Test performance in systemic sclerosis: anti-centromere and anti-Scl-70 antibodies

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Authors' objectives
To determine the sensitivity and specificity of anti-centromere (ACA) and anti-Scl-70 (AS70) antibodies as diagnostic tests for systemic sclerosis (SSc).

Searching
MEDLINE was searched from 1966 to 1994 for English language papers; the bibliographies of the original papers and review articles retrieved were examined for additional studies. Exploded MeSH terms were used: ‘systemic sclerosis’, ‘circumscribed systemic sclerosis’, ‘antinuclear antibody’, ‘nuclear proteins’, ‘autoantibodies’, ‘autoantigens’ and ‘DNA-binding proteins’, ‘centromere’, ‘kinetochore’, ‘Scl-70’, ‘Scl-86’, ‘Sc195/100’ and ‘topoisomerase1’.

Study selection
Study designs of evaluations included in the review
Articles focusing on methodology or techniques were excluded. There were no further inclusion criteria relating to the study design.

Specific interventions included in the review
Article describing a method known to detect either ACA or AS70 antibodies were eligible for inclusion.

Reference standard test against which the new test was compared
The included articles were required to use an appropriate reference standard: identification of a cohort of patients with SSc. Articles where diagnosis was based on a positive antibody test were excluded.

Participants included in the review
The included articles were required to have both a diseased (SSc) and a non-diseased (any group of patients that did not have SSc) cohort of participants. Articles where the patient population was poorly characterised were excluded.

Outcomes assessed in the review
No inclusion criteria relating to the outcome measures were specified. The outcome measures reported by the review were the sensitivity and specificity.

How were decisions on the relevance of primary studies made?
Two independent authors selected the papers for the review.

Assessment of study quality
Validity was assessed using a published diagnostic test evaluation scale (see Other Publications of Related Interest) and 16 additional weighted criteria. These criteria included: adequacy of sample size, participant selection and characteristics, adequacy of description and appropriateness of index test and reference standard, treatment of uninterpretable results, and blinding. Overall quality scores were calculated for each article. Two independent authors assessed the papers for validity, with any discrepancies resolved independently by a third author.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. 2x2 tables, for both ACA and AS70 antibodies, were reconstructed for each included study, based on the reported sensitivity and specificity.
Methods of synthesis

How were the studies combined?
Combined overall measures of sensitivity were calculated for ACA and AS70 antibodies. Specificity measures were stratified based on four categories of non-SSc control group studies: nondiseased normals, first-degree relatives, non-SSc connective tissue disease controls, and other co-morbid diseases. In studies reporting mutually exclusive CREST (calcinosis, Raynaud's phenomenon, oesophageal dysmotility sclerodacty, and telangiectasis) or limited cutaneous (lcSSc) and diffuse cutaneous (dcSSc) subsets of SSc patients, the sensitivity for ACA and AS70 antibodies in lcSSc and dcSSc, respectively, and the specificity of each relative to the other SSc subset, were determined.

How were differences between studies investigated?
Differences between the studies were investigated through a subgroup analysis, based on the different subsets of SSc patients.

Results of the review
Thirty studies were included. There was no information on the characteristics of the primary studies included.

The Validity Quality Rating scores for the 30 studies ranged from 0.9 to 71 (standard deviation 16) on a scale from +100 to -100. The proportion of studies satisfying standards for each of the 16 evaluation criteria ranged from 19 to 100%.

ACA antibodies were found in 441 of the 1,379 SSc patients, representing a sensitivity of 32% (range: 17 to 56). When restricted to patients with lcSSc, sensitivity improved to 57% (range: 32 to 96). AS70 antibodies were found in 366 of the 1,074 patients, representing a sensitivity of 34% (range: 3 to 75). As with ACA, when limited to patients with dcSSc, sensitivity improved to 40% (range: 0 to 77). The combined overall sensitivity, i.e. the presence of either antibody, was 58% among 670 patients in which both antibodies were measured (30% had ACA, 29% had AS70 and 0.4% had both).

The specificity of ACA and AS70 antibodies was high, but varied with the control group. ACA and AS70 antibodies were present in 5 and 2%, respectively, of patients with other connective tissue diseases, but fewer than 1% of disease-free controls had either antibody present. The specificities of the antibodies in discriminating lcSSc from dcSSc were 92% (range: 71 to 100) for ACA in dcSSc patients and 83% (range: 56 to 100) for AS70 in lcSSc patients.

Authors’ conclusions
Both ACA and AS70 antibodies were highly specific as individual diagnostic tests in SSc. Each performed somewhat better as a discriminator of clinical subsets for patients in whom a diagnosis of SSc has already been established. Clinicians can rely on a positive test result as being specific in the detection of disease, but 40% of SSc patients are likely to have neither antibody present; in addition, a negative result does not exclude diagnosis. The clinician is reminded that in patients who present with a group of signs and symptoms that suggest SSc, the low sensitivity of these assays means that their use should be considered subordinate to clinical features in diagnosing and classifying SSc.

CRD commentary
The review addressed a clearly stated question, and appropriate inclusion criteria were reasonably well defined. The restriction of the literature search to English language articles indexed in MEDLINE means that relevant articles may well have been overlooked. In addition, publication bias was not discussed and no attempt was made to identify unpublished data. The review was severely weakened by the absence of certain key information, specifically, details of the primary studies included within the review, the patients’ characteristics, and a discussion of the methods of data extraction and analysis. In the absence of either details of the included primary studies or any examination of heterogeneity, it is difficult to judge whether the pooling of these studies was appropriate at all. Further, assuming that the pooling of the primary studies was a reasonable strategy, the lack of any detail on the methods of analysis make any assessment of the appropriateness of the methodology impossible.
The authors' conclusions, whilst generally cautious, seem somewhat over optimistic with respect to the possibility of using antibody testing to rule in disease, given the ranges in specificity reported.

**Implications of the review for practice and research**

Practice: The authors stated that the measurement of ACA or AS70 antibodies should be considered secondary to clinical features when making a diagnosis of SSc. Research: The authors did not state any implications for further research.

**Bibliographic details**


**PubMedID**

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**Other publications of related interest**


**Indexing Status**

Subject indexing assigned by NLM

**MeSH**

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.