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ORIGINAL ARTICLE

Impact of Degree of Human Leucocyte Antigen Mismatch on Live Donor Kidney Transplant Recipients

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ABSTRACT

Background: The human leukocyte antigen (HLA) system plays a crucial role in the activation and function of the immune system. HLA mismatches may lead to activation of alloreactive T-cells and development of donor-specific HLA antibodies (DSA), thereby significantly impairing kidney graft survival.
Methods: From March 1976 and August 2019, 2200 kidney transplant recipients were included, and were divided according to the degree of HLA mismatch into three groups.
Results: Acute rejection episodes were more frequent in groups 2 and 3. Chronic rejection was revealed in group II, and III graft biopsies more than in group I. Incidence of post-transplant hypertension and diabetes mellitus was higher in group III. Median serum creatinine was more elevated in group III after 2, 3, 4, and 5 years' post-transplantation with subsequent lower creatinine clearance. The majority of patients were alive with functioning graft at last follow-up, especially in group I. More patients were alive with failed graft at the last follow-up in group III. On the other hand, the 5, 10, and 15 years of graft and patient survival showed statistically significant differences between the three groups with better survival for group I.
Conclusions: The degree of mismatch affected the choice of the immunosuppressive regimen. Higher HLA mismatch was associated with a higher incidence of diabetes and hypertension and lower patient and graft survival.
Keywords: HLA Mismatch; Transplantation; Graft Survival.

INTRODUCTION

Several databases, representing thousands of kidney transplant patients from a large number of collaborating centers, showed strong evidence for the importance of HLA matching in kidney transplantation [1], and many studies had shown associations between HLA-DR mismatches and rejection, transplant glomerulopathy, graft failure, and death with functioning graft following kidney transplantation [2]. Furthermore, it was found that HLA-DR mismatch is an independent risk factor for the development of de novo DSA and T-cell mediated rejection in elderly kidney transplant recipients [3]. However, some studies suggested that HLA mismatch did not influence graft survival. In a cohort of 2600 deceased donor kidney transplants in Spain, **Morales et al**. found no effect of HLA mismatch on graft survival [4]. Many current practices in kidney transplantation revolve around controlling the immune system, including immunosuppression strategies, rejection treatment, and tolerance understanding. In this current study, we will highlight the impact of the different degrees of HLA mismatch on both patient and graft survival.

METHODS

This current study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies that involve humans. A retrospective cohort study was conducted at the Urology and Nephrology Centre, Mansoura University.

Ethical consideration: Our study is a retrospective study. The data was retrieved from our patient information system at the Urology and Nephrology Center after an agreement from the head of the department and director of the center. We confirm that we do not use patients' names, initials, or hospital

numbers. The medical research and ethics committee of Zagazig University approved the study. The work was carried out under The Code of Ethics of the World Medical Association. Written informed consent was obtained from all participants. The ethical research committee approved the study of the Faculty of Medicine, Zagazig University.

Subjects: The data of kidney transplant recipients who underwent renal transplantation in the Urology & Nephrology Center, Mansoura University, Egypt, from March 1976 to August 2019, were retrospectively analyzed. After excluding recipients aged less than 18 years and patients with no baseline data about HLA, 2200 kidney transplant recipients were included in the study.

Immunosuppression Protocols: Patients received different regimens of induction therapy:

Anti-Thymocyte Globulin (ATG) (1.5 mg/kg/day was administered by IV infusion for 7 to 14 days), Basiliximab (Simulect, 20 mg infused over 20-30 minutes by central or peripheral intravenous administration; the first 20 mg dose was given within 2 hours prior to transplantation surgery, the recommended second 20 mg dose was given 4 days after transplantation), the role in our center is preserving ATG for recipients with high immunological risk like high PRA or low HLA match and also for some patients with high risk of recurrence of original kidney disease. all patients received Calcineurin -Inhibitors (CNI)-based immunosuppressive therapy, consisting mainly of Cyclosporine (CsA) or Tacrolimus. Cyclosporine was introduced either in dual therapy with Prednisolone by a dose of 12 mg/kg/day or triple therapy protocol with Prednisolone and Azathioprine or MMF in a dose 10 mg/kg/day, Targeted Cyclosporine (CsA) levels between 200 and 400 ng/ml, in the first two months, at a level between 125 and 175 ng/ml, Tacrolimus was introduced to the patients in a dose of 0.15 mg/kg in two divided doses. Tacrolimus was used as rescue therapy in some patients or as a substitution of CsA in case of inevitable side effects. A trough level between 5 and 10 ng/ml was targeted for Tacrolimus. All acute rejections were biopsy-proven and managed by pulses of Methylprednisolone 500 mg/day for five days. Anti-Thymocyte Globulin (ATG) or Orthoclone (OKT3) were used in cases of Steroid-resistant rejections.

Follow-Up: The patients were divided into three main groups according to the degree of HLA mismatch: the first group includes 0, 1, and 2 HLA mismatch (568 patients) while the second group involves 3 and 4 HLA mismatch (1462 patients), and the last group has those with 5 HLA mismatch (170 patients). The demographic data of the recipients and donors, pre-transplant co-morbidities, original kidney disease (OKD), immunosuppression regimens, number of biopsy-proven acute rejection episodes, post-transplant hypertension, diabetes mellitus, infections, hepatic problems, the occurrence of malignancies. graft function was followed up to 5 years' post-transplantation, graft and patient survival up to 25 years' post-transplantation.

STATISTICAL ANALYSIS

The findings were recorded, tabulated, and analyzed using SPSS statistics version 21 for Windows (SPSS Inc. Chicago). T-test was used to compare the continuous normally distributed data between the three groups. Kruskal-Wallis test was used to compare abnormally distributed continuous data. Categorical data were compared using the chi-square test. The graft and patient survival were computed using the Kaplan-Meier technique. P-value < 0.05 was considered statistically significant.

RESULTS

There was no statistical significant difference among the studied group regarding recipient and donor age and sex. 95.2% of cases in group **I** were related donors ***(table 1).*** Ischemia time was comparable, and over 90% of the patients had immediate diuresis. The degree of HLA mismatch affected the choice of induction therapy as lymphocyte depleting agent (ATG) was used more frequently in group **III** (7%, 11.6% higher than group **II** and **I**, respectively). In comparison, Basiliximab was used more frequently in group **I** (9.1%, 14.1% higher than group **II** and **III**, respectively)**.** Patients in group **I** were maintained on dual immunosuppressive protocols more frequently than the other two groups, where triple immunosuppressive protocols were commonly used**.** The Tacrolimus-based protocol was used

more among group **I** while the Cyclosporine-based regimen was often used among group **III**. Acute rejection episodes were more frequent with groups **II** and **III (p-value 0.001).** Chronic rejection was revealed in graft biopsies of groups **II** and **III** more than group **I.** The incidence of post-transplant Hypertension and Diabetes mellitus was higher in group **III (p-value: 0.004, 0.016 respectively).** Median serum creatinine after one-year follow-up didn't differ significantly between the studied groups. However, serum creatinine was higher in group **III** after 2, 3, 4, and 5 years' post-transplantation with subsequent lower creatinine clearance ***(table 2).*** The majority of patients were alive with functioning graft at last follow-up, especially in group **I** with the statistically significant difference among the three groups**.** More patients were alive with failed graft at the last follow-up in group **III** than in the other two groups with a statistically significant difference**.** A comparable percentage of patients among the three groups were died either with functioning or with failed graft. On the other hand, 5, 10, and 25 years for graft and patient survival showed statistically significant differences between the three groups with a better survival in group **I (figure 1, 2).**

Table (1): demographic data of studied groups

	Group I (568 KTRs)	Group II (1462 KTRs)	Group III (170 KTRs)	p-value
Recipient age Mean ± SD	31.1 ± 8.3	31.5 ± 9.4	32.1 ± 9.2	0.48
Recipient Sex: Male (n, %)	417 (73.4%)	1096 (75%)	138 (81.2%)	0.121
Donor age Mean ± SD	35.1 ± 10.3	33.4 ± 10.7	32.4 ± 7.8	0.1
Donor Sex: Male (n, %)	295 (51.9%)	682 (46.6%)	82 (48.2%)	0.101
Consanguinity: Related (n, %)	541 (95.2%)	1193 (81.6%)	107 (62.9%)	**0.001**

*ANOVA test

Table (2): Serum creatinine follow-up over 5 years after transplantation

Serum creatinine (mg/dl)	Group I (568 KTRs)	Group II (1462 KTRs)	Group III (170 KTRs)	p-value	Post-hoc analysis
after 1 year Median (min, max)	1.2 (0.6, 8.9)	1.3 (0.4, 11.7)	1.3 (0.8, 4)	0.211	
after 2 years Median (min, max)	1.3 (0.6, 8.8)	1.3 (0.6, 11.9)	1.3 (0.8, 6.3)	**0.007**	Group I>II>III
after 3 years Median (min, max)	1.3 (0.5, 11.5)	1.4 (0.6, 9.1)	1.3 (0.9, 6.3)	**0.044**	Group I>II>III
after 4 years Median (min, max)	1.3 (0.5, 8.3)	1.4 (0.5, 13.3)	1.3 (0.9, 6.5)	**<0.0001**	Group I>II>III
after 5 years Median (min, max)	1.3 (0.6, 8.3)	1.4 (0.5, 10.7)	1.3 (0.9, 4)	**<0.00008**	Group I>II>III
at last follow-up Median (min, max)	1.3 (0.5, 12.3)	1.5 (0.5, 12.4)	1.4 (0.5, 12.4)	**< 0.0001**	Group I>II>III
Creatinine clearance (ml/min) at last follow up Median (min, max)	65 (4, 116)	60 (3, 118)	60 (3, 117)	0.052	

Table (3): condition at last follow-up

	Group I (568 KTRs) (n, %)	Group II (1462 KTRs) (n, %)	Group III (170 KTRs) (n, %)	p-value
Live with functioning graft	364(64.1%)	800(54.7%)	91(53.5%)	**0.001**
Live with failed graft	114(20.1%)	327(22.4%)	46(27.2%)	**0.003**
Died with functioning graft	58(10.2%)	224(15.3%)	20(11.6%)	0.188
Died with failed graft	32(5.6%)	111(7.6%)	13(7.7%)	0.252

*ANOVA test

Table (4): rejection episodes

	Group I (568 KTRs) (n, %)	Group II (1462 KTRs) (n, %)	Group III (170 KTRs) (n, %)	p-value
Acute rejection:				
Hyper-acute rejection	6 (1.1%)	7 (0.5%)	0 (0%)	
Acute cellular rejection	118 (20.8%)	528 (36.1%)	57 (33.6%)	**0.001**
Acute antibody-mediated rejection	10 (1.7%)	55 (3.8%)	14 (8.2%)	
Number of rejection episodes:				
1-2	194 (34.2%)	681 (46.6%)	73 (42.9%)	**0.001**
3-4	28 (4.9%)	130 (8.9%)	18 (10.6%)	
5-6	1 (0.2%)	9 (0.6%)	0 (0%)	
Acute tubular necrosis	23 (4%)	76 (5.2%)	6 (3.5%)	0.404
Chronic antibody-mediated rejection	103 (18.1%)	336 (23%)	33 (19.4%)	**0.046**

* ANOVA test

Table (5): Primary plan for immunosuppressive medications

	Group I (568 KTRs) (n, %)	Group II (1462 KTRs) (n, %)	Group III (170 KTRs) (n, %)	p-value
Dual therapy	192 (33.8%)	453 (31%)	39 (22.9%)	
Triple therapy	376 (66.2%)	1009 (69%)	131 (77.1%)	**0.027**

Table (6): post-transplant hypertension and diabetes mellitus

	Group I (568 KTRs) (n, %)	Group II (1462 KTRs) (n, %)	Group III (170 KTRs) (n, %)	p-value
Hypertension	283 (49.8%)	825 (56.4%)	106 (62.4%)	**0.004**
Diabetes Mellitus	33 (5.8%)	107 (7.3%)	21 (12.4%)	**0.016**

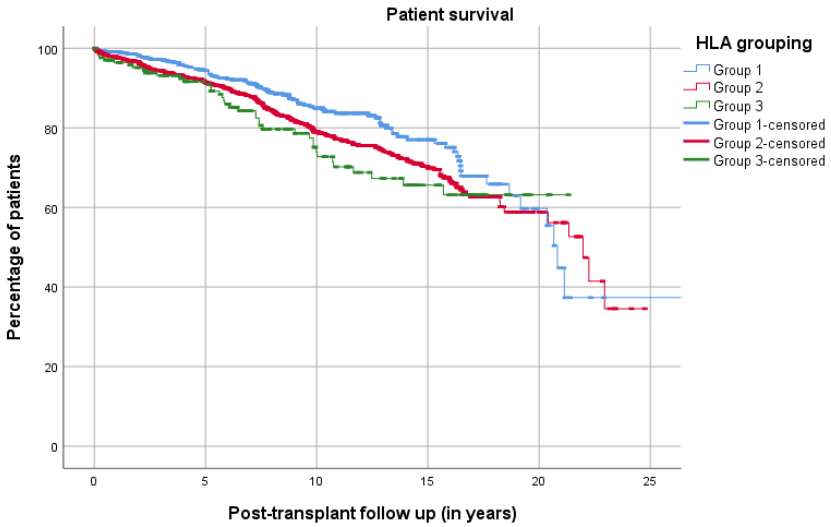

Figure (1): Kaplan Meyer curve showing graft survival among the studied groups.

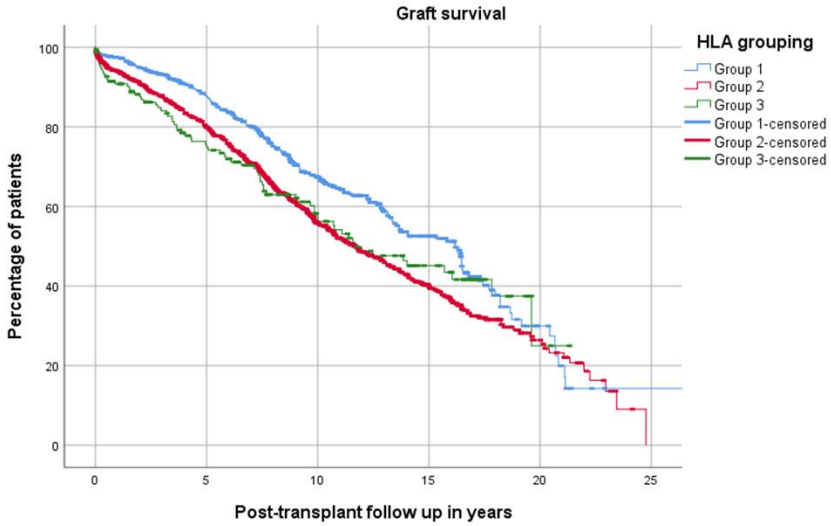

Figure (2): Kaplan Meyer curve showing patient survival among the studied groups.

DISCUSSION

the percentage of unrelated couples was higher in group III (37.1%) than group I and II (4.8% and 18.4%, respectively). This agrees with other investigators as the number of live related transplants with better HLA match are significantly higher than in the live unrelated transplants [5, 6]. Couples with the same blood group received kidney transplantation were more frequent in group1 and showed better graft survival. Some investigators found that blood group matching has no significant impact on graft survival [7]. The longer duration of follow-up could explain this difference, and a more considerable number of patients followed up at our study. Our research found that hepatitis C infection occurred more frequently among group I which includes kidney transplant recipients with better HLA match and, consequently, better graft survival. Others disagreed with our finding and found a significant decrease in graft survival in recipients transplanted with positive hepatitis C virus antibodies (HCV Abs) recipients [8]. A difference between the three groups was found that can be explained by; Anti-Thymocyte Globulin was used more frequently in group III while Basiliximab was used more frequently in group I. Some investigators found that ATG is preferred in high-risk recipients and is associated with a lower risk of acute rejection [9, 10]. Group I received a dual immunosuppressive protocol (Tacrolimus, MMF) more frequently than the other two groups, and triple immunosuppressive protocol (Steroid, Tacrolimus, MMF or Azathioprine) was less. This can be explained as more HLA mismatch in groups II and III requires strong induction and maintenance of immunosuppression. Others [11, 12] reported that

early and late steroid withdrawals were well tolerated in selected low-risk renal allograft recipients treated with potent modern immunosuppression. Acute rejection episodes (cellular and antibody-mediated) was more frequent in groups II and III. Other investigators proved that higher HLA mismatches were associated with a greater risk of acute rejection [2, 13]. Post-transplant hypertension and DM were higher in group III, with a statistically significant difference between the three groups **(p-value: 0.004, 0.016 respectively);** this can be explained by more dependence on Steroid and Calcineurin inhibitor-based regimens of immunosuppression which known to cause the development of hypertension and DM. Regarding hypertension, some authors agreed with our finding [14, 15]. Tacrolimus was used more with group I (p-value: 0.002), while Cyclosporine was used more with group III (p-value: 0.001). Remarkably; some studies reported that patients receiving Tacrolimus had a higher frequency of post-transplant DM than those taking Cyclosporine [16, 17]. This could be due to impaired insulin release or increased insulin resistance, islet cell damage in the form of cytoplasmic swelling, and vacuolization due to CNI therapy. There was a better graft and patient survival in our center with a higher degree of HLA match. Median serum creatinine after one-year follow-up didn't differ significantly between the studied groups. However, serum creatinine showed more elevation in group III after 2, 3, 4, and 5 years' post-transplantation with subsequent lower creatinine clearance.

5, 15 up to 25 years' graft and patient survival showed statistically significant difference among the three groups with better survival for group I. Some studies agreed that the better HLA matching, the longer will be the graft survival [14, 18]. Others suggested that HLA mismatch did not influence graft survival; in a cohort of 2600 deceased donor kidney transplants in Spain, **Morales et al**. found no effect of HLA mismatch on graft survival [4].

The current study had a higher power due to long-duration follow-up, it included all kidney transplant recipients from March 1976 to August 2019. Our study had some limitations as it was a retrospective study, lack of randomization, a single-center study, and all patients in our center received their kidney grafts from living donors; therefore, results might differ and could not be applied to the general transplant societies where cadaveric donors represent the primary source of kidney grafts. Results could be used on similar renal recipients from our geographic area not with different ethnic compositions.

We recommend giving attention to Proper HLA matching to decrease rejection episodes, the burden of immunosuppression, and improve both patient and graft survival.

CONCLUSION

A better HLA match between donor and recipient plays a crucial role in successful renal transplantation, long-term graft, and patient survival.

Conflict of Interest: Nothing to declare.

Financial Disclosures: Nothing to declare.

REFERENCES

1. Shi X, Lv J, Han W, Zhong X, Xie X, Su B, Ding J. What is the impact of human leukocyte antigen mismatching on graft survival and mortality in renal transplantation? A meta-analysis of 23 cohort studies involving 486,608 recipients. BMCN 2018;19(1):116.
2. Sapir-Pichhadze R, Tinckam K, Quach K, Logan AG, Laupacis A, John R et al. HLA-DR and -DQ eplet mismatches and transplant glomerulopathy: a nested case-control study. AJT 2015;15(1):137-48.
3. Halleck F, Khadzhynov D, Liefeldt L, Schrezenmeier E, Lehner L, Duerr M et al. Immunologic outcome in elderly kidney transplant recipients: is it time for HLA-DR matching? Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant AERA 2016;31(12):2143-9.
4. Morales JM, Marcén R, Andrés A, Molina MG, Del Castillo D, Cabello M et al. Renal transplantation in the modern immunosuppressive era in Spain: four-year results from a multicenter database focus on post-transplant cardiovascular disease. KIS 2008;(111):S94-9.
5. Mac Guad R, Eng HS. Renal Transplant Outcomes in Spousal and Living-Related Donors in Malaysia. AAMS 2019;48(12):403-11.
6. Matter YE, Nagib AM, Lotfy OE, Alsayed AM, Donia AF, Refaie AF et al. Impact of Donor Source on the Outcome of Live Donor Kidney Transplantation: A Single Center Experience. NUM 2016;8(3):e34770.
7. El-Husseini AA, Foda MA, Shokeir AA, Shehab El-Din AB, Sobh MA, Ghoneim MA. Determinants of graft survival in pediatric and adolescent live donor kidney transplant recipients: a single center experience. PT 2005;9(6):763-9.
8. Elmenyawia AA, Donia A, Ahmed TT. The impact of Recipient and Donor Characteristics on Kidney Transplant Graft Survival. JMSR 2021;4(1):11-25.
9. PATEL S, Gohel DK, Patel DB. Comparison of Induction Therapy Using Antithymocyte Globulin and Using Basiliximab for Live Donor Kidney Transplant Recipients: A Single Centre Prospective Cohort Study. AJP and CR 2016;9(6):187-91.
10. Gill, J, Sampaio, M, Gill, JS, et al. Induction immunosuppressive therapy in the elderly kidney transplant recipient in the United States. CJASN 2011;6(5):1168-78.

11. Gill J, Sampaio M, Gill JS, Dong J, Kuo HT, Danovitch GM et al. Low-dose Rituximab and Thymoglobulin Induction With Steroid-free Maintenance Immunosuppression and Protocol Biopsies Improves Long-term Patient and Graft Survival After Kidney Transplantation: Survival and Safety Outcomes in More Than 1100 Patients From a Single Center. TD 2019;5(8):e475.

12. **H**aller MC, Royuela A, Nagler EV, Pascual J, Webster AC. Steroid avoidance or withdrawal for kidney transplant recipients. The Cochrane database of systematic reviews 2016;(8):Cd005632.

13. Lim WH, Chadban SJ, Clayton P, Budgeon CA, Murray K, Campbell SB et al. Human leukocyte antigen mismatches associated with increased risk of rejection, graft failure, and death independent of initial immunosuppression in renal transplant recipients. CT 2012;26(4):E428-37.

14. Williams RC, Opelz G, Weil EJ, McGarvey CJ, Chakkera HA. The Risk of Transplant Failure With HLA Mismatch in First Adult Kidney Allografts 2: Living Donors, Summary, Guide. TD2017;3(5):e152.

15. Dragun D, Müller DN, Bräsen JH, Fritsche L, Nieminen-Kelhä M, Dechend R et al. Angiotensin II type 1-receptor activating antibodies in renal-allograft rejection. NElJM 2005;352(6):558-69.

16. Mohammad KG, Idrees MK, Ali T, Akhtar F. Posttransplant diabetes mellitus among live-related kidney transplant recipients: SJKD and T 2018;29(6):1320-25.

17. Palepu, S, Prasad, GV. New-onset diabetes mellitus after kidney transplantation: Current status and future directions. WJD 2015;6(3):445-55.

18. Ashby VB, Leichtman AB, Rees MA, Song PX, Bray M, Wang W et al. A Kidney Graft Survival Calculator that Accounts for Mismatches in Age, Sex, HLA, and Body Size: CJASN 2017;12(7):1148-60.

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