

Scleroderma Renal Crisis: Risk Factors for an Increasingly Rare Organ Complication

Pia Moinszadeh, Kathrin Kuhr^{ID}, Elise Siegert, Norbert Blank^{ID}, Cord Sunderkoetter, Jörg Henes, Martin Krusche^{ID}, Marc Schmalzing^{ID}, Margitta Worm^{ID}, Tim Schmeiser, Claudia Günther, Elisabeth Aberer, Laura Susok, Gabriela Riemekasten, Alexander Kreuter^{ID}, Gabriele Zeidler, Aaron Juche, Denitsa Hadjiski^{ID}, Ulf Müller-Ladner, Noemi Gaebelein-Wissing, Jörg H.W. Distler, Miklós Sárdy, Thomas Krieg, and Nicolas Hunzelmann

ABSTRACT. Objective. Scleroderma renal crisis (SRC) is a severe life-threatening manifestation in patients with systemic sclerosis (SSc). However, the knowledge about risk factors for SRC is limited. We determined here the frequency of SRC and identified risk factors for the prediction of SRC.

Methods. Based on regular followup data from the German Network for Systemic Scleroderma, we used univariate and multivariate generalized estimating equations to analyze the association between clinical variables, SSc subsets, therapy [i.e., angiotensin-converting enzyme inhibitors (ACEi), corticosteroids], and the occurrence of SRC.

Results. Data of 2873 patients with 10,425 visits were available for analysis with a mean number of registry visits of 3.6 ± 2.8 and a mean time of followup of 3.6 ± 3.8 years. In total, 70 patients developed SRC (70/2873, 2.4%). Of these patients, 57.1% (40/70) were diagnosed with diffuse cutaneous SSc, 31.4% (22/70) with limited cutaneous SSc, and 11.4% (8/70) with SSc-overlap syndromes. Predictive independent factors with the highest probability for SRC were positive anti-RNA polymerase antibodies (RNAP), a history of proteinuria prior to SRC onset, diminished DLCO, and a history of hypertension. Interestingly, positive antitopoisomerase autoantibodies did not predict a higher risk for SRC. Further, patients with SRC were significantly more frequently treated with ACEi and corticosteroids without being independently associated with SRC.

Conclusion. In this cohort, SRC has become a rare complication. By far the highest risk for SRC was associated with the detection of anti-RNAP and proteinuria. (First Release August 15 2019; J Rheumatol 2020;47:241–8; doi:10.3899/jrheum.180582)

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From the Department of Dermatology and Venereology, University Hospital Cologne; Institute of Medical Statistics and Computational Biology, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne; Department of Rheumatology, Charité Universitätsmedizin Berlin; Department of Dermatology and Allergology, Immanuel Krankenhaus Berlin-Buch, Berlin; Department of Rheumatology, University Hospital Heidelberg, Heidelberg; Department of Dermatology and Venereology, University Hospital Muenster, Muenster; University Hospital Halle, Halle; Centre for Interdisciplinary Clinical Immunology, Rheumatology and Auto-inflammatory Diseases; Department of Internal Medicine II (Oncology, Hematology, Immunology, Rheumatology, Pulmonology), University Hospital Tuebingen, Tuebingen; Department for Internal Medicine, Rheumatology, Immunology and Nephrology, Asklepios Clinic Altona, Hamburg; Department of Rheumatology, University Hospital Wuerzburg, Wuerzburg; Department of Rheumatology, Krankenhaus St. Josef; Department of Dermatology, HELIOS University Hospital Wuppertal, Wuppertal; Department of Dermatology, University Hospital Carl Gustav Carus, Dresden; Department of Dermatology and Venereology, Ruhr-University-Bochum, Bochum; Department of Rheumatology, University Medical Center-UKSH, Luebeck; Department of Dermatology, Venereology and Allergology, HELIOS St. Elisabeth Hospital Oberhausen, University Witten-Herdecke, Witten; Department of Rheumatology, Johanniter-Krankenhaus im Flaeming Treuenbrietzen, Treuenbrietzen; University Medical Center Freiburg, Freiburg; Department of Rheumatology, Justus Liebig University Giessen, Kerckhoff Clinic, Bad Nauheim; Department of

Rheumatology, University Hospital Erlangen, Erlangen; Department of Dermatology and Allergology, Ludwig Maximilian University, Munich, Germany; Department of Dermatology, Medical University of Graz, Graz, Austria.

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P. Moinszadeh, MD, Department of Dermatology and Venereology, University Hospital Cologne; K. Kuhr, Dr. rer. nat, Institute of Medical Statistics and Computational Biology, Faculty of Medicine and University Hospital Cologne, University of Cologne; E. Siegert, MD, Department of Rheumatology, Charité Universitätsmedizin Berlin; N. Blank, MD, Department of Rheumatology, University Hospital Heidelberg; C. Sunderkoetter, MD, Department of Dermatology and Venereology, University Hospital Muenster, Muenster, and University Hospital Halle; J. Henes, MD, Centre for Interdisciplinary Clinical Immunology, Rheumatology and Auto-inflammatory Diseases, and Department of Internal Medicine II (Oncology, Hematology, Immunology, Rheumatology, Pulmonology), University Hospital Tuebingen; M. Krusche, MD, Department for Internal Medicine, Rheumatology, Immunology and Nephrology, Asklepios Clinic Altona; M. Schmalzing, MD, Department of Rheumatology, University Hospital Wuerzburg; M. Worm, MD, Department of Dermatology and Allergology, Charité Universitätsmedizin Berlin; T. Schmeiser, MD, Department of Rheumatology, Krankenhaus St.

Previously, scleroderma renal crisis (SRC) was reported to occur in up to 15% of patients with systemic sclerosis (SSc)^{1,2,3,4}. In more recent years, however, declining frequencies have been observed^{5,6}. SRC is a medical emergency for patients and a challenge for the treating clinician. The high mortality and morbidity rates observed in the past, especially outside specialized centers, have significantly decreased since the 1970s^{6,7,8}. This is possibly because of (1) the introduction of angiotensin-converting enzyme inhibitors (ACEi), (2) the reduced use of high doses of systemic corticosteroids in patients with SSc, (3) an improvement in SRC knowledge, and simultaneously, an increased research interest in this rare condition. Another reason could be because of more extensive clinical care and an earlier identification of patients at risk of developing this life-threatening organ manifestation. Steen and Medsger reported in 2007 that the 5-year survival of SSc patients with renal crisis improved from < 10% to 65% after the introduction of ACEi⁷. Patient registries, national and international networks combined with a better understanding of the disease, and an intense exchange of knowledge may have spurred this change.

Immediate identification of patients with renal crisis as well as direct initiation of therapy with ACEi can help to improve the outcome of these patients^{2,8,9,10,11,12}. The UK Scleroderma Study Group has published guidelines on diagnosis and therapy of SRC and recommended that ACEi therapy should be continued in patients with SRC independently, whether they need renal replacement therapy or not¹³. Fortunately, renal recovery after renal crisis can still occur up to 3 years after developing SRC (most often between 12–18 months)¹³.

The International Scleroderma Renal Crisis Survey collected incident cases of renal crisis being reported from centers specialized in SSc care on all continents. They

showed that patients who were treated with ACEi prior to the onset of SRC had a higher probability of death afterward¹⁴. This triggered the debate of whether ACEi may obscure the initial clinical signs of an SRC and therefore cause a worse outcome^{15,16,17,18}. Further, the survey indicated that a higher risk of developing SRC exists in patients having the diffuse form of SSc, those with an early onset and progressive course of the disease (typically within the first 3–5 yrs after the onset of non-Raynaud signs¹⁹), as well as patients with tendon friction rubs/large joint contractures²⁰, positive antitopoisomerase (ATA)^{20,21}, anti-RNA polymerase antibodies (RNAP)^{4,6,21,22,23,24}, and recent corticosteroid exposure^{14,18,25}.

In our study, prospectively collected data of more than 2800 patients were analyzed to assess the frequency of SRC and its association with clinical and therapeutic characteristics in a large central European multidisciplinary cohort.

MATERIALS AND METHODS

The patient registry of the German Network for Systemic Scleroderma (DNSS) was founded in 2003 and involves, to date, more than 40 clinical centers consisting of different subspecialties such as rheumatologists, dermatologists, pulmonologists, and nephrologists. Followup visits and regular investigations (e.g., echocardiography, electrocardiogram, lung function test) are recommended at least once per year, depending on the severity of organ manifestations and the course of the disease. The 4-page disease- and organ-specific questionnaire collects a core set of clinical data to determine the current disease status, including information on sex, date of birth, onset of organ manifestations, as well as current signs and symptoms together with characteristic laboratory data such as antinuclear antibodies^{26,27,28,29}. Information on therapy including corticosteroid dosage, immunosuppressive treatment, as well as the use of ACEi and vasodilative drugs are part of the questionnaire^{26,27,28,29}. In particular, SRC has been defined by (1) increased systolic pressure (> 140/90 mmHg), a fast increase of the systolic/diastolic pressure of > 30 mmHg/20 mmHg compared to baseline in addition to (2) an increase of serum creatinine and a decrease of the glomerular filtration rate of $\geq 30\%$. Proteinuria, hematuria, and/or the development of thrombocytopenia, hemolysis, and hypertensive encephalopathy might also be present. Further, kidney involvement (subclinical renal impairment) was defined as renal insufficiency with an age-related creatinine clearance of < 80 ml/min and/or proteinuria as defined by albuminuria ≥ 30 mg/24 h or ≥ 20 mg/l; proteinuria ≥ 300 mg/24 h or ≥ 200 mg/126.

Hypertension (HTN) has been defined as repeatedly increased blood pressure of > 140/90 mmHg at rest or already well-adjusted blood pressure being treated with, for example, calcium channel blockers, ACEi, AT1 receptor antagonists, β blocker, and/or diuretics.

Raynaud phenomenon (RP) was defined by recurrent vasospasms of small digital arterioles/arteries at the fingers and/or toes. The age of RP onset has been defined as the age at which the RP first appeared. The first non-RP onset has been considered the timepoint of first skin or organ involvement.

Skin involvement was evaluated using the modified Rodnan skin score (mRSS) to assess the skin thickness by manual palpation of 17 different anatomic areas, scaling the thickness in 0–3.

Pulmonary manifestation includes pulmonary interstitial fibrosis and/or isolated pulmonary arterial hypertension (PAH).

Isolated pulmonary HTN was defined as clinical evidence of right-heart failure and/or increased mean pulmonary arterial pressure (mPAP > 25 mmHg at rest or PAP > 30 mmHg during exercise), determined by right-heart catheterization. Echocardiography was used to identify likely PAH (estimated right ventricular systolic pressure > 40 mmHg).

Lung fibrosis was established when bilateral basal fibrosis, confirmed by chest radiograph and/or high-resolution computed tomography scan,

Josef; C. Günther, MD, Department of Dermatology, University Hospital Carl Gustav Carus; E. Aberer, MD, Department of Dermatology, Medical University of Graz; L. Susok, MD, Department of Dermatology and Venereology, Ruhr-University-Bochum; G. Riemekasten, MD, Department of Rheumatology, University Medical Center-UKSH; A. Kreuter, MD, Department of Dermatology, Venereology and Allergology, HELIOS St. Elisabeth Hospital Oberhausen, University Witten-Herdecke; G. Zeidler, MD, Department of Rheumatology, Johanniter-Krankenhaus im Flaeming Treuenbrietzen; A. Juche, MD, Department of Rheumatology, Immanuel Krankenhaus Berlin-Buch; D. Hadjiski, MD, University Medical Center Freiburg; U. Müller-Ladner, MD, Department of Rheumatology, Justus Liebig University Giessen, Kerckhoff Clinic; N. Gaebele-Wissing, MD, Department of Dermatology, HELIOS University Hospital Wuppertal; J.H. Distler, MD, Department of Rheumatology, University Hospital Erlangen; M. Sárdy, MD, Department of Dermatology and Allergology, Ludwig Maximilian University; T. Krieg, MD, Department of Dermatology and Venereology, University Hospital Cologne; N. Hunzelmann, MD, Department of Dermatology and Venereology, University Hospital Cologne.

Address correspondence to Dr. P. Moinszadeh, Department of Dermatology and Venereology, University of Cologne, Kerpener Str. 62, 50937 Cologne, Germany. E-mail: pia.moinszadeh@uk-koeln.de

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occurred together with restrictive pulmonary abnormalities on pulmonary function tests (total lung capacity < 80%). We defined a normal DLCO level as > 75%, and a low level as ≤ 75%.

Gastrointestinal (GI) involvement included GI motility disturbance, dysphagia, nausea, malabsorption, esophageal stenosis, gastroesophageal reflux, or intestinal pseudo-obstruction.

Heart involvement was defined by heart palpitation, conduction disturbance, and/or diastolic dysfunction.

Skeletal muscle involvement was present in case of proximal muscle weakness and/or atrophy recorded on clinical evaluation and raised serum muscle enzyme levels [creatinine kinase (CK)] and/or articular involvement. The articular involvement included synovitis with swelling, with or without tenderness to palpation in 1 or > 1 joint.

Digital ulcers were defined as loss of dermis and epidermis of at least 2 mm of tissue at the fingertips.

Tendon friction rubs were defined as palpable, leathery crepitus in combination with active and passive movements of the joints^{26,28}.

The Ethics Committee of the coordinating center, i.e., the Cologne University Hospital, approved the patient information and consent form of the DNSS registry (approval number 04-037), which was used by all participating centers to receive the approval of their local ethics committees prior to registering patients. To participate in the study, all patients have provided written informed consent.

The registry encompasses several subsets of SSc including early undifferentiated forms and SSc sine scleroderma. For this analysis, we focused on patients with limited cutaneous SSc (lcSSc), diffuse cutaneous SSc (dcSSc), and SSc overlap syndromes. Using this selection, data of 2873 patients with 10,425 followup visits were present for analysis registered between 2003 and 2017.

In addition to the separation into the 3 main SSc subsets, we also screened for those patients who had at least once a defined history of renal crisis. Association of SRC with other clinical data was evaluated, descriptively comparing patients with and without SRC (cross-sectional data analysis). For changeable patient characteristics, we used aggregated information (first to last visit) to include followup data, i.e., ever/never documented for dichotomous variables and minimum or maximum values for ordinal and continuous variables (worst value documented). To estimate the extension of these associations, we used generalized estimating equations (GEE), considering the repeated measures structure (outcome = SRC, probability distribution = binomial, link = logit, working correlation matrix structure = AR-1). The originally measured values at the related visit cycles were used to fit the models (longitudinal data analysis).

Univariable models for all variables of interest, as well as a multivariable model including variables showing a *p* value < 0.1 in univariable models, were fitted. Further, we analyzed the prognostic value of possible risk factors (i.e., proteinuria, HTN, ACEi, and corticosteroids) with the risk of developing SRC. Only data prior to SRC onset were used for the analysis of the prognostic significance. Accordingly, patients treated with corticosteroids and/or ACEi were included within this analysis only if they were receiving ACEi and/or corticosteroids prior to the onset of SRC. The same applies for the onset of HTN and proteinuria, defined as a history of proteinuria and a history of HTN.

We used univariable and multivariable GEE in the same manner, but we considered data only until the first documentation of SRC, instead of considering all visits. For GEE, the data given are OR and adjusted OR (aOR), corresponding 95% CI, and *p* values (Wald test). All reported *p* values are 2-sided. To avoid type I error from multiple testing, only *p* values below 0.01 were considered to indicate statistical significance. Calculations and figures were carried out using SPSS (IBM Corp.) and Excel (Microsoft Corp.).

RESULTS

Complete datasets on SRC were available for 2873 patients and 10,425 visits, with a mean number of registry visits of

3.6 ± 2.8 , respectively. In total, 70 patients developed an SRC (2.4%, 70/2873). Of these, 57.1% (40/70) were diagnosed with dcSSc, while 31.4% (22/70) were diagnosed with lcSSc and 11.4% (8/70) with SSc overlap syndromes. The male/female ratio was equivalent to the distribution within the whole SSc cohort with a clear predominance of women (3:1, 76.5% vs 23.5%). All clinical features of patients with SRC are listed in Table 1.

The mean age at disease onset did not show any significant difference between patients with (48.0 ± 12.4 yrs) or without (47.8 ± 14.4 yrs) a history of SRC. Throughout the observation time, patients with SRC had, on average, 1.5 more visits than those without SRC (mean 5.1 ± 3.4 vs 3.6 ± 2.8 visits). The time between the onset of the first non-Raynaud symptom and the first visit to a specified clinical center was shorter for patients developing SRC (mean 5.2 ± 6.5 vs 7.2 ± 7.9 visits). The disease duration, starting from the onset of the first non-Raynaud symptom, was shorter for patients with SRC (8.5 ± 8.0 yrs vs 11.0 ± 8.8 yrs). No significant difference could be observed for the body mass index, sex distribution, simultaneous occurrence of lung fibrosis, GI involvement, tendon friction rubs, or digital ulcerations.

The unadjusted univariable GEE analysis clearly showed an association between key variables and the risk of SRC onset. Using the limited form of SSc as reference value, patients having dcSSc developed SRC significantly more often, resulting in a 3-fold increased probability (OR 2.545, CI 1.424–4.549, *p* = 0.002; Table 2A and Table 2B). Patients with anticentromere antibodies (ACA) showed a significantly lower probability of developing SRC (OR 0.459, 95% CI 0.248–0.853, *p* = 0.014), while patients with anti-RNAP (16.7% vs 2.3%) had a 7-fold increased risk of SRC (OR 7.298, 95% CI 3.181–16.743, *p* < 0.001; Table 2A and Table 2B).

Patients with SRC were more often associated with a higher mRSS (worst mRSS > 10) with frequencies of 4.1% versus 1.3%. This difference was more pronounced after selecting patients with worst mRSS of > 15 (5.4% vs 1.5%) or > 20 (6.5% vs 1.8%). For instance, mRSS of > 15 was associated with a 2-fold higher probability of developing SRC (OR 2.058, 95% CI 1.104–3.836, *p* = 0.023). A decreased diffusion capacity level (worst DLCO ≤ 75%, 3.2% vs 1.1%) was also associated with an increased SRC probability (OR 4.419, 95% CI 2.018–9.674, *p* < 0.001; Table 2A and Table 2B). We could not find any relationship between the development of digital ulcerations, tendon friction rubs, lung fibrosis, or GI involvement and the manifestation of SRC.

A further analysis examined all prognostic factors (history of proteinuria, history of HTN, treatment with corticosteroids and/or ACEi prior to SRC onset), including all visits until SRC was first documented. Patients with a history of proteinuria had a 6-fold increased probability of developing SRC (OR 5.559, 95% CI 3.436–8.994, *p* < 0.001). The mean

Table 1. Patient characteristics comparing those with or without a history of SRC (ever/never; epidemiological factors).

Variable	Value	Total n	SRC, Never, % (n)	SRC, Ever, % (n)
Analysis set	Total	2873	97.6 (2803)	2.4 (70)
No. visits	Valid n	2873	2803	70
	Mean \pm SD	3.6 \pm 2.8	3.6 \pm 2.8	5.1 \pm 3.4
Age at disease onset, yrs	Valid n	2321	2257	64
	Mean \pm SD	47.8 \pm 14.3	47.8 \pm 14.4	48.0 \pm 12.4
Disease duration at first visit, yrs	Valid n	2355	2290	65
	Mean \pm SD	7.2 \pm 7.9	7.2 \pm 7.9	5.2 \pm 6.5
Disease duration at occurrence of SRC or last visit, resp., yrs*	Valid n	2355	2290	65
	Mean \pm SD	10.9 \pm 8.8	11.0 \pm 8.8	8.5 \pm 8.0
Sex	Male	540	97.0 (524)	3.0 (16)
	Female	2260	97.7 (2209)	2.3 (52)
	Total	2800	97.6 (2732)	2.4 (68)
Highest BMI	Valid n	2760	2691	69
	Mean \pm SD	25.2 \pm 5.0	25.1 \pm 5.0	25.9 \pm 4.5
Lowest BMI	Valid n	2760	2691	69
	Mean \pm SD	23.9 \pm 4.7	23.9 \pm 4.7	23.0 \pm 4.3
Diagnosis	LcSSc	1465	98.5 (1443)	1.5 (22)
	DcSSc	1064	96.2 (1024)	3.8 (40)
	Overlap-S.	344	97.7 (336)	2.3 (8)
	Total	2873	97.6 (2803)	2.4 (70)
ANA+, first visit	No	259	97.7 (253)	2.3 (6)
	Yes	2415	97.6 (2356)	2.4 (59)
	Total	2674	97.6 (2609)	2.4 (65)
Scl-70+, first visit	No	1713	97.3 (1666)	2.7 (47)
	Yes	800	98.0 (784)	2.0 (16)
	Total	2513	97.5 (2450)	2.5 (63)
ACA+, first visit	No	1580	97.1 (1534)	2.9 (46)
	Yes	958	98.2 (941)	1.8 (17)
	Total	2538	97.5 (2475)	2.5 (63)
RNAP+, first visit	No	2573	97.7 (2513)	2.3 (60)
	Yes	42	83.3 (35)	16.7 (7)
	Total	2615	97.4 (2548)	2.6 (67)
Worst mRSS > 15	No	2048	98.5 (2018)	1.5 (30)
	Yes	745	94.6 (705)	5.4 (40)
	Total	2793	97.5 (2723)	2.5 (70)
Worst DLCO \leq 75	No	563	98.9 (557)	1.1 (6)
	Yes	1827	96.8 (1769)	3.2 (58)
	Total	2390	97.3 (2326)	2.7 (64)
Worst ESR > 20/30 mm/h	No	1646	98.7 (1625)	1.3 (21)
	Yes	819	95.2 (780)	4.8 (39)
	Total	2465	97.6 (2405)	2.4 (60)
Digital ulcerations, ever	No	1674	98.0 (1641)	2.0 (33)
	Yes	1181	97.0 (1145)	3.0 (36)
	Total	2855	97.6 (2786)	2.4 (69)
CK elevation, > 3 times, ever	No	2313	97.7 (2259)	2.3 (54)
	Yes	331	96.1 (318)	3.9 (13)
	Total	2644	97.5 (2577)	2.5 (67)
Tendon friction rubs, ever	No	2446	98.1 (2400)	1.9 (46)
	Yes	410	94.1 (386)	5.9 (24)
	Total	2856	97.5 (2786)	2.5 (70)
PAH, ever	No	2263	98.0 (2218)	2.0 (45)
	Yes	595	96.0 (571)	4.0 (24)
	Total	2858	97.6 (2789)	2.4 (69)
Lung fibrosis, ever	No	1540	98.0 (1509)	2.0 (31)
	Yes	1322	97.1 (1284)	2.9 (38)
	Total	2862	97.6 (2793)	2.4 (69)
GI involvement, ever	No	2143	98.2 (2105)	1.8 (38)
	Yes	718	95.7 (687)	4.3 (31)
	Total	2861	97.6 (2792)	2.4 (69)

*SRC, never: at last visit; SRC, ever: at first visit with documented SRC. Of note: for 22/70 patients with SRC, SRC was present at first visit, thus disease duration might be overestimated. SRC: scleroderma renal crisis; BMI: body mass index; ANA: antinuclear antibody; ACA: anticentromere antibodies; RNAP: RNA polymerase antibodies; mRSS: modified Rodnan skin score; ESR: erythrocyte sedimentation rate; CK: creatine kinase; PAH: pulmonary arterial hypertension; GI: gastrointestinal.

Table 2A. Association between patient characteristics and SRC development. Longitudinal data analysis using GEE with target variable “SRC,” including all visits (univariable analysis).

Variable	Univariable GEE		
	p	OR	95% CI
Age at disease onset	0.734	1.003	0.986–1.020
Disease duration, yrs	0.447	0.985	0.949–1.023
Disease duration ≤ 5 yrs	0.267	1.294	0.821–2.038
Sex, male vs female	0.063	0.502	0.243–1.038
BMI	0.162	0.958	0.902–1.017
Diagnosis	0.004		
Overlap vs lcSSc	0.848	1.087	0.463–2.554
DcSSc vs lcSSc	0.002	2.545	1.424–4.549
ANA	0.922	0.958	0.406–2.262
Anti-Scl 70	0.879	0.944	0.450–1.980
ACA	0.014	0.459	0.248–0.853
Anti-RNAP	< 0.001	7.298	3.181–16.743
mRSS, total score	0.001	1.043	1.019–1.069
mRSS > 10	0.008	1.934	1.186–3.153
mRSS > 15	0.023	2.058	1.104–3.836
mRSS > 20	0.066	1.865	0.959–3.628
DLCO ≤ 75%	< 0.001	4.419	2.018–9.674
Elevated ESR	0.004	2.500	1.349–4.633
Digital ulceration	0.414	1.238	0.742–2.064
CK elevation	0.020	2.247	1.134–4.452
Tendon friction rubs	0.158	1.885	0.782–4.541
PAH	0.004	2.082	1.263–3.430
Lung fibrosis	0.066	1.609	0.969–2.670
GI involvement	0.070	1.767	0.955–3.269

SRC: scleroderma renal crisis; GEE: generalized estimating equations; BMI: body mass index; lcSSc: limited cutaneous systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis; ANA: antinuclear antibody; ACA: anticentromere antibodies; anti-RNAP: anti-RNA polymerase antibodies; mRSS: modified Rodnan skin score; ESR: erythrocyte sedimentation rate; CK: creatine kinase; PAH: pulmonary arterial hypertension; GI: gastrointestinal.

Table 2B. Association between patient characteristics and SRC development. Longitudinal data analysis using GEE with target variable “SRC,” including all visits (multivariable analysis).

Variable	Multivariable GEE*		
	p	aOR	95% CI
Sex	0.119	0.559	0.269–1.161
Diagnosis	0.609		
Overlap vs lcSSc	0.935	1.042	0.390–2.785
DcSSc vs lcSSc	0.385	1.379	0.668–2.846
ACA	0.410	0.753	0.383–1.480
Anti-RNAP	< 0.001	5.856	2.599–13.193
mRSS > 15	0.412	1.337	0.668–2.675
DLCO ≤ 75%	0.012	2.544	1.226–5.279
Elevated ESR	0.084	1.607	0.939–2.751
CK elevation	0.538	1.340	0.528–3.397
PAH	0.036	1.912	1.044–3.504
Lung fibrosis	0.598	1.186	0.630–2.233
GI involvement	0.037	1.966	1.042–3.708

*Missing was included as category in case of > 10% missing values (data not shown). SRC: scleroderma renal crisis; GEE: generalized estimating equations; lcSSc: limited cutaneous systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis; ACA: anticentromere antibodies; anti-RNAP: anti-RNA polymerase antibodies; mRSS: modified Rodnan skin score; ESR: erythrocyte sedimentation rate; CK: creatine kinase; PAH: pulmonary arterial hypertension; GI: gastrointestinal; aOR: adjusted OR.

time between the onset of proteinuria and the onset of SRC was 3.71 ± 2.83 years. Patients with a history of HTN ($> 140/90$ mmHg) had a 4-fold increased probability of SRC (OR 4.198, 95% CI 2.488–7.084, $p < 0.001$). The mean time between the onset of HTN and the onset of SRC was 3.83 ± 2.15 years. Patients who were treated with systemic corticosteroids had about a 2-fold increased risk of developing SRC (OR 1.932, 95% CI 1.202–3.107, $p = 0.007$). Sufficient data were not available for a more in-depth analysis of corticosteroid dosage. Similarly, patients with SRC were significantly more frequently treated with ACEi prior to the onset of SRC, versus those without SRC (OR 2.709, 95% CI 1.676–4.379, $p < 0.001$; Table 3).

Clinical characteristics included in the multivariable GEE model were SSc subsets, ACA, anti-RNAP, mRSS > 15, DLCO ≤ 75%, PAH, GI involvement, elevated erythrocyte sedimentation rate (ESR), history of HTN, proteinuria, ACEi, and corticosteroids. This additional analysis step clearly indicated that these factors remained independently associated with an increased probability of SRC: a history of proteinuria (aOR 4.024, 95% CI 2.343–6.912, $p < 0.001$), anti-RNAP (aOR 5.856, 95% CI 2.599–13.193, $p < 0.001$), diminished DLCO levels (aOR 2.544, 95% CI 1.226–5.279, $p = 0.012$), PAH (aOR 1.912, 95% CI 1.044–3.504,

Table 3. Prognostic factors for SRC development. Longitudinal data analysis using GEE with target variable "SRC," including all visits until first documentation of SRC.

Variable	Univariable GEE			Multivariable GEE*		
	p	OR	95% CI	p	aOR	95% CI
Hypertension	< 0.001	4.198	2.488–7.084	< 0.001	2.793	1.570–4.970
Proteinuria	< 0.001	5.559	3.436–8.994	< 0.001	4.024	2.343–6.912
ACEi	< 0.001	2.709	1.676–4.379	0.162	1.492	0.851–2.616
Corticosteroids	0.007	1.932	1.202–3.107	0.067	1.656	0.966–2.841

*Adjusted for diagnosis, anti-RNA polymerase antibodies, modified Rodnan skin score, DLCO, erythrocyte sedimentation rate elevation, pulmonary arterial hypertension, and gastrointestinal involvement. Missing was included as category in case of > 10% missing values (data not shown). SRC: scleroderma renal crisis; GEE: generalized estimating equations; ACEi: angiotensin-converting enzyme inhibitors; aOR: adjusted OR.

p = 0.036), GI involvement (aOR 1.966, 95% CI 1.042–3.708, p = 0.037), and a history of HTN (aOR 2.793, 95% CI 1.570–4.970, p = 0.001; Table 2B and Table 3). The association of dcSSc, mRSS > 15, intake of ACEi, and corticosteroids was not stable after adjusting for the key clinical characteristics.

DISCUSSION

Our study underlines that renal crisis has become a rare complication in SSc. A number of aspects appear to be relevant for the observed decline compared to previous studies. These include a more judicious use of corticosteroids, the decreased use of potentially harmful immunosuppression such as cyclosporine, and the increased use of vasodilators. Nevertheless, SRC remains an important cause of morbidity and mortality, in which risk factors are still poorly understood. After metaanalyses of papers addressing SRC, Hoa, *et al* pointed out that a consensus definition is urgently needed to standardize the collection of clinical data of patients with SRC in the future; lack of a definition is clearly a limitation when data collected under different circumstances are compared²⁵. The variables collected in this registry did not include hypertensive encephalopathy, seizures, microangiopathic hemolytic anemia, thrombocytopenia, or characteristic changes on renal biopsy. Hoa, *et al* focused on classification criteria of SRC and found 23 original papers assessing clinical predictors for SRC, which included shorter disease duration, diffuse skin manifestation, high levels of mRSS, joint contractures, anti-RNAP antibodies, and recent exposure to corticosteroids²⁵. In our cohort, we found that SRC occurred relatively early in the disease. However, this was not statistically significant.

Predictive independent factors for SRC in our patient cohort included a history of proteinuria prior to SRC onset, and positive anti-RNAP, followed by diminished DLCO levels as well as a medical history of HTN prior to SRC onset. The association between positive anti-RNAP antibodies and the occurrence of SRC was in line with other reports^{4,21,24}. Those studies also supported our observation that ATA and ACA antibodies were not strongly associated

with the development of SRC^{21,24}. Further, our data are in line with and support the observations by Gordon, *et al*, who recently reported the association between a medical history of HTN and/or proteinuria and SRC³⁰. It is also not known yet whether symptoms associated with kidney damage, such as HTN and proteinuria, could serve as indicators predicting an increased risk for SRC. This study shows, in analogy to other systemic diseases, that proteinuria may also be an indicator of early organ damage and morbidity in SSc³¹. Therefore, HTN and proteinuria could serve as signs of early kidney damage preceding SRC. However, just in a specific subset of patients, this organ involvement will then progress to SRC. In this context, it is important to mention that proteinuria belongs to the strongest predictors of mortality known in SSc³².

Further, diminished DLCO was observed to indicate an increased risk, which might reflect in part the vasculopathy underlying SRC, which has not been identified yet. Recent exposure to corticosteroids was associated with an increased risk for SRC in the univariate analysis. Unfortunately, we did not have sufficient data for a more in-depth analysis on the potential effect of the corticosteroid dosage on the risk for SRC. However, after performing a multivariate analysis, adjusting for diagnosis, anti-RNAP, mRSS, DLCO, ESR elevation, GI involvement, and PAH, the effect of corticosteroids prior to the onset of SRC was less pronounced, which is not in line with previous reports^{33,34,35}.

When a multivariate analysis was performed, a higher probability for SRC was not predicted by ATA, a specific disease subset, tendon friction rubs, elevated CK serum levels, increased mRSS, or the consumption of ACEi or corticosteroids. Controversial data exist regarding the association of ACEi intake with a higher probability of developing SRC and the risk of postponing the diagnosis of SRC with a higher risk of death^{14,36,37}. Our study clearly shows no direct association with the development of SRC after multivariate analysis, which is in line with the observation of Wangkaew, *et al*³⁴. At present, the question of whether ACEi in some patients are associated with a worse outcome cannot yet be answered with our cohort. However, it should be noted that

the frequency of renal crisis was still remarkably low despite the high frequency of ACEi prior to the onset of SRC use in this cohort (1087/2839, i.e., 38.3%, and reported by Moinzadeh, *et al*)²⁹.

These data clearly indicate that the highest independent risk for SRC is associated with the existence of anti-RNAP and the history of proteinuria prior to SRC onset, followed by a history of HTN and a decreased DLCO level. It is known that in up to 25% of cases, diagnosis has been made at the time of SRC development. SRC remains an emergency situation^{6,16,38}. Therefore, it would be ideal to identify and protect patients at an earlier stage, and at best, prior to the manifestation of SRC. It is known that the usual manifestation of SRC occurs together with acute or moderate-to-severe onset of HTN and renal failure with oliguria^{1,6,39}. On the other hand, it needs to be emphasized that up to 10% of patients with SRC are normotensive^{16,40}, which reflects the urgent need of other predictive markers and their incorporation into clinical care to identify high-risk patients.

There are several limitations of our study. SRC was diagnosed by clinical data only, and results of kidney pathology, as suggested by Hoa, *et al*, were not available to fully ascertain the diagnosis. When the registry was founded in 2003, no generally accepted, standardized definition for SRC was available. We strongly support the idea of a uniform standardized definition for SRC, as published in 2017 by Hoa, *et al*²⁵. Data obtained within the registry did not allow differentiating patients with normotensive SRC from hypertensive SRC. Further, anti-RNAP was not measured in all patients, which was presumably because of reduced availability and cost restraints. Finally, the (fortunately) low number of events in this large cohort limited statistical analysis.

The data presented show that SRC has become a rare complication of SSc and recent development of proteinuria and HTN, as well as positive RNAP, are the strongest risk factors for SRC.

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