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Original Article

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Is the ABO Blood Group a Predictor of Renal Allograft Survival in ABO Identical Donor Recipients?

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ABSTRACT

Objective: The effect of the ABO blood group on renal allograft survival (AS) is unclear. We assessed the influence of the ABO blood group on AS and performed a comparative analysis of AS in kidney transplant recipients with different ABO blood groups.

Methods: The 239 renal transplant recipients who underwent transplantation in a single center were stratified into the 3 groups: blood group O (84, 35.14%), blood group A (104, 43.51%), and due to the low number of blood group AB patients, blood groups B and AB were classified as blood group B (51, 21.3%). Clinical outcomes and patient demographics were investigated and compared between groups.

Results: The AS of blood group O recipients was significantly longer than that of blood group B recipients (P = .001). Correlation analyses revealed that recipient age (P = .002), donor age (P = .013), creatinine level (P = .022), estimated glomerular filtration rate (eGFR) (P = .005), human leukocyte antigen (HLA) mismatches (P = .001), blood group O (P < .0001), blood group B (P < .0001), cyclosporine A (P < .0001), and sirolimus treatment (P = .032) were predictors of AS. Multivariate regression analyses indicated that blood group B (β = −0.618, P < .0001) and cyclosporine A-based immunosuppression (β = −0.924, P < .0001) were negative predictors of AS.

Conclusion: The data presented here showed that eGFR, low recipient age, low donor age, patient gender (male), and 3 HLA mismatches were correlated with long-term AS. In contrast, shorter AS was associated with the blood group B and cyclosporine A treatment.

Keywords: ABO blood group, allograft, graft survival, kidney transplantation

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INTRODUCTION

Avoiding the placement of kidney grafts into recipients with pre-existing anti-donor antibodies has been considered important for more than 50 years. ABO isoagglutinins were among the first well-characterized targets of naturally occurring antibody reactivity, with other antibody classes, such as cytotoxic antibodies, now recognized as emerging threats.[1-3]

Allo-immunization of the human leukocyte antigen (HLA) may arise as a result of several different events, all of which can lead to sensitization. Multiple blood transfusions, pregnancies, and previous graft rejections are among the more common risk factors for sensitization. Allosensitized kidney transplant patients have an increased risk of graft rejection, making the panel reactive antibody (PRA) rate one of the most critical assays prior to kidney transplantation. For this reason, a serological crossmatch is routinely performed before kidney transplantation.[4] Although the specific role of ABO antigens in transplantation was first reported in the early 1960s, the effects of ABO blood groups on renal allograft survival (AS) remain unclear.[5,6] Some multivariate analyses have demonstrated no significant

difference in graft survival among recipients of various blood types.[7] However, a study by Port et al.[8] reported that transplantation in compatible blood groups carried a 9% higher relative risk for initial graft loss compared to transplantation between identical blood types. In 1985, Klouda and Bradley suggested that the ABO blood group influences sensitization in terms of the development of lymphocytotoxic antibodies.[9] Cicciarelli reported that the development of PRAs increases in association with an increasing number of blood transfusions as a result of active immunologic suppression, clonal deletion, and/or clonal anergy.[5] Here, we assess the influence of the ABO blood group on kidney graft survival. Also, we compared AS between kidney transplant recipients with an ABO identical donor and pretransplantation PRA-negative recipient combinations with negative serological crossmatch results.

METHODS

Design, Setting, and Study Population

After approval from the Clinical Research Ethical Committee of The Bozok University Hospital (no: 2017-KAEK-189._2019. 09.25_07), this retrospective analysis of prospectively acquired data from a nephrology-transplantation clinic was performed in accordance with the ethical guidelines of the Declaration of Helsinki. The files of the first-time kidney transplant recipients who came to our nephrology-transplantation outpatient clinic for routine follow-up and underwent transplantation in the same single renal transplant center between May 1, 1993 and June 1, 2014 were examined. Informed consent was obtained from all individuals included in the study.

Between 1993 and 2014, 273 kidney transplantations were performed. A total of 239 kidney transplant recipients with an ABO identical donor (≥18 or ≤60 years of age; deceased or first-degree relative living donor) and pretransplantation PRA-negative recipient combinations with negative serological crossmatch results were included in the study. The patients were stratified into the following groups: blood group A (n = 104, 43.5%) comprised 68 males (65.4%) and 91 living donors (87.5%); 47 patients (45.9%) received tacrolimus (TAC), 21 received cyclosporine A (CyA), and 36 received sirolimus-based immunosuppression (SRL), blood group O (n = 84, 35.14%) comprised 57 males (67.9%) and 78 living donors (92.9%); 44 patients (52.4%) received TAC, 14 received CyA, and 31 received SRL. The blood groups of the donor of the blood group AB, B, O, and A transplant recipients were AB, B, O, and A, respectively.

Due to the low number of blood group AB patients, blood groups B and AB were classified as blood group B. Blood group B (n = 51, 21.3%) comprised 39 males (76.5%) and 42 living donors (82.4%); 22 patients (43.1%) received TAC, 4 received CyA, and 22 received SRL. Variables investigated included the age and sex of recipients and donors, the number of HLA mismatches, AS (mean duration of follow-up for patients with a functioning allograft from the first day after transplantation to the time of data extraction from the clinical follow-up database), the proportion of living/cadaver donors, urinary protein excretion for 24 h, estimated glomerular filtration rate (eGFR), serum creatinine, cholesterol, triglyceride levels, and CyA/SRL/TAC-based immunosuppression drugs. Blood transfusion was not performed in our patients; intensive intravenous or subcutaneous antianemic treatment was used in the pretransplantation period and also if required in the post-transplant period.

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM SPSS Corp.; Armonk, NY, USA) Categorical variables were expressed as counts and percentages; continuous variables were expressed as means (standard deviation; SD) or medians (minimum and maximum). The normality of the numerical variables was analyzed using the Kolmogorov–Smirnov test, whereas the similarity of group variances was examined using Levene's test. Means were compared using one-way analysis of variance, Tukey's honestly significant difference test, the Games Howell or Dunn test, or independent-samples t-tests. Median values were compared using the Kruskal–Wallis H-test and the Bonferroni-corrected Mann–Whitney U-test (as appropriate). We expressed relationships between numerical and ordinal variables by calculating Pearson or Spearman correlation coefficients. Cox proportional hazard regression models were used to identify prognostic factors for allograft survival. Significance was set at $P < .05$, and Bonferroni correction was used for multiple comparisons.

RESULTS

The 239 kidney transplant recipients were stratified into 3 groups according to the blood group. During the study period, no graft rejection occurred between our patients. There were no differences between the blood groups in terms of the recipient or donor age or sex, eGFR rate, serum creatinine, cholesterol and triglyceride levels, HLA mismatches, or the proportions of living/cadaver donors. Although the SRL use in group B was 49 %, no difference (P = .138) between the blood groups in terms of drug (CyA/TAC/SRL) use was found (Table 1). However, blood group O recipients had a significantly longer allograft follow-up

Main Points

- The effects of ABO blood groups on renal AS remain unclear.
- Recipient age, donor age, donor sex, number of HLA mismatches eGFR, immunosuppressive drugs, and ABO blood group influence renal allograft survival.
- Low recipient age, low donor age, donor gender (male), 3 HLA mismatches, eGFR, sirolimus treatment were correlated with long-term allograft survival.
- Blood group B and cyclosporine A treatment were associated with shorter AS.
- Present study highlights the association between the ABO blood group and AS and sheds light on the epidemiological aspect of renal transplant graft survival.

Table 1. Demographic and Clinical Characteristics and Post Transplantation Laboratory Test Results of Kidney Recipients and Donors

Patient group (*n*)	A (*n* = 104)	B (*n* = 51)	O (*n* = 84)	*P*
Recipient gender, male, *n* (%)	68 (65.4)	39 (76.5)	57 (67.9)	.370
Donor gender, male, *n* (%)	51 (49.9)	25 (49.0)	35 (41.7)	.448
Recipient age, years	33.3 ± 10.7	34.6 ± 11.4	32.8 ± 12.0	.654
Donor age, years	41.1 ± 10.9	43.92 ± 11.21	40.8 ± 11.0	.229
Graft follow-up, months	86.5 (16-256)	77.0 (21-131)*	117.5(15-269)*	**.0001***
HLA mismatch, number of patients (%)	3-69 (66.3%)	3-29 (56.9%)	3-58 (69.0%)	.398
Serum creatinine, mg/dL	1.25 ± 0.43	1.22 ± 0.37	1.19 ± 0.42	.720
Cholesterol, mg/dL	196.1 ± 48.7	198.4 ± 49.3	186.6 ± 48.9	.290
Triglyceride, mg/dL	137.5 (39-581)	144.0 (48-519)	139 (53-290)	.924
eGFR, mL/min/1.73 m^2	69.1 (11.5-157.6)	67.0 (26.5-130.3)	72.4 (11.6-198)	.751
Proteinuria, mg/day	100.5 (10-990)	75.0 (10-860)	102 (19-990)	.833
Living donor, *n* (%)	91 (87.5)	42 (82.4)	78 (92.9)	.174
Drug (CyA/TAC/SRL), n	21/47/36	4/22/25	14/44/26	.138

Values are presented as means ± SD, medians (range) or *n* (%).
HLA, human leukocyte antigen; eGFR, estimated glomerular filtration rate; *n*, number; SD, standard deviation; CyA, cyclosporine A; TAC, tacrolimus; SRL, sirolimus.
*$P < .016$.

time than blood group B recipients ($P = .001$; Table 1, Fig. 1). The association between allograft follow-up time and clinicopathologic characteristics was analyzed by correlation analysis and multivariate ($\chi^2 = 89.17$, $P < .0001$) Cox regression model.

Correlation analyses revealed that AS was correlated significantly with recipient age ($P = .002$, correlation coefficient (r) = −0.200), donor age ($P = .013$, $r = −0.161$), creatinine level ($P = .022$, $r = −0.148$), eGFR ($P = .005$, $r = −.183$), HLA mismatches ($P = .001$, $r = −0.215$), blood group O ($P < .0001$, $r = .227$), blood group B ($P < .0001$, $r = −0.219$), CyA-based immunosuppression ($P < .0001$, $r = −0.293$), and SRL-based immunosuppression ($P = .032$, $r = 0.139$). Multivariate Cox regression analyses (Table 2) indicated that low recipient age ($P < .0001$), low donor age ($P = .027$), donor gender (male; $P = .003$), 3 HLA mismatches ($P = .006$), eGFR ($P < .0001$), blood group B ($P < .0001$), blood group O ($P = .046$) and CyA-based immunosuppression ($P < .0001$) were all significant predictors of AS. Multivariate regression analyses also indicated that CyA-based immunosuppression (β = −0.924, $P < .0001$) and group B (β = −0.618, $P < .0001$) were significant negative predictors of AS.

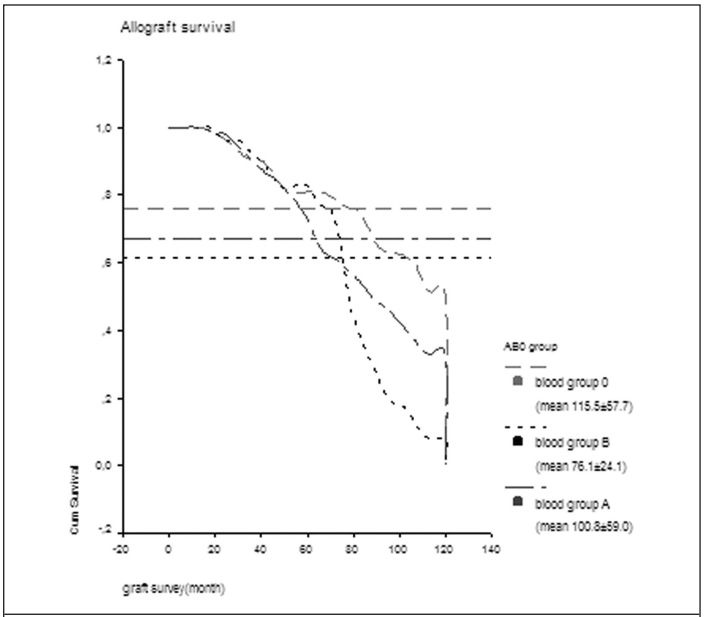

Figure 1. Graphical form of renal survival mean values. cum survival, cumulative survival.

DISCUSSION

Worldwide and in our country, 34 and 37.8% of persons are of blood group A, 38 and 29.8% are of blood group O, 9 and 14.2% are of blood group B, and 3 and 7.2% are blood group of AB, respectively. The most prevalent blood group among renal failure patients is A (45.7%).[6] Moreover, the most prevalent blood group among kidney transplant recipients is A (41.91%), with blood group A recipients exhibiting a significantly higher 5-year graft survival rate (76.5%).[10] In the present study, blood group A was also the most prevalent (43.51%) group, with a median AS of 86.5 months (range: 16-256 months). It has been reported that individuals with blood group B or AB have a higher incidence of sensitivity than those with blood group O or A.[7] These observations are consistent with the significantly higher renal graft survival rates seen in blood group O recipients compared to blood group A, B, and AB recipients.[7,10,11] The prevalence of patients with blood group O in our study was 35.14%, with a median AS of 117.5 months (range: 15-259 months),

Table 2 Factors Affecting Graft Survival: Results of Multivariate Cox Regression Analysis

Factors	Beta	Regression Coefficient Beta (95% CI)	*P*	R^2	Significance of Model
CyA	−0.924	0.397 (0.269 to 0.585)	.0001	89.17%,	0.0001
Recipient age	0.023	1.023 (1.011 to 1.035)	.0001		
Donor age	0.014	1.014 (1.002 to 1.026)	.027		
eGFR	0.015	1.015 (1.009 to 1.022)	.0001		
HLA mismatch	0.174	1.190 (1.051 to 1.347)	.006		
Group B	−0.618	0.539 (0.375 to 0.775)	.001		
Group 0	0.303	1.353 (1.005 to 1.823)	.046		
Donor gender (male)	0.416	1.516 (1.151 to 1.997)	.003		

eGFR, estimated glomerular filtration rate; CyA, cyclosporine A; HLA, human leukocyte antigen.
$P < .05$.

significantly longer than that seen in blood groups A and B. The poorest graft survival was seen in blood group B, where belonging to this blood group was a strong negative predictor of AS in the present study.

Hassan et al. reported that before transplantation, 60% of blood group AB patients had a PRA > 50%, followed in order by blood groups B, O, and A. The differences in the incidence and degree of sensitization among blood groups may be attributed to various factors. The higher incidence of sensitization in blood group B patients might be responsible for their poor graft survival rates and vice versa for blood group O patients.[12] Some reports in the literature conflict in this regard. Cecka reported that there is no difference in graft survival according to recipient blood type.[13] Multiple blood transfusions increase the formation of PRA; however, when the number of blood transfusions decreases as a result of intensive intravenous or subcutaneous antianemic therapy, the higher incidence of sensitization is reduced or eliminated.[5] Dialysis patients in the O blood group typically endure long waiting times until transplantation, due to a lower chance of a blood group-compatible donor.[14] During the long waiting period experienced by some patients, exposure to multiple blood transfusions may increase the likelihood of developing PRA or lymphocytotoxic antibodies due to sensitization of the ABO blood system.[5,9] Instead of blood transfusion, intensive intravenous or subcutaneous antianemic treatment was used to prevent sensitization in our patients. Various risk factors, such as poorer kidney function early after transplantation, proteinuria and uncontrolled hypertension, older age of the donor and recipient, donor source (living vs. cadaver), and 5 or 6 HLA mismatches, may be associated with the duration of kidney AS.[15,16] Many efforts have been made to increase long-term graft survival rates. Long-term graft survival rates are influenced by several well-established risk factors including donor and recipient age, donor and recipient gender, and HLA mismatch. It is known that kidney transplant outcomes can be affected by donor age, which may be an indicator of functional renal mass.[13,17] Previous results showed that, for renal transplant, a donor of younger age is more important to graft outcome than the age of the recipient.[15-17] Possibly due to careful selection of patients and cautious follow-up, no graft rejection or hemodialysis need occurred among our patients during the mean follow-up period. In this study, the low recipient and donor age, donor sex (male), 3 HLA mismatches, eGFR, and blood group O were significant positive predictors of AS, and blood group B and CyA immunosuppressive drug were a significant negative predictor of AS. Tacrolimus is the immunosuppressant of choice, being preferred over cyclosporine and sirolimus. Tacrolimus-based regimens show a low acute rejection rate and good long-term allograft function.[18] In the present study, 52.3% of recipients with blood group O compared to 43.1% of those with blood group B received tacrolimus-based immunosuppression.

The limitations of our study included its retrospective nature and the small number of ABO identical donors and recipients. Although the study provided no information about why and how the ABO blood group affects AS, our data suggest that the ABO blood group is independently associated with AS in ABO identical kidney donor recipients. ABO blood group has not been previously recognized as a known predictor of survival in renal transplants. Our study highlights the relationship between the ABO blood group and AS and sheds light on the epidemiological aspect of renal transplant graft survival.

In conclusion, blood group O recipients had a significantly longer follow-up time than blood group B recipients. Our analysis indicates that recipient age, donor age, donor sex, number of HLA mismatches eGFR, immunosuppressive drugs, and ABO blood group influence AS. Further studies with larger populations are required to assess the effects of blood group on AS in ABO identical donor and pretransplantation PRA-negative recipient combinations with negative serological crossmatch results.

Ethics Committee Approval: Ethics Committee Approval was received from the Clinical Research Ethical Committee of the Bozok University Hospital (2017-KAEK-189._2019.09.25_07).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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