Marked Revision (revisions indicated) | Note: must be .DOC(X) or .RTF
Click here to download Marked Revision (revisions indicated) | Note: must be .DOC(X) or .RTF Scleroderma ERA-EDTA

Characteristics and outcomes of patients with systemic sclerosis (scleroderma) requiring renal replacement therapy in Europe: results from the ERA-EDTA Registry

Hruskova Zdenka, **Pippias** Maria, **Stel** Vianda S., **Abad-Díez** Jose M., **Benítez Sánchez** Manuel, **Caskey** Fergus J., **Collart** Frederic, **De Meester** Johan, **Finne** Patrik, **Heaf** James G., **Magaz** Angela, **Palsson** Runolfur, **Reisæter** Anna Varberg, **Salama** Alan D., **Segelmark** Mårten, **Traynor** Jamie P., **Massy** Ziad A., **Jager** Kitty J., **Tesar** Vladimir.

Hruskova Zdenka MD PhD, Department of Nephrology, 1st Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic. email: zd.hruskova@gmail.com

Pippias Maria MBChB, ERA-EDTA Registry, Department of Medical Informatics, Academic Medical Center, Amsterdam Public Health Research Institute, University of Amsterdam, Amsterdam, the Netherlands. email: m.pippias@amc.nl

Stel Vianda S. PhD, ERA-EDTA Registry, Department of Medical Informatics, Academic Medical Center, Amsterdam Public Health Research Institute, University of Amsterdam, Amsterdam, the Netherlands. email: v.s.stel@amc.nl

Abad-Díez Jose M. MD MPH, Renal Registry of Aragon, Aragon Health Service, Spain. email: jmabaddiez@gmail.com

Benítez Sánchez Manuel MD, Hospital Juan Ramón Jiménez.Huelva. Andalusia. Spain. email: manuelbenitezsanchez@gmail.com

Caskey Fergus J. MD, 1.UK Renal Registry, Southmead Hospital, Bristol, BS10 5NB, UK. 2. Population Health Sciences, University of Bristol, Bristol, BS8 2PS, UK. email: mdfjc@bristol.ac.uk

Collart Frederic MD, French-Belgian ESRD Registry, Brussels, Belgium. email: Frederic.collart@chu-brugmann.be

De Meester Johan MD PhD, Department of Nephrology, Dialysis and Hypertension, Dutch-speaking Belgian Renal Registry (NBVN), Sint-Niklaas, Belgium. email: Johan.DeMeester@aznikolaas.be

Finne Patrik MD PhD, 1.Department of Nephrology, Helsinki University and Helsinki University Hospital, Helsinki, Finland, 2. Finnish Registry for Kidney Diseases, Helsinki, Finland. email: patrik.finne@helsinki.fi

Heaf James G. MD DMSc, Department of Medicine, Zealand University Hospital, Roskilde, Denmark. email: heaf@dadlnet.dk

Magaz Angela PhD: Unidad de Información sobre Pacientes Renales de la Comunidad Autónoma del País Vasco (UNIPAR), Basque country, Spain. email: amagaz@gac.com.es

Palsson Runolfur MD, 1. Division of Nephrology, Landspitali - The National University Hospital of Iceland, Reykjavik, Iceland, 2. Faculty of Medicine, School of Health Sciences, University of Iceland, Reykjavik, Iceland. email: runolfur@landspitali.is

Reisæter Anna Varberg MD, PhD, Department of Transplantation Medicine, Oslo University Hospital, Rikshospitalet, Norway. email: areisate@ous-hf.no

Salama Alan David MBBS PhD FRCP, University College London Centre for Nephrology, Royal Free Hospital, London, United Kingdom. email: a.salama@ucl.ac.uk.

Segelmark Mårten MD PhD, Department of Medical and Health Sciences and Department of Nephrology, Linköping University, Linköping, Sweden. email: marten.segelmark@liu.se

Traynor Jamie P. MD, Scottish Renal Registry, ISD Scotland, 5 Cadogan Street, Glasgow, G2 6QE, Scotland. email: jamie.traynor@nhs.net

Massy Ziad A. MD, PhD, 1. Division of Nephrology, Ambroise Paré University Hospital, APHP, Boulogne-Billancourt, France. 2. Institut National de la Santé et de la Recherche Médicale (INSERM) U1018, Team 5, CESP UVSQ, and University Paris Saclay, Villejuif, France. email: ziad.massy@aphp.fr

Jager Kitty J., MD PhD, ERA-EDTA Registry, Department of Medical Informatics, Academic Medical Center, Amsterdam Public Health Research Institute, University of Amsterdam, Amsterdam, the Netherlands. email: k.j.jager@amc.nl

Tesar Vladimir MD PhD, Department of Nephrology, 1st Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic. email: Vladimir.Tesar@vfn.cz

Corresponding author:

Maria Pippias, ERA-EDTA Registry, Department of Medical Informatics, Academic Medical Center, Amsterdam Public Health Research Institute, University of Amsterdam, Amsterdam, the Netherlands. email: m.pippias@amc.nl

Word count: Abstract: 298. Main text: 3,481

Short title: Scleroderma and ESRD in the ERA-EDTA Registry

ABSTRACT

Rational & Objective: Data on outcomes of patients with end-stage renal disease (ESRD) secondary to systemic sclerosis (scleroderma) requiring renal replacement therapy (RRT) is limited. We examined the incidence, prevalence and outcomes of European patients starting RRT for ESRD due to scleroderma.

Study Design: Cohort study.

Setting & Participants: Nineteen renal registries providing data to the ERA-EDTA Registry between 2002-2013.

Predictor: Patients with scleroderma versus two age- and sex-matched control groups without scleroderma (diabetes mellitus and disease other than diabetes).

Outcomes: Incidence, prevalence and survival.

Analytic approach: Incidence and prevalence was standardised to the European Union of 2005. Survival analyses were performed using Kaplan Meier and Cox regression.

Results: 342 patients with scleroderma (0.14% incident RRT patients) were included. The adjusted annual incidence of RRT for ESRD due to scleroderma varied between 0.11-0.26 per million population and the adjusted prevalence between 0.73-0.95. Recovery of independent renal function was greatest in the scleroderma group (7.6% vs. 0.6% in diabetes and 2.1% in non-diabetes, both P<0.001), though time required to achieve recovery was longer. In patients with scleroderma, 5-year survival probability from day 91 of RRT was 38.9% (95% confidence interval (CI):32.0%-45.8%), 5-year post-transplant patient survival was 88.2% (95%CI:75.3%-94.6%) and 5-year allograft survival was 72.4% (95%CI:55.0%-84.0%). The adjusted mortality from day 91 on RRT was higher in patients with scleroderma than in both control groups (hazard ratio: 1.25, 95%CI:1.05-1.48, and 2.00 95%CI=1.69-2.39). In contrast, patient and graft survival after kidney transplantation did not differ between patients with scleroderma and other groups.

Limitations: No data on extra-renal manifestations, treatment or recurrence.

Conclusions: Survival in patients with scleroderma from day 91 of ~~on~~ RRT was worse than in other causes of ESRD. Patient survival after transplantation was similar to the control groups. In this study, patients with scleroderma had higher renal function recovery rates than controls.

Index words: incidence, dialysis, end-stage renal disease, outcomes, scleroderma, kidney transplantation

Summary: Scleroderma is a rare chronic connective tissue disease with multi-organ involvement. There is limited published data on the outcomes of patients with end-stage renal disease (ESRD) secondary to scleroderma requiring renal replacement therapy (RRT); i.e. dialysis or kidney transplantation. In this European matched-cohort study we examined the incidence, prevalence and outcomes of 342 patients receiving RRT for ESRD due to scleroderma between 2002-2013. The matched controls had a diagnosis of diabetes mellitus or all other diagnoses except diabetes mellitus or scleroderma. Patients with scleroderma receiving RRT had a higher rate of kidney function recovery than the matched controls, though their overall survival was worse. Transplanted patients with scleroderma showed similar survival to the matched-controls, supporting the practice of kidney transplantation in these patients. However, given that these patients had a relatively high rate of recovery of their kidney function after starting dialysis we recommend a period of observation before kidney transplantation is performed.

INTRODUCTION

Systemic sclerosis (also referred to as scleroderma) is a rare chronic connective tissue disease with multi-organ involvement characterized by immune activation, vasculopathy, fibroblast dysfunction and excessive collagen accumulation in the skin and internal organs [1-3].

Renal disease in patients with scleroderma, particularly scleroderma renal crisis, result in significant morbidity and mortality [1]. Scleroderma renal crisis typically manifests with an acute onset of accelerated hypertension, rapidly progressive renal failure, frequently accompanied by microangiopathic haemolytic anaemia and thrombocytopenia. Occurring in approximately 3-10% of the scleroderma population, severe renal disease is commonly seen in patients with diffuse rather than limited cutaneous scleroderma [1, 4]. Until the 1970s, scleroderma renal crisis was recognized as the main cause of death in patients with scleroderma, though since the introduction of treatment with ACE inhibitors and reduction of corticosteroid doses the prognosis has substantially improved [4]. Nevertheless, about 25-50% of patients with scleroderma renal crisis will develop end-stage renal disease (ESRD) and the mortality associated with this condition remains high [1, 3-7].

There is limited knowledge regarding the prevalence of scleroderma renal crisis requiring renal replacement therapy (RRT) [8] and due to the infrequency of this condition there are a limited number of large multicentre or registry-based studies available [3-7, 9-11]. While the outcome of patients with scleroderma on dialysis seems to be uniformly worse than that of patients with other causes of ESRD [7, 11], the outcomes of kidney transplantation are less clear. It is known that renal function may recover after commencing RRT and there is an ongoing discussion regarding the optimal timing of kidney transplantation in patients with scleroderma [5, 12, 13].

We analysed the trends in incidence and prevalence of RRT for ESRD due to scleroderma in the European Renal Association - European Dialysis and Transplant Association (ERA-

EDTA) Registry and determined the patient characteristics, patient survival on RRT, patient and graft survival after kidney transplantation and causes of death in a large cohort of European patients initiating RRT between 2002 and 2013.

METHODS

Patients and data collection

The ERA-EDTA Registry collects data annually on patients starting RRT from national and regional renal registries in Europe. Renal registries sending individual patient level data to the ERA-EDTA Registry between 2002 and 2013, with at least 50% percent coverage of the general population were included in the study. The renal registries included were Austria, Dutch-speaking Belgium, French-speaking Belgium, Denmark, Finland, Greece, Iceland, the Netherlands, Norway, the Spanish regional renal registries of Andalusia, Aragon, Asturias, Basque Country, Cantabria, Castile and León, Catalonia, and Valencia, Sweden, United Kingdom: England, Northern Ireland and Wales, and United Kingdom: Scotland. The details of methods of data collection and data processing are described elsewhere [14]. The cause of death was defined and categorized according to the ERA-EDTA coding system [14]. All national and regional registries contributing data to the ERA-EDTA Registry followed national legislation with regard to ethics committee approval. Additional informed patient consent was not required for this study due to the de-identified nature of the information obtained.

Cases and matched control groups

The incidence, prevalence and patient survival on RRT analyses refer to patients starting RRT for ESRD due to "systemic sclerosis (scleroderma)" (ERA-EDTA primary renal disease [PRD] code 87 [14]), as recorded by the responsible physician. Patient and graft survival after

kidney transplantation refer to all patients with a diagnosis of scleroderma, or the matched controls (described below) who received their first kidney-only transplant between 1st January 2002 and 31st December 2013. This included patients who commenced RRT for ESRD before 2002. Age and sex were compared between scleroderma and non-scleroderma patients. We then formed two matched control groups of patients without scleroderma: 1) diabetes mellitus as a primary renal disease (PRD codes 80 and 81); and 2) patients without scleroderma and without diabetes mellitus ("non-diabetes") as a primary renal disease. Due to the low number of scleroderma patients, we matched 10 controls to 1 case. We matched on age group at the start of RRT (5-year age groups) and sex, when comparing patients receiving RRT. When comparing transplant recipients we matched on age group at the time of kidney transplantation (5-year age groups) and sex.

Statistical analysis

Time trends in the incidence of RRT per million population (pmp) were studied by year according to the date of RRT onset for all participating European countries/regions combined. Incidence was then assessed by country/region for the whole study period. Time trends in the prevalence of RRT pmp by year, defined as the number of patients alive and receiving RRT on 31st December of that year, divided by the mid-year general population, were studied for all participating European countries/regions. Incidence and prevalence rates were adjusted for age and sex using the European Standard Population of 2005 as a reference [15]. The time trends for the incidence rates and prevalence were estimated using Poisson regression, with the observed rate as the outcome and the year as the explanatory variable. The mean percentage annual change (MPAC) and its 95% confidence interval were computed from each model as $[\exp(\beta)-1] \times 100$, where β denotes the regression coefficient of time (i.e., change in the event rate per year). To examine whether the trends were linear, we performed Joinpoint

regression analysis. Joinpoint regression allows the identification of points in time where a significant change in the linear slope of a trend occurs. The analysis starts with zero joinpoints (i.e. a straight line) and then tests whether one or more joinpoints are significantly different and must be added to the model [16]. This was performed using the Joinpoint software (version 4.0.4) [17].

To compare the characteristics of scleroderma patients receiving RRT with each of the matched control groups separately, the Wilcoxon signed-rank test was used for continuous variables with a skewed distribution, and the McNemar square test for categorical variables. A two-tailed p-value <0.05 was considered as statistically significant. The first treatment modality was defined as treatment at day 91 after the start of RRT, as some patients received haemodialysis (HD) for a short period, while preparations were made for peritoneal dialysis (PD).

The Kaplan-Meier method and Cox regression analysis were used for the survival analyses. The patient survival on RRT was examined for individuals who initiated RRT for ESRD due to scleroderma between 2002 and 2013, and was compared with each of the matched control groups separately. Day 91 after the onset of RRT was taken as the starting point for these survival analyses. The death of the patient was the event studied. Follow-up time was censored at recovery of renal function, loss to follow-up and the end of the follow-up period (31st December 2013). Within the Cox regression analysis we took the strata (matched groups) into account. Patient survival on RRT was adjusted for time period (with three intervals, 2002-2005, 2006-2009 and 2010-2013) and country. Patient and graft survival after kidney transplantation was examined for patients who received their first transplant between 2002 and 2013 (regardless of the RRT start date). The scleroderma group was compared with each of the matched control groups separately. In these analyses the date of the first kidney transplant was defined as the first day of follow-up. For patient survival after transplantation,

the event studied was death, and in case of graft survival, the events were graft failure and death. Reasons for censoring were loss to follow-up and the end of follow-up period (31st December 2013). In the Cox regression analysis, patient and graft survival were adjusted for time period (as described above), country and donor type.

All analyses were performed using SAS 9.3.

RESULTS

Incidence and prevalence

A total of 342 patients with scleroderma were identified; comprising 0.14% of 236,082 patients starting RRT between 2002 and 2013.

The adjusted incidence of RRT for ESRD due to scleroderma between 2002 and 2013 was 0.18 pmp, ranging from 0.0 to 0.25 pmp between regions/countries (*Table 1*). The adjusted incidence of RRT for ESRD due to scleroderma was 0.26 pmp in 2002 and 0.12 pmp in 2013 (*Table 2*). There was a trend towards a decline in the incidence pmp over time but this did not reach statistical significance (MPAC = -3.6; [95%CI: -7.9; 0.8]).

During the study period, the adjusted prevalence of RRT for ESRD due to scleroderma varied between 0.73 and 0.95 pmp per year (*Table 2*) with a statistically significant increase in the prevalence pmp (MPAC = 2.0; [95%CI: 1.0; 2.9]).

Patient characteristics

Patients commencing RRT for ESRD due to scleroderma were significantly younger than patients (before matching) with other diagnoses (median age [25th-75th percentile] 59.9 [50.2-68.2] years for patients with scleroderma vs. 67.2 [54.4-76.1] years for all non-scleroderma patients; P<0.001). The proportion of women within the scleroderma group was higher than that of non-scleroderma group (68.1% vs. 38.2%; P<0.001).

~~Baseline~~ The group characteristics for the first 90 days or beyond the first 90 days are displayed in *Table 3* for patients initiating RRT for ESRD due to scleroderma and for the control groups, matched on age group and sex. The treatment modality at day 91 after the start of RRT was different in patients with scleroderma compared with the matched control groups, with a higher percentage of HD in the scleroderma patients (*Table 3*; P≤0.01 for both comparisons).

A higher number of deaths during the first 90 days on RRT was observed in the scleroderma patients compared with both matched control groups (12.6% vs. 3.9% and 4.0%, respectively, *Table 3*; P<0.001 for both comparisons).

The percentage of patients who achieved dialysis independency during the first 90 days on RRT did not differ between the scleroderma patients and the matched control groups. However, a higher proportion of patients with scleroderma recovered renal function beyond this time period (7.6% vs. 0.7% and 2.0% in the matched control groups diabetes and non-diabetes, respectively; both P<0.001). In patients who recovered renal function, the time to recovery was longer in those with a diagnosis of scleroderma than in both matched control groups (median 255.5 days [25^{th}-75^{th} percentile]: 130-454] vs. 112.0 [40.5-178] days (diabetes) and 167.5 [60-353] days (non-diabetes); both P<0.05) . The vast majority of patients who recovered renal function were female; 80.8% in patients with scleroderma, 83.2% for the matched control group with diabetes mellitus (p<0.05) and 60.0% in the non-diabetics matched control group (p<0.001). Median age was significantly lower in patients with scleroderma who recovered renal function than in both matched control groups (median 52.1 [25^{th}-75^{th} percentile: 47.9-56.8] vs. 64.6 [54.8-71.7] (diabetes) and 60.6 [50.4-66.3] (non-diabetes) (p<0.05). A total of 46 of the 342 (13.7%) scleroderma patients who started RRT between 2002 and 2013 received a kidney transplant during the study period. This percentage

was 18.7% for the control group diabetes mellitus and 27.1% for the control group non-diabetes mellitus (both p<0.001 in comparison with scleroderma patients).

Patient survival on RRT

Figure 1a depicts the 5-year patient survival on RRT after day 91 for patients who started RRT for ESRD due to scleroderma (38.9% [95%CI: 32.0% - 45.8%]) and for the matched control groups diabetes mellitus (46.0% [95%CI: 43.9% - 48.0%]), and non-diabetes mellitus (63.6% [95% CI: 61.6% - 65.6%]).

After adjustment for time period and country, the mortality from day 91 after the commencement of RRT was higher in patients with scleroderma than in both matched control groups (i.e. diabetes and non-diabetes, HR= 1.25 [95%CI: 1.05 – 1.48] and 2.00 [95%CI: 1.69-2.39], respectively; Figure 2a).

Patient and graft survival after kidney transplantation

Of the 57 patients with scleroderma who received their first kidney transplant between 2002 and 2013, the percentage of patients with a living donor transplant was 35.6% in the scleroderma group, and 17.8% and 29.8% in the matched control groups of diabetes and non-diabetes, respectively.

The median time on dialysis before receiving their first transplant was significantly greater in the patients with scleroderma (2.9 years [25^{th}-75^{th} percentile:1.6-4.7]) compared with the matched control groups (diabetes: 1.6 years [0.8-2.9]; and non-diabetes: 1.6 years [0.5-3.6], both p<0.001).

Figure 1b and 1c present the 5-year patient and graft survival after receiving a first kidney transplant, respectively, for patients with scleroderma (88.2% [95%CI: 75.3% - 94.6%] and 72.4% [95%CI: 55.0% - 84.0%]) and for the matched control groups with diabetes mellitus

(84.3% [95%CI: 80.5% - 87.4%] and 76.5% [95%CI: 72.2% - 80.3%]) and non-diabetes patients (89.3% [95%CI: 86.0% - 91.8%] and 81.5% [95%CI: 77.6% - 84.8%]), matched on age group at kidney transplantation and sex.

The risk of death for patients with scleroderma after kidney transplantation, adjusted for country, time period and donor type, did not differ from patients with diabetes or non-diabetes (Figure 2b). Similarly, graft survival adjusted for country, time period and donor type did not differ between the patients with scleroderma and the matched control groups (Figure 2c).

Causes of death

Table 4 shows the causes of death for patients who started RRT for ESRD due to scleroderma and for the matched control groups since day 91. Patients with scleroderma had fewer deaths due to cardiovascular events (particularly myocardial ischemia and cardiac arrest) compared with the matched control group of patients with diabetes. Compared with the matched control group of patients with non-diabetes, there were fewer deaths due to malignancy and cardiac arrest among the patients with scleroderma. Conversely, there were more deaths due to heart failure. A large proportion of deaths in the patients with scleroderma were reported as "miscellaneous" or unknown.

DISCUSSION

Systemic sclerosis is a very rare cause of ESRD, and as such analysis of this condition requires multi-centre, multi-national studies performed over a long period of time. This study describes the characteristics and outcomes of patients with scleroderma requiring RRT in a large European cohort. We found that the age and sex adjusted incidence of RRT for ESRD due to scleroderma between 2002 and 2013 was only 0.18 pmp. There was a trend towards a decline in the incidence over time but this did not reach statistical significance. Conversely

the prevalence significantly increased over the time period from 0.80 pmp in 2002 to 0.89 pmp in 2013. Furthermore, we observed that survival on RRT in patients with scleroderma was worse than in other causes of ESRD, whilst transplant recipients with scleroderma showed a similar survival to the control groups.

Scleroderma is a rare disease with an estimated annual incidence of 10-20 pmp and a prevalence of about 30-300 pmp. The occurrence of scleroderma is presumed to be higher in North America or Australia than in Europe or Asia, even though epidemiological studies are difficult to perform due to the low incidence and heterogeneity of the disease [18, 19]. The overall prevalence of scleroderma in the general population has been reported to increase, probably due to a greater awareness of the disease and improved patient survival [20], whereas there is in more recent studies some evidence suggesting a lower incidence of scleroderma renal crisis [1]. In keeping with this observation, we observed a non-statistically significant trend towards a decline in the incidence of RRT for ESRD due to scleroderma over time. However, as frequently seen in rare diseases with low numbers of patients, the number of cases in each year fluctuated. In Australia and New Zealand the incidence of patients with scleroderma requiring RRT for ESRD declined significantly between 2002 and 2013, from 0.51 pmp to 0.18 pmp [21]. The prevalence of RRT for ESRD caused by scleroderma increased during the study period. This is most likely explained by the improved survival of patients with scleroderma receiving RRT.

In this study, patients with scleroderma were less likely to be treated with PD than haemodialysis when compared with the matched control groups. This is in contrast to the data from the Australian and New Zealand registry where the use of PD was more common in patients with scleroderma than in patients with other causes of ESRD. However, PD is also a more frequent treatment option for ESRD in Australia than in Europe [11]. The choice of the

"optimal" modality of RRT in patients with scleroderma is generally considered problematic [22].

Scleroderma has long been recognized as a condition with a relatively high probability of renal recovery, even in patients requiring long-term dialysis [23]. This has important implications regarding the timing of kidney transplantation and some authors have recommended treating patients initially with dialysis for up to two years [13], whereas, for instance, the Canadian guidelines suggest that kidney transplantation could be considered in patients with scleroderma who have had quiescent disease for at least six months off cytotoxic agents and have limited extra-renal disease [12]. Previous reports have described renal recovery in patients with scleroderma to be as high as 38% [1, 6]. However the Australian and New Zealand Registry, which includes patients with presumed ESRD [11], reported renal recovery at 10%, which is similar to the 7.6% observed in our study. The proportion of patients with presumed ESRD who recovered renal function in this study was higher in patients with ESRD secondary to scleroderma than in patients with other causes of ESRD. It has been previously noted that systemic autoimmune diseases commonly show higher recovery rates than other PRDs [24, 25]. Importantly, 25% of patients who recovered renal function in the current study discontinued dialysis after more than 15 months of RRT, supporting the recommendation of delaying kidney transplantation in these patients. This may explain why the time spent on dialysis before transplantation was longer in patients with scleroderma than in the matched control groups in our study.

In previous studies exploring the survival of patients with scleroderma receiving RRT, a diagnosis of scleroderma mostly showed unfavourable outcomes [7, 11, 25] and was even identified as an independent predictor of death (HR of 2.47) [11]. Similarly, in the present study, we confirmed that both early and long-term mortality of patients with scleroderma receiving RRT remains high, and that the prognosis is worse than that of RRT patients with

diabetes. Among the causes of death, cardiovascular events, especially ischemic heart disease, were much less common in patients with scleroderma than in patients with diabetes. Nevertheless, detailed evaluation of the causes of death was limited due to the high number of unknown or miscellaneous causes reported in the patients with scleroderma.

Interestingly, patient and graft survival after kidney transplantation did not differ between patients with scleroderma and other PRDs. Given the poorer survival outcomes in patients with scleroderma, but similar post-transplant survival outcomes one must consider it likely that bias towards transplanting patients with scleroderma without major comorbidities i.e. the healthiest patients exists. Furthermore given the small samples size one cannot rule out a possible type 2 error. Nevertheless, our findings support the use of kidney transplantation in at least some patients with scleroderma, preferably those without major extra-renal complications, although transplantation should be delayed due to the aforementioned chance of renal recovery. The 5-year graft survival rate of 72.4% in our study is greater than the 3-year graft survival of 60.3% in the study by Gibney et al. [9], or the 5-year graft survival of 56.7% in the study by Pham et al. [26], both using United States (US) data. Although direct comparison is hardly possible, it may suggest improving survival over time, even though there are known geographical differences, with a somewhat better graft survival in Europe than in the US [27].

We are aware of the potential limitations of this study that include the registry-based nature of the data with a lack of detailed information regarding the disease course of individual patients, for example, disease duration prior to RRT, renal biopsy results, extent of extra-renal involvement, administered treatment, or disease recurrence after kidney transplantation. As such there are known and unknown factors which we cannot take into account within this study. It is known that ESRD in some patients with scleroderma is not necessarily caused solely by scleroderma renal crisis, they may have for example normotensive renal crisis,

penicillamine-associated nephropathy, scleroderma-associated vasculopathy, a mixed disease and overlap with for example, ANCA-associated vasculitis, in which case their renal survival and renal outcomes may be different [1, 28]. However, we were not able to distinguish such mixed causes of ESRD. Furthermore, on occasion it may be difficult to differentiate between acute cases of kidney failure requiring short-term (but prolonged) dialysis from true ESRD in patients with a diagnosis of scleroderma. The view regarding such patients may differ between registries, some of which may not enter patients who recovered renal function as ESRD into the database, even though the time on dialysis exceeded three months which is typically the cut-off point for entering a patient requiring long-term RRT into the ESRD registry. In addition we do not have access to comorbidity data including diabetic status (beyond diabetes mellitus as a cause of ESRD). Having data on patient co-morbidities is required to further differentiate patients, for example, this information could have in part, accounted for the differences in transplantation rates and time to transplantation between patients with a diagnosis of scleroderma and the control groups. Nor do we have data on vascular access. Problems related to vascular access in patients with scleroderma may have contributed to differences in RRT outcomes when compared to control patients, which we are not aware of. On the other hand, the ERA-EDTA Registry provides a unique opportunity to analyse a large cohort of European patients with scleroderma receiving RRT and also allows for the direct comparison of patients with scleroderma with other causes of ESRD.

In conclusion, we show that the overall survival of patients with scleroderma receiving RRT is worse than that of patients with ESRD due to diabetes or other PRDs. Although limited by a relatively low number of patients, our results suggest that kidney transplantation may be a sound therapeutic option in some patients with ESRD due to scleroderma, as graft and patient survival rates in this study were comparable with other non-diabetic causes of ESRD.

Acknowledgements

Contributions: research area and study design: ZH, MP, VSS, ADS, KJJ, VT; data acquisition: JMAD, MBS, FJC, FC, JDM, PF, JGH, AM, RP, ARV, MS, JPT; data analysis and interpretation: ZH, MP, VSS, JMAD, MBS, FJC, FC, JDM, PF, JGH, AM, RP, AVR, ADS, MS, JPT, ZAM, KJJ, VT; statistical analysis: ZH, VSS; supervision or mentorship: VSS, KJJ, VT. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

We would like to thank the patients and the staff of the dialysis and transplant units for contributing the data via their national and regional renal registries. We would also like to thank the following registries for the contribution of data: Austrian Dialysis and Transplant Registry [OEDTR] (R. Kramar); Dutch-speaking Belgian Society of Nephrology [NBVN] (B. De Moor and F. Schroven); French-speaking Belgian Society of Nephrology [GNFB] (JM. des Grottes); Danish Nephrology Registry [DNS]; Finnish Registry for Kidney Diseases; Greek Renal Registry ; Icelandic End-Stage Renal Disease Registry; Dutch End-Stage Renal Disease Registry [RENINE] (M. Hemmelder); Norwegian Renal Registry (T. Leivestad, and A. Åsberg); the Spanish regional registries of Andalusia [SICATA] (P. Castro de la Nuez), Aragon (J.M. Abad Diez), Asturias (J.R. Quirós, and RERCA Working Group), Basque Country [UNIPAR] (I. Moina), Cantabria (M. Arias Rodríguez), Castile and León, Catalonia [RMRC] (E. Arcos, and J. Comas), and Valencian region [REMRENAL]; Swedish Kidney Registry [SNR] (K.G. Prütz, M. Stendahl, M. Evans and S. Schön; UK Renal Registry (All the staff of the UK Renal Registry and of the renal units submitting data); Scottish Renal Registry [SRR] (All of the Scottish renal units); and the other ERA-EDTA Registry committee members not mentioned above for their advice in the analysis and the drafting of

this paper: A. Więcek, C. Couchoud, J.W. Groothoff, J. Harambat, M. Nordio, and I. Rychlik; and A. Kramer, in the AMC Registry office for data collection and management.

The ERA-EDTA Registry is funded by the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA). This article was written by Zdenka Hruskova, Maria Pippias, Vianda S. Stel, Jose M. Abaz, Manuel Benítez Sánchez, Fergus J.Caskey, Frederic Collart, Johan De Meester, Patrik Finne, James G. Heaf, Angela Magaz, Runolfur Palsson, Anna Varberg Reisæter, Alan Salama, Mårten Segelmark, Jamie P. Traynor, Ziad A. Massy, Kitty J. Jager, and Vladimir Tesar, on behalf of the ERA-EDTA Registry which is an official body of the ERA-EDTA.

Financial Disclosure: The ERA-EDTA Registry is funded by the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA). The funders of this study had no role in study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication. There are no conflicts of interest.

REFERENCES

1. Shanmugam VK, Steen VD. Renal disease in scleroderma: an update on evaluation, risk stratification, pathogenesis and management. Curr Opin Rheumatol 2012; 24(6): 669-676.
2. Saketkoo LA, Magnus JH, Doyle MK. The primary care physician in the early diagnosis of systemic sclerosis: the cornerstone of recognition and hope. Am J Med Sci. 2014; 347(1): 54-63.
3. Guillevin L, Bérezné A, Seror R, et al. Scleroderma renal crisis: a retrospective multicentre study on 91 patients and 427 controls. Rheumatology (Oxford). 2012; 51(3): 460-7.

4. Cozzi F, Marson P, Cardarelli S, et al. Prognosis of scleroderma renal crisis: a long-term observational study. Nephrol Dial Transplant. 2012; 27(12): 4398-403.
5. Steen VD, Medsger TA, Jr. Long-term outcomes of scleroderma renal crisis. Ann Intern Med 2000; 133(8): 600-603.
6. Penn H, Howie AJ, Kingdon EJ, et al. Scleroderma renal crisis: patient characteristics and long-term outcomes. QJM 2007; 100(8): 485-494.
7. Abbott KC, Trespalacios FC, Welch PG, Agodoa LY. Scleroderma at end stage renal disease in the United States: patient characteristics and survival. J Nephrol 2002; 15(3): 236-240.
8. Guillevin L, Mouthon L. Scleroderma Renal Crisis. Rheum Dis Clin North Am. 2015; 41(3): 475-88.
9. Gibney EM, Parikh CR, Jani A, Fischer MJ, Collier D, Wiseman AC. Kidney transplantation for systemic sclerosis improves survival and may modulate disease activity. Am J Transplant 2004; 4(12): 2027-2031.
10. Chang YJ, Spiera H. Renal transplantation in scleroderma. Medicine (Baltimore) 1999; 78(6): 382-385.
11. Siva B, McDonald SP, Hawley CM, et al. End-stage kidney disease due to scleroderma--outcomes in 127 consecutive ANZDATA registry cases. Nephrol Dial Transplant 2011; 26(10): 3165-3171.
12. Knoll G, Cockfield S, Blydt-Hansen T, et al. Canadian Society of Transplantation consensus guidelines on eligibility for kidney transplantation. CMAJ 2005; 173(10): 1181-1184.
13. Teixeira L, Mahr A, Berezne A, Noel LH, Guillevin L, Mouthon L. Scleroderma renal crisis, still a life-threatening complication. Ann N Y Acad Sci 2007; 1108: 249-258.

14. ERA-EDTA Registry: ERA-EDTA Registry Annual Report 2013. Academic Medical Center, Department of Medical Informatics, Amsterdam, the Netherlands, 2015
15. Eurostat: http://epp.eurostat.ec.europa.eu/portal/page/portal/population/data/database. Table: Average population by sex and five-year age groups. Date of extraction: July 15, 2010.
16. Kim HJ, Fay MP, Feuer EJ, et al. Permutation tests for joinpoint regression with applications to cancer rates. Stat Med 2000; 19(3): 335–351.
17. Joinpoint Regression Program, Version 4.0.4. May 2013; Statistical Research and Applications Branch, National Cancer Institute. Available at http://srab.cancer.gov/joinpoint [Accessed 2015-10-09].
18. Ranque B, Mouthon L. Geoepidemiology of systemic sclerosis. Autoimmun Rev. 2010; 9(5): A311-8.
19. Mayes MD. Scleroderma epidemiology. Rheum Dis Clin North Am. 2003; 29(2): 239-54.
20. Chifflot H, Fautrel B, Sordet C, Chatelus E, Sibilia J. Incidence and prevalence of systemic sclerosis: a systematic literature review. Semin Arthritis Rheum. 2008; 37(4): 223-35.
21. ANZDATA (Australia and New Zealand Dialysis and Transplant Registry) Annual Report. Available at http://www.anzdata.org.au/v1/annual_reports_download.html. [Accessed 2017-08-15].
22. Brown N, Summers A, Venning MC, Bruce IN. The challenges of dialysis in systemic sclerosis: between the devil and the deep blue sea? Case Rep Nephrol. 2012; 2012:865193.
23. Chu JK, Folkert VW. Renal function recovery in chronic dialysis patients. Semin Dial. 2010; 23(6): 606-13.

24. Hruskova Z, Stel VS, Jayne D, et al. Characteristics and Outcomes of Granulomatosis With Polyangiitis (Wegener) and Microscopic Polyangiitis Requiring Renal Replacement Therapy: Results From the European Renal Association-European Dialysis and Transplant Association Registry. Am J Kidney Dis. 2015; 66(4): 613-20.

25. Nissenson AR, Port FK. Outcome of end-stage renal disease in patients with rare causes of renal failure. III. Systemic/vascular disorders. Q J Med. 1990; 74(273): 63-74.

26. Pham PT, Pham PC, Danovitch GM, et al. Predictors and risk factors for recurrent scleroderma renal crisis in the kidney allograft: case report and review of the literature. Am J Transplant. 2005; 5(10): 2565-9.

27. Gondos A, Döhler B, Brenner H, Opelz G. Kidney graft survival in Europe and the United States: strikingly different long-term outcomes. Transplantation. 2013; 95(2): 267-74.

28. Derrett-Smith EC, Nihtyanova SI, Harvey J, Salama AD, Denton CP. Revisiting ANCA-associated vasculitis in systemic sclerosis: clinical, serological and immunogenetic factors. Rheumatology (Oxford). 2013; 52(10): 1824-31.

Table 1. Incidence of renal replacement therapy (RRT) for end-stage renal disease secondary to scleroderma, by country/region from 2002 to 2013

	All RRT	Scleroderma			
Country	N	N	%	N pmp	N pmp*†
Austria	14650	12	0.08	0.12	0.12
Belgium: Dutch-speaking	13968	16	0.11	0.22	0.20
Belgium: French-speaking	9943	11	0.11	0.20	0.23
Denmark	8431	17	0.20	0.26	0.25
Finland	5775	8	0.14	0.13	0.11
Greece	26181	31	0.12	0.23	0.21
Iceland	295	0	0	0	0
Netherlands	22131	37	0.17	0.19	0.19
Norway	5923	5	0.08	0.09	0.08
Spain: Andalusia	11817	11	0.09	0.11	0.12
Spain: Aragon	2031	3	0.15	0.19	0.18
Spain: Asturias	1772	2	0.11	0.15	0.14
Spain: Basque Country	3052	5	0.16	0.20	0.17
Spain: Cantabria	833	0	0	0	0
Spain: Castile and León	3654	8	0.22	0.27	0.23
Spain: Catalonia	12298	20	0.16	0.23	0.24
Spain: Valencian region	8582	7	0.08	0.12	0.12
Sweden	13640	19	0.14	0.17	0.17
United Kingdom	71106	130	0.18	0.19	0.19
All countries	**236082**	**342**	**0.14**	**0.18**	**0.18**

*Pmp=per million population.

†N pmp are adjusted for the age and sex distribution using the European Standard Population of 2005 as reference.

Table 2. Incidence and prevalence of renal replacement therapy for end-stage renal disease secondary to scleroderma per million population by year from 2002 to 2013, and the mean percentage annual change (MPAC) with 95% confidence interval (95%CI) for all countries/regions combined, adjusted for age and sex using the European Standard Population of 2005 as a reference.

Year	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**MPAC (95%CI)**
Incidence	0.26	0.22	0.20	0.20	0.17	0.20	0.20	0.11	0.15	0.27	0.14	0.12	-3.6 (-7.9; 0.8)
Prevalence	0.80	0.75	0.73	0.81	0.81	0.90	0.89	0.88	0.85	0.95	0.95	0.89	2.0 (1.0; 2.9)

Table 3. Characteristics of patients with end-stage renal (ESRD) disease secondary to a primary renal disease of scleroderma, or diabetes mellitus, or a primary renal disease other than scleroderma or diabetes mellitus ("non-diabetes"). The latter two groups form the matched-control groups which were matched on day 1 of renal replacement therapy (RRT), based on age group and sex*. The first part (shaded region) of the table refers to the first 90 days of commencing RRT for ESRD. The second part of the table (unshaded) refers to the group characteristics beyond 90 days of commencing RRT for ESRD.~~Characteristics and treatment modality at day 91 after the onset of renal replacement therapy (RRT) in patients with end-stage renal disease secondary to scleroderma and control groups matched on age group and sex*~~

	Scleroderma	Control group DM#	Control group Non-DM
First 90 days of commencing RRT for ESRD			
Patients at day 1 of RRT, N	342	3420	3420
Female at day 1 of RRT, %	68.1	68.1	68.1
Median age at day 1 of RRT, years [25th-75th percentile]	59.9 [50.2-68.2]	59.8 [50.3-68.1]	59.8 [50.3-68.2]
Patients in whom renal function recovered within 90 days, N [%])	3 (0.9)	21 (0.6)	38 (1.1)
Patients who died within 90 days, N [%]	43 (12.6)	135 (3.9)	138 (4.0)
Loss to follow-up/missing data within 90 days, N [%])	0 (0)	7 (0.2)	15 (0.4)
Treatment discontinued/ limited care within 90 days, N [%]	0 (0)	4 (0.1)	5 (0.2)
Beyond 90 days of commencing RRT for ESRD			
Patients at day 91 after start of RRT, N [% of number of patients at day 1]	296 (86.5)	3253 (95.1)	3224 (94.3)
Female at day 91 of RRT, %	67.2	67.9	68.4
Median age at day 91 of RRT, years [25th-75th percentile]	58.6 [49.4-68.1]	59.9 [50.2-68.2]	59.6 [49.9-68.1]
Treatment modality at day 91			
Haemodialysis, %	83.4	75.9	70.4
Peritoneal dialysis, %	14.9	20.6	22.5
Transplantation, %	1.7	3.5	7.1

* Control groups were matched on 5-year age groups and sex at day 1 after the initiation of RRT.

DM = diabetes mellitus as primary renal disease; the matched control groups did not include patients with scleroderma.

Table 4. Causes of death in patients starting renal replacement therapy (RRT) for end-stage renal disease secondary to scleroderma and the matched control groups since day 91

	Scleroderma n=296	Control group* DM n=3,253		Control group* Non-DM n= 3,224	
Number of deaths (%)	156 (52.7)	1,613 (49.6)		1,134 (35.2)	
Cause of death	%	%	P value#	%	P value#
Cardiovascular disease	21.2	36.3	**<0.001**	23.8	0.5
Myocardial ischaemia/infarction	4.5	12.8	**0.002**	5.5	0.6
Heart failure	8.3	5.3	0.1	4.4	**0.03**
Cardiac arrest; other cause/unknown	3.9	12.0	**0.002**	9.1	**0.03**
Cerebrovascular accident	4.5	6.2	0.4	4.9	0.8
Infection	14.1	17.3	0.3	15.4	0.7
Suicide/refusal of dialysis	3.9	1.7	0.06	2.6	0.4
Withdrawal from dialysis	5.8	5.8	0.9	5.6	0.9
Cachexia	3.9	1.6	0.04	2.0	0.2
Malignancy	1.9	3.8	0.2	10.4	**<0.001**
Miscellaneous	19.2	12.7	**0.02**	16.3	0.4
Unknown/unavailable/missing	30.1	20.8	0.007	23.9	0.09

Percentages may not add up to 100% because of rounding off. DM = diabetes mellitus as primary renal disease.

*Control groups are matched on 5-year age groups and sex; # comparison of control group with patients with scleroderma. The matched control groups did not include patients with scleroderma.

Legends to Figures

Figure 1

a. Kaplan-Meier survival analyses of patient survival on renal replacement therapy (RRT) for end-stage renal disease secondary to scleroderma (n=296) from day 91, and for the matched control groups with diabetes mellitus (DM; n=3253) and without diabetes mellitus (non-DM; n=3224) as primary renal disease. Control groups are matched on 5-year age groups at the onset of RRT and sex. Median age was 59.9 years and 68.1% were female in the scleroderma group and in each matched control group. The matched control groups did not include patients with scleroderma.

b. Kaplan-Meier survival analyses of patient survival after kidney transplantation for end-stage renal disease secondary to scleroderma (n=57), and for the matched control groups with diabetes mellitus (DM) and without diabetes mellitus (non-DM) as primary renal disease (n=565 for each matched control group). Control groups are matched on 5-year age groups at the time of transplantation and sex. Median age was 49 years and 62.7% were female in the scleroderma group and in each matched control group. The matched control groups did not include patients with scleroderma.

c. Kaplan-Meier survival analyses of graft survival after kidney transplantation for end-stage renal disease secondary to scleroderma (n=57), and for the matched control groups with diabetes mellitus (DM) and without diabetes mellitus (non-DM) as primary renal disease (n=565 for each matched control group). Control groups are matched on 5-year age groups at the time of transplantation and sex. Median age was 49 years and 62.7% were female in the scleroderma group and in each matched control group. The matched control groups did not include patients with scleroderma.

Figure 2.

a. Hazard ratios (HR; 95% confidence intervals) for death on RRT from day 91 for patients with scleroderma versus the matched control groups, unadjusted and adjusted for time period and country. Control groups with diabetes mellitus (DM) and without diabetes mellitus (non-DM) as primary renal disease are matched on 5-year age groups at the onset of renal replacement therapy and sex. The scleroderma group and each matched control group had a median age of 59.9 years and 68.1% were female. The matched control groups did not include patients with scleroderma.

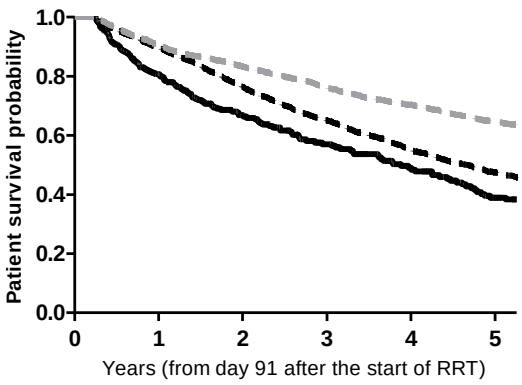
b. Hazard ratios (HR; 95% confidence intervals) for death after kidney transplantation for patients with scleroderma versus the matched control groups, unadjusted and adjusted for time period, country and donor type. Control groups with diabetes mellitus (DM) and without diabetes mellitus (non-DM) as primary renal disease are matched on 5-year age groups at the time of transplantation and sex. The scleroderma group and each matched control group had a median age of 49 years and 62.7% were female. The matched control groups did not include patients with scleroderma.

c. Hazard ratios (HR; 95% confidence intervals) for graft failure after kidney transplantation in patients with scleroderma versus the matched control groups, unadjusted and adjusted for time period, country and donor type. Control groups with diabetes mellitus (DM) and without diabetes mellitus (non-DM) as primary renal disease are matched on 5-year age groups at the time of transplantation and sex. The scleroderma group and each matched control group had a median age of 49 years and 62.7% were female. The matched control groups did not include patients with scleroderma.

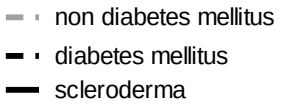
Figure 1

Click here to download Figure
Scleroderma_Figure_1.pdf

a

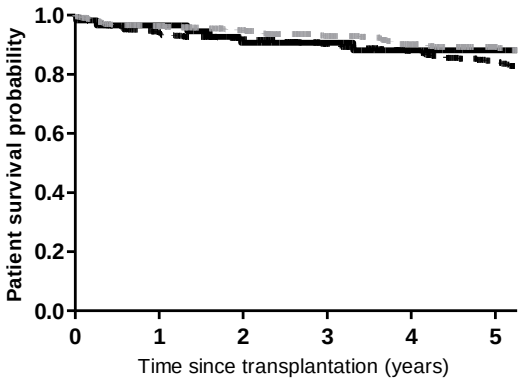


Non-DM	3224	2986	2326	1924	1549	1250
DM	3253	3046	2372	1783	1331	982
Scleroderma	296	272	180	127	95	75

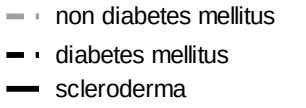


From day 91 of RRT start	Non diabetes	Diabetes	Scleroderma
1 year	88.0 (86.7; 89.1)	86.6 (85.3; 87.9)	76.4 (70.1; 81.1)
2 year	81.6 (80.1; 83.0)	73.3 (71.6; 74.9)	63.7 (57.4; 69.3)
3 year	74.4 (72.7; 76.0)	62.3 (60.4; 64.1)	56.5 (48.8; 61.5)
4 year	68.8 (67.0; 70.6)	53.3 (51.3; 55.2)	49.1 (42.2; 55.5)
5 year	63.6 (61.6; 65.6)	46.0 (43.9; 48.0)	38.9 (32.0; 45.8)

b

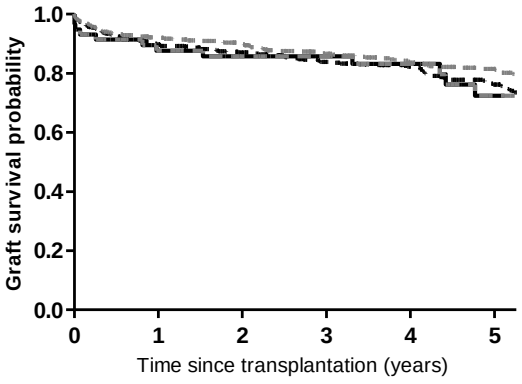


Non-DM	565	487	420	351	291	242
DM	565	477	407	348	284	220
Scleroderma	57	50	42	35	27	22

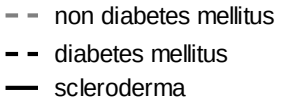


From day 91 of RRT start	Non diabetes	Diabetes	Scleroderma
1 year	96.3 (94.4; 97.6)	94.0 (92.2; 96.0)	90.7 (86.9; 99.1)
2 year	95.0 (92.8; 96.5)	91.6 (89.3; 93.9)	90.7 (86.9; 99.1)
3 year	92.9 (90.3; 94.8)	90.3 (87.4; 92.5)	90.7 (86.9; 99.1)
4 year	90.2 (87.1; 92.6)	88.0 (84.8; 90.6)	88.2 (75.3; 94.6)
5 year	89.3 (86.0; 91.8)	84.3 (80.5; 87.4)	88.2 (75.3; 94.6)

c



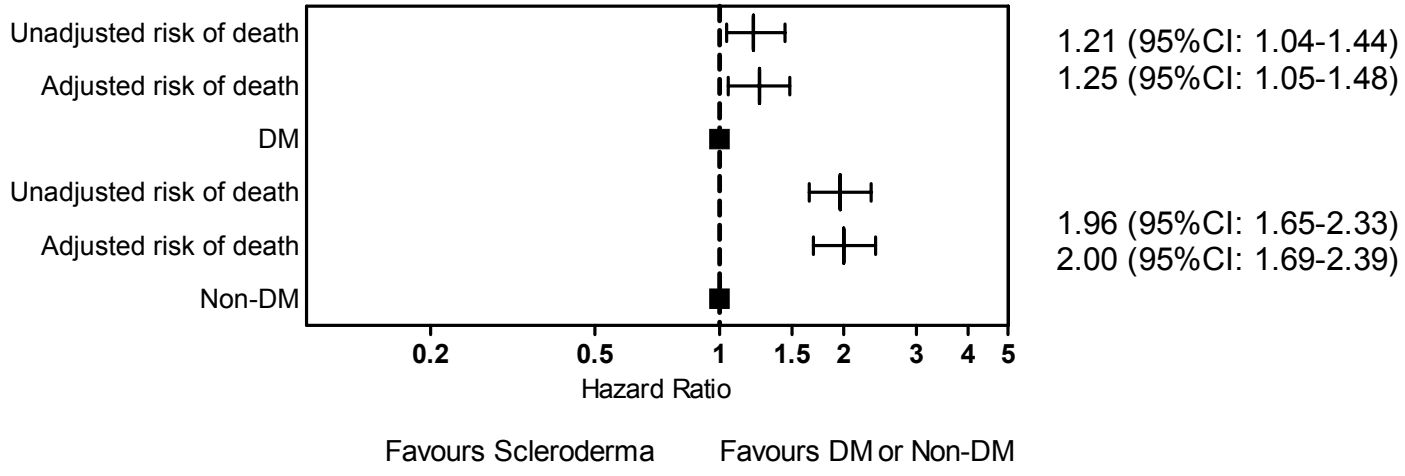
Non-DM	565	454	385	322	265	119
DM	565	466	398	328	272	221
Scleroderma	57	46	39	32	25	17



From day 91 of RRT start	Non diabetes	Diabetes	Scleroderma
1 year	92.2 (89.7; 94.1)	90.1 (87.3; 92.2)	89.6 (78.3; 95.2)
2 year	90.0 (87.2; 92.2)	87.1 (84.0; 89.6)	85.8 (73.5; 92.6)
3 year	86.7 (83.4; 89.3)	84.9 (81.0; 87.2)	85.8 (73.5; 92.6)
4 year	86.7 (83.4; 89.3)	82.6 (79.1; 85.6)	83.2 (69.9; 91.0)
5 year	81.5 (77.6; 84.8)	76.5 (72.2; 80.3)	72.4 (55.0; 84.0)

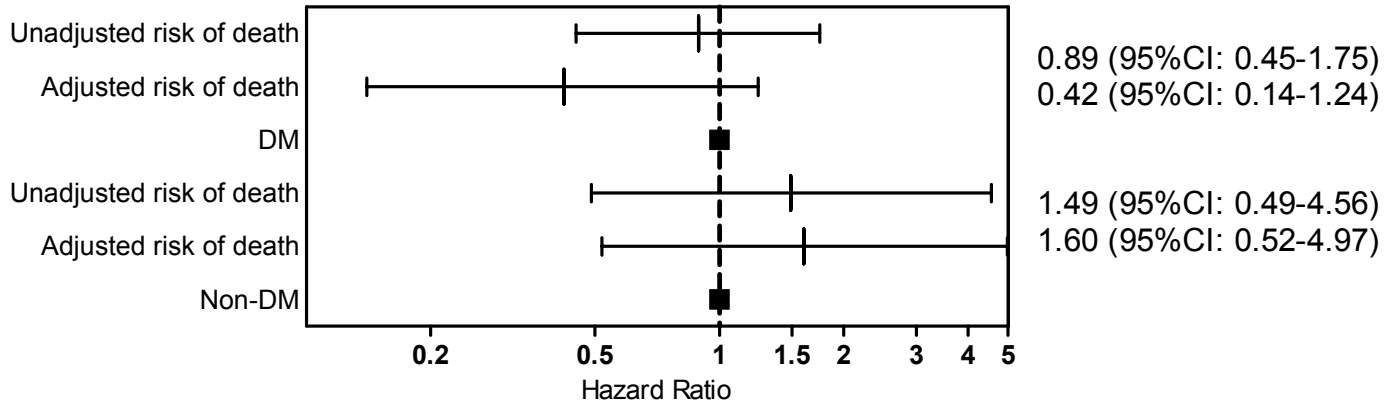
Figure 2 Click here to download Figure Figure_2.pdf

a. Risk of death after day 91 of commencing RRT: patients with scleroderma versus matched DM or Non-DM groups.



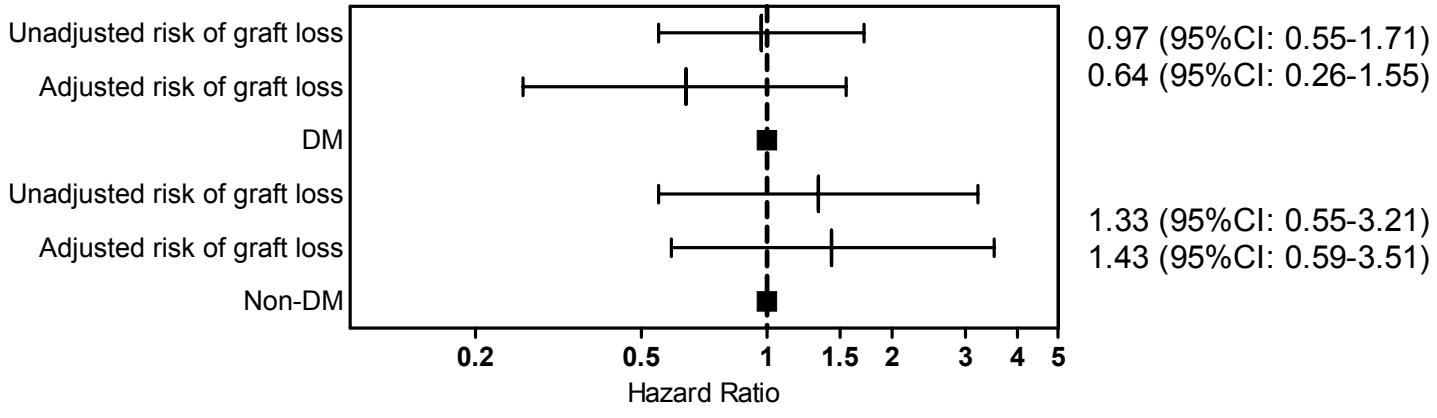
Favours Scleroderma Favours DM or Non-DM

b. Risk of death after kidney transplantation: patients with scleroderma versus matched DM or Non-DM groups.



Favours Scleroderma Favours DM or Non-DM

c. Risk of graft failure after kidney transplantation: patients with scleroderma versus matched DM or Non-DM groups.



Favours Scleroderma Favours DM or Non-DM

Marked Revision (revisions indicated) | Note: must be .DOC(X) or .RTF

Click here to access/download
Unmarked Revision | Note: must be .DOC(X) or .RTF
Scleroderma ERA-EDTA Registry_Clean.doc