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Original Article

The impact of early and late acute rejection on graft survival in renal transplantation

Eun Hee Koo [1], Hye Ryoun Jang [1], Jung Eun Lee [1], Jae Berm Park [2], Sung-Joo Kim [2], Dae Joong Kim [1], Yoon-Goo Kim [1], Ha Young Oh [1], Wooseong Huh [1,*]

[1] Nephrology Division, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[2] Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

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Abstract

Background: Advances in immunosuppression after kidney transplantation have decreased the influence of early acute rejection (EAR) on graft survival. Several studies have suggested that late acute rejection (LAR) has a poorer effect on long-term graft survival than EAR. We investigated whether the timing of acute rejection (AR) influences graft survival, and analyzed the risk factors for EAR and LAR.
Methods: We performed a retrospective cohort study involving 709 patients who underwent kidney transplantation between 2000 and 2009 at the Samsung Medical Center, Seoul, Korea. Patients were divided into three groups: no AR, EAR, and LAR. EAR and LAR were defined as rejection before 1 year and after 1 year, respectively. Differences in graft survival between the three groups and risk factors of graft failure were analyzed.
Results: Of the 709 patients, 198 (30%) had biopsy-proven AR [EAR = 152 patients (77%); LAR = 46 patients (23%)]. A total of 65 transplants were lost. The 5-year graft survival rates were 97%, 89%, and 85% for patients with no AR, EAR, and LAR, respectively. These differences were significant ($P < 0.001$ for both by log-rank test). In time-dependent Cox regression analysis, EAR (hazards ratio, 3.37; 95% confidence interval, 1.90–5.99) and LAR (hazards ratio, 5.32; 95% confidence interval, 2.65–10.69) were significantly related to graft failure. When we set LAR as standard and compared it with EAR, there was no statistical difference between EAR and LAR ($P = 0.21$).
Conclusion: AR, regardless of its timing, significantly worsened graft survival. Treatments to reduce the incidence of AR and improve prognosis are needed.

Introduction

It has been demonstrated that an acute rejection (AR) episode is a major risk factor of graft loss. However, not all rejection episodes have the same effect. Severity of rejection, as described using the Banff system, timing of rejection as early (EAR) or late acute rejection (LAR), and whether the allograft recovers to the baseline function after rejection are known to affect the long-term graft outcome.

Several studies have evaluated the difference between EAR and LAR in terms of impact on long-term graft survival. Some studies have suggested that LAR has a poorer effect on long-term graft survival than EAR [1–3], and recent studies showed that EAR was not the cause of graft failure [4,5]. It has been proposed that differences in immunologic activity and triggering factors such as

* Corresponding author. Division of Nephrology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-dong, Gangnam-gu, Seoul 135-710, Korea.
E-mail address: wooseong.huh@samsung.com (W Huh).

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infection or nonadherence to immunosuppressive medication may be the reasons for these distinctions [2,5].

Rates of AR and graft survival have steadily improved over time, but AR still occurs frequently and is a major risk factor for graft failure. Although several studies have compared EAR and LAR, we realized that the definitions of AR and the criteria for EAR and LAR varied across these studies. It is important to know the prognosis of AR to determine the treatment strategy and to improve the graft outcome. The aim of the present study was to identify whether the timing of AR influences graft survival and to analyze the risk factors for EAR and LAR.

Methods

Patients

We performed a retrospective cohort study involving 709 patients who underwent kidney transplantation between 2000 and 2009 at the Samsung Medical Center, Seoul, Korea. Follow-up lasted until June 2011. Indication of transplanted kidney biopsy was when acute or chronic renal allograft rejection is suspected. The main clinical indicator of rejection is a trend toward increasing serum creatinine level above baseline. Besides, other clinical indicators such as oliguria or proteinuria not related to glomerulonephritis could be an indication of biopsy depending on the clinical situation. Protocol biopsy was not performed in our study period. We used initial biopsy displaying AR to define EAR and LAR. EAR and LAR were defined as rejection before 1 year and after 1 year, respectively. Patients were divided into three groups: no AR, EAR, and LAR. The standard immunosuppression regimen consisted of prednisolone and cyclosporine or tacrolimus plus mycophenolic acid or azathioprine. Recipients younger than 18 years, patients with multiple organ transplants (e.g., kidney and liver, or kidney and pancreas), repeated kidney transplantation, primary nonfunctioning transplants, follow-up loss, and death with a functioning graft were excluded. There were five patients who had both EAR and LAR. We included them in the LAR group considering that EAR could be a risk factor of LAR.

Definition

AR was defined clinically by an acute deterioration in allograft function and confirmed with tissue diagnosis. Banff borderline AR was not considered as an AR episode. Graft failure was defined as transplant nephrectomy, retransplantation, or return to long-term dialysis. Delayed graft function was defined as the need for dialysis in the 1st week.

Statistical analysis

The clinical characteristics of the groups without AR, with EAR, and with LAR were compared using the chi-square test or the Fisher exact test. Where there were significant differences between the three groups, we compared two groups. For statistical comparisons between the means from different groups, we used the Kruskal–Wallis test. Multinomial logistic regression analysis was performed to determine the predictive values of EAR and LAR. Recipient age, sex, body mass index, underlying diabetes, preformed panel-reactive lymphocytotoxic antibodies (PRAs), induction protocol, dialysis duration, human leucocyte antigen (HLA) mismatches, cold ischemic time, immunosuppressive regimens, donor age, donor type, and donor gender were used for the univariable analysis. Variables with a value of $P < 0.2$ in either the EAR or LAR groups in the univariable analysis were selected for the multivariable analysis. The graft survival rates of the three groups were compared using time-dependent Cox regression analysis. Univariable and multivariable analyses were performed to evaluate the predictive factors of graft survival; age, gender, body mass index, underlying diabetes, PRA, induction protocol, dialysis duration, HLA mismatches, cold ischemic time, immunosuppressive regimens, donor age, donor type, and donor gender were used as variables. Significant predictors (P value < 0.2) of graft survival in the univariable analysis were fitted into a multivariable model. The results are presented as hazard ratios (HRs) with 95% confidence interval (CI). The P values were corrected using the Bonferroni method because of multiple testing. A value of $P < 0.05$ was considered to be significant. Statistical analysis was executed using SPSS for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Study population

In total, 709 patients were included in the analysis. Of these, 198 (28%) had biopsy-proven AR, 152 (21%) had EAR, 46 (7%) had LAR, and 511 (72%) did not have a rejection episode. Demographic characteristics of the patient population studied are listed in Table 1.

Recipient sex and age, dialysis duration, positive PRA (> 30%), HLA mismatches, and donor type were significantly different between the three groups. Patients with EAR were more likely to be male than the no AR group ($P < 0.001$) and LAR group ($P < 0.001$). Patients with LAR were more likely to be PRA positive than the no AR group ($P = 0.01$) and EAR ($P = 0.01$) group. The no AR group had more HLA-A, HLA-B, and HLA-DR complete matches than the EAR group ($P < 0.001$). The proportion of living donors was higher in the EAR group than in the no AR group ($P = 0.003$). The LAR group was younger than the no AR group ($P = 0.03$). The EAR group had a short dialysis duration than the no AR group ($P = 0.05$).

Graft survival

Allograft failure occurred in 65 patients. The 5-year graft survival rates were 97%, 89%, and 85% for patients with no AR, EAR, and LAR, respectively (Fig. 1). The patients with EAR or LAR showed lower graft survival rates than those with no AR ($P < 0.001$ for both by log-rank test). The graft survival rates were not different between the EAR group and LAR group ($P = 0.22$ by log-rank test).

Risk profile of EAR and LAR

In univariable analysis, EAR was related to male sex, HLA mismatch, living donor, and short cold ischemic time. The variable predictive of LAR was young recipient age and positive PRA (Table 2). By multivariable analysis, EAR was related to male sex [odds ratio (OR), 1.89, 95% CI, 1.18–3.00], HLA mismatch (OR, 12.27; 95% CI, 2.46–64.19), and older donor age (OR, 1.02; 95% CI, 1.00–1.04). LAR was associated with

Table 1. Characteristics of the study population

	No AR (n=511)	EAR (n=152)	LAR (n=46)	P
Recipient age (y)	42 (34–50)*	41 (31–48)	36 (31–47)*	0.02
Male recipient	267 (52)†	104 (68)†,‡	17 (37)‡	< 0.001
Recipient BMI (kg/m^2)	22 (20–25)	23 (20–25)	22 (20–25)	0.06
Diabetes	73 (14)	20 (13)	6 (13)	0.92
Dialysis duration (mo)	15 (3–53)§	9 (2–34)§	19 (5–51)	0.03
PRA > 30%	32 (6)‖	7 (5)¶	8 (17)‖,¶	0.008
HLA—no mismatch	67 (13)**	2 (1)**	1 (1)	< 0.001
Deceased donor	125 (25)††	18 (12)††	10 (22)	0.004
Donor age (y)	40 (31–47)	42 (33–50)	42 (33–50)	0.15
Male donor	280 (55)	82 (54)	30 (65)	0.37
Cold ischemic time (min)	65 (48–155)	62 (45–87)	70 (52–121)	0.08
Induction	155 (30)	34 (22)	17 (37)	0.08
Immunosuppression				
CsA	237 (46)	75 (49)	22 (48)	0.78
FK	269 (53)	74 (49)	24 (52)	
Delayed graft function	25 (5)	6 (4)	4 (9)	0.43
Cellular rejection				
Banff grade IA		79 (52)	23 (50)	0.37
IB		27 (18)	14 (30)	
IIA		28 (18)	6 (13)	
IIB		6 (4)	1 (2)	
Antibody-mediated rejection		12 (8)	2 (4)	0.40

* No AR vs. LAR, P = 0.03. † No AR vs. EAR, P < 0.001. ‡ EAR vs. LAR, P < 0.001. § No AR vs. EAR, P = 0.05. ‖ No AR vs. LAR, P = 0.01. ¶ EAR vs. LAR, P = 0.01. ** No AR vs. EAR, P < 0.001. †† No AR vs. EAR, P = 0.003.
Data are presented as n (%) or median (interquartile range 25–75%).
By multiple testing, P value was corrected with the Bonferroni method.
CsA, cyclosporine; EAR, early acute rejection; FK, tacrolimus; HLA, human leucocyte antigen; LAR, late acute rejection; No AR, no acute rejection; PRA, panel-reactive lymphocytotoxic antibody.

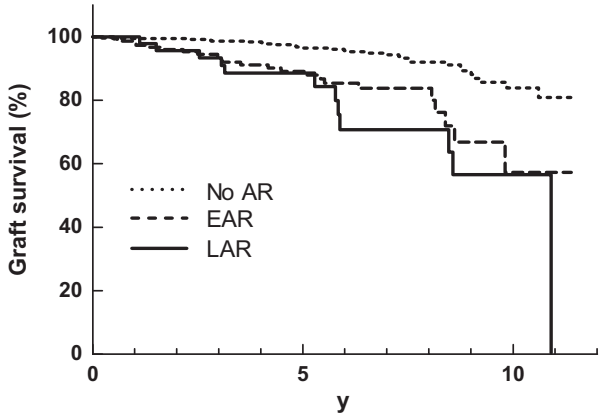

Figure. 1. Kaplan–Meier graft survival for transplants without AR, with EAR, and with LAR. AR, acute rejection; EAR, early acute rejection; LAR, late acute rejection.

younger recipient age (OR, 0.95; 95% CI, 0.91–0.98) and positive PRA (OR, 2.72; 95% CI, 1.20–10.48) (Table 2).

Graft failure risk factor

Univariable and multivariable Cox regression analyses were used to identify independent variables associated with poor transplant outcomes. Rejection was regarded as a time-dependent variable. In univariable analysis, EAR (HR, 3.27; 95% CI, 1.88–5.66), LAR (HR, 5.10; 95% CI, 2.59–10.08), longer dialysis duration (HR, 1.01; 95% CI, 1.00–1.00), and deceased donor (HR, 1.84; 95% CI, 1.02–3.31) were significant risk factors for graft failure.

In multivariable analysis, EAR (HR, 3.37; 95% CI, 1.90–5.99) and LAR (HR, 5.32; 95% CI, 2.65–10.69) were significantly related to graft failure (Table 3). When we set LAR as standard and compared it with EAR, there were no statistical difference between EAR and LAR (P = 0.21).

Discussion

In this study, we found that EAR, as well as LAR, had negative effects on long-term graft survival. In a time-dependent Cox regression test to evaluate the risk factors for graft survival, both EAR and LAR were significant risk factors for graft failure compared with the no AR group. Unlike other studies that showed that EAR was not the cause of graft failure, EAR was a significant risk factor for graft failure in our study [4,5]. Recently, El Ters et al [6] showed that early acute cellular rejection was not a single acute event but triggered a persistent alloimmune response that might result in long-term graft injury and graft loss years after the acute event. These findings are consistent with our observation.

Many studies have been conducted to explore whether the timing of AR affects graft survival. The majority of these studies reported that LAR was correlated with poor long-term graft survival [1–3]. However, reports about the impact of EAR are inconsistent. We thought that the reason for variable results might be that each study used different methods and populations, with the cutoff for EAR being particularly variable. Some studies used a 3-month cutoff to divide EAR and LAR [1,3]. Others used 6- or 12-month cutoffs [7,8]. Most studies categorized EAR and LAR by the onset of the first AR [1,2]. One study used the timing of the last treated AR [3]. Definitions of AR were also inconsistent. Some studies included AR diagnosed using clinical biopsy or using either

Table 2. Logistic regression model for predicting EAR and LAR

	Univariable analysis						Multivariable analysis					
	EAR			LAR			EAR			LAR		
	Exp(B)	*P*	95% CI*	Exp(B)	*P*	95% CI*	Exp(B)	*P*	95% CI *	Exp(B)	*P*	95% CI*
Recipient age	0.99	0.29	0.97–1.01	0.96	0.01	0.92–0.99	0.99	0.26	0.96–1.01	0.95	0.002	0.91–0.98
Male recipient	1.98	< 0.001	1.28–3.07	0.54	0.10	0.26–1.09	1.89	0.004	1.18–3.00	0.59	0.23	0.27–1.26
BMI	1.06	0.06	0.99–1.12	0.96	0.81	0.86–1.07	1.05	0.18	0.99–1.12	0.99	0.75	0.89–1.12
Diabetes	0.91	0.73	0.50–1.67	0.81	0.82	0.32–2.50						
Dialysis duration	0.99	0.07	0.99–1.00	1.00	0.89	0.99–1.00	0.99	0.65	0.99–1.00	1.00	> 0.99	0.99–1.01
PRA > 30%	0.63	0.90	0.28–1.89	3.15	0.02	1.20–8.26	1.16	> 0.99	0.41–3.23	3.54	0.02	1.20–10.48
HLA mismatch ≥ 1	11.3	0.002	2.24–57.32	6.79	0.12	0.69–66.73	12.55	0.002	2.46–64.19	8.38	0.08	0.83–84.94
Deceased donor	0.42	0.002	0.23–0.76	0.86	0.68	0.37–1.98	0.81	> 0.99	0.26–2.52	0.71	> 0.99	0.14–3.54
Donor age	1.02	0.11	1.00–1.03	1.01	0.65	0.98–1.04	1.02	0.05	1.00–1.04	1.02	0.54	0.99–1.05
Male donor	0.97	> 0.99	0.64–1.46	1.55	0.35	0.75–3.18.						
Cold ischemic time	0.99	0.002	0.99–1.00	0.99	0.68	1.00–1.00	1.00	0.08	0.99–1.00	1.00	0.88	0.99–1.00
Induction	0.66	0.11	0.41–1.08	1.35	0.71	0.66–2.76	1.19	> 0.99	0.58–2.44	2.02	0.27	0.71–5.78
FK (vs. CsA)	0.87	0.47	0.61–1.26	0.97	0.91	0.53–1.77						
Delayed graft function	0.80	> 0.99	0.28–2.26	0.83	0.55	0.53–6.53						

* 95% CI for odds ratio was corrected with the Bonferroni method because of multiple testing.
BMI, body mass index; CI, confidence interval; CsA, cyclosporine; EAR, early acute rejection; FK, tacrolimus; HLA, human leucocyte antigen; LAR, late acute rejection; PRA, panel-reactive lymphocytotoxic antibody.

Table 3. Univariable and multivariable analyses of risk factors associated with graft survival

	Univariable analysis			Multivariable analysis		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Rejection (vs. No AR)						
EAR	3.27	1.88–5.66*	< 0.001	3.37	1.90–5.99*	< 0.001
LAR	5.10	2.59–10.08*	< 0.001	5.32	2.65–10.69*	< 0.001
Recipient age	0.99	0.97–1.02	0.39			
Male recipient	1.22	0.74–2.00	0.47			
Diabetes	1.47	0.82–3.18	0.17	1.60	0.80–3.18	0.18
Dialysis duration	1.01	1.00–1.01	0.04	1.00	1.00–1.01	0.27
PRA > 30%	1.05	0.33–3.36	0.94			
HLA mismatch ≥ 1	3.63	0.89–14.85	0.07	2.11	0.51–8.79	0.31
Deceased donor	1.84	1.02–3.31	0.04	1.54	0.54–4.43	0.42
Donor age	1.02	1.00–1.04	0.08	1.02	0.99–1.04	0.15
Male donor	1.18	0.72–1.92	0.52			
Cold ischemic time	1.00	1.00–1.00	0.18	1.00	1.00–1.00	0.81
Induction	1.41	0.75–2.66	0.29			
FK (vs. CsA)	1.27	0.77–2.09	0.36			
Delayed graft function	1.43	0.45–4.57	0.55			

* 95% CI for odds ratio was corrected with the Bonferroni method because of multiple testing.
AR, acute rejection; CI, confidence interval; CsA, cyclosporine; EAR, early acute rejection; FK, tacrolimus; HLA, human leucocyte antigen; LAR, late acute rejection; PRA, panel-reactive lymphocytotoxic antibody.

clinical or protocol biopsy [5]. Others used clinical AR that was not biopsy proven [3,7]. Study populations also differed; some studies selected only deceased-donor kidney transplants [1–3], whereas others enrolled both living- and deceased-donor kidney transplants [5,6].

In this study, AR was diagnosed using clinical biopsy. We excluded the Banff borderline to overcome the bias from misdiagnosis [9]. The 1-year cutoff was used. Although it was arbitrary from 3-month to 1-year cutoff, we could identify the inflection points at 1 year on the Kaplan–Meier curve of AR (Fig. 2). There were five patients who had experienced both EAR and LAR. In consideration of the EAR as a risk factor of LAR, we included them to the LAR group. When we put them into either the EAR group or excluded them, their influence on the study results was statistically insignificant (data not shown). Because AR is a time-dependent variable and not a baseline characteristic, the effect of rejection on survival is not constant over time. We chose the time-dependent Cox regression test for survival analysis, which could be more appropriate than the Kaplan–Meier estimate or Cox regression analysis, and found that EAR and LAR were independent risk factors for graft survival.

We found that EAR was associated with male sex, HLA mismatch, and older donor. LAR was associated with young recipient age and positive PRA. HLA mismatches are well-known risk factors for AR. HRs in the range of 1.39–3.78 have been described for one or more HLA-A, HLA-B, and HLA-DR mismatches [10]. Older donor and positive PRA are also known risk factors for AR [11]. Older donor age is known to be related to inflammation in grafts, which is associated with later chronic graft damage [12]. The association of young recipient age and LAR could be partly explained by noncompliance or increased immune responsiveness [3,5]. In our study, male sex was associated with EAR. Evidence for the effect of sex is by no means consistent in many studies [13,14].

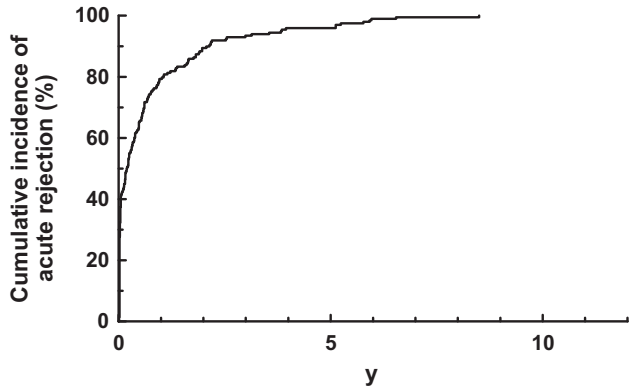

Figure 2. Kaplan–Meier plot of the cumulative incidence of acute rejection.

There were several limitations of this investigation. First, the study was retrospective, and association does not prove causality. Second, antibody-mediated rejection (AMR) was not included as a graft failure risk factor, although it has been identified as the cause of graft failure in many studies [5,7,8]. Because the Banff 2001 classification included criteria for AMR, AMR has been increasingly recognized. In the early study period, distinguishing AMR from acute cellular rejection was not precise. This is one reason why the incidence of AMR in our study was lower than that of the published data [5]. In addition, it was difficult to show the statistical difference because the number of events was small. Third, clinical factors, such as recovery from AR and type of treatment, were not included in the analysis. These may be different because of the timing of AR and could influence graft survival rates. As a retrospective study, determining recovery from AR through a chart review has the risk of bias. Additional prospective studies with recent data to carefully distinguish AMR through microcirculation inflammation and C4d staining could show clearer results.

The study is significant in two main ways. First, the EAR and LAR categories were clearly defined. All AR episodes were confirmed with biopsy. If we had included clinical rejection, the incidence of AR would be overestimated. Furthermore, we recognized the patients who had both EAR and LAR, included them in each group, and excluded them to see if there is a statistical difference in each cases. Second, the study emphasizes that the risk of EAR on graft survival is of importance. Nowadays, EAR is thought to be of no particular importance in graft survival. Because of the side effects of immunosuppressants, a reduction in medication is a positive trend in the management of EAR, but EAR is still a significant risk factor for graft failure.

In conclusion, these observations suggest that we should still consider EAR to be a major barrier to improving long-term graft survival. Graft biopsy, either clinical biopsy or protocol biopsy, has been the gold standard for diagnosing EAR. However, it is invasive and cannot predict AR. For the prevention and early detection of EAR, a noninvasive immunologic monitoring method should be developed. Major histologic types of LAR may include AMR [5]. At this time, education for noncompliant patients is important in the prevention of AMR. The development of a noninvasive immunologic monitoring method is also necessary for early detection.

Conflicts of interest

The authors declare no conflict of interest.

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