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ORIGINAL ARTICLE

Kidney transplantation in patients with systemic sclerosis: a nationwide multicentre study

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SUMMARY

Kidney transplantation is one of the therapeutic options for end-stage renal disease (ESRD) in systemic sclerosis (SS). Current evidence demonstrates poorer patient and graft survival after transplantation in SS than in other primary kidney diseases. All the patients presenting ESRD associated with SS who had received a kidney allograft between 1987 and 2013 were systematically included from 20 French kidney transplantation centres. Thirty-four patients received 36 kidney transplants during the study period. Initial kidney disease was scleroderma renal crisis in 76.4%. Extrarenal involvement of SS was generally stable, except cardiac and gastrointestinal involvements, which worsened after kidney transplantation in 45% and 26% of cases, respectively. Patient survival was 100%, 90.3% and 82.5% at 1, 3 and 5 years post-transplant, respectively. Pulmonary involvement of SS was an independent risk factor of death after transplantation. Death-censored graft survival was 97.2% after 1 and 3 years, and 92.8% after 5 years. Recurrence of scleroderma renal crisis was diagnosed in three cases. In our study, patient and graft survivals after kidney transplantation can be considered as excellent. On this basis, we propose that in the absence of extrarenal contraindication, SS patients presenting with ESRD should be considered for kidney transplantation.

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Key words

graft and patient survival, kidney transplantation, systemic sclerosis

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Introduction

Systemic sclerosis (SS) is a connective tissue disorder involving multiple organs and characterized by excessive collagen deposition, autoimmunity, vascular hyperreactivity and obliterative microvascular phenomena [1]. Vascular injury manifests as Raynaud's phenomenon (RP), digital ischaemia, pulmonary arterial hypertension and scleroderma renal crisis (SRC) [2]. Renal involvement in SS most frequently presents as rapidly progressive renal failure with malignant hypertension and oliguria, known as SRC. SRC is associated with limited skin involvement in 1% SS patients, and with diffuse skin involvement in 5% cases. The introduction of angiotensin-converting enzyme (ACE) inhibitors has tempered the poor renal and overall prognosis associated with SRC, and often leads to reversal of the syndrome [3–5]. However, up to 50% of patients still require long-term dialysis, and in this situation, kidney transplantation may be a valuable therapeutic option [6]. Nevertheless, data available show poorer patient and graft survival than in other primary renal diseases [7]. Here, we report an observational study on 34 patients with SS who underwent renal transplantation. We report patient and graft outcomes, and, for the first time, evolution of extrarenal involvement after transplantation.

Materials and methods

This retrospective multicentre nationwide study was performed in all the 20 kidney transplantation centres in France. A questionnaire was sent to each department in order to ensure a systematic data collection for every patient with systemic sclerosis having received a kidney transplant between 1987 and 2013. The number of patients with SS transplanted during this period was confirmed with the national database of kidney transplantation Cristal. Diagnosis of SS was performed in each centre according to the diagnostic criteria used in the concerned period. During the inclusion period, from 1987 to 2013, four classification criteria were successively used [8–11]. Scleroderma renal crisis (SRC) was defined by a severe arterial hypertension associated with microangiopathic haemolytic anaemia, thrombocytopenia and accelerated oliguric renal failure, confirmed or not by a renal biopsy, according the diagnostic criteria reported by Steen in 2003 [12,13].

The medical charts and demographics were recorded, including age, gender, weight, comorbidities, type of dialysis before transplantation, cause of the renal

disease, kidney histology, history of scleroderma, HLA immunization and date of transplantation. Data regarding the renal transplantation and outcomes were collected, including patient and graft survival, evolution of scleroderma after transplantation, immunosuppressive therapy, acute rejection episodes, causes of graft loss and patient death.

Extrarenal involvement of systemic sclerosis was defined as following:

- 1 Cardiac involvement: presence or history of myocardial infarction and/or pericarditis
- 2 Pulmonary involvement: presence or history of interstitial and/or pulmonary fibrosis and/or pulmonary artery hypertension
- 3 Gastrointestinal involvement: presence or history of reflux, oesophagitis, gastritis, pancreatitis, oesophageal sclerosis or dysmotility syndrome.
- 4 Rheumatologic involvement: presence or history of polyarthralgia or tendonitis
- 5 Cutaneous involvement: presence or history of cutaneous sclerosis and/or Raynaud phenomenon and/or digital ischaemia.

Clinical records were specifically reviewed for the evolution of lesions related to SS after kidney transplantation. Worsening, improvement or stability of extrarenal involvement was considered on the basis of the available data from each centre.

Quantitative data were presented as mean (SD) or median (range) when data were not normally distributed. Qualitative data were presented as percentages. Survival data were assessed by Kaplan–Meier analysis. Cox regression analysis was used to evaluate potential risk factors for patient survival. All factors with $P < 0.1$ in the univariate analysis were included in the multivariate model. A P value < 0.05 was considered statistically significant. All analyses were performed using STATVIEW version 5.0 (SAS Institute, Cary, NC, USA).

Results

Thirty-four patients (36 kidney transplantations) were included. Two kidney allografts came from living donors. The patients' characteristics at the time of transplantation are described in Table 1. Characteristics of extrarenal involvement are summarized in Table 2. Cardiac involvement was associated in 11 of 34 patients (32.3%), whereas pulmonary involvement was present in 13 of 34 recipients (38.2%). Gastrointestinal and rheumatic involvement was associated, respectively, in 53% and 20.6% cases. All the patients demonstrated

cutaneous involvement. There were no specific contraindications to transplantation regarding disease activity, serological markers or active extrarenal manifestations of SS. Nevertheless, in the case of too advanced cardiac or pulmonary involvement, kidney transplantation was not considered, but these criteria varied between centres.

The initial renal disease was scleroderma renal crisis in 76.4% (26/34) patients (Table 1). A biopsy was carried out in 18 of 34 patients. It showed evidence of scleroderma renal crisis in 13 of 18 patients. Three patients developed a biopsy-proven MPO ANCA vasculitis (8.8%). The two remaining biopsies showed chronic vascular changes with fibrosis and tubular atrophy. Systemic sclerosis and kidney disease were simultaneously diagnosed in 16 patients, and in 62% (10/16) with a diagnosis of SRC. Renal failure appeared after a mean period of time of 24 months (0–283) after systemic sclerosis had been diagnosed. At the time of renal diagnosis, 15 of 34 patients (44.1%) required dialysis immediately. Twenty-eight patients of 34 underwent haemodialysis (82%), while six (18%) were on peritoneal dialysis. In three of 34 patients, dialysis was transiently withdrawn because of a spontaneous recovery of renal function, but all the patients were on dialysis supportive treatment at the time of transplantation.

Kidney transplantation was performed 45 months (5–153) after the initiation of dialysis, and 25 months (3–141) after registration on the waiting list (Table 1). It was the first transplantation in 34 of 36 cases. Only one of 36 grafts (2.7%) had a primary nonfunction. Five (13.9%) presented a delayed graft function, and five (13.9%) presented an early episode of rejection. No patient died immediately after surgery. Induction of immunosuppressive therapy included antilymphocyte serum in 17 of 36 grafts (47.2%), anti-IL-2 receptor antibodies in 14 (38.9%), calcineurin inhibitors in 33 (91.7%) and mycophenolate mofetil in 28 (77.8%). Induction also included steroids in 32 of 36 (88.9%) cases, and high dose (60 mg prednisolone to 500 mg methylprednisolone) was given in 27 cases (84%). Steroids were stopped in 11 of 30 cases (36.7%), after an average period of time of 6.4 months (1.0–12.5). Immunosuppressive therapy is summarized in Table 3.

Renin–angiotensin–aldosterone system blockers were largely prescribed (27/36, 75%), introduced after a mean period of time of 10.1 months after kidney transplantation.

We observed seven graft losses after a mean 82.2 months (1.5–167). Four were secondary to chronic

Table 1. Characteristics of patients at transplantation.

Variable	
Age (year)	52.9 (27.7–75.5)
Sex ratio M/F	11/23
BMI (kg/m ²)	21.5 (13.0–27.8)
Diabetes – <i>n</i> (%)	1 (2.8)
Hypertension – <i>n</i> (%)	23 (63.9)
Active smoking – <i>n</i> (%)	12 (33.3)
Coronary artery disease – <i>n</i> (%)	0 (0)
Initial renal disease	
Scleroderma renal crisis – <i>n</i> (%)	26 (76.5)
ANCA vasculitis – <i>n</i> (%)	3 (8.8)
Other – <i>n</i> (%)	5 (14.7)
Extrarenal involvement of scleroderma before transplantation	
Pulmonary – <i>n</i> (%)	13 (38.2)
Cutaneous – <i>n</i> (%)	34 (100)
Cardiac – <i>n</i> (%)	11 (32.4)
Rheumatologic – <i>n</i> (%)	7 (20.6)
Digestive – <i>n</i> (%)	19 (55.8)
Time frame	
Between RRT and registration on waiting list (months)	25 (3–141)
Between RRT and RTx (months)	45 (5–153)

RRT, renal replacement therapy; RTx, renal transplantation.

antibody-mediated rejection (positive for donor-specific antibody), one to scleroderma renal crisis recurrence, one to a tumour of the graft (renal cell carcinoma) and one was due to an infectious disease (urinary septic shock). Death-censored graft survival was 97.2% after 1 and 3 years and 92.8% after 5 years (Fig. 1).

Patient survival was 100%, 90.3% and 82.5% at 1, 3 and 5 years post-transplant, respectively. One patient died due to extrarenal involvement of systemic sclerosis, two to infectious diseases, three to cardiovascular disease and one to cancer. Death occurred after an average of 61.7 months (16.5–150.7 months) (Fig. 2).

Three cases of scleroderma renal crisis recurrence were suspected clinically, ascertained by a renal graft biopsy: the first biopsy showed typical lesions of thrombotic microangiopathy, and the two others showed fibroproliferative endarteritis with ischaemic glomeruli and interstitial fibrosis. They occurred, respectively, 1, 4 and 57 months after transplantation. The characteristics of patients with disease recurrence are presented in Table 4. In the 26 patients with SRC as initial renal disease, 14 (54%) experienced a renal graft biopsy during their follow-up, after a mean of 16 months. Three biopsies demonstrated the three suspected recurrence of SRC. In the 11 other kidney biopsies performed, no vascular change

Table 2. Characteristics of extrarenal involvements and evolution after kidney transplantation.

Patient	SRC	Heart		Lung		Digestive tract		Joint and muscular		Skin	Follow-up after KT (months)
		Type	After KT	Type	After KT	Type	After KT	Type	After KT		
1	No	Pericarditis	Improve (NR)	ILD	Stable	Reflux/gastritis	Stable		Yes	Stable	57
2	Yes	Constrictive pericarditis	Stable						Yes	Stable	62.8
3	Yes	Pericarditis	Stable	PAH	Stable	Reflux/gastritis	Worsening		Yes	Stable	150.8
4	Yes	Myocardiodiopathy	Worsening	PAH	Stable	Reflux	Stable	Polyarthralgia	Yes	Stable	50.6
5	Yes	Myocardiodiopathy	Worsening	PAH	Worsening	Reflux/oesophageal sclerosis	Stable	Polyarthralgia	Yes	Stable	10.2
6	Yes	Myocardiodiopathy	Worsening			Reflux	Stable	Polyarthralgia	Yes	Stable	0.9
7	Yes	Pericarditis	Improve (NR)			Oesophagitis	Stable	Polyarthralgia	Yes	Stable	77.8
8	No	Pericarditis/myocardiodiopathy	Worsening				Worsening		Yes	Worsening	63.1
9	Yes	Pericarditis	Worsening (tamponade)	ILD	Stable				Yes	Stable	30.2
10	Yes	Pericarditis	Improve (NR)	ILD + PAH	Improve	Gastritis	Stable		Yes	Stable	17.8
11	Yes	Myocardiodiopathy	Stable	Pleurisy	Improve (NR)				Yes	Stable	60.1
12	Yes	Pericarditis	Stable	ILD	Stable	Pancreatitis	Stable		Yes	Improve	19.4
13	No	Myocardiodiopathy	Stable	ILD	Stable	Reflux	Worsening		Yes	Stable	68
14	Yes	Pericarditis	Stable	ILD	Stable	Oesophagitis	Stable		Yes	Stable	60.3
15	No	Pericarditis	Worsening	ILD	Improve	Dysmotility Syndrome	Improve	Polyarthralgia	Yes	Stable	56.6
16	Yes	Pericarditis	Stable	PAH	Stable				Yes	Stable	60.9
17	Yes	Pericarditis	Stable	ILD	Stable	Reflux/oesophagitis	Stable		Yes	Stable	18.3
18	No	Pericarditis	Stable					Polyarthralgia	Yes	Stable	76.3
19	Yes	Pericarditis	Stable						Yes	Stable	10.6
20	No	Pericarditis	Stable						Yes	Stable	14.8
21	Yes	Pericarditis	Stable			Reflux/oesophagitis	Stable		Yes	Stable	160.6
22	Yes	Pericarditis	Stable			Reflux/gastritis	Worsening		Yes	Stable	21.2
23	No	Pericarditis	Stable						Yes	Stable	30.4
24	Yes	Pericarditis	Stable						Yes	Stable	96.3
25	Yes	Pericarditis	Stable						Yes	Stable	166.5
26	Yes	Pericarditis	Stable			Reflux	Stable		Yes	Stable	96
27	Yes	Pericarditis	Stable			Reflux/oesophagitis	Stable		Yes	Stable	71.9
28	Yes	Pericarditis	Stable			Reflux	Stable		Yes	Worsening	16.5
29	Yes	Pericarditis	Stable						Yes	Stable	104.7
30	No	Pericarditis	Stable						Yes	Worsening	50.5
31	Yes	Pericarditis	Stable			Reflux/oesophagitis	Stable	Tendonitis	Yes	Worsening	96.6
32	Yes	Pericarditis	Stable			Reflux/oesophagitis	Worsening		Yes	Worsening	69
33	Yes	Pericarditis/myocardiodiopathy	Worsening						Yes	Stable	167.4
34	Yes	Pericarditis/myocardiodiopathy	Worsening						Yes	Stable	118.8
Total (%)	26/34	11/34		13/34		19/34		7/34	34/34		
	76.40%	32.40%		38.20%		55.80%		20.60%	100%		

PAH, pulmonary artery hypertension; ILD, interstitial lung disease; SRC, scleroderma renal crisis; NR, no recurrence; KT, kidney transplantation.

(fibroproliferative endarteritis or thrombotic microangiopathy) matching with a renal involvement of SS was observed.

The evolution of extrarenal involvement is depicted in Table 2. No patient developed new extrarenal manifestation after kidney transplantation. After a mean follow-up of 65.7 months (0.9–167.4 months), cutaneous, pulmonary, cardiac, rheumatic and digestive involvements remained stable or improved in 85.3%, 92.3%, 54.5%, 85.7% and 72.2% cases, respectively. Five of 11 patients showed cardiac worsening, and five of 18 showed digestive worsening.

To determine the risk factors for patient death after kidney transplantation, we performed a Cox regression analysis. Univariate and multivariate analyses revealed that the presence of pulmonary involvement associated with SS [HR = 10.5, 95% CI (1.1–96.7); $P = 0.03$] was an independent risk factor (Table 5).

Discussion

The first kidney transplantation performed in a patient with systemic sclerosis was reported by Richardson [14]. At that time, kidney transplantation was considered safe for patients whose primary organ involvement by scleroderma was renal, and whose other lesions were relatively stable. Many years later, Gibney *et al.* [6] confirmed that kidney transplantation improved patient survival. They studied 258 ESRD patients with a diagnosis of SS, of whom 142 were transplanted, while the other patients remained

on the waiting list [United Network for Organ Sharing (UNOS) registry from 1985 to 2002]. Patient survival with a transplant was, respectively, 90.1% and 79.5% after 1 and 3 years, significantly higher compared with SS patients on the waiting list (81.1% and 54.6%, respectively). Unfortunately, the authors did not provide information regarding the severity of the systemic disease, and whether SS was the cause of ESRD was unknown. Based on the current literature, it is therefore difficult to know which ESRD patients with systemic sclerosis would most probably benefit from kidney transplantation, and whether specific extrarenal involvements should be a contraindication to kidney transplantation.

As reported in the literature, survival in patients with ESRD SS is dramatically poor [12,15–17]. According to the French ESRD patients' database (REIN registry: Réseau épidémiologie et information en néphrologie), 98 patients with SS were dialysed between 2001 and 2013, of which 81% had ESRD secondary to a scleroderma renal crisis. In this French cohort, patient survival was, respectively, 75%, 55% and 32% after 1, 3 and 5 years. Pham *et al.* [18] reported a patient survival of, respectively, 89.8%, 81.1%, 72.7% and 53.7% at 1, 3, 5 and 10 years post-transplant in 260 kidney allograft recipients from UNOS registry, whose transplantation was performed between 1987 and 2004. Bleyer *et al.* [7] analysed the relationship between the underlying renal disease and renal transplantation outcomes in 23 838 living and 67 183 deceased donor renal transplantations from the UNOS registry between 1987 and 1996, and found that outcomes (patient and graft survival) in patients with SS were reduced, compared to the patients transplanted because of another renal disease. In comparison, in our study, the patient survival was excellent after transplantation. The absence of a control group including patients with SS remaining on the waiting list is an important limit. We therefore cannot ascertain which patients with SS may most probably benefit from kidney transplantation. However, these meaningful data could help clinicians to better define the ideal recipient for transplantation. In addition, a potential selection bias is that our population might have undergone a more selective screening before registration on the waiting list. Nevertheless, the severity of SS was confirmed by extrarenal involvement of SS.

Non-death-censored graft survival in our study was, respectively, 97.2%, 87.8% and 76.6% after 1, 3 and 5 years, superior to the survival reported by Gibney *et al.* [6], respectively, 68.0% and 60.3% after 1 and 3 years post-transplant (UNOS registry from 1985 to

Table 3. Immunosuppressive therapy after kidney transplantation.

Induction immunosuppressive therapy	%
Induction	86.1
Antilymphocyte serum (%)	47.2
Anti-IL-2 receptor (%)	38.9
Steroids (%)	88.9
Steroid pulse (%)	84.0
Maintenance immunosuppressive therapy	
Steroids (%)	83.3
Steroid weaning (%)	30.5
CNI (%)	91.7
Ciclosporin	30.7
Tacrolimus	61.0
Antimetabolites (%)	91.7
MMF	77.8
Azathioprine	13.9
Sirolimus (%)	5.5

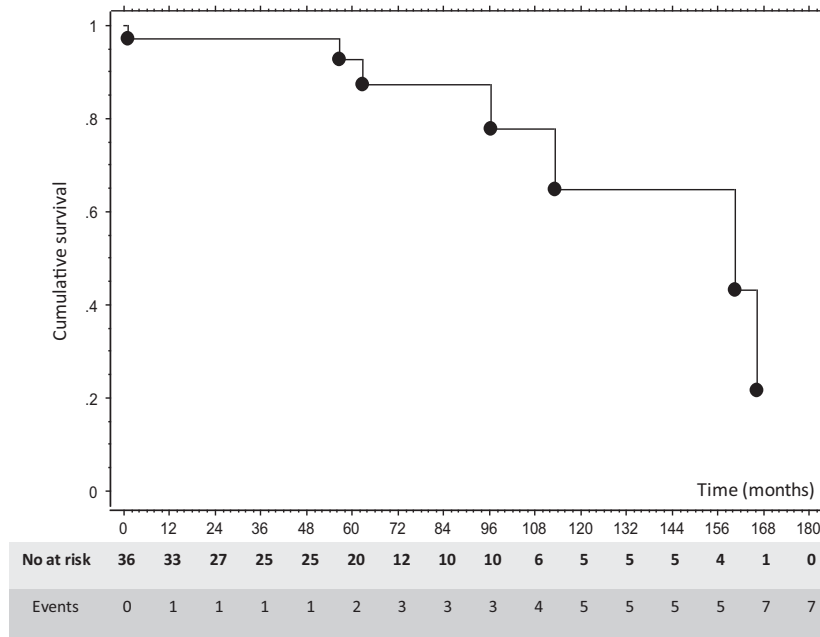


Figure 1 Death-censored graft survival. Death-censored graft survival was 97.2% after 1 and 3 years and 92.8% after 5 years post-transplant.

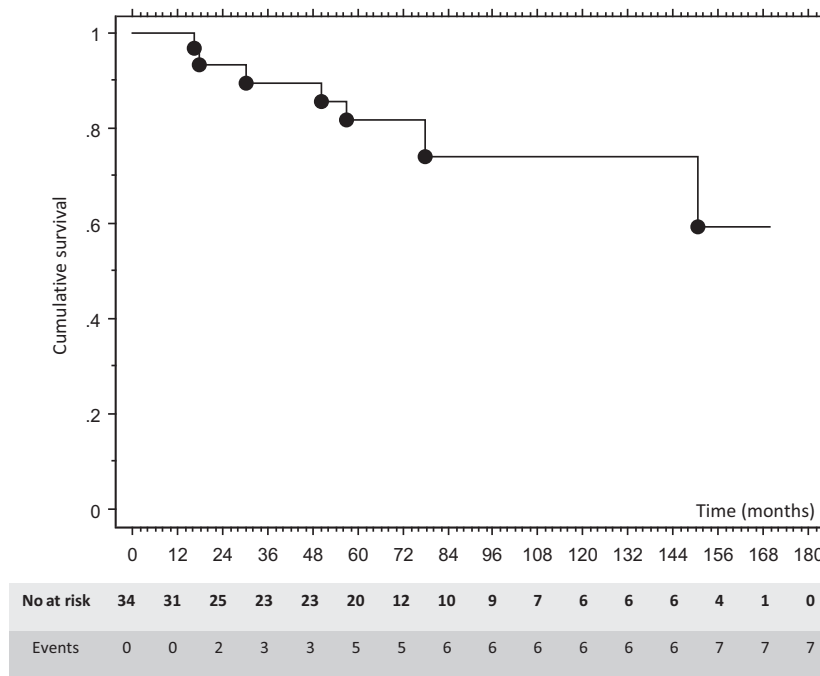


Figure 2 Patient survival. Patient survival was 100%, 93.8% and 82.5% at 1, 3, and 5 years post-transplant, respectively.

2002). In this study, early graft loss was common, occurred more often within 90 days of transplantation and was related to death with functioning graft in the majority of cases. Moreover, the results reported on the causes, and the frequency of early graft loss, suggest that patients with SS are particularly susceptible to early

death, acute rejection and thrombosis. In our study, there was no early death with a functioning graft, and primary nonfunction due to a possible recurrence of SRC was reported in only one recipient. Pham *et al.* [18] reported a graft survival (non-death-censored) at 1, 3, 5 and 10 years post-transplant, respectively, of 78.7%,

Table 4. Characteristics of patients with a scleroderma renal crisis recurrence.

	Patient 1	Patient 2	Patient 3
Gender	F	F	F
Age	56	47	34
Initial renal disease	SRC	SRC	SRC
Biopsy	Yes	Yes	Yes
Graft loss	Yes	No	No
Year of transplantation	1989	1997	2013
Time frame			
Between start of renal disease and RRT	2.0 months	0.3 month	1.2 month
Between RRT and Tx	10 months	24 months	33 months
Between Tx and recurrence	1 month	57 months	4 months
Immunosuppressive therapy			
CNI	Ciclosporin	Ciclosporin	Tacrolimus
Steroids	Yes	Yes	Yes
ACEi	Yes	Yes	Yes

F, female; RRT, renal replacement therapy; RTx, renal transplantation; CNI, calcineurin inhibitors; ACEi, Angiotensin-converting enzyme inhibitors.

Table 5. Risk factors for patient death after transplantation. Cox analysis

	Univariate analysis <i>P</i> value	Multivariate analysis		
		HR	95% CI	<i>P</i> value
Sex (M/F)	0.9			
Patient age	0.65			
SRC (initial renal disease)	0.58			
Time frame between RRT and KT	0.53			
Immunization (anti-HLA antibody positivity)	0.96			
Use of antilymphocyte serum	0.29			
Use of tacrolimus	0.69			
Use of ciclosporin	0.57			
Steroids weaning	0.68			
Acute rejection in the first year after transplantation	0.66			
Cardiac involvement	0.54			
Pulmonary involvement	0.03	10.5	1.1–96.7	0.03
Gastrointestinal involvement	0.9			
Rheumatic involvement	0.9			

SRC, scleroderma renal crisis; RRT, renal replacement therapy; KT, kidney transplantation. Bolds values: independent risk factor for death.

68.6%, 56.7% and 26.7% (UNOS registry from 1987 to 2004), which was far below the results we report. According to Bleyer *et al.* [7], graft survival in patients with SS was largely below that found in other kidney diseases (79.5% and 71.8% after 1 and 3 years post-transplant). Both European and US reports have demonstrated poorer graft survival than in other primary renal diseases [7,19]. In our study, death-censored graft survival was excellent and comparable to those of the global French cohort of kidney transplantations performed between 1993 and 2010, respectively, at 91.2% after 1 year, and 79.7% after 5 years (Agence de

Biomédecine, annual report). An important point to underline is that our data are collected from a more recent period (1987–2012) than the data reported in the previous literature, which could partly explain the better results in our population. Indeed, the more efficient immunosuppressive therapy for rejection, but also for systemic sclerosis, and the better selection of the kidney transplant recipients during this period probably improved graft survival.

Our work is limited by the number of patients transplanted during the study period. Nevertheless, it provides relevant information, especially about extrarenal

involvement in patients with SS and evolution after kidney transplantation. Gibney *et al.* [6] reported the evolution of skin lesions in four patients with SS having received a kidney allograft, who presented a subsequent improvement of Rodnan score. It would have been interesting to compare the disease activity before and after kidney transplantation. Unfortunately due to the retrospective multicentre design of this study, standardized clinical and biological data at baseline were not available. Nevertheless, the present study reports, for the first time, broader data on extrarenal involvement at time and after transplantation. Although this systemic disease is generally stable or improved, these results also highlight the fact that special attention should be paid to cardiac and gastrointestinal involvement, which may worsen after transplantation. On this basis, we consider that a close monitoring of extrarenal involvement is necessary before and after kidney transplantation, but suggest that kidney transplantation could be a highly valuable option in systemic sclerosis patients with stable extrarenal involvement. The multicentre nature of our study enhances this conclusion. Furthermore, pulmonary involvement of SS was found to be an independent risk factor of death after kidney transplantation in our study. Pulmonary disease in patients with SS can be classified into two main groups: (i) primary pulmonary disease (i.e. lung parenchyma involvement and pulmonary hypertension) and (ii) secondary pulmonary disease (i.e. airway illness due to broncho-aspiration that is secondary to gastro-oesophageal reflux, toxicity due to medications, and infections, among others) [20–22]. The presence of parenchymal lung disease (HR = 2.9, $P = 0.023$), pulmonary hypertension (HR = 4.78, $P = 0.002$) and renal disease (HR = 2.78, $P = 0.016$) is associated with increased mortality in patients with SS [23] in the nontransplant setting. The presence of ILD or PH is responsible for 60% of the mortality in these patients [23]. According to our findings, in the transplant setting, pulmonary involvement seems to have the same impact on mortality. Therefore, special caution should be paid before kidney transplantation to find and explore any parenchymal lung disease and pulmonary hypertension. This could constitute a contraindication for kidney transplantation.

In our study, there were three cases of suspected recurrence of SRC (3/36 kidney transplantation, 8.3%) between 1 and 57 months post-transplant. One recurrence caused graft loss. At time of recurrence, all three patients were under CNI, steroids and ACE inhibitors. Furthermore, there were no subclinical vascular changes in the other follow-up biopsies performed in this study.

In the literature, six cases are reported and the incidence of recurrence of SRC causing graft loss based on UNOS database was very low, estimated to be 1.9% (5/260 kidney transplantations performed) [18]. It is possible that published case series may over-report the recurrence rate, because of a bias in publications of more difficult cases, with worse outcomes, while UNOS may under-report the actual recurrence rate. One of the most important facts concerning the recurrence of SRC is the potential differential diagnosis (acute or chronic antibody-mediated rejection and CNI toxicity [24]). It is therefore challenging to ascertain the final diagnosis, especially in retrospective studies. In the nontransplant setting, the suggested predictors for SRC are quite well defined [12,25–27]. In the transplant setting, progression of diffuse skin thickening, new onset anaemia and cardiac complications may be predictive for SRC occurrence [18]. These points also have to be considered with caution because of important bias in previous publications and the very low number of cases. The literature review and the UNOS data suggest that most recurrences occur within a few months, usually before the end of the second year post-transplantation. A close monitoring for evidence of recurrence within the first 2 years after transplantation is therefore warranted. Nevertheless, our study shows that nephrologists also must be cautious for a recurrence of SRC after this period of time (57 months after transplantation for one patient in our cohort). The detection of RNA polymerase III might be a useful tool to screen patients with higher risk for SRC recurrence [28,29].

The immunosuppressive regimen used in kidney transplantation may have an important role in the improvement of the systemic manifestations of the disease. There is no consensus in this specific setting. In 1991, Ruiz *et al.* [24] suggested cyclosporine be avoided in systemic sclerosis after kidney transplantation, mainly to reduce superimposed vascular toxicity, as endothelial lesions are suspected to participate to the pathophysiology of the disease. In our study, a large majority (91.7%) of the kidney transplant recipients were treated with CNI (22 patients with tacrolimus and 11 with ciclosporin), without serious adverse events. We therefore believe that the use of CNI in SS transplanted patients should be considered as generally safe. The same conclusion could be drawn with corticosteroids: 88.9% of the cohort received high-dose corticosteroids as an induction before kidney transplantation, followed by low-dose corticosteroids, which were continued in 63.3% of patients. Steroid therapy is a classical risk factor of SRC in systemic sclerosis, but whether the use of

high-dose steroids may precipitate SRC in renal transplant recipients is currently debated. Although no general recommendation can be made, steroids appear as a reasonable immunosuppressive option in this context. Due to the relatively limited number of patients, the present study cannot conclude on the best immunosuppressive regimen to use in this setting. The most frequent combination was the use of an induction therapy including antilymphocyte serum or anti-IL-2 receptor, and a maintenance immunosuppressive therapy with tacrolimus, mycophenolate mofetil and steroids. Steroids were weaned in a large number of cases. Importantly, outcomes with this standard combination were clearly acceptable, with a rejection rate at 1 year of 13.8% (5/36) and a SRC recurrence rate of 8.3%. We speculate that using an immunosuppressive combination therapy with reduced vascular toxicity, including mTOR inhibitors or belatacept rather than CNI, could be beneficial in SS, but neither the present study nor previous literature has specifically addressed this issue.

In a series of chronic dialysis-dependent patients, Siva *et al.* [30] reported that a recovery of renal function occurred in 10% ($n = 13$) scleroderma patients, as compared to 1% ($n = 437$) ESRD patients with other causes of kidney disease ($P < 0.001$). Recovery was most likely in the first 12–18 months following dialysis initiation. On this basis, several authors have recommended to wait at least 2 years after beginning dialysis, before enrolling patients on the waiting list. In our study, 76% of the patients were on the waiting list before the 2-year limit, and none of these patients recovered renal function before kidney transplantation. Altogether, the time between dialysis initiation and transplantation was 45 months. We believe that postponing the enrolment on the waiting list after 6 months of dialysis for a reason unsupported by clear current evidence can increase both the time of dialysis and the overall risk of mortality in this setting.

In summary, our observational study provides valuable information about kidney transplantation in patients with systemic sclerosis and shows that outcomes may potentially be better than previously thought. This study provides original information on the presence and evolution of extrarenal involvement and immunosuppressive strategy in transplanted SS patients. Pulmonary involvement was an independent risk factor of death after transplantation, and a rigorous exploration should be performed before listing patient for transplantation. Special care should be taken regarding the presence and the evolution of cardiac and gastrointestinal disease in this setting. Further studies including larger cohorts would be useful to better define the ideal recipient for kidney transplantation in systemic sclerosis.

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Conflict of interest

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