Impact of age, gender and race on patient and graft survival following renal transplantation — developing country experience

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Background. Optimising renal allograft survival is crucially important in developing countries because of limited resources to treat irreversible renal failure. However, although many factors can be manipulated to improve outcome, certain demographic factors are immutable in individual patients. The present study evaluated the impact of age, gender and race on the outcome of renal transplantation.

Methods. Relevant data were reviewed for 542 patients receiving primary renal allografts over a 23-year period. The survival of patients and grafts were calculated using the Kaplan-Meier method. Both univariate and multivariate analyses were used to determine the association between the demographic factors and patient and graft survival.

Results. Actuarial survival of both patients and grafts decreased with increasing age. The most striking differences were demonstrated when patients older than 40 years were compared with younger patients. However, when patient survival was censored for death with functioning grafts — a very important cause of graft loss — then actuarial graft survival improved with increasing age. There was no gender difference in graft survival, but female recipients of renal allografts had a higher mortality than their male counterparts. There were no racial differences in either patient or graft survival.

Conclusions. Age is an important determinant of outcome after renal transplantation, but race is not. Gender does not influence graft survival, but females do have a higher overall mortality rate following renal transplantation at our centre.

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Optimising the survival of renal allografts is of crucial importance, especially in developing countries where donor organs are at a premium and alternative forms of treatment for end-stage renal failure are often not readily available. Patient survival is one of the most important determinants of graft survival and it has been estimated that 9 - 30% of patients die with functioning grafts,[1,2] making patient mortality one of the most important causes of graft loss.[2] Numerous factors are known to influence the survival of recipients of renal allografts as well as their transplanted organs.[3] Much emphasis has been placed on the impact of immunosuppressive agents[4] and HLA compatibility[5] on outcome, while there is a paucity of information on those factors over which the patient and physician have no control. In this study we undertook to investigate the impact of certain demographic factors, namely age, race and gender, on the outcome of renal transplantation.

Most reports detailing outcome of renal transplantation originate from developed countries where there is generally ready access to renal replacement treatment and other resources. In contrast, patients with irreversible renal failure in developing countries have very limited, if any, access to any form of renal replacement treatment, and renal transplantation is often the only long-term option — provided that patients have a suitable living donor. In this setting there is a bias towards treating younger patients, and males have greater access to treatment than females.[6]

In common with other developing countries South Africa has limited resources and only a fraction of patients with irreversible renal failure receive treatment. However, unlike many other developing countries South Africa has had an active cadaveric renal transplant programme for several decades. In one of the earliest reports of graft and patient survival our sister hospital (Groote Schuur Hospital) reported its experience with ciclosporin.[7] Although the number of patients treated was small and the follow-up short, the 1-year patient and graft survival rates were impressive, being 88% and 94%, respectively. Our own renal transplant programme was initiated in 1976 and is an important complement to our chronic dialysis programme.

This study looked specifically at the influence of demographic factors on both patient survival and the survival of renal allografts since the inception of our programme. Our experience confirms the importance of age in the survival of both patients and renal allografts and the lack of impact of race on survival.

Subjects and methods

The study population consisted of all patients receiving first cadaveric renal transplants at Tygerberg Academic Hospital,

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which is attached to the University of Stellenbosch, for the period April 1976 to March 1999. Over the 23-year period 542 patients received 623 renal allografts: 64 patients received a second graft, 7 received a third, and 1 patient a fourth. The demographic details of the patients are shown in Table I.

Geographically the hospital serves approximately 50% of the Western Cape, which has a population of almost 4 million inhabitants (census 1996). The population served is racially heterogeneous, with the mixed race group (coloured) forming 56% of the population and whites 21%. The number of blacks in the Western Cape is relatively small (22%) compared with other South African provinces because of the enforced racial segregation policy of the previous South African government that confined certain race groups to particular areas.

All patients with end-stage chronic renal failure at our institution are assessed by a committee comprising the attending physician, social worker, nephrologists and other renal unit staff. Patients are accepted for transplantation with a living related donor (of which there are relatively few) or to the waiting list for cadaveric transplantation, with the same criteria. Cadaveric organs are allocated based mainly on time on the waiting list within each blood group. The average waiting time is 12 months for cadaveric transplantation. At our hospital, as in most public hospitals offering renal replacement treatment in South Africa, patients not suitable for renal transplantation for any medical reason such as severe cardiac disease, psychiatric disease or malignant disease are not offered dialysis or transplantation. In addition, social factors are taken into consideration and patients who live in rural areas where there are no haemodialysis facilities and who do not have access to running water are also denied treatment. Patients over the age of 60 years are also generally treated conservatively.

Table I. Demographic characteristics of renal allograft recipients, 1967 - 1999 (*N* (%))

Race		
Black	56 (10.3)	
White	185 (34.1)	
Coloured	301 (55.5)	
Gender		
Male	294 (54.2)	
Female	248 (45.7)	
Age (years)		
< 20	36 (6.6)	
20 - 29	126 (23.2)	
30 - 39	151 (27.9)	
40 - 49	160 (29.5)	
> 50	69 (12.7)	
Immunosuppression		
Azathioprine	123	
Ciclosporin	419	
Primary renal disease	White (*N* = 185)	Coloured & black (*N* = 357)
Chronic glomerulonephritis	58 (31)	161 (48)
Hypertension	10 (5)	91 (27)
Cystic kidney disease	35 (19)	16 (5)
Analgesic nephropathy	7 (4)	3 (1)
Diabetes mellitus	13 (7)	8 (2)
Hereditary kidney disease	5 (3)	0
Systemic lupus erythematosus	5 (3)	5 (1)
Miscellaneous	5 (3)	12 (3)
Unknown	9 (5)	12 (3)

No discrimination is made on the basis of gender. Immunological factors (panel-reactive antibodies, re-transplants) do not jeopardise access to the programme but are taken into consideration when allocating cadaveric organs. Despite this, there is no significant gender difference in the number of patients receiving organs compared with the general population and the dialysis population. In our institution the mean waiting period for females on dialysis before receiving an organ for transplantation is, however, (statistically) significantly longer than that of males (14 months compared with 10 months).

Patients with diabetic nephropathy are subjected to additional very stringent investigation before acceptance. At this time diabetic nephropathy is not the major problem in South Africa that it is in industrialised countries[8] and in our renal transplant population it accounted for less than 4% of renal allograft recipients, reflecting the strict selection criteria used for these patients.

The standard immunosuppressive regimen used until October 1983 was azathioprine at 1 - 2 mg/kg per day and methylprednisolone at doses varying between 1 mg/kg and 2 mg/kg per day over the years. A total of 123 patients received conventional treatment over the 7-year period. From October 1983, ciclosporin was included as part of triple therapy and was administered to 419 patients. Patients were maintained on ciclosporin for the life of the graft. The dose of ciclosporin was regularly monitored and the dose adjusted to maintain whole blood trough levels between 250 and 350 ng/l. The dose of ciclosporin was reduced at 3 - 6 months and whole blood trough levels were maintained between 150 and 250 ng/l. Cytochrome P450 inhibitors such as ketoconazole and diltiazem were not used routinely to allow reduction in the dose of ciclosporin. Under the triple immunosuppressive regimen oral methylprednisolone was reduced at 3 - 6 months to a maintenance dose of 8 mg per day. Azathioprine was administered at doses of 50 - 100 mg per day, with the majority of patients receiving the lower dose. Acute rejection was treated with intravenous 'pulses' of methylprednisolone 250 - 500 mg per day for 3 consecutive days. Polyvalent anti-thymocyte globulin or antilymphocyte globulin as well as OKT3 monoclonal antibodies were used individually (and occasionally sequentially) to treat steroid-resistant rejection as part of rescue therapy.

Initially, antimicrobial prophylaxis was only used in patients with a history or radiological evidence of tuberculosis. Since 1996 isoniazid prophylaxis (300 - 400 mg/day) has been used routinely in the first year after transplantation. Cytomegalovirus (CMV) infections started becoming a problem in out unit approximately 10 years ago and still remain a uncommon cause of mortality in our patients. Since 1999 aciclovir has been used for the first 6 - 12 months in all renal transplant patients who are serologically CMV-positive or where the organ donor is positive. *Pneumocystis carinii* pneumonia (PCP) has occurred in 20 patients after transplantation, all within the last decade. It has therefore become routine practice in our unit to use prophylactic co-trimoxazole (1 tablet daily) in the first year. Records of all the patients transplanted since the inception of our programme have been entered into a computer-based database. All patient-related data are entered into the database as well as the point of failure of the graft. The database was locked in March 1999 to allow follow-up of at least 2 years after transplantation. The mean follow-up period was 6.3 years.

Statistical methods

Values are expressed as means with 95% confidence intervals (CIs). The means of normally distributed data were compared using the Student's *t*-test. The chi-square (X^2) test was used to examine categorical data. Cumulative survival of patients and grafts was calculated using Kaplan-Meier plots, and significance of difference between groups using either the log-rank test or the X^2-test. Multivariate regression analysis of demographic factors prognostic of patient and graft survival was performed with proportional hazards analysis, using stepwise elimination to select variables for the model. For the purposes of this study, allograft failure was defined by the institution of long-term dialysis after transplantation or patient death.

Results (Table II)

The mean age of renal allograft recipients at the time of first kidney transplant was 37.0 years (CI: 36.0 - 37.9), with no significant gender or racial differences. Patient survival deteriorated progressively with advancing age (Fig. 1). However, patients over the age of 40 years seemed to have very similar outcomes. The survival of patients over 40 was significantly greater than that of younger patients. More importantly, the discrepancy in survival between the older and younger group increased with time (Fig. 2). The commonest

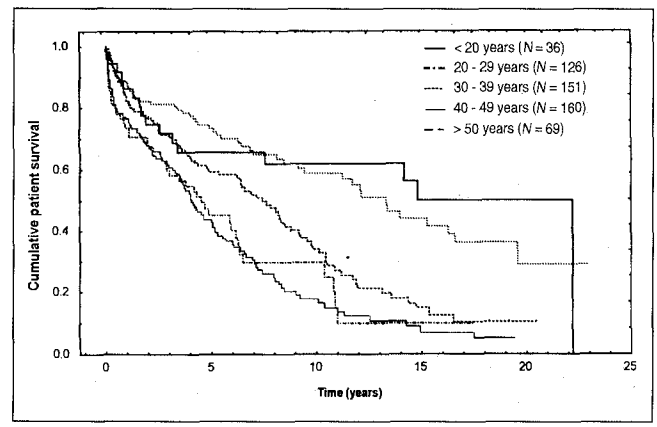

Fig. 1. Influence of recipient age on the survival of patients following renal transplantation ($p = 0.0000$, $\chi^2 = 35.2$, *degrees of freedom (df) = 4).*

Table II. Estimated relative risks for the Cox proportional hazard model considering demographic factors that influence patient and graft survival after renal transplantation

	Patient survival			Graft survival		
	RR	95% CI	*p*-value	RR	95% CI	*p*-value
Age (yrs)						
< 20	0.88	0.50 - 1.54	0.645	1.12	0.70-1.78	0.646
20 - 29	1.00			1.00		
30 - 39 yrs	1.94	1.38 - 2.74	0.0001	1.30	0.97 - 1.74	0.083
40 - 49	2.92	2.09 - 4.07	< 0.0001	1.50	1.12 -1.99	0.006
≥ 50	2.95	1.96 - 4.45	< 0.0001	1.59	1.11 -2.28	0.012
Gender						
Male	1.00			1.00		
Female	1.39	1.11 - 1.74	0.005	1.16	0.94 -1.37	0.154
Race						
White	1.00			1.00		
Coloured	1.28	1.01 - 1.64	0.043	1.10	0.88 - 1.37	0.394
Black	1.29	0.87 - 1.91	0.205	1.01	0.70 -1.44	0.974

RR = relative risk; CI = confidential interval.

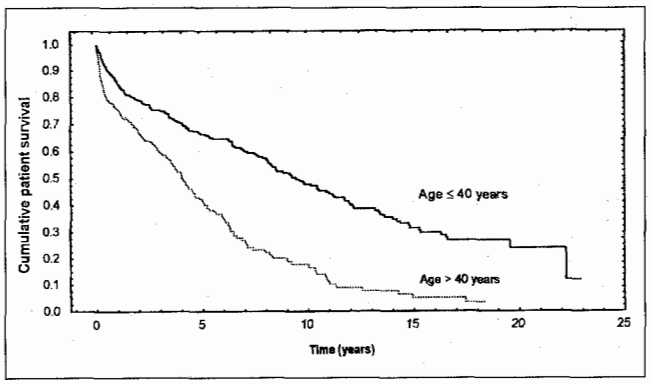

Fig. 2. Survival of renal allograft recipients aged 40 years and less compared with those aged more than 40 years at the time of transplantation (p = 0.0000, log-rank test).

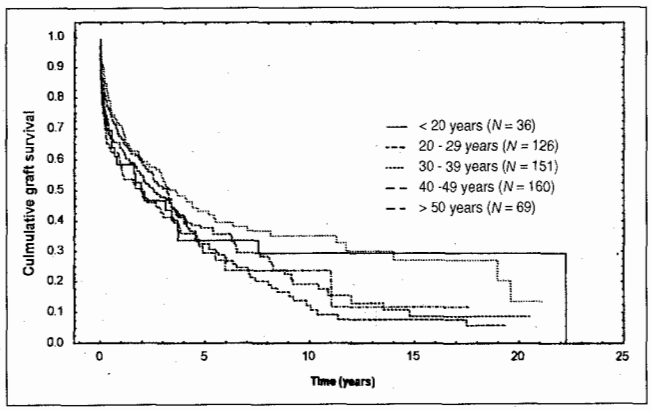

Fig. 3. Renal allograft survival in patients in different age percentiles (p = 0.15, χ^2 = 6.7, df = 4).

cause of death was infection, which accounted for 43% of deaths (Table III). The main cause of mortality was infection, both under conventional therapy and triple therapy. However, there was no significant difference in infective mortality under the two forms of treatment. Septicaemia and pulmonary infections together accounted for almost 70% of all infections. In the patients under ciclosporin, infections competed with cardiovascular disease as the main cause of patient mortality. Of the 542 patients transplanted, 321 (59%) had died by 31 March 1999. Of these, 180 (56%) died with functioning grafts. Expressed differently, at closure of the database 380 grafts had failed, with patient death accounting for 180 (47.3%) of all grafts lost. The remaining patients lost renal function progressively over months to years due to chronic allograft nephropathy.

Table III. Causes of patient mortality after kidney transplantation (*N* = 180)*

Parameter	*N*	%
Cardiovascular disease	65	36.1
Infections	72	40.0
Septicaemia	33	46†
Lung infection‡	24	33
Tuberculosis	7	9.7
Other	29	16.1
Malignancy	3	1.6
Unknown	11	6.1

* The cause of mortality was not available for 116 patients (39.2%).
† Percentage of infections.
‡ All but 4 infections were bacterial: 3 patients had fungal infections and 1 had a viral infection; included are 4 patients with *Pneumocystis carinii* pneumonia (PCP).

Renal allograft survival also deteriorated with advancing age (Fig. 3) and mirrored the patient survival curves. The exception was the group of patients aged under 20 years who fared as poorly as those over 50 years initially, but whose renal allograft survival improved later. The pattern of the renal allograft survival curves suggested that death of patients with functioning grafts was an important determinant of graft survival. Indeed, over the 23-year period of this study, death with functioning grafts occurred in 44% of patients aged over 40 years and 26% of those younger than 40 years. When the impact of death was censored for, renal allograft survival curves were dramatically different (Fig. 4). The older patients then had better graft survival than the younger patients, although the difference failed to reach statistical significance. Graft loss was due to death in 31% of women and 35% of men; the difference was not significant.

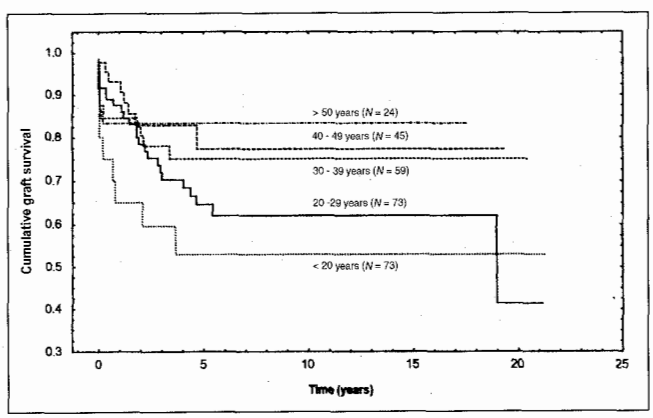

Fig. 4. Renal allograft survival in patients censored for death with functioning grafts (p = 0.18, χ^2 = 6.2, df = 4). See Table I for multivariate analysis.

There was no significant difference in either patient (not shown) or graft survival (Fig. 5) in the different race groups by univariate analysis, although using Cox's regression patient survival was significantly better in coloured than white patients. Patient and graft survival by race group remained virtually parallel throughout the study period. Survival of both patients (Fig. 6) and grafts (not shown) were better in males than females. However, only patient survival achieved statistical significance (Table II).

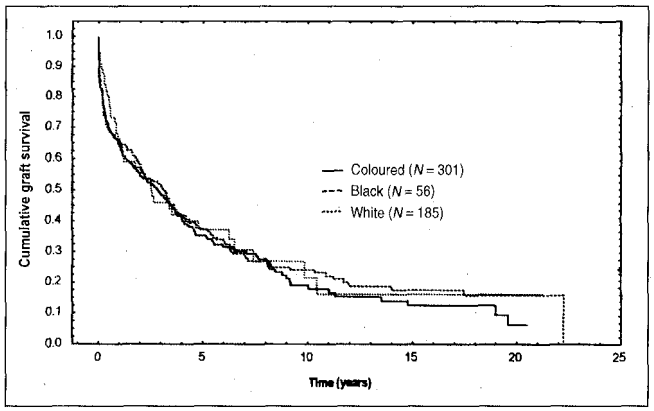

Fig. 5. Renal allograft survival in recipients of different race groups. There was statistically no difference in survival rates ($p = 0.74$, $\chi^2 = 0.60$, $df = 2$).

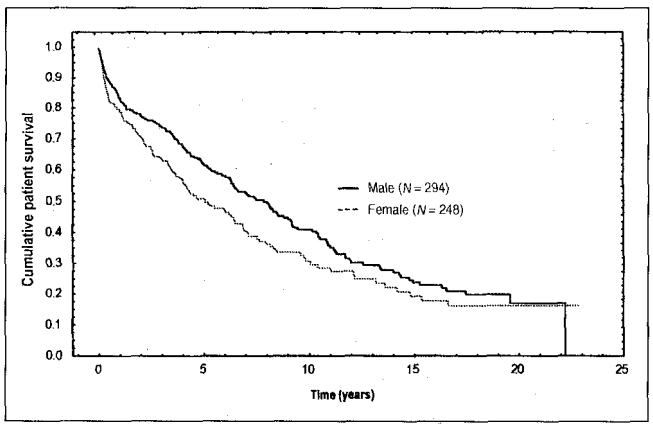

Fig. 6. Patient survival on the basis of gender ($p = 0.025$, *log rank test).*

Discussion

In a developing country setting where resources are limited it is crucial that renal allograft survival be optimised. However, it is important to appreciate that there are certain factors over which neither the patient nor the physician has any control. Our data demonstrate the superiority of patient and graft survival in younger patients. Our data also suggest that the loss of grafts in older patients is closely related to patient mortality. Death accounted for one in three of all grafts lost in our study. In a recent larger survey Ojo *et al.*[1] reported that 38% of more than 18 000 deaths were deaths with graft function and that this accounted for 43% of graft loss. Interestingly, infections (mostly of the lungs and septicaemia) were the commonest cause of death in our cohort even after the first year. In very young patients who experience greater graft loss early on, discrepancies in kidney size leading to vascular problems may account for the early loss of grafts; the higher propensity for acute rejection is perhaps the other explanation for the high early graft loss. The explanation for these causes of graft loss is strongly supported by our observation that when graft loss is censored for loss due to patient death, the graft survival improves with age. This observation confirms the findings of others.[9] The most likely explanation for this is declining immunological function, which results in improved graft survival.[10] However, this same mechanism may account for the increased susceptibility to infection in older patients that leads to early death. With these observations in mind it seems appropriate to suggest that immunosuppression should be reduced in older patients. Several factors have been identified as being predictors of reduced graft survival in the elderly patient, including increasing patient age, a pre-transplant history of non-skin cancer, time on the waiting list of less than 1 year, and tobacco use.[9]

Much more controversial is the impact of gender on patient and graft survival following renal transplantation. Our own finding of a higher mortality in female patients is corroborated by evidence presented by Troppmann *et al.*[11] who found that females had a 25% greater risk of dying than males but that the difference was not significant. An earlier report by Gorlén *et al.*,[12] who followed up patients for a mean period of 9.5 years, also found a non-significant increase in mortality in female patients (60% compared with 39%). These findings contrast with those of Arend *et al.*[13] who report a lower mortality among women, both in the first year post-transplant as well as during long-term follow-up. Woo *et al.*,[14] reporting on ciclosporin-treated patients, found that women had a lower mortality than men (hazard ratio: 0.66). In a more recent study,[1] male patients had a 16% higher risk of dying with graft function relative to females. The higher mortality observed in our cohort remains difficult to explain. One possibility is that since a standard immunosuppressive regimen was used throughout, female patients received relatively more immunosuppression for their body mass and were therefore more prone to the complications of over-immunosuppression.

Even more controversial are ethnic differences in the outcome of renal transplantation. In the present study, in contrast to reports both from South Africa[15] and elsewhere,[16] coloured and black patients taken together, and specifically black patients, had the same graft survival as white patients. The long-term survival of renal allografts in black patients has been reported to lag behind that of all other race groups.[17] In the latter study the
1-year and projected 10-year survival of first cadaver donor transplants were 84% and 47%, respectively, in white recipients compared with 81% and 23% in a similar-sized cohort of black recipients in the same age range. After the first year the rate of graft loss was more than double that of white recipients (half-life of 10.8 years versus 4.9 years). Earlier studies indicated that racial differences appeared shortly after transplantation, with more early rejection and 8 - 10% more graft loss in blacks at 1 year. The half-life of grafts in blacks was 30 - 40% that of whites.[18] Although this situation has improved and rates of

early rejection and graft loss now approximate those of whites, this has not resulted in improved long-term success as blacks remain at risk of late graft loss.[17,18] Important determinants of outcome may be histocompatibility differences,[16] possibly poorer blood pressure control and socioeconomic factors. As regards immunological issues, Asian patients who have similar difficulties finding histocompatible donors experience superior graft survival rates to those of white patients.[19] A higher incidence of late graft rejection among black recipients may be an indication of greater difficulty in maintaining adequate immunosuppression for these patients.[20] Most studies of outcome of renal transplantation in black patients are based on the African-American population. The reason that South African black patients respond differently to their American counterparts is uncertain. Hypertension, which is a key factor in the aetiology of end-stage renal failure in African Americans, is also a key predisposing cause in our population.[21] This continues to be a problem in our patients even after transplantation. Although several studies have sought an association between poorly controlled blood pressure and the survival of allografts,[22,23] none have established a cause-and-effect relationship. Young and Gaston[21] have suggested that poor socioeconomic status is a predictor of poorer outcome. Black patients suffer the worst socioeconomic deprivations of all race groups in our country, are the least educated and have the least access to medical care. Our observation of equal outcome among white patients and coloured and black patients challenges the validity of arguments that the racial discrepancies are related to issues such as socioeconomic factors, educational level and compliance with treatment. Although not part of this study, our small pool of transplant recipients makes it very difficult to obtain good HLA matching on any of the patients. Very few blacks are donors, with most organs being obtained from whites and coloureds in our province. Despite this the outcome of renal transplantation was comparable. One important difference between our situation and that in North America is that we pre-select transplant patients as indicated above. Patients with a history of poor compliance, very poor socioeconomic conditions that preclude regular commuting to a dialysis centre, or social conditions that do not allow the institution of continuous ambulatory peritoneal dialysis are not accepted for renal replacement treatment. However, even after this selection process, South African black patients are much worse off socioeconomically than their white counterparts.[24]

Much less is known about the survival of black patients after renal transplantation. Our own experience reported here failed to show a racial discrepancy in outcome, either early after transplantation or after prolonged follow-up. This supports the findings of the US Renal Data System 1999 Annual Report[8] which showed that patient survival after renal transplantation was virtually identical in black and white patients; the survival rate at 1 year was 96.5% and 95.7%, respectively, in recipients of cadaveric donor allografts and even better in recipients of kidneys from living donors. Another recent study[1] found that African American and other minority race groups had a lower risk of death, after controlling for other factors, than their white counterparts.

Comparisons with other developing countries are more problematic. In contrast to the developed countries, where most transplants are from cadaveric donors, most developing countries,[6] perhaps with the exception of the Latin American countries,[25] perform related or unrelated living-donor renal transplants, which often form the basis of their renal replacement programmes. In the few developing countries that do perform cadaveric transplants, the 1-year survival rates of patients range from 75% to 91% and 1-year graft survival rates range from 66% to 79%.[6] Recently, Opelz[25] reviewed the renal allograft survival experience in Latin America and found cadaveric donor transplant recipients to have a 1-year survival of 74%, while patient survival was over 80%. There was a relatively modest influence of age on graft survival but patient survival decreased strikingly with advancing age. Unlike the current study, graft survival censored for patient survival was not studied.

In sum, our report is one of the first from a developing country to look at the impact of certain demographic factors on the outcome of patients and grafts following renal transplantation. We have shown that race does not appear to be an important factor in determining the survival of either renal transplant patients or their grafts. Age, on the other hand, is an important determinant of renal allograft outcome but has an even more striking influence on patient survival. If graft survival is censored for patient death then graft survival is better in older patients. Gender differences in patient and graft survival are less impressive.

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Overt hypoadrenalism is uncommon in patients with stage 3 and 4 bronchogenic carcinoma

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Introduction. Lung cancer is the leading cause of cancer mortality in most countries. The adrenal glands are common sites of metastatic lung cancer as approximately 40% of subjects with stage 4 bronchogenic carcinoma have adrenal metastases. The prevalence of biochemical hypoadrenalism is, however, remarkably poorly documented.

Objectives. Our study aimed to determine the prevalence of primary hypoadrenalism, as defined by a subnormal cortisol response to the 250 µg adrenocorticotrophic hormone (ACTH) stimulation test, in patients with stage 3 and 4 lung cancer.

Methods. Thirty patients with stage 3 and 4 bronchogenic carcinoma were prospectively recruited from the bronchus clinic. Demographic data and electrolytes were recorded and each patient had a 250 µg ACTH stimulation test to determine the prevalence of overt adrenal insufficiency, defined as a +30 minute cortisol of less than 550 nmol/l.

Results. The median age and quartile deviation was 62 (10) years and the median basal cortisol was 429.5 (321) nmol/l. The median peak cortisol was 828.5 (342) nmol/l (range 536 - 1 675 nmol/l). Twenty-eight patients (93.3%) had an appropriate rise of cortisol to greater than 550 nmol/l following 250 µg ACTH stimulation. Two patients (6.7%) had mild primary adrenal failure with a peak cortisol between 500 and 550 nmol/l associated with a raised plasma ACTH concentration (131.4 and 10.5 pmol/l, normal 2.2 - 10 pmol/l). Twenty-eight patients (92.9%) were normonatraemic, while the two hyponatraemic patients had biochemical evidence of the syndrome of inappropriate antidiuretic hormone secretion.

Conclusion. In conclusion, despite evidence that the adrenal glands of patients with disseminated bronchogenic carcinoma are frequently affected by metastatic disease, biochemical evidence of clinically significant hypoadrenalism is relatively uncommon and is not accurately predicted by electrolyte abnormalities.

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Lung cancer is the leading cause of cancer mortality in most countries, with the global incidence increasing by 0.5% per year.[1] The adrenal glands are common sites of metastases, as evidenced by a series of 500 consecutive cancer necropsies, where 42% of metastatic lung cancers involved the adrenal glands. This high prevalence of adrenal metastases may reflect the rich sinusoidal blood supply and high local concentration of glucocorticoids, which may promote implantation of metastases.[2]