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Predictors of graft outcome in renal transplant recipients with antibody-mediated rejection

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Abstract. Active and chronic antibody-mediated rejection (ABMR) is a common cause of graft failure. Prognostic markers of this complication are not well defined. We aimed to find out the demographic, histopathological and clinical characteristics of transplant recipients who developed ABMR and evaluate the impact of these features, and anti-rejection treatment modalities on graft survival.

Methods. Thirty-two patients who developed ABMR (22 male; mean age 40.59 ± 12.52 years) were included in this study. Data were evaluated retrospectively and graft survival was analyzed. All transplant biopsies were evaluated according to Banff's 2013 classification.

Results. Among the 32 cases, 26 were transplanted from living donors. Mean serum creatinine at the time of biopsy was 1.99 ± 0.09 mg/dL. Proteinuria was 1566.06 ± 353.92 mg/day at the time of biopsy. The need for hemodialysis was significantly related with initial creatinine ($p = 0.003$); creatinine after three months ($p < 0.001$) and final creatinine ($p < 0.001$) as well as initial proteinuria ($p = 0.005$); proteinuria after three months ($p < 0.001$) and final proteinuria ($p < 0.001$). 6 cases showed diffuse C4d positivity, 26 cases showed focal c4d positivity. Five of 6 patients with diffuse C4d staining in renal biopsy were hemodialyzed at first and third months despite anti-rejection therapy ($p=0.029$ and 0.041 , respectively).

Mean survival time was 1654.67 ± 220.40 (95% CI 1222.68-2086.66) days for focal staining C4d cases and 366.16 ± 36.44 (95% CI 294.73-437.60) days for diffuse staining C4d cases. The difference was statistically significant ($p=0.012$). Two of the patients died, 15 experienced graft loss and 17 survived with functioning grafts. Mean survival time between anti-rejection treatment modalities showed no statistical significance ($p=0.15$).

Conclusions. Serum creatinine, proteinuria at the time of biopsy, diffuse peritubular C4d staining were significantly associated with graft survival. Early diagnosis is important to improve success in the treatment of ABMR and graft survival

Keywords: renal transplantation, antibody-mediated rejection, graft survival.

Conflict of interest statement. The authors declare no competing interest.

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Предиктори виживаності ниркового трансплантату у реципієнтів з антитіло-опосередкованим відторгненням

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Резюме. Активне та хронічне відторгнення, опосередковане антитілами (АОВ) є поширеною причиною відмови ниркового трансплантата. Прогностичні маркери відторгнення є нечітко визначеними. Поточне дослідження мало на меті визначити демографічні, гістопатологічні та клінічні характеристики реципієнтів з АОВ, та оцінити вплив цих ознак на виживання ниркового трансплантата.

Методи. До дослідження включено 32 реципієнти ниркового трансплантата, у яких розвинулася АОВ, з яких 22 чоловіки; середній вік $40,59 \pm 12,52$ років. Дані оцінювали ретроспективно та аналізували виживання трансплантата. Усі біопсії при трансплантації оцінювали за класифікацією Banff 2013 року.

Результати. Серед 32 включених у дослідження випадків було 26 трансплантацій від живого донора. Середній рівень креатиніну сироватки крові на момент біопсії становив $1,99 \pm 0,09$ мг/дл. Протеїнурія на момент біопсії становила $1566,06 \pm 353,92$ мг/добу. Необхідність гемодіалізу була значною мірою пов'язана з початковим креатиніном ($p = 0,003$); креатинін після трьох місяців ($p < 0,001$) та остаточний креатинін ($p < 0,001$), а також початкова протеїнурія ($p = 0,005$); протеїнурія через три місяці ($p < 0,001$) та остаточна протеїнурія ($p < 0,001$). 6 випадків показали дифузний позитив C4d, 26 випадків - фокальний C4d позитив. П'ятеро з 6 пацієнтів з дифузним забарвленням C4d при біопсії нирки були піддані гемодіалізу протягом першого та третього місяців, незважаючи на антивідторговуючу терапію ($p = 0,029$ та $0,041$ відповідно).

Середній час виживання становив $1654,67 \pm 220,40$ (95% ДІ 1222,68-2086,66) днів для випадків фокального фарбування C4d та $366,16 \pm 36,44$ (95% ДІ 294,73-437,60) днів для випадків дифузного фарбування C4d. Різниця була статистично значущою ($p = 0,012$). Двоє пацієнтів померли, 15 зазнали втрати трансплантата, а 17 вижили із функціонуючими трансплантатами. Середній час виживання між методами лікування проти відторгнення не показав статистичної значущості ($p = 0,15$).

Висновки. Креатинін сироватки крові, протеїнурія на момент біопсії, дифузне перитубулярне фарбування C4d були значною мірою пов'язані з виживанням трансплантата. Рання діагностика важлива для поліпшення успіху в лікуванні АМР та виживання трансплантата

Ключові слова: трансплантація нирок, антитіло-опосередковане відторгнення, виживання трансплантата.

Introduction. Active and chronic antibody-mediated rejection (ABMR) is a common cause of graft failure. In previous reports, the incidence of ABMR has been defined to vary between 5.6% and 23%. ABMR frequently occurs as a reaction to donor HLA antigens and seldom to non-HLA antigens [1, 2].

ABMR's revised Banff 2017 classification specifies histological evidence of acute and chronic damage, recent antibody interaction with the vascular endothelium, and conditions associated with donor-specific antibodies (DSA) to human leukocyte (DSA) definitions as HLA or non-HLA antigens [3]. B cell and plasma cell activation lead to the production of DSAs that bind to HLA or non-HLA molecules expressed on endothelial cells in the renal allograft [4].

Active ABMR contributes to peritubular capillaritis, glomerulitis, and rapid decline in allograft function [4]. Chronic ABMR manifests histologically as transplant glomerulopathy and results in a progressive decline in kidney function [5].

The diagnosis of ABMR is based on three key criteria: (1) histological evidence of acute-chronic tissue damage, (2) evidence of antibody interaction with vascular endothelium (peritubular capillary C4d accumulation), and (3) determination of circulating DSAs [6].

Multiple studies have shown an association between peritubular c4d staining, DSA and pathological findings in patients with ABMR [7]. ABMR treatment after diagnosis is based on 2 basic mechanisms: (1) Suppression of B cells or plasma cells, (2) removal of donor-specific antibodies.

The study aim. In the current study, we aimed to find out the demographic, histopathological and clinical characteristics of transplant recipients who developed ABMR and to evaluate the impact of these features as well as anti-rejection treatment modalities on graft survival.

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Subjects and methods. Patients. The data from 306 kidney transplantations performed between January 2012 and June 2018 were retrospectively analysed; 32 recipients have been found to develop ABMR. The data from files of these patients were evaluated and demographic, histopathological and clinical characteristics were recorded.

Demographic data including age and gender, clinical data including the underlying etiology for chronic kidney disease, duration of dialysis, renal replacement therapy, laboratory data including serum creatinine, urinary protein, immunological characteristics and histopathological features of rejected kidney were recorded. The biopsies from transplanted organs were evaluated according to Banff's 2013 classification. PRA classes 1 and 2 were studied during diagnosis and in 3 months after treatment; DSA detection could not be performed due to financial problems. According to the protocol of our transplant center, all patients received induction therapy with anti-thymocyte globulin (ATG). As a standard immunosuppression regimen, 30 of the 32 patients were taking tacrolimus+mycophenolic acid derivative+prednisolone, two patients receiving tacrolimus+mycophenolic acid derivative. Treatments given after diagnosis of ABMR were analyzed retrospectively.

The local ethics committee approves the study.

Statistical analysis. Statistical analysis was performed by Statistical Package for Social Sciences for Windows version 17.0 (SPSS Inc, Chicago, IL) software. Quantitative data were expressed as mean values and standard deviations (mean \pm SD). Graft survival was evaluated by using Kaplan–Meier method, and Cox regression analysis was used for finding out independent factors. Chi-square and T-tests were used for the comparison of the 2 groups. A P-value of less than 0.05 was considered statistically significant.

Results. Demographic and clinical features. Among 306 kidney transplantations performed in our centre, 32 recipients have been found to develop ABMR (10.4 %). The study population consisted of 22 male and 10 female patients. The mean duration of renal replacement therapy (RRT) was 27.22 ± 18.62 months. The mean age at the time of diagnosis was 40.59 ± 12.52 (20–63) years. The majority of the patients ($n = 26$, 81.3 %) have been transplanted from living donors. Five female patients' past medical history was characterized by pregnancies, while 12 patients received a blood transfusion. The patients' demographic characteristics are shown in Table 1.

Table 1

The patients' demographic characteristics

Parameter	Patients
Mean age \pm SD (range) (year)	40.59 \pm 12.52 (20–63)
Male/female	22/10
Underlying disease	
Glomerulonephritis	7
DM	6
Hypertension	4
Polycystic kidney disease	3
Systemic lupus erythematosus	2
Undetected	10
Living/deceased donor (n-%)	26/6 (80.6/19.4)
Time on dialysis(month)	27.22 \pm 18.62

Laboratory data. Mean serum creatinine level was 1.99 ± 0.09 (1.36–3.70) mg/dL. Proteinuria was 1566.06 ± 353.92 mg/day at the time of biopsy. Laboratory and immunological parameters of the patients at the time of biopsy are given in Table 2.

Table 2

Laboratory and immunological parameters of the patients at the time of biopsy

	Initial	Week 1	Week 2	Month 3	Final
Creatinine (mg/dL)	1.99 \pm 0.09	2.01 \pm 0.11	2.13 \pm 0.15	2.49 \pm 0.24	3.58 \pm 0.44
Protinuria (g/24 hours)	1566.06 \pm 353.92	1402.84 \pm 275.58	1618.15 \pm 300.37	2112.03 \pm 431.05	2190.37 \pm 398.30
PRA Class 1(%)	30.41 \pm 4.57			26.89 \pm 5.13	
PRA Class 2(%)	60.06 \pm 3.63			49.48 \pm 6.22	

Pre-transplant and at the moment of biopsy immunological characteristics are shown in Table 3.

Table 3

Pre-transplant and at the moment of biopsy immunological characteristics

Parameter	Patients
ABO (compatible/incompatible)	32/0
CDC CM (negative/positive)	32/0
T cell FC CM (negative/positive)	32/0
B cell FC CM (negative/positive)	32/0
PRA class 1 (negative/positive)	31/1
PRA class 2 (negative/positive)	30/2
HLA mismatches (mean/minimum-maximum) At time of biopsy	3.56 \pm 1.45 (0–6)
PRA class 1 (negative/positive)	11/21
PRA class 2 (negative/positive)	1/31

ABMR was diagnosed at a mean of 38.34 ± 29.23 (6-120) months post-transplantation. Half of the cases were diagnosed as active AMR ($n=16$); 7 of these cases were started hemodialysis in the first month (43.8 % of acute AMR cases). Of 16 chronic AMR cases, 6 cases (37.5 %) underwent hemodialysis at the first month after treatment. The difference between these two groups

was not statistically significant ($p = 0.71$). In the third month, 7 of 16 active AMR (43.8%) and 8 of chronic AMR cases (50.0 %) underwent hemodialysis. The difference between these two groups was not statistically significant ($p = 0.72$).

Histopathologic data. The histopathology of the allograft biopsy specimens with ABMR is shown in Table 4.

Table 4

The histopathology of the allograft biopsy specimens with AMR

Case	V	I	t	G	PTC	MVI	TG	C4d	IF	TA
1	0	2	2	2	2	4	0	Focal	0	0
2	0	0	0	2	1	3	3	Focal	2	2
3	0	2	1	2	1	3	0	Focal	0	0
4	0	2	1	2	1	3	2	Focal	1	1
5	0	0	0	2	2	4	3	Focal	2	1
6	1	1	1	3	3	6	0	Focal	0	0
7	1	0	0	2	2	4	0	Focal	0	0
8	0	0	0	1	3	4	2	Focal	0	0
9	0	1	1	2	1	3	1	Focal	0	0
10	0	2	1	1	3	4	0	Focal	1	0
11	0	3	2	3	3	6	1	Diffuse	0	1
12	0	1	1	3	3	6	0	Focal	0	0
13	0	1	1	2	2	4	3	Focal	0	0
14	0	1	1	2	1	3	1	Focal	0	0
15	0	0	0	2	2	4	3	Focal	0	0
16	1	1	1	2	2	4	2	Focal	1	1
17	0	2	1	1	3	4	0	Focal	1	0
18	0	0	1	2	1	3	1	Focal	0	1
19	0	2	1	2	2	4	2	Focal	3	2
20	1	1	0	2	3	5	0	Diffuse	1	0
21	0	2	1	2	2	4	3	Diffuse	0	0
22	1	2	2	2	2	4	0	Diffuse	0	0
23	1	0	0	3	3	6	3	Focal	0	0
24	3	3	2	3	1	4	0	Focal	1	1
25	0	1	1	2	2	4	2	Focal	1	1
26	1	0	0	2	2	4	0	Diffuse	0	0
27	0	3	2	1	3	4	2	Diffuse	0	0
28	2	0	0	2	3	5	0	Focal	0	0
29	0	2	1	3	3	6	1	Focal	1	1
30	0	1	1	2	2	4	2	Focal	0	1
31	0	1	1	2	1	3	0	Focal	0	0
32	0	0	0	2	2	4	2	Focal	0	0

C4d deposition in PTC was observed in all cases as either diffuse (6) or focal (26) staining.

No significant difference was determined in terms of graft survival when we divided our patients into two groups based on microvascular inflamma-

tion (MVI) score (patients with MVI score ≤ 3 and >3) ($p = 0.086$).

The frequency of dialysis need despite treatment at the third month did not differ between the transplant glomerulopathy (TG) group and the non-TG group ($p = 0.83$).

Therapeutic and clinical features. Anti-rejection treatment options received by ABMR patients and outcomes are demonstrated in Table 5.

Table 5

Anti-rejection treatments and outcomes received by AMR patients

Therapy after rejection	N (%)	Hemodialysis despite treatment after 1 month(N-%)	Hemodialysis despite treatment after 3 months(N-%)
Corticosteroids+Plasmapheresis+IVIG	8 (25)	4(30.8)	5(33.3)
Corticosteroids +IVIG+ Rituximab	13 (40.6)	3(23.1)	4(26.7)
Corticosteroids+Plasmapheresis+IVIG+Rituximab	11 (34.4)	6(46.2)	6(40.0)

As anti-rejection therapy, the patients have received one or more of the following: pulse steroid, intravenous immunoglobulin (IVIG), rituximab, plasmapheresis. After initiation of anti-rejection therapy, 13 (40.6%) patients were administered hemodialysis in 1 month and 15 (46.9) patients in the 3 months. Two patients (6.3%) were deceased.

Thirteen patients (61.9%) who were positive for PRA class 1 at the time of renal biopsy returned to hemodialysis despite anti-rejection treatment after one month ($p < 0.001$). All 15 cases who underwent hemodialysis in 3 months were positive for PRA class 1 ($p < 0.001$) and PRA class 2. Five of 6 patients with diffuse C4d staining in renal biopsy were hemodialyzed

at first and third months despite rejection therapy ($p = 0.029$ and 0.041 , respectively).

When we compared the groups with and without TG, the response to anti-rejection treatment was not significantly different ($p = 0.68$)

The need for hemodialysis was significantly related with initial creatinine ($p = 0.003$) level; creatinine after three months ($p < 0.001$) and final creatinine ($p < 0.001$) as well as initial proteinuria ($p = 0.005$); proteinuria after three months ($p < 0.001$) and final proteinuria($p < 0.001$).

Kaplan–Meier survival analyses based on anti-rejection treatment modalities and C4d staining are demonstrated in Fig. 1 and 2, respectively.

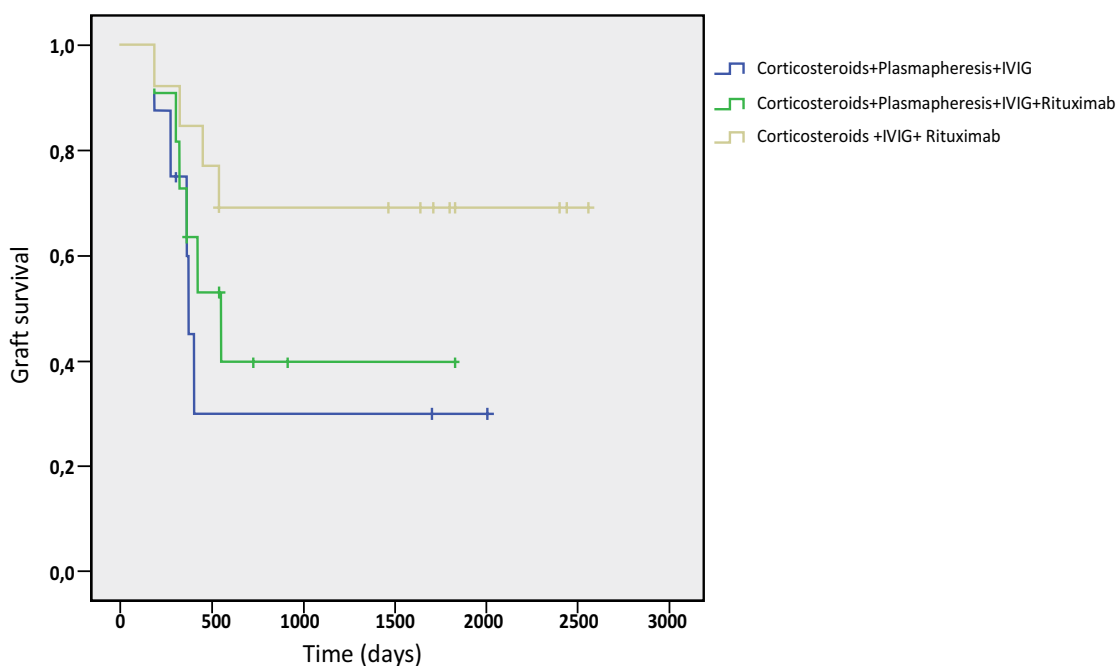


Fig. 1. Survival functions according to anti-rejection treatment

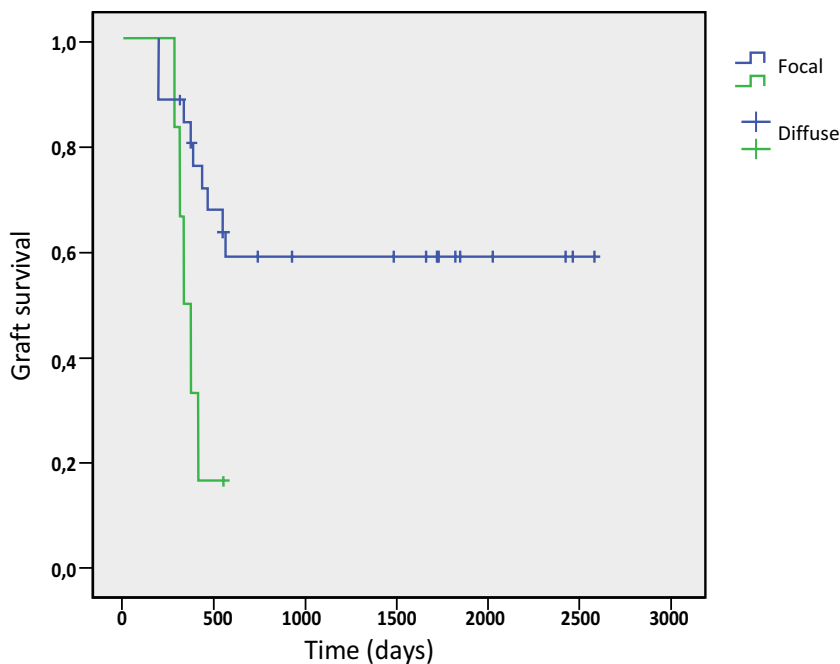


Fig. 2. Survival functions according to C4d staining

Mean survival time and SD values were 1654.67 ± 220.40 (95% CI 1222.68-2086.66) days for focal staining C4d cases and 366.16 ± 36.44 (95% CI 294.73-437.60) days for diffuse staining C4d cases. The difference was statistically significant ($p = 0.012$). Mean survival time concerning anti-rejection treatment modalities were as follows: 827.25 ± 294.59 (95% CI 249.84-1404.65) days for those who received corticosteroids, plasmapheresis, IVIG; 949.22 ± 234.80 (95% CI 489.00-1409.44) days for those who corticosteroids, plasmapheresis, IVIG and rituximab and 1883.46 ± 280.15 (95% CI 1068.49-1861.51) days for those who received corticosteroids, IVIG and rituximab. The difference between these three groups showed no statistical significance ($p = 0.15$).

By multivariate analyses, none of the covariates was found to have an independent impact on graft survival.

Discussion. Active and chronic antibody-mediated rejections are dangerous entities with significant effects on patient and graft survival. In our study, a statistically significant relationship was detected between creatinine, proteinuria, PRA percentage at the beginning of rejection and diffuse C4d staining in renal biopsy and graft survival. In our patients, the mean serum creatinine levels at the time of biopsy were 1.99 mg/dl. In previous studies, there are data on mean serum creatinine levels of 1.6–1.7 mg/dl (8-9).

Akagün et al studied 52 ABMR patients and found serum creatinine ratio to be 3.8 mg/dl at the time of biopsy [10]. An important finding in our study is a negative correlation between mean serum creatinine levels at the time of biopsy and graft survival. In line with our findings, Akagün et al also showed that serum creatinine levels at the time of biopsy were correlated with graft survival [10]. In our cohort, the mean serum cre-

atinine values were 2.49 ± 0.24 mg/dl in the third month of treatment. In the study conducted by Yılmaz et al, the mean blood creatinine value was 3.1 ± 1.4 at the last follow-up visit and mean proteinuria was 2300 (1300-3300) mg/day [11]. These results were in line with our results.

The mean time to diagnosis of rejection was 38.34 ± 29.23 months in our cases. In other words, it can be considered as late acute rejection. Consistent with our study, Akagün et al found the posttransplant ABMR diagnosis time as 34,5 months [10]. Yılmaz et al showed that the mean duration between transplantation and the development of ABMR was 31.9 ± 25.9 months [11]. However, any significant difference was not found in terms of graft survival between cases in which rejection occurred in the acute period and those in which it occurred in the chronic period ($p = 0.72$).

We have demonstrated that graft survival was significantly shorter in PRA-positive cases at biopsy time. That finding is consistent with another study which showed that graft function and high PRA levels during biopsy were predictors of graft loss [12]. The mean creatinine was 1.93 mg/dl in the group with focal C4d staining, whereas it was 2.23 mg/dl in the group with diffuse C4d staining.

Several studies on the association between graft survival and C4d staining have reported different results. The diffuse positivity of C4d in peritubular capillaries is known to be a poor prognostic factor [13]. We have demonstrated shorter graft survival in C4d positive cases, consistent with previous studies [13, 14].

When we divided our patients into two groups based on MVI (glomerulitis+peritubular capillaritis) score (MVI score ≤ 3 and >3), one recent mode of assessment in biopsies of renal transplant patients (15),

we have found no significant difference in terms of graft survival. Our results may not have reached statistical significance due to our low case numbers.

In a study involving 8 patients, Faguer et al have reported a 75% of graft survival rate over a 10-month follow-up period following plasmapheresis and rituximab treatment [8]. In another study, the graft survival rate in 569 days following administration of plasmapheresis and IVIG has been reported to be 81% [15]. In our study, there was no relationship between treatment modalities and graft survival.

In previous researches, IVIG therapy has generally been administered in combination with plasmapheresis and rituximab [8, 9].

Plasmapheresis was administered to 19 of 32 patients in our research, and IVIG to 32. However, in our study, there was no statistical significance among IVIG-containing treatment groups. Consistent with these results, treatment modalities specific ABMR must be administered.

The loss of graft due to AMR was found to be 15.3% in a study conducted by Yalçıntaş et al [16]. In another study, seven (50%) patients lost their grafts [11]. This ratio was 46.9% in our study. This may be due to the patient's late referral to the transplant unit for allograft biopsy, and may also be a feature of the destructive process of ABMR.

In a study published in 2007, the estimated patient survival was 99% and the graft survival was 80%

over an average follow-up period of 18 months [17]. In our study, despite the treatment, the loss of grafts was 46.9% in the mean follow-up period of 31 months. In our study, two patients (6.3%) died. The patient survival rate was 100% in the study conducted by Yılmaz et al [11]. In our study, the patient survival rate was 93.75 %.

There are several limitations of our study. First, our study was retrospective. Second, our study did not contain as many cases as to make clearer statistical comments. Third, the DSA cannot be studied due to financial problems.

Conclusions. ABMR had a significant and negative effect on graft survival. In our study, serum creatinine level, proteinuria at the time of biopsy, C4d staining adversely affected graft survival. Early diagnosis is important to improve success in the treatment of ABMR and graft survival. As a result, regular creatinine, proteinuria, PRA follow-up and rapid renal biopsy are recommended in case of possible rejection.

Authors' contributions.

Ergün Parmaksız: study concept and design, data analysis, manuscript writing and editing, research management;

Meral Meşe, Serap Yadigar & Kübra Aydın Bahat: data collection and clinical data analysis, manuscript editing.

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