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Recommendations and metaanalyses

# Anti-citrullinated peptides antibodies in systemic sclerosis: Meta-analysis of frequency and meaning

Guillaume Laustriat[a], Adeline Ruyssen-Witrand[a,b], Arnaud Constantin[a,c], Thomas Barnetche[d], Daniel Adoue[a,e], Alain Cantagrel[a,c], Yannick Degboé[a,c,*]

[a] Centre de rhumatologie, hôpital Pierre-Paul-Riquet, CHU de Toulouse, place du Dr-Baylac, TSA 40 031, 31059 Toulouse cedex 9, France
[b] Pharmaco-épidémiologie, évaluation de l'utilisation et du risque médicamenteux, Inserm UMR 1027, faculté de médecine, 37, allées Jules-Guesde, 31000 Toulouse, France
[c] CPTP, Inserm UMR 1043, CHU Purpan, BP 3028, 31024 Toulouse cedex 3, France
[d] Service de rhumatologie, FHU Acronim, CHU Pellegrin, place Amélie-Raba-Léon, 33000 Bordeaux, France
[e] Service d'immunologie clinique, IUCT, oncopole, CHU de Toulouse, 1, avenue Irène-Joliot-Curie, 31059 Toulouse cedex 9, France

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ABSTRACT

*Objectives:* Diagnosis of systemic sclerosis (SSc) is partially determined by the presence of specific auto-antibodies often associated with specific clinical features. Recent studies report the presence of ACPA in SSc. We aimed to evaluate the prevalence of ACPA in SSc and to assess their influence on clinical presentation of SSc.
*Methods:* A systematic literature search was performed using PubMed and Cochrane databases' publications between 1999 and March 2017. Search terms were: "systemic sclerosis [MeSH] AND (ACPA OR anti-CCP OR rheumatoid factor OR cohort OR value diagnostic)". In a first step, we selected cohorts with > 50 SSc patients with ACPA identification, for ACPA frequency determination. In a second step, we included studies that analysed clinical profiles according to ACPA status. Meta-analyses were performed when at least two studies were available.
*Results:* First, we identified 13 observational studies with a total of 1231 SSc patients. The mean prevalence of ACPA in SSc was 9.2%. Secondly, we identified nine studies reporting clinical aspects according to ACPA status. Our meta-analyses showed a significant association between ACPA positivity and the presence of arthritis (odds ratio (*OR*) = 22.48 [10.71–47.21]), joint erosions seen on X-rays (*OR* = 14.79 [6.38–34.28]), pulmonary fibrosis (*OR* = 2.75 [1.21–6.24]), oesophagus involvement (*OR* = 2.72 [1.05–7.07]), and diffuse skin involvement (*OR* = 2.21 [1.21–4.03]).
*Conclusions:* The prevalence of ACPA in scleroderma is 9.2%. Our meta-analysis shows an increased risk for erosive arthritis, pulmonary fibrosis, oesophagus involvement and diffuse skin involvement, in patients with ACPA-positive SSc. ACPA should be systematically included in SSc assessment.


## 1. Introduction

Systemic sclerosis (SSc) is a rare chronic immune disorder of unknown origin, more frequently observed in women, and is characterised by vascular damage, extensive fibrosis and immune activation. SSc presents with considerable clinical heterogeneity. Among the types of cutaneous sclerosis, two major subsets of systemic sclerosis are distinguished:

- limited cutaneous SSc;
- diffuse cutaneous SSc.

Apart from skin lesions, different organs can be involved associated with the severity of the disease:

- lung fibrosis;
- pulmonary arterial hypertension;
- digestive lesions;
- erosive or non-erosive arthritis;
- renal crisis;
- neurological disorders [1].

* Corresponding author. Centre de rhumatologie, hôpitaux de Toulouse, hôpital Pierre-Paul-Riquet, 1, place du Dr-Baylac, 31059 Toulouse cedex 9, France.
*E-mail address:* degboe.y@chu-toulouse.fr (Y. Degboé).

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Diagnosis of SSc is generally made using two main sets of classification criteria. The first is the classification of the American College of Rheumatology, published in 1980, based on clinical symptoms:

- sclerodactyly;
- digital ulcers;
- pulmonary fibrosis [2].

The second is the classification proposed by LeRoy et al., in which capillaroscopy and immunological features have been included [3]. Autoantibodies against a variety of self-antigens have been detected in SSc patients. Antinuclear antibodies (ANA) are present in more than 90% of SSc patients. Among these ANA, some are specific, such as anti-topoisomerase I, anticentromere or anti-RNA polymerase I, II and III antibodies and so are useful in diagnosis. Autoantibodies other than ANA can be present and associated with particular clinical manifestations:

- anti-phospholipid antibodies with vascular occlusion;
- antibodies from the anti-phosphatidyl-serine-prothrombin complex with peripheral ischemia;
- autoantibodies against endothelial cell antigens with digital scars or ulcers [4].

Anti-citrullinated peptide antibodies (ACPA) selectively recognize citrullinated self-proteins. Citrullination is the posttranslational modification of proteins in which a positively charged peptidyl-arginine residue is converted into a neutral peptidyl-citrulline by calcium-dependent peptidyl-arginine deiminase. The result of citrullination is to change the affinity of peptide binding and to alter the presentation of self-peptides to CD4+ T cells, mounting thus an autoimmune reaction in a favourable HLA-DR context, producing ACPA [5]. ACPA provide the most relevant biomarker for RA in clinical practice and are detected in 50–75% of RA patients, with a very high specificity [6]. However, they can be detected less frequently in other diseases, such as psoriatic arthritis, lupus or scleroderma [7].

In the present work, we conducted a systematic analysis of the literature to establish the frequency with which ACPA are found in the course of SSc. We then assessed if ACPA could be a biomarker (as autoantibodies are) for specific clinical presentations of SSc.

## 2. Methods

This article has been written in compliance with the PRISMA criteria.

### 2.1. Identification of articles

A search was conducted using PubMed Medline and Cochrane databases and was restricted to English, French, Italian and Spanish language articles published between 1999 (first studies in which ACPA was assessed in routine practice) and 1st March 2017. We used the terms "Systemic Sclerosis [MeSH Term] AND (value diagnostic OR cohorts OR ACPA OR anti-CCP OR rheumatoid factor OR arthritis)". We excluded editorials, reviews and case-reports. A manual search completed the selection process. To determine the frequency of ACPA during SSc, we selected observational studies that included more than 50 patients to limit the risk of selection bias. To assess the association between ACPA and the clinical aspects of SSc, we selected observational studies that described the clinical manifestations of SSc according to ACPA status.

After duplicates were removed, two independent authors (GL and YD) reviewed all titles and abstracts and then full-text of the potentially relevant articles. Disagreements were resolved by a third party (AC). We chose to use the validated Cochrane Risk of Bias Tool for quality assessment of the selected studies at outcome level, even though it was designed to evaluate randomised trials (Table S1) [8].

### 2.2. Data acquisition

The types of data to be collected were established prior to selecting the published literature. Joint involvement was defined by:

- the detection of arthralgia or arthritis by clinical examination;
- lung fibrosis was defined by the presence of bi-basal fibrosis on CT-scan;
- pulmonary arterial hypertension was detected by echography;
- oesophagus involvement was defined in the case of hypomobility shown by barium radiography;
- cardiac involvement was defined by the presence of pericarditis (echography), or diastolic dysfunction (echography), or right ventricular hypertrophy (electrocardiography (ECG)), or the presence of reduced left ventricular ejection fraction (echography), or arrhythmia (ECG), or conduction disturbance (ECG).

### 2.3. Statistical analyses

When possible, the risk of a particular clinical manifestation as a result of positive ACPA was evaluated in a meta-analysis using the inverse-of-variance method with a hypothesis of homogeneity between the selected studies. Statistical heterogeneity amongst the included studies was assessed using the Cochrane Q test ($\chi^2$), using a significance level of 5% and carrying forward the value of the $I^2$ statistic for which important values were associated with the level of significant heterogeneity. Further methodological data are provided in [Appendix A, Table S1–S2 and Fig. S1; See the supplementary material associated with this article online].

## 3. Results

### 3.1. Prevalence of ACPA in systemic sclerosis

We selected 13 reports where cohorts included >50 patients with SSc [9–21], giving a total of 1231 patients (Fig. 1, Table 1, Table S2). In 11 of these 13 studies, results for RF were also specified [9–17,19,20]. Diagnosis of SSc was done according 1980 ACR criteria [2] for five studies [13,14,17,19,20] and the criteria of LeRoy et al. [3] for the other four studies [9,10,12,15]. The work by Wu et al. included only patients with CREST syndrome [21]. In the report by Morita et al., patients fulfilled the Japanese criteria derived from ACR criteria [16]. In two other publications, we did not find the criteria used to diagnose SSc [11,18].

The mean age of patients included in the different cohorts varied between 48.0 and 58.7 years. The mean duration of disease was $5.0 \pm 11.3$ years. The methods used to measure ACPA differed between studies: i.e. anti-CCP1 in one study, anti-CCP2 and anti-CCP3 in three studies each, anti-filaggrin in one study, anti-CCP ELISA without any other information in five studies. RF was determined in 11 reports using ELISA or nephelemetry. The frequency of ACPA in the 13 articles varied from 4.1 [11] to 28.8% [21]. For all 13 merged publications, the presence of positive ACPA was reported in 113 (9.2%) of the 1231 patients with SSc. Overall, RF was positive for 323 (29.3%) of the 1103 patients.

### 3.2. Clinical characteristics of positive-ACPA systemic sclerosis

We found nine studies that had clinical manifestations detailed enough to be analysed in relationship to positive ACPA (Fig. 1,

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