The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 4, 2003 VOL. 349 NO. 10

# Chronic Renal Failure after Transplantation of a Nonrenal Organ

Akinlolu O. Ojo, M.D., Ph.D., Philip J. Held, Ph.D., Friedrich K. Port, M.D., M.S., Robert A. Wolfe, Ph.D., Alan B. Leichtman, M.D., Eric W. Young, M.D., M.S., Julie Arndorfer, M.P.H., Laura Christensen, M.S., and Robert M. Merion, M.D.

## ABSTRACT

### BACKGROUND

Transplantation of nonrenal organs is often complicated by chronic renal disease with multifactorial causes. We conducted a population-based cohort analysis to evaluate the incidence of chronic renal failure, risk factors for it, and the associated hazard of death in recipients of nonrenal transplants.

### METHODS

Pretransplantation and post-transplantation clinical variables and data from a registry of patients with end-stage renal disease (ESRD) were linked in order to estimate the cumulative incidence of chronic renal failure (defined as a glomerular filtration rate of 29 ml per minute per 1.73 $m^2$ of body-surface area or less or the development of ESRD) and the associated risk of death among 69,321 persons who received nonrenal transplants in the United States between 1990 and 2000.

### RESULTS

During a median follow-up of 36 months, chronic renal failure developed in 11,426 patients (16.5 percent). Of these patients, 3297 (28.9 percent) required maintenance dialysis or renal transplantation. The five-year risk of chronic renal failure varied according to the type of organ transplanted — from 6.9 percent among recipients of heart–lung transplants to 21.3 percent among recipients of intestine transplants. Multivariate analysis indicated that an increased risk of chronic renal failure was associated with increasing age (relative risk per 10-year increment, 1.36; $P<0.001$), female sex (relative risk among male patients as compared with female patients, 0.74; $P<0.001$), pretransplantation hepatitis C infection (relative risk, 1.15; $P<0.001$), hypertension (relative risk, 1.18; $P<0.001$), diabetes mellitus (relative risk, 1.42; $P<0.001$), and postoperative acute renal failure (relative risk, 2.13; $P<0.001$). The occurrence of chronic renal failure significantly increased the risk of death (relative risk, 4.55; $P<0.001$). Treatment of ESRD with kidney transplantation was associated with a five-year risk of death that was significantly lower than that associated with dialysis (relative risk, 0.56; $P=0.02$).

### CONCLUSIONS

The five-year risk of chronic renal failure after transplantation of a nonrenal organ ranges from 7 to 21 percent, depending on the type of organ transplanted. The occurrence of chronic renal failure among patients with a nonrenal transplant is associated with an increase by a factor of more than four in the risk of death.

From the Scientific Registry of Transplant Recipients (A.O.O., P.J.H., F.K.P., R.A.W., A.B.L., E.W.Y., J.A., L.C., R.M.M.) and the Departments of Medicine (A.O.O., A.B.L., E.W.Y.), Biostatistics (R.A.W.), and Surgery (R.M.M.), University of Michigan, Ann Arbor. Address reprint requests to Dr. Ojo at the University of Michigan Medical School, Division of Nephrology, 3914 Taubman Ctr., Box 0364, Ann Arbor, MI 48109-0364, or at aojo@umich.edu.

N Engl J Med 2003;349:931-40.

Chronic renal failure is a recognized complication of organ transplantation.[1-8] Calcineurin-inhibitor therapy, a key component of immunosuppressive regimens for patients undergoing transplantation, has been implicated as a principal cause of post-transplantation renal dysfunction,[9,10] which may lead to severe tubular atrophy, interstitial fibrosis, and focal hyalinosis of small renal arteries and arterioles.[11-16] Furthermore, renal disease before transplantation, perioperative hemodynamic insults to the kidneys, nephrotoxic effects of other drugs, dyslipidemia, hypertension, and diabetes mellitus can all contribute to chronic renal failure in recipients of nonrenal organs.[17,18]

Renal failure after the transplantation of a nonrenal organ complicates medical management, leading to increased morbidity and mortality.[14,19-22] The incidence of chronic renal disease among recipients of nonrenal transplants varies widely, from 10 to 83 percent,[1,5,22-24] most likely owing to the lack of a standard definition of post-transplantation renal disease, differences in the types of transplantation studied, and variable periods of follow-up. Furthermore, occurrences of reversible postoperative acute renal failure are included in some reported estimates.

Reports of the progression of chronic renal failure to end-stage renal disease (ESRD) in recipients of nonrenal transplants have been contradicted by some reports suggesting a self-limited decrease in renal function without a measurable effect on patient outcomes.[2,6,11,15,25-28] We performed a population-based cohort analysis involving recipients of heart, lung, liver, and intestine transplants who were included in the Scientific Registry of Transplant Recipients (SRTR) in order to determine the incidence of chronic renal failure, the risk factors for this condition, and the risk of death associated with it and to describe the outcomes of approaches to renal replacement (dialysis or kidney transplantation).

## METHODS

### SOURCES OF DATA

Our study was based on data obtained from the SRTR, the Centers for Medicare and Medicaid Services (CMS), and the Death Master File of the Social Security Administration (SSA). The SRTR maintains a data base of all candidates for and recipients of solid-organ transplants in the United States. Patients on waiting lists for organ transplantation and those who receive organ transplants are tracked on a periodic basis with the use of data-collection forms completed by organ-transplantation programs and submitted to the Organ Procurement and Transplantation Network. These follow-up data, in addition to data from the network regarding patients on waiting lists and the allocation of organs, are included in the SRTR data base. The SRTR supplements information on vital status with data on deaths from the SSA's Death Master File and the Medicare Beneficiary Database maintained by the CMS. Data collection by the SRTR is exempt from oversight under the "public benefit or service program" provisions of the Code of Federal Regulations (45 CFR 46.101[b][5]), as approved by the institutional review board of the Health Resources and Services Administration of the Department of Health and Human Services.

The Death Master File includes updated information on all participants in the Social Security system. Information on deaths reported to the SSA for the administration of the death, disability, and retirement benefit programs is kept in the Death Master File data base.

The CMS maintains a data base of all patients treated for ESRD in the United States, which includes information about demographics, treatment, hospitalization, and costs for Medicare beneficiaries and other patients with ESRD who have received maintenance renal-replacement therapy.[29] This data base also includes records of any changes in vital status or method of renal replacement, including kidney transplantation.

### STUDY SUBJECTS

The study population for our analysis included patients who received a heart, lung, heart–lung, liver, or intestine transplant in the United States between January 1, 1990, and December 31, 2000. This period was chosen as a period of relevant clinical-practice experience and to ensure that the follow-up information would be complete. We excluded from the analysis patients in whom the transplantation of a kidney or pancreas preceded the transplantation of a heart, lung, liver, or intestine and those who underwent combined heart–liver, liver–kidney, or heart–kidney transplantation. The sample in the analysis included 69,321 patients who received a first nonrenal solid-organ transplant during the study period. Patients entered the study on the date of the transplantation of the nonrenal organ or or-

gans and were followed until death or December 31, 2001, whichever occurred first.

We constructed an analysis file containing information on the base-line demographic and clinical characteristics of the patients. These base-line data were linked to serum creatinine levels from post-transplantation follow-up forms in order to calculate the estimated glomerular filtration rate according to the four-variable formula used in the Modification of Diet in Renal Disease Study.[30] The analysis file was linked to the ESRD data base of the CMS in order to identify patients who received renal-replacement therapy after transplantation of a nonrenal organ. The date of placement on the waiting list for kidney transplantation was tracked for patients with nonrenal transplants in whom ESRD developed. The change from dialysis to transplantation was also tracked in order to identify patients who received a renal transplant from a living donor and those who received a cadaveric kidney.

### STATISTICAL ANALYSIS

The primary end point analyzed was chronic renal failure (defined as a glomerular filtration rate of 29 ml per minute per 1.73 $m^2$ of body-surface area or less, according to the clinical-practice guidelines of the National Kidney Foundation[31]) or the onset of ESRD (as determined by the initiation of dialysis therapy or preemptive kidney transplantation). An analysis of competing risks[32] was conducted to determine the cumulative incidence of chronic renal failure after transplantation. Variables for chronic renal failure and death were used to generate a curve showing the cumulative incidence of chronic renal failure among patients with each category of transplant.

A multivariate Cox regression model was used to analyze the relation between chronic renal failure and the following covariates: age; race; sex; the presence or absence of pretransplantation hepatitis, diabetes mellitus, or systemic hypertension; the use or nonuse of a calcineurin inhibitor (cyclosporine or tacrolimus) for immunosuppressive therapy during the initial hospitalization for transplantation; the presence or absence of postoperative acute renal failure (defined as a 50 percent decrease from base line in the glomerular filtration rate or the need for one or more dialysis treatments during the initial hospitalization for transplantation); and the type of nonrenal organ transplanted and year of transplantation.

A separate time-dependent Cox regression model was used to study the long-term effect of chronic renal failure on mortality. To avoid mingling the risk of death associated with the transplantation procedure with the relation that may exist between chronic renal failure and mortality, the analysis of the risk of death associated with chronic renal failure began three months after transplantation. Patients who died within three months after transplantation of a nonrenal organ were not included in the analysis of post-transplantation death rates.

Next, we evaluated the type of renal-replacement therapy provided to patients in whom chronic renal failure developed. We estimated the probability of receipt of a kidney transplant as treatment for ESRD among patients who had received a nonrenal transplant and in the general population of patients with ESRD by using a competing-risks model adjusted for age, race, cause of ESRD, and time since the onset of ESRD.

Finally, a time-dependent Cox regression model was used to estimate the effect of kidney transplantation on mortality among recipients of a nonrenal transplant who had ESRD and were on a waiting list for a kidney. The average relative risk of death after kidney transplantation was estimated at five time points after transplantation (days 30, 90, 183, 731, and 1825) for recipients of nonrenal transplants; the reference group for this analysis was the patients who were treated with dialysis. In this analysis, adjustment was made for the duration of ESRD before placement on the waiting list, as previously described.[33,34] All reported P values are two-sided, and a P value of less than 0.05 was considered to indicate statistical significance.

## RESULTS

### BASE-LINE CHARACTERISTICS

The base-line characteristics of the recipients of nonrenal transplants are summarized in Table 1. Recipients of liver and heart transplants accounted for 53.2 percent and 34.7 percent of the patients, respectively; recipients of intestine and combined heart–lung transplants accounted for less than 1 percent each. The average age at the time of transplantation of the nonrenal organ or organs was approximately 45 years, except among recipients of intestine and heart–lung transplants (19 years and 33 years, respectively). Coexisting conditions were present before transplantation in a substantial minority of the patients; these included drug-treated hypertension (in 10.2 percent of patients), diabetes

**Table 1. Base-Line Characteristics of Recipients of Nonrenal Organ Transplants in the United States, 1990 to 2000.***

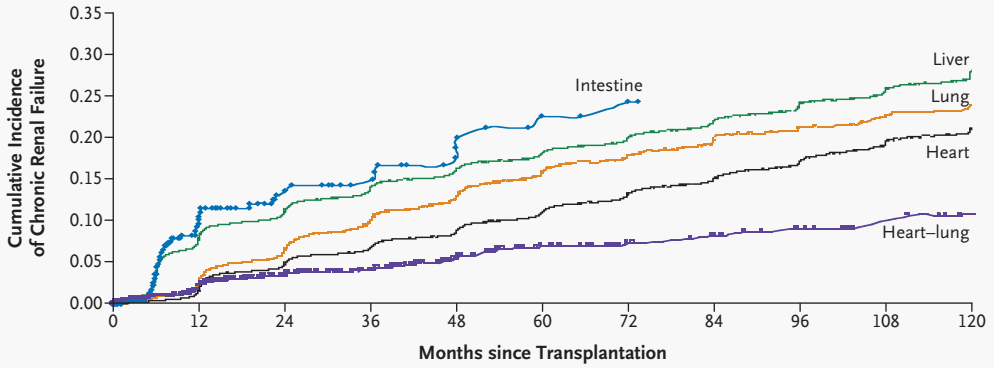
| Characteristic | Transplant Recipients | | | | | |
|---|---|---|---|---|---|---|
| | All Organs (N=69,321) | Liver (N=36,849) | Heart (N=24,024) | Lung (N=7644) | Heart–Lung (N=576) | Intestine (N=228) |
| Age — yr | 45±18 | 44±18 | 47±18 | 46±15 | 33±15 | 19±18 |
| Male sex — no. (%) | 43,688 (63.0) | 21,312 (57.8) | 18,285 (76.1) | 3729 (48.8) | 242 (42.0) | 120 (52.6) |
| Race — no. (%)† | | | | | | |
| White | 60,118 (86.7) | 31,714 (86.1) | 20,586 (85.7) | 7111 (93.0) | 518 (89.9) | 189 (82.9) |
| Black | 6,336 (9.1) | 3,039 (8.2) | 2,802 (11.7) | 433 (5.7) | 34 (5.9) | 28 (12.3) |
| Asian | 1,495 (2.2) | 1,126 (3.1) | 309 (1.3) | 45 (0.6) | 13 (2.3) | 2 (0.9) |
| Other | 1,372 (2.0) | 970 (2.6) | 327 (1.4) | 55 (0.7) | 11 (1.9) | 9 (3.9) |
| Height — cm | 161.9±29.8 | 158.5±31.7 | 164.5±30.1 | 165.5±17.1 | 157.6±24.4 | 142.0±39.4 |
| Weight — kg | 73.1±25.5 | 70.9±25.9 | 77.3±25.2 | 68.8±22.4 | 60.2±20.0 | 41.0±25.7 |
| Hypertension before transplantation — no. (%) | 7,047 (10.2) | 2,111 (5.7) | 4,343 (18.1) | 555 (7.3) | 36 (6.3) | 2 (0.9) |
| Diabetes mellitus before transplantation — no. (%) | 5,633 (8.1) | 3,347 (9.1) | 1,569 (6.5) | 675 (8.8) | 21 (3.6) | 21 (9.2) |
| Positive for hepatitis B surface antigen — no. (%) | 2,292 (3.3) | 2,069 (5.6) | 164 (0.7) | 56 (0.7) | 2 (0.3) | 1 (0.4) |
| Positive for hepatitis C antibody — no. (%) | 8,402 (12.1) | 7,901 (21.4) | 389 (1.6) | 97 (1.3) | 13 (2.3) | 2 (0.9) |
| Dialysis before transplantation — no. (%) | 1,059 (1.5) | 825 (2.2) | 230 (1.0) | 4 (0.1) | 0 | 0 |
| Pretransplantation glomerular filtration rate — no. (%) | | | | | | |
| ≥90 ml/min/1.73 m² | 35,196 (50.8) | 17,057 (46.3) | 12,497 (52.0) | 5100 (66.7) | 369 (64.1) | 173 (75.9) |
| 60–89 ml/min/1.73 m² | 17,626 (25.4) | 9,918 (26.9) | 5,558 (23.1) | 1979 (25.9) | 138 (24.0) | 33 (14.5) |
| 30–59 ml/min/1.73 m² | 13,088 (18.9) | 7,141 (19.4) | 5,373 (22.4) | 495 (6.5) | 62 (10.8) | 17 (7.5) |
| ≤29 ml/min/1.73 m² | 3,411 (4.9) | 2,733 (7.4) | 596 (2.5) | 70 (0.9) | 7 (1.2) | 5 (2.2) |
| Calcineurin inhibitor during initial hospitalization for transplantation — no. (%)‡ | | | | | | |
| Tacrolimus | 19,473 (28.1) | 16,407 (44.5) | 1,452 (6.0) | 1338 (17.5) | 86 (14.9) | 190 (83.3) |
| Cyclosporine | 41,797 (60.3) | 16,398 (44.5) | 19,196 (79.9) | 5789 (75.7) | 407 (70.7) | 7 (3.1) |
| Sirolimus treatment during initial hospitalization for transplantation — no. (%) | 590 (0.9) | 471 (1.3) | 78 (0.3) | 25 (0.3) | 2 (0.3) | 14 (6.1) |
| Year of organ transplantation — no. (%) | | | | | | |
| 1990–1993 | 20,980 (30.3) | 10,493 (28.5) | 8,490 (35.3) | 1761 (23.0) | 206 (35.8) | 30 (13.2) |
| 1994–1997 | 26,410 (38.1) | 13,780 (37.4) | 9,072 (37.8) | 3240 (42.4) | 232 (40.3) | 86 (37.7) |
| 1998–2000 | 21,931 (31.6) | 12,576 (34.1) | 6,462 (26.9) | 2643 (34.6) | 138 (24.0) | 112 (49.1) |

* Plus–minus values are means ±SD. Because of rounding, percentages may not sum to 100.
† Designations of race were submitted to the Organ Procurement and Transplantation Network by the individual transplantation centers.
‡ Data were missing for 8051 patients.

mellitus (in 8.1 percent), and hepatitis C infection (in 12.1 percent). The mean (±SD) glomerular filtration rate before transplantation was 75±31 ml per minute per 1.73 m²; the pretransplantation glomerular filtration rate was less than 60 ml per minute per 1.73 m² in 23.8 percent of the patients, and 1.5 percent of the patients had been treated with dialysis between registration for the transplantation of a nonrenal organ and the receipt of a transplant.

### INCIDENCE OF CHRONIC RENAL FAILURE

The median duration of follow-up from the time of transplantation of the nonrenal organ to the end of the cohort study was 36 months (mean, 46±38).




| No. at Risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Heart–lung | 576 | 375 | 295 | 219 | 194 | 156 | 133 | 107 | 72 | 46 | 30 |
| Heart | 24,024 | 19,885 | 17,238 | 14,687 | 12,341 | 10,022 | 7997 | 6104 | 4526 | 3096 | 1991 |
| Intestine | 228 | 152 | 110 | 84 | 57 | 33 | 23 | 13 | 8 | 5 | 5 |
| Liver | 36,849 | 28,495 | 24,041 | 19,508 | 15,724 | 12,564 | 9844 | 7345 | 5292 | 3614 | 2261 |
| Lung | 7,643 | 5,633 | 4,316 | 3,184 | 2,327 | 1,629 | 1136 | 745 | 468 | 258 | 133 |

**Figure 1. Cumulative Incidence of Chronic Renal Failure among 69,321 Persons Who Received Nonrenal Organ Transplants in the United States between January 1, 1990, and December 31, 2000.**

The risk of chronic renal failure was estimated with a noncompeting-risk model. Measurements of renal function were obtained at six-month intervals during the first year and annually thereafter.

During follow-up, chronic renal failure developed in 11,426 patients (16.5 percent). ESRD developed in 3297 of the patients with newly diagnosed chronic renal failure (28.9 percent). The risk of chronic renal failure increased over time among patients with all categories of nonrenal transplants (Fig. 1). Table 2 shows the five-year cumulative incidence of chronic renal failure for each category of nonrenal transplant, which ranged from 6.9 percent among patients with heart–lung transplants to 21.3 percent among patients with intestine transplants. ESRD occurred at a rate of 1.0 to 1.5 percent per year among patients with a nonrenal transplant.

### RISK FACTORS FOR CHRONIC RENAL FAILURE

Multivariate Cox nonproportional-hazards regression analysis revealed that the overall risk of chronic renal failure was associated with a number of variables, including the patient's age, race, and sex; the pretransplantation glomerular filtration rate; and the presence or absence of pretransplantation hypertension, diabetes mellitus, or hepatitis C infection (Table 3). When the glomerular filtration rate was analyzed as a continuous variable, a decrement of 10 ml per minute per 1.73 $m^2$ in the pretransplantation glomerular filtration rate was associated with an increase of 9 percent in the risk of chronic renal failure (relative risk, 1.09; 95 percent confidence interval, 1.07 to 1.10). Greater reductions in the pretransplantation glomerular filtration rate[31] were also associated with progressive increases in the risk of chronic renal failure. Overall, Asian patients and patients in the "other" category for race had a lower risk of chronic renal failure than white patients (relative risk, 0.77 and 0.73, respectively; $P<0.001$ for both comparisons). No independent effect of race on the risk of chronic renal failure was detected in a comparison of black and white patients.

Apart from the risk factors that were significant for all categories of nonrenal transplants, the susceptibility factors associated with individual types of nonrenal transplants varied (Table 3). In organ-specific multivariate Cox regression models, only age, sex, presence or absence of postoperative acute renal failure, presence or absence of diabetes mellitus, and the year of transplantation were significantly associated with the risk of chronic renal failure among patients with any of the four major categories of nonrenal transplants. We did not construct a separate model for patients with intestine transplants because of the relatively small number of these patients. A combined regression model was used for patients with heart transplants and those with heart–lung transplants because of the nearly identical findings for these two categories.

**Table 2. Cumulative Incidence of Chronic Renal Failure According to the Type of Transplanted Organ.***

| Type of Organ | Cumulative Incidence of Chronic Renal Failure after Transplantation | | | Relative Risk of Chronic Renal Failure (95% CI) |
|---|---|---|---|---|
| | 12 Mo | 36 Mo | 60 Mo | |
| | *percentage ±SE* | | | |
| Heart | 1.9±0.1 | 6.8±0.2 | 10.9±0.2 | 0.63 (0.61–0.66) |
| Heart–lung | 1.7±0.5 | 4.2±0.9 | 6.9±1.1 | 0.48 (0.36–0.65) |
| Intestine | 9.6±2.0 | 14.2±2.4 | 21.3±3.4 | 1.36 (1.00–1.86) |
| Liver | 8.0±0.1 | 13.9±0.2 | 18.1±0.2 | 1.00 (reference group) |
| Lung | 2.9±0.2 | 10.0±0.4 | 15.8±0.5 | 0.99 (0.93–1.06) |

* CI denotes confidence interval.

There was a record of treatment with a calcineurin inhibitor (cyclosporine or tacrolimus) during the initial hospitalization for transplantation for 88.4 percent of the patients. As compared with the patients for whom the calcineurin-inhibitor treatment status was known, those with missing or unknown data on such treatment (at the time of the initial hospitalization for transplantation) had a lower risk of chronic renal failure (relative risk, 0.87; P<0.001). Among patients who had received liver transplants, the excess risk of chronic renal failure associated with the use of a calcineurin inhibitor was greater with cyclosporine therapy than with tacrolimus therapy (relative risk, 1.25; P<0.001). In this subgroup, we found no association between sirolimus therapy and chronic renal failure. Less than 1 percent of recipients of all extrarenal organs (590 patients) received sirolimus, with or without a calcineurin inhibitor, during the initial hospitalization for transplantation.

In keeping with the well-established association between hepatitis C and various glomerulonephritides,[35] a positive result on a serologic test for hepatitis C before transplantation was significantly associated with an elevated risk of chronic renal failure (overall relative risk, 1.15; P<0.001), except among recipients of lung transplants. There was an elevated risk of chronic renal failure among patients with a previous diagnosis of hypertension (overall relative risk, 1.18; P<0.001), except among recipients of liver transplants. Diabetes mellitus was associated with chronic renal failure among patients with transplants of all categories (overall relative risk, 1.42; P<0.001). Postoperative acute renal failure (a 50 percent reduction in the glomerular filtration rate or a need for urgent dialysis treatment) occurred in 7.6 percent of the patients and was associated with an increase by a factor of more than two in the risk of chronic renal failure among patients with transplants of all categories (overall relative risk, 2.13; P<0.001).

### RISK OF DEATH AFTER CHRONIC RENAL FAILURE

The risk of death associated with the onset of chronic renal failure after the transplantation of a nonrenal organ was evaluated by means of a time-dependent Cox regression model, as described by Mauger et al.[33] and Wolfe et al.[34] In a comparison with transplant recipients who did not have chronic renal failure, and with allowance for at least three months of equivalent follow-up after transplantation, chronic renal failure was associated with an elevated risk of death after transplantation (relative risk, 4.55; 95 percent confidence interval, 4.38 to 4.74; P<0.001). The excess risk of death associated with chronic renal failure was not accounted for by the presence of ESRD alone, since patients who met the glomerular-filtration-rate criterion for chronic renal failure but in whom ESRD had not developed had a risk of death twice as high as that among transplant recipients who did not have chronic renal failure (data not shown).

### RENAL TRANSPLANTATION IN PATIENTS WITH NONRENAL ORGAN TRANSPLANTS

Forty-six percent (1516) of the patients with nonrenal transplants in whom ESRD developed were placed on a waiting list for kidney transplantation. In this subgroup, the adjusted annual incidence of kidney transplantation was 30.9 percent, as compared with 27.4 percent among all patients with ESRD on waiting lists for transplantation. The adjusted median time to kidney transplantation was 689 days for the patients who had received a nonrenal transplant, as compared with 771 days for the overall population of candidates for kidney transplants (P=0.02). Figure 2 shows the mortality rate among patients with nonrenal transplants who received a kidney transplant, as compared with patients with nonrenal transplants who were being treated with dialysis and awaiting kidney transplantation. An initial transient increase in mortality after kidney transplantation (relative risk at 30 days, 3.42; P=0.05) was followed by a progressive decrease in risk, so that 141 days after kidney transplantation, the patients who had received a kidney transplant had the same mortality rate as the patients still on

**Table 3. Risk Factors Associated with Chronic Renal Failure in Recipients of Nonrenal Organ Transplants.***

| Variable | Overall Relative Risk (95% CI) | P Value | Relative Risks in Subgroups of Recipients | | |
|---|---|---|---|---|---|
| | | | Liver Transplants | Heart and Heart–Lung Transplants | Lung Transplants |
| Age (per 10-year increment) | 1.36 (1.34–1.38) | <0.001 | 1.29 | 1.56 | 1.40 |
| Pretransplantation glomerular filtration rate | | | | | |
| ≥90 ml/min/1.73 m² | 1.00 (reference group) | | 1.00 | 1.00 | 1.00 |
| 60–89 ml/min/1.73 m² | 1.38 (1.30–1.46) | <0.001 | 1.54 | 1.16† | 1.00† |
| 30–59 ml/min/1.73 m² | 2.25 (2.12–2.39) | <0.001 | 2.54 | 1.92 | 1.00† |
| ≤29 ml/min/1.73 m² | 3.41 (3.15–3.70) | <0.001 | 3.78 | 2.82 | 1.42† |
| Missing or unknown | 1.33 (1.21–1.46) | <0.001 | 1.25 | 1.29 | 1.13† |
| Postoperative acute renal failure‡ | 2.13 (1.99–2.27) | <0.001 | 2.11 | 3.03 | 4.56 |
| Dialysis treatment before transplantation | 1.46 (1.27–1.68) | <0.001 | 1.45 | 1.25† | —§ |
| Male sex | 0.74 (0.71–0.77) | <0.001 | 0.71 | 0.78 | 0.68 |
| Race | | | | | |
| White | 1.00 (reference group) | | 1.00 | 1.00 | 1.00 |
| Black | 1.02 (0.95–1.10) | 0.57 | 1.01† | 1.05† | 0.91† |
| Asian | 0.77 (0.66–0.89) | <0.001 | 0.79 | 0.86† | 0.32† |
| Other | 0.73 (0.63–0.85) | <0.001 | 0.76 | 0.58 | 1.34† |
| Calcineurin-inhibitor treatment during initial hospitalization | | | | | |
| Tacrolimus | 1.00 (reference group) | | 1.00 | 1.00 | 1.00 |
| Cyclosporine | 1.24 (1.17–1.30) | <0.001 | 1.25 | 0.98† | 1.09† |
| Missing or unknown | 0.87 (0.80–0.95) | <0.001 | 0.63 | 1.04† | 1.10† |
| Sirolimus treatment during initial hospitalization | | | | | |
| No | 1.00 (reference group) | | 1.00 | 1.00 | 1.00 |
| Yes | 1.19 (0.94–1.52) | 0.16 | 1.21† | 1.82† | 0.36† |
| Hepatitis B | 1.06 (0.96–1.18) | 0.25 | 1.04† | 1.41† | 0.66† |
| Hepatitis C | 1.15 (1.08–1.23) | <0.001 | 1.22 | 1.34 | 1.07† |
| Hypertension before transplantation | 1.18 (1.10–1.26) | <0.001 | 1.04† | 1.24 | 1.26 |
| Diabetes mellitus before transplantation | 1.42 (1.33–1.51) | <0.001 | 1.39 | 1.51 | 1.53 |
| Year of transplantation | | | | | |
| 1998–2000 | 1.00 (reference group) | | 1.00 | 1.00 | 1.00 |
| 1994–1997 | 1.08 (1.02–1.14) | 0.008 | 1.23 | 0.80 | 0.84 |
| 1990–1993 | 1.31 (1.15–1.48) | <0.001 | 1.52 | 0.92† | 0.62 |

* Relative risks were calculated with multivariate Cox nonproportional regression models that included all variables in the table as covariates. CI denotes confidence interval.
† The relative risk was not significant (P≥0.05).
‡ Postoperative acute renal failure was defined as a 50 percent reduction from base line in the glomerular filtration rate or a need for dialysis treatment during the initial hospitalization for transplantation.
§ There were only four patients with lung transplants who had received dialysis treatment before transplantation, so an estimate of the relative risk is not available.

the waiting list. Thereafter, the patients who received a kidney transplant had a lower risk of death, which was sustained until five years after transplantation (relative risk at day 1825, 0.56; P=0.02). Because of the initial excess mortality associated with the kidney-transplantation procedure, the proportion of patients who survived in the group that received a kidney transplant did not match the proportion in the group of patients on the waiting list until 506 days after kidney transplantation.

## DISCUSSION

In our cohort study, chronic renal failure emerged as a relatively common complication in recipients of nonrenal transplants, affecting 7 to 21 percent with-

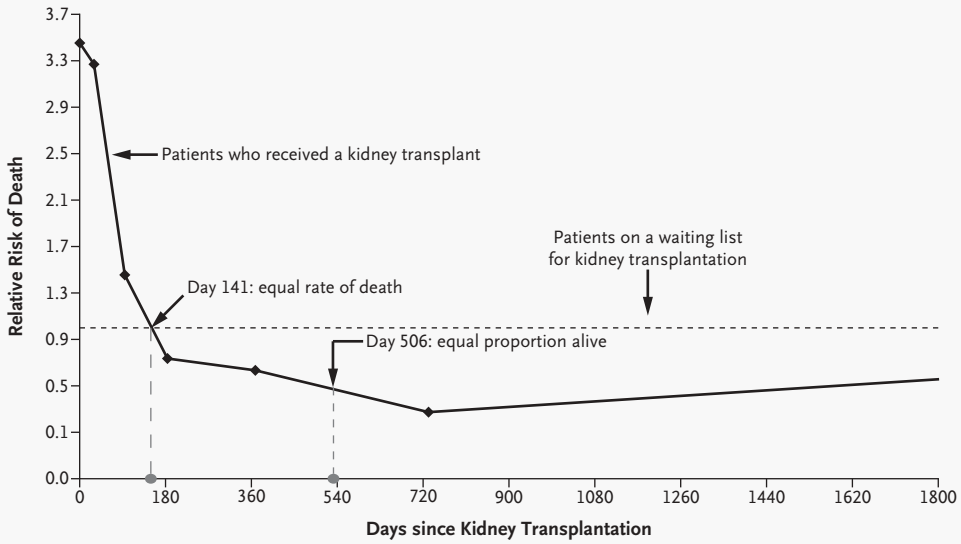



**Figure 2. Relative Risk of Death Associated with the Method of Renal Replacement (Dialysis or Kidney Transplantation) among Recipients of Nonrenal Organ Transplants Who Had Chronic Renal Failure.**

in five years after transplantation of a nonrenal organ. The risk of chronic renal failure and the need for long-term renal-replacement therapy will increase further, given the trend toward increasing longevity in the overall population of recipients of nonrenal transplants, which currently numbers more than 100,000. Such a trend has already been demonstrated in single-center studies showing an increasing rate of chronic renal failure in direct proportion to longevity among recipients of heart and liver transplants.[7,19,20,36] The potential for a greater caseload of patients with ESRD has serious fiscal implications for the ESRD program of Medicare, which currently spends $13 billion annually (approximately 6 percent of the total annual Medicare budget) on less than 1 percent of the 40 million Medicare enrollees (300,000 patients with ESRD).[29]

In our study of patients with nonrenal transplants, chronic renal failure was associated with an increase in mortality by a factor of more than four (relative risk of death, 4.55; 95 percent confidence interval, 4.38 to 4.74), which is consistent with more recent evidence of excess risk of death among patients with chronic renal insufficiency who have had an acute myocardial infarction or who have congestive heart failure.[37,38] In view of the high incidence of chronic renal failure and the excess risk of death associated with it, it seems prudent to counsel patients undergoing transplantation of a nonrenal organ about the likelihood of chronic renal failure, just as they are typically cautioned about the risks of other complications — such as post-transplantation cancer, which occurs much less frequently than chronic renal failure.

The risk of chronic renal failure in our study was higher among recipients of liver transplants who were treated with cyclosporine than among those who were treated with tacrolimus — a difference that was not evident among patients with other types of transplants. The results of studies comparing the risk of kidney failure among transplant recipients receiving cyclosporine-based immunosuppressive regimens with the risk among those receiving tacrolimus-based regimens have been contradictory.[39-43] Most comparative evaluations of calcineurin-induced nephrotoxic effects are of limited validity, because either the study patients were recipients of renal transplants (who lacked the sympathetic innervation of the allograft that has been implicated in the pathogenesis of toxic effects of calcineurin) or the study involved a switch from one calcineurin inhibitor to another after chronic renal failure had already been established.

The variability in risk among patients with different types of organ transplants in our study points to the existence of other important patient-specific and organ-specific susceptibility traits. Our data show that diabetes mellitus, hypertension, and hepatitis C

infection are independent risk factors in the aggregate, although their prevalence and effect varied according to the type of organ transplanted. For example, recipients of liver transplants had a prevalence of hepatitis C of 21.4 percent, with an associated 22 percent excess risk of chronic renal failure. In contrast, recipients of lung transplants had a prevalence of hepatitis C of about 1 percent, with no detectable associated increase in the risk of chronic renal failure. We did not measure certain cardiovascular risk factors (e.g., hyperlipidemia and insulin resistance) that are recognized side effects of immunosuppressive medications[44,45] and potential contributors to the progression of chronic renal failure in patients who have received different types of transplants.[8,20]

As in the general population of patients with ESRD,[34,46-49] the high mortality associated with ESRD was substantially mitigated by kidney transplantation among patients with nonrenal transplants in our study and in other studies.[50,51] In addition to the analysis of the influence of calcineurin inhibitors, attention to preexisting renal diseases, pretransplantation renal function, and modifiable cardiovascular risk factors might reduce the long-term risk of chronic renal failure after the transplantation of nonrenal organs.

Supported by a grant (HRSA 00-3691) from the Health Resources and Services Administration and a grant (K24 DK62234) from the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (to Dr. Ojo).

Dr. Ojo reports having received consulting fees from Novartis and lecture fees from Merck, Pfizer, AstraZeneca, and Pharmacia; Dr. Held a grant from Amgen; Dr. Port consulting fees from Optimal Renal Care and a grant from Amgen; and Dr. Wolfe a grant from PRO-West.

## REFERENCES

1. van Gelder T, Balk AH, Zietse R, Hesse C, Mochtar B, Weimar W. Renal insufficiency after heart transplantation: a case-control study. Nephrol Dial Transplant 1998;13:2322-6.
2. Waser M, Maggiorini M, Binswanger U, et al. Irreversibility of cyclosporine-induced renal function impairment in heart transplant recipients. J Heart Lung Transplant 1993;12:846-50.
3. Greenberg A, Thompson ME, Griffith BJ, et al. Cyclosporine nephrotoxicity in cardiac allograft patients — a seven-year follow-up. Transplantation 1990;50:589-93.
4. Zaltzman JS, Pei Y, Maurer J, Patterson A, Cattran DC. Cyclosporine nephrotoxicity in lung transplant recipients. Transplantation 1992;54:875-8.
5. Platz K-P, Mueller AR, Blumhardt G, et al. Nephrotoxicity following orthotopic liver transplantation: a comparison between cyclosporine and FK506. Transplantation 1994;58:170-8.
6. Pattison JM, Petersen J, Kuo P, Valantine V, Robbins RC, Theodore J. The incidence of renal failure in one hundred consecutive heart-lung transplant recipients. Am J Kidney Dis 1995;26:643-8.
7. Fisher NC, Nightingale PG, Gunson BK, Lipkin GW, Neuberger JM. Chronic renal failure following liver transplantation: a retrospective analysis. Transplantation 1998;66:59-66.
8. Sehgal V, Radhakrishnan J, Appel GB, Valeri A, Cohen DJ. Progressive renal insufficiency following cardiac transplantation: cyclosporine, lipids, and hypertension. Am J Kidney Dis 1995;26:193-201.
9. Bennett WM. Insights into chronic cyclosporine nephrotoxicity. Int J Clin Pharmacol Ther 1996;34:515-9.
10. Bennett WM, DeMattos A, Meyer MM, Andoh T, Barry JM. Chronic cyclosporine nephropathy: the Achilles' heel of immunosuppressive therapy. Kidney Int 1996;50:1089-100.
11. Myers BD. Cyclosporine nephrotoxicity. Kidney Int 1986;30:964-74.
12. Puschett JB, Greenberg A, Holley J, McCauley J. The spectrum of ciclosporin nephrotoxicity. Am J Nephrol 1990;10:296-309.
13. Iwatsuki S, Esquivel CO, Klintmalm GB, Gordon RD, Shaw BW Jr, Starzl TE. Nephrotoxicity of cyclosporine in liver transplantation. Transplant Proc 1985;17:191-5.
14. Porayko MK, Gonwa TA, Klintmalm GB, Wiesner RH. Comparing nephrotoxicity of FK 506 and cyclosporine regimens after liver transplantation: preliminary results from US Multicenter trial. Transplant Proc 1995;27:1114-6.
15. Wheatley HC, Datzman M, Williams JW, Miles DE, Hatch FE. Long-term effects of cyclosporine on renal function in liver transplant recipients. Transplantation 1987;43:641-7.
16. Young EW, Ellis CN, Messana JM, et al. A prospective study of renal structure and function in psoriasis patients treated with cyclosporin. Kidney Int 1994;46:1216-22.
17. Sehgal AR, Snow RJ, Singer ME, et al. Barriers to adequate delivery of hemodialysis. Am J Kidney Dis 1998;31:593-601.
18. Kasiske BL. Hyperlipidemia in patients with chronic renal disease. Am J Kidney Dis 1998;32:Suppl 3:S142-S156.
19. Brown RS Jr, Lombardero M, Lake JR. Outcome of patients with renal insufficiency undergoing liver or liver-kidney transplantation. Transplantation 1996;62:1788-93.
20. Wilkinson AH, Cohen DJ. Renal failure in the recipients of nonrenal solid organ transplants. J Am Soc Nephrol 1999;10:1136-44.
21. Rimola A, Gavaler JS, Schade RR, el-Lankany S, Starzl TE, Van Thiel DH. Effects of renal impairment on liver transplantation. Gastroenterology 1987;93:148-56.
22. Goldstein DJ, Zuech N, Sehgal V, Weinberg AD, Drusin R, Cohen D. Cyclosporine-associated end-stage nephropathy after cardiac transplantation: incidence and progression. Transplantation 1997;63:664-8.
23. Myers BD, Ross J, Newton L, Luetscher J, Perlroth M. Cyclosporine-associated chronic nephropathy. N Engl J Med 1984;311:699-705.
24. McCauley J, Van Thiel DH, Starzl TE, Puschett JB. Acute and chronic renal failure in liver transplantation. Nephron 1990;55:121-8.
25. Gonwa TA, Mai ML, Pilcher J, et al. Stability of long-term renal function in heart transplant patients treated with induction therapy and low-dose cyclosporine. J Heart Lung Transplant 1992;11:926-8.
26. Greenberg A, Egel JW, Thompson ME, et al. Early and late forms of cyclosporine nephrotoxicity: studies in cardiac transplant recipients. Am J Kidney Dis 1987;9:12-22.
27. McDiarmid SV, Ettenger RB, Hawkins RA, et al. The impairment of true glomerular filtration rate in long-term cyclosporine-treated pediatric allograft recipients. Transplantation 1990;49:81-5.
28. Van Buren DH, Burke JF, Lewis RM. Renal function in patients receiving long-term cyclosporine therapy. J Am Soc Nephrol 1994;4:Suppl:S17-S22.
29. Analytical methods. In: Renal Data System. USRDS 2001 annual data report: atlas of end-stage renal disease in the United States. Bethesda, Md.: National Institute of Diabetes and Digestive and Kidney Diseases, 2001:204-30.
30. Levey AS, Greene T, Kusek JW, Beck GJ, MDRD Study Group. A simplified equation to predict glomerular filtration rate from serum creatinine. J Am Soc Nephrol 2000;11:155A. abstract.

**31.** National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (K/DOQI) Advisory Board. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification: Kidney Disease Outcome Quality Initiative. Am J Kidney Dis 2002;39:Suppl 2:S1-S246.
**32.** Gray RJ. A class of k-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 1988;16:1141-54.
**33.** Mauger EA, Wolfe RA, Port FK. Transient effects in the Cox proportional hazards regression model. Stat Med 1995;14:1553-65.
**34.** Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med 1999;341:1725-30.
**35.** Baid S, Cosimi AB, Tolkoff-Rubin N, Colvin RB, Williams WW, Pascual M. Renal disease associated with hepatitis C infection after kidney and liver transplantation. Transplantation 2000;70:255-61.
**36.** Satchithananda DK, Parameshwar J, Sharples L, et al. The incidence of end-stage renal failure in 17 years of heart transplantation: a single center experience. J Heart Lung Transplant 2002;21:651-7.
**37.** Shlipak MG, Heidenreich PA, Noguchi H, Chertow GM, Browner WS, McClellan MB. Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. Ann Intern Med 2002;137:555-62.
**38.** Ruilope LM, van Veldhuisen DJ, Ritz E, Luscher TF. Renal function: the Cinderella of cardiovascular risk profile. J Am Coll Cardiol 2001;38:1782-7.
**39.** Israni A, Brozena S, Pankewycz O, Grossman R, Bloom R. Conversion to tacrolimus for the treatment of cyclosporine-associated nephrotoxicity in heart transplant recipients. Am J Kidney Dis 2002;39:E16 (Web only). (Accessed July 14, 2003, at http://www.ajkd.org.)
**40.** Khanna A, Plummer M, Bromberek C, Bresnahan BA, Hariharan S. Expression of TGF-beta and fibrogenic genes in transplant recipients with tacrolimus and cyclosporine nephrotoxicity. Kidney Int 2002;62:2257-63.
**41.** Waller JR, Murphy GJ, Metcalfe MS, Sandford RM, Pattenden CJ, Nicholson ML. Primary immunosuppression with tacrolimus is associated with a reduction in renal allograft fibrosis compared with neoral therapy. Transplant Proc 2002;34:1587-8.
**42.** Trompeter R, Filler G, Webb NJA, et al. Randomized trial of tacrolimus versus cyclosporin microemulsion in renal transplantation. Pediatr Nephrol 2002;17:141-9.
**43.** English RF, Pophal SA, Bacanu SA, et al. Long-term comparison of tacrolimus- and cyclosporine-induced nephrotoxicity in pediatric heart-transplant recipients. Am J Transplant 2002;2:769-73.
**44.** Kasiske BL. Risk factors for cardiovascular disease after renal transplantation. Miner Electrolyte Metab 1993;19:186-95.
**45.** Sakhuja V, Sharma UK, Jha V, Minz M, Chugh KS. High incidence of posttransplant diabetes mellitus in renal transplant recipients on triple-drug immunosuppression. Transplant Proc 1995;27:2728-30.
**46.** Arend SM, Mallat MJ, Westendorp RJ, van der Woude FJ, van Es LA. Patient survival after renal transplantation: more than 25 years follow-up. Nephrol Dial Transplant 1997;12:1672-9.
**47.** Brunner FP, Fassbinder W, Broyer M, et al. Survival on renal replacement therapy: data from the EDTA Registry. Nephrol Dial Transplant 1988;3:109-22.
**48.** Garcia-Garcia G, Deddens JA, D'Achiardi-Rey R, et al. Results of treatment in patients with end-stage renal disease: a multivariate analysis of risk factors and survival in 341 successive patients. Am J Kidney Dis 1985;5:10-8.
**49.** Port FK, Wolfe RA, Mauger EA, Berling DP, Jiang K. Comparison of survival probabilities for dialysis patients vs. cadaveric renal transplant recipients. JAMA 1993;270:1339-43.
**50.** Molmenti EP, Jain AB, Shapiro R, et al. Kidney transplantation for end-stage renal failure in liver transplant recipients with hepatitis C viral infection. Transplantation 2001;71:267-71.
**51.** Coopersmith CM, Brennan DC, Miller B, et al. Renal transplantation following previous heart, liver, and lung transplantation: an 8-year single-center experience. Surgery 2001;130:457-62.