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Incidence of Kidney Replacement Therapy and Subsequent Outcomes Among Patients With Systemic Lupus Erythematosus: Findings From the ERA Registry

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ABSTRACT

Rationale and objective: There is a dearth of data characterizing patients requiring kidney replacement therapy (KRT) for kidney failure due to systemic lupus erythematosus (SLE) and their clinical outcomes. The aim of this study was to describe trends in incidence and prevalence of KRT among these patients as well as to compare their outcomes to patients treated with KRT for diseases other than SLE.

Study design: Retrospective cohort study based on kidney registry data.

Setting & participants: Patients recorded in 14 registries of patients receiving kidney replacement therapy that provided data to the European Renal Association (ERA) Registry between 1992 and 2016.

Predictor: SLE as cause of kidney failure.

Outcomes: Incidence and prevalence of KRT, patient survival while receiving KRT, patient and graft survival after kidney transplantation, and specific causes of death.

Analytical Approach: Kaplan-Meier methods and Cox regression models were fit to compare patient survival between the SLE and non-SLE groups, overall KRT, dialysis and patient and graft survival after kidney transplantation.

Results: In total, 1826 patients commenced KRT for kidney failure due to SLE, representing an incidence of 0.80 per million population (pmp) per year. The incidence remained stable during the study period (annual percent change=0.1 [95%CI: -0.6 ; 0.8]). Patient survival among patients with SLE receiving KRT was similar to survival within the comparator group (HR=1.11 [95%CI: 0.99-1.23]). After kidney transplantation, the risk of death was greater among patients with SLE than among patients within the comparator group (HR=1.25 [95%CI: 1.02-1.53]), while the risk of all-cause graft failure was similar (HR=1.09 [95%CI: 0.95-1.27]). Ten-year

patient overall survival on KRT, and patient and graft survival after kidney transplantation improved over the study period (HR=0.71 [95%CI: 0.56-0.91], 0.43 [0.27-0.69] and 0.60 [0.43-0.84], respectively). Patients with SLE receiving KRT were significantly more likely to die from infections (24.8%) than patients in the comparator group (16.9%, p<0.001).

Limitations: No data were available on extrarenal manifestations of SLE, drug treatments, comorbidities, kidney transplant characteristics, or relapses of SLE.

Conclusion: The prognosis of patients with SLE receiving KRT has improved over time. Survival of patients with SLE requiring KRT was similar when compared to patients requiring KRT due to other causes of kidney failure. Survival following kidney transplantation was worse among patients with SLE.

Key words: Systemic lupus erythematosus, lupus nephritis, kidney failure, kidney replacement therapy, kidney transplantation, incidence, prevalence, survival

PLAIN-LANGUAGE SUMMARY

There is a dearth of information about incidence and prognosis among patients with SLE requiring kidney replacement therapy (KRT). We performed a study using data from the ERA Registry focusing on the period between 1992 and 2016 comparing patients with SLE who developed a need for KRT to patients also requiring KRT but from other causes of kidney disease (non-SLE patients). The overall survival of SLE patients receiving KRT was not identified to differ from the survival within the comparator group despite higher infection-related mortality, lower kidney transplantation rates, and higher patient mortality after kidney transplantation in the setting of SLE. Graft survival was also not different between groups. The incidence of patients with SLE on kidney replacement therapy in the European population studied remained stable over time.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease involving different organ systems. It is typically a disease of young women in reproductive age with a women-to-men ratio averaging about 9:1[1]. Lupus nephritis (LN) is one of the most frequent and important types of organ involvement in SLE with a negative impact on patient outcome, partly because of the morbidity and mortality associated with chronic kidney disease (CKD)[2]. The risk of developing LN varies significantly between regions and ethnicities, ranging from 10% to 70% of the SLE population[3-7]. Kidney failure has been reported in 10% to 30% of patients with LN[7, 8]. About 1% of patients undergoing kidney replacement therapy (KRT) in US[9] do so because of LN.

In recent decades, registry-based data on the outcomes of SLE patients on KRT have been presented by the US Renal Data System (USRDS)[9-16], the Taiwanese National Registry (NHIRD)[17,18], the French Registry of Renal Epidemiology and Information Network (REIN)[19] and the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA)[20]. These studies have shown mixed results, also for patient survival on dialysis and patient and allograft survival after kidney transplantation. To our knowledge, although SLE patients differ substantially from patients on KRT for kidney failure due to other causes, only a few of these studies used advanced analytical methods to compare patients with SLE patients receiving KRT to patients without SLE receiving KRT. Furthermore, no registry-based study has examined time trends in the incidence and mortality of SLE patients on KRT outside the US.

Using data from the European Renal Association (ERA) Registry, we aimed to compare patient characteristics, overall survival on KRT, survival after kidney transplantation, and causes of death for SLE patients starting KRT with their age-, sex- and time period-matched comparator group of patients without SLE. In addition, we aimed to explore the trends in incidence and

prevalence of KRT for kidney failure due to SLE and in survival of SLE patients over the past 25 years.

Methods

Data collection

The ERA Registry collects data annually on patients who initiate KRT from national and regional kidney registries in Europe. The details of data collection and data processing methods are described elsewhere[21]. For this study, data from kidney registries providing individual patient data to the ERA Registry for patients receiving KRT between 1992 and 2016 were used, including Andalusia (Spain), Austria, Basque country (Spain), Belgium (French-speaking), Catalonia (Spain), Denmark, Finland, Greece, Iceland, The Netherlands, Norway, Scotland (UK), Sweden and the Valencian region (Spain). Together, the Spanish regions covered 49.2% of the general population of Spain. Data on children were not available for French-speaking Belgium. All participating national and regional renal registries provided full coverage of the population within their corresponding region, accounting for 85 million Europeans in 1992 and 96 million in 2016. The national and regional registries complied with national legislation with regard to ethics committee approval and with European and national data protection regulations. Informed consent was not obtained separately for the present study, as data collection was part of the routine work of the participating registries for which – according to each country's rules and regulations – informed consent was or was not required. Cause of death was defined and categorized according to the ERA-EDTA coding system[21].

SLE patients and the matched comparison group

The analyses included data on patients requiring KRT (dialysis and kidney transplantation) for kidney failure due to SLE (ERA-EDTA primary renal disease code 84)[21] (**Figure S1**). These patients will hereafter be referred to as SLE patients, and all other patients will be indicated as non-SLE patients. The median age at the onset of KRT differed substantially between SLE patients (42.9 years) and non-SLE patients (66.4 years). Therefore we matched the entire cohort of SLE patients who started KRT between 1992 and 2016 to non-SLE patients starting KRT within the same period, by age at KRT initiation (per five years), by sex and year of KRT initiation (per five years) at a ratio of 1 to 5. In addition, we separately matched SLE patients who received a kidney transplant between 1992 and 2016 to non-SLE transplant recipients, by age at the time of kidney transplantation (per five years), sex and year of transplantation (per five years) at a ratio of 1 to 5. The same strategy was applied separately for recipients of living and deceased donor kidneys. SLE patients who started KRT between 1992 and 2016 and received a kidney transplant in the same period were included in both the KRT cohort and the kidney transplant cohort, however, the comparator group was assembled separately as the matching variables for the KRT cohort (e.g. age at KRT onset) and the kidney transplant cohort (e.g. age at kidney transplantation) differed.

Statistical analysis

The incidence of KRT per million population (pmp) was studied per country/region over the entire study period. For the time trend analysis the incidence rate was studied by year of KRT onset, and prevalence was assessed on 31 December of each year for all participating European countries/regions combined. To enable comparisons over time and between countries the adjusted incidence and prevalence were calculated using the age and sex distribution of the EU

Population in 2005. Time trends were examined using Joinpoint regression, with the observed rate as the outcome and year as the explanatory variable. The average annual percent change was computed using Poisson regression as provided by the Joinpoint Regression Program (National Cancer Institute; version 4.6.0).[22] To compare the characteristics of the SLE patients to the comparator group, the Mann-Whitney test was used for continuous variables and the chi-square test for categorical variables. A two-tailed p-value of less than 0.05 was considered as statistically significant.

The survival analyses were performed using the Kaplan-Meier method and Cox regression analysis, and were performed unadjusted and adjusted for age, sex, time period and country. In order to allow all patients to complete the follow-up period of ten years for all survival analyses, a subset of the initial 1992-2016 cohort was used, only including patients until 2006 (**Figure S1**). For patient survival on KRT, individuals who initiated treatment between 1992 and 2006 were included. The first day on KRT was defined as the starting point, and patient death was the event studied. Follow-up time included treatment changes from dialysis to kidney transplantation and vice versa, and was censored at recovery of kidney function (defined as interruption of dialysis - excluding kidney transplantation - for more than 30 days), at loss to follow-up, at the end of the follow-up period on 31 December 2016, or at ten years of follow-up, whichever occurred first. Patient survival on KRT was compared between SLE patients and the comparison group, between men and women with SLE, and among the periods of 1992-1996, 1997-2001 and 2002-2006. Furthermore, we examined the impact of time spent on dialysis versus with a functioning kidney transplant during follow-up on the risk of death in a sensitivity analysis in which treatment modality for kidney failure was incorporated as a time-dependent covariate in a Cox regression model that compared patients with SLE to the comparator group.

For patient survival on dialysis (hemodialysis or peritoneal dialysis), individuals who initiated dialysis between 1992 and 2006 were included. The starting point was defined as the first day on dialysis, and the event studied was patient death. Follow-up time was censored at recovery of kidney function, loss to follow-up, on the day of kidney transplantation (unless a patient restarted dialysis within 7 days after transplantation), at the end of the follow-up period on 31 December 2016, or at ten years of follow-up, whichever occurred first. Patient survival on dialysis was compared between SLE patients and the comparator group, between patients on hemodialysis and peritoneal dialysis at day 90, and among the periods of 1992-1996, 1997-2001 and 2002-2006.

Patient and graft survival after kidney transplantation was investigated for patients who received their first kidney transplant between 1992 and 2006. The date of the first kidney transplantation was defined as the first day of follow-up. For patient survival after kidney transplantation, the event studied was death, and for graft survival the event was all-cause graft failure (defined as return to dialysis, retransplantation or death). Patient and graft survival after kidney transplantation were compared between SLE patients and the comparator group, between recipients of living and deceased donor kidneys, and among the periods of 1992-1996, 1997-2001 and 2002-2006. Hazard ratios for patient and graft survival after kidney transplantation were additionally adjusted for dialysis vintage.

Competing risk analyses were carried out to calculate the cumulative incidence of kidney transplantation from the onset of KRT in SLE patients and the comparator group, taking into account the competing risk due to death. To examine the trend in the probability of transplantation over time, this analysis was done separately for patients starting KRT in the periods 1992-1996, 1997-2001 and 2002-2006.

All analyses were performed using SAS 9.4.

Results

Incidence and prevalence

Out of 280,892 patients who started KRT between 1992 and 2016, 1,826 commenced this treatment due to SLE-related kidney failure (0.65%, ranging from 0.46% to 1.00% in kidney registries across Europe) (**Table 1**). The age- and sex-standardized incidence of KRT for kidney failure due to SLE ranged from 0.46 pmp in Finland to 1.24 pmp in the Valencian region (Spain). **Figure 1** shows that the age-standardized incidence of KRT due to SLE was stable between 1992 and 2016, both overall (annual percent change: 0.1% [95% confidence interval [CI]: -0.6; 0.8]) and in men and women. The prevalence of KRT for kidney failure due to SLE increased from 5.5 pmp in 1992 to 12.1 pmp in 2016 (annual percent change: 3.0% [95%CI: 2.7; 3.3]).

Characteristics of SLE patients and the non-SLE comparator group

The 1826 SLE patients starting KRT between 1992 and 2016 were matched to 9130 patients without SLE by age (median 42.9 years), sex (79% women) and year of KRT initiation (**Table 2**). SLE patients more frequently started KRT with hemodialysis (73.8%) than matched non-SLE patients (70.4%; p=0.003), but after 90 days this difference became non-significant. By contrast, SLE patients underwent pre-emptive kidney transplantation less often (5.0%) than matched non-SLE patients (7.8%; p<0.001), and during the first ten years of follow-up after

KRT initiation fewer SLE patients (46.9%) received a first kidney transplant than matched non-SLE patients (51.9%, p<0.001).

In addition, 999 patients with SLE who received a first kidney transplant (SLE transplant recipients) between 1992 and 2016 were matched with 4995 without SLE (non-SLE transplant recipients) who received a first transplant **(Table 2)**. In the SLE transplant recipients, the median age at the time of kidney transplantation was 39.1 years (interquartile range [IQR]: 31.3-48.9), and 82.2% were women. SLE transplant recipients spent more time on dialysis before transplantation (median: 2.0 years [IQR: 0.9 – 3.9]), than matched non-SLE transplant recipients (1.5 years [IQR: 0.5-3.0], p<0.001).

Patient survival after KRT initiation

Within 90 days after commencing KRT, a larger proportion of SLE patients than matched non-SLE patients died (3.1% vs. 2.2%, p=0.03) (**Table 2**). The unadjusted patient survival on KRT in SLE patients and in the comparator group is shown in **Figure 2A and Table 3**. SLE patients showed lower survival probabilities during the first 10 years after KRT initiation than did the comparator group without SLE, and this was also the case for the patient and graft survival after a first kidney transplantation. Although increased, the difference in overall adjusted risk of death on KRT between SLE patients and matched non-SLE patients was not statistically significant (adjusted hazard ratio [HR]=1.11 [95%CI: 0.99-1.23], p=0.06). In sensitivity analyses additionally adjusting for treatment modality as time-dependent covariate, the HR was 1.04 (95%CI: 0.93-1.16). Within the group of SLE patients, survival on KRT tended to be worse in men, with an adjusted HR for women of 0.81 (95%CI: 0.64-1.02, p=0.07) (**Table S1**). As shown in **Table S2,** patient survival was better in both SLE patients and the comparator group who

started KRT between 2002 and 2006, than for those who initiated treatment between 1992 and 1996.

Patient and graft survival after kidney transplantation and access to kidney transplantation

Patient and graft survival after a first kidney transplantation in SLE patients and in the comparator group is shown in **Figures 2B** and **2C** and in **Table 3**. SLE patients had lower patient and graft survival probabilities during the first 10 years after a first kidney transplantation than the matched comparator group without SLE, but only the risk of death was statistically significantly higher for SLE patients (HR=1.25 [95%CI: 1.02-1.53], p=0.03). This increase in the risk of death for SLE kidney transplant recipients was also observed after deceased donor kidney transplantation (**Table S3**), while this difference was statistically insignificant after living donor kidney transplantation. The risk of all-cause graft failure was similar for SLE patients and matched non-SLE patients (HR=1.09 [95%CI: 0.95-1.27], p=0.2, **Table 3**), and this was also the case for both living and deceased donor kidney transplantation (**Table S3**). Within the group of SLE patients, patient mortality after a first kidney transplantation was similar for recipients of living and deceased donor grafts (HR for living versus deceased donor grafts =: 0.64 [95%CI: 0.38-1.08], p=0.09), while the risk of all-cause graft failure was lower for recipients of a living donor grafts (HR for living versus deceased donor grafts = 0.60 [0.41-0.88], p=0.009, **Table S1**). Patient and graft survival of patients receiving their first kidney transplant improved over time in both SLE patients and the non-SLE comparator group (**Table S2**). This finding was accompanied by an increase in the median age of SLE patients commencing KRT and undergoing transplantation (from 37.6 and 30.7 years in period 1992-1996 to 43.6 and 35.1 years in the most recent period, respectively).

Figure S2 shows a longer median time to a first kidney transplantation for SLE patients than within the non-SLE comparator group. However, as the median time to first kidney transplantation in the non-SLE comparator group increased over time, the difference in access to kidney transplantation between SLE patients and the comparator group became similar in the most recent period.

Causes of death

As shown in **Table 4**, the percentage of deaths due to cardiovascular diseases among patients on KRT was similar in the SLE group and the comparator group (31.1% vs. 34.3%, p=0.2). However, the percentage of deaths due to infection was significantly higher in SLE patients (24.8% vs. 16.9%, p<0.001). On the other hand, a higher percentage of patients in the non-SLE comparator group died from malignancy (8.7% vs. 5.4%, p=0.03). There was no statistically significant difference in the causes of death between the SLE group and the comparator group after kidney transplantation.

Discussion

In this study of a European cohort with SLE, we found a stable incidence of KRT for kidney failure. The results suggest similar patient survival of SLE patients on KRT when compared with an age- and sex-matched group of patients on KRT due to other causes of kidney failure. Patient survival after a first kidney transplantation appeared to be worse in SLE patients, although graft survival was similar. Cardiovascular disease was the most common cause of death

in both groups. A greater probability of death due to infection was observed in the SLE patients. Finally, we found significant improvement in patient survival on KRT over the studied period.

Our results show that though the **incidence** of KRT for kidney failure due to SLE varied between countries (0.46 to 1.24 pmp), it has remained stable over the last 25 years. This finding corresponds with the most recently reported data from the USRDS by Ward[23] and Sexton et al.[12], showing a stable or declining incidence of KRT among patients with SLE. However, it remains unclear whether the risk of kidney failure in patients with SLE and LN has changed over time. Lack of national data on the annual incidence and prevalence of LN precludes the opportunity to define the number of SLE patients at risk of kidney failure. Data from the first decade of the 21st century in a cohort from the UK[24] suggested a gradual decline in SLE incidence, which might result in a decreased incidence of LN and eventually also of SLE-related kidney failure, but this still needs to be determined. Nevertheless, a potential benefit of new therapies for LN introduced at the turn of century, such as mycophenolate mofetil and rituximab, could not be demonstrated, since the coverage of this era by the study period was too short. However, we observed an increase in the median age of SLE patients at the start of KRT over time by six years, implying that some improvement in the outcome of the disease has been achieved, although not yet reflected in the incidence of patients with LN-related kidney failure.

Our data show that the **survival of SLE patients on KRT** is similar when compared with patients with kidney failure due to other causes. Comparable mortality of SLE and non-SLE patients on KRT has also been published by Sexton and co-workers[12], even though the studied cohort included a high percentage of African-Americans who are expected to have a less favorable prognosis when diagnosed with SLE. The median follow-up of patients in this study was 4.4 years, which may not allow for the development of specific complications that are

unique to patients with SLE. A variety of factors may contribute to adverse outcomes in SLE patients such as history of aggressive immunosuppressive treatment and presence of antiphospholipid antibodies potentiating the risk of vascular access failure and thrombotic complications, including allograft thrombosis[25, 26]. Delayed wait-listing for kidney transplantation, causing the prolongation of time to transplant as shown in our study, likely due to persistent disease activity or complications arising from the disease itself[27] results in overall lower transplantation rate, including pre-emptive kidney transplantation.

While the survival of SLE patients after kidney transplantation was inferior when compared with the matched non-SLE comparator group in our study, there was no difference in graft survival, suggesting that SLE patients are more prone to fatal outcomes of complications, especially infections. Similar patient survival disadvantage after kidney transplantation and tendency to comparable graft survival was noted in two other registry studies[16,20]. Recurrence of LN does not appear to have significant clinical relevance[28]. Only a few registry studies have analyzed the prognosis of patients with SLE after kidney transplantation to date. Marked improvement in patient outcomes has recently been demonstrated by Jorge et al.[10] The investigators compared outcomes of SLE patients on KRT who were wait-listed for kidney transplantation and those who were eventually transplanted. Patients who received a kidney transplant had a 70% reduction in all-cause mortality, when compared with patients remaining on hemodialysis (adjusted HR, 0.30 [95% CI, 0.27 – 0.33]).

Although SLE has been shown to be among important non-traditional risk factors of CV disease, we found no difference in CV mortality in patients with SLE on KRT compared with matched non-SLE patients. Comparable CV morbidity measured by hospitalization rate in SLE patients on KRT was observed by Ward[29], suggesting that SLE might not increase the risk of CV

complications beyond the CV risk of patients on KRT in general. This notion could in part be a explained by burnt-out SLE in patients on dialysis[30,31], therefore not contributing to an inflammatory environment that could enhance the progression of atherosclerosis. Similar proportions of CV and infection-related deaths were observed by Zhang et al.[20], demonstrating that SLE patients were more prone to die from infections than the comparator group, but less likely to die due to CV complications. The higher risk of infectious diseases associated with immunosuppressive therapy might partly explain this increased mortality in SLE patients on KRT.

To our knowledge, this is the largest European study thus far on the outcomes of SLE patients on KRT, with almost 100% coverage in selected regions. An important strength of the study is matching of the SLE cohort to the comparator group to reduce possible confounding factors at the time of KRT initiation. Only a few registry studies have attempted to match comparator groups[12, 32], in some cases with certain shortcomings[19]. Other studies used adjustment methods to eliminate the effect of known confounding factors at the onset of KRT.

This study has certain limitations that are related to the registry-based nature of the data. The unavailability of information regarding the disease course, including duration before KRT, kidney biopsy results, severity of extrarenal involvement and treatment choices, as well as the lack of data on comorbidities, vascular access, race and socioeconomic status precludes the possibility of adjusting for these probable confounding factors. In addition, data on transplant-related characteristics such as time on the waiting list, presence of panel-reactive antibodies, cold ischemia time and immunosuppressive regimen as possible confounders were not available.

In conclusion, data from the ERA Registry show plateauing of the incidence of KRT for kidney failure due to SLE in this large European cohort. Our findings also suggest that the

prognosis of SLE patients on KRT has improved over recent decades. Finally, we show that SLE as an underlying cause of kidney failure has minimal effect on the overall patient survival after starting KRT, although it does have an unfavorable effect on overall patient survival after kidney transplantation. This may be caused by disease-specific complications but may also in part be due to complications arising from long-term immunosuppressive burden. Therapeutic advances resulting from better understanding of these complications have the potential to improve survival after kidney transplantation in patients with SLE.

Supplementary Material

Table S1 - Patient survival of systemic lupus erythematosus (SLE) patients after kidney replacement therapy (KRT) or dialysis initiation in 1992-2006, and patient and graft survival after a first kidney transplantation (KTx) in 1992-2006, analyzed for different subgroups.

Table S2 - Patient survival after kidney replacement therapy (KRT) or dialysis initiation, and patient and graft survival after a first kidney transplantation (KTx) in systemic lupus erythematosus (SLE) patients and in a matched non-SLE comparator group, compared for three time periods (1992-1996, 1997-2001, 2002-2006) according to the year of KRT initiation or the year of a first KTx.

Table S3 - Patient and graft survival after a first kidney transplantation (KTx) from a living or deceased donor in 1992-2006 among systemic lupus erythematosus (SLE) patients versus patients in the matched non-SLE comparator group.

Figure S1 - Flow diagram illustrating the number of patients selected for the analysis of the kidney replacement therapy (KRT) kidney transplant (KTx) cohorts. SLE patients and patients

with other causes of kidney failure (non-SLE patients) starting or receiving a in 1992-2016 were included in the comparison analyses. Only SLE patients and matched non-SLE patients starting KRT or receiving a KTx in 1992-2006 were included in the primary outcome analysis.

Figure S2 - Competing risk analysis comparing the time to first kidney transplantation (KTx) with death as competing event between patients starting kidney replacement therapy (KRT) for kidney failure due to systemic lupus erythematosus (SLE) during the time periods 1992-1996 (A), 1997-2001 (B), and 2002-2006 (C), and patients in the matched non-SLE comparator group initiating KRT during the time periods 1992-1996 (D), 1997-2001 (E), and 2002-2006 (F). The dotted lines represent the median time until the first kidney transplantation. Abbreviations: LD KTx, living donor kidney transplantation; DD KTx, deceased donor kidney transplantation; UD KTx, unknown donor type kidney transplantation.

Article information

Authors' contributions

Research idea and study design: OD, ZH, VT, KJJ, VSS, AK; data acquisition: MA, FC, PF, LFS, JH, MHH, KH, JK, JDM, RP, MS, RS, JPT, OZ, ZAM; data analysis/interpretation: OD, AK, KJJ, VSS, VT, ZH; supervision or mentorship: VT, KJJ. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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Table 1. Incidence of kidney replacement therapy (KRT) for kidney failure due to systemic lupus erythematosus (SLE), by country/region in 1992-2016.

	All KRT patients	SLE patients on KRT					
		Total group				Male patients	Female patients
Country/region	N total	N	%	Crude PMP	Adjusted PMP[a]	Adjusted PMP[a]	Adjusted PMP[a]
Andalusia (Spain)	21662	216	1.00	1.12	1.14	0.40	1.84
Austria	27644	166	0.60	0.81	0.81	0.32	1.27
Basque country (Spain)	5779	50	0.87	0.95	0.93	0.46	1.38
Catalonia (Spain)	24135	127	0.53	0.74	0.74	0.36	1.10
Denmark	16265	109	0.67	0.80	0.83	0.28	1.36
Finland	11342	59	0.52	0.45	0.46	0.19	0.72
French-speaking Belgium	17990	86	0.48	0.77	0.79	0.49	1.08
Greece	45724	209	0.46	0.77	0.76	0.34	1.16
Iceland	514	4	0.78	0.54	0.53	0	1.04
Norway	11214	106	0.95	0.91	0.95	0.52	1.37
Scotland (UK)	12839	77	0.60	0.60	0.61	0.20	0.99
Sweden	27613	198	0.72	0.87	0.91	0.34	1.45
the Netherlands	41787	278	0.67	0.69	0.70	0.35	1.03
Valencian region (Spain)	16384	141	0.86	1.25	1.24	0.35	2.09
All countries	280892	1826	0.65	0.80	0.82	0.35	1.26

Abbreviations: KRT, kidney replacement therapy; PMP, per million population.

[a] Adjusted for age and sex distribution using the European Standard Population of 2005 as reference population.

Table 2. Characteristics of systemic lupus erythematosus (SLE) patients and non-SLE patients, including patients in the matched comparator group, initiating kidney replacement therapy (KRT) by either dialysis or kidney transplantation, or receiving a first kidney transplant (KTx) in 1992-2016.

		Non-SLE		
	SLE	**Total**	**Matched comparator group[a]**	**p-value***
Kidney replacement therapy cohort				
Number of patients	1826	279066	9130	
Age at KRT onset, years				NA
median [25th-75th percentile]	42.9 [32.0-55.9]	66.4 [53.9-75.1]	42.9 [31.9-55.9]	
0 – 19, n (%)	72 (3.9)	4235 (1.5)	360 (3.9)	
20 – 64, n (%)	1533 (84.0)	125326 (44.9)	7665 (84.0)	
65+, n (%)	221 (12.1)	149505 (53.6)	1105 (12.1)	
Women, n (%)	1442 (79.0)	103633 (37.1)	7210 (79.0)	NA
Primary kidney disease				NA
Glomerulonephritis/sclerosis	0 (0)	35831 (12.8)	1779 (19.5)	
Pyelonephritis, n (%)	0 (0)	18391 (6.6)	928 (10.2)	
Polycystic kidney disease, adult type, n (%)	0 (0)	16779 (6.0)	772 (8.5)	
Diabetes mellitus, n (%)	0 (0)	63191 (22.6)	1830 (20.0)	
Hypertension/RVD, n (%)	0 (0)	45697 (16.4)	794 (8.7)	
Lupus nephritis, n (%)	1826 (100)	0 (0)	0 (0)	
Miscellaneous, n (%)	0 (0)	45831 (16.4)	1639 (18.0)	
Unknown/missing, n (%)	0 (0)	53346 (19.1)	1388 (15.2)	
Treatment modality at day 1				
HD, n (%)	1348 (73.8)	224377 (80.4)	6425 (70.4)	0.003
PD, n (%)	386 (21.1)	45526 (16.3)	1994 (21.8)	0.5
KTx, n (%)	92 (5.0)	9109 (3.3)	710 (7.8)	<0.001
Unknown, n (%)	0 (0.0)	54 (0.0)	1 (0.0)	NA
Patients who recovered kidney function within 90 days of initiating KRT, n (%)	46 (2.5)	4167 (1.5)	88 (1.0)	<0.001
Patients who died within 90 days of initiating KRT, n (%)	57 (3.1)	15982 (5.7)	205 (2.2)	0.03
Loss to follow-up within 90 days of initiating KRT, n (%)	7 (0.4)	663 (0.2)	27 (0.3)	0.5
KRT discontinued within 90 days of initiating KRT, n (%)	0 (0.0)	66 (0.0)	4 (0.0)	NA
Treatment modality at day 91 after initiating KRT				

HD, n (%)	1175 (64.3)	199546 (71.5)	5780 (63.3)	0.4
PD, n (%)	422 (23.1)	47340 (17.0)	2138 (23.4)	0.8
KTx, n (%)	119 (6.5)	11148 (4.0)	884 (9.7)	<0.001
Unknown, n (%)	0 (0.0)	154 (0.1)	4 (0.0)	NA
Kidney transplantation				
Patients who received a first KTx within 10 years after initiating KRT, n(%)	857 (46.9)	66644 (23.9)	4742 (51.9)	<0.001
Patients who received a second KTx within 10 years after initiating KRT, n(%)	49 (2.7)	3469 (1.2)	333 (3.6)	0.04
Kidney transplant cohort				
Number of patients	999	74359	4995	
Age at KTx, years				NA
median [25th-75th percentile]	39.1 [31.3-48.9]	50.9 [38.7-60.8]	39.2 [31.5-49.2]	
0 – 19, n (%)	31 (3.1)	3641 (4.9)	155 (3.1)	
20 – 64, n (%)	937 (93.8)	59466 (80.0)	4685 (93.8)	
65+, n (%)	31 (3.1)	11252 (15.1)	155 (3.1)	
Women, n (%)	821 (82.2)	26978 (36.3)	4105 (82.2)	NA
Primary kidney disease				NA
Glomerulonephritis/sclerosis, n (%)	0 (0)	18257 (24.6)	1289 (25.8)	
Pyelonephritis, n (%)	0 (0)	6428 (8.6)	583 (11.7)	
Polycystic kidney disease adult type, n (%)	0 (0)	9566 (12.9)	555 (11.1)	
Diabetes mellitus, n (%)	0 (0)	9761 (13.1)	687 (13.8)	
Hypertension/RVD, n (%)	0 (0)	7427 (10.0)	315 (6.3)	
Lupus nephritis, n (%)	999 (100)	0 (0)	0 (0)	
Miscellaneous, n (%)	0 (0)	11686 (15.7)	834 (16.7)	
Unknown/missing, n (%)	0 (0)	11234 (15.1)	732 (14.7)	
Pre-emptive KTx, n (%)	92 (9.2)	9151 (12.3)	693 (13.9)	<0.001
Dialysis vintage at KTx (years), median [25th-75th percentile]	2.0 [0.9-3.9]	1.7 [0.7-3.2]	1.5 [0.5-3.0]	<0.001
Donor type				
Living donor, n (%)	300 (30.0)	17738 (23.9)	1441 (28.8)	0.5
Deceased donor, n (%)	668 (66.9)	55212 (74.3)	3463 (69.3)	0.1
Unknown, n (%)	31 (3.1)	1409 (1.9)	91 (1.8)	0.009

Note: Unless otherwise indicated, values for categorical variables given as count, count (percentage), continuous variables given as median [25th-75th percentile].

[a] For SLE patients starting KRT the comparator group comprised of a subgroup of non-SLE patients starting KRT (matched by age group and sex). For SLE patients receiving a first KTx the comparator group comprised of a subgroup of non-SLE patients receiving a first KTx (matched by age group and sex).

* P-values are based on the comparison between SLE patients and the matched non-SLE comparator group.

Abbreviations: KRT, kidney replacement therapy; HD, hemodialysis; PD, peritoneal dialysis; KTx, kidney transplantation; RVD, renovascular disease.

Table 3. Patient survival after kidney replacement therapy (KRT) overall or dialysis initiation in 1992-2006, and patient and graft survival after a first kidney transplantation in 1992-2006, in systemic lupus erythematosus (SLE) patients versus age-, sex- and time period-matched non-SLE the group.

					Crude survival probabilities (95% CI)				Hazard ratios (95% CI)	
	Number at risk	**Number of events**	**Mean follow-up years**	**Event rate**	**1 year**	**2 year**	**5 year**	**10 year**	**Crude**	**Adjusted***
Patient survival on KRT										
SLE patients	1056	408	6.9	0.39	91.5(89.6-93.1)	84.2(81.8-86.3)	71.8(68.9-74.5)	58.9(55.8-61.9)	1.13(1.01-1.25)	1.11(0.99-1.23)
Matched comparator group	5280	1925	7.4	0.36	92.3(91.6-93.0)	86.5(85.6-87.4)	75.0(73.8-76.2)	62.4(61.1-63.8)	1 (ref)	1 (ref)
Patient survival on dialysis										
SLE patients	944	318	3.5	0.34	91.6(89.5-93.3)	83.4(80.5-85.8)	63.4(59.2-67.3)	33.8(28.7-39.0)	0.97(0.86-1.09)	1.00(0.89-1.13)
Matched comparator group	4683	1461	3.2	0.31	91.5(90.6-92.3)	84.1(82.8-85.2)	62.4(60.4-64.3)	33.1(30.7-35.6)	1 (ref)	1 (ref)
Patient survival after kidney transplantation										
SLE patients	559	122	8.9	0.22	96.1(94.1-97.4)	95.2(93.0-96.7)	90.1(87.3-92.3)	78.2(74.6-81.4)	1.32(1.08-1.61)	1.25(1.02-1.53)
Matched comparator group	2795	476	9.1	0.17	97.3(96.6-97.9)	96.1(95.3-96.8)	92.7(91.6-93.6)	82.9(81.4-84.2)	1 (ref)	1 (ref)
Graft survival after kidney transplantation										
SLE patients	559	225	7.5	0.40	87.8(84.8-90.3)	84.8(81.5-87.5)	74.9(71.0-78.3)	59.7(55.4-63.6)	1.14(0.99-1.32)	1.09(0.95-1.27)
Matched comparator group	2795	1030	7.8	0.37	90.8(89.6-91.8)	88.2(87.0-89.4)	79.7(78.2-81.2)	62.9(61.0-64.6)	1 (ref)	1 (ref)

* Adjusted for age, sex, time period, dialysis vintage (for patient and graft survival after kidney transplantation only) and country.

Table 4. Causes of death distribution among systemic lupus erythematosus (SLE) patients and patients in the matched non-SLE comparator group who died within ten years after starting kidney replacement therapy, or after receiving a first kidney transplant in 1992-2006.

	SLE patients		Matched comparator group[a]		
	N	%	N	%	p-value
KRT cohort					
Number of patients	1056		5280		
Number of deaths within 10 years	408		1925		
Cause of death					
Cardiovascular disease	127	31.1	661	34.3	0.2
Myocardial ischemia/infarction	35	8.6	200	10.4	0.3
Heart failure	23	5.6	124	6.4	0.5
Cardiac arrest; other cause/unknown	42	10.3	205	10.6	0.8
Cerebrovascular accident	27	6.6	132	6.9	0.9
Infection	101	24.8	325	16.9	<0.001
Suicide/refusal of treatment	10	2.5	50	2.6	0.9
Withdrawal of treatment	18	4.4	70	3.6	0.5
Cachexia	7	1.7	48	2.5	0.3
Malignancies	22	5.4	167	8.7	0.03
Miscellaneous	65	15.9	294	15.3	0.7
Unknown/unavailable/missing	58	14.2	310	16.1	0.3
Kidney transplant cohort					
Number of patients	559		2795		
Number of deaths within 10 years	121		476		
Cause of death					
Cardiovascular disease	36	29.8	150	31.6	0.7
Myocardial ischemia/infarction	12	9.9	36	7.6	0.4
Heart failure	8	6.6	31	6.5	0.9
Cardiac arrest; other cause/unknown	10	8.3	45	9.5	0.7
Cerebrovascular accident	6	5.0	38	8.0	0.3
Infection	32	26.4	94	19.7	0.1
Suicide/refusal of treatment	2	1.7	9	1.9	0.9
Withdrawal of treatment	0	0	8	1.7	0.2
Cachexia	0	0	4	0.8	0.3
Malignancies	14	11.6	49	10.3	0.7
Miscellaneous	23	19.0	83	17.4	0.7
Unknown/unavailable/missing	14	11.6	79	16.6	0.2

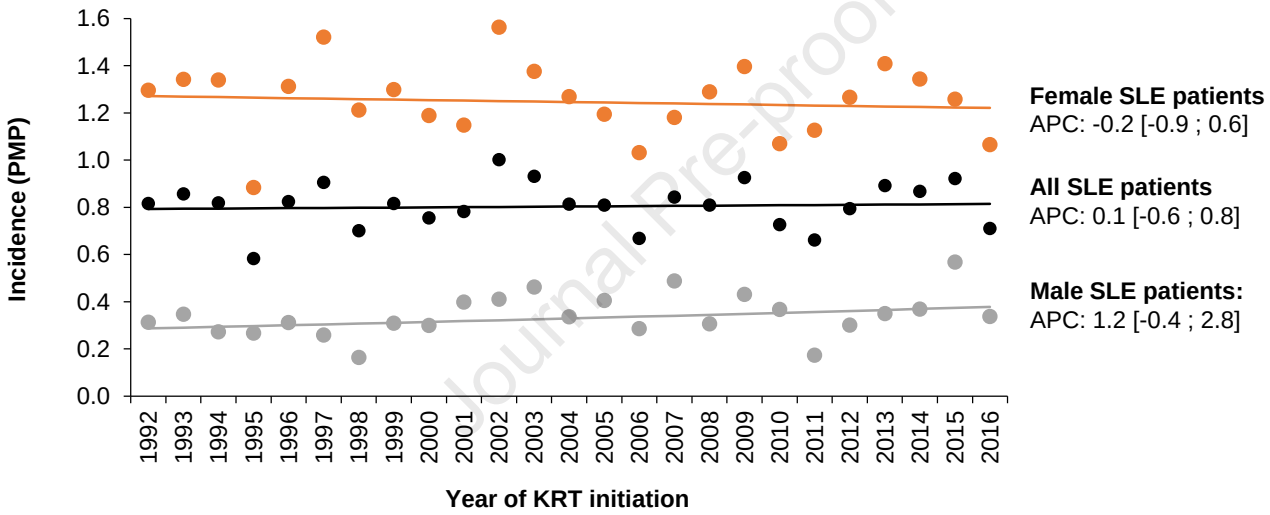
Note: Percentages may not add up to 100% because of rounding.

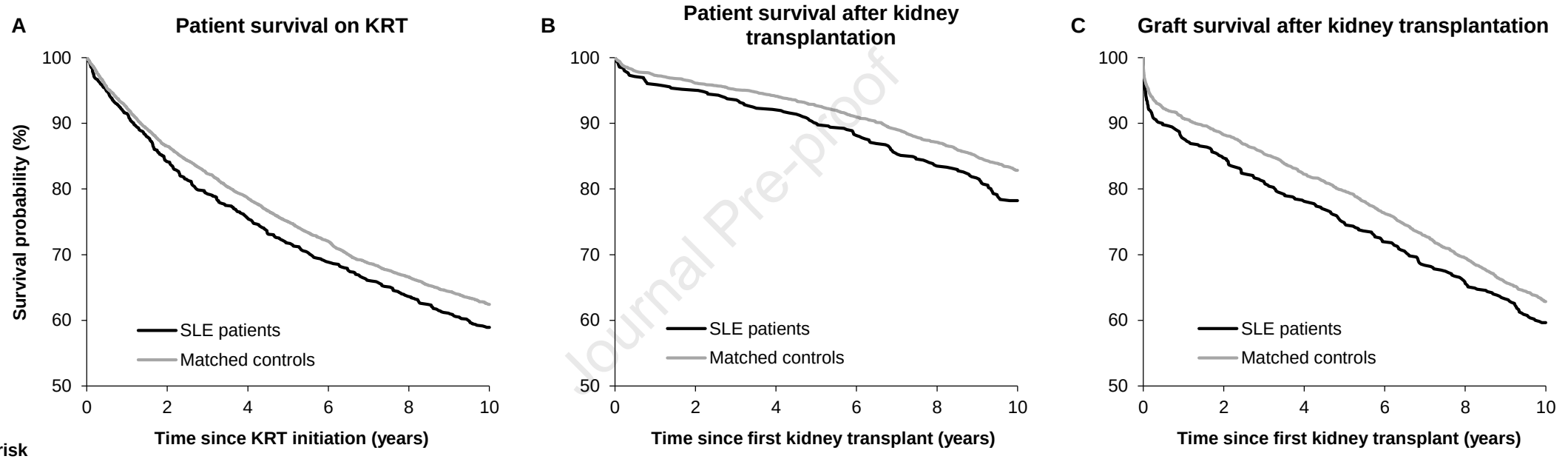
[a] For SLE patients starting kidney replacement therapy (KRT) the comparator comprised of non-SLE patients starting KRT, matched by age group and sex. For SLE patients receiving a first kidney transplant (KTx) the comparator group comprised of non-SLE patients receiving a first KTx, matched by age group and sex.

Figures

Figure 1. Trends in the incidence of kidney replacement therapy (KRT) due to kidney failure caused by systemic lupus erythematosus (SLE) per million population (pmp). The incidence rates (presented as dots) were adjusted for age and sex using the European Standard Population of 2005 as a reference. The solid line shows the estimated rates as modelled by Joinpoint. Abbreviations: APC, annual percent change; SLE, systemic lupus erythematosus.

Figure 2. Kaplan-Meier survival analysis, comparing (A) patient survival from day 1 after starting kidney replacement therapy (KRT) in 1992-2006, and (B) patient and (C) graft survival after first kidney transplantation in 1992-2006 in SLE patients and the matched comparator group.





Number at risk																		
SLE patients	1056	835	742	677	624	576	559	530	513	491	562	432	559	471	434	399	362	328
Matched controls	5280	4441	4017	3665	3377	3151	2795	2680	2618	2524	2412	2288	2795	2459	2284	2111	1914	1724