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ORIGINAL ARTICLE

# Influence of kidney function to the impact of acute rejection on long-term kidney transplant survival

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## Summary

In kidney transplantation, timing of an initial acute rejection (AR) is correlated with a variable risk of graft loss. However, it is unknown whether the increased risk for graft loss because of AR is conditioned by impaired graft function. A total of 730 cadaveric kidney transplant recipients were retrospectively evaluated from 1994 to 2001. When AR occurred, the risk ratio (RR) for graft loss was strongly time-dependent and increased, the later the rejection episode occurred. Compared with the reference group (no rejection) having an AR within 0–30, 31–365, or >365 days post-transplant conferred a 3.1-, 9.1- and 49.3-fold risk for subsequent graft loss ($P < 0.001$). By including serum creatinine as an indicator for graft function at the time of rejection RR decreased to 2.4-, 7.1- and 21.8-fold, but remained still significant ($P = 0.023$). In conclusion, the higher risk of graft loss after late AR is not fully explained by impaired graft function measured by serum creatinine.

## Introduction

Many risk factors are known to influence long-term graft survival such as age of the recipient, race, presence of diabetes, delayed graft function, human leukocyte antigen (HLA)-mismatch [1,2], whereas acute rejection (AR) has consistently been reported to be the most important risk factor leading to chronic allograft failure [3–5]. Although improvements have been made in preventing AR and in maximizing short-term graft survival in kidney transplantation, long-term graft survival has not improved as dramatically [6–8]. With the use of newer immunosuppressive drugs such as mycophenolate mofetil (MMF) and tacrolimus further reduction in the incidence of AR episodes has been attained [9,10], but regardless of the decrease in the incidence of AR, chronic allograft failure and kidney graft loss remain the most common cause of death censored graft loss after kidney transplantation [3,11,12]. Recent studies have been reported that an initial AR episode is linked with an increased risk of graft loss after kidney transplantation [8,13–16] and that the timing of the initial episode of AR has been evolved over time [7]. As a consequence, the association of AR with chronic allograft failure and graft loss has been shown to vary with the degree and the timing of the AR episode in a complex time-dependent manner [5,7,12,17–19].

Previous reports demonstrated that kidney graft function during the first year of transplantation is a useful prognostic tool for graft survival [2,20]. However, it has never been investigated whether the association between late AR episode and the increased risk for kidney graft loss can be explained by impaired graft function. The purpose of this retrospective study was therefore to document if the timing of an initial AR episode changes the risk for kidney graft loss and whether this time-dependent risk is correlated with increased serum creatinine as an indicator for kidney graft function.

## Material and methods

### Patients

A total of 730 consecutive recipients of a cadaver kidney transplant from January 1, 1990 to December 31, 2001 were included in the study. Data of cadaveric organ

donor (CAD) recipient were entered prospectively into a transplant-specific database at the time of transplantation. The generated data was used for this retrospective analysis. Inclusion criterion was at least one determination of serum creatinine within <30 days after transplantation. CAD recipients received quadruple sequential immunosuppression, including antithymocyte globulin or muromonab-CD3, corticosteroids, azathioprine (before 1995) and MMF (after 1995), and a calcineurin inhibitor (cyclosporine or tacrolimus).

### Definitions

*Acute graft rejection* was diagnosed based on histology. A kidney transplant biopsy was performed for the diagnosis of any significant increase of baseline serum creatinine that was clinically suspected to be caused by an AR episode before administering an antirejection corticosteroid bolus. Antithymocyte globulin or muromonab-CD3 was used at the discretion of the treating physician for steroid-resistant rejection. Only biopsy-proven episodes of AR were included in this analysis. *Graft loss* was considered as return to hemodialysis or loss of the transplanted organ.

### Analytical method

Based on the follow up in interval during which an initial AR episode occurred, the study cohort was divided into four groups as follows: no AR episode during the time of follow up (group A); first AR episode during the first 30 days after transplantation (group B); first AR episode between 1 month and 1 year (group C); and first AR episode more than 1 year after transplantation (group D). Consequently, graft recipients who had an early AR episode (groups B and C) also may have had an AR episode in the later time periods.

### Statistical analysis

The dynamic time-varying covariate approach in a non-proportional partial likelihood model was used to determine the association of AR and serum creatinine timing on the risk of kidney graft loss. Results are reported as the risk ratio (RR). A *P*-value of ≤0.05 was considered as significant. Data are reported as mean ± SD. All statistical analysis was performed using the SAS system (SAS Institute, Inc., Cary, NC, USA).

## Results

### Baseline characteristics

The clinical characteristics of the patients documented at baseline are shown in Table 1. The average age at time of transplantation was 47.3 ± 2.3 years. About 53.4% were male patients. During a follow up of 3.8 ± 1.7 years (range: 0.3–7), 284 patients (38.9%) did not encounter AR, whereas in 217 patients (29.7%) an AR episode occurred within the first 30 days after transplantation (group B), in 153 patients (20.9%) between 1 month and the first post-transplant year (group C), and in 76 patients (10.4%) after the first post-transplant year (group D) (Table 2).

**Table 1.** Baseline characteristics of first cadaveric kidney transplants ($n = 730$).

| Characteristic | Mean ± SD or *n* (% per category) |
|---|---|
| Recipient factors | |
| Age at transplantation (year) | 47.3 ± 2.3 |
| Male | 438 (60.0) |
| Race | |
| White | 621 (85.0) |
| Black | 58 (7.9) |
| Other | 51 (7.0) |
| Hemodialysis before transplantation | 663 (90.8) |
| Donor factors | |
| Age (year) | 37.3 ± 0.4 |
| Male | 465 (60.0) |
| Transplant factors | |
| Mean number of mismatches | |
| Human leukocyte antigen (HLA)-A | 1.1 ± 0.8 |
| HLA-B | 1.1 ± 0.8 |
| HLA-DR | 0.8 ± 0.7 |
| Delayed graft function | 161 (22.0) |
| Discharge serum creatinine | 1.75 ± 0.02 |

**Table 2.** Definition and size of study groups in respect to acute rejection (AR).

| Study group | Time of first AR (days) | Number of patients (%) |
|---|---|---|
| A | – | 284 (38.9) |
| B | 0–30 | 217 (29.7) |
| C | 31–365 | 153 (20.9) |
| D | >365 | 76 (10.4) |

### Time of first acute rejection episode and risk for kidney graft loss

Using group A (no rejection) as reference, RR for graft loss after an AR episode was strongly time-dependent and increased, the later an AR occurred (RR = 2.7, 5.7, and 17.6 in groups B, C, and D, respectively; $P < 0.001$) (Table 3). In addition, risk for graft loss was the highest immediately after AR and decreased, the later the AR episode occurred: in group B (AR <30 days: RR = 3.1; AR 31–365 days: RR = 2.8; AR >365 days: RR = 2.0), in group C (AR <30 days: RR = 9.1; AR 31–365 days:

**Table 3.** Risk ratios (RR) for kidney graft loss after a first acute rejection (AR) episode.

| | Groups (days) | | |
|---|---|---|---|
| Days since AR | B (0–30) | C (31–365) | D (>365) |
| Overall | 2.7 | 5.7 | 17.6 |
| 0–30 | 3.1 | 9.1 | 49.3 |
| 31–365 | 2.8 | 3.5 | 3.3 |
| >365 | 2.0 | 2.6 | 2.7 |

**Table 4.** Risk ratios (RR) for kidney graft loss after a first acute rejection (AR) episode adjusted by including serum creatinine.

| | Groups (days) | | |
|---|---|---|---|
| Days since AR | B (0–30) | C (31–365) | D (>365) |
| 0–30 | 2.4 | 7.1 | 21.8 |

RR = 3.5; AR >365 days: RR = 2.6), and in group D (AR <30 days: RR = 49.3; AR 31–365 days: RR = 3.3; AR >365 days: RR = 2.7) (Table 3). While an AR during the first 30 days after transplantation showed an almost equal RR for graft loss (RR = 3.1, 2.8, and 2.0, respectively; overall RR = 2.7), an AR after the first year of transplantation showed a significantly increased risk for graft loss (RR = 49.3, 3.3, and 2.7, respectively; overall RR = 17.6; $P < 0.001$; Table 3).

### Effect of graft function assessed by serum creatinine on late AR episode and risk for kidney graft loss

To evaluate how graft function accounted for the time-dependent impact of AR on graft loss, this risk was estimated by treating AR and serum creatinine as time-varying covariates in a nonproportional partial likelihood model. Adjusting RR for graft loss by including serum creatinine, the time dependency for late AR immediately within the first 30 days after an AR was reduced (AR <30 days: RR = 2.4; AR 31–365 days: RR = 7.1; AR >365 days: RR = 21.8), but still significant ($P = 0.023$) (Table 4).

## Discussion

Several studies have shown that both the occurrence of an AR episode and the number of such episodes strongly predict chronic rejection and long-term allograft failure [6–8]. Although it has been demonstrated that kidney graft function within the first year of transplantation is a useful prognostic tool for graft survival [2,20], it has never been investigated whether the association between a late AR and the increased risk for kidney graft loss is to be explained by impaired renal function assessed by an increase in serum creatinine.

In this retrospective study, we demonstrated that the risk for graft loss after an AR episode is strongly time-dependent and increased, the later an initial rejection episode occurred. These findings are consistent with those of other authors who have shown that late AR episodes are more harmful to long-term kidney graft survival than early rejection episodes [6–8,13–16,18]. We also demonstrated an increasingly detrimental impact of AR on short-, intermediate-, and long-term allograft survival. Considering these findings, we demonstrated that an initial AR episode after the first year of transplantation is at the highest risk immediately after the rejection (RR = 49.3) compared with 1 year after rejection, when the AR occurred during the first 30 days of transplantation (RR = 2.0). This pattern was present in all groups (B, C, and D) (Table 3), and demonstrated the complex interactions of immune and nonimmune events triggering an AR episode. Multiple nonimmune events, for example, may precipitate AR episodes.

Factors such as compliance with immunosuppressive and monitoring protocols, changes in the absorption or metabolism of immunosuppressant, or drug interactions may be also be involved in a significant fraction of recipients. These factors may help to explain the differences in timing and effect of AR episodes in our study. Early rejections, such as in group B, are more likely to be primarily immune-mediated, because patients undergo a supervised immunosuppressive protocol before discharge and, thus, are compelled to be compliant. Differences in absorption or metabolism may also contribute to these early rejection episodes. Later rejection episodes, on the other hand, may have a significant behavioral component. Noncompliance was shown to be a significant factor in transplant rejection, and is estimated to account for 11–23% of allograft losses [14,21]. Studies by Matas *et al.* and Didlake *et al.* showed that noncompliance is not only an important factor for rejection episodes and allograft loss, but also that it is also an important factor for late rejection episodes accounting for 24–50% of the allograft losses [14,21]. Thus, many of the later AR in our study may result from less than ideal immunosuppression due to patient noncompliance. We could not determine to which extent noncompliance was a factor in late AR.

Not all late rejection episodes are caused by noncompliance, changes in absorption, metabolism, or drug interactions. Several studies have suggested that primary immune factors account for 50–60% of allograft losses after the first year [14,15]. To some extent, impaired graft function may be an important factor triggering a late event of AR. Although several studies have

addressed factors which may be involved in the occurrence of a late AR [16,22–24], none of them examined whether late rejections appear to be more severe simply because they are occurring in patients with a greater degree of renal impairment. Given the fact that organ shortage for transplantation is increasing, the optimization of long-term allograft survival is becoming more and more important. Renal function within the first year of transplantation has been reported to be an important factor of graft survival [25,26]. Therefore, some effort has been made to develop easy and reliable tools to predict graft survival using serum creatinine levels in the past [2,20]. To evaluate how late AR episodes and the risk for kidney graft loss are correlated with impaired graft function, we recalculated the risk of graft loss by treating AR and serum creatinine as time-varying covariates in a nonproportional partial likelihood model. Our results showed that the higher risk of graft loss after late AR cannot be fully explained by impaired graft function represented by increased serum creatinine. On the contrary, whether an increase of serum creatinine levels reflects the ongoing rejection episode or could at least in part account for it, is still unknown.

A major weakness of this investigation and of most other studies [6,7,18] is the inability to include the timepoint at which the last AR episode occurred into the statistical calculations. Therefore, transplant recipients with a late AR episode who already had a rejection episode within the first year of transplantation appeared to be in the group of 'low'-risk for graft loss, although they had a more detrimental later rejection impact. This inability is caused by the design of most of the currently used transplant-specific databases.

In conclusion, late occurrence of an initial AR episode is associated with a higher risk of graft loss after kidney transplantation. This interrelation is cannot be fully explained by impaired graft function assessed by measurement of serum creatinine.

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## References

1. Shoskes DA, Cecka JM. Deleterious effects of delayed graft function in cadaveric renal transplant recipients independent of acute rejection. *Transplantation* 1998; **66**: 1697.
2. Hariharan S, Johnson CP, Bresnahan BA, Taranto SE, McIntosh MJ, Stablein D. Improved graft survival after renal transplantation in the United States, 1988 to 1996. *N Engl J Med* 2000; **342**: 605.
3. Almond PS, Matas A, Gillingham K, *et al.* Risk factors for chronic rejection in renal allograft recipients. *Transplantation* 1993; **55**: 752; discussion 756.
4. Paul LC. Chronic allograft nephropathy: an update. *Kidney Int* 1999; **56**: 783.
5. Humar A, Hassoun A, Kandaswamy R, Payne WD, Sutherland DE, Matas AJ. Immunologic factors: the major risk for decreased long-term renal allograft survival. *Transplantation* 1999; **68**: 1842.
6. Leggat JE Jr, Ojo AO, Leichtman AB, *et al.* Long-term renal allograft survival: prognostic implication of the timing of acute rejection episodes. *Transplantation* 1997; **63**: 1268.
7. Meier-Kriesche HU, Ojo AO, Hanson JA, *et al.* Increased impact of acute rejection on chronic allograft failure in recent era. *Transplantation* 2000; **70**: 1098.
8. Joseph JT, Kingsmore DB, Junor BJ, *et al.* The impact of late acute rejection after cadaveric kidney transplantation. *Clin Transplant* 2001; **15**: 221.
9. Sollinger HW. Mycophenolate mofetil for the prevention of acute rejection in primary cadaveric renal allograft recipients. U.S. Renal Transplant Mycophenolate Mofetil Study Group. *Transplantation* 1995; **60**: 225.
10. Pirsch JD, Miller J, Deierhoi MH, Vincenti F, Filo RS. A comparison of tacrolimus (FK506) and cyclosporine for immunosuppression after cadaveric renal transplantation. FK506 Kidney Transplant Study Group. *Transplantation* 1997; **63**: 977.
11. Kasiske BL. Immune and nonimmune clinical correlates of chronic renal allograft rejection. *Transplant Proc* 1997; **29**: 2557.
12. Ishikawa A, Flechner SM, Goldfarb DA, *et al.* Quantitative assessment of the first acute rejection as a predictor of renal transplant outcome. *Transplantation* 1999; **68**: 1318.
13. Basadonna GP, Matas AJ, Gillingham KJ, *et al.* Early versus late acute renal allograft rejection: impact on chronic rejection. *Transplantation* 1993; **55**: 993.
14. Matas AJ, Gillingham KJ, Payne WD, Najarian JS. The impact of an acute rejection episode on long-term renal allograft survival ($t1/2$). *Transplantation* 1994; **57**: 857.
15. Cole E, Naimark D, Aprile M, *et al.* An analysis of predictors of long-term cadaveric renal allograft survival. *Clin Transplant* 1995; **9**: 282.
16. Sijpkens YW, Doxiadis II, Mallat MJ, *et al.* Early versus late acute rejection episodes in renal transplantation. *Transplantation* 2003; **75**: 204.
17. Massy ZA, Guijarro C, Wiederkehr MR, Ma JZ, Kasiske BL. Chronic renal allograft rejection: immunologic and nonimmunologic risk factors. *Kidney Int* 1996; **49**: 518.
18. Heisey DM, Foong AP. Modelling time-dependent interaction in a time-varying covariate and its application to

rejection episodes and kidney transplant failure. *Biometrics* 1998; **54**: 712.
19. Pelletier RP, Cosio F, Henry ML, *et al.* Acute rejection following renal transplantation. Evidence that severity is the best predictor of subsequent graft survival time. *Clin Transplant* 1998; **12**: 543.
20. Hariharan S, McBride MA, Cherikh WS, Tolleris CB, Bresnahan BA, Johnson CP. Post-transplant renal function in the first year predicts long-term kidney transplant survival. *Kidney Int* 2002; **62**: 311.
21. Didlake RH, Dreyfus K, Kerman RH, Van Buren CT, Kahan BD. Patient noncompliance: a major cause of late graft failure in cyclosporine-treated renal transplants. *Transplant Proc* 1988; **20**(3 Suppl 3):63.
22. Reisaeter AV, Leivestad T, Vartdal F, *et al.* A strong impact of matching for a limited number of HLA-DR antigens on graft survival and rejection episodes: a single-center study of first cadaveric kidneys to nonsensitized recipients. *Transplantation* 1998; **66**: 523.
23. Mathew TH. A blinded, long-term, randomized multicenter study of mycophenolate mofetil in cadaveric renal transplantation: results at three years. Tricontinental Mycophenolate Mofetil Renal Transplantation Study Group. *Transplantation* 1998; **65**: 1450.
24. Pollard SG, Lear PA, Ready AR, Moore RH, Johnson RW. Comparison of microemulsion and conventional formulations of cyclosporine A in preventing acute rejection in de novo kidney transplant patients. The U.K. Neoral Renal Study Group. *Transplantation* 1999; **68**: 1325.
25. Nicol D, MacDonald AS, Lawen J, Belitsky P. Early prediction of renal allograft loss beyond one year. *Transpl Int* 1993; **6**: 153.
26. Humar A, Kerr S, Gillingham KJ, Matas AJ. Features of acute rejection that increase risk for chronic rejection. *Transplantation* 1999; **68**: 1200.