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Renal Transplantation for Patients 60 Years of Age or Older

A Single-Institution Experience

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Objective
The authors reviewed renal transplant outcomes in recipients 60 years of age or older.

Background
Before cyclosporine, patients older than 45 years of age were considered to be at high risk for transplantation. With cyclosporine, the age limits for transplantation have expanded.

Methods
The authors compared patient and graft survival, hospital stay, the incidence of rejection and rehospitalization, and the cause of graft loss for primary kidney recipients 60 years of age or older *versus* those 18 to 59 years of age. For those patients ≥ 60 years transplanted since 1985, the authors analyzed pretransplant extrarenal disease and its impact on post-transplant outcome. In addition, all surviving recipients ≥ 60 years completed a medical outcome survey (SF-36).

Results
Patient and graft survival for those ≥ 60 years of age *versus* those 18 to 59 years of age were similar 3 years after transplant. Subsequently, mortality increased for the older recipients. Death-censored graft survival was identical in the two groups. There were no differences in the cause of graft loss. Those 60 years of age or older had a longer initial hospitalization, but had fewer rejection episodes and fewer rehospitalizations. Quality of life for recipients 60 years of age or older was similar to the age-matched U.S. population.

Conclusion
Renal transplantation is successful for recipients 60 years of age or older. Most of them had extrarenal disease at the time of transplantation; however, extrarenal disease was not an important predictor of outcome and should not be used as an exclusion criterion. Post-transplant quality of life is excellent.

Cadaver kidney transplantation necessitates allocation of a scarce resource. With improved transplant outcomes, more patients with end-stage renal disease (ESRD) are opting for transplantation; consequently, the waiting list and resultant waiting time have increased annually. Many question whether transplants should be provided to high-risk patients, i.e., those whose chances of long-term success are diminished.[1]

Before cyclosporine (cyclosporin A [CsA])-based immunosuppressive protocols, cadaver kidney recipients older than 45 years of age were shown to be high risk.[2–8] But with CsA, patients between 50 and 60 years of age

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Table 1. CAUSE OF RENAL FAILURE BY AGE IN PRIMARY ADULT KIDNEY RECIPIENTS (1970–1993)

Cause	18–59 yr (n = 2184)	≥60 yr (n = 128)
Polycystic kidney disease	7%	15%
Hypertension	3%	14%
Type II diabetes	2%	14%
Type I diabetes	42%	5%
Chronic glomerulonephritis	17%	11%
Other glomerulonephritis*	2%	7%
Pyelonephritis	5%	4%
IgA nephropathy	2%	2%
Unknown	2%	8%
Other	16%	20%

* Focal sclerosis, membranous, or membranoproliferative.

routinely are transplanted. However, concurrent with the aging of the American population, an increasing number of older patients have renal failure. Currently, more than 50% of those with ESRD who require dialysis are older than 55 years of age.[9]

It is important to question whether kidneys should be allocated to this subgroup. In theory, a successful transplant in a 60-year-old patient does not have the same long-term potential as the same transplant in a 30-year-old. However, a 60-year-old person most likely has many quality years left. In the United States, the average 60-year-old person lives another 17 or more years.[9] Such patients should not be eliminated for transplant consideration on the basis of age alone. In this study, we reviewed the outcomes of kidney transplants at the University of Minnesota since 1970, comparing recipients 60 years of age or older with patients 18 to 59 years of age.

METHODS

Between January 1, 1970, and December 31, 1993, 2828 adults received 3103 kidney transplants at the University of Minnesota. Of these, 138 transplants (128 primary, 10 retransplants) were for patients 60 years of age or older. The cause of renal failure for recipients ≥ 60 years of age *versus* those 18 to 59 years of age is shown in Table 1.

Patient selection, surgical technique, and immunosuppressive protocols have been described in detail.[10] Routine evaluation of pretransplant patients ≥ 60 years of age and those 18 to 59 years of age was similar (Table 2). Recently, patients with diabetes or a history of cardiac disease routinely have undergone coronary angiography; stress thallium testing is considered for asymptomatic patients without a history of risk factors.

Immunosuppression

Between 1970 and 1980, immunosuppression for all kidney recipients (except human lymphocyte antigen [HLA]-identical siblings) consisted of Minnesota antilymphocyte globulin (MALG) (15–30 mg/kg/day for 14 days), prednisone (2 mg/kg/day tapered to 0.5 mg/kg/day by 1 month, and 0.3 mg/kg/day by 1 year), and azathioprine (AZA) (5 mg/kg/day tapered to 2.5 mg/kg/day by the fifth postoperative day). Routine pretransplant transfusions were introduced in 1978. Between 1980 and 1984, patients were randomized to receive MALG, prednisone, and AZA *versus* CsA (14 mg/kg/day for the first week, then 12 mg/kg/day) and prednisone. Since 1984, all living donor kidney recipients have received triple therapy—CsA (4 mg/kg/twice daily), prednisone (1 mg/kg/day tapered to 0.4 mg/kg/day by 1 month, and 0.15 mg/kg/day by 1 year), and AZA. Cadaver kidney recipients received sequential therapy—MALG (20 mg/kg/day for 7 days), prednisone, and AZA, with delayed introduction of CsA. The CsA dose was adjusted to maintain whole blood trough levels (by high-pressure liquid chromatography) between 150 and 200 ng/mL for the first 3 months. Between 1987 and 1991, OKT3 (5 mg/day for 7 days) was randomized *versus* MALG in the sequential therapy protocol;[11] there were no differences in 1-year graft survival, and the groups have been combined for this report. In addition, since August 1992, antithymocyte globulin (ATGAM, Upjohn Company, Kalamazoo, MI) has been substituted for MALG.

All acute rejection episodes were confirmed by percutaneous allograft biopsy; rejection treatment consisted of recycling the prednisone taper. Steroid-resistant rejec-

Table 2. ROUTINE EVALUATION OF PRETRANSPLANT PATIENTS

Laboratory studies
Blood typing
Human leukocyte antigen typing
Hepatitis B profile
Viral titers
CBC, electrolytes, liver function tests
Cholesterol, serum protein, albumin, triglycerides
VDRL, HIV
Electrocardiogram
Radiologic studies
Chest radiograph
Gallbladder ultrasonogram
Voiding cystourethrogram*
Upper gastrointestinal series*
Lower gastrointestinal series*
Cardiac catheterization*

CBC = complete blood count; VDRL = Venereal Disease Research Laboratory; HIV = human immunodeficiency virus.
* When indicated by patient history.

tions were treated by a 7- to 10-day course of antibody (MALG or OKT3).

Tissue Typing and Donor/Recipient Selection

All patients underwent serologic typing for HLA antigens. Donor/recipient typing was initiated in 1980. All patients underwent determination of panel-reactive antibody.

Patients accepted for transplantation were urged to find a living donor. If a number of potential donors volunteered, an HLA-identical (mixed lymphocyte culture [MLC]-nonreactive) match was preferred. All potential donors underwent careful medical screening.[12]

All patients awaiting cadaver transplantation had serum samples collected on a regular basis for preliminary crossmatching. For each cadaver kidney, potential recipients were called in after preliminary crossmatches were done. Since 1987, the extant United Network for Organ Sharing point system has been used to allocate cadaver kidneys.

Data Collection and Analysis

Patient data are maintained on a mainframe database. In addition, detailed information on patients transplanted since 1985 (including data on 108 transplants for patients ≥ 60 years of age) is maintained on a microcomputer database (DATAEASE, Software Solutions, Trumbull, CT).

We analyzed patient and graft survival and the cause of graft loss for primary kidney recipients 60 years of age or older *versus* those 18 to 59 years of age. For historic background, we also reviewed outcomes for patients older than 45 years of age who were transplanted before CsA immunosuppression. In addition, for the subset of CsA-immunosuppressed patients transplanted since 1985, we compared the length of initial hospitalization, the rate of rejection, the number of readmissions, and the total number of readmission days. For these analyses, only primary transplants were compared; patients readmitted for subsequent extrarenal transplants were not considered further.

For those patients 60 years of age or older who underwent transplants since 1985, we analyzed pretransplant extrarenal disease and its impact on posttransplant outcome. In addition, quality of life was assessed informally by a series of questions asked annually. Answers were entered in the computer database and tabulated for analysis.

Finally, surviving patients who underwent transplants when 60 years of age or older were sent a medical outcome survey (SF-36 Health Survey, The Health Institute, Boston, MA) in 1993.[13] All patients completed the survey by mail or by telephone. This survey was designed to represent the following eight important health concepts included in medical outcome studies: physical functioning; role-physical (role limitations caused by physical health problems); bodily pain; general health; vitality (energy/fatigue); social functioning; role-emotional (role limitations caused by emotional problems); and mental health (psychological distress and well-being). The survey is short and can either be self-administered or given over the telephone. National norms of the United States have been developed for each adult age group,[13] and profiles have been developed for a variety of chronic diseases.

Actuarial patient and graft survival rates were calculated by Kaplan-Meier methods, and Gehan's test was used for statistical comparisons.[14] Graft survival rates were calculated with and without death with function considered a graft loss.[15] Rejection rates were computed and compared in a similar manner. Other comparisons between groups were analyzed using the Student's t test, Wilcoxon rank sum test, and chi square or Fisher's exact tests. Responses to the survey were averaged and compared with the national norms for adults 55 to 64 years of age and those 65 to 74 years of age.[13]

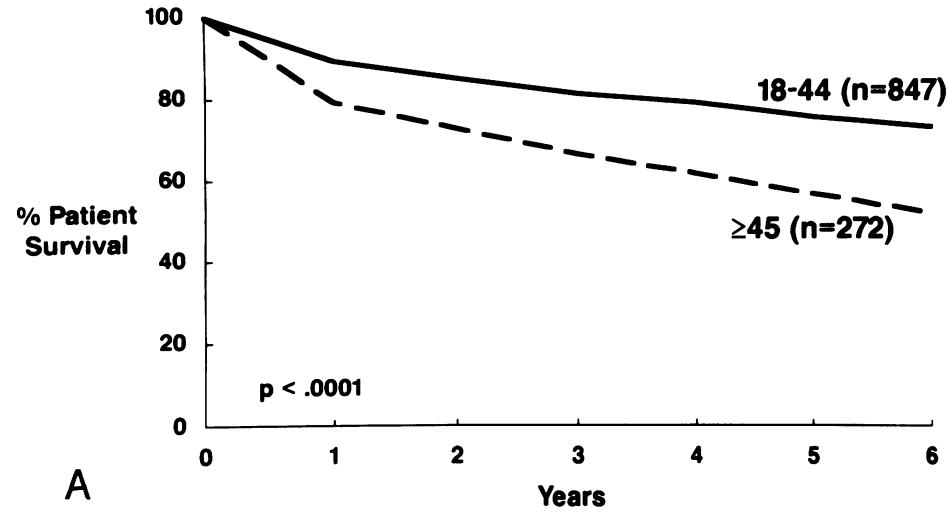
RESULTS

Pre-CsA Era

In the pre-CsA era, 272 patients 45 years of age or older underwent primary kidney transplants. Of these, 18 were 60 years of age or older. For patients ≥ 45 years, patient survival at 1 year (79%) and at 5 years (56%) was significantly worse than for those patients 18 to 44 years of age (89%, 75%, respectively; $p < 0.0001$; Fig 1A). When subdivided by diabetic status, patients 45 years of age or older (both diabetic and nondiabetic) also had significantly decreased survival *versus* those 18 to 44 years of age. For each age group, diabetic patients had significantly worse survival (Fig. 1B).

For patients 45 years of age or older, graft survival at 1 year (64%) and at 5 years (51%) was significantly worse than for those 18 to 44 years of age (77%, 65%, respectively; $p < 0.0001$; Fig. 2A). Again, when groups were subdivided by diabetic status, patients ≥ 45 years of age (both diabetic and nondiabetic) had significantly decreased graft survival compared with those 18 to 44 years of age ($p < 0.0001$). In addition, for each age group, patients with diabetes had decreased survival (Fig. 2B). When only living donor recipients were analyzed, outcome was not affected by recipient age (Fig. 3).[8] However, for cadaver recipients, patient and graft survival was significantly worse for those 45 years of age or older.

When death with a functioning graft was censored, graft survival was not significantly different between age



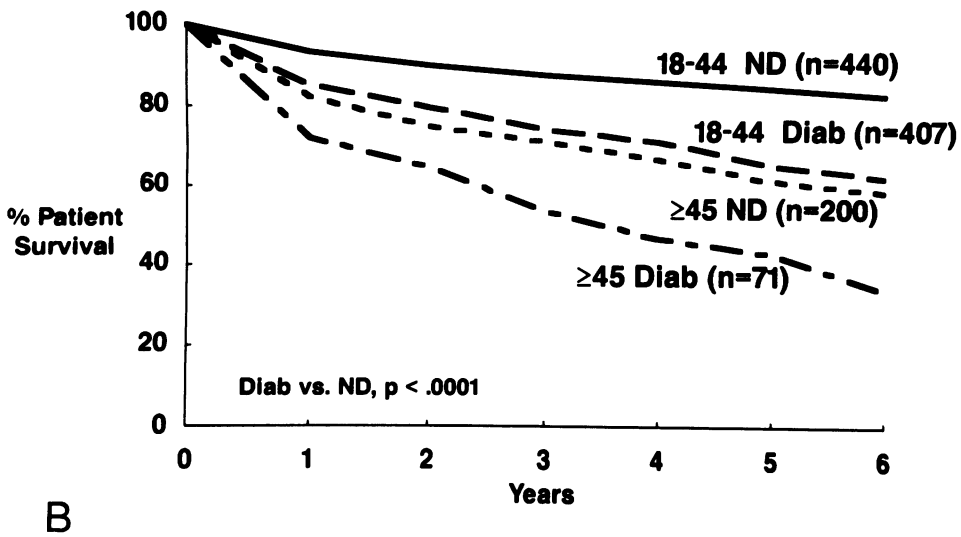


Figure 1. Patient survival, pre-CsA era. (A) Recipients ≥ 45 years had significantly decreased survival. (B) When subdivided by diabetic status, those ≥ 45 years had decreased survival. In addition, patients with diabetes had decreased survival *vs.* those with renal failure caused by other diseases.

groups. Thus, the major difference was an excess mortality rate for those 45 years of age or older. Causes of graft loss for patients ≥ 45 years of age compared with those 18 to 44 years of are shown in Table 3. Death with function was the leading cause of graft loss for both groups, but was responsible for a greater percentage of losses for those 45 years of age or older. Causes of death are shown in Table 3. There were no major differences for patients ≥ 45 years of age *versus* patients 18 to 44 years of age.

Only 18 patients 60 years of age or older (12 living donors, 6 cadavers) underwent transplants before CsA immunosuppression. Their patient survival at 1 year (78%) and at 5 years (56%) was significantly worse than for those patients 18 to 59 years of age ($p < 0.0001$).

CsA Era

In the CsA era, 108 patients 60 years of age or older received primary renal transplants. Detailed information on patients transplanted since 1985 (98 primary) is maintained on a microcomputer database. Their comorbid conditions are shown in Table 4. Extrarenal disease was common. Only 15% of recipients 60 years of age or older were free of any other problems.

For primary living donor recipients ≥ 60 years of age ($n = 32$), patient survival was 90% at 1 year and 90% at 3 years; for those 18 to 59 years of age ($n = 1082$), patient survival at 1 and 5 years was 96% and 92%, respectively (Fig. 4A). At 5 years, there is an increasing difference between the two groups ($p = 0.006$). Graft survival for those ≥ 60 years of age was 86% at 1 year and 86% at 3 years; for those 18 to 59 years of age, patient survival at 1 and 5 years was 96% and 86%, respectively ($p = 0.12$; Fig. 4B). However, when death with a functioning graft was censored, there was no difference in graft survival between the groups; for patients ≥ 60 years of age, survival was 93% at 1 year and 88% at 3 years; for those 18 to 59 years of age, 93% and 87%, respectively.

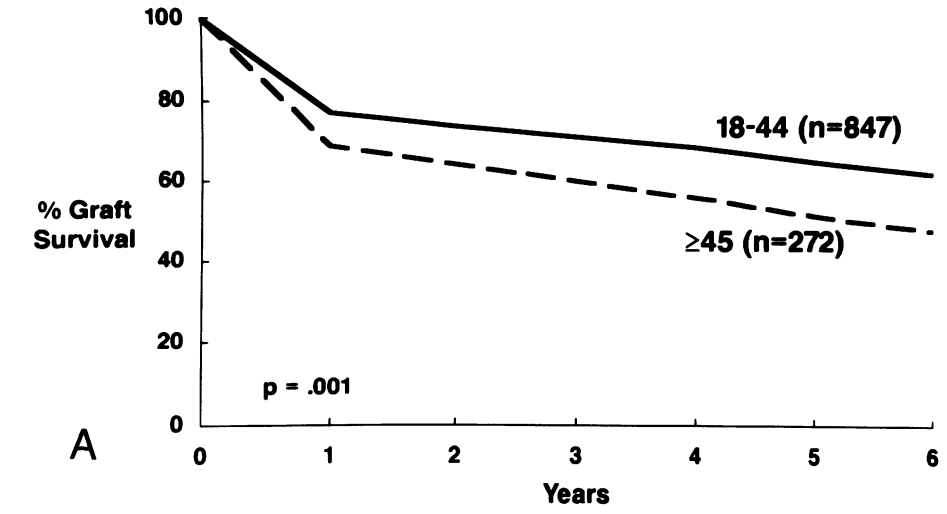
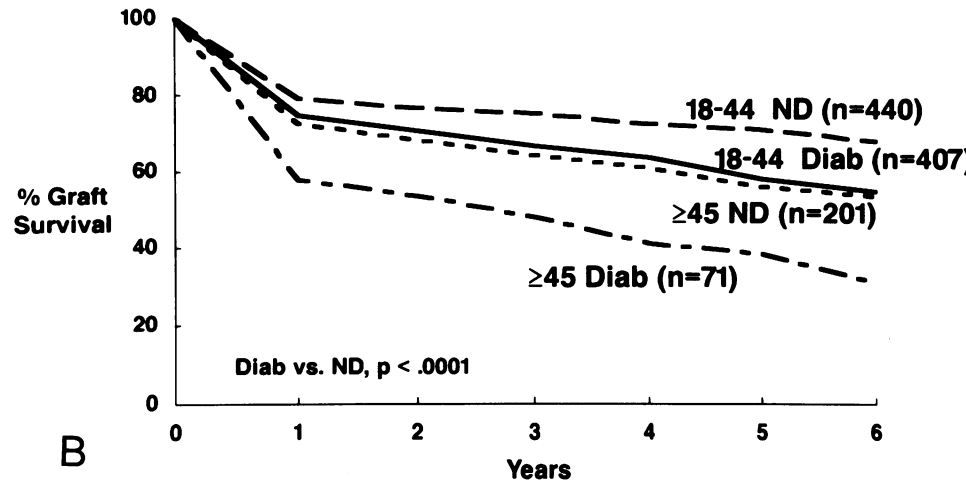


Figure 2. Graft survival, pre-CsA era. (A) Recipients ≥ 45 years had significantly decreased survival. (B) When subdivided by diabetic status, those ≥ 45 years had decreased survival. In addition, patients with diabetes had decreased survival *vs.* those with renal failure caused by other diseases.



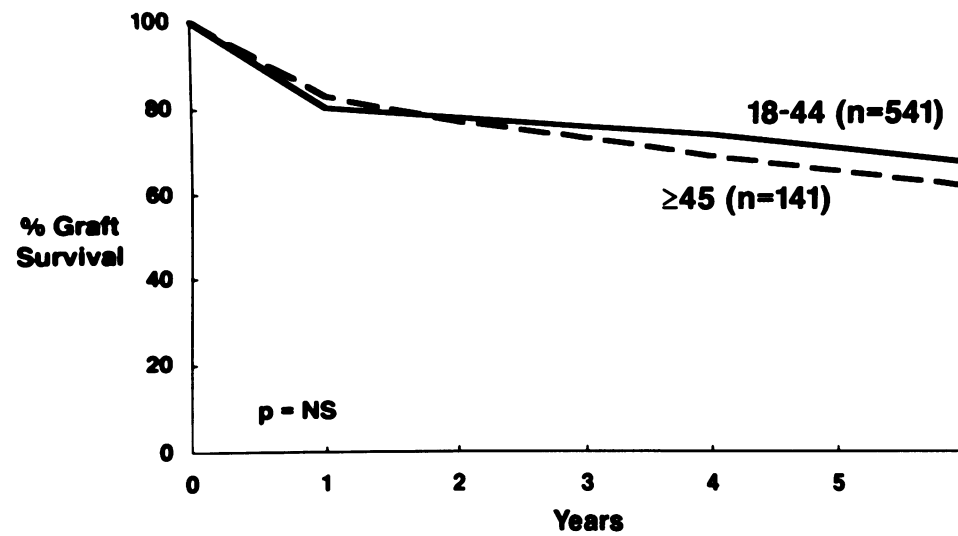


Figure 3. Living donor graft survival, pre-CsA era. There was no difference in survival for those ≥ 45 years *vs.* those between 18 and 44 years of age.

Table 3. CAUSE OF GRAFT LOSS AND DEATH BY DONOR SOURCE AND AGE (PRE-CsA ERA)

	Living Donor		Cadaver		All	
	18–44 yr (n = 310)	≥45 yr (n = 107)	18–44 yr (n = 224)	≥45 yr (n = 120)	18–44 yr (n = 554)	≥45 yr (n = 227)
Cause of graft loss						
Death with function	54%	79%	48%	63%	51%	71%
Acute rejection	8%	1%	12%	14%	10%	8%
Chronic rejection	21%	13%	22%	9%	22%	11%
Technical complications	5%	4%	4%	5%	4%	4%
Recurrence	5%	0%	2%	1%	4%	1%
	Living Donor		**Cadaver**		**All**	
	18–44 yr (n = 247)	**≥45 yr (n = 104)**	**18–44 yr (n = 187)**	**≥45 yr (n = 115)**	**18–44 yr (n = 434)**	**≥45 yr (n = 219)**
Cause of death						
Viral infection	6%	5%	8%	10%	7%	7%
Other infection	13%	15%	18%	27%	15%	22%
Myocardial infarction	15%	17%	8%	11%	12%	14%
Other cardiac disease	17%	15%	17%	12%	16%	14%
Stroke	4%	6%	5%	4%	5%	5%
Liver failure	4%	4%	4%	4%	4%	4%
Malignancy	8%	12%	10%	10%	9%	11%

For primary cadaver recipients 60 years of age or older (n = 76), patient survival was 91% at 1 year and 77% at 3 years; for those 18 to 59 years of age (n = 520), survival at 1 and 5 years was 93% and 86%, respectively (Fig. 4C). Again, at 5 years, there is an increasing difference between the two groups (p = 0.04). Graft survival for those ≥ 60 years of age was 83% at 1 year and 68% at 3 years; for those 18 to 59 years of age, 85% and 74% (p = 0.27) (Fig. 4D). Again, when death with a functioning graft was censored, there was no difference in graft survival between the groups (Fig. 5); for those ≥ 60 years of age, survival was 92% at 1 year and 84% at 3 years; for those 18 to 59 years of age, survival at 1 and 3 years was 90% and 83%, respectively. Unlike the pre-CsA era, there was no difference between diabetic and nondiabetic recipients.

Table 4. PRETRANSPLANT EXTRARENAL DISEASE IN PRIMARY KIDNEY RECIPIENTS ≥ 60 YEARS OF AGE WHO HAVE HAD TRANSPLANTS SINCE 1985

Hypertension	82%
Diabetes	26%
Gastrointestinal disease	39%
Liver/pancreas disease	35%
Peripheral vascular disease	21%
Respiratory disease	19%
Cardiac disease	63%
Malignancy*	9%

* 3 renal cell, 2 bladder (transitional cell), 1 skin, 1 chronic lymphocytic leukemia, 1 B cell lymphoma.

Immunosuppression

Although our immunosuppressive protocols are the same for older and younger adult recipients, those 60 years of age or older received less long-term immunosuppression (Table 5). Our pre-CsA experience suggested that, in older patients, there was less graft loss to rejection and more graft loss to death (Table 3).[16] Thus, we tend to use lower immunosuppressive dosages for patients ≥ 60 years of age. As seen in Table 5, patients 60 years of age or older received significantly less AZA and less prednisone 1, 2, and 3 years after transplant ($p < 0.05$). This is particularly striking because 51% of transplants for patients 18 to 59 years of age are from living donors *versus* 30% for those 60 years of age or older.

Cause of Graft Loss and Death

Cause of graft loss in the CsA era is shown in Table 6. Death with a functioning graft again was the leading cause of graft loss for both age groups, but was responsi-

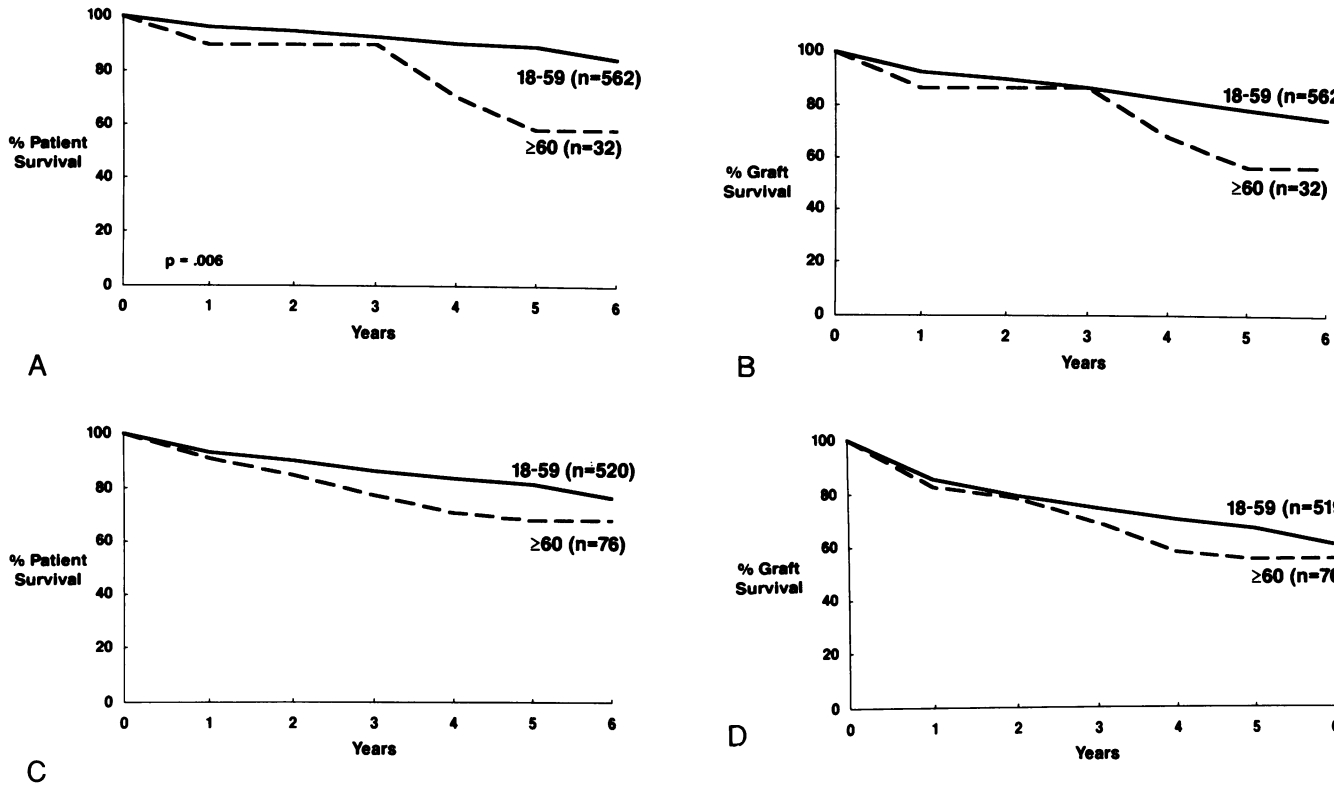


Figure 4. Patient and graft survival with CsA immunosuppression. (A) Living donor recipients ≥ 60 years had patient survival similar to those 18 to 59 years until 3 years, but more deaths after 3 years; (B) Living donor recipients ≥ 60 years had graft survival similar to those 18 to 59 years. For cadaver graft recipients, there was no difference in patient (C) or graft (D) survival for those ≥ 60 years *vs.* those 18 to 59 years of age.

ble for a greater percentage of losses for those 60 years of age or older. (In the pre-CsA era, there was a higher percentage of graft loss due to patient death [Table 3], but this may be caused by the longer follow-up for those patients.) Although the numbers are small, death with function was responsible for 82% of graft loss for living donor recipients ≥ 60 years of age in the CsA era. This may reflect our policy of accepting high-risk patients for living donor transplantation. We believe that if the donor, recipient, and family understand the risks, and realize that survival may be limited by extrarenal disease, transplantation may be an acceptable alternative to dialysis. Seventeen patients ≥ 60 years of age had graft failures more than 2 years after transplant—11 (65%) due to death, 5 (29%) due to chronic rejection, and 1 (6%) due to recurrent disease.

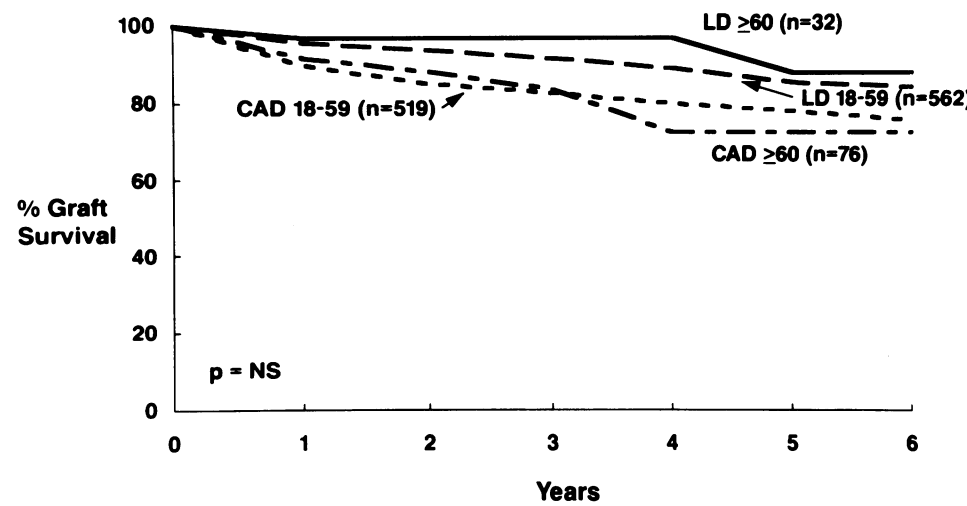


Figure 5. Graft survival with death with function censored. There was no difference between groups.

Table 5. IMMUNOSUPPRESSIVE DOSAGES BY AGE

Time Post-transplant	18–59 yr	≥60 yr
1 yr		
CsA level (ng/mL) (±S.E.)	116 ± 2	122 ± 7
mg/kg AZA (±S.E.)	2 ± 0.03	1.6 ± 0.1*
mg/kg P (±S.E.)	0.19 ± .01	0.17 ± 00*
2 yr		
CsA level (ng/mL) (±S.E.)	99 ± 4	104 ± 10
mg/kg AZA (±S.E.)	2 ± 0.04	1.6 ± .11*
mg/kg P (±S.E.)	0.16 ± .00	0.15 ± .00*
3 yr		
CsA level (ng/mL) (±S.E.)	83 ± 4	74 ± 9
mg/kg AZA (±S.E.)	2 ± 0.04	1.5 ± 0.13*
mg/kg P (±S.E.)	0.15 ± .00	0.14 ± .01*

CsA = cyclosporine; AZA = azathioprine; P = prednisone.
* $p < 0.05$.

Causes of death are shown in Table 6. There were no significant differences for those 60 years of age or older *versus* those 18 to 59 years of age.

Rejection

Recipients ≥ 60 years of age had fewer acute rejection episodes than those 18 to 59 years of age. At 3 months post-transplant, 76% of patients ≥ 60 years of age were free of rejection *versus* 69% of those 18 to 59 years of age. At 1 year after transplant, 72% of those ≥ 60 years of age were free of rejection *versus* 64% of those 18 to 59 years of age ($p = 0.15$). The average number of rejection episodes in recipients who had rejection was 1.36 ± 0.13 for those ≥ 60 years of age and 1.61 ± 0.05 for those 18 to 59 years of age ($p = 0.07$).

For primary cadaver recipients ($n = 76$), the difference in the incidence of rejection was statistically significant; 78% of those ≥ 60 years of age were rejection-free at 3 months *versus* 63% of those 18 to 59 years of age ($p = 0.008$). At 1 year post-transplant, 76% of those ≥ 60 years of age were rejection-free *versus* 58% of those 18 to 59 years of age ($p = 0.01$). The average number of rejections (in those experiencing rejection) was 1.53 ± 0.19 for those ≥ 60 years of age and 1.67 ± 0.08 for those 18 to 59 years of age.

To date, biopsy-proven chronic rejection has been documented for 10% of primary transplant recipients ≥ 60 years of age *versus* 13% for those 18 to 59 years of age.

Renal Function

In Table 7, serum creatinine level is compared for primary kidney transplant recipients ≥ 60 years of age *versus* those 18 to 59 years of age. From 3 months to 5 years post-transplant, there was no difference in renal function.

Table 6. CAUSE OF GRAFT LOSS AND DEATH BY DONOR SOURCE AND AGE (CsA ERA)

	Living Donor		Cadaver		All	
	18–59 yr (n = 128)	≥60 yr (n = 11)	18–59 yr (n = 202)	≥60 yr (n = 29)	18–59 yr (n = 330)	≥60 yr (n = 40)
Cause of graft loss						
Death with function	42%	82%	45%	52%	44%	60%
Acute rejection	9%	9%	6%	7%	7%	8%
Chronic rejection	24%	0%	23%	26%	24%	20%
Technical complications	5%	0%	5%	4%	4%	2%
Recurrence	2%	9%	2%	—	2%	3%
	Living Donor		**Cadaver**		**All**	
	18–59 yr (n = 78)	**≥60 yr (n = 10)**	**18–59 yr (n = 124)**	**≥60 yr (n = 22)**	**18–59 yr (n = 202)**	**≥60 yr (n = 32)**
Cause of death						
Viral infection	5%	0%	7%	0%	6%	0%
Other infection	14%	30%	11%	32%	12.5%	25%
MI	19%	20%	13%	18%	15%	19%
Other cardiac disease	23%	20%	26%	13%	25%	15%
Stroke	4%	20%	9%	9%	7%	13%
Liver failure	4%	0%	2%	0%	2.5%	0%
Malignancy	0%	10%	6%	18%	4%	16%

Table 7. SERUM CREATININE LEVEL BY AGE IN CSA-IMMUNOSUPPRESSED PRIMARY KIDNEY RECIPIENTS

Time Post-transplant (mo)	Serum Creatinine Level (mg% ± S.E.)	
	18–59	≥60
3	1.6 ± .6	1.6 ± .6
6	1.7 ± .5	1.6 ± .6
12	1.7 ± .6	1.6 ± .5
24	1.7 ± 1.2	1.5 ± .6
36	1.6 ± .6	1.5 ± .7
48	1.6 ± 1	1.4 ± .4
60	1.5 ± .6	1.5 ± .4

Hospitalization

The initial hospitalization was longer for primary recipients ≥ 60 years of age (15.4 ± 1.13 days) *versus* those 18 to 59 years of age (11.9 ± 0.25 days) (p = 0.003). However, only 58% of those 60 years of age or older have required readmission compared with 66% of those 18 to 59 years of age (p = 0.17). In addition, recipients ≥ 60 years of age were hospitalized fewer days after the transplant admission: 14.6 ± 3.0 days (*vs.* 16.6 ± 1.2 days for those 18 to 59 years of age).

Again, the difference was statistically significant for cadaver recipients: 55% of those ≥ 60 years of age required readmission compared with 72% of those 18 to 59 years of age (p = 0.008). Average number of readmission days was 14.1 ± 3.3 for those ≥ 60 years of age and 19.9 ± 1.7 for those 18 to 59 years of age (p < 0.05).

Post-Transplant Extrarenal Morbidity

Post-transplant extrarenal morbidity was common. Sixteen patients (16%) developed post-transplant diabetes; of these, 13 responded to diet and oral medications, and 3 required insulin. Another 7 patients developed avascular necrosis; 11 others had long bone fractures.

Cataracts were diagnosed post-transplant in 41 (42%) recipients. In nondiabetic recipients, cataracts developed in 24 of 62 patients (39%) without and 6 of 12 (50%) with previous histories of cataracts. In diabetic recipients, cataracts developed in 4 of 12 with and 6 of 12 (50%) without previous histories of cataracts.

Eighteen patients required treatment for cytomegalovirus disease; 4 of them died from mixed-organ infection. Nine patients developed herpes zoster infections post-transplant; 33 had bacterial infections, the most common site being the urinary tract.

Nine patients developed non-skin malignancies (three prostate, three bladder, one colon, one lung, one squamous cell of the mouth). Only one had had a pretransplant malignancy—i.e, a transitional cell tumor of the bladder that recurred and disseminated after transplant. Three patients died of their malignancies (colon, bladder, lung). Ten patients reported skin cancers (three basal, five squamous, two unknown).

Table 8. IMPACT OF PRETRANSPLANT EXTRARENAL DISEASE IN PRIMARY KIDNEY RECIPIENTS ≥ 60 YEARS OF AGE (SINCE 1985)

	Patient Survival			Graft Survival		
	1 yr	3 yr	5 yr	1 yr	3 yr	5 yr
Respiratory						
With (n = 24)	91%	87%	81%	83%	73%	65%
Without (n = 74)	89%	79%	56%	85%	73%	55%
Peripheral vascular						
With (n = 21)	80%	55%	37%*	65%	47%	22%†
Without (n = 77)	92%	87%	71%	89%	81%	67%
Liver/biliary tract						
With (n = 37)	89%	79%	59%	75%	63%	44%‡
Without (n = 61)	90%	80%	67%	90%	71%	67%
Cardiac						
With (n = 64)	87%	79%	60%	80%	73%	55%
Without (n = 34)	94%	82%	70%	91%	76%	68%
Gastrointestinal						
With (n = 44)	80%	83%	68%	79%	71%	55%
Without (n = 54)	91%	76%	60%	89%	75%	59%
All	88%	77%	57%	83%	70%	51%

* p = 0.02; † p = 0.004; ‡ p = 0.054.

Graft and patient survival for those with and without pretransplant respiratory, peripheral vascular, liver/biliary tract, cardiac, and gastrointestinal disease are shown in Table 8.

Cardiac disease was prevalent before transplant (63%). Forty-one patients (42%) had cardiac morbidity during follow-up. Of the 34 without pretransplant problems, 15 (44%) had post-transplant morbidity (6 myocardial infarcts, 5 arrhythmias, 1 heart failure, 1 angina, 2 others). Of 64 with pretransplant problems, 38 have had no post-transplant problems, whereas 26 have had continuing problems. Patients with pretransplant problems were further subdivided by the type of problem; of 4 with pretransplant cardiac failure, none have had post-transplant problems; of 7 with histories of myocardial infarctions, 2 have had post-transplant problems (1 failure, 1 arrhythmia); of 2 with valve dysfunctions, neither has had post-transplant problems; of 4 with arrhythmias, 3 have had ongoing post-transplant problems; of 11 treated for coronary disease by pretransplant coronary artery bypasses, 3 have had post-transplant problems (1 angina treated with medical therapy, 1 angina treated with angioplasty, and 1 myocardial infarction); of 7 with other types of

problems, 3 have had post-transplant problems; of 26 with multiple pretransplant cardiac problems, 15 have had ongoing post-transplant problems.

Importantly, cardiac disease was responsible for 2 deaths in the 34 recipients with no histories of pretransplant disease, and 5 deaths in the 64 with histories (p = NS). Pretransplant diseases did not significantly affect patient and graft survival (Table 8).

Peripheral vascular disease (arterial and venous) was diagnosed in 21% of patients before transplant and in 16% after transplant. Only one patient with a post-transplant problem had a history of pretransplant problems. However, patient and graft survival decreased significantly in patients with pretransplant peripheral vascular disease (Table 8). This was not because of an excessive number of cardiac deaths in this subgroup.

Respiratory and gastrointestinal pretransplant complications did not have an impact on post-transplant outcome (Table 8). However, patients with pretransplant liver/biliary tract disease had decreased survival. Of the 19 graft losses in this group, 10 were due to death with function. Of these ten, six were due to infections—a higher percentage of infectious deaths than in any other subgroup.

Quality of Life Survey

Surviving recipients ≥ 60 years of age were questioned annually about their quality of life (Table 9). At each interval, over 80% of recipients felt cheerful, independent, and healthy. They reported that health problems were either a minor drawback or no drawback to enjoying life, and 100% of them felt that opting for transplantation was the correct decision.

In addition, in 1993, all surviving patients completed the SF-36 Health Survey.[13] Table 10 compares the scores for recipients ≥ 60 years of age with the national norms. Although not significantly different, recipients ≥ 60 years of age scored lower than the national norms on the physical functioning and role-physical scales, measures of physical functioning and limitations due to physical health. Other scores were similar to the national norms.

DISCUSSION

The initial experience with kidney transplantation for older patients, especially with cadaver grafts, was dismal. In 1971, Simmons et al. reported that 1-year patient and graft survival for primary cadaver graft recipients ≥ 45 years of age was 40% and 20%, both considerably worse than for younger patients.[2] Others had similar experiences.[3–7] In each of these initial reports, survival for older patients after cadaver transplantation was worse than for comparable patients treated with dialysis. Survival for living donor recipients was better. Because of this, in 1977, Najarian et al. suggested that cadaver transplants should not be offered to patients older than 45 years of age.[8]

With the development of CsA-based immunosuppressive protocols, results improved; this improvement was particularly striking in high-risk groups. By 1987, Fryd et al. reported that outcomes for primary cadaver recipients ≥ 50 years of age were similar to outcomes for those < 50 years of age.[17] Since then, the age limits for transplantation have been extended further.[18–31] Our current analysis would suggest that immunologic graft loss for patients ≥ 60 years of age (death with function censored) is no different from those 18 to 59 years of age. Long-term patient and graft survival is lower for those 60 years of age or older, but this is because of increased mortality. Although patients ≥ 60 years of age have a somewhat longer initial hospitalization, they have significantly fewer readmissions, and more remain free of rejection. Quality of life is within the national norms for the age-matched population.

Should there be an upper age limit for kidney transplantation? The answer is complicated and revolves around many conflicting issues. First, concurrent with the aging of the American population is the aging of the subgroup with ESRD. It is projected that by the year 2000, more than 60% of ESRD patients in the United States will be older than 65 years of age.[32,33] Currently, 50% of new patients with ESRD are older than 61 years of age.[34]

Second, patients older than 60 years of age have the potential for many quality years. The average 60-year-old in the United States lives another 17 years or more.[9] Transplantation provides better quality of life than dialysis. Compared with dialysis, it is a more cost-effective treatment of ESRD.

Both of the above factors would support kidney transplantation for patients 60 years of age or older. However, other considerations also apply. It must be recognized that not all patients older than 60 years of age are equivalent transplant candidates. Physicians generally accept that chronologic age and "biologic" age, although difficult to quantitate, differ considerably. Most of our patients ≥ 60 years of age had at least one extrarenal system affected by disease, some perhaps due to the consequences of renal failure. Although cost effective when compared with dialysis, transplantation is expensive. Unlike dialysis, most transplant costs are in the first years. Thus, if it can be predicted that the potential for survival is limited severely by extrarenal disease, the expense of transplantation may not be justified.

At the same time, cadaver kidneys are a scarce resource. As a result, there is ongoing discussion about ethical allocation priorities. Should every patient on a waiting list have an equal opportunity to be transplanted? Or should kidneys be allocated to the patient with the best chance of long-term success?[1] If long-term success is the

Table 9. REPRESENTATIVE QUALITY OF LIFE QUESTIONS AND RESPONSES

Questions				
1. How do you feel currently?				
a) very cheerful	b) a little cheerful	c) a little depressed	d) very depressed	
2. How independent do you feel in managing your life?				
a) very independent	b) pretty independent	c) not very independent	d) dependent	
3. How would you label your health status?				
a) very healthy	b) pretty healthy	c) not very healthy	d) not at all healthy	
4. Health problems are:				
a) no drawback to enjoying life	b) a minor drawback	c) a major drawback	d) life is not worthwhile because of health problems	
5. Looking back, did you make the correct decision or a mistake by having a transplant?				

	Time Post-transplant					
	1–2 yr (n = 47)	2–3 yr (n = 36)	3–4 yr (n = 29)	4–5 yr (n = 18)	5–6 yr (n = 12)	6–7 yr (n = 9)
Responses						
Very/a little cheerful	91%	83%	90%	100%	100%	100%
Very/pretty independent	84%	89%	93%	94%	100%	89%
Very/pretty healthy	89%	83%	97%	94%	100%	78%
Health problems no/minor drawback	86%	86%	90%	94%	100%	89%
Transplant was correct decision	100%	100%	100%	100%	100%	100%

major goal, perhaps cadaver kidneys should be allocated to younger patients.

The answers are somewhat easier for patients with living donors. In this situation, the competing priorities of organ allocation are not a problem. We believe that the donor must be fully aware of the limitations of transplantation. However, rather than set arbitrary age limits, we continue to consider each case individually. If the recipient is otherwise healthy and is not tolerating dialysis (physically, emotionally, or because of limitations on quality of life) and the donor fully understands the risks and benefits, we consider older patients. Remember, the outcome with living donor transplantation must be compared with alternate treatments for the same patient subgroup. Our data suggest that for patients ≥ 60 years of age, the outcome of a primary transplant with a living donor is better than with a cadaver donor (Fig. 4) and better than dialysis. To date, the oldest recipient (transplanted ≥ 60 years of age) of a nonidentical living donor transplant in our series is currently 82 years old and is 19 years post-transplant.

Unfortunately, patients ≥ 60 years of age frequently do not have potential living donors. Many of the disease causing ESRD in older people (e.g., polycystic kidneys, hypertension) are familial. Many siblings already are too old or have renal or extrarenal disease that precludes donation. The patients themselves often are reluctant to accept kidneys from their children. Thus, only 30% of our recipients ≥ 60 years of age had living donor transplants (*vs.* 51% of those 18 to 59 years of age).

For CsA-immunosuppressed primary cadaver transplants in our series, patient survival was 91% at 1 year, 81% at 3 years, and 64% at 5 years. Results from other centers are shown in Table 11; patient survival at 5

Table 10. SF-36 HEALTH SURVEY SCORES

	Scale (mean ± SD)							
	PF	RP	BP	GH	VT	SF	RE	MH
Recipients ≥ 60 yr	61 ± 29	58 ± 46	68 ± 25	64 ± 24	58 ± 24	80 ± 27	73 ± 40	78 ± 20
National norms								
Age 55–64 yr	76 ± 26	74 ± 38	67 ± 26	64 ± 27	60 ± 23	81 ± 25	80 ± 34	75 ± 19
Age 65–74 yr	69 ± 26	65 ± 41	68 ± 26	63 ± 22	60 ± 22	81 ± 26	81 ± 35	77 ± 18

PF = physical functioning; RP = role-physical; BP = bodily pain; GH = general health; VT = vitality; SF = social functioning; RE = role-emotional; MH = mental health.

years ranged from 57% to 80%.[23-31] Transplant rates can be compared with the expected survival on dialysis: in the United States, for dialysis-treated Medicare patients 60 to 69 years of age, survival is 73% at 1 year and 24% at 5 years.[9] For patients 55 to 65 years of age, survival is 35% at 5 years.[33] It is difficult to determine if these transplant and dialysis patients are comparable. It is highly likely that patients with significant extrarenal disease that would limit life span are maintained on dialysis, whereas healthier patients are more likely to be considered for transplantation. However, in our series, most patients had significant extrarenal pretransplant disease. Fauchald et al. found that the survival rate for patients ≥ 60 years of age who were accepted for transplantation but maintained on dialysis while waiting was the same as for patients rejected for transplantation: 48% and 44% at 1 year, 29% and 30% at 2 years, respectively.[27] Ismail et al. recently compared transplant and dialysis outcomes in older patients[4,23] and suggested that definitive data are not available as to which is superior. However, they believed that transplantation should be offered as an option for patients 65 to 75 years of age.

Our finding of fewer acute rejections for patients ≥ 60 years of age is not new.[4,31] Immune competence decreases with age,[36-39] providing a possible explanation. Tesi et al. found that when patient death was censored, those ≥ 60 years of age had significantly better graft survival; their data suggest no immunologic graft loss after 36 months. But in our series, five patients ≥ 60 years of age lost their grafts to chronic rejection between 24 and 60 months post-transplant. One difference may be our tendency to use lower dosages of immunosuppression in older patients (Table 5). In our early (pre-CsA) experience, patient death from infections was a major cause of graft loss for older patients;[16] consequently, we are less aggressive in treating acute rejection episodes in these patients and, at the same time, tend to use lower late immunosuppressive dosages (Table 5).

The lower incidence of rejection in patients ≥ 60 years of age is associated with a lower rate of rehospitalization. More patients ≥ 60 years of age were readmission-free (statistically significant for cadaver recipients). Also, patients ≥ 60 years of age had fewer post-transplant readmission days.

Little data exist on the relationship of extrarenal disease to outcome. Schulak et al. subdivided their recipients ≥ 60 years of age into those free of both diabetes and cardiac disease (low-risk) (n = 14) *versus* those with either pretransplant diabetes or cardiac disease (n = 12).[27] The low-risk patients had better patient ($p = 0.055$) and graft survival rates. In our patient population, we were surprised to see so little impact of pretransplant cardiac disease; patient survival at 3 years differed by 3% in those with *versus* without identified cardiac disease; at 5 years, survival differed by 10% (Table 8). This would suggest that cardiac disease should not be an exclusion criterion for transplant consideration. Similarly, pretransplant respiratory or gastrointestinal disease had no impact on outcome. Our most striking findings involved recipients with pretransplant peripheral vascular disease (either arterial or venous) or liver/biliary tract disease (Table 8). The numbers in each of these subgroups, however, were small, and it was impossible to identify a specific increase in cause of death or cause of graft loss. Those with liver disease tended to have late failure because of sepsis.

Finally, there has been no data on quality of life for older transplant recipients. Our informal questionnaire (Table 9) suggests that patients are doing reasonably well. All continue to state that they made the correct decision in choosing transplantation. A more rigorous evaluation is provided by the SF-36 Health Survey,[13] designed to measure general health concepts that are "not age, disease, or treatment specific."[13(p2:3)] The SF-36 survey was designed from lengthier surveys with the goal of being short, practical (lower costs of data collection and analysis), and precise.[13] National norms have been developed for different adult age groups, and it is easy to compare any patient group with the U.S. population.[13] We found little difference in SF-36 scores for our recipients ≥ 60 years of age, compared with the national norms (Table 10). Although not statistically different, our recipients scored lower on two scales of physical functioning (physical functioning and role-physical). A limitation of our analysis is that it took place at a single time point—the time post-transplant varied from a few months to 8 years. Sequential analyses with larger numbers will be necessary to separate out immediate post-transplant issues and those related to age or the consequences of immunosuppression. Of note, recipients 60 years of age or older had scores identical to the national norms on scales of bodily pain, general health, vitality (energy level/fatigue), social functioning, and mental health.

Transplantation is successful for patients 60 years of age or older. Outcome is limited by patient survival. Death-censored graft survival is identical to graft survival for patients 18 to 59 years of age. Most recipients ≥ 60 years of age have extrarenal disease at the time of transplantation; however, extrarenal disease was not an important predictor of outcome and should not be used as an exclusion criterion. Recipients ≥ 60 years of age have a lower rate of rejection and fewer readmissions than those 18 to 59 years of age. In addition, quality of life for recipients 60 years of age or older is similar to the age-matched U.S. population.

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Table 11. RESULTS FROM OTHER CENTERS ON CSA RECIPIENTS ≥ 60 YEARS OF AGE

Author	n	Patient Survival			Graft Survival		
		1 yr	3 yr	5 yr	1 yr	3 yr	5 yr
Fauchild et al.[23]	122	76%	66%	—	67%	59%	—
Pirsch et al.[24]	34	91%	91%	—	74%	74%	—
Roza et al.[25]	28	91%	—	—	81%	—	—
Fehrman et al.[26]	55	71%	61%	57%	63%	54%	49%
Schulak et al.[27]	25	79%	79%	—	76%	71%	—
Morris et al.[28]	45	75%	58%	58%	72%	58%	58%
Vivas et al.[29]	22	89%	89%	—	73%	73%	—
Cantarovich et al.[30]	117	92%	90%	80%	86%	82%	80%
Tesi et al.[31]	133	85%	75%	68%	80%	70%	62%
Benedetti et al.	108	90%	81%	64%	84%	74%	55%

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Discussion

DR. CLYDE F. BARKER (Philadelphia, Pennsylvania): I'm pleased with the opportunity to comment on the accomplishments of one of our past presidents who in more ways than one remains a giant in the field of transplantation.

Perusal of past programs of the Association indicates that Dr. Najarian has presented many of his most important contributions in transplantation to the Association. Those include, to mention just a few, his demonstration in the 1960's that contrary to prevailing opinions diabetics can be transplanted safely and that they fare much better with transplantation than with dialysis; that pancreatic transplants can in fact be accomplished with results good enough to benefit patients; that polyclonal anti-T-cell agents are very effective when used as routine immunosuppressives.

Dr. Najarian has brought another such contribution to us today. As has frequently been true in the past his results are so good that they may be greeted at first with skepticism until the rest of us in the transplant field find that following his lead we can accomplish similar outcomes.

It may not be well known to those outside the field what a valuable resource Dr. Najarian's program at the University of Minnesota is to the world of transplantation. It's been recognized by the NIH for more than 25 years that his center grant in transplantation is a unique resource. Dr. Najarian and his associates have developed a tremendous data base and their well organized randomized and retrospective studies have provided us with information not easily attainable from the reports of other groups with smaller and less well-studied patient populations.

Another unique feature of their program is the emphasis under the leadership of the late Roberta Simmons on studying the important psychosocial effects of transplantation.

Today's paper is typical of Dr. Najarian's in that like his previous ones indicating the benefit of transplantation to diabetics, it indicates an unexpected benefit of transplantation in another high risk group, older patients. Those of us who are aging are happy to have this information.

However, even careful perusal of the manuscript leaves a few questions which I hope Dr. Najarian can answer. With regard to the difficult issue of allocation of the scarce resource of cadaveric kidneys, I wonder whether it's possible by modeling and use of his data base for Dr. Najarian to calculate the overall benefit of using a kidney in an older patient as compared to its use in a younger patient. He's certainly shown us that it is beneficial to the older patient to receive a transplant, but what about the benefit of that kidney as a resource to society? Unfortunately the sequence in some older patients is kidney transplantation and then death, since death was one of the prime causes of transplant failure in this older group in which failure from rejection was less common because of the immunodeficiency of age. In contrast the failures in younger patients often have a sequence something like this: kidney transplantation, rejection, dialysis, and then retransplantation. So what is the overall outcome in years of extending life likely to be when kidneys are used for older patients *versus* younger ones.

Secondly, was any analysis done on the age of the donors used? This is an interesting point in this series because at the University of Minnesota many living donors are used. Dr. Najarian's group uses living donors preferentially, as do we and many other groups because the outcome is better. But in this older age group fewer related donors can be found since there are fewer relatives who are medically acceptable as donors.

One solution to the shortage of related donors for older recipients that we've employed at the University of Pennsylvania over the last several years is the use of living unrelated donors. These have for the most part been older patients and the donors have been spouses. In some 27 patients transplanted with such donors we have so far had no failures. The lack of immunological failures, perhaps reflects the older age of the recipients, similar to Dr. Najarian's experience. It is also gratifying that thus far we've had no disastrous complications in the donors. I wonder if Dr. Najarian can tell us anything about the outcome of the living donors in his series and whether they've had increased complications because of being older.

Finally, with regard to the quality of life of the older recipients, was that compared to the quality of life of younger transplant patients or only to age-matched non transplant patients?

DR. ARNOLD G. DIETHELM (Birmingham, Alabama): Stimulated by this manuscript, I looked at our own experience. And, in the last 10 years or so, with 2,000 cadaveric transplants, 50 patients over the age of 60 received cadaveric kidneys and our results were the same as Dr. Najarian's in that age made no difference. We then looked at the recipients of living related donors over and under the age of 60 and again in our institution we found no difference in graft survival. But there are some important points to emphasize in the paper.

When you put a patient on a waiting list aged 60 or more, obviously they have more medical problems. In our institution we have a waiting list of about 600 patients, and if they have blood type B or O, a patient may wait 12 to 24 months. In the 60 or older age group, medical problems change in that period of time and often the patients that looked fine 2½ years ago present themselves and they are no longer in the same state of health. So we've had to put a considerable effort into contacting the referring nephrologist to be sure that the patient that was in good health a year ago is still the same.

Another point to discuss and a question for Dr. Najarian is