GENERATION OF A CORE SET OF ITEMS TO DEVELOP CLASSIFICATION CRITERIA FOR SCLERODERMA RENAL CRISIS USING CONSENSUS METHODOLOGY

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Abstract

Background: We undertook this project to generate a core set of items to develop classification criteria for 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 the 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 1-9 (1= very invalid/unfeasible, 5 = uncertain, 9 = very valid/feasible). In Round 3, participants reviewed the results and comments of Round 2, and were asked to provide final ratings. Items rated as highly valid and feasible (both median scores ≥7) in Round 3 were selected as the provisional core set of items. A nominal group discussion meeting followed to achieve final consensus on the core set of items.

Results: Overall, 99 experts from 16 countries participated in the Delphi exercise. Of the 31 items in the survey, consensus was achieved on 13, including hypertension, renal insufficiency, proteinuria and hemolysis. Eleven experts took part in the nominal group discussion, where consensus was achieved in 5 domains: blood pressure, acute kidney injury, microangiopathic hemolytic anemia, target organ dysfunction, and histopathology.

Conclusions: 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 uraemia, urinary abnormalities and/or mild uraemia attributable to other factors (e.g., concomitant comorbidities such as diabetes or exposure to nephrotoxic medications) are common in SSc (4,5). These conditions should not be confused with SRC.

SRC is relatively rare occurring in about 5% of all SSc patients (3). It is more common in patients with rapidly progressing diffuse cutaneous SSc (dcSSc) (11%) as compared to patients with limited cutaneous SSc (lcSSc) (4%) (6). SRC can be further sub-categorized into hypertensive or normotensive forms, representing approximately 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 ACE inhibitors, mortality rates have decreased significantly (10,11). Nevertheless, one-year outcomes remain poor, with over 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 of SRC.

In addition to rarity and heterogeneity, 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. 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 required 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 (13). The results of this review were used to inform this project, which consisted of two phases: 1) a modified online Delphi exercise to develop provisional consensus on a core set of items to define SRC and 2) a nominal group technique (NGT) meeting to develop final consensus for the core set. Ethics approval for this project was obtained from the Jewish General Hospital Research Ethics Board, Montréal, Quebec, Canada (Protocol # CODIM-MBM-17-104).

Phase 1: Delphi

To develop initial consensus, a modified, online, 3-round Delphi exercise was conducted (14). Two hundred and sixteen experts identified through the Scleroderma Clinical Trials Consortium (SCTC), European Scleroderma Trials and Research Group (EUSTAR), Canadian Scleroderma Research Group (CSRG) and Australian Scleroderma Interest Group (ASIG) were sent a letter of invitation to participate. In addition, pathologists and nephrologists known through these organizations with interest in SRC were invited to participate to provide additional perspective on key items pertaining to SRC.

All individuals interested in participating in the online Delphi were asked to explicitly accept the invitation by return email. All individuals who accepted were then considered study participants, and thereby constituted the denominator for the participation rates.

An online Delphi survey was developed and managed through the REDCap platform (Vanderbilt University, Nashville Tennessee). The survey consisted of 48 items identified by the scoping review, grouped in 11 categories: hypertension; renal insufficiency; proteinuria; hematuria; thrombocytopenia; hemolysis; encephalopathy; retinopathy; hyper-reninemia; cardiac dysfunction; and abnormal kidney biopsy.

The Delphi exercise consisted of three rounds. At the start of Round 1, consent to participate was obtained and contact, demographic and personal information was collected on participants. Subsequently, Round 1 asked participants to consider the items identified in the scoping review and requested them to clarify ambiguities, identify omissions and to provide comments. Items were modified, re-worded and re-organized according to the feedback from Round 1.

In Round 2, participants were asked to rate the scientific validity, empirical validity and feasibility of the items using Likert-type scales ranging from 1-9 (1= very invalid/unfeasible, 5 = uncertain, 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 as items supported by personal experience and knowledge of professional consensus. Feasibility was defined in terms of whether the item could be performed/tested in an easy or convenient matter. In addition, several questions interrogating various cut-offs were also included by way of exploratory

analysis, using multiple-choice question format. These questions pertained to blood pressure, serum creatinine, proteinuria, hematuria and thrombocytopenia.

In Round 3, the results of Round 2 were presented using summary statistics, including medians and interquartile ranges, and bar graphs. Participants were also shown their answers and anonymized comments from other participants in Round 2. After reviewing the results of Round 2, participants were then asked to provide their final rating on scientific validity, empirical validity and feasibility of the items.

Participants were informed of the timeline for the Delphi and given 2 weeks to complete the first round. Upon completion of Round 1, participants were prompted with a reminder of the upcoming rounds. After closing Round 1, results were analyzed and the survey modified accordingly during a 2-week period. Each round remained open for approximately two weeks. If an individual had agreed to participate, but did not complete Round 1 in the allotted time, they were still allowed to participate in Rounds 2 and 3, as the first round primarily gathered input and comments for a more structured second and third round. However, given the links between Rounds 2 and 3, only those who participated in Round 2 were presented with their answers. If an individual did not complete Round 2 in the allotted time, they were only provided with group summary statistics and comments in Round 3.

Consensus was defined as items rated highly scientifically valid and feasible (both median scores ≥7) in Round 3, and for which there was no disagreement, calculated using the RAND/UCLA Appropriateness Method formula. Disagreement exists when the inter-percentile range (IPR: difference between the 30^{th} and 70^{th} percentiles) is larger than the IPR adjusted for symmetry (IPRAS), calculated as follows:

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

Derivation of the formula is shown in the RAND/UCLA Appropriateness Method handbook (15).

Phase 2: NGT meeting

The second phase of this study was to develop final consensus using nominal group technique (NGT). Seventeen 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 (CA). Six were not available. Thus, the final panel consisted of 11 experts with an international representation in the fields of rheumatology, internal medicine and nephrology. All but one of the NGT participants were also participants in the prior Delphi exercise. Dr. Dinesh Khanna moderated the discussion based on expertise and previous experience in the fields of SRC and NGT techniques.

For the purposes of the NGT meeting, the 11 categories from the Delphi exercise were re-organized and collapsed into 5 domains (hypertension, renal dysfunction, microangiopathic hemolytic anemia with thrombocytopenia, target organ dysfunction [encephalopathy, retinopathy and cardiac dysfunction] and histopathology). Each domain 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 NGT meeting, it became clear that some items required content expertise beyond rheumatology, 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 core set items (and their definitions) was compiled and circulated among the participants of the NGT meeting for final approval.

Secondary objectives of the NGT were to define a list of SRC mimickers (to improve the specificity of the criteria) and to discuss how the classification criteria for hypertensive and normotensive SRC should be different. Although the former was achieved, the panel decided that distinction between hypertensive and normotensive SRC should be based on data collected in future data-driven phases of this project.

Results

Phase 1: Delphi

We contacted 216 professionals with an interest in SRC of which 99 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 three rounds of the exercise.

Participant characteristics are shown in Table 1 and the geographical distribution of those participants in Table 2. Participants were mainly rheumatologists (86%) with some internists, nephrologists and pathologists. Most participants worked as clinicians for >11 years, with only a few having less than 10 years of experience (13%). The majority of participants were from the United States (35%) followed by Canada (11%); 16 other countries were also represented.

The Delphi exercise consisted of 3 rounds in which Round 1 allowed participants to provide feedback on the content of the survey, Round 2 allowed participants to rate items for validity and feasibility, in addition to providing optional comments, and Round 3 allowed participants to review their own and the group's ratings from Round 2 and to provide final ratings for validity and feasibility. The median ratings and IQR for each item for Rounds 2 and 3

are presented in Table 3. 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 $\geq$ 7 on validity and feasibility with no disagreement). Disagreement, calculated with the IPRAS formula, was only present for hyper-reninemia. In any case, that item had not achieved consensus on feasibility 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.

In addition to the rating of items, questions pertaining to cut-offs for blood pressure, creatinine, proteinuria, hematuria and thrombocytopenia were included in Rounds 2 and 3 (Table 4). The results showed considerable variability, emphasizing the need to identify uniform cut-offs supported by evidence.

Phase 2: Nominal Group Technique meeting

The face-to-face NGT meeting was held in San Diego, California and consisted of 11 participants, 10 rheumatologists and 1 nephrologist, from the USA, Canada, UK, France, Netherlands and Australia. Prior to the NGT meeting, the 11 categories from the Delphi exercise were re-organized into 5 domains (hypertension, renal dysfunction [renal insufficiency, proteinuria, hematuria and hyper-reninemia], microangiopathic hemolytic anemia with thrombocytopenia, target organ dysfunction [encephalopathy, retinopathy and cardiac dysfunction] and histopathology). At the meeting, it was agreed that items should be defined as much as possible according to evidence and/or international guidelines.

After discussion, the participants at the NGT agreed that hypertension should be re-worded as *Rise in blood pressure* and defined according to international guidelines using cut-offs

of 140 mmHg for systolic blood pressure and 90 mmHg for diastolic blood pressure (16–18). Since "rise in blood pressure" is a concept that is intrinsic to SRC and is meant to include patients with blood pressure within normal ranges but with clinically significant rise over baseline and for which there are no established guidelines, cut-offs of 30 mmHg for systolic blood pressure and 20 mmHg for diastolic blood pressure were retained based on the consensus in the Delphi exercise (Table 4).

Similarly, the participants at the NGT agreed that renal dysfunction should be re-worded as *Acute Kidney Injury* and defined according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines (19). These guidelines define acute kidney injury as follows: increase in serum creatinine by > 26.5 umol/L (> 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; and urine volume < 0.5 ml/kg/h for 6 hours.

The panel discussed *Microangiopathic hemolytic anemia and thrombocytopenia* and *Target organ dysfunction (encephalopathy, retinopathy, cardiomyopathy)*. It was agreed that these items could be retained in the core set but that definitions should be finalized after consulting with content experts in hematology, neurology, ophthalmology, and cardiology. Following these consultations, the items were defined as follows:

Microangiopathic hemolytic anemia and thrombocytopenia (MAHAT) was defined as new or worsening anemia not due to other causes, schistocytes or other RBC fragments on blood smear, laboratory evidence of hemolysis that includes elevated lactate dehydrogenase (LDH) and reticulocytes and/or low/absent haptoglobin and a negative Coombs test. Thrombocytopenia was defined as a platelet count of $\leq$ 100,000 confirmed by blood smear (20, 21). There was discussion about including a specific cut-off for schistocytes, such as >1% (11, 22) or > 2 per

high-powered field (23). However, this was not retained because automated quantification is not widely available, manual quantification is subjective and neither of these cut-offs have been validated.

Encephalopathy was defined as headache, altered mental status, seizures, visual disturbances and/or other focal or diffuse neurologic signs not attributable to other cause. In the absence of an evidence-based definition of hypertensive encephalopathy, the definition proposed by Lamy and Mas (24) was felt to describe the syndrome best and was retained.

Retinopathy was defined as hemorrhages, hard and soft (cotton wool) exudates, and/or disc edema, not attributable to other causes and confirmed by an ophthalmologist. This definition was based on key items in the Keith-Wagener-Baker and Modified Scheie classification criteria (25,26), and required confirmation by an ophthalmologists because it has been shown that the reliability of these criteria is low when ophthalmoscopic exam is performed by other physicians (26).

Cardiomyopathy was divided into *Acute Heart Failure* and *Acute Pericarditis. Acute heart failure* is a syndrome and its definition was based on the US and Canadian guidelines for the management of heart failure (25–26). It is characterized by typical symptoms including breathlessness, ankle swelling and fatigue that may be accompanied by signs such as elevated jugular venous pressure, pulmonary crackles and peripheral edema. *Acute pericarditis* was defined according to the 2015 European Society of Cardiology Guidelines for the diagnosis and management of pericardial diseases. It is diagnosed with at least 2 of the 4 following criteria: 1) pericarditis chest pain; 2) pericardial rub; 3) new widespread ST-elevation or PR depression on ECG; 4) pericardial effusion (new or worsening) on cardiac echocardiography (27).

A detailed description of the histopathological changes in SRC was prepared by an experienced pathologist (30). It reads as follows: Histopathological findings on kidney biopsy consistent with SRC which may include the following: small vessel (arcuate and interlobular arteries) changes predominate over glomerular alterations. Glomerular changes of thrombotic micrioangiopahty may be present, with acute changes including fibrin thrombi and endothelial swelling, RBC fragments and mesangiolysis, and chronic changes including double contours of the GBM. Nonspecific ischemic changes with corrugation of the GBM, and even segmental or global sclerosis of glomeruli may occur. Early vascular abnormalities include intimal accumulation of myxoid material, thrombosis, fibrinoid necrosis, fragmented RBCs, sometimes resulting in cortical necrosis. Narrowing and obliteration of the vascular lumen lead to glomerular ischemia. Juxtaglomerular apparatus (JGA) 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 acutely, and later interstitial fibrosis and tubular atrophy. Since none of these findings are specific for SRC, the pathological diagnosis must be supported by appropriate clinical and serological data.

Of note, as a result of the NGT and consultation with content experts, some items that reached consensus (eg. proteinuria) in the Delphi exercise were not retained in the core set while others that did not achieve consensus in the Delphi exercise (eg. thrombocytopenia < 100,000 platelets/mm3 and elevated serum lactate dehydrogenase as part of the definition for microangiopathic hemolytic anemia) were included in the final core set.

The final core set of items (and definitions) is presented in Table 5. It was approved by the participants at the NGT.

Finally, as a secondary objective of the NGT, a list of SRC mimickers was compiled and approved by the panel (Table 6). Mimickers of SRC are associated with acute kidney injury and share other clinical features with SRC (13,31). Excluding patients with these conditions will improve the specificity of the future classification criteria.

Discussion

In this study, we generated a core set of items to define SRC using consensus methodology. This core set includes 5 domains and 14 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 NGT. Thus, the 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 AKI, proteinuria is not part the KDIGO definition of AKI, and proteinuria would compromise 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 NGT 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, 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 addition, our core set includes target organ dysfunction and a detailed histopathological description of SRC.

In 2016, the UK Scleroderma Study Group proposed criteria for the diagnosis of SRC. The criteria were divided into categories: diagnostic criteria (essential) and supportive evidence (desirable) with blood pressure and AKI as the former, MAHA and thrombocytopenia, hypertensive retinopathy, hematuria, oliguria or anuria, renal biopsy consistent with SRC features and flash pulmonary edema as the latter. Discrepancies with our proposed criteria are found in the slightly modified cut-off values for blood pressure (150/85 mmHg versus 140/90 mmHg) and additionally, there is no noted rise in DBP, only $\geq$20 mmHg for SBP which is lower than $\geq$30 mmHg proposed in this study. Further, the UK criteria includes hematuria. Additionally, oliguria and flash pulmonary edema are proposed each as a stand-alone items whereas in our list, these items are grouped into the AKI and acute heart failure definition respectively (42). Our core set provides a more in depth detailed definition for each item, specifically for AKI, MAHAT and renal biopsy.

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 two sets of criteria identified 70/70 subjects with hypertensive, but only 2/5 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 histopathological description to define the term “findings consistent with SRC”.

This study has some limitations. First, only 99/216 experts invited to participate accepted and 77 (78%), 60 (61%) and 69 (70%) of these participated in Rounds 1-3 of the Delphi, 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. 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 may have rated validity based more on empirical, rather than on scientific evidence. Nevertheless, we provided the Delphi 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 that rheumatologists who participated in the Delphi, it became clear at the NGT 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 NGT. The Delphi provided a cost-effective approach to survey a larger sample of international experts working

anonymously. The NGT meeting allowed for a time-efficient, face-to-face discussion of a smaller sample of experts led by an experienced moderator.

Conclusion and future steps

In conclusion, using consensus methodology, we generated a core set of items to be used in the development of classification criteria for SRC. Two future phases of this research project are now in planning. The first, modeled on the *International Scleroderma Renal Crisis Survey (ISRCS)* (12), will be to recruit an inception SRC cohort and collect the items in the core set. A comparison cohort consisting of subjects with conditions that mimic SRC (Table 6) 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 (43) 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.

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Table 1. Characteristics of Participants in the Delphi exercise

		N (%)
Specialty	Rheumatologist	61 (85.9)
	Nephrologist	2 (2.8)
	Pathologist	1 (1.4)
	Internist	5 (7.0)
	Other	2 (2.8)
Years as a clinician	1-10 years	9 (12.7)
	11-20 years	22 (31.0)
	21-30 years	24 (33.8)
	>30 years	16 (22.5)
Unique scleroderma patients seen each year	1-30 patients	10 (14.1)
	31-60 patients	8 (11.3)
	61-100 patients	12 (16.9)
	>100 patients	41 (57.7)
New scleroderma renal crisis (SRC) patients seen each year	0 patients	4 (5.6)
	1-2 patients	45 (63.4)
	3-5 patients	16 (22.5)
	>6 patients	6 (8.5)
Returning SRC patients seen each year	0 patients	5 (7.0)
	1-5 patients	26 (36.6)
	6-10 patients	23 (32.4)
	10-15 patients	14 (19.7)
	>15 patients	3 (4.2)

Table 2. Geographical distribution of participants in the Delphi exercise

	N (%)
Argentina	1 (1.4)
Australia	6 (8.5)
Belgium	2 (2.8)
Canada	8 (11.3)
Denmark	1 (1.4)
France	3 (4.2)
Germany	2 (2.8)
Israel	1 (1.4)
Italy	5 (7.0)
Japan	3 (4.2)
Mexico	1 (1.4)
Netherlands	2 (2.8)
Spain	2 (2.8)
Switzerland	2 (2.8)
United Kingdom	6 (8.5)
United States of America	25 (35.2)

Table 3. Results from Rounds 2 and 3 of the Delphi exercise and consensus achieved after Round 3. Values indicate median values (inter-quartile range)

Criteria Category	Question		Round 2		Round 3		Consensus
			Scientific Validity	Feasibility	Scientific Validity	Feasibility	
Hypertension	New onset or deterioration of pre-existing hypertension, defined as any of the following:	Systolic blood pressure ≥ 140 mmHg	7(2)	8(2)	7(1)	8(1)	yes
		Diastolic blood pressure ≥ 90 mmHg	7(2)	8(1)	7(0.5)	8(1)	yes
		Rise in systolic blood pressure ≥ 30 mmHg	7(2)	8(1)	7(1)	8(1)	yes
		Rise in diastolic blood pressure ≥ 20 mmHg	7(2)	8(2)	7(1)	8(0)	yes
	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 measurements should be measured on at least 2 occasions		7(3)	8(1)	7(1)	8(1)	yes
Renal Insufficiency	Increase in serum creatinine ≥50% over baseline or, if no baseline available, serum creatinine ≥120% (or 1.2 times) the upper limit of normal for local laboratory (with measurement repeated if necessary to rule out lab error).		7(2)	8(2)	7(1)	8(1)	yes
Proteinuria	New proteinuria defined as ≥ 1+ (30-100 mg/dL range) by urine dipstick or worsening proteinuria defined as a ≥ 1 point increase in protein on urine (1+ to ≥ 2+, 2+ to ≥ 3+, etc).		5(2)	7(2)	5(1)	7(1)	no
	New proteinuria defined as ≥ 2+ (100-300 mg/dL range) by urine dipstick or worsening proteinuria defined as a ≥ 1 point increase in protein on urine (2+ to ≥ 3+, 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 urine dipstick or worsening hematuria defined as a a ≥ 1 point increase on urine dipstick (1+ to ≥ 2+, 2+ to ≥ 3+, etc).		6(3)	8(1)	6(1)	8(1)	no
	New hematuria defined as ≥ 2+ by urine dipstick or worsening hematuria defined as a ≥ 1 point increase on urine dipstick (2+ to ≥ 3+, 3+ to ≥ 4+, etc).		6(3)	8(1)	6(1)	8(1)	no
	New hematuria defined as ≥ 10 RBCs/HPF 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/mm3		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	MAHA defined as new or worsening anemia not due to other causes and supported by the presence of one of the following:	Schistocytes or other RBC fragments on blood smear.	8(1)	8(1)	8(0)	8(0)	yes
		Reticulocyte count above normal range for local laboratory.	7(3)	7(1)	7(1)	7(1)	yes
		Serum LDH and/or indirect bilirubin above normal ranges for local laboratory.	6(2)	8(2)	6(1)	8(1)	no
		Serum haptoglobin below normal range for local laboratory.	7(2)	8(2)	7(1)	8(1)	yes
	MAHA defined as new or worsening anemia not due to other causes and supported by the presence of at least two lab abnormalities (RBC fragments, elevated reticulocyte count, elevated serum LDH/indirect bilirubin, low haptoglobin).		8(1)	8(1)	8(0)	8(0)	yes
	A direct Coombs test should be documented to rule out autoimmune hemolytic anemia.		7(3)	7(2)	7(0)	7(1)	yes

Table 3. Results from the Delphi exercise - Continued

Criteria Category	Question	Round 2		Round 3		Consensus
		Scientific Validity	Feasibility	Scientific Validity	Feasibility	
Encephalopathy	Encephalopathy defined by the American Academy of Neurology 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 IV (papilledema) retinopathy, according to Keith-Wagener classification	7(3)	6(3)	7(1)	6(2)	no
Hyperreninemia	Elevation of 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 judgement.	6(2)	7(2)	6(1)	7(0)	no
	Presence of symptomatic pericardial effusion based on all available information and clinical judgement.	6(2)	6(2)	6(1)	6(1)	no
Abnormal kidney Biopsy	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
	Histopathological findings on kidney biopsy consistent with SRC 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, fibrinoid necrosis, sometimes resulting in cortical necrosis. Narrowing and obliteration of the vascular lumen lead to glomerular ischemia. Juxtaglomerular apparatus (JGA) 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 pathological diagnosis must be supported by appropriate clinical and serological data.	8(2)	6(3)	8(0)	6(2)	no

Table 4. Results from the Delphi exercise for questions pertaining to cut-offs

		Round 2	Round 3
What are the most appropriate cutoffs for high blood pressure? - Absolute SBP	140 mmHg	16	13
	150 mmHg	**16**	**40**
	160 mmHg	9	7
	170 mmHg	1	0
	180 mmHg	1	0
	Other	2	0
What are the most appropriate cutoffs for high blood pressure? - Absolute DBP	**90 mmHg**	**24**	**38**
	100 mmHg	18	21
	110 mmHg	1	1
	120 mmHg	0	0
	130 mmHg	0	0
	Other	2	0
What are the most appropriate cutoffs for high blood pressure? - Increase in SBP	10 mmHg	0	0
	20 mmHg	11	5
	30 mmHg	**33**	**55**
	40 mmHg	1	0
	Other	0	0
What are the most appropriate cutoffs for high blood pressure? - Increase in DBP	10 mmHg	6	3
	20 mmHg	**35**	**57**
	30 mmHg	4	0
	40 mmHg	0	0
	50 mmHg	0	0
	Other	0	0
What are the most appropriate frequency and intervals for repeated measurements?	Only once is enough	1	1
	2 times	**30**	**51**
	3 times	13	8
	4 times	0	0
	Other	1	0
What are the most appropriate frequency and intervals for repeated measurements?	**12 hours apart**	**29**	**45**
	24 hours apart	7	3
	48 hours apart	2	0
	72 hours apart	2	0
	1 week apart	0	0
	Other	5	12
What are the most appropriate cutoffs for increase in serum creatinine? - Increase above baseline	20%	2	0
	30%	7	7
	40%	7	6
	50%	**25**	**43**
	60%	1	1
	70%	0	1
	80%	0	0
	90%	0	0
	100% (doubling)	2	0
	Other	0	1
What are the most appropriate cutoffs for increase in serum creatinine? - Increase above upper limit of local laboratory	**120%**	**21**	**41**
	130%	7	7
	140%	3	3
	150%	10	6
	175%	0	0
	200%	2	0
	Other	1	2
What are the most appropriate cutoffs for new proteinuria? - Dipstick	1+	3	2
	2+	**40**	**56**
	3+	0	0
	4+	0	0
	Other	0	1

Table 4. Results from the Delphi exercise for questions pertaining to cut-offs - Continued

Questions		Round 2	Round 3
What are the most appropriate cutoffs for new proteinuria? - urine protein:creatinine ratio	≥ 0.15 g/day	3	2
	≥ 0.5 g/day	**28**	**57**
	≥ 1.0 g/day	10	0
	≥ 2.0 g/day	1	0
	Other	1	0
What are the most appropriate cutoffs for worsening proteinuria? - Dipstick	a ≥ 1 point increase	18	6
	a ≥ 2 point increase	**25**	**51**
	Other	0	2
What are the most appropriate cutoffs for worsening proteinuria? - urine protein:creatinine ratio	**Doubling**	**37**	**51**
	Tripling	4	1
	Quadrupling	0	0
	Other	2	6
What are the most appropriate cutoffs for new hematuria? - Dipstick	1+	4	3
	2+	**37**	**55**
	3+	2	0
	4+	0	0
	Other	0	1
What are the most appropriate cutoffs for new hematuria? - Microscopy	**≥ 10 RBCs/HPF**	**28**	**50**
	≥ 20 RBCs/HPF	9	6
	≥ 30 RBCs/HPF	4	0
	≥ 50 RBCs/HPF	1	1
	Other	1	2
What are the most appropriate cutoffs for worsening hematuria? - Dipstick	a ≥ 1 point increase	20	8
	a ≥ 2 point increase	**22**	**48**
	Other	1	3
What are the most appropriate cutoffs for worsening hematuria? - Microscopy	**doubling**	**34**	**50**
	tripling	7	2
	quadrupling	1	0
	Other	1	7
What is the most appropriate cutoff for thrombocytopenia? - Range from 50,000 to 140,000 platelets/mm3	50 000 platelets/mm3	1	1
	60 000 platelets/mm3	2	0
	70 000 platelets/mm3	2	0
	80 000 platelets/mm3	0	1
	90 000 platelets/mm3	1	3
	100 000 platelets/mm3	**29**	**47**
	110 000 platelets/mm3	0	2
	120 000 platelets/mm3	7	3
	130 000 platelets/mm3	1	0
	140 000 platelets/mm3	0	0
	Other	0	0

Table 5. Final core set of items to develop classification criteria for SRC

Domain	Item	
Blood pressure	Acute rise in blood pressure defined as any of the following:	SBP ≥ 140 mmHg DBP ≥ 90mmHg A rise in SBP ≥ 30 mmHg A rise in DBP ≥ 20 mmHg
	Blood pressure measurement should be taken twice separated by at least 5 min. If blood pressure readings are discordant, repeat readings should be obtained until 2 consistent readings are obtained.	
Kidney injury	AKI defined as any of the following:	Increase in serum creatinine by ≥ 26.5 umol/L (≥ 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/h for 6 hours
MAHAT	New or worsening anemia not due to other causes. Schistocytes or other RBC fragments on blood smear. Thrombocytopenia <= 100,000, confirmed by manual smear. Laboratory evidence of hemolysis, including elevated lactate dehydrogenase, reticulocytosis and/or low/absent haptoglobin A negative Coombs 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-elevation or PR depression on ECG; 4) pericardial effusion (new or worsening) on cardiac echocardiography.	
Histopathology	Histopathological findings on kidney biopsy consistent with SRC which may include the following: small vessel (arcuate and interlobular arteries) changes predominate over glomerular alterations. Glomerular changes of thrombotic micrioangiopahty may be present, with acute changes including fibrin thrombi and endothelial swelling, RBC fragments and mesangiolysis, and chronic changes including double contours of the GBM. Nonspecific ischemic changes with corrugation of the GBM, and even segmental or global sclerosis of glomeruli may occur. Early vascular abnormalities include intimal accumulation of myxoid material, thrombosis, fibrinoid necrosis, fragmented RBCs, sometimes resulting in cortical necrosis. Narrowing and obliteration of the vascular lumen lead to glomerular ischemia. Juxtaglomerular apparatus (JGA) 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 acutely, and later interstitial fibrosis and tubular atrophy. Since none of these findings are specific for SRC, the pathological diagnosis must be supported by appropriate clinical and serological data.	

Table 6. SRC mimickers and similarities and differences with SRC

ANCA-associated glomerulonephritis	Typically characterized by renal insufficiency and the presence of proteinuria but lacks MAHAT and hypertension (8)
Thrombotic thrombocytopenic purpura /hemolytic uremic syndrome	Characterized by MAHAT and renal failure, however, hypertension findings remain key for distinguishing SRC from such alternative complications (32)
Membranous nephropathy	Proteinuria and edema (33), hypertension (34)
Drug-induced nephropathies (e.g. cyclosporin A)	Can result in acute kidney injury (35)
Other vasculitides (e.g. polyarteritis nodosa, mixed cryoglobulinemia, Goodpasture syndrome)	Criteria for characterization of polyarteritis nodosa includes hypertension and increase blood creatinine levels (36,37)
Oxalate nephropathy	Associated with kidney injury and hypertension (38)
Renal artery stenosis	Accelerated hypertension present as well (3,31)
Membranoproliferative nephropathy	Can present with hematuria, proteinuria and hypertension (39)
Pre-renal causes (e.g. sepsis, dehydration, cardiac or pulmonary vascular involvement)	Can result in renal abnormalities (ie, increase in serum creatinine from dehydration or cardiac involvement) (35)
Isolated renal abnormalities	Such as proteinuria and hypertension alone or explained by alternative cause not associated with SRC (35)
Eclampsia	If SRC happens to occur during pregnancy due to elevated blood pressure, increased protein in urine, and organ dysfunction that may be present in a patient (40,41)

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