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ORIGINAL RESEARCH

Risk of kidney failure in patients with systemic sclerosis: a nationwide population-based study

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ABSTRACT

Objective Data from a decade ago have shown that patients with systemic sclerosis (SSc) have a higher risk of kidney failure than the general population. However, as the incidence of kidney failure due to SSc has been declining, the comparative risk of kidney failure between patients with SSc and the general population could have changed over time. We investigated the risk of kidney failure in patients with SSc compared with the general population, up to more recent years.

Methods This was a nationwide population-based study using the Korean National Health Insurance Service database. Patients with claims data for SSc between 2010 and 2017 (n=2591) and 1:5 age-matched and sex-matched controls (n=12 955) were selected. The index date was the earliest date of claim for SSc between 2010 and 2017. The follow-up duration was from the index date to 2019. The adjusted HRs (aHRs) and 95% CI for kidney failure were estimated using multivariable Cox proportional hazard models.

Results Over 5.2±2.6 years, the incidence rates of kidney failure in patients with SSc and controls were 2.88 and 0.35 per 1000 person-years, respectively. Patients with SSc had a significantly higher risk of kidney failure than controls (aHR=7.244, 95% CI=4.256 to 12.329). The effect size was larger in patients diagnosed with SSc between 2014 and 2017 (aHR=9.754, 95% CI=3.254 to 29.235) than in those diagnosed before 2010 (aHR=6.568, 95% CI=2.711 to 15.571) or between 2010 and 2013 (aHR=6.553, 95% CI=2.721 to 15.781).

Conclusion The risk of kidney failure remains higher in patients with SSc than in the general population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The incidence of kidney failure in patients with systemic sclerosis (SSc) has been declining over time.
⇒ Although data from a decade ago have shown that the risk of kidney failure is higher in patients with SSc than in the general population, it is unclear whether the comparative risk has changed in more recent years.

WHAT THIS STUDY ADDS

⇒ In this nationwide cohort study, we assessed the comparative risk of kidney failure up to more recent years between patients with SSc and controls and found that patients with SSc have a sevenfold higher risk of kidney failure than controls.
⇒ The effect size was larger in those who were more recently diagnosed with SSc.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The risk of kidney failure remains higher in patients with SSc than in the general population, and therefore, careful monitoring for incident kidney failure on patients with SSc is needed.

INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune disorder characterised by vasculopathy and fibrosis of the skin and various internal organs.[1 2] Among the various internal organs, renal involvement causes considerable morbidity and mortality in patients with SSc.[3] Renal manifestations of SSc range from subclinical renal impairment to scleroderma renal crisis (SRC).[3 4] Subclinical renal impairment is common in patients with SSc, affecting approximately 50% of all patients.[3] The prevalence of SRC, which is the most severe form of renal involvement, is relatively low, affecting 1%–14% of the patients with SSc.[5–7] Despite the low prevalence, the disease burden due to SRC is high, as it is likely to progress to kidney failure.[3] Although the introduction of ACE inhibitors (ACEis) has greatly improved the prognosis of SRC,[8] 55% of cases still progress to kidney failure within a year.[9] Importantly, the mortality risk is 2.5-fold higher from kidney failure caused by SSc than from kidney failure caused by other conditions.[10] Therefore, kidney failure is an important renal complication in SSc, and it is crucial to understand whether the risk of kidney failure differs between patients with SSc and the general population.

Data comparing the risk of kidney failure between patients with SSc and the general population are limited. One population-based study from Taiwan reported a twofold higher

risk of kidney failure in patients with SSc compared with the general population.[11] In that study, patients diagnosed with SSc between 2000 and 2013 and their matched controls were followed up until 31 December 2013[11]; that is, the results of the study are based on data from a decade ago.[11] Considering that the incidence of kidney failure in patients with SSc has declined since 1996,[12] the risk of kidney failure in patients with SSc compared with the general population may have changed. Therefore, updated data on the risk of kidney failure in patients with SSc are needed. In this study, we used the Korean nationwide database to assess the risk of kidney failure in patients with SSc compared with the general population, up to more recent years. We also investigated whether the risk of kidney failure differs according to the time patients were diagnosed with SSc.

METHODS

Data source

We extracted data from the Korean National Health Insurance Service (NHIS) claims database. A detailed profile of the database has been described previously.[13] Briefly, the NHIS claims database contains vast amounts of data, including demographics, socioeconomic status, medical treatments and procedures, disease diagnoses according to the International Classification of Diseases—Tenth Revision (ICD-10) codes, and rare intractable disease (RID) codes.[14] The RID code is assigned to patients who fulfil a uniform diagnostic criterion provided by the NHIS. The fulfilment of the diagnostic criteria is thoroughly reviewed by the NHIS and the corresponding healthcare institution.[14] All individuals registered in the NHIS database are advised to undergo national health check-ups every 2 years. The health check-up data include anthropometric data, blood pressure, lifestyle factors, such as smoking, alcohol consumption and physical activity, and laboratory data, such as serum fasting glucose, cholesterol and creatinine levels.[15]

Study cohort

Patients with claims data for SSc between 1 January 2010 and 31 December 2017 were extracted from the NHIS database. SSc was defined as ICD-10 code M34 with RID code V.138.[16] A total of 5986 patients with SSc were identified. The index date was the earliest date with claims data for SSc between 1 January 2010 and 31 December 2017. The following patients were excluded: (1) age<20 years (n=277); (2) no check-up data within 2 years prior to the index date (n=3009); (3) history of kidney failure (n=23); and (4) kidney failure or death that occurred within 1 year from baseline (n=82). Patients with kidney failure that occurred within 1 year from baseline were excluded to avoid the possibility of misclassifying prevalent kidney failure cases as incident kidney failure cases. The remaining 2591 patients with SSc were used to select age-matched and sex-matched controls from the NHIS database at a ratio of 1:5. As a result, 2591 patients with SSc and 12 955 age-matched and sex-matched controls were included in the analysis (figure 1). All individuals were followed up until 31 December 2019.

Definition of kidney failure and covariates

Kidney failure was defined as a combination of ICD-10 codes (N18-19, Z49, Z94.0 and Z99.2) and an RID code assigned to patients with chronic kidney disease (CKD) that required haemodialysis (V001), peritoneal dialysis (V003) or kidney transplantation (V005).[17] Covariates were defined as described in previous studies (online supplemental table S1).[14 15]

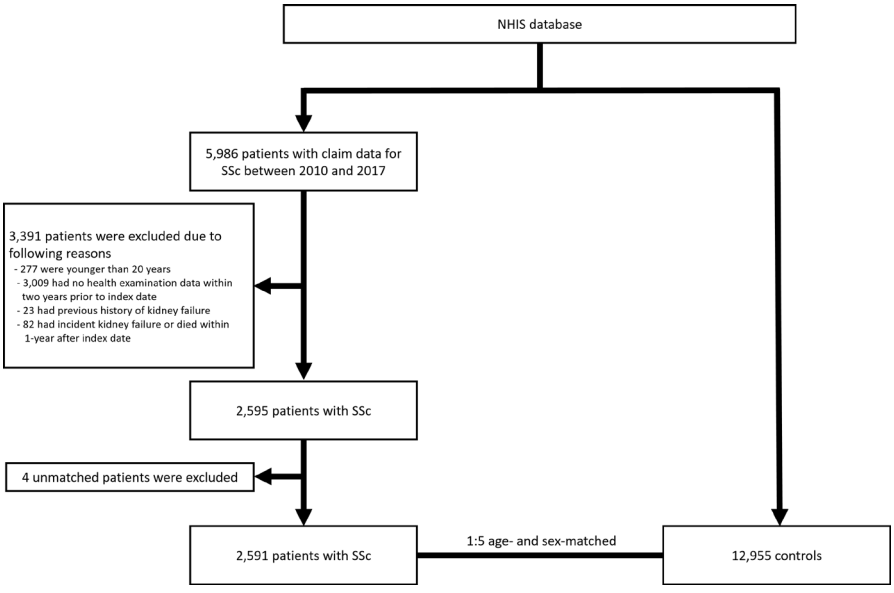

Figure 1 Selection of the study population from the NHIS database. NHIS, National Health Insurance Service; SSc, systemic sclerosis.

Statistical analysis

Continuous variables are expressed as mean±SD and categorical variables as numbers (%). Continuous and categorical variables were compared using the independent Student's t-tests and χ^2 tests, respectively. The incidence rate of kidney failure was expressed as the number of events per 1000 person-years. The cumulative incidences of kidney failure in patients with SSc and controls were visualised using the Kaplan-Meier curve and compared using the log-rank test. Cox proportional hazard models were used to estimate the HRs and 95% CIs for the incidence of kidney failure. Cox proportional hazard models were first performed in all patients with SSc and their matched controls. Next, to investigate whether the HR varies according to the time patients were diagnosed with SSc, Cox proportional hazard models were separately performed in patients with prevalent cases of SSc (diagnosed before 2010), incident cases of SSc between 2010 and 2013 and incident cases of SSc between 2014 and 2017 with their respective matched controls. Furthermore, to analyse the effect of different SSc treatments on the risk of incident kidney failure, we classified the patients with SSc according to the use of specific medications (methotrexate (MTX), mycophenolate mofetil (MMF), cyclophosphamide (CYC) or ACEi) during follow-up and additionally performed Cox proportional hazard models. Univariable and multivariable models were performed. Multivariable models were adjusted for multiple covariates, chosen either as confounders (age and sex[18 19]) or as explanatory variables (income, smoking status, alcohol consumption, physical activity, obesity, hypertension, type 2 diabetes, dyslipidaemia and CKD[19–22]). Model 1 was a univariable model. Model 2 was adjusted for age, sex, income, smoking status, alcohol consumption and physical activity. Model 3 was further adjusted for obesity, hypertension, type 2 diabetes and dyslipidaemia. Model 4 was additionally adjusted for CKD. Competing risk model accounting for the competing risk of death was also performed. Subgroup analyses stratified by multiple covariates were performed to evaluate whether the association between SSc and the risk of incident kidney failure is greater in a particular subgroup of patients. All p values were two sided, and a p value<0.05 was considered statistically significant. Statistical analyses were performed using SAS V.9.4.

RESULTS

Baseline characteristics

The baseline characteristics of the 2591 patients with SSc and their age-matched and sex-matched controls are shown in table 1. The mean age of the total study population was 55.9±10.7 years, and 14.6% were men. Patients with SSc were less commonly alcohol drinkers (23.1% vs 27.0%, p<0.001), less commonly exercised regularly (17.4% vs 19.4%, p=0.018) and were less commonly obese (25.5% vs 33.9%, p<0.001) than controls. The prevalence of type 2 diabetes (10.2% vs 11.7%, p=0.030) and dyslipidaemia (28.7% vs 31.1%, p=0.015) was lower, whereas the prevalence of hypertension (58.0% vs 34.9%,

Table 1 Baseline characteristics of the study population

	Total population (n=15546)	Patients with SSc (n=2591)	Controls (n=12955)	P value
Age, years	55.9±10.7	55.9±10.7	55.9±10.7	>0.999
<65 years, n (%)	12144 (78.1)	2024 (78.1)	10120 (78.1)	>0.999
≥65 years, n (%)	3402 (21.9)	567 (21.9)	2835 (21.9)	
Male sex, n (%)	2262 (14.6)	377 (14.6)	1885 (14.6)	>0.999
Female sex, n (%)	13284 (85.5)	2214 (85.5)	11070 (85.5)	
Low income*, n (%)	3707 (23.9)	625 (24.1)	3082 (23.8)	0.717
Current smoker, n (%)	1231 (7.9)	185 (7.1)	1046 (8.1)	0.110
Alcohol drinker, n (%)	4101 (26.4)	599 (23.1)	3502 (27.1)	<0.001
Regular physical activity, n (%)	2960 (19.0)	450 (17.4)	2510 (19.4)	0.018
Obesity, n (%)	5049 (32.5)	661 (25.5)	4388 (33.9)	<0.001
Hypertension, n (%)	6026 (38.8)	1502 (58.0)	4524 (34.9)	<0.001
Type 2 diabetes, n (%)	1776 (11.4)	264 (10.2)	1512 (11.7)	0.030
Dyslipidaemia, n (%)	4777 (30.7)	744 (28.7)	4033 (31.1)	0.015
CKD	878 (5.7)	169 (6.5)	709 (5.5)	0.035
Incident kidney failure, n (%)	61 (0.4)	37 (1.4)	24 (0.2)	<0.001
Follow-up duration, years	5.2±2.6	5.0±2.6	5.2±2.6	<0.001

Continuous variables are expressed in mean±SD.
*Lowest 25th percentile.
CKD, chronic kidney disease; SSc, systemic sclerosis.

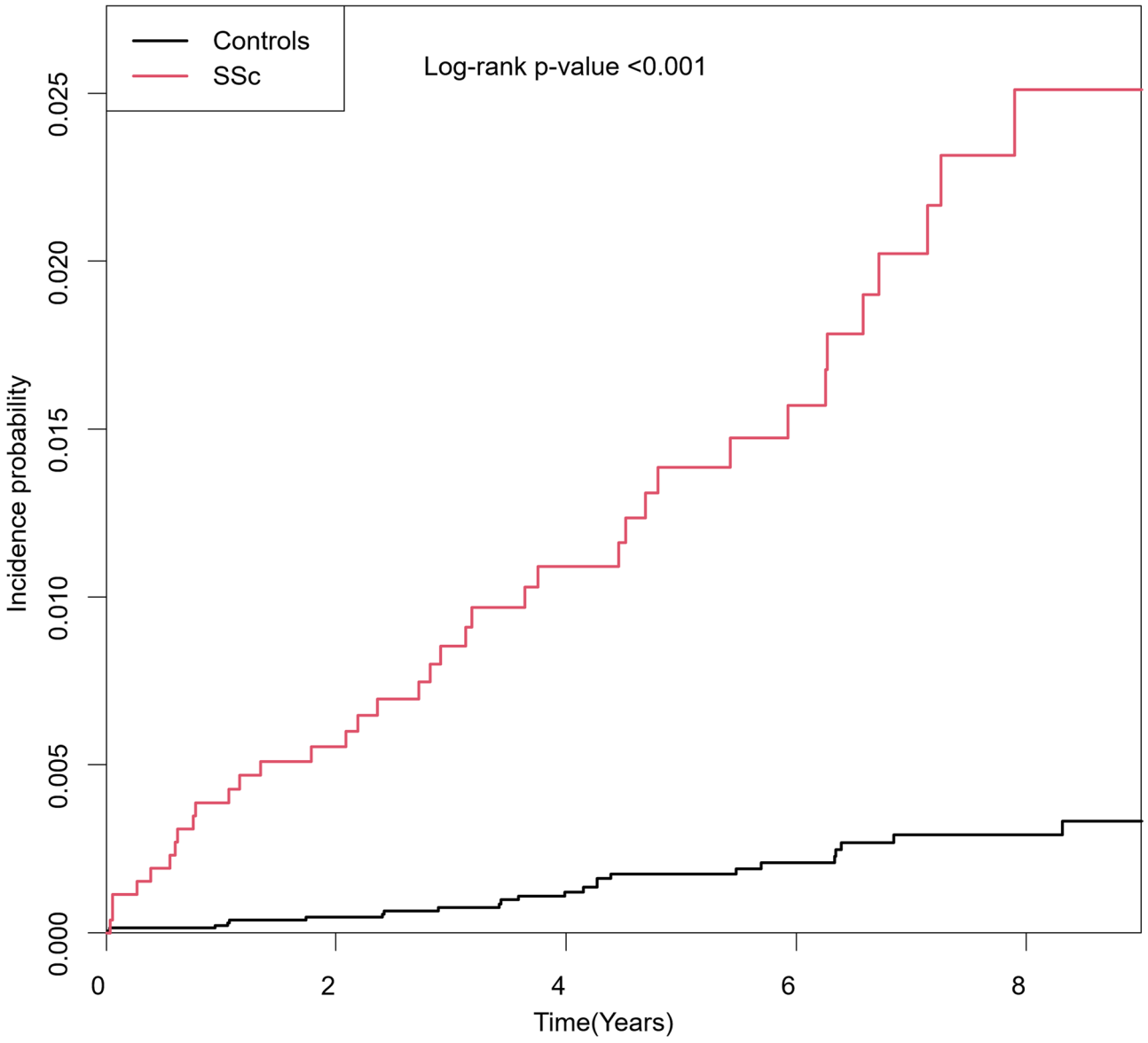

Figure 2 Cumulative incidences of kidney failure in patients with SSc and controls. SSc, systemic sclerosis.

p<0.001) and CKD (6.5% vs 5.5%, p=0.035) was higher, in patients with SSc than in controls.

Risk of kidney failure in patients with SSc and in controls

The study population was followed up for a mean of 5.2±2.6 years. The incidence rates of kidney failure in patients with SSc and in controls were 2.88 and 0.35 per 1000 person-years, respectively. The cumulative incidence of kidney failure was significantly higher in patients with SSc (figure 2, p<0.001). In the Cox proportional hazard model with no adjustments, patients with SSc had a higher risk of incident kidney failure than controls (model 1, unadjusted HR=8.144, 95% CI=4.872 to 13.614). This association was consistently observed in the multivariable models (model 2, adjusted HR (aHR)=8.174, 95% CI=4.885 to 13.678; model 3, aHR=7.141, 95% CI=4.195 to 12.156; and model 4, aHR=7.244, 95% CI=4.256 to 12.329) (table 2). Similar result was observed in the competing risk model accounting for the competing risk of death (aHR=6.817, 95% CI=4.052 to 11.467).

In the comparison between patients diagnosed with SSc before 2010 (prevalent cases) and their matched controls, the aHR (model 4) was 6.568 (95% CI=2.711 to 15.571). The aHR (model 4) for kidney failure was similar in patients diagnosed with incident SSc between 2010 and 2013 (aHR=6.553, 95% CI=2.721 to 15.781). Meanwhile, the aHR (model 4) for kidney failure was higher in patients diagnosed with incident SSc between 2014 and 2017 (aHR=9.754, 95% CI=3.254 to 29.235) (table 2). Similarly, the aHRs in the competing risk model comparing patients diagnosed with SSc before 2010, patients diagnosed with incident SSc between 2010 and 2013 and patients diagnosed with incident SSc between 2014 and 2017 with their respective matched controls were 5.976 (95% CI=2.523 to 14.157), 6.091 (95% CI=2.490 to 14.902) and 9.532 (95% CI=3.354 to 27.092), respectively.

Table 2 Comparison of risk of incident kidney failure between patients with systemic sclerosis and controls

	N	Incident kidney failure	Duration, pyrs	IR/1000 pyrs	Model 1	Model 2	Model 3	Model 4	Competing risk model*
Comparison of all patients with SSc versus controls									
Controls	12 955	24	67 654.22	0.35	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Patients with SSc	2591	37	12 836.61	2.88	8.144 (4.872, 13.614)	8.174 (4.885, 13.678)	7.141 (4.195, 12.156)	7.244 (4.256, 12.329)	6.817 (4.052, 11.467)
Comparison of patients with prevalent cases of SSc† versus controls									
Controls	2835	10	22 772.72	0.44	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Patients with SSc	567	13	4256.83	3.05	6.949 (3.047, 15.849)	7.337 (3.180, 16.925)	6.353 (2.657, 15.194)	6.568 (2.771, 15.571)	5.976 (2.523, 14.157)
Comparison of patients with incident cases of SSc between 2010 and 2013 versus controls									
Controls	4075	9	27 430.89	0.33	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Patients with SSc	815	13	5204.72	2.50	7.686 (3.285, 17.984)	7.695 (3.285, 18.025)	6.920 (2.891, 16.564)	6.553 (2.721, 15.781)	6.091 (2.490, 14.902)
Comparison of patients with incident cases of SSc between 2014 and 2017 versus controls									
Controls	6045	5	17 450.60	0.29	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Patients with SSc	1209	11	3375.06	3.26	11.331 (3.937, 32.613)	11.177 (3.881, 32.187)	9.911 (3.303, 29.741)	9.754 (3.254, 29.235)	9.532 (3.354, 27.092)

Model 1: non-adjusted.
Model 2: adjusted for age, sex, income, smoking status, alcohol consumption and physical activity.
Model 3: adjusted for age, sex, income, smoking status, alcohol consumption, physical activity, obesity, hypertension, type 2 diabetes and dyslipidaemia.
Model 4: adjusted for age, sex, income, smoking status, alcohol consumption, physical activity, obesity, hypertension, type 2 diabetes, dyslipidaemia and CKD.
*Competing risk model accounting for the competing risk of death. Adjusted for the same covariates as model 4.
†Patients diagnosed with SSc before 2010.
CKD, chronic kidney disease; IR, incidence rate; pyrs, person-years; SSc, systemic sclerosis.

Table 3 Risk of incident kidney failure according to the medications used

	N	Incident kidney failure	Duration, pyrs	IR/1000 pyrs	Model 1	Model 2	Model 3	Model 4
Controls	12955	24	67654.22	0.35	1 (Ref.)	1 (Ref.)	1 (Ref.)	1 (Ref.)
Patients with SSc without MTX	2042	32	10136.41	3.16	8.917 (5.252, 15.139)	8.865 (5.215, 15.071)	7.694 (4.460, 13.273)	7.700 (4.465, 13.278)
Patients with SSc with MTX	549	5	2700.20	1.85	5.239 (1.999, 13.732)	5.458 (2.080, 14.324)	4.809 (1.805, 12.810)	5.157 (1.931, 13.772)
Patients with SSc without MMF	2390	29	11948.54	2.43	6.854 (3.990, 11.772)	6.842 (3.980, 11.761)	6.029 (3.454, 10.523)	6.088 (3.488, 10.626)
Patients with SSc with MMF	201	8	888.07	9.01	25.732 (11.55, 57.331)	29.274 (13.025, 65.796)	24.656 (10.781, 56.390)	27.094 (11.791, 62.258)
Patients with SSc without CYC	2290	27	11282.67	2.39	6.761 (3.901, 11.718)	6.775 (3.906, 11.752)	5.939 (3.373, 10.454)	6.052 (3.439, 10.651)
Patients with SSc with CYC	301	10	1553.94	6.44	18.19 (8.697, 38.045)	18.766 (8.922, 39.470)	17.189 (8.009, 36.891)	17.122 (7.945, 36.899)
Patients with SSc without ACEi	2391	27	11817.12	2.28	6.460 (3.727, 11.196)	6.538 (3.768, 11.345)	5.905 (3.350, 10.407)	6.007 (3.409, 10.588)
Patients with SSc with ACEi	200	10	1019.49	9.81	27.382 (13.092, 57.268)	24.839 (11.812, 52.234)	18.067 (8.354, 39.075)	17.126 (7.968, 36.810)

Model 1: non-adjusted.
Model 2: adjusted for age, sex, income, smoking status, alcohol consumption and physical activity.
Model 3: adjusted for age, sex, income, smoking status, alcohol consumption, physical activity, obesity, hypertension, type 2 diabetes and dyslipidaemia.
Model 4: adjusted for age, sex, income, smoking status, alcohol consumption, physical activity, obesity, hypertension, type 2 diabetes, dyslipidaemia and CKD.
ACEi, ACE inhibitor; CKD, chronic kidney disease; CYC, cyclophosphamide; IR, incidence rate; MMF, mycophenolate mofetil; MTX, methotrexate; pyrs, person-years; SSc, systemic sclerosis.

Table 4 Subgroup analyses

Subgroup		SSc	N	Kidney failure	Duration (pyrs)	IR/1000 pyrs	HR* (95% CI)	P interaction
Sex	Male	No	1885	6	9819.71	0.61	1 (Ref.)	0.576
		Yes	377	7	1801.80	3.89	5.504 (1.840 to 16.463)	
	Female	No	11 070	18	57 834.51	0.31	1 (Ref.)	
		Yes	2214	30	11 034.81	2.72	7.848 (4.286 to 14.370)	
Age, years	<65	No	10 120	18	53 509.14	0.34	1 (Ref.)	0.243
		Yes	2024	25	10 251.88	2.44	5.903 (3.160 to 11.025)	
	≥65	No	2835	6	14 145.08	0.42	1 (Ref.)	
		Yes	567	12	2584.73	4.64	11.772 (4.376 to 31.670)	
Low income†	No	No	9873	19	51 526.14	0.37	1 (Ref.)	0.736
		Yes	1966	28	9863.55	2.84	6.908 (3.803 to 12.550)	
	Yes	No	3082	5	16 128.08	0.31	1 (Ref.)	
		Yes	625	9	2973.06	3.03	8.549 (2.828 to 25.846)	
Current smoker	No	No	11 909	20	62 204.03	0.32	1 (Ref.)	0.628
		Yes	2406	33	12 007.23	2.75	7.624 (4.298 to 13.521)	
	Yes	No	1046	4	5450.19	0.73	1 (Ref.)	
		Yes	185	4	829.38	4.82	5.268 (1.307 to 21.232)	
Alcohol drinker	No	No	9453	19	49 583.32	0.38	1 (Ref.)	0.690
		Yes	1992	31	9982.14	3.11	7.609 (4.233 to 13.680)	
	Yes	No	3502	5	18 070.90	0.28	1 (Ref.)	
		Yes	599	6	2854.47	2.10	5.817 (1.753 to 19.298)	
Regular physical activity	No	No	10 445	21	54 575.64	0.38	1 (Ref.)	0.190
		Yes	2141	28	10 634.58	2.63	6.063 (3.377 to 10.884)	
	Yes	No	2510	3	13 078.57	0.23	1 (Ref.)	
		Yes	450	9	2202.03	4.09	15.759 (4.246 to 58.486)	
Obesity	No	No	8567	10	44 786.80	0.22	1 (Ref.)	0.207
		Yes	1930	25	9522.67	2.63	10.015 (4.719 to 21.253)	
	Yes	No	4388	14	22 867.41	0.61	1 (Ref.)	
		Yes	661	12	3313.95	3.62	5.023 (2.308 to 10.931)	
Hypertension	No	No	8431	7	44 153.97	0.16	1 (Ref.)	0.418
		Yes	1089	9	5417.54	1.66	10.211 (3.798 to 27.454)	
	Yes	No	4524	17	23 500.25	0.72	1 (Ref.)	
		Yes	1502	28	7419.07	3.77	6.301 (3.383 to 11.735)	

Continued

Table 4 Continued

Subgroup		SSc	N	Kidney failure	Duration (pyrs)	IR/1000 pyrs	HR* (95% CI)	P interaction
Type 2 diabetes	No	No	11 443	12	60 157.04	0.20	1 (Ref.)	0.045
		Yes	2327	31	11 605.96	2.67	10.858 (5.458 to 21.598)	
	Yes	No	1512	12	7497.18	1.60	1 (Ref.)	
		Yes	264	6	1230.65	4.88	3.175 (1.182 to 8.527)	
Dyslipidaemia	No	No	8922	12	48 089.50	0.25	1 (Ref.)	0.330
		Yes	1847	26	9469.74	2.75	9.033 (4.462 to 18.286)	
	Yes	No	4033	12	19 564.72	0.61	1 (Ref.)	
		Yes	744	11	3366.87	3.27	5.289 (2.318 to 12.066)	
CKD	No	No	12 246	10	63 735.20	0.16	1 (Ref.)	0.002
		Yes	2422	31	11 982.01	2.59	14.229 (6.859 to 29.518)	
	Yes	No	709	14	3919.02	3.57	1 (Ref.)	
		Yes	169	6	854.60	7.02	2.163 (0.822 to 5.690)	

*Adjusted for age, sex, income, smoking status, alcohol consumption, physical activity, obesity, hypertension, type 2 diabetes, dyslipidaemia and CKD.
†Lowest 25th percentile.
CKD, chronic kidney disease; IR, incidence rate; pyrs, person-years; SSc, systemic sclerosis.

When patients with SSc were classified according to the specific medications used during follow-up, the risk of incident kidney failure was higher in patients with SSc than in controls, regardless of the medications used (table 3). However, the effect size differed across medications. The effect size was larger in patients with SSc treated with MMF (model 4, aHR=27.094, 95% CI=11.791 to 62.258), CYC (model 4, aHR=17.122, 95% CI=7.945 to 36.899) or ACEi (model 4, aHR=17.126, 95% CI=7.968 to 36.810), than in those treated with MTX (model 4, aHR=5.157, 95% CI=1.931 to 13.772).

Subgroup analyses

The results of subgroup analyses stratified by multiple covariates are summarised in table 4. The association between SSc and the risk of incident kidney failure was more prominent in those without type 2 diabetes than in those with type 2 diabetes (P interaction=0.045), as well as in those without CKD than in those with CKD (P interaction=0.002).

DISCUSSION

In this study, we assessed the risk of kidney failure in patients with SSc compared with the general population. The risk of kidney failure was higher in patients with SSc than in controls. The effect size was larger in patients who were more recently diagnosed with SSc than in those who were diagnosed with SSc earlier. The association between SSc and the risk of kidney failure was more robust in individuals without type 2 diabetes and in those without CKD compared with their respective counterparts. Our study is noteworthy in that it encompasses data up to the recent years (followed up up to 2019) and that the HRs according to the time of SSc diagnosis have been assessed.

In a study from Taiwan, in which the end of follow-up was 2013, the HR for kidney failure in patients with SSc was 2.12.[11] In our study, the end of follow-up was 2019, and the risk of kidney failure was also higher in patients with SSc than in the general population. However, the absolute incidence rate of kidney failure in patients with SSc in our study (2.88 per 1000 person-years) was relatively lower than that in the previous study (3.55 per 1000 person-years).[11] This is in line with a study that reported a declining incidence of kidney failure in patients with SSc.[12] Nonetheless, the effect size of SSc on incident kidney failure in our study was markedly greater (model 4, aHR=7.244) than that in the previous study.[11] This is likely attributable to the considerably lower absolute incidence rate of kidney failure in the general population in our study (0.35 per 1000 person-years) than that in the previous study (1.63 per 1000 person-years).[11] Although the absolute incidence of kidney failure in patients with SSc has been declining, these patients are still at significantly higher risk of developing kidney failure than the general population.

When patients with SSc were further categorised based on when they were diagnosed (before 2010, between 2010 and 2013 and between 2014 and 2017) and compared with their respective matched controls, the higher risk of kidney failure in patients with SSc was consistently observed in all comparisons. Interestingly, the effect size was similar in patients diagnosed before 2010 (model 4, aHR=6.568) and in those diagnosed between 2010 and 2013 (model 4, aHR=6.553) but greater in patients diagnosed between 2014 and 2017 (model 4, aHR=9.754). As the end of follow-up was 2019 for all patients, patients diagnosed later had a shorter follow-up period than those diagnosed earlier. The larger effect size in those diagnosed later suggests that the risk of kidney failure is particularly high early after the diagnosis of SSc. SRC manifests early in the disease course of SSc, with a mean of 3.2 years after diagnosis of SSc.[23] This could be a possible explanation for the larger effect size observed in patients with SSc diagnosed between 2014 and 2017. The impact of SRC may have attenuated with the longer follow-up period, as seen in patients diagnosed before 2010 and between 2010 and 2013.

In terms of effect of different SSc treatments on the risk of incident kidney failure, we found that use of MMF (model 4, aHR=27.094), CYC (model 4, aHR=17.122) or ACEi (model 4, aHR=17.126) had a higher effect size than that of MTX (model 4, aHR=5.157). It is possible that MMF or CYC could have been used for more rapidly progressive disease than MTX. Considering that rapidly progressive disease is a risk factor for SRC,[24] this could be a possible explanation for the larger effect size of MMF or CYC than MTX on the incidence of kidney failure. With regard to ACEi, it is likely that patients with SSc treated with ACEi are those who developed SRC. The larger effect size of ACEi on incident kidney failure could be explained by the higher incidence of SRC in these patients.

In the subgroup analyses, the impact of SSc on the incidence of kidney failure was more prominent in individuals without type 2 diabetes (model 4, aHR=10.858) than in those with type 2 diabetes (model 4, aHR=3.175). Type 2 diabetes is a leading cause of kidney failure[21 25]; therefore, the impact of SSc on kidney failure might have been blunted in individuals with underlying type 2 diabetes. Another significant finding observed in the subgroup analyses was the more pronounced impact of SSc on the incidence of kidney failure in individuals without CKD (model 4, aHR=14.229) than in those with CKD (model 4, aHR=2.163). CKD is another established risk factor for kidney failure,[21] and the effects of SSc on kidney failure might have been attenuated in those with underlying CKD. In addition, although statistically not significant, a similar trend was also observed in the subgroup analyses stratified by other known risk factors for kidney failure such as smoking, obesity, hypertension and dyslipidaemia[19 21 26–29]; that is, the impact of SSc on the incidence of kidney failure tended to be more pronounced in individuals without these risk factors than in those with these risk factors. Therefore, incident kidney failure should be closely monitored, especially in patients with SSc who do not have other risk factors for kidney failure.

Some limitations should be noted in our study. First, bias from unmeasured confounders could not be fully excluded. However, by using the health check-up data, we adjusted for various covariates, including smoking status, alcohol consumption, physical activity and obesity, which were not considered in the previous study.[11] Second, we lacked data on disease-specific characteristics of SSc, such as the modified Rodnan skin score or organs involved, and we were unable to analyse whether disease-specific characteristics of SSc are associated with a higher risk of kidney failure. Nonetheless, our study is meaningful in that we included a large number of patients and provided robust evidence that SSc is still associated with a higher risk of incident kidney failure, up to the recent years.

In conclusion, although the absolute incidence of kidney failure in patients with SSc has been declining, the risk of incident kidney failure is still higher in patients with SSc than in the general population. The impact of SSc on incident kidney failure was stronger in individuals who do not have known risk factors of kidney failure, particularly type 2 diabetes or CKD. Therefore, careful monitoring for incident kidney failure on patients with SSc is warranted, especially in those without other risk factors for kidney failure.

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