

**TOWARDS DEVELOPING CRITERIA FOR SCLERODERMA RENAL CRISIS:
A SCOPING REVIEW¹**

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¹ **Abbreviations:**

ANCA	Anti-neutrophil cytoplasmic antibody
HUS	Hemolytic uremic syndrome
MAHA	Microangiopathic hemolytic anemia
SRC	Scleroderma renal crisis
SSc	Systemic sclerosis
TTP	Thrombotic thrombocytopenic purpura

Funding:

S. Hoa is funded as a fellow by the Université de Montréal Rheumatology Program Abbvie educational grant and by a postdoctoral fellowship award from The Arthritis Society.

M. Hudson is funded by the Fonds de la recherche en Santé du Québec.

E. Stern is funded by the Medical Research Council, United Kingdom.

C. Denton is funded by...

The funding sources had no role in the design of the study, analysis of the data, preparation of the manuscript and decision to submit for publication.

ABSTRACT

Objective The absence of a gold standard for scleroderma renal crisis (SRC) has hindered our understanding of this problem. The objective of this scoping review was to identify the criteria used to define SRC in order to guide the development of a consensus definition for SRC.

Methods We conducted a search in three databases: Medline, Embase and non-Ovid Pubmed. Papers were eligible for inclusion if they were full-length articles in English whose main topic was SRC or scleroderma renal disease. Two reviewers independently screened eligible papers for final study selection. Data was extracted using a customized form. A web-based survey of members of the Scleroderma Clinical Trials Consortium was used to identify unpublished definitions of SRC.

Results We identified 415 papers that met inclusion criteria. Forty original definitions of SRC were identified from 36 studies, 9 reviews and 2 editorials. There was significant heterogeneity in definitions. As a rule, though, in addition to new-onset hypertension and acute kidney injury, other common items used to define SRC included hypertensive encephalopathy and seizures, microangiopathic hemolytic anemia and characteristic changes on kidney biopsy. The web-based survey identified unpublished definitions of SRC that were largely consistent with the results of the published literature.

Conclusion SRC was defined in a minority of studies and criteria were heterogeneous. A consensus definition of SRC is urgently needed to standardize data collection on SRC and further our understanding of this serious problem.

KEYWORDS

Scleroderma (or Systemic Sclerosis); Renal crisis; Definition; Scoping review

1. INTRODUCTION

Scleroderma renal crisis (SRC) is a rare complication of systemic sclerosis (SSc), affecting approximately 11% of diffuse and 4% of limited cutaneous SSc subjects. [1] Its clinical spectrum is broad, ranging from full-blown disease presenting as new onset of accelerated arterial hypertension and rapidly progressive oliguric renal insufficiency, to more modest elevations in blood pressure and renal dysfunction, and at times normotensive presentations. On the other hand, non-malignant hypertension without uremia, urine abnormalities and/or mild uremia attributable to other factors in the absence of SRC are common in SSc and should not be confused with it. [2, 3]

The absence of a gold standard for SRC has hindered our understanding of this problem. Outcomes of SRC have been reported to vary widely, but different studies have used different criteria to define SRC. Although a hallmark of SSc, SRC was not retained in the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2013 classification criteria for SSc because, although considered in the development and analysis of the criteria, it did not add to sensitivity and specificity of the final set of items retained. [4] This speaks not only to the rarity of SRC, but possibly also to the difficulty in ascertaining SRC. To date, two sets of criteria for SRC have been proposed and partially validated. [5, 6] We wish to build on these preliminary efforts to develop a consensus definition for SRC and improve systematic research in this condition.

The purpose of this paper was to undertake a scoping review to identify definitions and items that have been used to define SRC. A search of the published literature was conducted to identify papers whose main topic was SRC or scleroderma renal disease. This search was supplemented by a web-based survey of members of the Scleroderma Clinical Trials Consortium to identify unpublished definitions of SRC. The primary objective was to map out the range of formal definitions used to define SRC. The secondary objectives were to 1) examine clinical features or predictors that have been shown to characterize SRC, and 2) identify items that have been proposed to distinguish SRC from diseases that are part of its differential diagnoses. Results from this review will be used to guide the development of a consensus definition for SRC.

2. METHODS

This scoping review was conducted using the Arksey and O'Malley framework [7] and further guided by the methodology from recent scoping review publications [8]. The review included the following six key phases: 1) identifying the research question, 2) identifying relevant studies, 3) study selection, 4) charting the data, 5) collating, summarizing, and reporting the results, and 6) consultation exercise.

2.1. Research question

This scoping review was guided by the question, “What are the items that have been used to define, characterize or predict scleroderma renal crisis in the literature?”

2.2. Data sources and search strategy

The comprehensive search was implemented on June 17, 2016, in three electronic databases including MEDLINE (Ovid) (1946-present), EMBASE (Ovid) (1947-present) and Pubmed (1966-present) by one author (SH), with the assistance of a professional librarian. No limits on date, language, subject or type were placed on the database search. The search query was constructed to capture articles that addressed the topics of renal insufficiency or malignant hypertension in SSc. The search query was tailored to the specific requirements of each database (Supplementary File 1).

The reference lists of 15 pre-selected relevant review articles were manually searched to identify any further studies not yet captured. A “snowball” technique was also adopted in which citations within articles were searched if they appeared relevant to the review [8].

2.3. Citation management

Duplicate citations were initially removed in Ovid for citations from Medline and EMBASE. Citations from Ovid and Pubmed were then imported into the bibliographic manager EndNote X7.4 (Thomson Reuters) and duplicate citations were further removed manually following a 12-step method of de-duplication [9]. Citations were finally imported into Microsoft Excel 2010 for title and abstract relevance screening and data

extraction of full articles. Additional duplicates were removed when found later in the process.

2.4. Eligibility criteria

A two-stage screening process was used to assess the relevance of papers identified in the search. Papers were eligible for inclusion if they were full-length articles in English language whose main topic of study was SRC or scleroderma renal disease. Articles that did not present human data were excluded.

2.5. Title and abstract relevance screening

A primary screen of the papers retrieved by the search was conducted by two reviewers (SH and ES) working independently. Titles and abstracts were reviewed for eligibility using a customized study eligibility form. Titles for which an abstract was not available and/or for which the screening decision was uncertain were included for subsequent review of the full text. Any disagreements regarding the inclusion or exclusion of an article were resolved by consensus. All papers not meeting the eligibility criteria were excluded and the reason for their exclusion were noted.

2.6. Data characterization

All citations deemed relevant after title and abstract screening were procured for subsequent review of the full-text article. Papers that could not be obtained through institutional holdings available to the primary author were requested through interlibrary loans.

Data from included papers were charted by one reviewer (SH), using a pretested data charting form in Microsoft Excel 2010. Extracted data included: author(s), year of publication, publication type, main topic of the study, and data relevant to the specific objectives of this scoping review, i.e. 1) formal definitions of SRC used in the literature, 2) clinical features or predictors that have been shown to characterize SRC (limiting this question to original studies of at least 50 SSc subjects), and 3) items that distinguish SRC from its differential diagnoses.

2.7. Web-based survey of members of the Scleroderma Clinical Trials Consortium

With the aim of identifying unpublished working definitions of SRC, a web-based survey was sent out in September 2016 to members of the Scleroderma Clinical Trials Consortium, an international consortium representing the vast majority of researchers and clinicians who have particular interest and expertise in the care of, and research in, scleroderma. Members were invited to answer the following questions:

1. What criteria do you use to define SRC in research studies that you currently lead or have led in the past?

2. Have you participated in clinical trials that have used formal criteria to define SRC? (If yes, respondents were asked to provide the criteria or the name or details of the study).
3. Have you participated in observational studies that have used formal criteria to define SRC? (If yes, respondents were asked to provide the criteria or the name or details of the study).

2.8. Data summary and presentation

Tables and charts were produced to compile the data. Descriptive statistics were used to summarize the results. A list of candidate items to guide the development of a consensus definition for SRC was created. Results of the scoping review were presented to the Scleroderma Clinical Trials Consortium SRC working group at the American College of Rheumatology annual meeting on November 12, 2016 in Washington, D.C., USA.

3. RESULTS

3.1. Search results and study characteristics

The search identified 4146 potentially relevant citations. Twelve additional citations were identified through search of reference lists and the “snowball” technique. After de-duplication and relevance screening, 501 citations met the eligibility criteria based on title and abstract and 483 corresponding full-text articles were procured for review. After

full-text review, 415 papers met the inclusion criteria. The study selection process is presented as a flowchart in Figure 1.

General characteristics of included papers are presented in Table 1. Papers were published from 1952 to 2016, with the majority of studies being published in the last 2 decades. Among these, only 81 articles reported a formal definition of SRC.

3.2. Formal definitions of SRC

In total, 40 original definitions of SRC were identified from 36 original studies, 9 reviews and 2 editorials (Supplementary Table 2). There was significant heterogeneity in definitions. As a rule, though, in addition to new-onset hypertension and renal insufficiency, other common items used to define SRC included hypertensive encephalopathy and seizures, microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and characteristic changes on kidney biopsy. Kidney biopsy was reported to be of particular interest in the normotensive SRC subset.

3.3. Clinical predictors of SRC

Clinical predictors significantly associated with SRC were reported in 23 original studies of at least 50 subjects and included shorter disease duration, diffuse cutaneous involvement, high skin score, large joint contractures, anti-RNA polymerase III positivity and recent exposure to corticosteroids (Table 2) [10-31].

3.4. Differential diagnoses of SRC

Seventy-five (75) studies addressed differential diagnoses of SRC, the most common of which were anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis (37%) and thrombotic thrombocytopenic purpura (TTP) / hemolytic uremic syndrome (HUS) (21%). Other differential diagnoses reported included membranous (7%) and membranoproliferative (1%) nephropathies, other vasculitides (including polyarteritis nodosa, mixed cryoglobulinemia and Goodpasture syndrome) (7%), drug-induced nephropathies (due to D-penicillamine or cyclosporin A) (5%), oxalate nephropathy (4%), renal artery stenosis (4%) and pre-renal causes (e.g. sepsis, dehydration) (1%).

In ANCA-associated glomerulonephritis, presence of ANCA (especially MPO-ANCA, observed in >95%), pauci-immune necrotizing and crescentic glomerulonephritis on kidney biopsy, presence of other vasculitic manifestations (such as pulmonary hemorrhage, vasculitic skin rash and limb ischemia), and treatment response to immunosuppressive therapy were described as items that could distinguish this entity from SRC [32, 33]. In addition, ANCA-associated glomerulonephritis is reported in patients from all SSc subsets (including limited and sine scleroderma in 59%), with anti-Sc170 antibodies (77%) and with longer disease duration of SSc compared to SRC (8 ± 7.7 years vs. 7.5 months) [32, 33]. ANCA-associated glomerulonephritis patients also differed by their clinical presentation, being more frequently normotensive or with mildly

elevated systolic blood pressure (below 160 mmHg) (82%), and rarely had MAHA, thrombocytopenia or hyper-reninemia [33, 34].

In regards to TTP, deficiency of ADAMTS-13 activity with presence of anti-ADAMTS-13 autoantibodies, severe thrombocytopenia (especially $<50,000/\mu\text{l}$), hemorrhagic complications (such as purpura and gastrointestinal bleeding), fever and dramatic response to plasmapheresis were highlighted as items supporting a diagnosis of TTP rather than SRC [35, 36]. Such patients were also often normotensive and with limited SSc of long disease duration [37]. On kidney biopsy, studies reported the predominance of primary glomerular capillary microangiopathic changes in TTP-HUS, whereas in SRC, extra-glomerular small vessel lesions predominated [38].

Oxalate nephropathy should be suspected in SSc patients with severe gastrointestinal involvement leading to fat malabsorption or small intestinal bacterial overgrowth and need for antibiotics. Such patients are often normotensive, with no signs of hemolysis and an inactive urine sediment. Oxalate crystals on urinalysis, increased oxalate on 24-hour urine collection, and biopsy demonstrating diffuse intra-tubular deposits of calcium-containing birefringent crystals all point towards this diagnosis [39-41].

Renal artery stenosis should be suspected if there is significant and persistent worsening of renal function on ACE inhibitor therapy. Imaging of the renal arteries can confirm the diagnosis. This entity has been increasingly observed in elderly subjects, particularly those with diabetes mellitus [42].

Finally, for other differential diagnoses, suspicion was mostly based on compatible clinical context (e.g. for drug-induced nephropathies or pre-renal causes), laboratory findings (e.g. for mixed cryoglobulinemia and Goodpasture syndrome) and kidney biopsy results (e.g. for membranous and membranoproliferative nephropathies), particularly in patients with inadequate response to ACE inhibitors.

3.5. Web-based survey of members of the Scleroderma Clinical Trials Consortium

Twenty-eight (28/155, 18%) members of the Scleroderma Clinical Trials Consortium responded to the survey. Most (96%) were rheumatologists and one respondent was a nephrologist/internist. Respondents were mostly from North America (64%) and Europe (25%). Overall, 60% of respondents had led research studies requiring a definition for SRC. Among these, 35% defined SRC according to the treating physician, while 65% used preexisting definitions. In addition, 21% and 46% had participated in clinical trials and observational studies that had used formal criteria to define SRC.

Overall, this exercise identified unpublished definitions of SRC that were largely consistent with the results of the published literature. In addition, novel concepts included the stratification of SRC into definite SRC (defined as at least two of: new onset systemic hypertension, MAHA and rising creatinine) and suspected SRC (defined as new onset hypertension); the distinction between classic SRC and subacute forms of SRC (such as hypertension, renal insufficiency and renal sediment changes in the absence of MAHA);

the addition of ACE inhibitor responsiveness as a characteristic of hypertension (in probable SRC); and the addition of more specific time frames for measurement of blood pressure (taken twice, 2 hours apart, within 3 days of first event-associated observation).

* CAT-192 trial: Dr. Denton, could you provide us with study definition?

4. DISCUSSION

We conducted a rigorous scoping review of the literature to identify variables that were used to define, characterize or predict SRC. Definitions were heterogeneous and reported in a minority of studies. Several patient-specific, SSc-specific and SRC-specific variables predicted the presence or risk of developing SRC in SSc; however, included studies were of variable methodologic quality, with a number of limitations, including small, selected samples, retrospective designs, and paucity of controlled data or multivariate analyses. Nonetheless, we used this evidence base to generate a comprehensive list of potential candidate items that could be used to develop a definition for SRC (Table 3).

Given that we limited our search of the published literature to full-text articles published in English and whose main topic was SRC or scleroderma renal disease, it is possible that we missed some published definitions of SRC in other languages or in papers where SRC was a secondary interest. In particular, randomized controlled trials of therapies in SSc were not well captured in our scoping review, given that such studies most often did not look at SRC as a primary outcome. Furthermore, most experimental trials have

definitions of SRC in their protocol manuals, but these definitions are often not published. On the other hand, our search of the unpublished literature through a web-based survey of members of the Scleroderma Clinical Trials Consortium uncovered several definitions, in particular from randomized clinical trials. Moreover, these were consistent with the published literature and support the fact that our comprehensive review strategy most likely captured all of the relevant items used to define SRC.

In conclusion, criteria used to define SRC are used in a minority of studies and are highly heterogeneous. There is an increasing number of clinical trials in SSc being planned, many of which are in early diffuse disease. These represent unique opportunities to identify and study SRC. However, this will only be possible if investigators use a common definition of SRC. Hence, a consensus definition of SRC is urgently needed to standardize data collection on SRC. This scoping review will be used as a starting point to guide the development of a consensus definition for SRC.

ACKNOWLEDGEMENTS

***Investigators of the Scleroderma Clinical Trials Consortium Scleroderma Renal Crisis Working Group:** M. Baron, Montreal, Quebec, Canada; T. Frech, Salt Lake City, Utah, United States; C. Ghossein, Chicago, Illinois, United States; S. Johnson, Toronto, Ontario, Canada; L. Mouthon, Paris, France; S. Proudman, Adelaide, South Australia; V. Steen, Washington, District of Columbia, United States; J. Varga, Chicago, Illinois, United States.

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