Risk Factors for Future Scleroderma Renal Crisis at Systemic Sclerosis Diagnosis

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ABSTRACT. ***Objective.*** Systemic sclerosis (SSc) is a disease of autoimmunity, fibrosis, and vasculopathy. Scleroderma renal crisis (SRC) is one of the most severe complications. Corticosteroid exposure, presence of anti-RNA polymerase III antibodies (ARA), skin thickness, and significant tendon friction rubs are among the known risk factors at SSc diagnosis for developing future SRC. Identification of additional clinical characteristics and laboratory findings could expand and improve the risk profile for future SRC at SSc diagnosis.

Methods. In this retrospective cohort study of the entire military electronic medical record between 2005 and 2016, we compared the demographics, clinical characteristics, and laboratory results at SSc diagnosis for 31 cases who developed SRC after SSc diagnosis to 322 SSc without SRC disease controls.

Results. After adjustment for potential confounding variables, at SSc diagnosis these conditions were all associated with future SRC: proteinuria ($p < 0.001$; OR 183, 95% CI 19.1–1750), anemia ($p = 0.001$; OR 9.9, 95% CI 2.7–36.2), hypertension ($p < 0.001$; OR 13.1, 95% CI 4.7–36.6), chronic kidney disease ($p = 0.008$; OR 20.7, 95% CI 2.2–190.7), elevated erythrocyte sedimentation rate ($p < 0.001$; OR 14.3, 95% CI 4.8–43.0), thrombocytopenia ($p = 0.03$; OR 7.0, 95% CI 1.2–42.7), hypothyroidism ($p = 0.01$; OR 2.8, 95% CI 1.2–6.7), Anti-Ro antibody seropositivity ($p = 0.003$; OR 3.9, 95% CI 1.6–9.8), and ARA ($p = 0.02$; OR 4.1, 95% CI 1.2–13.8). Three or more of these risk factors present at SSc diagnosis was sensitive (77%) and highly specific (97%) for future SRC. No SSc without SRC disease controls had ≥ 4 risk factors.

Conclusion. In this SSc cohort, we present a panel of risk factors for future SRC. These patients may benefit from close observation of blood pressure, proteinuria, and estimated glomerular filtration rate, for earlier SRC identification and intervention. Future prospective therapeutic studies could focus specifically on this high-risk population. (J Rheumatol First Release July 15 2018; doi:10.3899/jrheum.171186)

Key Indexing Terms:
SYSTEMIC SCLEROSIS SCLERODERMA RENAL CRISIS RISK FACTORS
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Systemic sclerosis (SSc) is a complex autoimmune disease that can lead to fibrosis and vasculopathy of multiple organ systems[1]. Scleroderma renal crisis (SRC) is a rare and severe manifestation[2,3]. Previous retrospective cohort studies and case series have focused primarily on clinical and laboratory associations at SRC diagnosis as well as longterm outcomes[4-13]. Improved understanding of SRC risk factors at the time of SSc diagnosis could better instruct future clinical surveillance and prospective research. Corticosteroid exposure, presence of anti-RNA polymerase III antibodies (ARA), skin thickness, cardiac silhouette on radiograph, and significant tendon friction rubs are accepted risk factors for the development of SRC[5,8,14,15,16]. These conditions are associated with SRC at diagnosis but have not been extensively evaluated as SRC risk factors at the time of SSc diagnosis: anemia, thrombocytopenia, proteinuria, elevated erythrocyte sedimentation rate (ESR), hypertension (HTN), and kidney disease. Hypothyroidism and anti-Ro antibody seropositivity are associated with SSc but have not been

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studied specifically in an SRC subpopulation[17-24]. We sought to determine whether these clinical and serologic associations were risk factors for future SRC at the time of SSc diagnosis.

MATERIALS AND METHODS

We conducted a retrospective cohort study to compare clinical characteristics associated with future SRC versus SSc without renal crisis. The diverse cohort was derived from a global United States Department of Defense healthcare network composed of 9.6 million active and retired service members and their families[25]. This integrated health system allows its beneficiaries to be followed longitudinally, regardless of location[26]. The global health network includes 65 hospitals and 412 clinics. The majority of these locations began to use a universal electronic medical record (EMR) in 2005. We queried this EMR for SSc [International Classification of Diseases, 9th ed (ICD-9) code 710.1] between 2005 and 2016.

The initial ICD-9 code query identified 749 potential SSc cases. Each case was then reviewed for inclusion and exclusion criteria with a comprehensive EMR review. For inclusion, cases either met the American College of Rheumatology/European League Against Rheumatism 2013 classification criteria for SSc or had a documented diagnosis by a rheumatologist[27]. Cases were excluded if they had insufficient documentation to confirm SSc diagnosis (n = 144), had only skin disease (n = 32), had a different autoimmune disease (n = 57), or no autoimmune disease (n = 43). Alternative rheumatologic diagnoses included systemic lupus erythematosus, mixed connective tissue disease, undifferentiated connective tissue disease, Sjögren syndrome, and fibromyalgia. Of the remaining 461 SSc cases, 54 had SRC. But 9 SRC cases occurred before the advent of the military EMR and 14 cases manifested SRC at the time of SSc diagnosis, leaving 31 SRC cases for analysis. Of the 407 remaining SSc cases without SRC controls, 85 occurred before the advent of the military EMR, leaving 322 for analysis (Figure 1).

SRC was defined, using some of the most stringent measurements from previous studies[2-6,8-13], by at least 1 of the following criteria in the absence of another clinical explanation for acute kidney injury (AKI) and/or hypertensive emergency: (1) AKI requiring renal replacement therapy; (2) doubling of serum creatinine (SCr); (3) 50% rise in SCr with new-onset HTN [blood pressure (BP) ≥ 140/90 mmHg]; and (4) hypertensive urgency or emergency defined by an abrupt onset of BP ≥ 180/110 mmHg requiring hospitalization or evidence of end-organ damage. Fourteen confirmed SRC cases were excluded because both SSc and SRC were diagnosed concurrently. In total, 31 SRC cases and 322 SSc without SRC disease controls were included for comparison of clinical characteristics at the time of SSc diagnosis (Figure 1).

The following data were collected for the cases and disease controls when present: age, sex, race, year of SSc diagnosis, age at SSc diagnosis, year of SRC diagnosis, pulmonary fibrosis (pulmonologist documentation or chest computed tomography), pulmonary HTN (pulmonologist or cardiologist documentation or evidence on echocardiogram), cardiac involvement (pericarditis, pericardial effusion, or new and otherwise unexplained heart failure, documented by cardiology consultation or echocardiogram), Raynaud phenomenon, gastrointestinal involvement (gastroesophageal reflux disease or esophageal dysmotility), digital ulceration, prior corticosteroid use, and other immunosuppression therapy. At the time of SSc diagnosis, the following data were collected: presence of

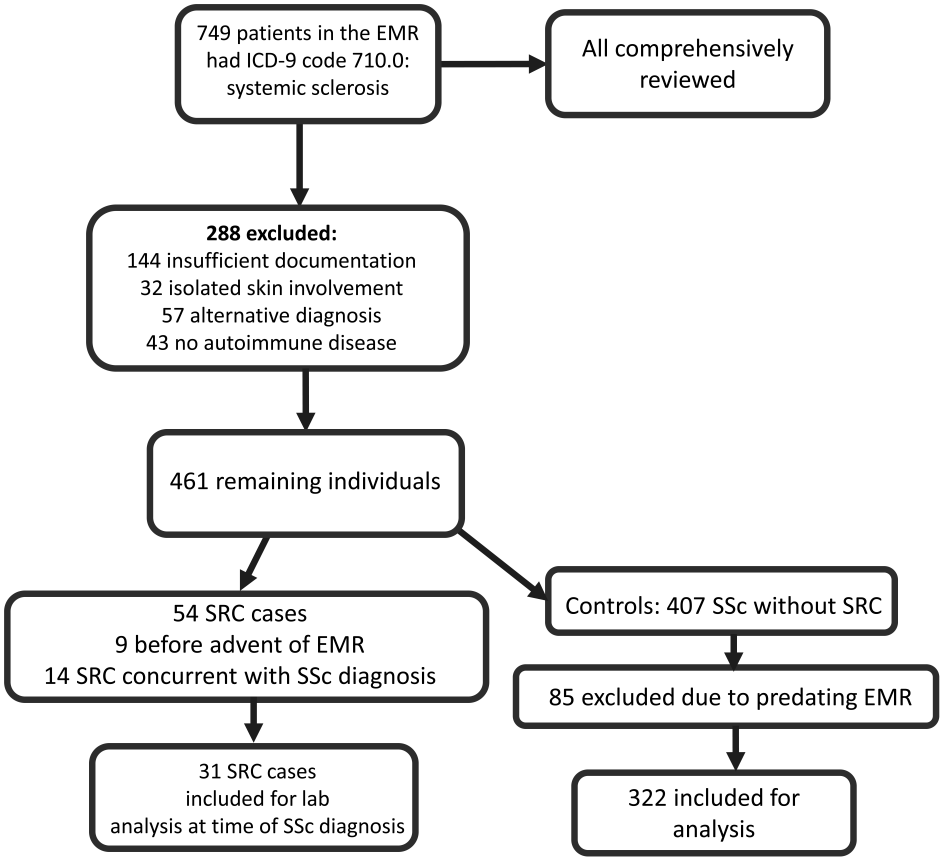

Figure 1. Flowchart of study participants. EMR: electronic medical record; ICD-9: International Classification of Diseases, 9th ed; SRC: scleroderma renal crisis; SSc: systemic sclerosis.

thyroid disease; presence of antinuclear (ANA), anticentromere (ACA), antitopoisomerase I (Scl-70), ARA, Ro, La, and anti-U3 RNP antibodies; proteinuria assessment by urinalysis (UA); BP; ESR; hemoglobin (Hgb); platelet concentration; SCr; and estimated glomerular filtration rate (eGFR). HTN was defined by prescription for antihypertensive medications, or ≥ 2 systolic or diastolic BP readings of ≥ 140 mmHg or ≥ 90 mmHg, respectively. Categorical variables were established for elevated ESR (> 27 mm/h), anemia (Hgb < 12.8 g/dl for men and < 11.5 g/dl for women), chronic kidney disease [CKD; eGFR < 60 ml/min/1.73 m^2 by the Modification of Diet in Renal Disease (MDRD) equation], low platelets (< 150×10^3/mcl), and proteinuria (≥ 1+ on UA). Abnormal thresholds were determined by accredited military laboratories. To further ensure that early SRC was not present at the time of SSc diagnosis, baseline SCr, systolic BP, and diastolic BP were identified about 5 years before SSc diagnosis and compared to values at SSc diagnosis. The earliest available values were used for patients with < 5 years of data prior to SSc diagnosis. All SRC patients with data available for analysis had baseline values obtained at least 2 years before SSc diagnosis. Hypothyroidism was defined by a documented diagnosis in the EMR with a prescription for levothyroxine in the medication history.

Analyses were performed using Stata 14 SE (Stata Corp.). Univariate analyses were performed with chi-square testing for categorical variables (Fisher exact test used for violations of Cochran's assumptions) and Wilcoxon rank-sum test for continuous variables with nonparametric distribution. A p value < 0.05 was considered statistically significant for univariate comparisons.

We conducted logistic regression analyses in forward stepwise fashion to evaluate factors independently associated with SRC. The area under the receiver-operating characteristic (ROC) curve ranged from 0.64 to 0.96 (c statistic), indicating acceptable discrimination of the outcome variable in the individual models. To test model calibration, we calculated the Hosmer-Lemeshow goodness-of-fit test; p values for the models were nonsignificant, indicating no evidence of poor fit[28].

The protocol for our study (#418335) was approved by the Walter Reed National Military Medical Center Department of Research Protection Institutional Review Board.

RESULTS

The SRC group was more advanced in age and had a larger proportion of blacks and males than the SSc group without SRC (Table 1). The SRC group also had higher rates of pulmonary HTN and cardiac manifestations. There was a median of 3 years (interquartile range 1 to 5 yrs) between SSc and SRC diagnosis (Table 1).

ARA and anti-Ro antibody seropositivity were more frequent in SRC cases, whereas ANA and ACA seropositivity were more frequent with SSc without SRC disease controls (Table 2).

At the time of SSc diagnosis, the cohort that subsequently developed SRC was significantly more likely to present with proteinuria [50% (14/28) vs 1% (3/312); OR 183, 95% CI 19.1–1750, p < 0.001], anemia [55% (17/31) vs 6% (18/309); OR 9.9, 95% CI 2.7–36.2, p = 0.001], elevated ESR [68% (17/25) vs 15% (38/261); OR 14.3, 95% CI 4.8–43.0, p < 0.001], HTN [81% (25/31) vs 22% (82/368); OR 13.1, 95% CI 4.7–36.6, p < 0.001], CKD [33% (9/27) vs 3% (8/312); OR 20.7, 95% CI 2.2–190.7, p = 0.008], and thrombocytopenia [23% (7/31) vs 3% (8/309); OR 7.0, 95% CI 1.2–42.7), p = 0.003] accounting for known confounding variables (Table 3 and Table 4). Univariate and multivariable analyses of all identified SRC and SSc without SRC cases to include those excluded (Figure 1) found the same variables to be significantly different, making any selection bias unlikely (Supplementary Tables 1 and 2, available from the authors on request). At SSc diagnosis, the presence of ≥ 2 risk factors was highly sensitive [94% (29/31) vs 16% (51/322), p < 0.001], and the presence of ≥ 4 risk factors was

Table 1. Demographic and clinical characteristics of scleroderma renal crisis (SRC) cases and systemic sclerosis (SSc) without SRC disease controls. Data are %, n/N unless otherwise specified.

Characteristics	SRC, n = 31	SSc without SRC, n = 322	p
Race			
White	48, 15/31	57, 158/279	NS
Black	42, 13/31	24, 66/279	0.03
Other	10, 3/31	20, 63/279	NS
Sex, % female	74, 23/31	84, 271/322	NS
Age, yrs, median (IQR)	53 (40–60)	46 (37–54)	0.01
Time between SSc and SRC, yrs, median (IQR)	3 (1–5)	NA	NA
SSc followup, yrs, median (IQR)	6 (3–8)	5 (2–8)	NS
Pulmonary fibrosis	42, 13/31	31, 100/322	NS
Pulmonary HTN	39, 12/31	12, 40/322	< 0.001
Cardiac involvement	23, 7/31	5, 17/322	0.002
GI involvement	77, 24/31	82, 265/322	NS
RP	90, 28/31	97, 313/322	NS
Digital ulcers	29, 9/31	23, 73/322	NS
Prior prednisone	65, 20/31	19, 62/322	< 0.001
Other IST	32, 10/31	32, 104/322	NS
Diffuse SSc	39, 12/31	16, 52/322	0.004
Limited SSc	61, 19/31	74, 237/322	NS
Sine SSc	0, 0/31	1, 4/322	NS
Unknown	0, 0/31	9, 29/322	NS

IQR: interquartile range; HTN: hypertension; GI: gastrointestinal; RP: Raynaud phenomenon; IST: immunosuppression therapy; NS: not significant; NA: not applicable; sine SSc: SSc sine scleroderma.

Table 2. Baseline serology for SRC cases and SSc without SRC disease controls, when available. Data are %, n/N.

Autoantibody	SRC, n = 31	SSc without SRC, n = 322	p
ANA	83, 25/30	95, 228/242	0.04
Speckled	41, 9/22	33, 73/221	NS
Nucleolar	27, 6/22	41, 90/221	NS
Homogeneous	18, 4/22	16, 36/221	NS
Centromere	4, 1/22	9, 20/221	NS
Other	9, 2/22	1, 2/221	NS
ARA	50, 7/14	19, 15/76	0.02
Centromere	5, 1/17	52, 100/192	< 0.001
Scl-70	5, 1/17	18, 40/183	NS
U3-RNP	21, 3/14	28, 11/40	NS
SSA	35, 9/26	13, 29/228	0.006
SSB	8, 2/26	4, 9/219	NS
C3/C4, % low	5, 1/21	7, 10/138	NS

SRC: scleroderma renal crisis; SSc: systemic sclerosis; ANA: antinuclear antibodies; ARA: anti-RNA polymerase III antibodies; NS: not significant.

Table 3. A comparison of variables at the time of SSc between a cohort that subsequently developed SRC and a cohort that did not develop SRC. Data are %, n/N unless otherwise specified.

Variables	SRC, n = 31	SSc without SRC, n = 322	p
Serum creatinine, mg/dl, median (IQR)	0.98 (0.9–1.1)	0.8 (0.7–0.9)	< 0.001
eGFR, cc/min/1.73 m^2, median (IQR)	76 (56–86)	96 (80–110)	< 0.001
CKD, < 60 cc/min/1.73 m^2	33, 9/27	3, 8/312	< 0.001
Hypertension, > 140/90 mmHg or meds	81, 25/31	24, 72/305	< 0.001
Proteinuria, ≥ +1 on UA	50, 14/28	1, 3/312	< 0.001
Average Hgb, g/dl, median (IQR)	11.8 (10.3–13.1)	13.4 (12.7–14.1)	< 0.001
Anemia	55, 17/31	6, 18/309	< 0.001
Average ESR, g/dl	35, 20/47	16, 8/20	< 0.001
ESR, % elevated	68, 17/25	15, 38/261	< 0.001
Average platelets, K/μl	244, 152/335	265, 216/304	0.03
Platelet, % low	23, 7/31	3, 8/309	< 0.001

SRC: scleroderma renal crisis; SSc: systemic sclerosis; IQR: interquartile range; eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; UA: urinalysis; ESR: erythrocyte sedimentation rate; Hgb: hemoglobin.

Table 4. Multivariable logistic regression model of clinical factors associated with scleroderma renal crisis.

Logistic Regression Models	OR	95% CI	p
CKD*	20.7	2.2–190.7	0.008
Hypertension**	13.1	4.7–36.6	< 0.001
Proteinuria†	183	19.1–1750	< 0.001
Anemia‡	9.9	2.7–36.2	0.001
ESR£	14.3	4.8–43.0	< 0.001
Thrombocytopenia‖	7.0	1.2–42.7	0.003
Hypothyroidism¥	2.8	1.2–6.7	0.01
ARA#	4.1	1.2–13.8	0.02
Ro antibody#	3.9	1.6–9.8	0.03

* Adjusted for hypertension, proteinuria, age, race, and ESR. ** Adjusted for age, race, sex, CKD, and hypothyroidism. † Adjusted for hypertension, ESR, and CKD. ‡ Adjusted for ESR, CKD, cancer, hypothyroidism, and low platelets. £ Adjusted for age, cancer, and CKD. ‖ Adjusted for hypertension, ESR, cancer, and anemia. ¥ Adjusted for age and sex. # Adjusted for ANA seropositivity. CKD: chronic kidney disease; ESR: erythrocyte sedimentation rate; ARA: anti-RNA polymerase III antibodies; ANA: antinuclear antibodies.

Table 5. The percentage of SRC cases with multiple risk factors from Table 4 present at SSc diagnosis compared to the SSc without SRC disease controls. Data are %, n/N.

No. Variables Present	SRC, n = 31	SSc without SRC, n = 322
≥ 2	94, 29/31	16, 51/322
≥ 3	77, 24/31	3, 11/322
≥ 4	66, 20/31	0, 0/322

All p values < 0.001. SRC: scleroderma renal crisis; SSc: systemic sclerosis.

highly specific [66% (20/31) vs 0% (0/322), p < 0.001] for future SRC (Table 5).

For the SRC cases, there was no evidence of early or smoldering SRC at SSc diagnosis. Median baseline systolic BP and diastolic BP before SSc diagnosis were not significantly different from those levels at SSc diagnosis (130 mmHg vs 125 mmHg, p = 0.68; and 77 mmHg vs 74 mmHg, p = 0.56, respectively). In addition, there were no SRC cases identified with newly diagnosed HTN during the 5 years before SSc diagnosis. There was also no significant change in antihypertensive medications between the 2 time periods.

For SRC cases, median baseline SCr before SSc diagnosis was also not significantly different from the level at SSc diagnosis (0.9 mg/dl vs 0.97 mg/dl, p = 0.45). None of the SRC cases experienced a rise in SCr or a decline in eGFR of > 25% that was consistent with AKI during the 5 years prior to SSc diagnosis. All 9 SRC cases with baseline eGFR < 60 ml/min/1.73m^2 at SSc diagnosis had an SCr 1.0–1.3 mg/dl and stage 3 CKD. All SSc without SRC cases with eGFR < 60 ml/min/1.73m^2 at SSc diagnosis had an SCr between 0.8–1.2 mg/dl and stage 3 CKD.

Hypothyroidism was more common in the SRC cohort [35% (9/26) vs 16% (29/228), p = 0.006) at SSc diagnosis. When adjusted for age and sex, hypothyroidism was significantly associated with SRC (OR 2.8, 95% CI 1.2–6.7, p = 0.01).

DISCUSSION

Our study advances existing literature with additional power to detect significant differences, multivariable analyses to address potential confounders, and comparisons of proportion of SRC cases with abnormal laboratory values versus SSc without SRC controls, to better inform clinical practice. It has not been previously reported, to our knowledge, that these factors at the time of SSc diagnosis are strongly associated with future SRC: chronic HTN, proteinuria, anemia, thrombocytopenia, elevated ESR, CKD (eGFR < 60 ml/min/1.73 m^2), hypothyroidism, and anti-Ro antibody seropositivity. Previous SSc retrospective cohort studies and SRC case series investigated similar potential risk factors for future SRC[5,8,16,29,30]. A previous study found a higher average prediagnostic systolic BP in the SRC group than the SSc without SRC group, while another found no difference[8,29]. Neither addressed the percentage of patients with documented HTN (BP ≥ 140/90 mmHg and/or taking antihypertensive medications). Taking into account listed SD and undocumented BP medication use, there was possibly a significant proportion of SRC patients with chronic HTN at SSc diagnosis. In a separate case series, 31% of SRC cases had prediagnostic BP > 160/90 mmHg, years before diagnosis in many cases[30]. The proportion of subjects with prediagnostic BP ≥ 140/90 was not reported.

Ours is the first study to report an association between CKD at SSc diagnosis and subsequent SRC. Prior studies have not described baseline eGFR, but their reported mean serum creatinines (0.8–1.0 mg/dl) and creatinine clearances (73–90 ml/min) values are both similar to those in our study, and because of listed SD, they are consistent with inclusion of SRC cases with previous baseline CKD (eGFR < 60 ml/min/1.73 m^2)[4,5,29,30]. In addition, in 1 study an abnormal serum creatinine was considered > 1.3 mg/dl, but values 1.0–1.3 mg/dl would correspond to an eGFR < 60 for the middle-aged non-black female majority of the study population[29]. One study reported that future patients with SRC had a lower average hematocrit but did not comment on anemia. Another study did not find anemia to be a risk factor for SRC; however, additional power may have established significance[8,29]. Elevated average ESR levels before SRC have been reported, but there was no comparison of percent of patients with elevated ESR at SSc diagnosis between the SRC group and the SSc without SRC group[8,29]. Previous literature describes normal average platelet levels at SSc diagnosis in both SRC cases and SSc without SRC cases but incidence of baseline thrombocytopenia was not evaluated[29]. Our finding that proteinuria is a risk factor for future SRC is novel. One previous study did not find an association between proteinuria and risk of SRC[29]. Race and timing of proteinuria evaluation may explain this discrepancy. Our study population had a significantly higher percentage of black patients than was previously described in that cohort (26% vs 6% overall). Black patients in our cohort were twice as likely to have ≥ 1 proteinuria than white patients, and our SRC subgroup had 42% blacks. There is a precedence for racial discrepancies associated with proteinuria-related comorbidities. Proteinuria was previously shown to be a more prevalent risk factor for coronary heart disease in blacks than whites[31]. In addition, our study only evaluated proteinuria at SSc diagnosis, whereas Steen, *et al* evaluated proteinuria between SSc and SRC diagnosis (often within 6 mos of SRC). Therapeutic interventions surrounding SSc diagnosis, to include renin-angiotensin system (RAS) inhibitors, may have resolved initial low-level proteinuria. Historically, D-penicillamine was associated with proteinuria, but none of the patients in our study received this therapy[32]. The relationship between proteinuria and SRC has not been elucidated. We propose that proteinuria arises from underlying systemic vascular pathology such as evolving scleroderma renal involvement. Literature supports this

theory. Studies have shown that proteinuria or increased albuminuria were significant independent predictors of cardiac events, progression to CKD, and death, even in populations without substantial comorbidities, suggesting chronic vascular damage[33,34,35].

In addition, we included comparative analysis for hypothyroidism, and anti-Ro antibody seropositivity. Thyroid disease is associated with SSc, present in up to 26% of cases[17,18,19]. Anti-Ro antibodies are associated with SSc, present in up to 37% of cases[20,21,22,23,24]. However, there has been no previous comparison of the presence of thyroid disease or anti-Ro antibody seropositivity at SSc diagnosis between cohorts that did and did not subsequently develop SRC, to our knowledge. The link between thyroid disease and SSc, or more specifically SRC, is unclear[17,18,19]. Autoantibody overlap, type, avidity, epitope specificity, and subclass may contribute. Others have postulated that a systemic fibrotic mechanism may also contribute based on tissue fibrosis seen in the histopathology of thyroid glands from patients with SSc. The contribution of anti-Ro antibodies to SSc pathophysiology is also unknown.

Early or subclinical SRC unappreciated at SSc diagnosis is a potential explanation for our results. A smoldering subclinical SRC milieu at SSc diagnosis is possible and is what our study strives to identify[36,37]. But there was no evidence of early developing SRC at SSc diagnosis using accepted definitions. The SRC cases with a history of chronic HTN and CKD had no significant change in BP, BP medications, or renal function over the 5 years leading up to SSc diagnosis.

Used in combination to offset known disease heterogeneity, the risk factors identified at SSc diagnosis in our study provide the most comprehensive predictive profile for SRC. This prognostic information, particularly if validated in other cohorts, could have important clinical and research implications. Patients deemed at high risk for SRC may benefit from shorter followup intervals with particular focus on subtle changes or abnormalities in proteinuria and eGFR, more aggressive home BP screening (to include 24-h ambulatory BP monitors), stricter corticosteroid avoidance, and earlier nephrology consultation. Because of the abrupt onset of SRC with substantial morbidity and mortality, future prevention studies would benefit from specifically enrolling patients with SSc at high risk for SRC. Despite being the primary treatment for SRC, previous studies have not shown a prophylactic benefit for RAS inhibition[15,38,39]. But it is possible that a benefit in small high-risk subgroups may have been masked by the inclusion of a much larger group of low-risk cases. Captopril may also have a therapeutic effect independent of the angiotensin-converting enzyme (ACE) inhibitor drug class. Endothelin 1 receptor antagonists could also prove to provide prophylactic benefit in the future[40,41].

Our study has limitations, many of which are inherent to retrospective cohort studies. Not all patients had data available for the study variables. Specifically, there may have been a selection bias for the antibodies tested based on each patient's clinical presentation. Some of the study subjects had a portion of their care outside the military system. Patients who require subspecialty care in regions without a major medical center are evaluated at local civilian medical centers with the required expertise. Many, but not all, of the outside medical records are subsequently scanned into the military electronic system, leaving some data inaccessible. If organ involvement was not evident in the available records, the assumption was made that it was not present. Therefore, the prevalence of organ involvement may have been underestimated. Pulmonary HTN diagnosis was sometimes based on subspecialty notes without the rigorous review of echocardiogram and right heart catheterization measures established as the gold standard in previous SSc literature[42]. There was a lower percentage of centromere pattern ANA than anticipated, potentially due to the use of the solid phase assay, the laboratory designation of actual centromere pattern ANA in the more nonspecific category of speckled ANA, or sample bias arising from SSc cases with ACA but no ANA pattern on record, or an ANA pattern on record but no ACA. The association between ARA antibody and SRC was weaker than anticipated but nonetheless significant. This was likely due to the small sample size and the absence of a recorded ARA antibody in many cases. Our data are based on the date of SSc diagnosis, but do not take into account that the symptoms or onset of disease can be months or years earlier. This was difficult to reliably and accurately ascertain for most cases. While still significantly associated with SRC, the incidence of diffuse skin involvement is lower in our SRC cases than previously reported. This is likely because we report skin involvement at the time of SSc diagnosis, while previous studies documented the extent of skin involvement at SRC diagnosis. The MDRD equation was used for eGFR because a large portion of the laboratory data were analyzed prior to the development of the superior CKD-Epidemiology Collaboration (CKD-EPI) creatinine and the CKD-EPI creatinine-cystatin C estimating equations. This limitation is mitigated by the use of an eGFR of < 60 ml/min/1.73 m^2 as the threshold for CKD designation, where the MDRD has better accuracy than for eGFR measurements of > 60 ml/min/1.73 m^2. UA was used for determination of proteinuria instead of more exact methods of proteinuria quantification because a UA was commonly obtained by the primary care provider or rheumatologist at the time of SSc diagnosis. Quantification of proteinuria most often only occurred at the time of SRC diagnosis. To compensate for this limitation, proteinuria was defined by at least +1 on UA to avoid false-positive trace values that may have reflected highly concentrated specimens. On multivariable analysis, we were unable to adjust for all significant univariate variables because of our small cohort with fewer outcome events (SRC) per adjustment covariate. However, known clinical confounders were included. Finally, there is no

universal definition of SRC, which affects interpretation of and comparison between studies[43]. As for most diseases, there is likely a spectrum of scleroderma renal involvement[36,37]. We sought to establish a specific, logical, transparent, and reproducible definition of SRC. It is paramount to standardize this definition going forward to maximize the utility of future studies[43].

Our study also has unique strengths. All confirmed SSc cases in the electronic military medical record were included in the study, which minimized selection bias. The cohort was ethnically diverse. The universal electronic military medical record allowed us to analyze one of the largest and most comprehensive SSc diagnostic data collections to determine risk factors for future SRC.

Future directions include a robust analysis of potential disease-modulating therapy in this cohort. A comprehensive description of the use, timing, type, dose, and duration of ACE inhibitors, angiotensin-receptor blockers, and calcium channel blockers prior to SRC diagnosis should expand our understanding of therapeutic agents that have questionable benefits and potential risks as prophylactic agents.

We present SSc demographic, clinical, and serologic diagnostic risk factors for future development of SRC. Future prospective studies should focus specifically on patients with SSc who are determined by our findings to be at high risk for SRC. This population may benefit from followup at closer intervals, more aggressive BP monitoring, more stringent avoidance of steroids, and potential future therapies.

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