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Clinical science

Scleroderma renal crisis, an increasingly rare but persistently challenging condition: a retrospective cohort study

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Abstract

Objective: Scleroderma renal crisis (SRC) is associated with high morbidity and mortality and there remain unmet needs regarding early identification and treatment. We aimed to assess risk factors for and the outcomes of SRC at a large Australian tertiary hospital.

Methods: Seventeen incident SRC cases were diagnosed between 2012 and 2022. Demographic, SSc manifestations and treatment data were extracted. Using data from the Australian Scleroderma Cohort Study ($n = 483$), logistic regression analysis was performed to identify risk factors for SRC.

Results: The prevalence of SRC was 3.52%. The median SSc disease duration at SRC onset was 2 years [interquartile range (IQR) 1–4]. Peak creatinine occurred at a median of 11 days (IQR 5–14) post-SRC diagnosis, with a median peak creatinine of 144 μmol/l (IQR 86–306). Nine (52.94%) SRC patients had evidence of acute neurologic and/or cardiac complications. Acute haemofiltration was required in 3 (17.65%) patients. Over the follow-up period, 7 (41.18%) SRC patients died 2.75 years (IQR 0.74–7.25) after SRC onset. Patients with SRC were more likely to be male [odds ratio (OR) 9.73 (95% CI 3.57, 26.56)], have diffuse disease [OR 23.16 (95% CI 5.22, 102.80)] and have antibodies to Scl70 [OR 3.34 (95% CI 1.24, 9.04)] or RNA polymerase III (RNAPIII) [OR 5.15 (95% CI 1.91, 13.89)].

Conclusion: SRC is an uncommon manifestation, but outcomes remain poor. A significant proportion of patients presenting with SRC in Australia are positive for Scl70 or RNAPIII antibody. Despite relatively low peak serum creatinine and rates of renal replacement therapy, SRC was still associated with significant mortality.

Lay Summary

What does this mean for patients?

Scleroderma renal crisis (SRC) is a rare but serious complication of systemic sclerosis (also known as scleroderma). There are certain factors that can increase the risk of SRC, including markers in the blood (antibodies), prolonged use of steroids and the diffuse (extensive skin thickening) form of scleroderma. SRC typically presents with a sudden increase in blood pressure (BP) that can lead to kidney problems. If not recognized and treated promptly with BP-lowering medication, SRC can lead to significant kidney, heart and neurologic complications. We reviewed cases of SRC at St Vincent's Hospital Melbourne from 2012 to 2022 to understand the presentation, treatment and outcomes of SRC in the modern era. Of the 483 patients with scleroderma in our cohort, only 17 went on to develop SRC (3.52%). This demonstrates that rates of SRC have declined significantly over the last few decades. At our centre, we noted that male patients and those with a particular blood marker (Scl70 antibody) are at increased risk of SRC. These risk factors have not been well described previously and add to known risk factors for SRC. Although rates of death and severe complications, such as the need for dialysis, were lower at our centre compared with previously published reports, SRC remains a serious complication that patients and their doctors should be aware of and treat early and aggressively.

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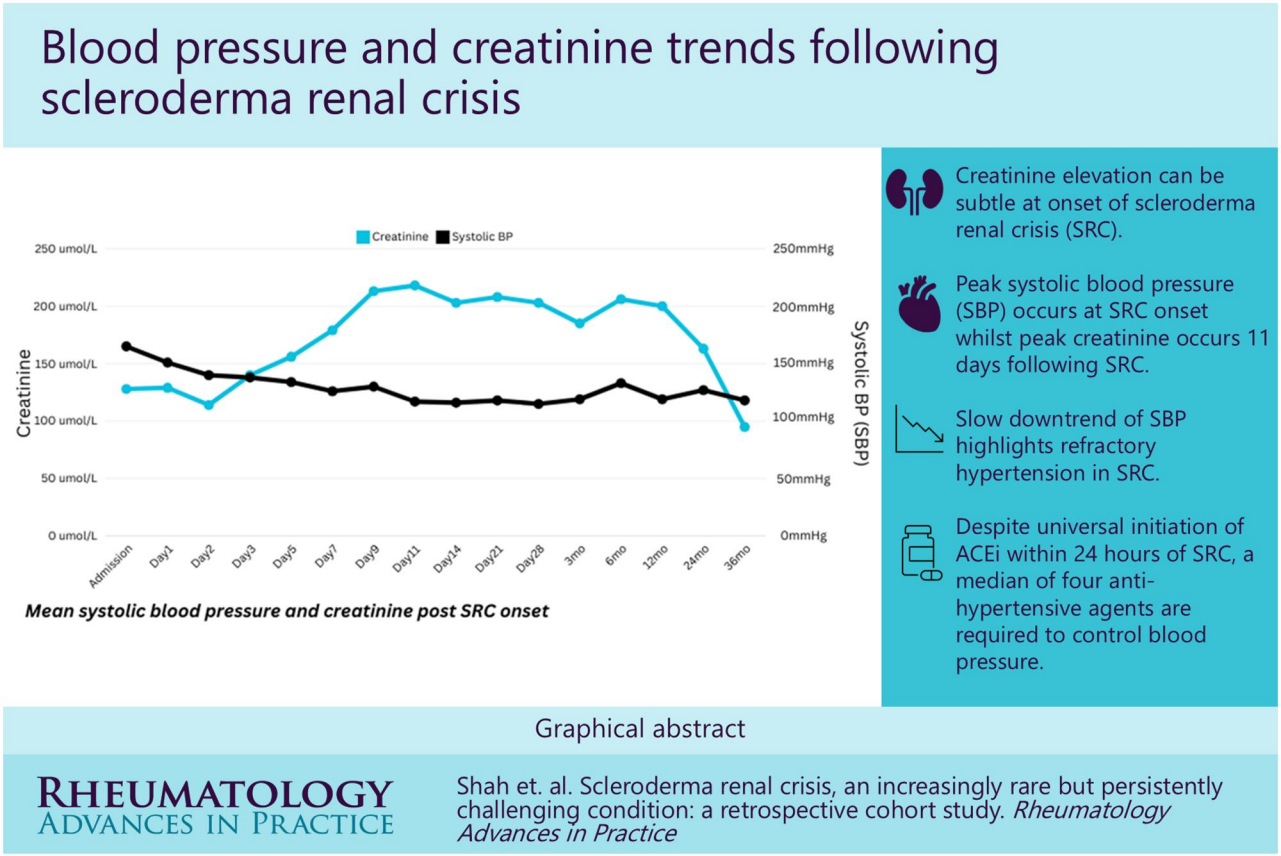
Graphical Abstract



Keywords: systemic sclerosis, scleroderma renal crisis, major organ involvement.

Key messages

- Scl-70 in addition to RNA polymerase III autoantibodies are associated with an increased risk of scleroderma renal crisis.
- Male sex may confer an increased risk of developing scleroderma renal crisis.
- Blood pressure management frequently requires multiple antihypertensive agents and early, aggressive control may improve overall clinical outcomes.

Introduction

Systemic sclerosis (SSc) is a rare autoimmune disorder causing fibrosis of the skin and internal organs [1]. Scleroderma renal crisis (SRC) is a feared complication of SSc and is a medical emergency. Characteristic features of SRC include accelerated hypertension, acute kidney injury and elevated serum creatinine with or without haemoproteinuria, haemolysis and end-organ dysfunction such as hypertensive encephalopathy [2, 3]. Heterogeneity in the presentation of SRC is observed, with up to 10% of patients presenting with a 'normotensive' SRC or with only modest derangements in renal function or limited evidence of haemolysis [2, 4]. A universally accepted definition of SRC does not exist, however, efforts are currently under way to develop SRC classification criteria [2, 5, 6].

The incidence of SRC is decreasing over time [5, 7]. Early studies reported the prevalence of SRC to be as high as 25% in diffuse cutaneous SSc (dcSSc). However, recent studies indicate that approximately 5–10% of patients with dcSSc and 1–4% of those with limited SSc suffer from SRC [5, 6]. The 12-month mortality associated with SRC has declined from 80% to 35% with the introduction of angiotensin-converting enzyme inhibitors (ACEis) [2, 4, 8]. Other factors associated with improved outcomes include earlier recognition of SRC and reduced use of high-dose glucocorticoids [3, 9]. Known SRC risk factors are diffuse and rapidly progressive skin disease, the presence of tendon friction rubs and inflammatory arthritis [8, 10], the presence RNA polymerase III (RNAPIII) antibodies and use of ≥15 mg prednisolone/day [3, 5]. Controversy remains regarding the risk posed by prior use of

ACEis, the presence of anti-topoisomerase I (Scl70) antibodies and pre-existing proteinuria or hypertension [5, 6, 9].

There remain significant unmet needs regarding early identification and treatment of SRC. Mortality rates remain high, with no further improvement in survival since the introduction of ACEi therapy [4, 11]. Early identification of SRC and treatment remain clinical challenges, particularly outside of tertiary centres. Therefore, we aimed to review all cases of SRC managed at an Australian SSc referral centre to describe the clinical presentation and clinical course of SRC in a contemporary era and to identify risk factors associated with the development of SRC.

Methods

We performed a retrospective medical records review of all patients diagnosed with SRC at St Vincent's Hospital Melbourne (SVHM) between 2012 and 2022. Cases were identified by searching for relevant International Classification of Diseases, Tenth Revision (ICD10) codes. This included systemic sclerosis (M34) in combination with at least one the following: hypertensive renal disease (I12), secondary hypertension (I15), haemolytic anaemia (D59), acute renal failure (N17) and hypertensive encephalopathy (I67.4). All cases were verified to be SRC after medical records review, according to expert opinion (L.R., W.S.). A case was considered to be SRC when there was documented evidence of rapidly progressive renal failure with no alternate cause identified and/or new-onset hypertension and/or microangiopathic haemolytic anaemia [1] and there was documentation that verified the patient fulfilled 2013 ACR/EULAR criteria for SSc [12]. Data pertaining to demographics, comorbidities, features of SSc, treatment of SRC, organ dysfunction secondary to SRC and clinical outcomes of SRC were extracted. Additionally, we collected all parameters included in the proposed SRC core item set [2]. Hypertensive encephalopathy was considered present if documented by the patient's treating physician in the context of unexplained headache or cognitive symptoms with or without supportive imaging findings. Haemolysis was assessed based on the presence of aberrant haemolysis biomarkers (bilirubin, lactate dehydrogenase, haptoglobin, reticulocytes) and evidence of haemolysis on blood film (presence of red blood cell fragments). SRC patient outcomes were followed up for a maximum of 60 months following SRC diagnosis.

The clinical characteristics of SSc patients with SRC were compared with the SSc patients with no history of SRC who were enrolled in the Australian Scleroderma Cohort Study (ASCS) at SVHM. The ASCS is a prospective cohort study that collects demographic, clinical and investigation data annually. All ASCS participants included in this study fulfilled the 2013 ACR/EULAR criteria [12] and had a definable disease subclass. A definition of SSc-associated organ involvement can be found in Supplementary Table S1, available at *Rheumatology Advances in Practice* online. This study was approved by the SVHM Human Research Ethics Committee (ID 90910), who also waived the requirement for informed consent.

Statistical analysis

Patient characteristics are reported as median and interquartile range (IQR) or number and percentage of patients for continuous and categorical data, respectively. The chi-squared test and two-sample Wilcoxon rank sum test were used for analysis of non-parametric variables. Kaplan–Meier survival curves were used to determine the effect of SRC on overall survival. Logistic regression analysis was used to assess clinical predictors of SRC, controlling for the presence of dcSSc given the recognized association between extensive skin thickening and SRC [3–5]. Statistical analyses were performed using Stata/SE 14.2 (StataCorp, College Station, TX, USA).

Results

We identified 17 new cases of SRC, with a median age at presentation of 53 years (IQR 43–58) and SSc disease duration of 2 years (IQR 1–4). In a cohort of 483 SSc patients, our SRC prevalence was 3.52%. Only one patient underwent a renal biopsy confirming a diagnosis of SRC. Ten patients (58.82%) were taking regular glucocorticoids when they presented with SRC at a median prednisolone dose of 5 mg/day (IQR 5–10). Two (11.76%) patients were taking >15 mg/day. Three patients (17.65%) were prescribed ACEi therapy prior to SRC. The reason for ACEi prescription or duration of therapy was not recorded in the patients' medical records. Seven (41.18%) SRC patients died at a median of 2.75 years (IQR 0.74–7.25) after SRC presentation. The clinical characteristics of the SRC patients compared with the general SVHM SSc cohort are presented in Supplementary Table S2, available at *Rheumatology Advances in Practice* online. Details of the clinical presentation and treatment of individuals with SRC are shown in Table 1.

Clinical and laboratory features of SRC

At SRC presentation, 16 patients (94.12%) had a systolic blood pressure (SBP) >140 mmHg [median SBP 169 mmHg (IQR 153–182)] with peak SBP occurring at the time of presentation with SRC. Achieving adequate control of BP was challenging; only six patients (35.29%) achieved a sustained SBP <120 mmHg within 7 days of SRC onset. Two patients (11.76%) had pre-existing hypertension. One of these patients died 8.45 years after SRC onset.

At SRC presentation, the median creatinine was 120 μmol/l (IQR 80–156). The median peak creatinine was 144 μmol/l (IQR 86–306), occurring 11 days (IQR 5–14) after SRC diagnosis. Only one patient had documented renal impairment, of unknown aetiology (creatinine >110 μmol/l), prior to SRC onset. Three (17.65%) patients required acute renal replacement therapy (RRT), defined as those needing RRT within 1 month of SRC onset. There was no significant difference between the serum creatinine on admission between those who did and did not require RRT (156 *vs* 126 μmol/l, $P = 0.35$). Three (17.65%) patients (including two who needed acute haemofiltration) required ongoing RRT, defined as those who required continuing RRT beyond 3 months after SRC onset. Two patients requiring ongoing RRT had been on ACEi therapy prior to SRC diagnosis. No patient who required long-term RRT was able to stop dialysis, with two patients dying at 3 months and 2.5 years post-SRC and the third patient continuing dialysis at the time of record review (12 months post-SRC). These two patients died of sepsis and complications of end-stage renal failure (ESRF), respectively. No patient proceeded to renal transplantation.

Ten patients (58.8%) had at least one aberrant biomarker of haemolysis. Of these, 5 (50.0%) had evidence of haemolysis on blood film. Six patients (35.29%) were diagnosed with hypertensive encephalopathy. All had central nervous system

Table 1. Clinical features and outcomes of SRC patients

Patient no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Age (years)	41	56	53	41	46	75	64	57	58	64	71	43	40	34	55	50	45
Sex	Female	Male	Male	Female	Male	Male	Female	Male	M	F	M	M	F	M	F	F	M
Disease subtype	Diffuse	Diffuse	Diffuse	Diffuse	Diffuse	Limited	Diffuse	Diffuse	Limited	Diffuse	Diffuse	Diffuse	Diffuse	Diffuse	Diffuse	Diffuse	Diffuse
Antibody profile	RNAP III	ANA(N) Scl70 ANCA	RNAP III	NA	RNAP III	ANA (other)	ANA(N) Scl70	ANA(N) Scl70	ANA(N) Scl70	RNAP III	ANA(N) Scl70	RNAP III	RNAP III	ANA(N) Scl70	RNAP III	RNAP III	ANA(N) Scl70 aPL Ab
Peak SBP (mmHg)	180	165	155	155	180	180	u/a	155	200	200	200	178	150	139	180	183	120
Peak creatinine (μmol/l)	89	72	186	222	126	140	449	144	272	312	362	38	88	117	394	103	299
Antihypertensive and maximal dose	CPT 100→ RMP 7.5 AMLO 10 FRS 40	CPT 150 DTZ 240 FRS 40	CPT 300 DTZ 360 IRB 75 FRS 40 MXN 400 μg PRZ 5	PRP 10 NIF 30 MXN 200 μg	PRP 15 NIF 150 MXN 200 μg GTN patch 25	PRP 10 BSP 1.25 AMLO 5	RMP 5	PRP 10 FRS 40	PRP 10 BSP 1.25 DTZ 240 FRS 240 GTN infusion	CPT 450 AMLO 10 HCT 12.5	CPT 450 ATN 50 AMLO 10 PRZ 1	PRP 20 AMLO 10 PRZ 6	PRP 15 NIF 30 FRS 40 PRZ 12	CPT 18.75	CPT 50→ RMP 10 AMLO 10 FRS 40 MXN 200 μg Methyldopa 250 GTN patch	PRP 10 MXN 200 μg	PRP 7.5
End-organ dysfunction	RETIN ENCEPH	RETIN	AHF		ENCEPH				AHF		ENCEPH	ENCEPH			ENCEPH AHF	ENCEPH	
Death within 12 months of SRC											Y						Y

ANA(N): ANA nucleolar; aPL Ab: anti-phospholipid antibodies; CPT: captopril; ATN: atenolol; AMLO: amlodipine; PRZ: prazosin; RMP: ramipril; FRS: frusemide; DTZ: diltiazem; IRB: irbesartan; MXN: moxonidine; PRP: perindopril; NIF: nifedipine; BSP: bisoprolol; HCT: hydrochlorothiazide; ENCEPH: encephalopathy; RETIN: retinopathy; AHF: acute heart failure; NA: not available.
Values from the first month following onset of SRC are represented for maximal medication doses, peak SBP and peak creatinine. Subsequent fluctuations in these values may not necessarily be related to SRC and its management.
Dose of medication is in milligrams, unless stated otherwise.
→ Indicates change from one ACEi to another (medications were not simultaneously administered).

imaging, but only one patient (16.67%) had imaging evidence of hypertensive encephalopathy. Only two patients underwent ophthalmic examination, and both patients had evidence of hypertensive retinopathy. Acute heart failure was observed in three (17.65%) patients at presentation. Two (11.76%) patients had a pericardial effusion detected at the time of admission. No patient had pericarditis.

Treatment of SRC

All 17 patients (100%) received ACEi therapy within 24 h of SRC diagnosis. Seven patients (41.18%) received captopril as first-line therapy, while the remaining patients received either ramipril or perindopril. Of the three patients who were on ACEi therapy prior to SRC onset, two remained on the same agent at an increased dose for management of SRC. The third patient switched from perindopril to captopril for a brief period before resuming long-term perindopril therapy at a higher dose than prior to SRC onset. A median of 4 (IQR 2–4) antihypertensive agents were required to achieve adequate BP control. Adjuvant antihypertensive agents used included calcium channel blockers ($n = 12$), moxonidine ($n = 5$) and prazosin ($n = 3$).

Patient outcomes

Three patients (17.65%) required admission to the intensive care unit, who were the same three patients who required acute RRT. Of the seven (41.18%) patients who died, two (11.76%) patients died within 1 year of diagnosis of SRC (one as a result of sepsis and the second death due to complications of SRC and anaphylaxis). One patient died as a result of ESRF secondary to SRC and another due to pulmonary haemorrhage of unclear aetiology. The cause of death was unknown in three (42.86%) patients. Complications of SRC accounted for the cause of death in two of seven (28.57%) deaths. Overall survival in those with SRC was poorer compared with the general SSc population (Fig. 1).

Risk factors for SRC

Diffuse SSc [odds ratio (OR) 23.16 (95% CI 5.22, 102.80), $P < 0.01$], male sex [OR 9.73 (95% CI 3.57, 26.56)] and antibodies to Scl70 [OR 3.34 (95% CI 1.24, 9.04)] or RNAPIII [OR 5.15 (95% CI 1.91, 13.89)] were strongly associated with the presence of SRC (Supplementary Table S3, available at *Rheumatology Advances in Practice* online). When controlling for disease subtype, only male sex significantly predicted the development of SRC [OR 5.70 (95% CI 1.99, 16.35), $P = 0.001$] (Supplementary Table S4, available at *Rheumatology Advances in Practice* online). Centromere antibodies and telangiectasia [OR 0.02 (95% CI 0.005, 0.07), $P < 0.001$] were both highly protective against SRC (Supplementary Table S2 and S4, available at *Rheumatology Advances in Practice* online, respectively), likely due to the association of these two features with limited cutaneous SSc. There were no cases of SRC in patients with centromere antibody–positive SSc.

Discussion

In this single-centre retrospective cohort study, we reviewed the presentation and clinical outcomes of 17 cases of SRC. Our results indicate that only subtle changes in renal function and BP may be seen in presentations of SRC. Despite this, adequate BP control was challenging to achieve, with only one-third of patients reaching a sustained SBP <120 mmHg within 7 days of SRC onset. Given our small sample size, we are unable to assert any firm conclusions regarding BP control and death or peak creatinine. In the post-ACEi era, SRC mortality rates have decreased, with published mortality rates suggesting ≈70% survival at 1 year and up to 50% survival at 5 years [8, 11]. The all-cause mortality rates observed in our cohort were lower than these reported rates, at 11.76% at 1 year and 29.41% at 5 years. Only one patient died of acute SRC complications in this series. While missing data preclude calculation of the precise mortality rate associated with SRC, we have observed a continued effect of SRC on all-cause mortality, with poorer overall survival in patients with a history of SRC compared with the general SSc patient population.

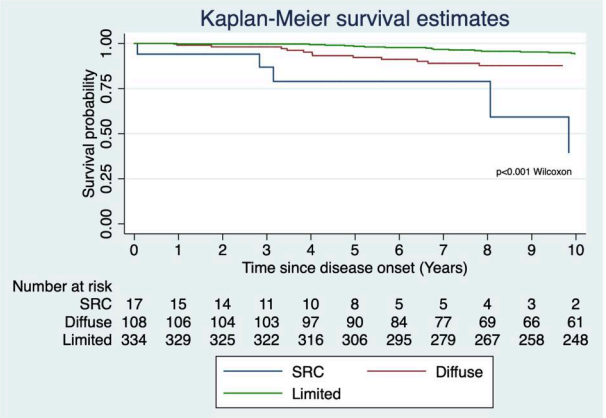


Figure 1. Kaplan–Meier survival analysis demonstrating reduced survival in SSc patients with SRC compared with those without SRC

Early administration of ACEis is associated with improved outcomes in SRC [13], and the universal administration of ACEis within 24 h of diagnosis and lower peak creatinine seen in this study may explain the lower rates of RRT and mortality observed. However, the excess mortality risk conferred by a diagnosis of SRC is somewhat in contrast to previous reports that have suggested that in patients who require only temporary or no dialysis, mortality rates are comparable to those of SSc patients without SRC [14]. Our sample size is too small to be able to explain this discordant result, but we have reported a higher percentage of patients who were Scl70 positive with SRC compared with historical reports [7, 10]. Recent data have indicated that Scl70 antibodies may be associated with worse SRC outcomes [15, 16] and, notably, the two patients who died within 12 months of their SRC were Scl70 positive. Asian and European populations demonstrate increased rates of Scl70 positivity and lower rates of RNAPIII than American SSc cohorts [3, 5, 10], which may account for the observed antibody associations in an Australian context.

RNAPIII antibodies are a well-established risk factor for SRC [3, 5], with up to 25% of patients with RNAPIII antibodies developing SRC [17]. However, half of the cases of SRC in our series were negative for RNAPIII antibodies. We also observed a significant risk of SRC associated with male sex, which is in contrast to previous reports that have reported a female preponderance of SRC cases consistent with the epidemiology of SSc generally [11, 16, 17]. Although there are no guaranteed mechanisms by which to prevent SRC, improved

understanding of SRC risk factors can help prompt increased vigilance for these patients [10]. Unfortunately, there is no clear guidance in the literature about efficacy or suggested surveillance strategies in patients at high risk for SRC, and this is an area that warrants further studies. In addition to patients with diffuse, rapidly progressive skin disease with RNAPIII antibodies, we propose that in the Australian context, patients with diffuse cutaneous involvement who are male or Scl70 positive should also be considered to be at increased risk of SRC.

There are no formal guidelines regarding the role of ophthalmic examination or CNS imaging in the clinical assessment of SRC. Ophthalmic and cerebral findings of acute hypertension are recognized complications of SRC; however, it is notable that no consensus was achieved for their inclusion as core set items for the development of SRC classification criteria [2]. The two patients in this series in whom a formal ophthalmic examination was performed both had signs of hypertensive retinopathy, whereas only one of six patients who underwent CNS imaging had documented changes of hypertensive encephalopathy. The relative utility of ophthalmic examination and/or CNS imaging in securing a diagnosis of SRC remains unstudied.

Our study is not without limitations, namely the small number of incident cases of SRC, limiting the statistical power of any analyses. Only one patient underwent a renal biopsy to confirm the diagnosis of SRC. All other cases of SRC were diagnosed based on the clinical presentation and expert physician assessment. This raises the possibility of misdiagnosis in some cases, particularly in the absence of classification criteria for SRC. However, a renal biopsy is not universally pursued in the diagnostic evaluation of possible SRC in our centre because of the risk of haemorrhage with biopsy in the setting of hypertension and/or thrombocytopaenia. This is consistent with published reports, in which renal biopsy rates are reported in 10–12% of cases [18, 19]. Expert recommendations have suggested undergoing a biopsy only if there are atypical features in the SRC presentation, such as normotension or unexpected urinalysis findings [8, 20]. The small size of our cohort precludes further evaluation of specific subgroups within our SRC cohort such as those who required a single antihypertensive agent compared with multiple agents, the need for acute RRT or analysis of the effect of ACEi treatment prior to the onset of SRC. While two of three patients prescribed ACEis died within 12 months of SRC onset and two of three patients requiring RRT died within 12 months, it is not possible to draw robust conclusions about the effect of preceding ACEi therapy or acute RRT on the overall disease course. The observational nature of our data precludes any conclusions about the relative efficacy of any individual treatment strategy. Additionally, due to the low frequency of SRC, our study lacks the power to include all variables statistically significant on univariable analysis in one multivariate model.

Conclusion

Aggressive BP management and lower peak creatinine improve SRC-associated morbidity and mortality, but these patients remain at increased risk of poor clinical outcomes overall. In addition to patients with dcSSc and RNAPIII antibodies, our results suggest men and those with Scl70 antibodies be considered at increased risk for SRC.

Supplementary material

Supplementary material is available at *Rheumatology Advances in Practice* online.

Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

Authors' contributions

Rushab C. Shah: Conceptualization, Methodology, Formal Analysis, Investigation, Writing – original draft preparation, Visualization; **Kathleen Morrisroe:** Conceptualization, Writing – review and editing; **Wendy Stevens:** Conceptualization, Writing – review and editing; **Nava Ferdowsi:** Resources, Writing – review and editing; **Susanna Proudman:** Resources, Writing – review and editing; **Mandana Nikpour:** Conceptualization, Resources, Writing – review and editing, Supervision; **Laura J. Ross:** Conceptualization, Methodology, Formal Analysis, Investigation, Writing – review and editing, Supervision.

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