AMERICAN COLLEGE
of RHEUMATOLOGY
Empowering Rheumatology Professionals

BRIEF REPORT

Generation of a Core Set of Items to Develop Classification Criteria for Scleroderma Renal Crisis Using Consensus Methodology

Emily-Ann Butler,[1] Murray Baron,[2] Agnes B. Fogo,[3] Tracy Frech,[4] Cybele Ghossein,[5] Eric Hachulla,[6] Sabrina Hoa,[7] Sindhu R. Johnson,[8] Dinesh Khanna,[9] Luc Mouthon,[10] Mandana Nikpour,[11] Susanna Proudman,[12] Virginia Steen,[13] Edward Stern,[14] John Varga,[5] Christopher Denton,[14] Marie Hudson,[15] and the Scleroderma Clinical Trials Consortium Scleroderma Renal Crisis Working Group

Objective. To generate a core set of items to develop classification criteria for scleroderma renal crisis (SRC) using consensus methodology.

Methods. An international, multidisciplinary panel of experts was invited to participate in a 3-round Delphi exercise developed using a survey based on items identified by a scoping review. In round 1, participants were asked to identify omissions and clarify ambiguities regarding the items in the survey. In round 2, participants were asked to rate the validity and feasibility of the items using Likert-type scales ranging from 1 to 9 (where 1 = very invalid/unfeasible, 5 = uncertain, and 9 = very valid/feasible). In round 3, participants reviewed the results and comments from round 2 and were asked to provide final ratings. Items rated as highly valid and feasible (median scores ≥7 for each) in round 3 were selected as the provisional core set of items. A consensus meeting using a nominal group technique was conducted to further reduce the core set of items.

Results. Ninety-nine experts from 16 countries participated in the Delphi exercise. Of the 31 items in the survey, consensus was achieved on 13, in the categories hypertension, renal insufficiency, proteinuria, and hemolysis. Eleven experts took part in the nominal group technique discussion, where consensus was achieved in 5 domains: blood pressure, acute kidney injury, microangiopathic hemolytic anemia, target organ dysfunction, and renal histopathology.

Conclusion. A core set of items that characterize SRC was identified using consensus methodology. This core set will be used in future data-driven phases of this project to develop classification criteria for SRC.

INTRODUCTION

Scleroderma renal crisis (SRC) is a life-threatening complication of systemic sclerosis (SSc) (1–4). It is usually characterized by malignant hypertension and acute kidney injury (3). However, the clinical spectrum of SRC is broad, ranging from full-blown disease presenting as new-onset accelerated arterial hypertension and rapidly progressive oliguric renal failure, to more modest elevations in blood pressure and renal dysfunction, and at times normotensive presentations. On the other hand, hypertension without uremia, urinary abnormalities, and/or mild uremia attributable to other factors (e.g., concomitant comorbidities such as diabetes or

[1]Emily-Ann Butler, BS (Hons): Dalhousie University, Halifax, Nova Scotia, Canada; [2]Murray Baron, MD: Jewish General Hospital, McGill University, Montreal, Quebec, Canada; [3]Agnes B. Fogo, MD: Vanderbilt University Medical Center, Nashville, Tennessee; [4]Tracy Frech, MD, MS: University of Utah, Salt Lake City; [5]Cybele Ghossein, MD, John Varga, MD: Northwestern University Feinberg School of Medicine, Chicago, Illinois; [6]Eric Hachulla, MD: University of Lille and Hôpital Claude Huriez, Lille, France; [7]Sabrina Hoa, MD: McGill University and Lady Davis Institute, Montreal, Quebec, Canada; [8]Sindhu R. Johnson, MD, PhD: Toronto Western Hospital, Mount Sinai Hospital and University of Toronto, Toronto, Ontario, Canada; [9]Dinesh Khanna, MD, MS: University of Michigan, Ann Arbor; [10]Luc Mouthon, MD, PhD: Cochin Hospital, Paris-Descartes University, Paris, France; [11]Mandana Nikpour, MD, PhD: University of Melbourne at St. Vincent's Hospital, Melbourne, Victoria, Australia; [12]Susanna Proudman, MB, BS (Hons): Royal Adelaide Hospital and University of Adelaide, Adelaide, South Australia, Australia; [13]Virginia Steen, MD: Georgetown University, Washington DC; [14]Edward Stern, MBBS, Christopher Denton, PhD, FRCP: Royal Free Hospital, London, UK; [15]Marie Hudson, MD, MPH: Jewish General Hospital, McGill University and Lady Davis Institute, Montreal, Quebec, Canada.

No potential conflicts of interest relevant to this article were reported.

Address correspondence to Marie Hudson, MD, MPH, Jewish General Hospital, 3755 Côte St. Catherine Road, Montreal, H3T 1E4 Quebec, Canada. E-mail: marie.hudson@mcgill.ca.

Submitted for publication July 11, 2018; accepted in revised form December 13, 2018.

exposure to nephrotoxic medications) are common in SSc (4,5). These conditions should not be confused with SRC.

SRC is relatively rare, occurring in ~5% of all SSc patients (3). It is more common in patients with rapidly progressing diffuse cutaneous SSc (11%) than in patients with limited cutaneous SSc (4%) (6). SRC can be further subcategorized into hypertensive or normotensive forms, representing ~90% and 10% of SRC cases, respectively (7,8). Historically, SRC was the leading cause of death in SSc (9). However, with the advent of angiotensin-converting enzyme inhibitors, mortality rates have decreased significantly (10,11). Nevertheless, 1-year outcomes remain poor, with >30% mortality and 25% of patients remaining dialysis dependent (12). There is an urgent need to undertake research to identify novel treatments and to improve outcomes in SRC.

In addition to heterogeneity and rarity, the absence of a gold standard and classification criteria are important challenges for research on SRC. To date, most studies of SRC have used ad hoc criteria that have varied considerably from study to study. In a scoping review of the literature, 40 original definitions of SRC, with significant heterogeneity among them, were identified (13). Only one study to date has partially validated criteria for SRC (12).

The Scleroderma Clinical Trials Consortium (SCTC) SRC Working Group was created to develop classification criteria for SRC. (See Appendix A for members of the SRC Working Group.) The objective of this phase of the study was to generate a core set of items to define SRC using consensus methodology. Future studies using data-driven methods will be needed to develop and validate classification criteria for SRC.

METHODS

A scoping review of the literature to identify items used to define SRC has been published previously (13). The results of that review were used to inform this project, which consisted of 2 phases: 1) a modified online Delphi exercise to develop provisional consensus on a core set of items to define SRC and 2) a consensus meeting using a nominal group technique to further reduce the core set. Ethics approval for this project was obtained from the Jewish General Hospital Research Ethics Board (protocol no. CODIM-MBM-17-104).

Delphi exercise. A modified, online, 3-round Delphi exercise was conducted (14,15). Experts from the SCTC, European League Against Rheumatism Scleroderma Trials and Research Group, Canadian Scleroderma Research Group, and Australian Scleroderma Interest Group were invited to participate. In addition, pathologists and nephrologists with an interest in SRC known through these organizations were invited to participate. Individuals interested in participating were asked to accept the invitation by return email. All individuals who accepted were then considered study participants, and thereby constituted the denominator for the participation rates.

The Delphi survey was developed and managed through the research electronic data capture (REDCap) platform (Vanderbilt University). In round 1, consent to participate was obtained and participant demographic and personal information was collected. Subsequently, round 1 asked participants to consider the items identified in the scoping review, clarify ambiguities, identify omissions, and provide comments. Items were modified accordingly.

In round 2, participants were asked to rate the scientific validity, empirical validity, and feasibility of the items using Likert-type scales ranging from 1 to 9 (where 1 = very invalid/unfeasible, 5 = uncertain, and 9 = very valid/feasible) and to provide comments. Participants were provided links to full-text copies of the scoping review and all of the papers included therein. Scientific validity was defined as items supported by published literature, and empirical validity was defined as items supported by personal experience and knowledge of professional consensus. Feasibility was defined in terms of whether the item could be performed or tested in an easy or convenient manner.

In round 3, the results of round 2 were presented using summary statistics, including the median and interquartile range (IQR), and bar graphs. Participants were also shown their answers and anonymized comments from other participants from round 2. The participants were then asked to provide their final rating on the scientific validity, empirical validity, and feasibility of the items.

Consensus was defined as items rated highly scientifically valid and feasible (median score ≥7 for each) in round 3, and for which there was no disagreement, calculated using the RAND/UCLA Appropriateness Method formula. Disagreement exists when the interpercentile range (IPR; difference between the 30th and 70th percentiles) is larger than the IPR adjusted for symmetry (IPRAS), calculated as follows:

$$IPRAS = 2.35 + [Asymmetry\ Index \times 1.5]$$

Derivation of the formula is shown in the RAND/UCLA Appropriateness Method handbook (16).

Consensus meeting using a nominal group technique. The second phase of this study was undertaken to reduce the number of items and achieve consensus using a nominal group technique (17). International experts, including rheumatologists, internists, and nephrologists, were invited to participate in a 2-hour face-to-face meeting held in November 2017 in San Diego, California. Dr. Dinesh Khanna moderated the discussion based on expertise and previous experience in the fields of SRC and nominal group techniques (17,18). Each item from the Delphi exercise was discussed in turn. Each panelist was invited to provide comments. At the end of the discussion, the panelists were asked to vote by a show of hands if the items should be included in the core set. A simple majority was required to include the item.

During the nominal group technique meeting, it became clear that some items required content expertise beyond rheu-

Table 1. Results from rounds 2 and 3 of the Delphi exercise and consensus achieved after round 3 for a core set of items to define SRC*

Criteria category and question	Round 2		Round 3		
	Scientific validity	Feasibility	Scientific validity	Feasibility	Consensus
Hypertension					
New onset or deterioration of preexisting hypertension, defined as any of the following:					
Systolic blood pressure ≥140 mm Hg	7 (2)	8 (2)	7 (1)	8 (1)	Yes
Diastolic blood pressure ≥90 mm Hg	7 (2)	8 (1)	7 (0.5)	8 (1)	Yes
Increase in systolic blood pressure of ≥30 mm Hg	7 (2)	8 (1)	7 (1)	8 (1)	Yes
Increase in diastolic blood pressure of ≥20 mm Hg	7 (2)	8 (2)	7 (1)	8 (0)	Yes
An increase in both systolic and diastolic blood pressure should be present	6 (3)	8 (2)	6 (2)	8 (0.5)	No
In the absence of signs and symptoms, blood pressure should be measured on at least 2 occasions	7 (3)	8 (1)	7 (1)	8 (1)	Yes
Renal insufficiency					
Increase in serum creatinine of ≥50% over baseline, or, if no baseline value is available, serum creatinine ≥120% (or 1.2 times) the upper limit of normal for the local laboratory (with measurement repeated if necessary to rule out laboratory error)	7 (2)	8 (2)	7 (1)	8 (1)	Yes
Proteinuria					
New proteinuria defined as ≥1+ (range 30–100 mg/dl) by urinary dipstick or worsening proteinuria defined as a ≥1 point increase in urinary protein (from 1+ to ≥2+, from 2+ to ≥3+, etc.)	5 (2)	7 (2)	5 (1)	7 (1)	No
New proteinuria defined as ≥2+ (range 100–300 mg/dl) by urinary dipstick or worsening proteinuria defined as a ≥1 point increase in urinary protein (from 2+ to ≥3+, from 3+ to ≥4+, etc.)	7 (2)	8 (1)	7 (1)	8 (1)	Yes
Proteinuria should be confirmed by urine protein:creatinine ratio	7 (2)	8 (2)	7 (1)	8 (0)	Yes
Proteinuria should be confirmed by 24-hour urine collection	6 (4)	6 (3)	6 (2)	6 (2)	No
Hematuria					
New hematuria defined as ≥1+ by urinary dipstick or worsening hematuria defined as a ≥1 point increase on urinary dipstick (from 1+ to ≥2+, from 2+ to ≥3+, etc.)	6 (3)	8 (1)	6 (1)	8 (1)	No
New hematuria defined as ≥2+ by urinary dipstick or worsening hematuria defined as a ≥1 point increase on urinary dipstick (2+ to ≥3+, 3+ to ≥4+, etc.)	6 (3)	8 (1)	6 (1)	8 (1)	No
New hematuria defined as ≥10 red blood cells per high-power field on urine microscopy or worsening hematuria defined as a doubling of baseline hematuria on urine microscopy	6 (2)	7 (2)	6 (2)	7 (1)	No
Thrombocytopenia					
≤100,000 platelets/mm^3	6 (3)	8 (1)	6 (1)	8 (1)	No
Thrombocytopenia should be confirmed by manual blood smear	6 (2)	6 (2)	6 (2)	6 (1)	No
Hemolysis					
Microangiopathic hemolytic anemia defined as new or worsening anemia not due to other causes and supported by the presence of one of the following:					
Schistocytes or other red blood cell fragments on blood smear	8 (1)	8 (1)	8 (0)	8 (0)	Yes
Reticulocyte count above normal range for the local laboratory	7 (3)	7 (1)	7 (1)	7 (1)	Yes
Serum lactate dehydrogenase and/or indirect bilirubin above normal ranges for the local laboratory	6 (2)	8 (2)	6 (1)	8 (1)	No
Serum haptoglobin below normal range for the local laboratory	7 (2)	8 (2)	7 (1)	8 (1)	Yes

Table 1. (*Cont'd*)

Criteria category and question	Round 2		Round 3		
	Scientific validity	Feasibility	Scientific validity	Feasibility	Consensus
Microangiopathic hemolytic anemia defined as new or worsening anemia not due to other causes and supported by the presence of at least 2 abnormal laboratory findings (red blood cell fragments, elevated reticulocyte count, elevated serum lactate dehydrogenase/indirect bilirubin, or low haptoglobin)	8 (1)	8 (1)	8 (0)	8 (0)	Yes
A direct antiglobulin test should be documented to rule out autoimmune hemolytic anemia	7 (3)	7 (2)	7 (0)	7 (1)	Yes
Encephalopathy, defined by the National Institute of Neurological Disorders and Stroke (21) as follows: "any diffuse disease of the brain that alters brain function or structure. The hallmark of encephalopathy is an altered mental state. Depending on the type and severity of encephalopathy, common neurological symptoms are progressive loss of memory and cognitive ability, subtle personality changes, inability to concentrate, lethargy, and progressive loss of consciousness. Other neurological symptoms may include myoclonus (involuntary twitching of a muscle or group of muscles), nystagmus (rapid, involuntary eye movement), tremor, muscle atrophy and weakness, dementia, seizures, and loss of ability to swallow or speak"	6 (3)	7 (2)	6 (1)	7 (1)	No
Retinopathy					
Retinopathy typical of malignant hypertension	7 (2)	6 (3)	7 (1)	6 (1)	No
Grade III (flame-shaped hemorrhages and/or cotton-wool exudates) or grade IV (papilledema) retinopathy, according to the Keith-Wagener classification system	7 (3)	6 (3)	7 (1)	6 (2)	No
Hyperreninemia, defined as an elevation in plasma renin activity ≥2 times the upper limit of normal	7 (3)	4 (4)	7 (1)	5 (2)	No
Cardiac dysfunction					
Presence of flash pulmonary edema based on all available information and clinical judgment	6 (2)	7 (2)	6 (1)	7 (0)	No
Presence of symptomatic pericardial effusion based on all available information and clinical judgment	6 (2)	6 (2)	6 (1)	6 (1)	No
Abnormal kidney biopsy findings					
Findings consistent with SRC (microangiopathy)	8 (2)	6 (4)	8 (0)	6 (2)	No
Accumulation of mucoid (myxoid) in interlobular arteries (indistinguishable from accelerated hypertension) and/or fibrinoid necrosis of arteries	7 (2)	6 (4)	7 (1)	6 (2)	No
Histopathologic findings on kidney biopsy consistent with SRC, which may include the following: Small vessel (arcuate and interlobular arteries) changes predominate over glomerular alterations. Early vascular abnormalities include intimal accumulation of myxoid material, thrombosis, and fibrinoid necrosis, sometimes resulting in cortical necrosis. Narrowing and obliteration of the vascular lumen lead to glomerular ischemia. Juxtaglomerular apparatus hyperplasia, while relatively rare (10%), can be observed. Late changes are manifested by intimal thickening and proliferation (which lead to characteristic vascular "onion-skin" lesions), glomerulosclerosis, and interstitial fibrosis. Since none of these findings are specific for SRC, the pathologic diagnosis must be supported by appropriate clinical and serologic data.	8 (2)	6 (3)	8 (0)	6 (2)	No

* Values are the median (interquartile range). SRC = scleroderma renal crisis.

matology, internal medicine, and nephrology. Thus, some items were conditionally included, pending further review with content experts. Experts in hematology, neurology, ophthalmology, and cardiology were then contacted and asked to provide input and published evidence to define items in those domains. A final list of a core set of items (and their definitions) was compiled and cir-

culated among the participants of the nominal group technique meeting for final approval.

RESULTS

Results of the Delphi exercise. We contacted 216 people with an interest in SRC, and 99 of them agreed to participate in the modified online Delphi exercise. Of those, 77 (78%), 60 (61%), and 69 (70%) participated in rounds 1, 2, and 3, respectively, and 49 (49%) completed all 3 rounds of the exercise. Participants were mainly rheumatologists (86%) but also included some internists, nephrologists, and pathologists. Most participants had worked as clinicians for >11 years, with only a few having <10 years of experience (13%). Most of the participants were from the US (35%) or Canada (11%); 16 other countries were also represented.

A total of 31 items in 11 categories were included in the Delphi exercise. Of these, 13 items in 4 categories (hypertension, renal insufficiency, proteinuria, and hemolysis) achieved consensus in round 3 (median ratings ≥7 for scientific validity and feasibility with no disagreement). Disagreement on feasibility was only present for hyperreninemia. In any case, consensus on feasibility was not achieved for that item either. Of note, all items that reached consensus in round 2 also reached consensus in round 3, with no additional items reaching consensus in round 3. However, the IQR for the majority of items became smaller in round 3, demonstrating growing consensus. The median ratings and IQR for each item for rounds 2 and 3 are presented in Table 1.

Results of the nominal group technique. Seventeen international experts were invited to participate in a face-to-face nominal group technique meeting. Six were not available. Thus, the panel consisted of 11 participants (10 rheumatologists and 1 nephrologist) from the US, Canada, UK, France, The Netherlands, and Australia. Prior to the nominal group technique meeting, the 11 categories from the Delphi exercise were reorganized into 5 domains (hypertension, renal dysfunction [renal insufficiency, proteinuria, hematuria, and hyperreninemia], microangiopathic hemolytic anemia with thrombocytopenia, target organ dysfunction [encephalopathy, retinopathy, and cardiac dysfunction], and renal histopathology). Prior to and at the meeting, it was agreed that items should be defined as much as possible according to evidence and/or international guidelines. Content experts in hematology, neurology, ophthalmology, and cardiology were contacted to provide input on the definitions of the items included in the core set. The final core set of items and their definitions are presented in Table 2 and were approved by the nominal group technique participants.

DISCUSSION

In this study, we generated a core set of items to classify SRC using consensus methodology. This core set includes 5 domains

and 13 items. The definitions for each item were evidence based or, in the absence of evidence, determined in consultation with content experts.

The progress made to date to develop classification criteria for SRC demonstrates the importance of using the best evidence available. A scoping review of the literature identified 40 heterogeneous definitions of SRC using more than 40 items with variable definitions (13). The Delphi exercise led to consensus on 13 of these items. However, the need to go beyond consensus in the rheumatology community and to get the input of content experts emerged as a critical factor at the nominal group technique meeting. Thus, input from content experts was sought to finalize the core set. Proteinuria is a perfect example of how this approach allowed the core set to evolve. Indeed, low-level proteinuria is common in SSc (4), dipstick and urine protein-to-creatinine ratio are not reliable in acute kidney injury, proteinuria is not part the Kidney Disease Improving Global Outcomes definition of acute kidney injury (19), and proteinuria would compromise the specificity of SRC criteria. Thus, despite the fact that there was consensus to include proteinuria in the core set after the Delphi exercise, this item was excluded after the nominal group technique meeting and discussion with nephrologists.

A core set of variables to define SRC was proposed by experts in 2003 (7). It included items for systolic and diastolic blood pressure, serum creatinine level, proteinuria, hematuria, microangiopathic hemolytic anemia, and renal histopathology. These are known as the Ancona criteria for SRC. Our core set has similarities to the Ancona criteria, in particular with respect to blood pressure. However, there are also notable differences in defining acute kidney injury (including the exclusion of proteinuria and hematuria in the present study). In addition, our core set includes target organ dysfunction and a detailed histopathologic description of SRC.

In 2016, the UK Scleroderma Study Group proposed criteria for the diagnosis of SRC (20). The criteria were divided into the categories diagnostic criteria (essential) and supportive evidence (desirable). The diagnostic criteria included blood pressure and acute kidney injury, and the supporting evidence consisted of microangiopathic hemolytic anemia with thrombocytopenia, hypertensive retinopathy, hematuria, oliguria or anuria, renal biopsy findings consistent with SRC features, and flash pulmonary edema. Discrepancies between the UK criteria and our proposed criteria are found in the slightly modified cutoff values for blood pressure (150/85 mm Hg in the UK criteria versus 140/90 mm Hg in our core set). Additionally, the UK criteria do not include an increase in diastolic blood pressure, only an increase of ≥20 mm Hg for systolic blood pressure, which is lower than the ≥30 mm Hg proposed in this study. Further, the UK criteria included hematuria. Additionally, oliguria and flash pulmonary edema were proposed as stand-alone items, whereas in our list, these items are grouped into the acute kidney injury and acute heart failure definitions, respec-

Table 2. Final core set of items to develop classification criteria for SRC*

Blood pressure

  Acute increase in blood pressure defined as any of the following:

    Systolic blood pressure ≥140 mm Hg

    Diastolic blood pressure ≥90 mm Hg

    An increase in systolic blood pressure of ≥30 mm Hg above normal

    An increase in diastolic blood pressure of ≥20 mm Hg above normal

  Blood pressure measurement should be taken twice, separated by at least 5 minutes; if blood pressure readings are discordant, repeat readings should be taken until 2 consistent readings are obtained

Kidney injury†

  Acute kidney injury defined as any of the following:

    Increase in serum creatinine of ≥26.5 μmoles/liter (≥0.3 mg/dl) within 48 hours

    Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days

    Urine volume <0.5 ml/kg/hour for 6 hours

Microangiopathic hemolytic anemia and thrombocytopenia

  New or worsening anemia not due to other causes

  Schistocytes or other red blood cell fragments on blood smear

  Thrombocytopenia ≤100,000 platelets/mm^3, confirmed by manual smear

  Laboratory evidence of hemolysis, including elevated lactate dehydrogenase, reticulocytosis, and/or low or absent haptoglobin

  A negative direct antiglobulin test

Target organ dysfunction

  Hypertensive retinopathy (hemorrhages, hard and soft [cotton-wool] exudates, and/or disc edema, not attributable to other causes), confirmed by an ophthalmologist

  Hypertensive encephalopathy, characterized by headache, altered mental status, seizures, visual disturbances, and/or other focal or diffuse neurologic signs not attributable to other causes

  Acute heart failure, characterized by typical symptoms (e.g., breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles, and peripheral edema)

  Acute pericarditis, diagnosed with at least 2 of the 4 following criteria: 1) pericarditis chest pain; 2) pericardial rub; 3) new widespread ST segment elevation or PR segment depression on electrocardiography; 4) pericardial effusion (new or worsening) on cardiac echocardiography

Renal histopathology

  Histopathologic findings on kidney biopsy consistent with SRC, which may include the following: Small vessel (arcuate and interlobular arteries) changes that predominate over glomerular alterations. Glomerular changes of thrombotic microangiopathy may be present, with acute changes including fibrin thrombi and endothelial swelling, red blood cell fragments, and mesangiolysis, and chronic changes including double contours of the glomerular basement membrane. Nonspecific ischemic changes with corrugation of the glomerular basement membrane, and even segmental or global sclerosis of glomeruli may occur. Early vascular abnormalities include intimal accumulation of myxoid material, thrombosis, fibrinoid necrosis, and fragmented red blood cells, sometimes resulting in cortical necrosis. Narrowing and obliteration of the vascular lumen lead to glomerular ischemia. Juxtaglomerular apparatus hyperplasia, while relatively rare (10%), can be observed. Late changes are manifested by intimal thickening and proliferation (which lead to characteristic vascular "onion-skin" lesions), glomerulosclerosis, and interstitial fibrosis. Nonspecific tubular changes may also occur, including acute tubular injury in the early stage of injury, and later interstitial fibrosis and tubular atrophy. Since none of these findings are specific for SRC, the pathologic diagnosis must be supported by appropriate clinical and serologic data.

* SRC = scleroderma renal crisis.
† This is the definition of acute kidney injury from the Kidney Disease Improving Global Outcomes guidelines (19).

tively. Our core set provides a more in-depth detailed definition for each item, specifically for acute kidney injury, microangiopathic hemolytic anemia with thrombocytopenia, and renal histopathology.

Only one study to date has attempted to validate the Ancona criteria and another slightly different set of criteria for SRC that included encephalopathy (12). In that study, a diagnosis of SRC confirmed by a study physician was used as the gold standard

for SRC. Compared to the gold standard, the 2 sets of criteria identified 70 of 70 subjects with hypertensive SRC, but only 2 of 5 subjects with normotensive SRC. We believe that our core set, which was developed using robust consensus methodology and evidence-based content, represents a significant advancement over these definitions. In addition, it defines target organ involvement and provides a detailed histopathologic description to define the term "findings consistent with SRC".

This study has some limitations. First, only 99 of 216 experts invited to participate accepted, and 77 (78%), 60 (61%), and 69 (70%) of these participated in rounds 1–3 of the Delphi exercise, respectively. We cannot exclude some response bias. Part of the reason for the low response rates may have been that the Delphi exercise was conducted during the summer and early fall in the Northern hemisphere. Numerous out of office replies were returned. On the other hand, to mitigate this source of bias, reminder emails were sent to optimize participation rates and the final sample was still substantial and representative. Second, there are large gaps in knowledge on SRC. Hence, participants in the Delphi exercise may have rated validity based more on empirical, rather than scientific, evidence. Nevertheless, we provided the Delphi exercise participants with the scoping review and all of the original papers included therein in every round for easy access to the available literature. Third, recruitment of participants with a broad range of expertise is critical to the success of a consensus-building exercise. Although there were a few specialists other than rheumatologists who participated in the Delphi exercise, it became clear at the nominal group technique meeting that content expertise in hematology, neurology, ophthalmology, and cardiology was lacking. We therefore recruited experts in all of these fields to help finalize the relevant items.

This study has substantial strengths. The emphasis on evidence and input from content experts ensured that the final core set had face and content validity. The geographic range of participants contributed to the generalizability of the results. There was important complementarity in the use of both a Delphi exercise and a semi-structured nominal group technique consensus meeting. The Delphi exercise provided a cost-effective approach to survey a larger sample of international experts working anonymously. The nominal group technique meeting allowed for a time-efficient, face-to-face discussion of a smaller sample of experts led by an experienced moderator.

In conclusion, using consensus methodology, we generated a core set of items, and the definitions of those items, to be used in the development of classification criteria for SRC. To determine if and how these items should be incorporated into classification criteria for SRC, 2 future phases of this research project are now being planned. The first, modeled on the *International Scleroderma Renal Crisis Survey* (12), will be to recruit an inception cohort of SRC patients and obtain data on the items in the core set. A comparison cohort consisting of subjects with conditions that mimic SRC will also be assembled. These data will be used to develop and validate classification criteria

for SRC. The second will be a forced choice study using multi-criteria decision analysis methods to assign weights to the items in the criteria and to set probability values for definite, probable, and possible SRC. The resulting classification criteria will facilitate rigorous research in SRC. In the meantime, SSc researchers who are designing new studies (either observational studies or trials) are encouraged to collect these items in their data sets. These will be useful for future external validation of the criteria.

ACKNOWLEDGMENTS

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Hudson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Denton, Hudson.
Acquisition of data. Butler, Baron, Fogo, Frech, Ghossein, Hachulla, Hoa, Johnson, Khanna, Mouthon, Nikpour, Proudman, Steen, Stern, Varga, Denton, Hudson.
Analysis and interpretation of data. Butler, Baron, Fogo, Frech, Ghossein, Hachulla, Hoa, Johnson, Khanna, Mouthon, Nikpour, Proudman, Steen, Stern, Varga, Denton, Hudson.

REFERENCES

1. Denton CP, Khanna D. Systemic sclerosis. Lancet 2017;390:1685–99.

2. Helfrich DJ, Banner B, Steen VD, Medsger TA Jr. Normotensive renal failure in systemic sclerosis. Arthritis Rheum 1989;32:1128–34.

3. Mouthon L, Bérezné A, Bussone G, Noël LH, Villiger PM, Guillevin L. Scleroderma renal crisis: a rare but severe complication of systemic sclerosis. Clin Rev Allergy Immunol 2011;40:84–91.

4. Steen VD, Syzd A, Johnson JP, Greenberg A, Medsger TA. Kidney disease other than renal crisis in patients with diffuse scleroderma. J Rheumatol 2005;32:649–55.

5. Caron M, Hudson M, Baron M, Nessim S, Steele R. Longitudinal study of renal function in systemic sclerosis. J Rheumatol 2012;39:1829–34.

6. Nihtyanova SI, Schreiber BE, Ong VH, Rosenberg D, Moinzadeh P, Coghlan JG, et al. Prediction of pulmonary complications and long-term survival in systemic sclerosis. Arthritis Rheumatol 2014;66:1625–35.

7. Steen VD, Mayes MD, Merkel PA. Assessment of kidney involvement. Clin Exp Rheumatol 2003;21:S29–31.

8. Steen VD. Scleroderma and renal crisis. Rheum Dis Clin North Am 2003;29:315–33.

9. Traub YM, Shapiro AP, Rodnan GP, Medsger TA, McDonald RH, Steen VD, et al. Hypertension and renal failure (scleroderma renal crisis) in progressive systemic sclerosis. Medicine (Baltimore) 1983;62:335–52.

10. Guillevin L, Berezne A, Seror R, Teixeira L, Pourrat J, Mahr A, et al. Scleroderma renal crisis: a retrospective multicentre study on 91 patients and 427 controls. Rheumatology (Oxford) 2012;51:460–7.

11. Teixeira L, Mouthon L, Mahr A, Berezné A, Agard C, Mehrenberger M, et al. Mortality and risk factors of scleroderma renal crisis: a French retrospective study of 50 patients. Ann Rheum Dis 2008;67:110–6.

12. Hudson M, Baron M, Tatibouet S, Furst DE, Khanna D, Hummers L, et al. Exposure to ACE inhibitors prior to the onset of scleroderma renal crisis-results from the international scleroderma renal crisis survey. Semin Arthritis Rheum 2014;43:666–72.

13. Hoa S, Stern EP, Denton CP, Hudson M, Baron M, Frech T, et al. Towards developing criteria for scleroderma renal crisis: a scoping review. Autoimmun Rev 2017;16:407–15.

14. Barber CE, Marshall DA, Alvarez N, Mancini GB, Lacaille D, Keeling S, et al. Development of cardiovascular quality indicators for rheumatoid arthritis: results from an international expert panel using a novel online process. J Rheumatol 2015;42:1548–55.

15. Schmajuk G, Hoyer BF, Aringer M, Johnson SR, Daikh DI, Dörner T, on behalf of the SLE Classification Criteria Steering Committee and the International SLE Expert Panel of the Initiative. Multicenter Delphi exercise to identify important key items for classifying systemic lupus erythematosus. Arthritis Care Res (Hoboken) 2018;70:1488–94.

16. Fitch K, Bernstein SJ, Aguilar MD, Burnand B, LaCalle JR, Lazaro P, et al. The RAND/UCLA appropriateness method user's manual. Santa Monica: RAND; 2001.

17. Fransen J, Johnson SR, van den Hoogen F, Baron M, Allanore Y, Carreira PE, et al. Items for developing revised classification criteria in systemic sclerosis: results of a consensus exercise. Arthritis Care Res (Hoboken) 2012;64:351–7.

18. Johnson SR, Khanna D, Cervera R, Costedoat-Chalumeau N, Gladman DD, Hahn BH, et al. Use of consensus methodology to determine candidate items for systemic lupus erythematosus classification criteria. J Rheumatol. E-pub ahead of print.

19. Kellum J, Lameire N, Aspelin P, Barsoum RS, Burdmann E, Goldstein SL, et al. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012;2:1–138.

20. Lynch BM, Stern EP, Ong VH, Harber M, Burns A, Denton CP. UK Scleroderma Study Group (UKSSG) guidelines on the diagnosis and management of scleroderma renal crisis. Clin Exp Rheumatol 2016;34 Suppl 100:106–9.

21. National Institute of Neurological Disorders and Stroke. Encephalopathy Information Page. URL: https://www.ninds.nih.gov/Disorders/All-Disorders/Encephalopathy-Information-Page.

APPENDIX A: THE SCLERODERMA CLINICAL TRIALS CONSORTIUM SCLERODERMA RENAL CRISIS WORKING GROUP

Members of the Scleroderma Clinical Trials Consortium Scleroderma Renal Crisis Working Group are as follows: April Barnado (Vanderbilt University Medical Center, Nashville, Tennessee), Murray Baron (Jewish General Hospital, McGill University, Montreal, Quebec, Canada), Elana J. Bernstein (Columbia University Medical Center, New York, New York), Francesco Boin (University of California, San Francisco), Yolanda Braun-Moscovici (Rheumatology Institute, Rambam Health Care Campus, Rappaport Faculty of Medicine, Technion, Haifa, Israel), Flavia V. Castelino (Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts), Luis J. Catoggio (Hospital Italiano de Buenos Aires, Buenos Aires, Argentina), Marco Matucci-Cerinic (University of Florence, Florence, Italy), Lorinda Chung (Palo Alto VA Health Care System, Stanford University, Stanford, California), Philip Clements (University of California, Los Angeles), Mary Ellen Csuka (Medical College of Wisconsin, Milwaukee, Wisconsin), Ellen De Langhe (University Hospital Leuven, Leuven, Belgium), Christopher Denton (Royal Free Hospital, London, UK), Jörg Distler (Friedrich-Alexander-University, Erlangen-Nürnberg, Germany), Oliver Distler (University Hospital Zurich, Zurich, Switzerland), Dominique Claire Farge (AP-HP, St. Louis Hospital, Université Denis Diderot, Paris, France), Aryeh Fischer (University of Colorado, Aurora, Colorado), Agnes B. Fogo (Vanderbilt University Medical Center, Nashville, Tennessee), Tracy Frech (University of Utah, Salt Lake City), Armando Gabrielli (Università Politecnica delle Marche, Ancona, Italy), Cybele Ghossein (Northwestern University Feinberg School of Medicine, Chicago, Illinois), Eric Hachulla (University of Lille and Hôpital Claude Huriez, Lille, France), Minoru Hasegawa (University of Fukui, Fukui, Japan), Samina Hayat (Louisiana State University, Baton Rouge, Louisiana), Ariane Herrick (University of Manchester, Manchester, UK), Roger Hesselstrand (Lund University Hospital, Lund, Sweden), Sabrina Hoa (McGill University and Lady Davis Institute, Montreal, Quebec, Canada), Vivien Hsu (Rutgers-RWJ Medical School, New Brunswick, New Jersey), Marie Hudson (Jewish General Hospital, McGill University and Lady Davis Institute, Montreal, Quebec, Canada), Michael Hughes (University of Manchester, Manchester, UK), Nicolas Hunzelmann (University of Cologne, Cologne, Germany), Laura Hummers (Johns Hopkins University, Baltimore, Maryland), Florenzo Iannone (University of Bari, Bari, Italy), Francesca Ingegnoli (Università degli Studi di Milano, Milan, Italy), Soren Jacobsen (Rigshospitalet, Copenhagen, Denmark), Sindhu R. Johnson (Toronto Western Hospital, Mount Sinai Hospital, and University of Toronto, Toronto, Ontario, Canada), Yasushi Kawaguchi (Tokyo Women's Medical University, Tokyo, Japan), Dinesh Khanna (University of Michigan, Ann Arbor), Martial Koenig (University of Montreal, Montreal, Quebec, Canada), Masataka Kuwana (Nippon Medical School, Tokyo, Japan), Jan Lenaerts (University Hospital Leuven, Leuven, Belgium), Thierry Martin (National Referral Center for Systemic Autoimmune Diseases, Strasbourg University Hospital, Strasbourg, France), Maureen D. Mayes (University of Texas McGovern Medical School, Houston), Zsuzsanna McMahan (Johns Hopkins University, Baltimore, Maryland), Thomas Medsger (University of Pittsburgh, Pittsburgh, Pennsylvania), Peter Merkel (University of Pennsylvania, Philadelphia, Pennsylvania), Sonali Narain (Northwell Health, New York, New York), Mandana Nikpour (University of Melbourne at St. Vincent's Hospital, Melbourne, Victoria, Australia), Voon Ong (University College London, London, UK), John D. Pauling (Royal National Hospital for Rheumatic Diseases, University of Bath, Bath, UK), Janet Pope (University of Western Ontario, St. Joseph's Health Care, London, Ontario, Canada), Susanna Proudman (Royal Adelaide Hospital and University of Adelaide, Adelaide, South Australia, Australia), Carlos de la Puente Bujidos (Hospital Ramón y Cajal, Madrid, Spain), Maureen Rischmueller (Queen Elizabeth Hospital, University of Adelaide, Adelaide, South Australia, Australia), Tatiana Sofía Rodríguez-Reyna (Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico), Joanne Sahhar (Monash Health, Monash University, Melbourne, Victoria, Australia), Lesley Ann Saketkoo (New Orleans Scleroderma and Sarcoidosis Patient Care and Research Center, Tulane University Lung Center, New Orleans, Louisiana), Jean-Luc Senécal (University of Montreal Scleroderma Research Chair, Centre Hospitalier de l'Université de Montréal, Montreal, Quebec, Canada), Ankoor Shah (Duke University, Durham, North Carolina), Ami A. Shah (Johns Hopkins University, Baltimore, Maryland), Walter Alberto Sifuentes-Giraldo (Hospital Ramón y Cajal, Madrid, Spain), Richard Silver (Medical University of South Carolina, Charleston, South Carolina), Virginia Steen (Georgetown University, Washington, DC), Edward Stern (Royal Free Hospital, London, UK), Wendy Stevens (St. Vincent's Hospital, Melbourne, Victoria, Australia), Evelyn Sutton (Dalhousie University, Halifax, Nova Scotia, Canada), Vivek Thakkar (Macquarie University, Sydney, New South Wales, Australia), Gabriele Valentini (Università degli Studi della Campania, Naples, Italy), Jeska de Vries-Bouwstra (Leiden University, Leiden, The Netherlands), Madelon Vonk (Radboud University, Nijmegen, The Netherlands), and Ulrich A. Walker (Basel University Hospital, Basel, Switzerland).