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Racial differences in renal allograft survival: The role of systemic hypertension

FERNANDO G. COSIO, JOHN J. DILLON, MICHAEL E. FALKENHAIN, RAYMOND J. TESI, MITCHELL L. HENRY, ELMAHDI A. ELKHAMMAS, ELIZABETH A. DAVIES, GINNY L. BUMGARDNER, and RONALD M. FERGUSON

Divisions of Nephrology and Transplantation, Departments of Internal Medicine and Surgery, The Ohio State University, Columbus, Ohio, USA

Racial differences in renal allograft survival: The role of systemic hypertension. The rate of decline in the number of functioning renal allografts beyond the first year after transplantation has changed little in the last 25 years, and during long-term follow-up most allografts are lost due to chronic transplant rejection or patient death. The recipient race correlates with allograft survival, and African American recipients have a lower allograft survival than Caucasians. The goal of the present study was to identify clinical variables present during the first six months after transplantation that predict the loss of renal allografts beyond six months after transplantation, and in particular to determine the role of systemic hypertension on renal allograft survival in black and white recipients. This study includes 547 recipients of first cadaveric renal allografts performed at The Ohio State University. All patients were treated with a uniform immunosuppressive protocol and had a follow-up of at least three years. By multivariate analysis the following variables correlate with poor allograft survival: an elevated serum creatinine concentration measured six months after transplantation (SCr_{6mo}) ($P < 0.0001$); black race ($P < 0.0001$); increasing numbers of acute rejection episodes (ATR) ($P = 0.002$); and young recipients ($P = 0.026$). Allograft survival is significantly worse in black (mean allograft half-life of 7.7 ± 1.3 years) than in white recipients (24 ± 3 years) ($P < 0.0001$). Black recipients also have a significantly higher six month average mean arterial blood pressure (MAP) (105 ± 8 mm Hg) than white recipients (102 ± 7 mm Hg) ($P = 0.002$). However, the prevalence of hypertension is not significantly different in black (33%) than in white recipients (26%). Furthermore, increasing MAP levels correlate with a shorter allograft half-life in black recipients ($P = 0.0002$), but not in white recipients ($P = 0.84$). Allograft survival was eight times shorter in hypertensive black (3.1 ± 0.7 years) than in hypertensive white recipients (24.6 ± 7 years). In contrast, allograft survival was not statistically different between normotensive black and white patients. In conclusion, the presence of poorly controlled systemic hypertension, early after renal transplantation, correlates with poor allograft survival in black recipients. Thus, systemic hypertension may explain, in part, differences in renal allograft survival between black and white patients.

Over the last 20 years, renal allograft survival rates during the first year after transplantation have improved dramatically. In contrast, the rate of decline in the number of functioning renal allografts beyond one year post-transplant has improved little in the recent past [1, 2]. The two leading causes of late renal allograft loss are patient death and chronic transplant rejection (CTR). Despite new immunosuppressive medications and regimens, the incidence of CTR remains unchanged, and long-term patient survival has improved little since 1985 [1–3]. Clearly, future improvements in renal allograft survival will depend on a better understanding and treatment of CTR and in the prevention of both CTR and patient death.

CTR is an ill-defined entity characterized clinically by progressive deterioration of renal allograft function late after transplantation and, pathologically, by interstitial scarring, tubular atrophy, fibrointimal hyperplasia of blood vessels, and glomerulosclerosis [3, 4]. These diagnostic criteria are non-specific, and consequently it is likely that several pathogenic mechanisms contribute to the development of CTR. For example, acute rejection episodes [2, 5–7] and histocompatibility (HLA) mismatching [8, 9] correlate with the development of CTR, suggesting that immunologic mechanisms contribute to the pathogenesis of CTR. Nonimmunologic mechanisms may also play a role in the pathogenesis of CTR [2, 10]. Thus, it has been postulated that reductions of renal mass, secondary to any etiology, may lead to glomerular hypertension, hyperfiltration and hypertrophy, alterations that under other clinical and experimental circumstances may lead to progressive glomerular damage and loss of renal function [10]. In addition, the prolonged use of cyclosporine (CsA) may be associated with progressive renal allograft damage [11, 12]. In contrast, recent studies did not demonstrate a progressive deterioration of glomerular filtration rate in renal allograft recipients treated with CsA [13].

In some patients the treatment of CTR, once the serum creatinine begins its progressive rise, is only effective in slowing down the progression of the disease [14–16]. Thus, a more successful therapeutic approach to CTR will require a better understanding of its pathogenesis and an early diagnosis. In the present study we tested the postulate that long-term renal allograft survival can be predicted by clinical variables during the first six months after renal transplantation. Furthermore, we postulate that systemic hypertension may be a risk factor for renal allograft loss. Previous studies have shown that systemic hypertension is common after transplantation [17] and that poorly controlled blood pressure, beyond one year after transplantation, is associated with poor allograft survival [14, 18, 19]. However, to

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our knowledge, no previous study has evaluated whether hypertension, early after transplantation, correlates with long-term renal allograft survival, nor whether there is an association between systemic hypertension and the survival of renal allografts in black and white recipients. The postulate that systemic hypertension may be particularly deleterious for the renal allografts in black recipients is suggested by the higher incidence of hypertensive nephrosclerosis in black patients [20], and it is indeed possible that allograft nephrosclerosis has a negative impact on the survival of renal transplants in black recipients.

Methods

Patient selection

The present study is based on a retrospective analysis of clinical records from 547 patients who received their first cadaveric (CAD) renal transplant at The Ohio State University between September 1982 to July 1990, at least three years before the initiation of the present study. All patients were treated with a uniform immunosuppression protocol that included [21], in the immediate post-transplant period, Minnesota anti-lymphocyte globulin at a dose of 15 mg/kg for at least five days, prednisone starting at 2 mg/kg p.o., and azathioprine at 1 to 2 mg/kg. Cyclosporine (CsA) was initiated at a dose of 8 to 10 mg/kg p.o. when the serum creatinine reached a concentration of 2.5 mg/dl. Subsequently, the CsA dose was adjusted downward if the serum creatinine concentration increased. Based on previous studies [22], no rigid HLA matching criteria were used to allocate renal allografts to particular recipients. Ninety-three percent of donors were Caucasians.

Acute transplant rejection (ATR) was diagnosed in all patients who had acute deterioration of renal allograft function and demonstrated, by kidney biopsy, the presence of ATR [4]. Because the purpose of the present study is to assess the predictive value of clinical events during the first six months post-transplant, only those ATR episodes that occurred during those first six months were analyzed as risk factors for graft losses that occurred beyond six months post-transplant. The return of a patient to hemodialysis or peritoneal dialysis on a permanent basis was considered as an allograft loss. Patients dying with functioning allografts were not considered as allograft failures; that is, data were right censored at patient death.

Systemic blood pressures (BP) were measured by the patients at home and reported to our post-transplant office. A total of 40,130 BP recordings were reported by 97% of the patients during the first six months post-transplant corresponding to a mean of 60 ± 18 SD BP determinations per patient. For each patient, the BP was calculated as the average of all mean arterial pressures [MAP = (systolic BP − diastolic BP)/3 + diastolic BP] recorded over the first six months after transplantation. We considered a MAP ≥ 107 (approximately 140/90) as indicative of hypertension. Most patients included in the study were receiving antihypertensive medications. Thus, the designation of a patient as hypertensive should be interpreted as a patient whose BP was poorly controlled on medications.

Statistical analysis

Data are expressed as the mean ± standard deviation (SD) except where designated as mean ± standard error (SEM). Student *t*-tests were used to compare two means and Fisher's exact tests were used to compare two proportions. All tests were two-tailed. Allograft survival data were analyzed with the Cox proportional hazards. The impact of covariates on graft survival was tested using first univariate and then multivariate regression analysis assuming that the rate of allograft losses beyond six months follows an exponential curve. Statistical significance was calculated as the significance of the coefficients in the proportional hazards model. Allograft half-lives, that is the number of years of follow-up after the first six months required to lose 50% of the allografts, were calculated as ln(2)/k, where k is the hazard function expressed as the fractions of grafts lost per year (number of grafts lost/total of months of follow-up for the population) [2, 23]. Survival curves were calculated using the Kaplan-Meier method [24].

Table 1. Clinical characteristics of the study population

Patient's characteristics	
Gender	
Males	330
Females	217
Race	
Whites	429
Blacks	104
Other	14
Age	43 ± 13[a] years
Follow-up (after 1st 6 months)	4.6 ± 2.6 years
Systolic BP (average 1st 6 months)	143 ± 13 mm Hg
Diastolic BP (average 1st 6 months)	82 ± 8 mm Hg
MAP (average 1st 6 months)	102 ± 8 mm Hg
CsA dose (average 1st 6 months)	6.2 ± 1.4 mg/kg/day

[a] Values represent means ± SD.

Results

Patient characteristics

Table 1 displays the characteristics of the patient population. Ninety-two patients (17%) died during the follow-up period. Ninety-three grafts (17%) were lost after a mean follow-up of 33 ± 25 months (range 6 to 104 months). During the first six months post-transplant, 234 patients (43%) had ATR episodes. Of those patients, 107 (20% of the total population) had one ATR, 58 patients (11%) had two, and 59 patients (13%) had three or more.

Relationships between long-term graft survival and clinical parameters during the first six months post-transplant

Table 2 displays the univariate and multivariate analysis of early post-transplant clinical parameters versus long-term allograft survival. As can be seen by multivariate regression analysis, four variables predicted the loss of renal allograft: higher serum creatinine concentration six months after transplantation (SCr_{6mo}) ($P < 0.0001$); more ATR episodes during the first six months post-transplant ($P < 0.0001$); black recipient race ($P = 0.007$); and younger recipient age ($P = 0.01$). It should be noted that MAP was significantly associated with allograft survival when considered in a univariate analysis but not when it was considered in a multivariate analysis together with the recipient race.

The SCr_{6mo} concentration increased progressively in patients with increasing numbers of ATR episodes ($r = 0.346, P < 0.0001$); however, neither variable completely explained the effect of the other on allograft survival. This is best demonstrated in Figure 1

Table 2. Relationship between clinical parameters collected during the first 6 months after transplant and long-term allograft survival

Parameter	Regression analysis	
	Univariate	Multivariate
Recipient gender	0.3[a]	—
Recipient age	0.003	0.01
Recipient race	0.007	0.007
MAP (1st 6 months)	0.002	0.08
HLA matching (AB+DR)	0.3	—
ATR (1st 6 months)	<0.0001	<0.0001
CsA dose	0.01	0.14
Cr_{6mo}	<0.0001	<0.0001

[a] *P* values < 0.05 were considered as statistically significant

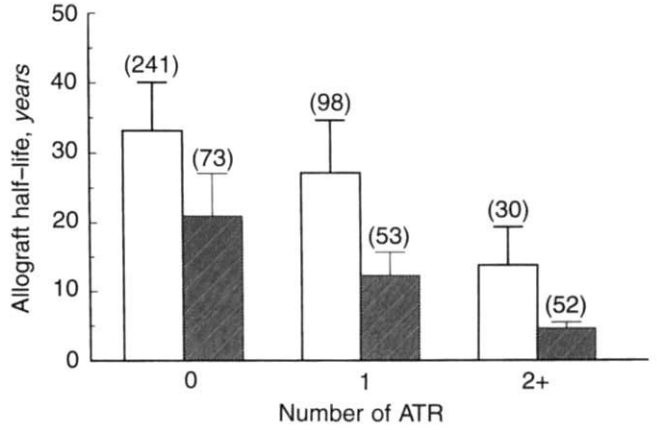

Fig. 1. *Relationships between SCr_{6mo}, ATR number and renal allograft survival, the latter expressed as allograft half-life (mean ± SEM, y axis).* The number of ATR, 0, 1, or 2 and more ATR (2+), is displayed in the x axis. Patients are subdivided into two groups: those with SCr_{6mo} < 2 mg/dl (□) and patients with SCr_{6mo} ≥ 2 mg/dl (▨). Numbers in parenthesis above the bars represent the numbers of patients in each group.

which displays allograft survival, expressed as allograft half-life, in patients with zero, one, or two or more episodes of ATR and a SCr_{6mo} lower or higher than 2 mg/dl. As can be seen in Figure 1, increasing numbers of ATR episodes were associated with a progressive decline in allograft half-life both in patients with SCr_{6mo} <2 mg/dl and in patients with SCr_{6mo} ≥2 mg/dl (P < 0.0001 both groups). In addition, patients with a SCr_{6mo} ≥2 mg/dl demonstrated a lower allograft half-life than patients with SCr_{6mo} <2 mg/dl, even when patients had the same number of ATR episodes (P < 0.0007) (Fig. 1). Although not shown here, allograft half-lives did not differ significantly between patients with two ATR and those with more than two ATR.

The effects of race and systemic hypertension on long-term allograft survival

The recipient race was a major predictor of allograft survival. For example, graft losses occurred in 34 out of 104 (33%) black recipients and in 59 out of 429 (14%) white recipients (P = 0.00007). Expressed in other terms, the calculated allograft half-life was 7.7 ± 1.3 SEM years in black recipients and 24.1 ± 3 years in white recipients (P < 0.0001). The study population included 14 transplant recipients who were not African American or Caucasian, a number insufficient to analyze the relationship between these other races and allograft survival.

Table 3. Prevalence of factors potentially associated with poor allograft survival in black and white recipients

Parameter	Recipient race		
	African American	Caucasian	*P*
SCr_{6mo}, *mg/dl*	2.0 ± 1.4[a]	1.8 ± 0.7	0.04
Number of ATR/patient	1.1 ± 1.6	0.9 ± 1.5	NS[e]
Recipient's age	44.3 ± 12	42.4 ± 14	NS
Delayed graft function[b]	11%	6%	NS
HLA matching (A,B)[c]	0.9 ± 0.9	1.4 ± 1.1	0.0001
HLA matching, (DR)[c]	0.4 ± 0.6	0.6 ± 0.7	0.001
CsA dose, *mg/kg*[d]	6.3 ± 1.5	6.2 ± 1.3	NS
CsA level, *ng/ml*[d]	73 ± 52	66 ± 48	NS
Diabetes, %	24%	23%	NS
MAP, *mm Hg*[f]	104.7 ± 7.6	102 ± 7.5	0.001

[a] Values represent means ± SD.
[b] Delayed graft function is defined as the need of hemodialysis, for any period of time, during the first 2 weeks following transplantation.
[c] Average number of HLA matches between donor and recipient.
[d] Average dose, or level, of CsA during the first six months after transplantation.
[e] NS is Not statistically significant.
[f] Average MAP during the first 6 months of transplantation.

In an attempt to explain racial differences in allograft survival, we examined the presence of variables potentially associated with poor allograft outcomes in black and white recipients (Table 3). Among those variables, the SCr_{6mo} concentration was significantly higher in black than in white patients, and HLA matching was significantly worse in black than in white patients. However, by multivariate analysis, these differences explained little of the effects of recipient race in allograft survival. In addition, the six month average MAP was significantly higher in black recipients (104.7 ± 7.6 mm Hg) than in white recipients (102 ± 7.5 mm Hg) although the difference was small. There were no differences between black and white recipients in the number of ATR episodes per patient, the recipient's age, the incidence of delayed allograft function, the dose of CsA, the average CsA levels for the first six months post-transplant, and the percentage of patients with diabetes (Table 3). Furthermore, there was no objective evidence of differences in patient compliance between black and white recipients. Thus, (1) the number of CsA level determinations per patient, during the first six months post-transplant, was not different in black (15.8 ± 14) or white recipients (15.8 ± 13); (2) The number of times that the CsA level was below the detectable range for the assay was also not different in black patients (9% of all determinations) and white patients (12%); (3) 96% of black recipients and 96.5% of white recipients recorded their BP at home and reported those results to the post-transplant office; and (4) the number of BP determinations per patient was similar in black (62 ± 24 measurements per patient) and white recipients (69 ± 20).

Based on the results noted above, we performed an analysis of risk factors for allograft loss independently in black and in white recipients. Table 4 summarizes the results of this analysis. In white recipients, as in the overall population, the following variables predicted the loss of the allograft: an elevated SCr_{6mo}; more ATR episodes during the first six months; and a younger recipient. In black recipients an elevated SCr_{6mo} and a younger recipient were

Table 4. Relationships between clinical variables during the first 6 months after transplantation and allograft survival in black and white recipients

Parameter	White recipients		Black recipients	
	Univariate	Multivariate	Univariate	Multivariate
Recipient gender	0.17[a]	—	0.86	—
Recipient age	0.013	0.03	0.008	0.006
SCr_{6mo}, *mg/dl*	<0.0001	<0.0001	<0.0001	<0.0001
Number of ATR	<0.0001	0.001	0.07	—
MAP (average 1st 6 months)	0.15	—	<0.0001	0.0009
HLA matching	0.88	—	0.45	—
CsA dose	0.06	—	0.2	—

[a] *P* values derived from Cox regression analysis

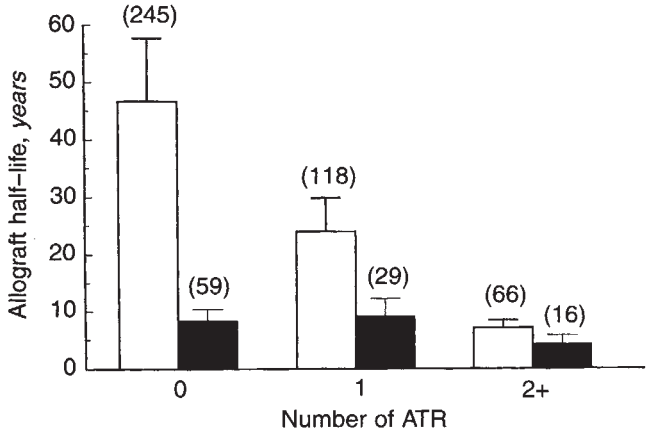

Fig. 2. *Relationships between ATR number, race and renal allograft survival, the latter expressed as half-life (mean ± SEM, y axis), in white (□) and black recipients (■).* Numbers in parenthesis above the bars represent the numbers of patients in each group.

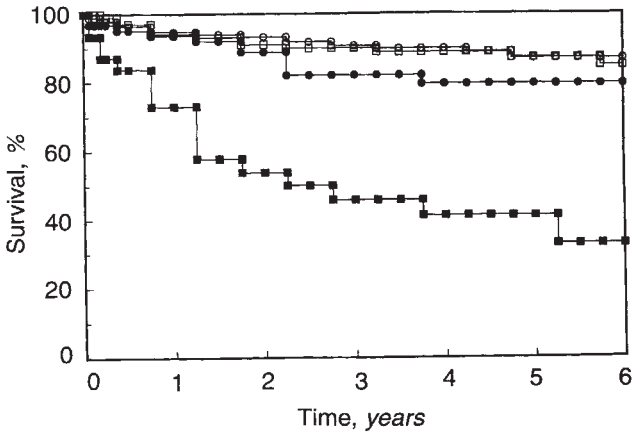

Fig. 3. *Kaplan-Meier plots of renal allograft survival in normotensive Caucasians (MAP < 107) (○----○), hypertensive Caucasians (MAP ≥ 107) (□----□), normotensive African American (●----●), and hypertensive African American (■----■).*

also associated with a poor allograft outcome. However, the number of ATR was not statistically related to allograft survival in black recipients. Furthermore, the allograft survival in black recipients was also adversely affected by poorly controlled systemic hypertension during the first six months following transplantation.

The relationship between ATR number and allograft survival in black and white recipients is re-examined in Figure 2. In white recipients, increasing numbers of ATR were associated with a progressive decline in allograft half-life ($P < 0.0001$). In contrast, the same relationship was not demonstrable in black recipients ($P = 0.21$). It is interesting to note that the largest difference in allograft survival between black and white recipients occurred in those patients who had no ATR episodes ($P < 0.0001$). Indeed, in patients who had two or more ATR episodes, the allograft survival was not statistically different between black and white recipients. These results suggest that factors other than number of ATR are important determinants of the difference in allograft survival between black and white recipients.

Based on the above observations, we next assessed the effects of poorly controlled systemic hypertension on renal allograft survival in black and in white recipients. The prevalence of poorly controlled hypertension was not significantly different in black (33%) and white recipients (26%). However, the six month average MAP was significantly higher in black than in white patients (Table 3), and hypertensive black recipients had significantly higher blood pressure levels than hypertensive white recipients (112.8 ± 5.1 and 110.6 ± 3.7 mm Hg, respectively) ($P = 0.009$). Figure 3 displays Kaplan-Meier allograft survival curves in black and in white recipients subdivided according to the presence or absence of hypertension. It can be seen that hypertensive black recipients had significantly lower allograft survival than the three other groups of patients ($P < 0.0001$ vs. all groups). In contrast, there were no significant differences in allograft survival among normotensive black recipients and normotensive or hypertensive white recipients.

The relationship between poorly controlled hypertension and allograft survival in black recipients was not due to poor compliance in this particular group of patients. Thus, objective parameters of patient compliance (including number of CsA level determinations per patient, number of times that the CsA level was below detectable levels, percent of patients reporting BP, and number of reported BP per patient) were not significantly different between hypertensive black recipients and other groups of patients (data not shown).

Discussion

The present analysis identified risk factors present during the first six months after renal transplantation that predict the loss of cadaveric renal allografts during long-term follow-up. Among those risk factors, we showed that the presence of poorly controlled systemic hypertension early after transplantation is associated with poor allograft survival in black recipients. Furthermore, the present results support the postulate that the relationship between hypertension and poor survival is due to the deleterious effects of hypertension on the renal allograft. For example, the relationship between blood pressure and graft survival was statistically independent of renal function (Table 4) and was demonstrated only in black recipients. The postulated role of hypertension on renal allograft survival in black recipients is also consistent with the observation that hypertensive nephrosclerosis of native kidneys is more common in African Americans than in Caucasians [20]. It has been suggested that the racial

disparity in the prevalence of hypertensive nephrosclerosis may be due to higher levels of blood pressure in black than in white patients, racial differences in the characteristics of hypertension, and/or racial differences in the renal responses to hypertension [20]. The present studies may help clarify these mechanisms. Thus, in the present patient population MAP levels were higher in hypertensive black recipients than in white recipients. However, that small difference (mean of 2 mm Hg) cannot explain the striking racial differences on the effects of hypertension on renal allograft survival. Furthermore, 93% of black recipients in the present study received kidneys from white donors. Thus, the poor allograft outcomes in hypertensive black recipients cannot be ascribed to a special sensitivity of the kidney of African Americans to hypertension. Supporting this conclusion, analysis of large databases did not show a significant impact of donor race on long-term allograft survival [2].

The lack of statistically significant correlation between MAP and renal allograft survival in white recipients should be interpreted with caution. We believe that these data indicate not that hypertension is unimportant in white recipients, but rather that other factors are relatively more important determinants of allograft survival in Caucasians. Indeed, we believe that hypertension should be treated aggressively in any allograft recipient. In the present study we did not do a detailed analysis of the antihypertensive medications used in our patients. However, the large majority of transplant patients in our institution are treated with primarily with diuretics and calcium channel blockers, and angiotensin converting enzyme inhibitors are avoided early after transplantation.

Previous studies suggested that racial differences in allograft survival may be explained, in part, by immunologic differences between black and white recipients [25]. Indeed, in this patient population there were significant racial differences in HLA matching between black and white recipients. However, the present analysis does not support the contention that these HLA matching differences explain the poor allograft outcomes of black recipients. In fact, in the present study HLA matching did not correlate with allograft survival in either black or white patients. These results are in contrast with previous studies [25], and this discrepancy may be due to the fact that our patients were poorly HLA matched, thus limiting the power to detect the effects of HLA matching on allograft survival. Also, against the contention that racial differences in allograft survival are mainly due to immunologic differences, is the observation that the number of ATR was not different in black and in white recipients. In fact, the most striking racial difference in allograft survival was demonstrated in individuals who never had an ATR episode. Previous studies agree with our conclusion that HLA matching cannot explain the shorter allograft survival in African Americans compared to Caucasians [26, 27]. In addition, this and other studies have identified additional factors that may partially explain racial differences in allograft survival. Those factors include an effect due to the transplant center, socioeconomic factors, recipient age, and patient compliance [25, 28–30]. The results of the present single center study suggest that the relationship between poorly controlled hypertension and allograft survival in black patients cannot be attributed to differences in the recipient's age or the patient's compliance. The present analysis is consistent with the postulate that several pathogenic events participate in the development of CTR. Furthermore, it is possible that the relative importance of each these pathogenic factors may vary among transplant centers due to differences in the patient population and/or clinical practices.

We and others have previously demonstrated that increasing numbers of ATR have a negative impact on long-term renal allograft survival [2, 5, 6]. The present analysis extends those observations by demonstrating that allograft survival is particularly poor in those individuals who have both ATR and an elevated SCR_{6mo}. In fact, the present study indicates that SCR_{6mo} prognosticates allograft survival independently from ATR number. This concept is also supported by previous studies showing that the S_{Cr} concentration on discharge from the hospital after renal transplantation predicts allograft survival [31, 32]. The reasons for the relationship between SCr_{6mo} and allograft survival may vary according to the etiology of the elevated SCr_{6mo}. For example, in some patients an elevated SCr_{6mo} may be due to allograft damage that occurred in the past, perhaps at the time of transplantation, or may be related to preexisting pathology in the donor organ. In those patients, the correlation between SCr_{6mo} and allograft survival may be due to the long-term deleterious effects of the hemodynamic adaptation to reduced functional renal mass [10]. In other patients, a persistently elevated S_{Cr} may be an indicator of ongoing immunologic and/or non-immunologically mediated allograft damage which eventually results in allograft loss. For example, an elevated S_{Cr} early after transplantation may be indicative of ongoing subclinical episodes of ATR [33], CsA toxicity, and/or hypertensive nephrosclerosis. Based on these considerations, we believe that persistent elevations in S_{Cr} (>2 mg/dl) early after transplantation should be investigated, and that investigation may require the performance of a kidney biopsy.

Previous studies showed that at the time of diagnosis, patients who had CTR were taking a lower dose of CsA than were those patients without evidence of CTR [5]. The present analysis cannot evaluate this relationship because in our transplant program the dose of CsA is adjusted according to the serum creatinine level, and consequently patients with high creatinine levels are treated with lower CsA doses.

The findings of the present study and other studies [31, 32] highlight the concept that the pathogenic mechanisms responsible for CTR are initiated early after transplantation. Consequently, clinical variables, such as those described here, can be used to identify patients at higher risk for CTR early after transplantation. This early identification will allow us, in the future, to perform prospective studies to test the effectiveness of preventive measures and therapeutic maneuvers for CTR. This study also suggests that BP control after transplantation may have profound beneficial effects in the survival of cadaveric renal allografts in black recipients.

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Reprint requests to Fernando G. Cosio, The Ohio State University, Division of Nephrology, N210 Means Hall, 1654 Upham Drive, Columbus, Ohio 43210-1228, USA.

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