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End-stage kidney disease due to scleroderma—outcomes in 127 consecutive ANZDATA registry cases

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Abstract

Background. Scleroderma is an uncommon cause of end-stage kidney disease (ESKD) which carries significant morbidity and mortality risks. The aim of this study was to determine the prevalence, treatment and outcomes of scleroderma patients with ESKD.

Methods. A study was conducted of all ESKD patients enrolled in the ANZDATA registry, who commenced dialysis between 15 May 1963 and 31 December 2005, and remained on dialysis for at least 90 days.

Results. Of the 40 238 patients who commenced dialysis during the study period, 127 (0.3%) patients had ESKD secondary to scleroderma. Scleroderma ESKD patients were more likely than other ESKD patients to be female (72% versus 43%, $P < 0.001$), Caucasian (98% versus 79%, $P < 0.001$) and of lower BMI (22.7 ± 4.7 versus 26.0 ± 5.9, $P < 0.001$) with a higher prevalence of chronic lung disease (36 versus 14%, $P < 0.001$) and lower prevalence of diabetes mellitus (10% versus 32%, $P < 0.001$) and coronary artery disease (23% versus 35%, $P = 0.01$). Median survival was significantly shorter in scleroderma ESKD (2.43 years, 95% confidence interval (CI) 1.75–3.11 years) than other ESKD (6.02 years, 95% CI 5.89–6.14 years, log-rank score 55.7, $P < 0.001$). Renal recovery was more likely in scleroderma patients (10% versus 1%, $P < 0.001$) with a shorter time to recovery. Scleroderma was found to be an independent predictor for mortality (HR 2.47, 95% CI 1.99–3.05) and renal recovery (HR 11.1, 95% CI 6.37–19.4). Five year deceased donor and live donor renal allograft survival rates of recipients with scleroderma were 53 and 100%, respectively.

Conclusions. Scleroderma is an uncommon cause of ESKD, which is associated with increased risks of both spontaneous renal recovery and mortality.

Keywords: end-stage renal failure; kidney failure, chronic; outcomes; progressive systemic sclerosis; renal function recovery

Introduction

Scleroderma is a devastating multi-system connective tissue disorder that is characterized by excessive collagen deposition in the skin and internal organs and by vasculopathy. Renal manifestations of this disorder, which include accelerated hypertension, mild proteinuria and abnormal renal function, are found in at least 50% of the patients [1, 2]. The development of accelerated renal failure and malignant hypertension signifies scleroderma renal crisis, which carries a much poorer prognosis. Progression to ESKD is seen in ~20 to 50% patients despite therapy with angiotensin-converting enzyme (ACE) inhibitors [3, 4]. Previous reports of the course and outcomes of ESKD patients with scleroderma have been limited [3, 5].

The aim of the present study was to investigate the characteristics, treatments and outcomes of all cases of ESKD due to scleroderma in the Australian and New Zealand dialysis populations, using data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry.

Patients and methods

Patient population

The cohort study included all patients with ESKD enrolled in the ANZDATA registry, who commenced dialysis between 15 May 1963 and 31 December 2005, and remained on dialysis for at least 90 days. All patients entered into the ANZDATA registry were considered by their treating nephrologists to have ESKD and therefore thought to require long-term renal replacement therapy at the time they were enrolled in the registry.

Dialysis modality was assigned at 90 days following commencement of RRT. The primary outcomes examined were recovery of dialysis-independent renal function, time from dialysis commencement to recovery of renal function, overall patient survival and renal allograft survival. Recovery of dialysis-independent renal function was considered to have occurred if the treating renal unit had recorded that the patient had recovered renal function and completed dialysis therapy. The onset of recovery was defined as the date of the last dialysis treatment. A secondary outcome measure was time to renal death (patient death or recommencement of renal replacement therapy [RRT]) following recovery of dialysis-independent renal function.

For potentially related comorbidities, 'Suspected' was combined with 'Yes' for analyses. Dialysis era was determined by the dialysis commencement date: pre-CAPD era (15 May 1963 to 31 March 1976; patients receiving intermittent peritoneal dialysis (PD) or haemodialysis (HD) only), second decade (1 April 1976 to 31 March 1986), third decade (1 April 1986 to 31 March 1996) and fourth decade (1 April 1996 to 31 December 2005). Initial glomerular filtration rate (GFR) was determined from serum creatinine at initiation of dialysis, patient age and gender, using the four-variable Modification of Diet in Renal Disease equation [6] and expressed as mL/min/1.73m^2. Body mass index (BMI) was calculated from weight/height^2 and expressed in kg/m^2.

Statistical analysis

Results were expressed as frequencies and percentages for categorical variables, mean ± SD for continuous normally distributed variables and median (interquartile range) for non-parametric data. Dichotomous and categorical data were compared using chi-square tests. Continuous parametric data were compared using two-tailed unpaired *t*-tests. Continuous non-parametric data were compared using Mann–Whitney tests. The independent predictors of scleroderma ESKD were assessed by multivariate logistic regression analysis. Time to renal functional recovery was evaluated by Kaplan–Meier and multivariate Cox proportional hazards survival analyses. The covariates included in the model for the entire cohort were age, gender, racial origin, dialysis modality, ESKD cause, state/country of treatment and dialysis era. In light of the possibility of informative censoring due to differential rates of renal function recovery between patients with and without scleroderma, multivariate Cox proportional hazards survival analysis using a competing risks approach was also performed. This involved fitting the Cox model on an augmented dataset, as described by Lunn and McNeil [7]. A supplementary analysis was also conducted using a contemporary cohort (1990s onwards), in whom data were available on comorbidities, including BMI, smoking status, history of hypertension, cerebrovascular disease, ischaemic heart disease, diabetes, peripheral vascular disease and calculated GFR at dialysis onset. Adjusted survival curves were estimated using the Cox average covariate method, which calculates predicted survival probabilities at the mean levels of the covariates. Data were censored at the time of death, renal transplantation or end of study (31 December 2005). Patient survival and renal allograft survival was estimated by Kaplan–Meier analysis. Data were analysed using the software package SPSS for Mac OSX release 13.0 (SPSS Inc., North Sydney, Australia). P-values <0.05 were considered statistically significant.

Results

Patient characteristics

Between 15 May 1963 and 31 December 2005, 40 238 individuals started dialysis for ESKD. Of these, 127 (0.3%) had ESKD secondary to scleroderma, while 40 111 (99.7%) had ESKD due to other causes. The baseline characteristics of the two groups are displayed in Table 1. Compared with other causes of ESKD, patients with ESKD secondary to scleroderma were more likely to be female, Caucasian, have chronic lung disease, lower BMI, higher baseline estimated GFR (eGFR) at dialysis onset, referred to a renal unit <3 months before dialysis commencement and treated with PD at Day 90. Scleroderma patients also had a lower prevalence of baseline vascular disease and were more likely to be

hypertensive and commenced on dialysis in the most recent decade (1996–2005). Using multivariate logistic regression analysis, scleroderma ESKD was significantly associated with female gender [odds ratio (OR) 4.17, 95% CI 2.38–7.30], lower BMI (OR 0.92, 95% CI 0.88–0.97), late referral (early referral OR 0.20, 95% CI 0.12–0.33), lung disease (OR 2.83, 95% CI 1.64–4.90), peripheral vascular disease (OR 4.19, 95% CI 2.23–7.68), absence of coronary artery disease (OR 0.39, 95% CI 0.20–0.77), absence of cerebrovascular disease (OR 0.20, 95% CI 0.06–0.67) and absence of diabetes mellitus (OR 0.32, 95% CI 0.14–0.71).

Survival on dialysis

Death occurred in 85 (67%) scleroderma ESKD patients and 22 882 (57%) patients with ESKD due to other causes ($P < 0.05$). The causes of death in the scleroderma group were cardiovascular ($n = 35$ or 28%), dialysis withdrawal ($n = 17$ or 13%), infection ($n = 11$ or 9%), respiratory failure ($n = 5$ or 4%), cachexia ($n = 5$ or 4%), malignancy ($n = 3$ or 2%), viscus perforation ($n = 2$ or 2%), dialysis dementia ($n = 1$ or 1%) and other ($n = 6$ or 5%).

Median survival was significantly shorter in scleroderma ESKD (2.43 years, 95% CI 1.75–3.11 years) than other ESKD (6.02 years, 95% CI 5.89–6.14 years, log-rank score 55.7, $P < 0.001$) (Figure 1). Respective survival rates in the two groups were 72 versus 90% at 1 year, 55 versus 79% at 2 years and 29 versus 55% at 5 years. Patient survival improved significantly during each decade of the study period (log-rank score 23.3, $P < 0.001$, Figure 2), although survival of scleroderma ESKD patients was always significantly inferior to that of the patients with ESKD due to other causes for each time period ($P < 0.001$).

Using multivariable Cox proportional hazards model analysis, scleroderma was a strong independent predictor of mortality on dialysis [adjusted hazard ratio (HR) 2.47, 95% CI 1.99–3.05, Figure 3]. The other independent predictors of dialysis mortality were older age, Aboriginal and Torres Strait Islander racial origin, Maori and Pacific Islander racial origin and commencement of dialysis prior to 2001. In light of the possibility of informative censoring due to a higher rate of renal recovery in the scleroderma group, a multivariate Cox proportional hazards model analysis was undertaken using a competing risks approach. In this analysis, scleroderma remained a strong independent predictor of mortality (HR 2.93, 95% CI 1.93–4.47). Supplementary analysis using a more contemporary cohort in which complete data were available on comorbidities ($n = 19529$ including 68 scleroderma patients) revealed similar results. In particular, scleroderma remained strongly associated with mortality on dialysis (HR 1.88, 95% CI 1.31–2.70). The other risk factors for mortality were older age, Aboriginal and Torres Strait Islander racial origin, Maori and Pacific Islander racial origin, commencement of dialysis prior to 2001, referral to a renal unit within 3 months of dialysis commencement, current cigarette smoking, lung disease, coronary artery disease, peripheral vascular disease, cerebrovascular disease and diabetes mellitus. Higher BMI was associated with a lower risk of mortality on dialysis. Within the scleroderma group, the only significant independent predictor of mortality was age (HR/10 years 1.68, 95% CI 1.14–2.47). There was a trend towards improved survival with referral to a renal unit within 3 months of dialysis commencement (HR 0.50, 95% CI 0.23–1.07).

Table 1. Characteristics of all patients with ESKD secondary to scleroderma or other causes in Australia and New Zealand 1963–2005

Characteristic	Scleroderma ESKD ($n = 127$)	Other ESKD ($n = 40111$)	P-value
Age	54.7 ± 11.1	53.4 ± 17.0	0.4
Male gender	35 (28%)	23018 (57%)	<0.001
Racial origin			
European	124 (98%)	31843 (79%)	<0.001
ATSI	1 (1%)	2115 (5%)	
MPI	0 (0%)	3522 (9%)	
Asian	0 (0%)	1447 (4%)	
Other	2 (2%)	1184 (3%)	
Dialysis era			
1963–1976	1 (1%)	2189 (5%)	
1976–1986	14 (11%)	5951 (15%)	
1986–1996	34 (27%)	11 324 (28%)	
1996–2001	33 (26%)	9162 (23%)	
2001–2005	45 (35%)	11 485 (29%)	0.06
Ever smoked[a]	13/95 (13%)	3964/29263 (14%)	0.9
Hypertension[a]	79/86 (92%)	23034/27196 (85%)	0.09
Diabetes mellitus[a]	10/99 (10%)	10575/32592 (32%)	<0.001
Coronary artery disease[a]	23/100 (23%)	11091/31378 (35%)	0.01
Peripheral vascular disease[a]	32/97 (33%)	7274/31270 (23%)	0.03
Cerebrovascular disease[a]	6/99 (6%)	4028/21301 (13%)	0.002
Lung disease[a]	36/99 (36%)	4304/31293 (14%)	<0.001
BMI (kg/m^2)[a]	22.7 ± 4.7	26.0 ± 5.9	<0.001
eGFR at initiation[a] ($mL/min/1.73m^2$)	5.9 (4.7–7.7)	5.4 (3.9–7.5)	0.02
Late referral[a]	48/85 (56%)	5812/26369 (22%)	<0.001
PD at 90 days	50%	40%	0.03
Follow-up (years)	1.6 (0.7–3.8)	3.6 (1.6–7.8)	<0.001

[a]Characteristics included in contemporary cohort supplemental analyses (complete supplementary data available in 68 scleroderma and 19461 non-scleroderma ESKD patients).

Recovery of renal function

Recovery of dialysis-independent renal function occurred in 13 (10%) scleroderma ESKD patients and 437 (1%) ESKD patients with other forms of renal disease ($P < 0.001$). Recovery was most likely in the first 12–18 months following dialysis commencement (Figure 4). Mean time to renal recovery was significantly shorter in scleroderma ESKD (14.1 versus 39.1 months, log-rank score 132, $P < 0.001$). Using multivariable Cox proportional hazards model analysis, scleroderma was a significant independent predictor of renal function recovery (HR 11.1, 95% CI 6.37–19.4) (Figure 4). Within the scleroderma group, there were no significant independent predictors of renal recovery. The likelihood of renal function recovery was not influenced by dialysis era (log-rank score 2.2, $P = 0.54$).

Of the 13 scleroderma patients who recovered dialysis-independent renal function, 7 (54%) died and 4 (31%) returned to dialysis.

Renal transplantation

A total of 22 (17%) patients with scleroderma (20 females) received 24 renal allografts during the study period (18

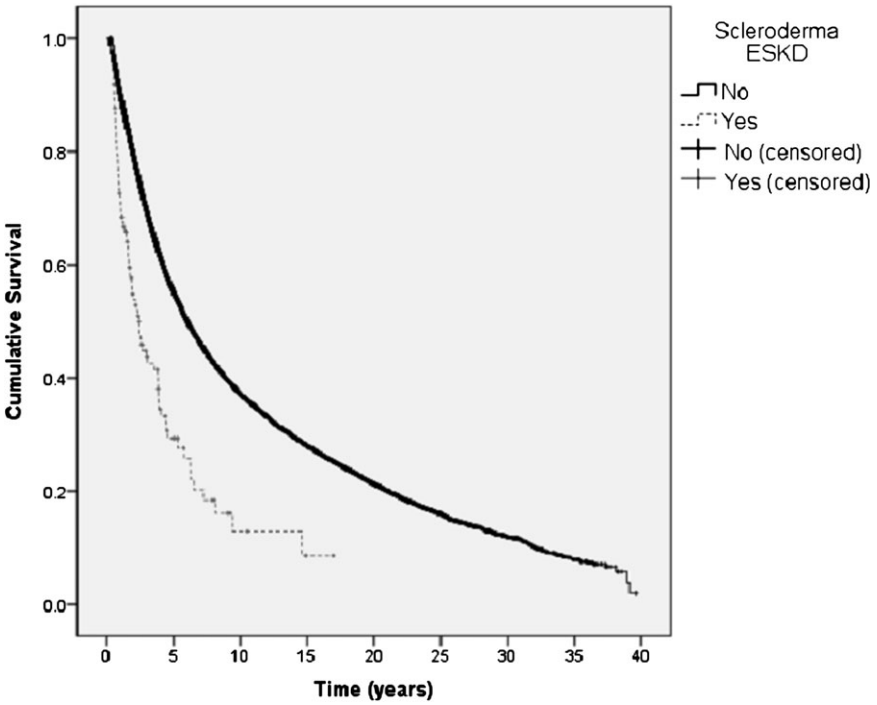

Fig. 1. Kaplan–Meier survival curves for scleroderma ESKD and other causes of ESKD in Australian and New Zealand dialysis patients 1963–2005. The difference between the groups was statistically significant (log-rank score 55.7, $P < 0.001$).

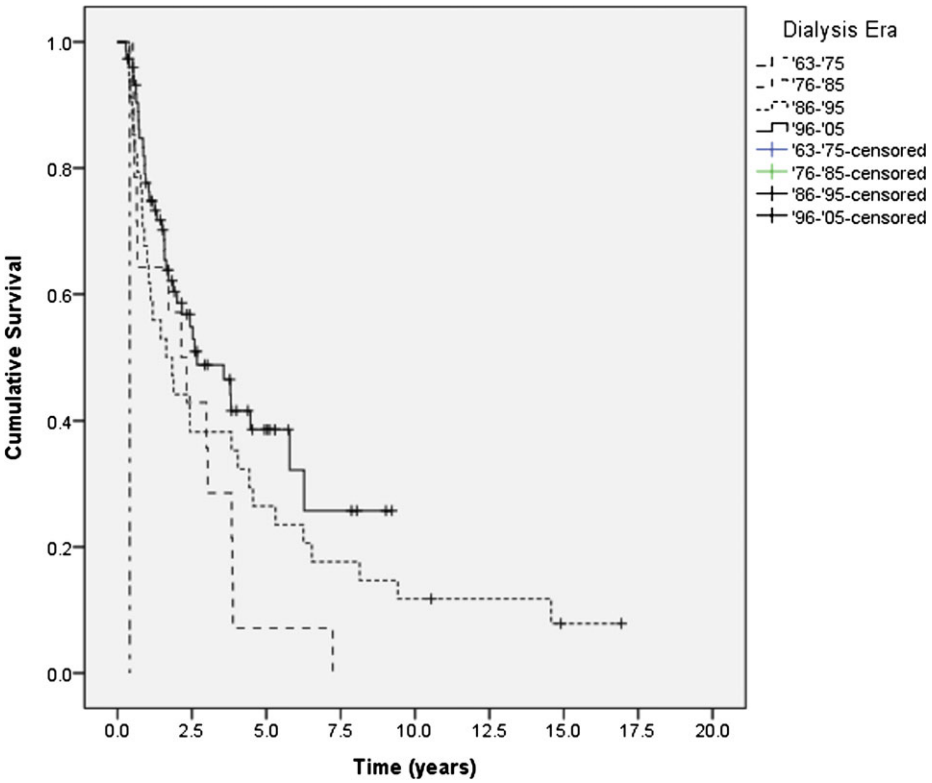

Fig. 2. Kaplan–Meier survival curves for scleroderma ESKD in Australian and New Zealand dialysis patients 1963–2005, according to decade in which RRT was commenced. The difference between the groups was statistically significant (log-rank score 23.3, $P < 0.001$).

deceased donor grafts and 6 live donor grafts). This was comparable to the proportion of ESKD patients without scleroderma who received a renal transplant (17%, $P = 0.9$). The baseline characteristics of these patients are shown in Table 2. The bulk of deceased donor and living donor transplants had been performed since 2000 (56 and 50%, respectively), while

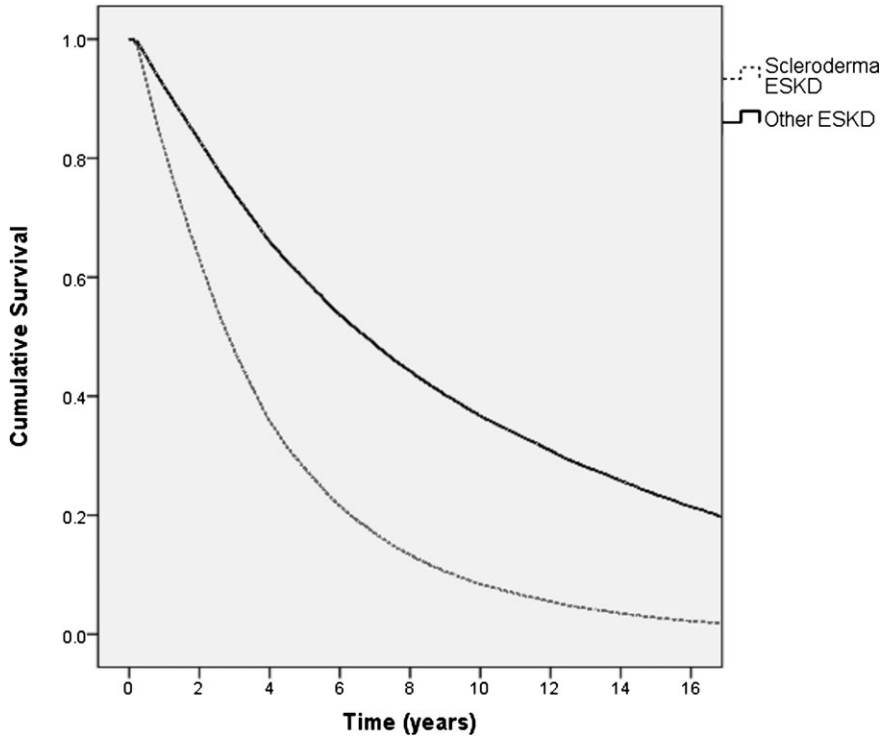

Fig. 3. Cox-adjusted survival curves for scleroderma ESKD and other causes of ESKD in Australian and New Zealand dialysis patients 1963–2005. Curves are adjusted for age, gender, racial origin, dialysis era, state/country of residence and dialysis modality at day 90. Scleroderma was a strong independent predictor of mortality on dialysis (HR 2.47, 95% CI 1.99–3.05).

smaller proportions were performed in the 1990s (28 and 33%), 1980s (17 and 0%) and 1970s (0 and 17%). Using Kaplan–Meier analysis, deceased donor renal allograft survival in scleroderma recipients was 78% at 1 year, 53% at 5 years and 28% at 10 years. All the six living donor renal allografts were still functioning at the end of the study, despite four allografts having been followed for at least 10 years.

Discussion

This retrospective analysis examined the outcomes of 127 patients with scleroderma ESKD compared to 40 111 patients with ESKD due to other causes in the ANZDATA registry. Although the overall prevalence of scleroderma as a cause of ESKD was low at 0.3%, it had a greater impact on the end points that were studied. The rising prevalence of patients with ESKD due to scleroderma with increasing dialysis era may be due to improved survival associated with the increasing use of ACE inhibitors since the late 1970s [4, 8, 9].

Scleroderma ESKD patients were significantly more likely than other ESKD patients to be female, Caucasian, have a lower BMI and have chronic lung disease or peripheral vascular disease. More patients with scleroderma were treated with PD at 90 days, which may have either reflected the poor vascular access that is associated with this disease or a propensity of clinicians to put scleroderma patients on PD because of the anticipated recovery of renal function. Diabetes mellitus, coronary artery disease and cerebrovascular disease were less common in ESKD patients with scleroderma.

Despite a lower prevalence of diabetes mellitus and cardiovascular burden, ESKD patients with scleroderma experienced a higher mortality rate than ESKD due to other causes (67 versus 57%, respectively, $P < 0.05$) and a relatively short time to death (2.43 years, 95% CI 1.753.11). On multivariate Cox proportional hazards model analysis, scleroderma was found to be a strong independent risk factor for mortality on dialysis (adjusted HR 2.47, 95% CI 1.99–3.05). This risk persisted even after consideration of renal function recovery as a competing risk. These findings are consistent with those of a previous United States Renal Data System (USRDS) study of 820 ESKD patients with scleroderma who initiated RRT between 1992 and 1997 [5]. Similar to our results, scleroderma ESKD patients were more likely to be female and Caucasian and less likely to have coronary artery or cerebrovascular disease than patients with ESKD due to other causes. In spite of this and the overall improvement in outcomes following ACE inhibitor therapy and aggressive blood pressure management [8, 9], scleroderma was associated with significantly worse survival compared with other ESKD patients (unadjusted 2-year survival 49 versus 64%).

Although mortality was greater in ESKD patients with scleroderma, this group was also more likely to experience dialysis-independent renal function recovery. A single-centre retrospective observational cohort study by Steen and Medsger [3] reported that more than half of the patients with scleroderma who initially required dialysis were able to discontinue it 3–18 months (mean 8 months) after initiation of dialysis. Similarly, Penn *et al.* [4] showed that although 64% of his patients with scleroderma renal crisis

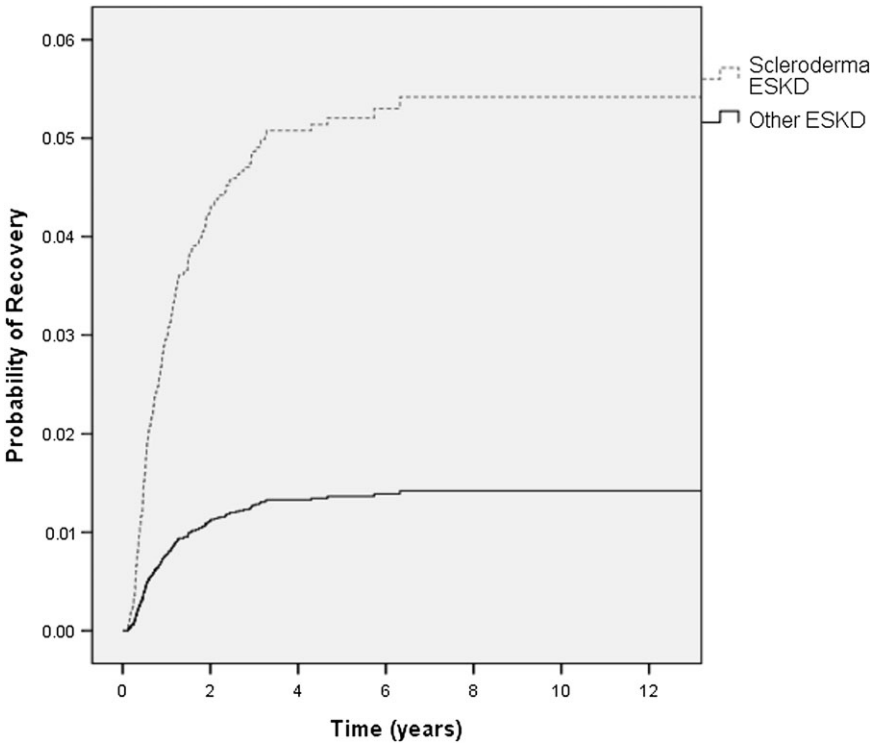

Fig. 4. Cox-adjusted survival curves for probability of renal recovery in Australian and New Zealand dialysis patients 1963–2005, according to underlying cause of renal disease (scleroderma or other). Curves are adjusted for age, gender, racial origin, dialysis era, dialysis modality at 90 days and state/country of residence. Scleroderma was a significant independent predictor of renal function recovery (HR 11.1, 95% CI 6.37–19.4).

Table 2. Baseline characteristics of all patients with ESKD secondary to scleroderma in Australia and New Zealand who underwent renal transplantation 1963–2005

Characteristic	Scleroderma ESKD transplant recipients ($n = 22$)
Age	47.7 ± 10.3
Male gender	3 (14%)
European racial origin	22 (100%)
Ever smoked	5/15 (33%)
Hypertension	16/16 (100%)
Diabetes mellitus	0/19 (0%)
Coronary artery disease	1/19 (5%)
Peripheral vascular disease	6/19 (32%)
Cerebrovascular disease	0/19 (0%)
Lung disease	5/19 (26%)
BMI (kg/m^2)	21.6 ± 4.2
Late referral	5/17 (29%)
Second renal allograft	2 (9%)

required RRT, approximately one-third of the patients were able to discontinue dialysis with a median time to renal recovery of 11 months (range 1–34 months). The probability of renal recovery was somewhat lower (10%) in our study possibly because patients needed to receive dialysis for at least 3 months before being considered to have ESKD. Consequently, a number of patients who recovered renal function prior to this were considered to have acute kidney failure and were not included in the ANZDATA registry analysis. Nevertheless, the appreciable incidence of recovery of dialysis-independent renal function in the first 12–18 months of dialysis initiation suggests that clinicians should be circumspect about proceeding with renal transplantation during this early period.

The overall proportion of scleroderma ESKD patients who received a renal transplant during the study period (17%) was comparable with that of other ESKD patients (17%). Deceased donor renal allograft survival in recipients with scleroderma ESKD was reasonable with observed 1-, 5- and 10-year survival rates of 78, 53 and 28%, respectively. These figures were very similar to those reported by Pham *et al.* [10] (79, 57 and 27%, respectively) and suggest that transplantation is a reasonable option in selected patients with scleroderma. The number of live donor renal transplant operations performed in scleroderma patients in this study (6) was too small to draw firm conclusions, although overall allograft survival was excellent.

The strengths of this study included its very large sample size and inclusiveness. We included all scleroderma patients receiving RRT in Australia and New Zealand during the study period, such that a variety of centres were included with varying approaches to the treatment of scleroderma and ESKD. This greatly enhanced the external validity of our findings. These strengths should be balanced against the study's limitations, which included limited depth of data collection. ANZDATA does not collect important information, such as severity of comorbidities, scleroderma activity indices, concomitant medications (such as ACE inhibitors), patient compliance, individual unit management protocols and laboratory values (such as C-reactive protein and autoantibody measurements). Even though we adjusted for a large number of patient characteristics, the possibility of

residual confounding could not be excluded. In common with other registries, ANZDATA is a voluntary Registry and there is no external audit of data accuracy, including the diagnosis of scleroderma.

In conclusion, scleroderma is an uncommon cause of ESKD, which is associated with significantly increased risks of both dialysis-independent renal function recovery and patient mortality compared with other causes of ESKD. In selected patients, renal transplant graft survival outcomes are reasonable, although should not be considered too early after commencement of dialysis in view of the appreciable likelihood of spontaneous renal function recovery.

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Conflict of interest statement. None declared.

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