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The Assessment of HLA Sensitization Effect on Graft Function and Survival in Renal Transplant Recipients

Böbrek Transplant Alıcılarında HLA Hassasiyetinin Greft Fonksiyonuna ve Hayatta Kalmaya Etkisi

Özgün Araştırma
Research Article

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ABSTRACT

Objective: *Anti-human leukocyte antibodies (HLA) play an important role in graft survival, particularly in kidney transplantation. Preformed anti-HLA antibodies, especially donor specific antibodies can cause acute and chronic rejections. In this study, it was aimed to assess the effects of anti-HLA antibodies in kidney patients before transplant on graft function, failure, and patient survival.*
Methods: *PRA (Panel Reactive Antibody) levels were monitored using bead based methods such as Luminex and flow cytometry. Post-transplant estimated glomerular filtration ratios (eGFR) among first, third, and fifth year patient survivals and graft failures were statistically analyzed.*
Results: *In this study, it was observed that related transplants had low levels of PRAs, and their eGFRs were at normal reference range. The patients without acute rejection episode (ARE) had higher eGFR values than those with ARE. When five year-graft survival terms were evaluated, it was found that 65.6±9.8% and 86.5±3.2% graft survival terms were detected in anti-HLA Class I/II positive and negative patients, whereas 74.8±6.4% and 84.3 ±2.6% graft survival terms were observed in ARE positive and negative patients, respectively. eGFR value is a predictor of graft failure and patient survival. Our Cox regression analyses (HR=0.843, p=0.00) also supported this information.*
Conclusion: *The study concluded that although the correlation between PRA positivity and graft survival were not significant, the shortest graft survival was observed in PRA positive patients in the whole cohort and ARE positive patients. The importance and requirement of pre- and post-transplant PRA tests continue.*

Keywords: *Chronic renal disease, PRA, Glomerular filtration rate, acute renal rejection, graft survival*

ÖZ

Amaç: *Anti-insan lökosit antikorları (HLA) greft sağkalımında özellikle de böbrek nakillerin önemli bir role sahiptir. Nakil öncesinde oluşan anti-HLA antikorları, özellikle donöre spesifik antikorlar, akut ve kronik rejeksiyona sebep olabilir. Bu çalışmada, böbrek nakli olmuş hastalarda nakil öncesinde bulunan anti-HLA antikorlarının greft fonksiyonu, kaybı ve hasta sağkalımı üzerindeki etkilerinin değerlendirilmesi amaçlanmıştır.*
Yöntem: *PRA (panel reaktif antikor) seviyeleri Luminex ve Flow sitometri gibi boncuğa dayalı yöntemlerle izlenmiştir. Hastaların nakil sonrası glomerular filtrasyon oranları (GFR) ve birinci, üçüncü ve beşinci yıllardaki greft kayıplarıyla hasta sağkalımları istatistiksel olarak değerlendirilmiştir.*
Bulgular: *Bu çalışma, akrabadan nakil olan hastaların daha düşük anti-HLA antikor seviyelerine ve daha yüksek eGFR değerlerine sahip olduklarını göstermiştir. Akut rejeksiyon atağı (ARE) geçirmiş hastalar geçirmemiş hastalara göre daha düşük eGFR değerlerine sahiptir. Beş yıllık greft sağkalımı incelendiğinde, anti-HLA Sınıf I/II pozitif hastalarda ve negatif hastalarda sırasıyla %65.6±9.8 ve %86.5±3.2%, ARE pozitif ve negatif hastalarda ise sırasıyla %74.8±6.4% ve %84.3±2.6 olarak bulunmuştur. Greft ve hasta sağkalımı cox regresyon testiyle analiz edildiğinde, eGFR değerinin greft kaybının göstergesi olduğu belirlenmiştir (HR=0.843, p=0.00).*
Sonuç: *Bu çalışmada, anti-HLA antikor karakterizasyonuyla greft sağkalımı arasında istatistiksel olarak anlamlı bir korelasyon bulunmamasına rağmen, anti-HLA sınıf I/II pozitifliği olan bütün hastalar ile ARE pozitif hastalarda en kısa greft sağkalımı gözlenmiştir. Nakil öncesinde ve sonrasında PRA testlerinin periyodik olarak yapılmasının önemi ve gerekliliği devam etmektedir.*

Anahtar kelimeler: *Kronik böbrek hastalığı, PRA, glomerüler filtrasyon hızı, akut renal rejeksiyon, greft sağkalımı*

INTRODUCTION

Renal transplantation is an important option for treating patients with end-stage chronic renal disease. Anti-human leukocyte antigen (HLA) antibodies may be produced due to alloimmunization factors (blood transfusion, pregnancy, or organ transplantation) [1,2].

It is known that anti-HLA antibodies are associated with high rejection risk and short graft survival for solid organ transplantation. Anti-HLA antibodies (Panel Reactive Antibodies-PRA) play a crucial role during graft rejection [3-6]. Patel and Terasaki (1969) showed the effect of a complement-dependent lymphocytotoxic crossmatch (CDCXM) technique on the detection of immunological risk in kidney transplantation [7]. This standard method is currently used for the detection of pre-transplantation antibodies. However, in the course of time it was observed that this method could not detect all pre-existing anti-HLA antibodies. Recently, solid-phase immunoassays (flow cytometry or a Luminex fluoroanalyzer multiple/single-antigen bead assays), known as more sensitive methods, have been used.

While a positive CDCXM test result is an accurate contraindication factor for transplantation, positive results obtained by only solid phase assays may increase acute rejection and graft failure risk. In addition, the development of anti-HLA antibodies is positively associated with chronic rejection of renal allografts. Currently, long-term graft and patient survival are unsatisfactory, although the acute rejection ratio decreases [8].

There are limited number of compatible donors. Thus, the patients on the waiting list may become sensitized. This is a growing problem for many transplant centers [9]. Some treatments (intravenous immunoglobulin (IVIG), plasmapheresis, etc.) and tests (single antigen bead test, HLA matchmaker program, and acceptable mismatch tests) are available in order to give a transplantation chance to the hypersensitive patients [10].

The aim of this study was to determine the effect of pre-transplantation anti-HLA antibodies, which are major barriers to allogeneic transplantation, on graft survival and to investigate the effect of HLA sensitization on long-term allograft survival.

MATERIAL and METHODS

Patients

Our Tissue typing laboratory supports three education and research hospitals in the Aegean region of Turkey for related and deceased transplantation. This study was planned retrospectively, and 2878 patients (2517 patients waiting for transplantation and 361 transplanted patients) were included in the study. The patients with chronic kidney failure (2517 patients; female 1089; 43.3%, male 1428; 56.7%) were tested for anti-HLA antibodies. We evaluated the correlation of pre-transplantation PRA results of 361 transplant patients (229 cadaveric transplant; 131 males, 98 females and 132 related transplant; 80 males, 52 females) and their graft survivals. Demographic information of the patients and donors were shown in Table 1. PRA test was performed regularly twice a year for patients with chronic kidney failure (CKF) on the waiting list. PRA tests were performed by Luminex PRA (85%) and Flow PRA (15%) methods. The test results involved in this study were the highest anti-HLA antibody screening results of the patients. All of the patients (n=2878) were divided into four groups: anti-HLA class I positive, anti-HLA class II positive, anti-HLA class I/II positive, and anti-HLA negative. Graft and patient survival durations were calculated from the transplantation date of the patients. Follow up durations were 35.76±23.28 and 36.24±24.12 months for deceased and related transplantations, respectively. Return to dialysis or glomerular filtration ratios (GFR) <15 mg/dl were accepted as graft failure.

Written and verbal permissions were obtained from all patients during their registry. The study was approved by the Committee on Medical Ethics in accordance with Helsinki Declaration.

Immunosuppression

All recipients were pre- operatively exposed to high dose of steroids (500 mg). The prednisolone dose was gradually decreased to 5 mg at the end of the 6 months and stopped at the end of the first year. Induction therapy for the patients with high immunological risk (such as high mismatch, PRA positivity, older donor, etc.) and deceased donors was 4-5 mg/kg ATG, preoperatively. And two more doses of 2-3 mg/kg ATG were used post-operatively according to CD3, lymphocyte, and platelet levels of the patients.

Two doses of basiliximab (preoperatively and on postoperative 4th day) were used for the patients with low immunological risk (low HLA mismatch, PRA negative, young donors, living donors). An anti-metabolite (mycophenolatemofetil) and a calcineurin inhibitor (cyclosporine or tacrolimus) were used during treatment maintenance. The target blood level of cyclosporine and tacrolimus were 250-350 ng/ml and 10-15 ng/ml at 6th month, and thereafter, it was 100-175 ng/ml and 6-10 ng/ml respectively.

Diagnosis of Rejection

Allograft biopsy was performed to evaluate the rejection episodes. Only biopsy-proven cases were included in this study. In our clinic, protocol biopsies have been routinely performed in the sixth month after transplantation since 2004. In addition, diagnostic biopsy was performed for the suspected rejection cases. The first option for treatment of acute rejection (AR) was three boluses of 500 mg methylprednisolone. ATG (1-1.5 mg/kg doses for 3-7 days) was used for the treatment of steroid-resistant rejections.

Luminex PRA

PRA test was performed by Lifecodes LifeScreen Deluxe Kit (Immucorgamma, Waukesha, WI, USA) [11]. The procedure was performed according to the commercial kit instructions. MFI (Mean Fluorescent Intensity) >1000 values were accepted as positive.

Flow PRA

FlowPRA kit (OneLambda, Hannover, Germany) was used for this test [3]. The procedure was conducted according to the manufacturer's instructions. The samples were analyzed by Facs Calibur Flow Cytometry instrument (BD, San Jose, CA, USA). The fluorescent values >3% were accepted as positive.

Estimated Glomerular Filtration Rate (eGFR)

GFR is very beneficial for renal function assessment. Ethnicity, gender, and age may affect the values. eGFRs of transplanted patients were calculated by modification of diet in renal disease formula (MDRD) using their creatinine values at 1st month (the average coming out of hospital time) and at their last control time [MDRD= 175 * (Serum creatinine mg/dl)-1.154 * (age)-0.203 * (0.742 if female) * (1.210 if African American)] [12,13].

Statistical Analyses

Statistical analyses were performed using IBM SPSS version 21.0 for Windows (SPSS, Chicago, Ill, United States). In addition to descriptive and frequency analyses, Chi-square and Fisher's exact tests were used to compare percentages of the groups. PRA-positive ratios between the groups were compared by Independent Samples t-test. In a one-way Anova, multiple mean values were compared by Tukey's multiple comparison tests. Univariate General Linear Model was used in order to measure the common effect of more than one independent variable on a dependent variable. Multivariate analysis of variance (MANOVA) model was used to investigate the differentiation status of more than one dependent variable according to more than one independent variable at the same time. The cumulative probability of patient and graft survival analysis was carried out using Kaplan-Meier estimates. A log-rank test was used for the differences in survival. A Cox proportional hazards analysis was used for predicting patients and graft loss. $p<0.05$ was accepted as statistically significant with a 95% confidence interval.

RESULTS

Demographic features and anti-HLA characterizations of all patients were shown in Table 1 and Table 2, respectively. Pre-transplantation negative anti-HLA antibody ratio was significantly higher ($p<0.05$) in the patient group with related transplantation (70.97%) than the patients transplanted from deceased donors (68.42%) and the patients waiting for kidney transplant (59.48%). In addition, when the patients were evaluated according to anti-HLA antibody percentages, it was found that 36.63%, 26.88%, and 28.95% of the patients in the waiting list, transplanted from related and deceased donor had >10% PRA, respectively (Table 2).

The eGFR mean values of transplanted patients at post-transplantation 1st month and at the last control time were given in Table 3. The lowest eGFR values among PRA positive transplanted patients were observed in the 1st month and the last control. The eGFR mean values were not significant ($p>0.05$) in each group and between the groups for all transplanted patients.

Of the transplanted patients, 19.40% had acute rejection episodes. eGFR mean values according to rejection episode and HLA sensitization at post-transplantation 1st month and the last control time were shown in Table 4.

First month eGFR values of anti-HLA negative patients with cadaveric transplant and without ARE were significantly ($p<0.05$) lower than the patients with related transplants, while last control eGFR values of anti-HLA Class I/II positive patients with cadaveric transplants and ARE were significantly ($p<0.05$) lower than the patients with related transplants.

This study investigated the effect of HLA sensitization on graft and patient survival, and analyzed using Life Tables and Kaplan-Meier method. Renal graft survival of all recipients who were followed up for 7 seven years were 92±1%, 87±2% and 80±3% in 1st, 3rd and 5th years, respectively. Patients' survivals were 97±1%, 95±1% and 93±2% in 1st, 3rd and 5th years, respectively (Figure 1).

Cumulative renal graft and patient survival were calculated according to HLA sensitizations of

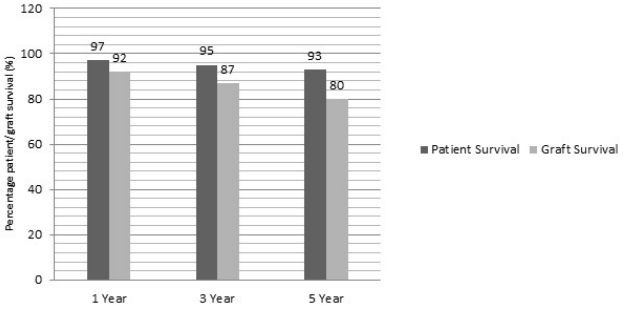

Figure 1. Patient and graft survival (%) of all patients in post-transplantation 1st, 3rd and 5th years, p>0.05.

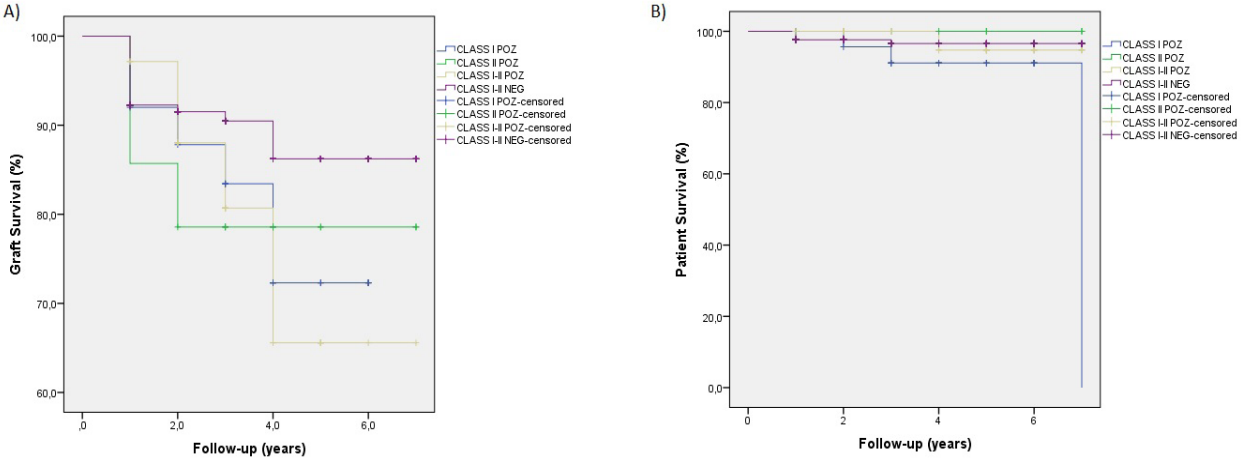

Figure 2. A) Kaplan-Meier analysis of graft survival due to HLA sensitization of transplanted patients, p=0.108 B) Kaplan-Meier analysis of patient survival due to HLA sensitization of transplanted patients, p=0.911.

Table 1. Frequencies of the patient data.

			Waiting List (n=2517)	Cadaveric Transplantation (n=229)	Related Transplantation (n=132)	p
Recipient Gender %	Male		58.4 (1470)	57.2 (131)	60.6 (80)	NS*
	Female		41.6 (1047)	42.8 (98)	39.4 (52)	
Donor Gender %	Male		-	73.81 (170)	44.30 (58)	<0.05
	Female		-	26.19 (59)	55.70 (74)	
Recipients Age (year)			49.94±14.73	42.34±11.09	37.77±11.64	<0.05
Donor age (year)			-	39.12±17.82	50.00±13.93	NS
Recipient Blood Groups %	A		42.2 (1062)	32.2 (74)	44.0 (58)	NS
	B		17.3 (436)	16.8 (38)	23.8 (31)	
	AB		7.5 (189)	9.8 (22)	9.5 (13)	
	0		33.0 (830)	41.3 (95)	22.6 (30)	
Donor Blood Groups %	A		-	31.8 (73)	44.3 (59)	NS
	B		-	16.4 (37)	23.6 (31)	
	AB		-	9.6 (22)	9.1 (12)	
	0		-	42.2 (97)	23 (30)	
Alloimmun. histories %	BTH		56.4 (1420)	52.0 (522)	76.36 (101)	NS
	TH		5.7 (143)	3.2 (7)	2.1 (3)	
	P	Birth	75.17 (1892)	41.67 (95)	53.12 (70)	
		Curetage	28.82 (725)	11.11 (25)	28.13 (37)	NS
		Abortus	26.38 (664)	11.11 (25)	21.87 (29)	
Dialyze Time (month)			51.75±50.35	79.82±57.32	25.97±32.77	<0.05
Acute Rejection Episode %			-	23.50 (54)	20.00 (27)	NS

**NS; not significant, BTH: Blood Transfusion History, TH: Transplantation history, P: Pregnancy*

transplanted patients (Figure 2). Graft survivals were observed as being low in HLA sensitized patients, particularly patients with anti-HLA class I/II sensitizations (65.6±9.8%) while it was observed that HLA class I sensitization had no significant effect on graft and patient survival (respectively p=0.108, p=0.911) (Table 5). Survival of patients were determined according to ARE. Patients with ARE were lower than patients without ARE. In particular, anti HLA class I/II sensitized patients had the lowest survival (48.9±19.2%) but the results were statistically non-significant (p>0.05) (Table 5).

Table 2. Anti-HLA characterizations of the patients in the waiting list and transplanted patients.

	Waiting List % (n= 2517)	Cadaveric Transplantation % (n= 229)	Related Transplantation % (n= 132)	P
Anti-HLA Class I Pos	12.55 (316)	11.18 (25)	9.68 (13)	NS
Anti-HLA Class II Pos	8.78 (221)	6.58 (15)	4.30 (6)	NS
Anti-HLA Class I/II Pos	19.19 (483)	13.82 (32)	15.05 (20)	NS
Anti-Class I/II Neg	59.48 (1497)	68.42 (157)	70.97 (93)	<0.05

NS; not significant; Pos: positive; Neg: negative

Table 3. Graft function analysis of transplanted patients by eGFR (mL/min/1.73 m²) according to HLA sensitization.

		Deceased Tx n:229	Related Tx n:132	Total n:361
Post-tx 1st Month GFR	**Anti-HLA Class I**	56.70±29.42 (25)	61.41±19.63 (13)	58.4±25.97 (38)
	Anti-HLA Class II	61.32±55.0 (15)	63.86±22.64 (6)	62.1±46.33 (21)
	Anti-HLA Class I/II	49.97±23.16 (32)	46.92±26.26 (20)	48.77±24.07 (52)
	Anti-Class I/II Neg	56.23±27.46 (157)	61.02±26.78 (93)	58.13±27.21 (250)
Last control GFR	**Anti-HLA Class I**	56.50±25.34 (25)	52.97±24.34 (13)	55.23±24.53 (38)
	Anti-HLA Class II	44.57±27.17 (15)	38.93±29.29 (6)	42.84±26.72 (21)
	Anti-HLA Class I/II	41.43±30.29 (32)	44.33±25.6 (20)	42.57±28.15 (52)
	Anti-Class I/II Neg	52.17±23.95 (157)	54.63±19.57 (93)	53.15±22.29 (250)

Tx: transplant, p>0.05

Table 4. Comparison of eGFR values of transplanted patients with and without ARE according to their HLA sensitizations.

		Anti-HLA Class I Pos (n)	Anti-HLA Class II Pos (n)	Anti-HLA Class I/II Pos (n)	Anti-HLA Class I/II Neg (n)
Cadaveric Tx		**(n:25)**	**(n:1 5)**	**(n:32)**	**(n:157)**
1st month eGFR	**ARE Pos**	**28.61±11.86 (7)**	**21.43± 21.91 (4)**	**46.60 ±20.53 (13)**	**60.09±26.68 (30)**
	ARE Neg	63.38±29.41 (18)	72.72±57.19 (11)	49.74 ±25.03 (19)	53.67±25.76[a] (127)
Last eGFR	**ARE Pos**	**44.06±40.20 (7)**	**15.47±11.24 (4)**	**15.80±10.31[a] (13)**	**45.76±22.17 (30)**
	ARE Neg	62.79±20.23 (18)	52.48±24.81 (11)	59.23±25.62 (19)	53.62±24.41 (127)
Related Tx		**(n:13)**	**(n:6)**	**(n:20)**	**(n:93)**
1st month eGFR	**ARE Pos**	**44.52±22.00 (3)**	**-(0)**	**42.15±13.35 (7)**	**45.96±22.96 (16)**
	ARE Neg	66.24±17.63 (10)	63.86±22.64 (6)	47.06±32.36 (13)	63.41±23.05[b] (77)
Last eGFR	**ARE Pos**	**48.76±.314 (3)**	**-(0)**	**58.63±24.88[a] (7)**	**39.88±20.18 (16)**
	ARE Neg	54.17±27.97 (10)	38.93±29.29 (6)	36.99±26.07 (13)	58.34±14.04 (77)

[a]: p =0.002, [b]: p =0.01, ARE: Acute Rejection Episode, Pos: Positive, Neg: Negative, Tx: Transplant

Table 5. Kaplan-Meier analysis of five year-survivals total and ARE due to HLA sensitization of kidney transplanted patients.

	Graft Survival % (n:361)	Patient Survival % (n:361)	ARE Pos Graft Survival % (n:80)	ARE Pos Patient Survival % (n:80)	ARE Neg Graft Survival % (n:281)	ARE Neg Patient Survival % (n:281)
Anti-HLA Class I Pos	73.6±9.4 (38)	75.9±14.7 (38)	66.7±19.2 (10)	100 (10)	72.2±12.1 (28)	73.5±14.9 (28)
Anti-HLA Class II Pos	78.6±11 (21)	100 (21)	66.7±27.2 (4)	100 (4)	81.8±11.6 (17)	100 (17)
Anti-HLAClass I/II Pos	65.6±9.8 (52)	94.7 ± 5.1 (52)	48.9±19.2 (20)	83.3±15.2 (20)	76.2±10.9 (32)	100 (32)
Anti-HLA Neg	86.5±3.2 (250)	96.6±1.6 (250)	80.3±10.6 (46)	93.5±4.4 (46)	89.4±3.4 (204)	97.7±1.7 (204)

ong rank p>0.05, Pos: Positive, Neg: Negative ARE: Acute Rejection Episode

Table 6. Cox Regression analysis for the prediction of survivals.

	Univariate Model			Multivariable Model		
	Hazard Ratio	95 % CI	P Value	Hazard Ratio	95 % CI	P Value
Graft Survival						
Post-tx 1st month eGFR	0.96	0.95-0.98	0.00	1.00	0.99-1.02	0.81
Last control eGFR	0.92	0.91-0.94	0.00	0.84	0.78-0.91	0.00
Dialyze Time	1.00	1.00-1.01	0.18	1.01	1.00-1.02	0.15
HLA Sensitizations						
Class I/II Neg / Class I Pos	1.86	0.73-4.70	0.19	2.22	0.57-8.66	0.25
Class I/II Neg / Class II Pos	1.77	0.52-6.02	0.36	1.50	0.30-7.44	0.62
Class I/II Neg / Class I/II Pos	2.16	0.97-4.81	0.06	1.51	0.48-4.72	0.48
Patient Survival						
Post-tx 1st month eGFR	0.97	0.95-0.99	0.01	0.96	0.89-1.02	0.19
Last control eGFR	0.97	0.96-0.99	0.01	0.97	0.92-1.03	0.35
Dialyze Time	1.00	0.99-1.01	0.37	0.99	0.97-1.01	0.54
HLA Sensitizations						
Class I/II Neg / Class I Pos	3.55	0.84-15	0.08	2.22	0.19-25.62	0.52
Class I/II Neg / Class II Pos	0	0-	0.98	0	0-	0.99
Class I/II Neg / Class I/II Pos	0.81	0.09-6.95	0.85	0.72	0.06-8.22	0.79

Tx: transplant, Cl: Coefficient Interval, Neg: Negative, Pos: Positive

The role of HLA sensitization on predicting graft and patient survival was analyzed by Cox proportional hazard method (Table 6). Post-transplantation 1st month and last eGFR values were found statistically significant (p<0.05) by univariate analysis among the variables such as post-transplantation 1st month eGFR, last control eGFR, dialysis time and HLA sensitizations. These variables were also analyzed by stepwise multivariable model, and it was observed that only last eGFR was an independent marker for graft failure (HR=0.843, p=0.00).

DISCUSSION

This study showed the effect of pre-transplantation anti-HLA antibody characterization in the clinic by evaluating graft function, failure, and patient survival.

Of the patients on the waiting list in the US, 28.4% and 13.9% had ≥20% PRA in 2002 and 2012, respectively. In 2014, 18% of Eurotransplant registries had >5% PRA and 25.7% of transplanted patients in Spain had>10% PRA in 2012, whereas this ratio was 15.2% in the USA [14,15]. The ratio of patients with >5% PRA was 12.6% in Europe. In this study, 36.63% of patients on the waiting list had >10% PRA, whereas 26.88% and 28.95% of the patients transplanted from related and deceased donor had >10% PRA. Pre-transplantation negative PRA ratio in the patients with related transplants (70.97%) was significantly higher than the patients waiting in the list (59.48%) and the patients with cadaveric transplants (68.42 %). In general, the duration of kidney patients awaiting cadaveric transplantation was longer than related transplantation. Thus, their alloimmunization probability might increase.

In related transplantations, if the patient has a full match first-degree relative, the patient has a high chance of transplantation. Also in cadaveric transplantations, the patients with frequently observed alleles have high chance for kidney transplantation.

It has been known that renal transplant patients with pre-transplantation anti-HLA antibodies have decreased graft survival [16]. In our study, the lowest eGFR values were detected in anti-HLA class I/II positive patients in total transplanted patients at post-transplantation 1st month and the last control time. The lowest eGFR values were detected in anti-HLA class I/II positive patients in both transplant groups at post-transplantation 1stmonth (Table 3). Cadaveric- and related-transplanted patient groups were evaluated according to their last control eGFRs. The lowest eGFR values were observed in anti-HLA class I/II positive patients in cadaveric-transplanted group. The lowest eGFR values were found in anti-HLA class II positive patients transplanted from related donors. In this study, we assessed only pre-transplantation PRA results retrospectively. In fact, de novo anti-HLA antibodies produced after transplantation may have affected GFR values. A number of studies have reported that de novo donor-specific anti-HLA antibodies, which were produced after transplantation, were associated with allograft rejection [16-18]. They also revealed that ARE ratios were higher in patients with de novo donor-specific anti-HLA antibodies after transplantation.

eGFR results were better in related transplantation than deceased-donor transplantation. In other studies, eGFR is usually accepted as the most beneficial tool for renal function assessment [19,20].

In addition, it was determined that GFR was an independent predictor by Cox regression analysis that was performed in order to predict the risk factor for graft and patient survival. This has been reported in several medical literatures, particularly those containing a great number of patients. Opelz et al. [21] observed that the best renal allograft survival was from identical twins; the second was from haplo-identical couples, and the poorest survival was from deceased donors [22]. However, multiple risk factors such as donor age, delayed graft function, number of HLA mismatches, infections, and de novo anti-HLA antibodies also affect graft survival, in addition to pre-transplantation antibody characteristics [23].

In our study, we compared the eGFR results and acute rejection episodes in all transplanted patients based on anti-HLA antibody groups (Table 4). It was generally determined that eGFRs of the patients with acute rejection episode were lower than the patients who have no acute rejection episode. The prevalence and clinical characteristics of PRAs were assessed for acute allograft rejection in several studies [24,25]. It was reported that post-transplantation acute rejection episodes were increasing factors for chronic rejection development [5,26]. In this study, the difference between the last control eGFR values of anti-HLA class I/II positive cadaveric and related transplant patients with ARE were significant ($p<0.05$). The difference between the 1st month eGFR values of anti-HLA class I/II negative cadaveric and related transplants without ARE were significant ($p<0.05$). Lower eGFR values of

patients with ARE can be explained by low number of patients and younger patients in HLA sensitization groups. The previous studies found that eGFR was decreased in aging healthy individuals [19,20].

Gondos et al. [27] evaluated the graft survival in patients transplanted from related and deceased donors. They reported that 1st year graft survival of the patients was 91% in US and Europe. Fifth year graft survival was 77% and 56% in Europe and US, respectively [13]. In our study, post-transplantation 1st, 3rd, and 5th year graft survivals were 92±1%, 87±2%, 80±3%, respectively. It was observed that our results were closer to the graft survival of Europe.

Renal function decrease is related to long-term graft and patient survival. Especially early-phase renal function is an important indicator for long term graft and patient survival [28-30].

This study perhaps reflects limited results due to being retrospective and consisting of insufficient data because of the difficulty in collection of clinical data from different organ transplantation centers. In this study, it was found that graft and patient survival were compatible with each other. The lowest graft survival was observed in PRA positive patients.

When the data obtained from this study were evaluated according to pre-transplant anti-HLA sensitization characteristics;

i. Post-transplant 1st month the lowest eGFR values were detected in anti-HLA Class I/II positive patients
ii. Post-transplant last control the lowest eGFR values were detected in anti-HLA Class I/II positive patients
iii. The lowest graft and patient survival were detected in anti-HLA Class I/II positive patients among all transplanted patients
iv. The poorest graft and patient survival of patients with ARE were detected in PRA positive patients

These results emphasized the effect of anti-HLA antibody characterization on allograft and patient survival, and show that PRA tests should be pursued in a controlled manner before transplantation. Post-transplantation anti-HLA antibody characterization also affects the success of the transplantation.

These data should be confirmed by further investigations including larger numbers of patients without any limitations.

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