donor kidney transplants have a higher rate of early graft function than unrelated ones. Moreover, Van Arendonk *et al*. [33] report on pediatric recipients revealed the same. Park *et al.* [34] confirmed that graft survival was better

for LR donor transplants than for unrelated in a retrospective study of 779 renal transplants.

Regarding LUR donor, kidney transplants showed higher rates of HLA MM. In contrary with our study, Berger *et al.* [21] revealed that unrelated donor was associated with a decreased risk. This is explained by their adjustment of HLA-B and HLA-DR mismatch.

The study by Holscher *et al*. [35] showed that renal transplant from offspring donors has a better graft outcome than nonoffspring donors. This is consistent with our data. The reason is the younger donor age and HLA matching of offspring donors but continuous donor evaluation is very important for the potential risk of future kidney disease, especially if the cause of recipient renal failure is genetic disease. However, Cohen *et al.* [36] concluded that nonoffspring kidneys had lower risk of graft failure than offspring kidneys. This is may be owing to analyzing only recipients with 3 HLA MM. Most parent-offspring pairs had mismatches less than 3 and might be expected to have a lower risk of graft failure. If a recipient has two donors with the same age and HLA MM number, and only differ by one of them being the offspring of the recipient, there is lower risk of graft failure with the non-offspring donor.

Human HLA genes are located on 6th chromosome. It codes for MHC class I and II alleles. Polymorphisms in HLA, especially HLA-A, HLA-B (class I), HLA-DR (class II) loci, have an important role in renal transplant. Low HLA MM number leads to decreased recognition and rejection. The effect of HLA matching is reduced by using strong immunosuppressant [37]. However, Croke *et al.* [38] found high graft loss risk with more HLA MM in 12 622 recipients. The study by Massie *et al.* [20] showed that HLA-DR and HLA-B mismatches were significantly associated with poor graft survival. Our results are consistent with these prior studies. We demonstrated that most of the recipients having renal failure were with 3–5 MM with or without DR MM. The studies by Yacoub *et al*. [39] and Shi *et al.* [40] confirmed that HLA mismatching was a powerful prognostic factor that influences graft survival, mainly HLA-DR, whereas HLA-A mismatching has less insignificant effect on graft survival. The study by Shi *et al.* [41] also proved that HLA-DR and HLA-A and HLA-B are crucial determinants for graft outcome in 26 000 pediatric recipients in their meta-analysis study involving 18 studies. Brennan *et al.* [42] showed that more than 3 HLA MM were significantly associated with nearly two times more risk of rejection.

The study by Casey *et al*. [43] disagreed with ours. The study showed that in unrelated living donor kidney transplants, zero-HLA MM had no effect on patient survival, as it needs HLA matching of the nontraditional major and minor histocompatibility antigens, which was not included in their study. Living related transplants typically have fewer HLA MMs than living unrelated transplants. Moreover, zero-HLA mismatching advantage is that it remains a minor risk of post-transplant sensitization, so second transplant may have a good chance [44].

However, HLA DR MM might cause lymphoproliferative diseases in pediatric recipients after transplantation [45] and may lead to death [46].

Panel-reactive antibody (PRA) is defined as the percentage of HLA antigens as a single or in association out of a panel interacting with a patient's serum and may show the number of donors expected to react with the patient's serum. Evaluation of the PRA proportion according to donor specificity is relevant to minimize risk of rejection after transplant [47]. Our study showed increase of renal complications in recipients with high PRA titer. There was significant six times increased risk of renal complication at 5-year survival rate, and seven times increase in HCV-negative recipients. Luminex assays are the most sensitive (78–98% for flow T-cell cross-match (XM) and 88–98% for flow B-cell XM) and specific (93–100% of flow T-cell XM and 91–100% for flow B-cell XM) compared with CDC and flow cytometry XM to determine the risk of sensitization for patients with a living donor [48].

If we have a positive cytotoxic cross-match, this indicated a high antibody level. A positive flow-cytometric assay with a negative cytotoxic cross-match indicated a moderate antibody level, and a positive Luminex assay with a negative flow-cytometric cross-match indicated a low DSA level [9].

Higher PRA at second transplant among adults and children leads to longer waiting times for a second graft and a higher risk of loss of the second graft [49]. In agreement with this, we found an increase in second graft failure and renal complication in our patients. Sensitization causes dysfunction and death risk owing to long period of dialysis [50]. However, Orandi *et al.* [9] revealed that patients transplanted with HLA-incompatible live donors kidney had a considerable survival benefit when compared with patients who did not undergo transplantation.

Single antigen (SA) estimation by Luminex platform is very important in highly sensitized recipients with antibodies against several various HLA alleles, owing to its elevated resolution capability, and it is a unique method that shows accurate HLA antibody properties [51]. We found insignificant association of positive SA test with both renal graft loss and renal complication, which might be owing to low sample size.

SA bead assays allow us to take a practical cross-match by guessing responses against HLA alleles. Both SA assay and Luminex Donor-specific antigen (DSA) Xm using donor lysates can be used to detect the presence of anti-HLA DSA in patient sera. The presence of DSA against any HLA locus can tell us donor typing. This enrolls natural human antigens and is much cheaper than the SA bead assays [52].

The DSA Xm examination revealed great association with the SA test for assessment of de novo DSA. Presence of de novo DSA is a predictor of rejection and gives positive DSA Xm [53].

The progress in tissue-typing methods has given rise to novel opinion of HLA matching at the epitope level. Epitopes are arrangement of polymorphic amino acid remnants that are

identified by B cells, and antibodies interact with these epitopes causing graft failure [54]. HLA epitope matching is more predictive for the development of DSA after transplantation than traditional HLA antigen matching [55]. Epitope matching helps prevent formation of de novo DSA and election of a preferable allograft for extremely sensitized patients by DSA Xm. There are two types of epitopes: private epitopes, which present on a single HLA, or public epitopes, which present on multiple antigens. This explains the cross-reactivity phenomenon in HLA testing, that is, public epitopes, an antibody targeting an epitope that shows positive reaction with all antigens sharing the epitope. Crystalized HLA molecule modeling and amino acid sequence comparisons between HLA alleles permit seeing structural descriptions, referred to in the HLA Matchmaker program as eplets, which are essential components of HLA epitopes [56]. Accurate characterization of anti-HLA DSAs, involving their complement binding ability and IgG subclass formation, could put on their predictive benefit for allograft loss on the basis of their evaluation of intensity by mean fluorescence intensity (MFI) level [57]. The hazard of antibody-mediated rejection and allograft loss may be significantly minimized by avoiding HLA-incompatible transplant across preformed C1q binding and/or IgG3-positive anti-HLA DSAs. Epitope specificity analyses have showed that 3 HLA-DR and 3 HLA-DQ epitopes were independent multivariate predictors of class II de novo DSAs [8].

The study by Reindl-Schwaighofer *et al.* [58] revealed that a median of 1892 mismatches in different genetic aberrants that result in protein polymorphisms per recipient and donor pair found in 477 transplant patients by genotyping array (without genetic variants in the HLA region on chromosome 6). The report by Reindl-Schwaighofer *et al.* [59] confirmed that these non-HLA mismatches amount was independently correlated with graft failure in a multivariable analysis adjusted for HLA serotype and eplet mismatch. Polymorphic amino acid sequences represent probable epitopes that can be identified by alloreactive antibodies as eplets in HLA.

However, the most important disadvantages of Luminex are its inability to quantitate the amount of anti-HLA antibodies in sera, different reports of MFI results between laboratories owing to dissimilar standards of laboratories, different antigen density among beads, variability in the sera preparation before assay, false negative or positive results probability, and shared epitopes between single-antigen beads [60].

Several studies revealed that ABO incompatibility had significant association of increase risk of graft loss and renal complications after LRD transplant [3,20,61].

In our patients, HCV-positive recipients were significantly associated with increased risk of worse graft survival and had graft failure eight times and increase risk of renal complications three times when compared with HCV-negative patients. This was supported by Ashbey *et al*. [4], who found increase risk of graft loss in their analyzed recipients.

The strengths of our study are that there were nearly no missing data. We found that most of living donor kidney transplants had their donor relationship obtainable and of unrelated living donor kidney recipients had their HLA condition accessible.

A limitation of the study is the low size sample and being a single-center study. It is known that other HLA loci, such as HLA-DQ locus, may lead to graft loss [19], but our study only included the HLA-A, -B and, -DR loci.

Conclusion

We concluded that recipient and donor characteristics have important roles on kidney transplant graft survival and also on renal complications such as renal impairment.

Recommendation

Further studies on a larger scale should be conducted on HLA MM and DSAs to confirm this effect on renal graft outcome of living donor kidney transplant.

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Conflicts of interest

There are no conflicts of interest.

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