

RACIAL DIFFERENCES IN THE SURVIVAL OF CADAVERIC RENAL ALLOGRAFTS

Overriding Effects of HLA Matching and Socioeconomic Factors

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Abstract Background. The long-term survival of cadaveric renal allografts is lower in black recipients than in white recipients, although the one-year graft survival is similar in these racial groups. We sought to determine what factors account for this disparity.

Methods. We studied 100 consecutive recipients of primary cadaveric renal allografts (57 were black and 43 white) at least 1 year after transplantation (mean, 40 months); all had received identical immunosuppressive therapy. We evaluated differences in the cause and duration of end-stage renal disease, the number of pretransplantation transfusions, age, matching for HLA-A, B, and DR antigens, race of the donor, insurance coverage, and compliance to assess their effect on graft survival in both groups.

Results. Allograft survival after one year was significantly lower in black than in white patients ($P = 0.025$). According to univariate analysis, only the recipient's age at transplantation, the number of mismatches for HLA antigens, the type of insurance coverage, the source of referral for transplantation, and the degree of compliance cor-

related significantly with the rate of graft survival. The frequency of all variables that reduced graft survival was higher among the blacks. According to proportional-hazards analysis, the only factors contributing to a lower rate of graft survival were age of less than 30 years at transplantation (relative risk, 2.3; 95 percent confidence interval, 1.3 to 4.6), mismatches for all six HLA antigens as compared with three or fewer mismatches (relative risk, 5.6; 95 percent confidence interval, 3.3 to 9.6), and coverage by Medicaid or Medicare (relative risk, 2.2; 95 percent confidence interval, 1.5 to 3.2). Race had no additional effect. Noncompliance was more frequent among blacks (16 percent vs. 2 percent) and could substitute for insurance status in the model.

Conclusions. When immunosuppression is equivalent in black and white transplant recipients, apparently race-related differences in the long-term survival of renal cadaveric allografts appear to be related to other factors that affect graft survival unfavorably, notably poor HLA matching and unfavorable socioeconomic factors. (N Engl J Med 1992;327:840-5.)

THE survival of cadaveric renal allografts is significantly lower in black transplant recipients than in white recipients.^{1,2} Before cyclosporine became available, the lower rate of graft survival in blacks was related to poorer HLA matching, unfavorable socioeconomic factors, and differences in immunologic responsiveness.³ The introduction of cyclosporine led to improvement in graft survival in both blacks and whites and a narrowing of the difference between the two races.³

In a recent review,² we found that the routine use of antithymocyte globulin in recipients of primary cadaveric renal allografts, together with cyclosporine in a triple-drug or quadruple-drug regimen, eliminated the differences in one-year allograft survival between black and white patients, but that long-term allograft survival in blacks remained significantly lower than that in whites. Differences in immunologic responsiveness, therefore, might be responsible for the unequal one-year survival rates, but other factors might be especially important in long-term graft survival. We undertook the present study to determine whether any of the factors previously reported to influence differences between blacks and whites in one-year survival of primary cadaveric renal allografts also influenced differences between these groups in long-term graft survival (survival for two to five years), either alone or in conjunction with other variables.

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METHODS

All recipients of first cadaveric renal allografts transplanted at the University of Mississippi Medical Center between January 1985 and April 1991 who received cyclosporine as part of their immunosuppressive regimen and had undergone transplantation at least 1 year previously (mean follow-up [\pm SD], 40 ± 17 months) were included in the study. Immunosuppressive therapy³ consisted of methylprednisolone (1 g on the day of transplantation, 500 mg the next day, and 250 mg on the second day after transplantation), azathioprine (3 mg per kilogram of body weight on the day of transplantation, followed by 2 mg per kilogram per day thereafter, with adjustment of the dose if leukopenia and thrombocytopenia occurred), and prednisone (100 mg per day, starting on the second post-transplantation day, with reduction of the dose by 10 mg every other day to 50 mg per day, and then by 5 mg every other day to a maintenance dose of 25 mg per day). Cyclosporine (6 mg per kilogram per day in divided doses) was administered when the allograft began to function, as demonstrated by an increase in urine volume to more than 1500 ml per day and a decrease in serum creatinine concentration, without dialysis, to less than 4 mg per deciliter (350 μ mol per liter). If allograft function was delayed, rabbit antithymocyte globulin was given until renal function was established, as noted above, and then for two days after the initiation of cyclosporine.

We collected data on the following: the recipient's race and the donor's race, the cause and duration of end-stage renal failure, the number of pretransplantation transfusions, the percentage of a panel of lymphocytes with different antigenic properties with which serum obtained from the recipient at the time of transplantation reacted (percentage of panel-reactive antibodies), the total number of mismatches for HLA-A, B, and DR antigens, the total number of mismatches for Lewis antigens, the dialysis unit referring the patient for transplantation, socioeconomic status, and compliance.

The patients' insurance coverage at the time of transplantation was used as a rough guide to their socioeconomic status and access to medications and to follow-up care. On the basis of this information, the recipients were divided into three coverage groups: those covered by Medicaid with or without Medicare, those covered by Medicare only, and those covered by private insurance

with or without Medicare. Their actual socioeconomic status was not retrospectively evaluated.

We assumed that patients with both Medicare and private insurance would have the highest socioeconomic status, the most education, and the greatest potential for compliance, and that those with Medicaid, with or without Medicare, would have the lowest socioeconomic status, since their income would have had to be less than \$6,864 per year per person or \$9,120 per year per family for them to qualify for this coverage. Patients with only Medicare were assumed to be intermediate in terms of socioeconomic status and education, but to have the greatest burden of cost sharing, especially after the first year. We did not determine whether the status of any patient subsequently changed. Noncompliance with therapy was indicated by one or more of the following: three or more consecutive missed clinic visits; unmeasurable blood cyclosporine concentrations on two consecutive visits, without other explanation; or leaving the hospital against medical advice. Ten patients met these criteria, three of whom also abused drugs overtly. Two of the latter died as a consequence of drug abuse, and one returned to dialysis because of chronic graft rejection. Lesser degrees of noncompliance were not evaluated.

The duration of graft survival was defined as the interval between transplantation and the reinitiation of dialysis or death. Only one patient was totally lost to follow-up after two years. Data on six patients were obtained from their referring dialysis unit after the third year after transplantation, and follow-up data on all other patients (93 percent) were obtained from our clinic.

The chi-square test was used to analyze differences in outcome,⁴ and Student's t-test to compare group means.⁵ Survival curves were constructed with the Kaplan–Meier method⁶ and were compared by the log-rank test.⁷ Linear-regression analysis was performed according to standard methods, and significance was assessed as described by Shavelson.⁸ Multivariate analysis of demographic and clinical factors prognostic of graft survival was performed with proportional-hazards analysis, in which both forward and backward stepwise elimination was used to select variables for the model.⁹

RESULTS

Characteristics of the Study Groups

The demographic and clinical characteristics of the 57 black and 43 white graft recipients who met the study criteria are shown in Table 1. The blacks differed significantly from the whites only in the total number of mismatched HLA antigens, the percentage of panel-reactive antibodies at the time of transplantation, and the causes of end-stage renal failure, among which hypertension was significantly more common in blacks than in whites. Although previous studies indicated that blacks waited longer for transplantation than did whites after their names were placed on a waiting list,¹⁰ we found no difference between the races when we used the initiation of hemodialysis as a starting point.

There was no difference between the races in graft survival one year after transplantation. However, long-term allograft survival (Fig. 1) was significantly lower among blacks ($P = 0.025$). Both immunologic and nonimmunologic causes of graft failure were more common among blacks than among whites at all times after transplantation, and graft loss due to acute graft rejection occurred only among blacks (Table 2).

Univariate analysis revealed that of the other factors defined in the Methods section, only age at transplantation, the number of HLA-antigen mismatches,

Table 1. Characteristics of Black and White Recipients of Cadaveric Renal Allografts.*

CHARACTERISTIC	BLACK RECIPIENTS (N = 57)	WHITE RECIPIENTS (N = 43)
Age (yr)	34±13	38±13
Sex ratio (M:F)	1.4:1	2:1
Duration of dialysis (mo)	26±25	27±36
No. of pretransplantation transfusions	3.3±2.1	3.3±1.4
Percentage of panel-reactive antibodies at transplantation	4.4±6.9	11.1±18.8†
No. of HLA-antigen mismatches/patient	4.6±1.0	3.7±1.4‡
No. of HLA-DR-antigen mismatches/patient	1.2±0.9	1.0±0.9
Lewis-antigen mismatch (%)	42	37
Donor-race ratio (white:black)	5.3:1	7.6:1
Donor age (yr)	30±16	27±15
Graft function (no. of patients)		
Immediate	31	23
Delayed	25	19
No function	1	1
Cause of end-stage renal disease (% of group)§		
Hypertension	37	12¶
Chronic glomerulonephritis	40	42
Polycystic kidney disease	4	16
Diabetes mellitus	11	12
Chronic interstitial nephritis	2	7
Hereditary or congenital disorder	7	12

*Plus-minus values are means ±SD.
 † $P < 0.025$ for the comparison with black recipients.
 ‡ $P < 0.001$ for the comparison with black recipients.
 §Percentages may not total 100 because of rounding.
 ¶ $P < 0.05$ for the comparison with black recipients.

socioeconomic status, degree of compliance, and the referring dialysis unit were also significantly related to overall graft survival. The frequency of all variables with unfavorable effects on graft survival was higher among blacks (Table 3).

As a group, patients less than 30 years old had significantly worse long-term graft survival than those 30

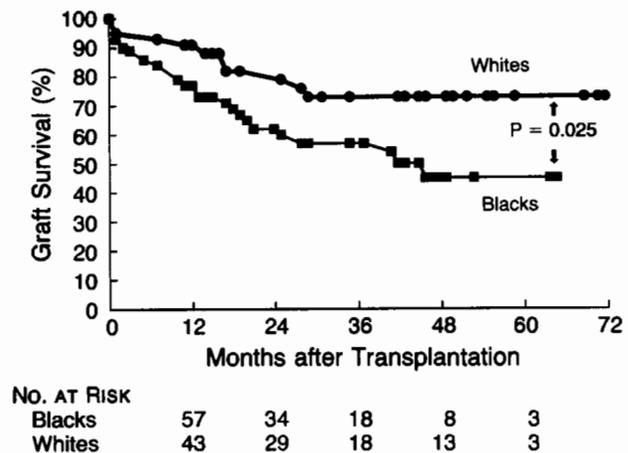


Figure 1. Long-Term Survival of Renal Allografts in Relation to the Race of Transplant Recipients.

Graft survival in black patients was significantly lower than in white patients. The numbers at the bottom of the figure are the numbers of patients at risk each year after transplantation.

Table 2. Causes of Graft Loss.

CAUSE	BLACK	WHITE
	RECIPIENTS	RECIPIENTS
	<i>no. of patients</i>	
Primary nonfunction	1	1
Vascular thrombosis	1	1
Acute rejection	8	—
Chronic rejection	7	5
Infection	3	1
Cancer	—	1
Recurrent glomerular disease	—	1
Cardiovascular disease	2	—
Substance abuse	3	—
Unknown	1	—
Noncompliance	9	1

or older (40 percent vs. 67 percent, $P < 0.025$). The percentage of blacks less than 30 years old was slightly but not significantly higher (42 percent vs. 26 percent) (Table 3).

Overall graft survival also correlated with the total number of HLA-antigen mismatches. Because the number of patients studied was small, they were grouped according to the number of HLA antigens for which donors and recipients were mismatched — i.e., six antigens, four or five antigens, or three or fewer antigens (Fig. 2). Patients with mismatches of four or five HLA antigens had significantly lower graft-survival rates than those with three mismatches or fewer; those with mismatches of six antigens fared significantly worse than all others ($P = 0.005$). Although more blacks than whites had more than three mismatches (84 percent vs. 56 percent, $P = 0.004$), there was no significant difference in graft survival between the racial groups at any level of HLA mismatching (data not shown).

Patients covered by private insurance had significantly better graft survival than those in either of the other coverage groups (Fig. 3). Patients with only Medicare coverage had the poorest outcome. There was little difference between blacks and whites except that blacks covered by Medicare or Medicaid tended to have worse graft survival (Table 3). Blacks with private insurance, like whites, had excellent five-year graft survival (blacks, 85 percent; whites, 75 percent;

Table 3. Distribution of Factors with Negative Effects on Overall Graft Survival.

NEGATIVE FACTOR	BLACK	WHITE	P VALUE
	RECIPIENTS	RECIPIENTS	
	<i>% of group</i>		
Age less than 30 yr	42	26	0.07
More than 3 HLA-antigen mismatches	84	56	0.004
Coverage by Medicaid, Medicare, or both	67	47	0.056
Noncompliance	16	2	0.054

however, a smaller percentage of blacks had private insurance (33 percent vs. 54 percent).

Noncompliance with treatment was more common among blacks than among whites (16 percent vs. 2 percent) and contributed significantly more to graft loss among blacks than among whites (36 percent vs. 10 percent, $P < 0.05$). Among blacks, noncompliance was more common in patients without private insurance (21 percent vs. 6 percent for those with private insurance, $P < 0.05$), whereas among whites all patients without private insurance complied with treatment.

Allograft survival was also significantly related to the referring dialysis unit. The five-year graft survival rate in patients from the five largest referral units ranged from 22 percent to 84 percent, correlating with a similar diversity in the distribution of patients with private insurance (range, 21 percent to 55 per-

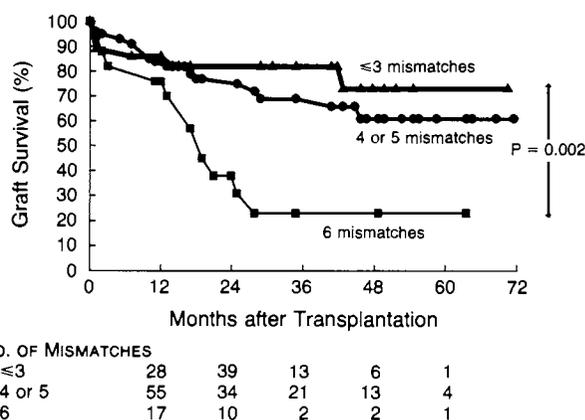


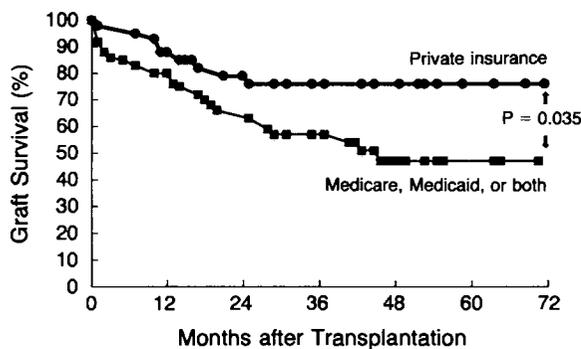
Figure 2. Long-Term Survival of Renal Allografts in Relation to the Degree of HLA Mismatching.

Graft survival was significantly higher in patients with three or fewer HLA mismatches than in those with four or five mismatches or those with six mismatches (total mismatching). Although significantly more blacks had more than three HLA mismatches, there was no difference in graft survival between blacks and whites at any level of HLA mismatching (data not shown).

When graft survival among the patients referred from each of these five units was plotted against the percentage of patients with private insurance, the correlation was linear at each post-transplantation year — e.g., as in blacks three years after transplantation (Fig. 4).

Multivariate analysis was performed with the proportional-hazards method. Before this analysis, the degree of homogeneity among the referring dialysis centers was tested by evaluating the patients' outcomes to determine whether the centers should be included as covariates. Statistically,¹¹ there were no significant differences between the referral centers, implying that most of the variation was due to other factors. The centers were therefore excluded from the model.

Analysis of the remaining covariates showed that the factors significantly associated with unfavorable long-term graft-survival rates were age of less than 30 years ($P = 0.014$), mismatching for more than three HLA antigens ($P = 0.002$), and coverage by Medicaid or Medicare ($P = 0.044$) (Fig. 5). When the values for graft survival were adjusted for the above factors, race no longer had an effect ($P = 0.37$). Thus, the difference represented by the curves in Figure 1 is misleading; graft survival is more appropriately represented by the modeled curves in Figure 5. In addition, a second model was generated with use of the degree of compliance; this model also showed that age and the number of HLA-antigen mismatches had predictive value, but that insurance coverage did not, indicating a strong interaction between this variable and the degree of compliance.



Private funds	41	29	14	11	3
Public funds	59	34	22	10	3

Figure 3. Long-Term Survival of Renal Allografts in Relation to Insurance Coverage.

Graft survival was significantly higher in patients with private insurance than in those with Medicaid, Medicare, or both. Within these coverage groups, there was no significant difference between black and white patients.

The relative risk of graft failure was calculated on the basis of the above variables. Patients less than 30 years of age had a relative risk of graft loss of 2.3 as compared with older patients (95 percent confidence interval, 1.3 to 4.6). Recipients with total HLA mismatching (all six antigens) had a relative risk of 5.6 (95 percent confidence interval, 3.3 to 9.6) as compared with recipients with three or fewer mismatches. Patients with Medicaid or Medicare coverage at the time of transplantation had a relative risk of 2.2 (95 percent confidence interval, 1.5 to 3.2) as compared with patients with private insurance.

The model generated from these calculations predicted that the best five-year graft-survival rate would be 90 percent among patients 30 years old or older with fewer than four HLA-antigen mismatches and private insurance, and that the worst rate would be 5 percent among patients less than 30 years old with six antigen mismatches and only Medicaid or Medi-

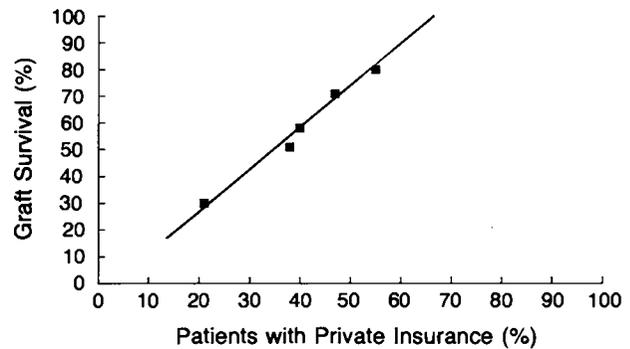


Figure 4. Renal-Allograft Survival among the Black Patients in the Five Largest Referring Dialysis Units, in Relation to the Percentage of Patients with Private Insurance.

Graft survival varied greatly among the referral units and was correlated strongly with the percentage of patients who had private insurance ($r = 0.92$, $P < 0.005$). From 8 to 16 patients were at risk for graft loss at each data point.

care insurance coverage. The race of the recipient did not significantly alter the outcome at either extreme.

DISCUSSION

In the past, when immunosuppressive treatment consisted primarily of prednisone and azathioprine, the rate of survival of cadaveric renal allografts during the first year after transplantation was lower in black recipients than in white recipients, but this difference disappeared after cyclosporine was introduced.^{3,12} The rate of long-term graft survival (survival for more than one year) is still lower in blacks, even though they receive immunosuppressive treatment equivalent to that given whites.¹³⁻²² We studied some of the factors that might contribute to this disparity in long-term graft-survival rates, realizing the limitations of con-

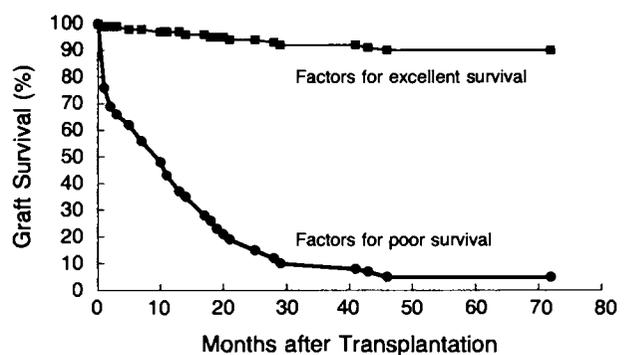


Figure 5. Renal-Allograft Survival in Relation to Factors Prognostic of Poor and Excellent Graft Survival, According to Multivariate Analysis.

Significant factors contributing to poor graft survival were age less than 30 years ($P = 0.014$), four or more HLA-antigen mismatches ($P < 0.002$), and coverage by Medicaid or Medicare insurance ($P = 0.044$). After adjustment for these factors, race no longer had an effect ($P = 0.37$). Factors contributing to excellent graft survival were age of 30 years or older, three or fewer antigen mismatches, and private insurance coverage, regardless of race.

clusions based on relatively small numbers of patients and the variability between centers in patients' characteristics.

We found that long-term graft survival was significantly lower in blacks and that noncompliance and substance abuse contributed to this lower rate. Didlake et al.²² also noted that noncompliance was more frequent among blacks, particularly during the first year after transplantation. Compliance is difficult to measure except as reflected by the blood cyclosporine concentration, and the noncompliance that we detected was undoubtedly a minimum. A number of factors contribute to noncompliance, including inability to pay for medications.²³⁻²⁷ Kalil et al.²⁴ observed that poor graft survival was associated with low income in the precyclosporine era, and suggested that an increase in the rate of substance abuse, a lower level of education, and a reduced ability to pay for medications contributed to undetected noncompliance. In our study, 40 percent of the black patients and 21 percent of the white patients were at the poverty level, on the basis of their eligibility for Medicaid at the time of transplantation. Another 26 percent of both blacks and whites had only Medicare coverage and thus found it a financial burden to pay for medications and follow-up care. Long-term graft survival was significantly lower in these patients than in patients with private insurance, and long-term graft survival in blacks with both favorable HLA matching and private insurance was equivalent to that in whites, supporting the suggestion that socioeconomic status may be the most important determinant of graft survival in blacks.²¹

Overall graft survival was also lower in patients less than 30 years old; such lower survival may be related to lower socioeconomic status as well as to a greater frequency of noncompliance and substance abuse. Poorer graft survival in younger recipients has been noted previously, especially in blacks.^{2,28}

Not surprisingly, overall graft survival was also directly related to HLA matching. Patients with mismatching for six HLA antigens had exceedingly poor graft survival, whereas those with three or fewer mismatches had excellent long-term graft survival, with no difference between the races at any level of mismatching. Blacks, however, had significantly more mismatches than whites. Although data from transplant registries^{13,14,28} continue to suggest that HLA matching affects allograft survival in patients of both races, results from individual transplantation centers generally do not support an association between matching and survival, perhaps because of differences in patients' characteristics, socioeconomic factors, and protocols for immunosuppression. Our findings suggest that HLA matching may be of greatest importance to graft survival in patients whose low socioeconomic status precludes ready access to medications and follow-up care, since we

found no HLA-associated difference in graft survival among patients with private insurance.

Multivariate analysis of risk factors affecting graft survival indicated that superior outcome was associated with older age, less HLA incompatibility, and private insurance coverage, and the analysis eliminated race as a significant variable. Thus, race had no predictive value in terms of either good or bad survival. When compliance was substituted for insurance status, the predicted survival was nearly identical, largely because noncompliance occurred almost exclusively among patients with only Medicare coverage. This finding suggests that the apparent differences in graft survival between blacks and whites receiving current immunosuppressive therapy are not related to race itself but rather to differences in other predictive variables. Poorer HLA matching and lower socioeconomic status, with greater noncompliance, emerged as the major factors predicting lower rates of long-term graft survival in blacks. That noncompliance was significantly associated with coverage by Medicare alone further suggests that noncompliance was related to a lack of funds for medications and follow-up care. That this was not the only factor is suggested by the observation that none of the white patients with only Medicare coverage had graft loss due to noncompliance.

These results require confirmation and may not agree with results at centers where the distribution of socioeconomic factors among patients is different. Nevertheless, they strongly suggest that race alone is not a determinant of long-term survival of primary cadaveric renal grafts, and they support the importance of HLA matching and socioeconomic factors. Attempts to encourage organ donation among members of minority groups, to maintain an organ-distribution system based on HLA matching, and to extend the breadth and depth of Medicare entitlements for transplant recipients may reduce apparent racial differences in renal-allograft survival.

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