Defining anti-synthetase syndrome: a systematic literature review


Abstract

Objective

Anti-synthetase syndrome (ASSD) is a heterogeneous autoimmune disease characterised by multi-system involvement with a wide variety of manifestations. Validated classification criteria are necessary to improve recognition and prevent misclassification, especially given the lack of reliable and standardised autoantibody testing. We systematically reviewed the literature to analyse proposed ASSD criteria, characteristics, and diagnostic performance.

Methods

We searched PubMed and Embase databases (01/01/1984 to 06/11/2018) and the ACR and EULAR meeting abstracts (2017-2018). Sensitivities, specificities, positive, negative likelihood ratios and risk of bias were calculated for ASSD criteria and key variables reported in the literature. We performed meta-analysis when appropriate.

Results

We retrieved 4,358 studies. We found 85 proposed ASSD criteria from a total of 82 studies. All but one study included anti-synthetase autoantibody (ARS) positivity in the ASSD criteria. Most studies required only one ASSD feature plus anti-ARS to define ASSD (n=64, 78%), whereas 16 studies required more than one ASSD variable plus anti-ARS. The only criteria not including anti-ARS positivity required 5 ASSD clinical features. We found limited data and wide variability in the diagnostic performance of each variable and definition proposed in the literature. Given these limitations we only meta-analysed the performance of individual muscle biopsy and clinical variables in diagnosing ASSD, which performed poorly.

Conclusion

The current ASSD criteria include a variety of serological, clinical, and histological features with wide variability amongst proposed definitions and the performance of these definitions has not been tested. This systematic literature review suggests the need for additional data and consensus-driven classification criteria for ASSD.

Key words

anti-synthetase syndrome, systematic literature review, diagnosis
Introduction

Anti-synthetase syndrome (ASSD) is a rare and heterogeneous systemic autoimmune disease (SAID) characterised by the positivity of anti-aminocyl-tRNA synthetase (anti-ARS) autoantibodies, including anti-Jo-1, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ, anti-KS, anti-Zo, anti-YRS/HA and by the occurrence of a broad spectrum of clinical features involving many organs, including the muscle, lung, joints and skin (1-3).

ASSD was defined as a distinct clinical entity for the first time in 1990 by Marguerie et al. as the presence of idiopathic inflammatory myositis, interstitial lung disease (ILD) and other clinical manifestations such as arthritis, Raynaud’s phenomenon (RP), keratoconjunctivitis sicca, and subcutaneous calcinosis in patients with anti-ARS autoantibodies (4). Since then, ASSD has been considered a subtype of idiopathic inflammatory myopathy (IIM) due to being closely associated with myositis and myositis associated ILD, arthritis, and other clinical features (5). The first criteria sets for the diagnosis of ASSD, based on expert opinion, were proposed in 2010 by Connors et al. (2). A subsequent definition was proposed in 2011 by Solomon et al. (6), and in 2015 by Lega et al. (7) (Table I). The presence of anti-ARS autoantibodies was mandatory for an ASSD diagnosis in all these criteria sets. In recent years, several studies analysed the clinical and prognostic heterogeneity among cohorts of patients with different anti-ARS autoantibodies with highly variable results (8-15).

Despite the quite unique clinical phenotypes associated with anti-ARS autoantibodies (16-22) and few proposed definitions, ASSD is not universally recognised as an autonomous and established disease entity. Moreover, anti-ARS autoantibodies are not universally considered to be a diagnostic marker of this syndrome, as demonstrated by the classification criteria for both IIM (23) and interstitial pneumonia with autoimmune features (IPAF) (24), that may lead to misclassification of patients positive for anti-ARS antibodies, as polymyositis or IPAF, and not ASSD specifically. Moreover, the results of many commercial assays used to detect anti-ARS autoantibodies are limited by a high rate of false positive or negative results, particularly in cases of weak positivity or low pre-test likelihood (25-27). Similar to most classification criteria in rheumatic disease, ASSD classification criteria should also require some combination of characteristic clinical features and/or serological markers with definite and probable thresholds.

The lack of a data driven and validated set of classification criteria for ASSD may lead to under-recognition and misclassification of this syndrome which is associated with high mortality and morbidity. An effort to overcome these limitations has led to the ACR/EULAR Classification of Anti-Synthetase Syndrome (CLASS) project with the goal to develop and validate a data and consensus-driven classification criteria set for ASSD using clinical and/or serological features. In this study, we performed a systematic literature review of the available definitions and unique variables of ASSD which could be evaluated as candidate definitions and variables for the development of classification criteria.

Material and methods

Two research questions were identified (Q1: How is ASSD defined in the literature? Q2: What is the diagnostic performance of the definition?). The population, intervention, comparison, outcomes and study type (PICOs) for inclusion were predetermined (Supplementary Table S1), following the Preferred Reporting Items for Systematic Literature Reviews (SLR) and Meta-analyses (PRISMA) guidelines (28). A protocol for the SLR was circulated among authors, although not registered.

Literature search

PubMed and Embase were searched from January 1, 1984 (when anti-ARS autoantibodies were first described) to November 6, 2018, following the strategy derived from PICOs (Supplementary Table S2). Abstracts from the EULAR and ACR 2017 and 2018 meetings, as well as references within the included studies, were hand-searched.
Articles in English, French, Spanish and Italian were included. No restriction based on quality was applied. All references were transferred into a reference manager software and duplicates were eliminated.

**Study selections**

Two independent reviewers (S.F.K. and G.Z.) screened the titles and abstracts following the criteria defined by the PICO.s. Papers were considered for full-text review when the two reviewers agreed that patients with ASSD were included. Subsequently, the full-text review selected only studies in which an explicit definition of ASSD was provided. Reasons for exclusion were standardised, prioritised, and specified for every excluded study. Disagreements about inclusion/exclusion or reason for exclusion were resolved by a third reviewer (G.S.).

**Data extraction and quality assessment**

We extracted the variables used to define ASSD (clinical, serological, and histological features) into pre-specified forms, and information about study design, sample number, and follow-up duration. We collected the number of the studies reporting each variable used to define ASSD, alone or in combination with others. For studies answering both Q1 and Q2, we considered the variables used to identify ASSD as the definition given by the author (answering Q1), while the diagnostic performances of other variables were tested against this definition. To assess the diagnostic accuracy, 2x2 tables were made when possible and sensitivity, specificity, likelihood ratios with 95% CIs were calculated.

For Q2, when the accuracy of a variable was evaluated by at least by 2 studies, sensitivities and specificities were presented as forest plots and sensitivity/specificity graphs. When the performance of a variable was assessed in at least four homogeneous studies, meta-analysis for data synthesis was conducted, using STATA (Stata Statistical Software: Release 11. College Station, TX: StataCorp LP). The results of each study were presented in the summary of findings tables.

The methodological quality and the risk of bias were estimated with different tools depending on study design: ROBINS (29) for systematic literature reviews, QUADAS-2 (30) for diagnostic accuracy studies, and Newcastle-Ottawa scale (31) for observational studies.

**Results**

**Study selection**

After the exclusion of duplicates, 4358 studies were retrieved, and the full text
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A total of 82 studies were included. Most studies (79 out of 82) provided a single definition of ASSD. Three studies provided two definitions (3, 12, 32) for a total of 85 definitions. The complete list of variables retrieved is displayed in Figure 2.

In every included study, the presence of anti-ARS autoantibodies was used to define ASSD. Almost half of the studies used more than one (median of only three) anti-ARS autoantibody in their analysis (44 studies, 54%), while 37 only one anti-ARS autoantibody (25 anti-Jo-1, four anti-PL-12, four anti-PL-7, three anti-EJ, and one anti-KS).

In only two studies, the presence of anti-ARS autoantibodies was sufficient to define ASSD (33, 34), whereas only one study defined ASSD without including anti-ARS positivity. (32).

Most studies required only one variable in association with anti-ARS autoantibodies to define ASSD (64 studies, 78%), thus fitting Connor’s criteria for ASSD.

Fig. 2. List of variables used to define ASSD.

ARS-Ab: anti aminoacyl-RNA-synthetase autoantibodies; ILD: interstitial lung disease; HRCT: high resolution computed tomography; NSIP: non-specific idiopathic pneumonia; UIP: usual interstitial pneumonia; GGO: ground glass opacities; LIP: lymphoid interstitial pneumonia; PFT: pulmonary function tests; EMG: electromyography; CPK: creatine phosphokinase; DM: dermatomyositis; PM: polymyositis; MRI: magnetic resonance imaging; MHC: major histocompatibility complex.

Fig. 3. Available definitions of anti-synthetase syndrome, based on the combination of autoantibodies and other variables. ARS-Ab: anti-synthetase autoantibodies; CTD: connective tissue disease.

of 375 was assessed to define eligibility. Among them, 77 met the criteria for inclusion. Three additional studies were included from the 2017 and 2018 EULAR abstracts and two from the hand search. The selection process is shown in Figure 1. Seventy-two studies were included only in Q1, and ten in both Q1 and Q2.
ASSD. The variable was myositis in 30 studies (10, 32, 35-61), ILD in 14 (3, 62-74), and arthritis in one (75). The remaining 19 studies required one of the following features: myositis, ILD, arthritis, fever, skin rash or mechanic’s hands, and RP (12, 76-93). Among the remaining definitions, 16 studies defined ASSD as the presence of more than one variable associated with anti-ARS positivity (11, 12, 94-107). In two studies, ASSD was defined as having a connective tissue disease (CTD) diagnosis and simultaneous positive anti-ARS (3, 108). The only definition that did not encompass anti-ARS positivity required all five clinical features (myositis, ILD, arthritis, RP and mechanic’s hands) to define ASSD (32).

The frequency of use for each variable, alone or in combination with others, is reported in Figure 3 and Table II. Among the features of the clinical triad of ASSD, myositis was the most frequently used (64 studies) (10-12, 32, 35-61, 76-107, 109), followed by ILD (49 studies) (3, 11, 12, 32, 62-74, 76-107) and arthritis (26 studies) (11, 12, 32, 75-77, 79, 80, 83-90, 93-101, 104).

Interestingly, the presence of myositis was defined predominantly as a combination of features, often fulfilling Bohan and Peter’s criteria (31 studies). However, 21 studies did not report how myositis was defined. The remaining 13 definitions were obtained by a combination of muscle enzyme elevation (10 studies), electromyographic alterations (9 studies), muscle weakness (8 studies), and MRI alterations (2 studies). One study defined myositis using a single variable, muscle biopsy (61).

Nine studies used muscle biopsy findings for ASSD definition (41,55,61,76,83,86-88,90). Details of histological findings were available only in four papers. In particular, perifascicular atrophy and diffuse necrosis were the most used variables. Supplementary table S3 includes the list of all muscle biopsy variables. ILD was mainly defined by high resolution computed tomography (HRCT) (39/49 studies), alone (15 studies), or in combination with pulmonary function tests (PFTs) (21 studies) or symptoms (three studies). ILD was not clearly defined in five studies. In four studies, ILD was defined by chest x-ray abnormalities and PFTs or by the presence of dyspnea and acute respiratory failure (two studies each). Lung biopsy, mostly in combination with other variables, was performed in seven studies. Among the 39 studies using HRCT, seven did not report any details about radiographic features or patterns. Supplementary Fig. S1 demonstrates the list of HRCT findings and patterns used to define ILD.

HRCT findings were reported in 21 studies. Ground-glass opacities (GGO) were included in all studies. Reticulation was reported in 17 studies, parenchymal consolidation in 14, honeycombing in 11, traction bronchiectasis in 10, and septal thickening in seven. Only 16 studies reported the ILD pattern. Among these, 16 reported non-specific interstitial pneumonia (NSIP), 14 organising pneumonia (OP), 11 usual interstitial pneumonia (UIP), and six overlaps between NSIP and OP.

Among the 26 studies that included the articular involvement, ten provided no details on how this was defined, whereas six studies defined joint symptoms as the presence of either arthritis or arthralgia, and nine studies required joint swelling. Morning stiffness was considered a sufficient criterion in one study. Polyarticular involvement was required in four studies. Other clinical findings were used to define ASSD in only a smaller number of studies. Only 14 studies used skin manifestations (mechanic’s hands, Gottron papules, heliotrope rash) as part of the definition (11, 12, 32, 84, 85, 88, 94-98, 100, 101, 104). We noted similar observations for RP (13 studies) (11, 32, 75-77, 79, 80, 83-90, 93-101, 104).

### Table II. Frequency of variables used to define anti-synthetase syndrome.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Variable alone (exclusive)</th>
<th>Variable alone (not exclusive)</th>
<th>Variable in association with others</th>
<th>Total (Total definitions n=85)</th>
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</thead>
<tbody>
<tr>
<td>Anti-synthetase autoantibodies</td>
<td>Anti-Jo1 0 0 0 67</td>
<td>Anti-PL12 0 0 0 46</td>
<td>Anti-PL7 0 0 0 40</td>
<td>Anti-EJ 0 0 0 23</td>
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<tr>
<td></td>
<td>Anti-OJ 0 0 0 16</td>
<td>Anti-KS 0 0 0 10</td>
<td>Anti-Zo 0 0 0 1</td>
<td></td>
</tr>
<tr>
<td>Myositis</td>
<td>Overall definitions</td>
<td>30 19 16 65</td>
<td>31</td>
<td>10</td>
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<td></td>
<td>DM/PM Bohan and Peter</td>
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<td>9</td>
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<td></td>
<td>CPK</td>
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<td></td>
<td>EMG</td>
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<tr>
<td></td>
<td>Biopsy</td>
<td></td>
<td>2</td>
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<td></td>
<td>Weakness</td>
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<td></td>
<td>Aldolase</td>
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<td></td>
<td>MRI</td>
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<td></td>
<td>Not defined/Other definitions</td>
<td></td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>ILD</td>
<td>Overall definitions</td>
<td>14 19 16 49</td>
<td>39</td>
<td>23</td>
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<tr>
<td></td>
<td>HRCT</td>
<td></td>
<td>7</td>
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<td>6</td>
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<td></td>
<td>Biopsy</td>
<td></td>
<td>4</td>
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<tr>
<td></td>
<td>Clinical</td>
<td></td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Other clinical manifestations</td>
<td>Arthritis/arthralgia 1 14 11 26</td>
<td>Raynaud’s phenomenon 0 3 10 13</td>
<td>Skin manifestations 0 4 10 14</td>
<td>Fever 0 2 5 7</td>
</tr>
<tr>
<td></td>
<td>Mechanic’s hands 0 3 8 11</td>
<td>Sclerodactyly 0 0 2 2</td>
<td></td>
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</tr>
</tbody>
</table>

*exclusive: the variable was considered sufficient and necessary for ASSD diagnosis; **not exclusive: the variable was sufficient but not necessary to make the diagnosis.

EMG: electromyography; CPK: creatine phosphokinase; DM: dermatomyositis; PM: polymyositis; MRI: magnetic resonance imaging; HRCT: high resolution computed tomography; PFT: pulmonary function tests.
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Perifascicular atrophy/necrosis

Study | N | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI)
--- | --- | --- | --- | --- | --- | --- | --- | --- | ---
Aouizerate | 50 | 15 | 9 | 18 | 3 | 0.45 [0.28, 0.64] | 0.47 [0.23, 0.72] | --- | ---
Cerbelli | 19 | 8 | 3 | 4 | 4 | 0.67 [0.35, 0.90] | 0.57 [0.18, 0.90] | --- | ---
Mescam-Mancini | 82 | 12 | 17 | 8 | 4 | 0.63 [0.38, 0.84] | 0.71 [0.59, 0.82] | --- | ---
Moazzafar | 48 | 11 | 27 | 0 | 10 | 1.00 [0.72, 1.00] | 0.27 [0.14, 0.44] | --- | ---
Pinal-Fernandez | 98 | 12 | 38 | 8 | 40 | 0.60 [0.36, 0.81] | 0.51 [0.40, 0.63] | --- | ---
Uruha | 108 | 6 | 33 | 24 | 45 | 0.20 [0.08, 0.39] | 0.58 [0.46, 0.69] | --- | ---

Perimysial fragmentation

Study | N | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI)
--- | --- | --- | --- | --- | --- | --- | --- | --- | ---
Aouizerate | 50 | 26 | 14 | 7 | 3 | 0.73 [0.61, 0.91] | 0.18 [0.00, 0.43] | --- | ---
Cerbelli | 18 | 9 | 5 | 2 | 2 | 0.82 [0.48, 0.98] | 0.29 [0.04, 0.71] | --- | ---
Mescam-Mancini | 82 | 14 | 17 | 5 | 46 | 0.74 [0.49, 0.91] | 0.73 [0.60, 0.83] | --- | ---

Perimysial inflammation

Study | N | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI)
--- | --- | --- | --- | --- | --- | --- | --- | --- | ---
Cerbelli | 18 | 6 | 6 | 5 | 1 | 0.55 [0.23, 0.83] | 0.14 [0.00, 0.58] | --- | ---
Mescam-Mancini | 82 | 19 | 59 | 0 | 24 | 1.00 [0.82, 1.00] | 0.38 [0.26, 0.51] | --- | ---

Diffuse myofiber necrosis

Study | N | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI)
--- | --- | --- | --- | --- | --- | --- | --- | --- | ---
Cerbelli | 19 | 8 | 3 | 4 | 4 | 0.67 [0.35, 0.90] | 0.57 [0.18, 0.90] | --- | ---
Mescam-Mancini | 82 | 17 | 52 | 2 | 11 | 0.89 [0.67, 0.99] | 0.17 [0.09, 0.29] | --- | ---
Pinal-Fernandez | 98 | 2 | 13 | 18 | 65 | 0.10 [0.01, 0.32] | 0.83 [0.73, 0.91] | --- | ---

Perifascicular C5b-9 deposition

Study | N | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI)
--- | --- | --- | --- | --- | --- | --- | --- | --- | ---
Cerbelli | 18 | 8 | 6 | 3 | 1 | 0.73 [0.39, 0.94] | 0.14 [0.00, 0.58] | --- | ---
Mescam-Mancini | 82 | 5 | 51 | 14 | 12 | 0.26 [0.09, 0.51] | 0.19 [0.10, 0.31] | --- | ---

Sarcolemmal C5b-9 deposition on non-necrotic fibres

Study | N | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI)
--- | --- | --- | --- | --- | --- | --- | --- | --- | ---
Aouizerate | 48 | 17 | 3 | 15 | 13 | 0.53 [0.35, 0.71] | 0.81 [0.54, 0.96] | --- | ---
Mescam-Mancini | 82 | 16 | 47 | 3 | 16 | 0.84 [0.60, 0.97] | 0.25 [0.15, 0.38] | --- | ---

Mitochondrial disfunction

Study | N | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI)
--- | --- | --- | --- | --- | --- | --- | --- | --- | ---
Cerbelli | 18 | 0 | 7 | 11 | 0 | 0.00 [0.00, 0.28] | 0.00 [0.00, 0.41] | --- | ---
Pinal-Fernandez | 98 | 4 | 23 | 16 | 55 | 0.20 [0.06, 0.44] | 0.71 [0.59, 0.80] | --- | ---

HLA ABC expression

Study | N | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI)
--- | --- | --- | --- | --- | --- | --- | --- | --- | ---
Aouizerate | 60 | 31 | 17 | 2 | 10 | 0.94 [0.80, 0.99] | 0.37 [0.19, 0.58] | --- | ---
Mescam-Mancini | 82 | 15 | 18 | 4 | 45 | 0.79 [0.54, 0.94] | 0.71 [0.59, 0.82] | --- | ---

Perivascular inflammation

Study | N | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI)
--- | --- | --- | --- | --- | --- | --- | --- | --- | ---
Moazzafar | 71 | 2 | 10 | 31 | 30 | 0.03 [0.00, 0.16] | 0.75 [0.59, 0.87] | --- | ---
Pinal-Fernandez | 91 | 9 | 35 | 4 | 47 | 0.69 [0.38, 0.90] | 0.57 [0.46, 0.68] | --- | ---

Fig. 4. Studies included in Q2, assessing the performance of muscle biopsy variables to diagnose ASSD.

Q2: What is the accuracy of the different definitions for diagnosing ASSD?

Ten studies were included for Q2. As a pre-specified inclusion criterion, all studies tested accuracy against the reference standard of a clinical diagnosis of ASSD, based on the presence of anti-ARS plus one or more typical clinical manifestations. In one study, anti-ARS was defined as the presence of anti-ARS autoantibodies and CTD diagnosis, characterised as IIM, SSC, SLE, RA, UCTD or MCTD (3). Supplementary Table S5 includes results of these studies. The majority were cohort studies (49, 54-56, 58, 59, 62, 92), except for one systematic review with meta-analysis (3) and one diagnostic accuracy study (57).

The tested variables mostly derived from muscle biopsy (7/10 studies). The only two variables assessed in at least four studies were perifascicular necrosis/atrophy and perimysial connective tissue fragmentation. Meta-analysis was performed only for the perifascicular necrosis/atrophy (six studies) (49, 54, 56-59), showing a pooled sensitivity of 0.54 (95%CI 0.3-0.76) and a pooled specificity of 0.55 (95%CI 0.43-0.66).
The pooled positive likelihood ratio (LR+) was 1.21 (95% CI: 0.68-2.14) and the pooled negative likelihood ratio (LR-) was 0.83 (95% CI: 0.44-1.55) (Supplementary Fig. S3). It was not possible to perform a meta-analysis for perimysial connective tissue fragmentation due to model instability.

We were only able to test the diagnostic accuracy of individual variables rather than the accuracy of the provided definitions of ASSD due to the inherent nature of these studies. We extracted data on accuracy for muscle biopsy variables. Perifascicular atrophy/necrosis demonstrated a highly variable sensitivity, from 0.2 to 1, and a similar specificity, from 0.27 to 0.71 (49, 54, 56-59). Perimysial fragmentation showed a relatively high sensitivity (0.74-1) and a variable specificity (0.18-0.73) (49, 54, 57, 59). Diffuse myofibre necrosis also showed highly variable sensitivity (0.1-0.89) and specificity from 0.17 to 0.83 (49, 56, 57). Perimysial inflammation showed a sensitivity from 0.55 to 1 and a specificity from 0.14 to 0.46 (49, 57, 59). Perimysial distribution of C5b-9 deposition on non-necrotic fibres was assessed in two studies (54, 57) and showed a sensitivity from 0.53 to 0.84 and a specificity from 0.25 to 0.81. The perifascicular distribution of C5b-9 was assessed in two studies (49, 57) and displayed a sensitivity from 0.26 to 0.72 and a specificity from 0.14 to 0.19. Mitochondrial dysfunction showed a sensitivity from 0 to 0.2 and a specificity from 0 to 0.71 (49, 56, 59). HLA-ABC expression had a sensitivity from 0.79 to 0.94 and a specificity from 0.37 to 0.71 (54, 57). Results are summarised in Figure 4.

The biopsy variable with the best performance was the presence of nuclear actin inclusion, which discriminated ASSD from other myositis subsets with good sensitivity and specificity (0.8 and 1, respectively) (55). HLA-DR deposition was also able to discriminate ASSD from DM in one study, showing a sensitivity of 0.84 and a specificity of 0.72 (54). Only one study analysed the performance of a composite definition of muscle biopsy parameters, combining the presence of perifascicular necrosis, atrophic fibres, and perimysial fragmentation. This definition was tested against a population of other myositis subsets and provided an area under the curve of 0.91 (57).

The diagnostic accuracy for clinical variables was calculated only from two studies that defined ASSD as anti-ARS+CTD diagnosis (3) and anti-ARS+ILD (62). These variables were tested against very different control populations; IIM patients with MSA positivity other than anti-ARS and IPF patients, respectively. The sensitivity of arthritis/arthritis ranged from 0.15 to 0.62 with a specificity of 0.64 to 0.98. The sensitivity of fever ranged from 0.15 to 0.43, with a specificity of 0.64 to 0.95. The sensitivity of RP ranged from 0.08 to 0.47, with a specificity of 0.55 to 0.98. The sensitivity of cutaneous symptoms, including Gottron sign and heliotrope rash, was around 0.31 with a specificity of 0.46 to 0.98. Mechanic’s hands’ performance was retrievable in only one study (3), with a sensitivity of 0.27 and a specificity of 0.98. The accuracy of ILD in differentiating ASSD from other IIMs was tested in the first study (3) and displayed a sensitivity of 0.7 and a specificity of 0.85.

Only one study analysed the performance of muscle MRI to diagnose ASSD (defined as anti-ARS autoantibodies plus ILD or myositis) against healthy controls. The sensitivity and specificity of muscle oedema was 0.38 and 0.87, fascial oedema 0.29 and 0.93, fatty replacement 0.41 and 0.96, and muscle mass reduction 0.14 and 0.93 (92).

The assessment of the risk of bias for the studies included in Q2, performed by QUADAS-2, revealed a high risk of bias, especially for patient selection. In particular, most were case-control studies, including patients with an established diagnosis and not incident cases. The risk of bias and applicability concerns are summarised in Supplementary Fig. S2.

Discussion

This SLR highlights that proposed definitions of ASSD in the literature are highly variable, purely eminence-based and lack any supporting data or consensus. ASSD appears to be a very heterogeneous condition with a variety of phenotypic and prognostic features, mimicking many other conditions clinically such as DM, RA and IPF. However, recent findings suggest that ASSD is a unique entity with a different immunopathogenic pathway, risk profile and prognostic factors compared to other forms of myositis. Therefore, it may be appropriate to consider ASSD a distinct syndrome from its mimickers, since individual manifestations of ASSD, such as mechanic’s hands, may be indistinguishable from other diseases (110). Unfortunately, the result of this SLR confirms the lack of adequate data and/or a consensus-driven validated criterion for ASSD. The most widely used definitions of ASSD, fulfilling Connor’s criteria (2), consisted of anti-ARS autoantibodies plus one feature of the classical clinical triad (arthritis, myositis, or ILD). Although useful in clinical practice, this approach comes from expert opinion and lacks validation or performance assessment. This systematic review was also unable to retrieve or confirm any measure of diagnostic performance for these expert-proposed definitions. This relates to the nature of the published ASSD studies that are primarily observational, describing the clinical phenotype of anti-ARS positive patients. Moreover, anti-ARS autoantibodies appear necessary for ASSD diagnosis, since every study except one (32) used them to define the disease.

The over-reliance on autoantibody results without establishing pre-test probability of the syndrome based on comprehensive set of clinical feature poses significant challenges. That is, the diagnosis of ASSD is not feasible if the clinician has no access to a reliable anti-ARS assay or lacks the expertise to interpret the results correctly as well as create significant dilemma in cases of false positive and negative results, which itself a significant challenge due to lack of standardised and reliable autoantibody testing (25-27, 110). In addition, there are significant delays in receiving timely anti-ARS test results when done by validated assays using reliable laboratories, or by the gold standard method (immunoprecipitation) which is rarely available in clinical practice. Moreover, the search
for these antibodies is often neglected especially when other diagnoses are possible, as recently reported in a cohort of ASSD patients misdiagnosed as having rheumatoid arthritis for 3-20 years (111). Furthermore, the different ASSD manifestations, when taken singularly, may not be specific for ASSD, even in the case of anti-ARS autoantibody positivity as highlighted in the two studies that allowed the assessment of the diagnostical performance of various clinical variables (3, 62). These variables were tested singularly and against different control populations, thus making their performance poorly comparable to each other and, in any case, far from being satisfactory. The performance of muscle MRI was also evaluated (92), revealing a high specificity but poor sensitivity in detecting ASSD-related myositis compared to healthy controls. Most muscle variables were not able to distinguish ASSD from other types of myositis with optimum sensitivity and specificity (49, 54-59) with the exception of nuclear action aggregation, which, however, has only been examined in one study (55). Moreover, all studies included in Q2 displayed a high risk of bias related to patient selection and a case-control design that tends to overestimate diagnostic accuracy. It should also be noted that a number of ASSD patients do not undergo muscle biopsy or never develop clinical myositis. Therefore, the information emerging from these studies might not reflect a typical clinical setting.

This SLR has highlighted how ASSD, since its first description, has been defined by a pleiotropic combination of clinical, laboratory, histological, and imaging measures. However, there have been absolutely no data or consensus driven attempt to develop a formal validated and widely accepted definition for ASSD, despite recent findings suggest that ASSD is a unique entity with a different immunopathogenic pathway, risk profile and prognostic factors compared to other forms of myositis or ILD (16, 17, 22), although individual manifestations of ASSD, such as mechanic’s hands, may be indistinguishable from other diseases (112). Meanwhile, there is a lack of performance data of the most used eminence-based definitions proposed for ASSD.

To the best of our knowledge, this is the first SLR regarding ASSD definition. However, there are several limitations to the present work, mostly related to the limitations of the primary studies. In particular, the scarcity of studies reporting the diagnostic performance has limited quantitative synthesis of the results, resulting in limited evidence. More importantly, it was not possible to test a definition of ASSD based on multiple variables. This is of utmost importance since the lack of a data-driven definition of ASSD reflects the impossibility of establishing a confident and early diagnosis. The absence of a universal definition hinders the design of interventional trials in ASSD, with a major consequence on the availability of effective treatments for this condition. The present work, therefore, underpins the need to develop a data-driven and consensus led definition of ASSD as the first step of a long process with an ideal positive impact on the early diagnosis and prognosis improvement of this disease. In our view, it is necessary to develop classification criteria of probable and definite ASSD (even in the absence of serological data), a syndrome encompassing a variety of clinical manifestations, with subsequent serological confirmation. This is crucial, especially given that the complete syndrome is not always fully expressed at the time of presentation, and the symptoms may evolve over time.

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Definition of anti-synthetase syndrome / G. Zanframundo et al.


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