

Defining anti-synthetase syndrome: a systematic literature review

Supplementary online only material

Table S1. PICO_s? developed to drive the literature review.

Research Question	<i>Q1: How has ASSD been defined in the available literature?</i>	<i>Q2: What is the accuracy of the different definitions for diagnosing ASSD?</i>
Population	People with suspected ASSD (adults) Patients with confirmed ASSD (adults)	People with suspected ASSD (adults) Patients with confirmed ASSD (adults)
Interventions	Definition of ASSD by clinical, laboratory, imaging, instrumental testing, and histology features (alone or combined)	Definition of ASSD by clinical, laboratory, imaging, instrumental testing, and histology features (alone or combined)
Comparators (if applicable – not required for inclusion)	Other definitions of ASSD	Diagnosis of ASSD by expert opinion
Outcomes	N/A	Sensitivity Specificity Positive and negative predictive values Positive and negative likelihood ratios Diagnostic Odds Ratio
Study type	Systematic literature reviews, meta-analyses, RCTs, controlled trials, non-controlled trials, diagnostic accuracy studies, cohort studies, cross-sectional studies, and case-control studies	Systematic literature reviews, meta-analyses, RCTs, controlled trials, non-controlled trials, diagnostic accuracy studies, cohort studies, cross-sectional studies, and case-control studies

ASSD: anti-synthetase syndrome; RCT: randomized clinical trial; N/A: not applicable.

Table S2. Search strategies for the SLR

<p>PubMed</p>	<p>#1. antisynthetase syndrome [supplementary concept] OR "Antisynthetase syndrome" OR ASSD OR "antisynthetase antibodies" OR "antisynthetase antibody" OR "antiaminoacyl-tRNA synthetase antibodies" OR "anti-aminoacyl-tRNA synthetase antibody" #2. "Myositis/complications"[Majr] #3. "Lung Diseases, Interstitial/complications"[Majr] OR "interstitial pneumonia with autoimmune features" OR IPAF #4. "Anti jo1" OR "Anti SSA/RO 52" OR "Anti OJ" OR "Anti EJ" OR "Anti PL 12" OR "Anti PL 7" OR "Anti KS" OR "Anti Zo" OR "Anti Ha") #5. #1 OR #2 OR #3 OR #4 #6. #5 NOT "Case reports"[Publication Type]</p> <p>Filters: Publication date from 1984/01/01 to 2018/11/06; English; French; Italian; Spanish</p>
<p>Embase</p>	<p>#1. 'antisynthetase syndrome'/exp OR 'Antisynthetase syndrome' OR ASSD OR 'antisynthetase antibod*' OR 'anti aminoacyl-tRNA synthetase antibod*' #2. 'Myositis'/mj AND complications/lnk #3. 'Interstitial Lung Disease'/mj AND 'complications'/lnk #4. 'interstitial pneumonia with autoimmune features' OR IPAF #5. 'Anti jo1' OR 'Anti SSA/RO 52' OR 'Anti OJ' OR 'Anti EJ' OR 'Anti PL 12' OR 'Anti PL 7' OR 'Anti KS' OR 'Anti Zo' OR 'Anti Ha' #6. (#1 OR #2 OR #3 OR #4 OR #5) #6 NOT 'case report'/exp #7. AND [1984-2018]/py AND ([english]/lim OR [french]/lim OR [italian]/lim OR [spanish]/lim)</p>

Table S3. Muscle biopsy variables retrieved by the SLR and number of studies including them

	N studies using variable for definition (Q1)	N studies using assessing variable performance (Q2)	Total (n= 11)
NECROSIS/REGENERATION			
Perifascicular necrosis	2	3	5
Diffuse necrosis	3	2	5
perimysial necrosis/regeneration	0	1	1
perivascular necrosis/regeneration	0	1	1
perifascicular mitochondrial disfunction	0	1	1
INFLAMMATION			
perimysial inflammation	1	3	4
perivascular inflammation	0	2	2
endomysial inflammation	1	3	4
ATROPHY/FRAGMENTATION			
perimysial fragmentation	0	4	4
perifascicular atrophy	0	6	6
diffuse atrophy	0	1	1
MHC/C5B-9 EXPRESSION			
MHC I diffuse expression	1	3	4
MHC I perifascicular expression	0	1	1
MHC II diffuse expression	0	1	1
C5b-9 diffuse expression	1	2	3
C5b-9 perifascicular expression	0	2	2
OTHER FINDIGNS			
microinfarcts	0	1	1
ischemic myosinolisis*	0	1	1
actin filament inclusion	0	1	1
mitochondrial disfunction	0	3	3
MxA sarcoplasmic expression	0	1	1
RIG-1 expression	0	1	1

* defined as punched-out vacuoles or myofibrillar rarefaction areas, corresponding to foci of myosin filament proteolysis.

Figure S1. Histogram of HRCT findings used in ASSD definition

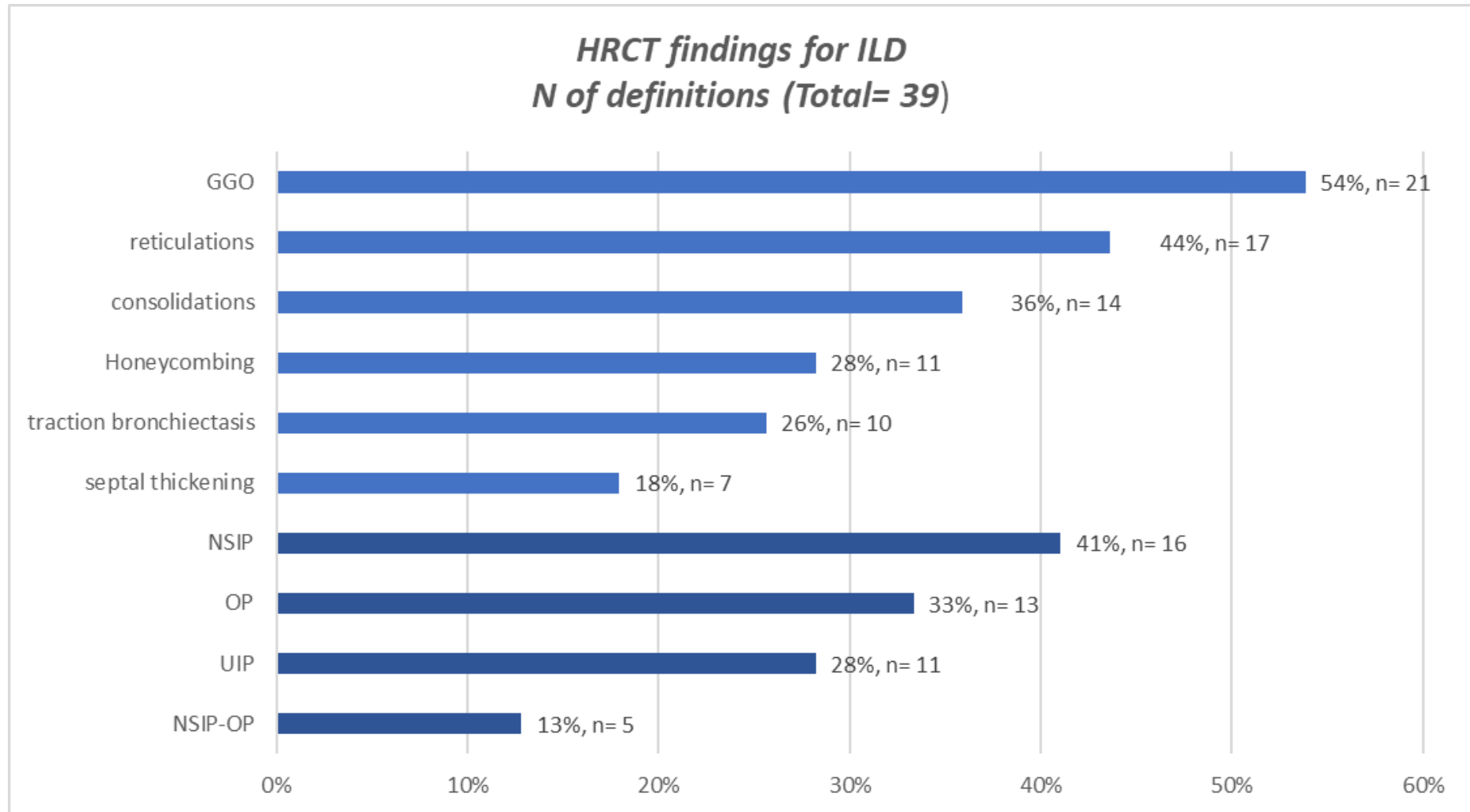


Table S4. Summary of findings – Q1 How has ASSD been defined in the available literature?

RoB: risk of bias; DM: dermatomyositis; PM: polymyositis; GGO: ground glass opacification; NSIP: nonspecific interstitial pneumonia; OP: organizing pneumonia; ILD: interstitial lung disease; HRCT: high resolution computed tomography; PFT: pulmonary function test; ARS: aminoacyl tRNA synthetase; ATS: American thoracic society; UIP: usual interstitial pneumonia; LIP: lymphocytic interstitial pneumonia; CK: creatinine kinase; RP: Raynaud’s phenomenon; MH: mechanic’s hands; EMG: electromyography; MRI: magnetic resonance imaging.

The Risk of Bias was evaluated by the Newcastle-Ottawa Scale for cohort studies or case-control studies, according to study design. S: Selection Items; C: comparability items; O: Outcome items. The symbol “*” indicates the score for each component of the scale. ‡: risk of bias assessed by QUADAS-2.

Study	Number of pts	Population	Study design	Index test (variables)	RoB
La Corte 2006 (1)	21	Patients with ASSD from a single Rheumatology center in Italy	Retrospective cross-sectional cohort	<ul style="list-style-type: none"> • Anti Jo1 • Myositis <ul style="list-style-type: none"> ○ Bohan and Peter criteria for probable or definite DM/PM ○ EMG* 	S** C O**
Marie I 2013 (2)	91	Anti Jo1 patients from 4 academic centers	Retrospective, longitudinal cohort	<ul style="list-style-type: none"> • Anti Jo1 • myositis <ul style="list-style-type: none"> ○ Bohan and Peter criteria for PM/DM 	S** C** O**
Debray 2014 (3)	33	ASSD from 4 tertiary centers specialized in rare lung diseases without any previous immunosuppressive therapy	Retrospective, longitudinal cohort	<ul style="list-style-type: none"> • Anti Jo1 • Anti PL 12 • Anti PL7 • ILD <ul style="list-style-type: none"> ○ HRCT <ul style="list-style-type: none"> ▪ GGO ▪ Reticulations ▪ Bronchiectasis ▪ Consolidations ▪ Honeycombing ▪ NSIP ▪ NSIP-OP ▪ OP 	S** C O**

Study	Number of pts	Population	Study design	Index test (variables)	RoB
Aguilera Cros C. 2018 (4)	27	ASSD from a single center	Retrospective, cross-sectional cohort	<ul style="list-style-type: none"> • Jo-1 • PL-12 • PL-7 • Myositis • arthritis • ILD HRCT <ul style="list-style-type: none"> ○ NSIP ○ UIP ○ OP • Fever • Raynaud’s phenomenon • mechanic’s hand 	S** C O
Hervier B. 2016 (5)	33	ASSD from a single center	Cross sectional cohort	<ul style="list-style-type: none"> • Jo-1 (22/33) • PL-12 (6/33) • PL-7 (3/33) • EJ (1/33) • OJ (1/33) • Myositis • ILD • rheumatic symptoms 	S** C O
Sasano H 2016 (6)	12	Consecutive patients with ASSD from a single center	Retrospective, longitudinal cohort	<ul style="list-style-type: none"> • Anti EJ • ILD <ul style="list-style-type: none"> ○ HRCT <ul style="list-style-type: none"> ▪ GGO ▪ Reticulations ▪ Consolidations ▪ Septal thickening 	S* C O**

Study	Number of pts	Population	Study design	Index test (variables)	RoB
				<ul style="list-style-type: none"> ▪ HC ▪ Emphysema ○ Biopsy <ul style="list-style-type: none"> ▪ Cellular NSIP ▪ fibrosing NSIP ▪ unclassifiable • myositis • arthritis • fever • RP • MH 	
Andersson H 2015 (7)	22	ASSD patients from single centre register	Retrospective, longitudinal cohort	<ul style="list-style-type: none"> • Anti Jo-1 • PL-12 • PL-7 • ILD <ul style="list-style-type: none"> ○ HRCT <ul style="list-style-type: none"> ▪ GGO ▪ Septal thickening ▪ Consolidations ▪ reticulations ○ PFT • myositis <ul style="list-style-type: none"> ○ B&P criteria for PM/DM <ul style="list-style-type: none"> ▪ CPK ▪ Weakness (MMT-8) 	S* C O**
Cobo-Ibanez T 2018 (8)	50	Consecutive ASSD patients from Europe8 88ntre registry???	Retrospective longitudinal cohort	<ul style="list-style-type: none"> • Jo-1 • PL-7 	S** C** O**

Study	Number of pts	Population	Study design	Index test (variables)	RoB
				<ul style="list-style-type: none"> • PL-12 • myositis <ul style="list-style-type: none"> ○ Bohan and Peter ○ Tanimoto criteria for PM/DM 	
Bachmeyer C. 2007 (9)	7	ASSD from single center registry	Retrospective longitudinal cohort	<ul style="list-style-type: none"> • anti Jo-1 • ILD <ul style="list-style-type: none"> ○ Cough ○ dyspnea • arthritis • Myositis 	S* C O**
Marie I 2013 (10)	5	Patients with anti PL12 antibodies from a single center	Retrospective longitudinal cohort	<ul style="list-style-type: none"> • Anti PL-12 	S* C O**
Uruha A. 2016 (11)	50	Patients with ARS positivity and myositis	Cross sectional cohort	<ul style="list-style-type: none"> • Anti Jo-1 • Anti PL-7 • Anti PL-12 • Anti-EJ • Anti-OJ • Anti-KS • Myositis <ul style="list-style-type: none"> ○ Biopsy (Perifascicular necrosis/atrophy) 	S* C O
Pinal-Fernandez I 2015 (12)	21	ASSD patients from a single Rheumatology center cohort	Cross sectional cohort	<ul style="list-style-type: none"> • Anti Jo1 • Anti PL7 • Anti PL12 • ILD <ul style="list-style-type: none"> ○ HRCT <ul style="list-style-type: none"> ▪ GGO ○ PFT 	S** C O

Study	Number of pts	Population	Study design	Index test (variables)	RoB
				<ul style="list-style-type: none"> ○ Clinical* ○ Biopsy* • Myositis • Arthritis • Raynaud’s phenomenon • Mechanic’s Hands • fever 	
Rojas-Serrano J 2015 (13)	43	ASSD patients from a single pneumology center in Europe	Longitudinal cohort	<ul style="list-style-type: none"> • Jo1 • EJ • OJ • PL 7 • PL 12 • ILD <ul style="list-style-type: none"> ○ PFT ○ HRCT <ul style="list-style-type: none"> ▪ GGO ▪ Consolidations ▪ reticulations • Myositis <ul style="list-style-type: none"> ○ Bohan and Peter • Fever • Mechanic’s hands • arthritis 	S * C * O **
Hervier B 2013 (14)	203	ASSD patients from 9 French university hospitals	Retrospective longitudinal cohort	<ul style="list-style-type: none"> • Anti Jo-1 • Anti PL-7 • Anti PL-12 • Anti EJ 	S * C ** O **

Study	Number of pts	Population	Study design	Index test (variables)	RoB
				<ul style="list-style-type: none"> • Anti OJ • myositis by Bohan and Peter criteria • ILD <ul style="list-style-type: none"> ○ HRCT <ul style="list-style-type: none"> ▪ NSIP ▪ UIP ▪ OP ○ PFT • arthritis 	
Andersson H 2016 (15)	68	ASSD patients from a single center cohort in Europe	Cross sectional	<ul style="list-style-type: none"> • Anti Jo-1 • Anti PL-7 • Anti PL-12 • ILD <ul style="list-style-type: none"> ○ PFT ○ HRCT <ul style="list-style-type: none"> ▪ GGO ▪ Reticulation ▪ UIP ▪ Opacities ▪ Emphysema ▪ Subpleural curvilinear lines and parenchymal bands ▪ Wedge shaped • Myositis <ul style="list-style-type: none"> ○ Probable or definite PM/DM (Bohan and Peter) 	S** C O**
Schneider F 2018 (16)	12	Anti PL 12 patients from a single center myositis register from US	Retrospective cross sectional cohort	<ul style="list-style-type: none"> • Anti PL-12 • Myositis 	S* C O**

Study	Number of pts	Population	Study design	Index test (variables)	RoB
				<ul style="list-style-type: none"> ○ Probable or definite PM/DM (Bohan and Peter) 	
Schneider F 2014 (17)	4	Anti EJ patients from a single center myositis register from US	Retrospective cross sectional cohort	<ul style="list-style-type: none"> • Anti-EJ • Myositis ○ Probable or definite PM/DM (Bohan and Peter) 	S* C O**
Doyle T J 2018 (18)	25	Consecutive ASSD patients from 2 US centers	Retrospective longitudinal cohort	<ul style="list-style-type: none"> • Jo-1 • PL-7 • PL-12 • ILD <ul style="list-style-type: none"> ○ PFT ○ HRCT <ul style="list-style-type: none"> ▪ NSIP ▪ Fibrotic NSIP/UIP ▪ NSIP/OP ▪ DAD 	S* C O**
Bauhammer J 2016 (19)	61	Anti Jo1 patients from 2 Rheumatology centers in Europe	Retrospective longitudinal cohort	<ul style="list-style-type: none"> • Anti Jo1 positivity • Myositis <ul style="list-style-type: none"> ○ Bohan and Peter's criteria for PM/DM 	S** C O**
Marie I 2012 (20)	7	patients with ASSD and ILD from a single center in France	Retrospective longitudinal cohort	<ul style="list-style-type: none"> • Anti Jo1 • Myositis <ul style="list-style-type: none"> ○ Bohan and Peter's criteria for definite PM/DM 	S* C O**
Sem M. 2009 (21)	11	Patients with ASSD and ILD from a tertiary center in Europe	Retrospective longitudinal cohort	<ul style="list-style-type: none"> • Anti Jo-1 • Anti PL-12 • ILD <ul style="list-style-type: none"> ○ HRCT <ul style="list-style-type: none"> ▪ GGO ▪ Reticulations ▪ Consolidations 	S* C O**

Study	Number of pts	Population	Study design	Index test (variables)	RoB
				<ul style="list-style-type: none"> ▪ HC ○ PFT 	
Couture P. 2018 (22)	10	Patients with ASSD and diagnosis of sarcoidosis from 10 French university hospitals	Longitudinal cohort	<ul style="list-style-type: none"> • Anti Jo1 • Anti PL12 • Anti PL 7 • ILD <ul style="list-style-type: none"> ○ HRCT <ul style="list-style-type: none"> ▪ NSIP ▪ NSIP/OP ▪ emphysema • myositis 	S** C O**
Lefevre G. 2015 (23)	73	ASSD patients from a multicentric French cohort	Retrospective longitudinal cohort	<ul style="list-style-type: none"> • Anti Jo1 • Anti PL7 • Anti PL12 • Anti EJ • ILD <ul style="list-style-type: none"> ○ HRCT ○ PFT* • Myositis <ul style="list-style-type: none"> ○ CPK ○ EMG ○ biopsy • arthritis 	S* C O**
Marie I 2012 (24)	89	Consecutive anti Jo1 patients from 4 French academic centers	Longitudinal cohort	<ul style="list-style-type: none"> • Anti Jo1 • Myositis <ul style="list-style-type: none"> ○ Bohan and Peter's criteria for PM/DM 	S** C O**
Noguchi E. 2017 (25)	51	ASSD from all over Japan	Cross sectional	<ul style="list-style-type: none"> • Anti Jo1 	S** C

Study	Number of pts	Population	Study design	Index test (variables)	RoB
				<ul style="list-style-type: none"> • Anti PL7 • Anti PL12 • Anti OJ • Anti EJ • Anti KS • Myositis <ul style="list-style-type: none"> ○ weakness ○ EMG ○ MRI ○ Biopsy* <ul style="list-style-type: none"> ▪ Perifascicular necrosis ▪ Diffuse necrosis ▪ Perimysial inflammation ▪ HLA ABC deposition ▪ C5b-9 expression 	O **
Gofrit S G 2018 (26)	15	ARS positive patients from a medical center database	Cross sectional	<ul style="list-style-type: none"> • Anti Jo1 • anti PL7 • anti PL12 • myositis • ILD • RP • Skin rash • Arthritis/arthritis 	S * C O *
Lilleker James B. 2018 (27)	512	ASSD from Euromyositis register	Multicentric cross sectional cohort	<ul style="list-style-type: none"> • Anti Jo1 • Anti PL7 • Anti PL12 • Anti OJ 	S ** C * O **

Study	Number of pts	Population	Study design	Index test (variables)	RoB
				<ul style="list-style-type: none"> • Anti EJ • Anti KS • Anti Zo • Myositis <ul style="list-style-type: none"> ○ Bohan and Peter’s criteria • Arthritis • ILD <ul style="list-style-type: none"> ○ HRCT ○ X rays ○ PFTs • mechanic’s hands • Raynaud’s phenomenon • fever 	
Späth M. 2004 (28)	12	antiJo1 patients from a Neurology department	Longitudinal cohort	<ul style="list-style-type: none"> • Myositis <ul style="list-style-type: none"> ○ CPK elevation ○ Clinical weakness (NA) • Anti Jo1 	S* C O**
Yousem S.A. 2014 (29)	8	PL7 patients from a single center in US	Retrospective longitudinal cohort	<ul style="list-style-type: none"> • • Anti PL7 CTD diagnosis 	S* C O**
Brillard Pocard A S 2018 (30)	10	ASSD from one Argentinian university hospital	Retrospective cross sectional cohort	<ul style="list-style-type: none"> • Arthritis • Raynaud’s phenomenon • mechanic hands • myositis <ul style="list-style-type: none"> • elevated CK • muscle weakness • ILD 	S** C O

Study	Number of pts	Population	Study design	Index test (variables)	RoB
				<ul style="list-style-type: none"> • antisynthetase antibodies 	
Carrasco Cubero MC 2018 (31)	5	Anti Jo1 ASSD from a single center in Spain	Retrospective cross sectional study	<ul style="list-style-type: none"> • myositis • anti Jo1 • fever • arthritis • Raynaud’s phenomenon • mechanic’s hands • ILD <ul style="list-style-type: none"> ○ HRCT <ul style="list-style-type: none"> ▪ NSIP ▪ UIP ▪ Respiratory bronchiolitis interstitial lung disease (RB-ILD) 	S* C O**
Casal-Dominguez M (32)	16	ASSD patients from a single center in Spain	Cross sectional	<ul style="list-style-type: none"> • Anti Jo1 • Anti PL7 • Anti PL12 • Myositis <ul style="list-style-type: none"> • Probable or definite PM/DM by Bohan and Peter 	S** C** O
Araujo P.A.O. 2018 (33)	42	ASSD patients from a single center in Brazil	Cross sectional	<ul style="list-style-type: none"> • Anti Jo1 • Anti EJ • Anti OJ • Anti PL7 • Anti PL12 • Myositis <ul style="list-style-type: none"> • PM/DM by Bohan and Peter’s criteria • ILD <ul style="list-style-type: none"> • HRCT 	S*** C O

Study	Number of pts	Population	Study design	Index test (variables)	RoB
				<ul style="list-style-type: none"> ▪ GGO ▪ Incipient pneumonia ▪ fibrosis • dyspnea • Arthritis • RP • MH • fever 	
Hervier 2012 (34)	233	ASSD patients from 8 centers in France	longitudinal	<ul style="list-style-type: none"> • anti Jo1 • anti PL7 • anti PL12 • ILD <ul style="list-style-type: none"> • HRCT • PFT • myositis <ul style="list-style-type: none"> • CK elevation • Muscle weakness • EMG • Muscle biopsy (diffuse myofiber necrosis/regeneration) • Arthritis/arthralgia 	S * C O **
Marie 2013 (35)	86	consecutive anti-Jo1 patients with ASS reviewed in 4 academic centers	longitudinal	<ul style="list-style-type: none"> • Myositis <ul style="list-style-type: none"> • PM/DM by Bohan and Peter • Anti Jo1 	S * C O **
Allenbach 2015 (36)	10	ASSD patients from 4 French adult internal medicine departments enrolled for a Phase II trial	open-label, prospective, multicenter phase II study	<ul style="list-style-type: none"> • myositis <ul style="list-style-type: none"> • proximal weakness • EMG • biopsy 	S * C O **

Study	Number of pts	Population	Study design	Index test (variables)	RoB
				<ul style="list-style-type: none"> ▪ muscle fibre necrosis and regeneration ▪ inflammatory cell infiltrate <ul style="list-style-type: none"> • anti-Jo-1 • anti-PL-7 • anti-PL-12 	
Lepri G. 2016 (37)	15	ASSD from 8 centers in Europe	multicentre retrospective longitudinal	<ul style="list-style-type: none"> • anti-synthetase antibodies • ILD <ul style="list-style-type: none"> • HRCT <ul style="list-style-type: none"> ○ GGO ○ Reticulations ○ honeycombing 	S** C O**
Marie I. 2012 (38)	95	ASSD patients from a single center in France	Retrospective longitudinal	<ul style="list-style-type: none"> • myositis <ul style="list-style-type: none"> • PM/DM by Bohn and Peter • Anti Jo1 • Anti PL7 • Anti PL12 	S* C O**
Cavagna L. 2015 (39)	225	anti Jo1 patients from 24 centers in Europe	Retrospective longitudinal	<ul style="list-style-type: none"> • Anti Jo1 • ILD <ul style="list-style-type: none"> • PFT • HRCT • Myositis <ul style="list-style-type: none"> • CK elevation • EMG • Biopsy • Arthritis 	S** C O**
Gomard-Menesson 2007 (40)	14	ASSD patients from a monocentric cohort of anti Jo1 subjects	Retrospective cross sectional	<ul style="list-style-type: none"> • Anti Jo1 • Myositis 	S** C* O

Study	Number of pts	Population	Study design	Index test (variables)	RoB
				<ul style="list-style-type: none"> • CPK • EMG • ILD <ul style="list-style-type: none"> • PFT • HRCT • RP • arthritis 	
Shi 2017 (41)	124	Consecutive ASSD patients from a single center	Retrospective longitudinal	<ul style="list-style-type: none"> • Anti Jo1 • Anti PL7 • Anti PL12 • Anti EJ • Myositis <ul style="list-style-type: none"> ○ DM/PM diagnosis according to Bohan and Peter • ILD <ul style="list-style-type: none"> ○ HRCT <ul style="list-style-type: none"> ▪ UIP ▪ NSIP ▪ OP • Arthritis • RP • MH 	S* C** O**
Kalluri 2009 (42)	31	Anti PL 12 patients from a multicentric cohort in US	Cross sectional	<ul style="list-style-type: none"> • Anti PL12 • Myositis <ul style="list-style-type: none"> ○ DM/PM diagnosis according to Bohan and Peter • ILD <ul style="list-style-type: none"> ○ PFT ○ HRCT 	S* C O

Study	Number of pts	Population	Study design	Index test (variables)	RoB
				<ul style="list-style-type: none"> • GGO • Septal thickening • HC ○ Biopsy <ul style="list-style-type: none"> • UIP • NSIP • OP • Arthritis • RP • MH • fever 	
Hervier B. 2010 (43)	17	anti PL12 patients from three university hospitals	longitudinal	<ul style="list-style-type: none"> • Anti PL12 • ILD <ul style="list-style-type: none"> ○ Cough ○ dyspnea ○ HRCT <ul style="list-style-type: none"> ▪ NSIP ▪ OP ○ Biopsy* ○ BAL* • Myositis <ul style="list-style-type: none"> ○ Clinical ○ EMG ○ CK ○ Biopsy* • Fever • RP 	S* C O**

Study	Number of pts	Population	Study design	Index test (variables)	RoB
				<ul style="list-style-type: none"> • MH • Weight loss • Esophageal involvement • PH 	
Marie 2013 (44)	15	anti PL 7 patients from 5 university hospitals in France	Retrospective longitudinal	<ul style="list-style-type: none"> ○ Anti PL7 ○ myositis <ul style="list-style-type: none"> ○ DM/PM according to Bohan and Peter ○ Sontheimer criteria for ADM 	S* C O**
Trallero-Araguas 2016 (45)	148	anti Jo1 patients from 18 Spanish centers	Retrospective longitudinal	<ul style="list-style-type: none"> ○ Anti Jo1 ○ Myositis <ul style="list-style-type: none"> ○ DM/PM according to Bohan and Peter ○ ILD <ul style="list-style-type: none"> ○ HRCT ○ PFT ○ arthritis 	S* C O**
Bartoloni 2017 (46)	165	anti Jo1 patients from a multicentric European cohort	Retrospective longitudinal	<ul style="list-style-type: none"> ○ Anti Jo1 ○ Arthritis ○ ILD <ul style="list-style-type: none"> ○ PFT ○ HRCT <ul style="list-style-type: none"> ▪ GGO ▪ Fibrosis ○ Myositis <ul style="list-style-type: none"> ○ CK elevation ○ aldolase ○ EMG 	S* C O**

Study	Number of pts	Population	Study design	Index test (variables)	RoB
				○ Biopsy*	
Cen X 2013 (47)	134	Patients with IIM, diagnosis based on the criteria of the ENMC workshop, and anti JO1	Retrospective cross sectional study	<ul style="list-style-type: none"> ● Anti Jo1 ○ Myositis ○ ILD <ul style="list-style-type: none"> ○ HRCT ○ Arthritis 	S** C* O
Pinal-Fernandez I 2017 (48)	292	IIM testing positive for anti-synthetase antibodies	Retrospective cross sectional study	<ul style="list-style-type: none"> ● Anti Jo1 ● Anti PL7 ● Anti PL12 ● Anti EJ ● Anti OJ ○ Anti Ro52 ○ myositis 	S** C O*
Chartrand S 2016 (49)	33	ASSD suspected based on multi-disciplinary assessment	Retrospective cross sectional study	<ul style="list-style-type: none"> ● ILD <ul style="list-style-type: none"> ● PFT* ● HRCT <ul style="list-style-type: none"> ▪ NSIP ▪ NSIP-OP ▪ OP ▪ UIP ● Anti Jo1 ● Anti PL7 ● Anti PL12 ● Anti EJ ● Anti OJ 	S** C O*
Cerbelli B 2018 (50)	18	Cases: Consecutive patients with anti ARS antibodies and suspected	Case-control	<ul style="list-style-type: none"> ● Anti Jo1 ● Anti PI7 	S** C O*

Study	Number of pts	Population	Study design	Index test (variables)	RoB
		myositis referred for histological evaluation. Controls: DM according to the ENMC criteria.		<ul style="list-style-type: none"> • Myositis <ul style="list-style-type: none"> ○ ENMC 2004 proposed criteria <ul style="list-style-type: none"> • Weakness • CPK • EMG • MRI ○ biopsy <ul style="list-style-type: none"> ○ Necrosis ○ Regeneration ○ Atrophy ○ Endomysial infiltrates ○ Perimysial inflammation+ ○ Perimysial fragmentation ○ MHC enhancement ○ C5B9 sarcolemmal positivity <ul style="list-style-type: none"> ▪ COX deficient fibers 	
Shinjo SK 2010 (51)	18	ASSD with anti Jo1	Retrospective cross sectional study	<ul style="list-style-type: none"> • Myositis <ul style="list-style-type: none"> ○ PM/DM by Bohan and Peter ○ Anti Jo1 	S* C O**
Labirua-Iturburu A 2012 (52)	18	ASSD with anti PL7	Retrospective cross sectional study	<ul style="list-style-type: none"> ○ Anti PL7 ○ Myositis <ul style="list-style-type: none"> ○ PM/DM by Bohan and Peter ○ Sontheimer criteria for ADM 	S** C O**
Fischer A 2007 (53)	9	Consecutive patients with ILD suspicious for ASSD with negative anti Jo1 antibodies	Prospective cohort	<ul style="list-style-type: none"> • ILD <ul style="list-style-type: none"> ○ HRCT <ul style="list-style-type: none"> • GGO • Reticulations 	S** C O**

Study	Number of pts	Population	Study design	Index test (variables)	RoB
				<ul style="list-style-type: none"> • Consolidations • Bronchiectasis • NSIP • OP ○ PFTs • Anti PL7 • Anti PL12 	
Targoff IN 1992 (54)	5	Patients with available serum samples, PM/DM criteria and positive anti EJ antibodies	Retrospective cross sectional study	<ul style="list-style-type: none"> • Myositis <ul style="list-style-type: none"> ○ PM/DM by Bohan and Peter • ILD <ul style="list-style-type: none"> ○ Chest X rays ○ PFTs ○ Anti EJ 	S ** C O **
Cavagna L 2010 (55)	12	Patients with anti Jo1 positive ASSD	Cross-sectional cohort	<ul style="list-style-type: none"> ○ Anti Jo1 ○ ILD <ul style="list-style-type: none"> ○ HRCT ○ PFT ○ Myositis ○ MH ○ arthritis 	S * C O **
Hervier B 2011 (56)	12	Patients testing twice positive for anti PL7 with one or more symptoms of ASSD	Retrospective cross sectional study	<ul style="list-style-type: none"> • ILD <ul style="list-style-type: none"> ○ Dyspnea ○ Cough ○ HRCT <ul style="list-style-type: none"> • GGO • Bronchiectasis • Consolidations 	S * C O **

Study	Number of pts	Population	Study design	Index test (variables)	RoB
				<ul style="list-style-type: none"> • NSIP • OP • Obliterative bronchiolitis • Myositis ○ Anti PL7 	
Mumm GE 2010 (57)	6	New onset inflammatory polyarthritis and anti-synthetase autoantibodies	Retrospective Case series	<ul style="list-style-type: none"> • Arthritis • Anti Jo1 ○ Anti OJ ○ Anti PL12 	S C O **
Stanciu R 2012 (58)	48	Anti Jo1 antibodies with at least 1 year of follow-up	Retrospective cohort	<ul style="list-style-type: none"> ○ Anti Jo1 	S ** C O *
Dieval C 2012 (59)	14	ASSD with positive anti-synthetase autoantibodies	Retrospective Case series	<ul style="list-style-type: none"> • Anti Jo1 • Anti PL7 ○ Anti PL12 ○ Myositis ○ ILD ○ Arthritis ○ RP ○ MH 	S * C O **
Maturu V 2016 (60)	9	Patients retrieved from the medical record database of a single tertiary center	Retrospective cohort	<ul style="list-style-type: none"> • Anti Jo1 • ILD <ul style="list-style-type: none"> ○ HRCT <ul style="list-style-type: none"> • NSIP • UIP • OP ○ PFTs* • Myositis 	S * C O **

Study	Number of pts	Population	Study design	Index test (variables)	RoB
				<ul style="list-style-type: none"> ○ PM/DM by Bohan and Peter ○ Weakness* ○ CPK* ○ EMG* ○ Biopsy* ● Arthritis 	
Zamarron E 2017 (61)	11	Patients with pulmonary involvement and anti synthetase antibodies positivity	Prospective cohort	<ul style="list-style-type: none"> ● Anti Jo1 ● Anti PL12 ● ILD <ul style="list-style-type: none"> ○ HRCT <ul style="list-style-type: none"> ● GGO ● Reticulations ● Bronchiectasis ○ PFTs 	S* C O**
Waseda Y 2016 (62)	64	Patients with ILD and anti synthetase antibodies positivity	Retrospective cross sectional study	<ul style="list-style-type: none"> ● ILD <ul style="list-style-type: none"> ○ GGO ○ reticulations ○ consolidations ○ septal thickening ○ HC ○ NSIP ○ OP ○ NSIP/OP ○ UIP ● Anti JO1 ● Anti EJ ● Anti PL7 	S* C O**

Study	Number of pts	Population	Study design	Index test (variables)	RoB
				<ul style="list-style-type: none"> • Anti PL12 • Anti OJ • Anti KS 	
Labirua-Itruburu A 2013 (63)	15	Patients with ASSD and ILD, treated with calcineurin inhibitors	Retrospective cohort	<ul style="list-style-type: none"> • ILD <ul style="list-style-type: none"> ○ HRCT <ul style="list-style-type: none"> • GGO • RETICULATIONS • Septal thickening • HC ○ PFTs • Anti Jo1 • Anti PL12 • myositis <ul style="list-style-type: none"> ○ PM/DM by Bohan and Peter 	S * C O **
Vancsa A 2009 (64)	27	Patients with IIM and anti Jo1	Retrospective cohort	<ul style="list-style-type: none"> • Myositis <ul style="list-style-type: none"> ○ PM/DM by Bohan and Peter • Anti Jo1 	S ** C O **
Karadimitrakis S 2009 (65)	17	Patients with IIM and anti Jo1	Retrospective cohort	<ul style="list-style-type: none"> • Myositis <ul style="list-style-type: none"> ○ PM/DM by Bohan and Peter • Anti Jo1 	S * C O **
Hirakata M 2007 (66)	8	Patients with PM/DM, with likely IM, with ILD without any other cause and anti-KS antibodies	Cross-sectional cohort	<ul style="list-style-type: none"> • Myositis <ul style="list-style-type: none"> ○ PM/DM by Bohan and Peter ○ weakness • ILD <ul style="list-style-type: none"> ○ Chest X rays ○ PFTs • Anti KS 	S ** C O **

Study	Number of pts	Population	Study design	Index test (variables)	RoB
Johnson C 2014 (67)	41	PM/DM, presence of ILD and at least 6 months of follow-up	Retrospective cohort	<ul style="list-style-type: none"> • Myositis <ul style="list-style-type: none"> ○ PM/DM by Bohan and Peter • ILD <ul style="list-style-type: none"> ○ PFTs ○ biopsy ○ HRCT <ul style="list-style-type: none"> ○ GGO ○ Reticulations/fibrosis • Anti Jo1 • Anti PL7 • Anti PL 12 • Anti EJ • Anti OJ 	S** C* O*
Koreeda Y 2010 (68)	14	Patients with ILD and anti synthetase antibodies positivity	Prospective cohort	<ul style="list-style-type: none"> • ILD <ul style="list-style-type: none"> ○ HRCT <ul style="list-style-type: none"> • GGO • Septal thickening • Bronchiectasis • Consolidations • HC • Anti Jo1 • Anti PL12 • Anti EJ • Anti OJ • Anti KS 	S** C O*
Yura H 2017 (69)	38	Patients with interstitial pneumonia of unknown cause not fulfilling classification criteria	Retrospective cohort	<ul style="list-style-type: none"> • ILD <ul style="list-style-type: none"> ○ HRCT 	S** C O**

Study	Number of pts	Population	Study design	Index test (variables)	RoB
				<ul style="list-style-type: none"> • Reticulations • HC • Bronchiectasis • GGO • Consolidations • Septal thickening • UIP • OP • NSIP • DAD • Anti Jo1 • Anti PL12 • Anti PL7 • Anti OJ • Anti EJ • Anti KS 	
Lecouffe-Despret M 2018 (70)	9	Patients with a request for myositis specific autoantibodies	Retrospective cross sectional study	<ul style="list-style-type: none"> • myositis • ARS <ul style="list-style-type: none"> ○ jo1 ○ pl12 	S* C O**
Vuillard C 2018 (71)	28	Patients admitted to the ICU for acute respiratory failure	Retrospective cohort	<ul style="list-style-type: none"> • Anti Jo1 • Anti PL7 • Anti PL12 • Anti EJ • ILD <ul style="list-style-type: none"> ○ Clinical (acute respiratory failure) 	S* C O**
Zamora AC 2016 (72)	104	ASSD with positive anti Jo1 and ILD	Retrospective cohort	<ul style="list-style-type: none"> • Anti JO1 	S*

Study	Number of pts	Population	Study design	Index test (variables)	RoB
				<ul style="list-style-type: none"> • myositis • ILD <ul style="list-style-type: none"> ○ GGO ○ HC ○ Reticulations ○ Bronchiectasis ○ Consolidations ○ UIP ○ NSIP ○ OP ○ NSIP/OP • Biopsy* <ul style="list-style-type: none"> ○ NSIP ○ OP ○ UIP ○ DAD • PFT* 	C * O **
Ben- Salem T 2018 (73)	9	Patients with ASSD and ILD	Retrospective cohort	<ul style="list-style-type: none"> • Anti Jo1 • Anti PI12 • ILD 	S * C O **
Aouizerate J. 2014 (74)	33	Patients with myositis and ARS positivity	Case-control	<ul style="list-style-type: none"> • Anti Jo1 • Anti PI12 • Anti PI7 • Anti EJ • Myositis 	§

Study	Number of pts	Population	Study design	Index test (variables)	RoB
Stenzel W 2015 (75)	21	Patients with myositis and ARS positivity	Case-control	<ul style="list-style-type: none"> • Myositis • Anti Jo1 • Anti PI12 • Anti PI7 	§
Lega J. 2014 (76)	1462	Patients with diagnosis of CTD and ARS positivity	Systematic review	<ul style="list-style-type: none"> • Anti Jo1 • Anti PL7 • Anti PI12 • Anti KS • Anti OJ • Anti EJ • CTD diagnosis • ILD 	§
Pinal-Fernandez I 2015 (77)	20	Patients with definite or probable DM/PM by B&P + anti Jo1	Cross-sectional study	<ul style="list-style-type: none"> • myositis <ul style="list-style-type: none"> ○ PM/DM diagnosis according with Bohan and Peter • Anti Jo1 	§
Mescam-Mancini L 2015 (78)	19	Anti Jo1 patients	diagnostic accuracy studies	<ul style="list-style-type: none"> • Anti Jo1 • myositis 	§
Uruha 2018 (79)	30	Patients with myositis and ARS positivity	Case-control	<ul style="list-style-type: none"> • Myositis • Anti EJ • Anti OJ • Anti KS 	§
Andersson 2017 (80)	66	Patients with ARS positivity, ILD or myositis	Case-control	<ul style="list-style-type: none"> • anti Jo1 	§

Study	Number of pts	Population	Study design	Index test (variables)	RoB
				<ul style="list-style-type: none"> • Anti PI12 • Anti PI7 • ILD <ul style="list-style-type: none"> ○ HRCT ○ PFTs • Myositis <ul style="list-style-type: none"> ○ PM/DM by Bohan and Peter 	
Watanabe 2011 (81)	13	Patients with ILD and ARS positivity	Retrospective longitudinal	<ul style="list-style-type: none"> • Anti Jo1 • anti PI12 • anti PI7 • anti EJ • anti OJ • anti KS • ILD <ul style="list-style-type: none"> ○ HRCT <ul style="list-style-type: none"> ▪ Septal thickening ▪ GGO ▪ Reticulations ▪ Bronchiectasis ▪ Consolidations 	§
Mozaffar 2000 (82)	11	Anti Jo1 + myositis	Case-control	<ul style="list-style-type: none"> • Anti Jo1 • myositis 	§

Table S5. Summary of findings – Q2 What is the accuracy of the different definitions for diagnosing ASSD?

Summary of findings of studies included in research question 2. ARS anti-RNA synthetase, ASSD anti synthetase syndrome, CTD connective tissue disease, DM dermatomyositis, GGO ground glass opacity, HRCT high resolution computed tomography, IBM inclusion body myositis, ILD interstitial lung disease, IMNM immune-mediated necrotizing myopathy, MH mechanic’s hands, NSIP nonspecific interstitial pneumonia, OP organising pneumonia, PFT pulmonary function tests, PM polymyositis, RP Raynaud’s phenomenon, UIP usual interstitial pneumonia.

Study	Number of pts	Population	Controls	Study design	Reference standard	Index test (variables)	Diagnostic performance
Aouizerate J. 2014 (74)	33 cases 27 controls	Patients with myositis and ARS positivity	17 patients with DM 10 patients with fibromyalgia	Case-control	ASSD diagnosed by Myositis AND ARS positivity	<ul style="list-style-type: none"> HLA-DR myofiber expression C5b-9 deposition on non-necrotic myofibers 	<p>HLA-DR myofiber expression</p> <p>Sensitivity 84.21% 95%CI (72.13-92.52%) Specificity 79.49% 95%CI (63.54-90.7%) PPV 85.71% 95%CI (76.2-91.83%) NPV 77.5% 95%CI (64.94-86.5%) DOR 20.67 95%CI (7.2-59.3) P < 0.0001 LR+ 4.11 95%CI (2.19-7.69) LR- 0.2 95%CI (0.11-0.37)</p> <p>C5b-9 deposition on non-necrotic myofibers</p> <p>Sensitivity 53.12% 95%CI (34.74-70.91%) Specificity 81.25% 95%CI (54.53-95.95%) PPV 85% 95%CI(66-94.3%) NPV 46.43% 95%CI (35.88-57.31%) DOR 4.91 95%CI (1.169-20.61) P = 0.0297 LR+ 2.83 95%CI (0.97-8.27) LR- 0.58 95%CI (0.37-0.89)</p> <p>Perimysial connective tissue fragmentation</p> <p>Sensitivity 78.8% 95%CI (61.1-91%) Specificity 17.65% 95%CI (3.8-43.3%) PPV 65% 95%CI (58.34-71.13%) NPV 30% 95%CI (11.24-59.2%) DOR 0.79 95%CI (0.177-3.57) p= 0.7656</p>

Study	Number of pts	Population	Controls	Study design	Reference standard	Index test (variables)	Diagnostic performance
						<ul style="list-style-type: none"> Perimysial connective tissue fragmentation Perifascicular atrophy Microinfarcts Ischemic myosinolysis (punched out vacuoles) 	<p>LR+ 0.96 95%CI (0.72-1.27) LR- 1.2 95%CI (0.36-4.07)</p> <p>Perifascicular atrophy Sensitivity 45.45% 95%CI (28.11-63.65%) Specificity 47.06% 95%CI (22.98-72.2%) PPV 62.5% 95%CI (48.18-74.9%) NPV 30.77% 95%CI (19.72-44.56%) DOR 0.741 95%CI (0.23-2.4) p= 0.6161 LR+ 0.86 95%CI (0.48-1.54) LR- 1.16 95%CI (0.64-2.1)</p> <p>MICROINFARTS Sensitivity 6.06% 95%CI (0.74-20.23%) Specificity 58.82% 95%CI (32.92-81.56%) PPV 22.22% 95%CI (6.23-55.13%) NPV 24.39% 95%CI (17.68-32.64%) DOR 0.092 95%CI (0.0164-0.518) p= 0.0068 LR+ 0.15 95%CI (0.03-0.63) LR- 1.6 95%CI (1.06-2.4)</p> <p>Ischemic myosinolysis Sensitivity 6.06% 95%CI (0.74-20.23%) Specificity 64.71% 95%CI (38.33-85-8%) PPV 25% 95%CI (7-60%) NPV 26.19% 95%CI (19.82-33.75%) DOR 0.118 95%CI (0.021-0.674) p= 0.0163 LR+ 0.17 95%CI (0.04-0.76) LR- 1.45 95%CI (1.01-2.08)</p> <p>HLA-ABC Sensitivity 93.94% 95%CI (79.77-99.26%) Specificity 37.04% 95%CI (19.4-57.63%) PPV 64.58% 95%CI (62.58-66.54%) NPV 83.33% 95%CI (54.46-95.43%)</p>

Study	Number of pts	Population	Controls	Study design	Reference standard	Index test (variables)	Diagnostic performance
						<ul style="list-style-type: none"> HLA-ABC expression 	DOR 9.12 95%CI (1.79-46.51) p=0.0078 LR+ 1.49 95%CI (1.1-2.02) LR- 0.16 95%CI (0.04-0.68)
Stenzel W 2015 (75)	21 case patient 53 controls	Patients with myositis and ARS positivity	14 DM 14 NAM 14 IBM 11 nonspecific myositis	Case-control	<ul style="list-style-type: none"> ARS antibody + Clinically significant myositis 	presence of myonuclear actin filament inclusions	Sensitivity 80.95% 95%CI (58.09-94.55%) Specificity 100% 95%CI (93.28-100%) PPV 100% NPV 92.98% 95%CI (84.58-96.97%) DOR 416.1 p= 0.0001 95% CI(21.32-8120.8) LR+ LR- 0.19 95%CI (0.08-0.46)
Lega J. 2014 (76)	1462 case 559 controls	Patients with diagnosis of CTD and ARS positivity	154 Mi2 144 SRP 116 PM-Sci 226 U1RNP 61 Ku	Meta-analysis	<ul style="list-style-type: none"> Diagnosis of CTD anti ARS positivity 	<ul style="list-style-type: none"> Arthralgia ILD Fever 	Arthralgia Sensitivity 61.97% 95%CI (59.43-64.47%) Specificity 64.05% 95%CI (60.37-67.61%) PPV 78.24% 95%CI (76.37-80%) NPV 44.68% 95%CI (42.57-46.81%) DOR 2.9 95%CI (2.4-3.5) LR+ 1.72 95%CI (1.55-1.92) LR- 0.59 95%CI (0.54-0.65) ILD Sensitivity 69.97% 95%CI (67.55-72.31%) Specificity 85.16% 95%CI (82.31-87.71%) PPV 90.77% 95%CI (89.14-92.18%) NPV 57.63% 95%CI (55.56-59.67%) DOR 13.37 95%CI (10.56-16.94) LR+ 4.72 95%CI (3.94-5.65) LR- 0.35 95%CI (0.32-0.38) Fever Sensitivity 43.02% 95%CI (40.47-45.61%) Specificity 64.19% 95%CI (60.52-67.75%) PPV 71.48% 95%CI (69.07-73.77%) NPV 35.07% 95%CI (33.47-36.71%) DOR 1.35 95%CI (1.12-1.63) LR+ 1.2 95%CI (1.07-1.35) LR- 0.89 95%CI (0.83-0.95)

Study	Number of pts	Population	Controls	Study design	Reference standard	Index test (variables)	Diagnostic performance
						<ul style="list-style-type: none"> RP 	<p>RP</p> <p>Sensitivity 46.99% 95%CI (44.41-49.59%)</p> <p>Specificity 55.35% 95%CI (51.58-59.07%)</p> <p>PPV 68.7% 95%CI (66.54-70.78%)</p> <p>NPV 33.36% 95%CI (31.56-35.21%)</p> <p>DOR 1.098 95%CI (0.917-1.317)</p> <p>LR+ 1.05 95%CI (0.95-1.16)</p> <p>LR- 0.96 95%CI (0.88-1.04)</p>
						<ul style="list-style-type: none"> MH 	<p>MH</p> <p>Sensitivity 27.98% 95%CI (25.69-30.35%)</p> <p>Specificity 97.57% 95%CI (96.15-98.58%)</p> <p>PPV 96.01% 95%CI (93.72-97.48%)</p> <p>NPV 39.38% 95%CI (38.57-40.19%)</p> <p>DOR 15.63 95%CI (9.53-25.63)</p> <p>LR+ 11.54 95%CI (7.16-18.58)</p> <p>LR- 0.74 95%CI (0.71-0.76)</p>
						<ul style="list-style-type: none"> DM rash 	<p>DM rash</p> <p>Sensitivity 32.01% 95%CI (29.62-34.47%)</p> <p>Specificity 45.93% 95%CI (42.2-49.71%)</p> <p>PPV 55.25% 95%CI (52.74-57.74%)</p> <p>NPV 24.47% 95%CI (22.88-26.12%)</p> <p>DOR 0.4 95%CI (0.33-0.48)</p> <p>LR+ 0.59 95%CI (0.54-0.66)</p> <p>LR- 1.48 95%CI (1.36-1.62)</p>
						<ul style="list-style-type: none"> Sclerodactyly 	<p>Sclerodactyly</p> <p>Sensitivity 11.97% 95%CI (10.35-13.74%)</p> <p>Specificity 59.91% 95% CI (56.18-63.57%)</p> <p>PPV 38.38% 95%CI (34.54-42.37%)</p>

Study	Number of pts	Population	Controls	Study design	Reference standard	Index test (variables)	Diagnostic performance
						<ul style="list-style-type: none"> cancer 	NPV 24.6% 95%CI (23.45-25.8%) DOR 0.2 95%CI (0.16-0.25) LR+ 0.3 95%CI (0.25-0.35) LR- 1.47 95%CI (1.38-1.57%) cancer Sensitivity 9.03% 95%CI (7.61-10.62%) Specificity 92.44% 95%CI (90.23-94.29%) PPV 71.35% 95%CI (64.72-77.18%) NPV 32.76% 95%CI (32.18-33.35%) DOR 1.21 95%CI (0.87-1.69) LR+ 1.19 95%CI (0.88-1.62) LR- 0.98 95%CI (0.96-1.01)
Pinal-Fernandez I 2015 (77)	20 patients 78 controls	Patients with definite or probable DM/PM by B&P + anti Jo1	25 Anti-TIF1-γ 17 NXP2 12 Mi2 5 MDA5 9 PM-Scl 22 Ro52 15 seronegative myositis	Cross-sectional study	Expert opinion (definite or probable DM/PM by B&P + anti Jo1)	<ul style="list-style-type: none"> Perivascular inflammation Perifascicular atrophy Primary inflammation (endomysial inflammation) 	Perivascular inflammation Sensitivity 75% 95%CI (50.9-91.34%) Specificity 39.74% 95%CI (28.83-51.46%) PPV 24.19% 95%CI (18.96-30.33%) NPV 86.11% 95%CI (73.45-93.29%) DOR 1.98 95%CI(0.64-6) p= 0.2278 LR+ 1.24 95%CI (0.91-1.7) LR- 0.63 95%CI (0.28-1.41) Perifascicular atrophy Sensitivity 60% 95%CI (36.05-80.88%) Specificity 51.3% 95%CI (39.69-62.77%) PPV 24% 95%CI (17.12-32.55%) NPV 83.33% 95%CI (73.71-89.92%) DOR 1.58 95%CI (0.58-4.3) p= 0.37 LR+ 1.23 95%CI (0.81-1.88) LR- 0.78 95%CI (0.44-1.39) Primary inflammation Sensitivity 40% 95%CI (19.12-63.95%) Specificity 78.21% 95%CI (67.41-86.76%) PPV 32% 95%CI (19.22-48.2%) NPV 83.56% 95%CI (77.72-88.11%) DOR 2.4 95%CI (0.83-6.78) p=0.1014 LR+ 1.84 95%CI (0.93-3.63)

Study	Number of pts	Population	Controls	Study design	Reference standard	Index test (variables)	Diagnostic performance
							LR- 0.77 95%CI (0.53-1.12) Accuracy 70.4% 95%CI (60.34-79.21%) Necrotizing myopathy Sensitivity 10% 95%CI (1.23-31.7%) Specificity 83.33% 95%CI (73.2-90.8%) PPV 13.33% 95%CI (3.64-38.55%) NPV 78.13% 95%CI (75.16-81.16%) DOR 0.55 95%CI (0.115-2.7) p=0.4652 LR+ 0.6 95%CI (0.15-2.45) LR- 1.08 95%CI (0.91-1.29) Mitochondrial dysfunction Sensitivity 20% 95%CI (5.73-43.66%) Specificity 70.51% 95%CI (59.11-80.3%) PPV 14.81% 95%CI (6.35-30.83%) NPV 77.46% 95%CI (72.57-81.71%) DOR 0.6 95%CI (0.18-1.98) p=0.4 LR+ 0.68 95%CI (0.26-1.74) LR- 1.13 95%CI (0.87-1.47)
Mescam-Mancini L 2015 (78)	19 cases 63 controls	Anti Jo1 patients	20 DM 21 IMNM 22 IBM	diagnostic accuracy studies	Expert opinion (anti Jo1 AND clinical manifestation of ASSD including ILD or myositis or arthritis/arthralgia)	<ul style="list-style-type: none"> myofibre necrosis perifascicular necrosis 	myofibre necrosis Sensitivity 89.47% 95%CI (66.86-98.7%) Specificity 17.46% 95%CI (9.05-29.01%) PPV 24.64% 95%CI (21.26-28.36%) NPV 84.62% 95%CI (57.15-95.78%) DOR 1.8 95%CI (0.37-8.92) p=0.473 LR+ 1.08 95%CI (0.9-1.31) LR- 0.6 95%CI (0.15-2.49) perifascicular necrosis Sensitivity 78.95% 95%CI (54.43-93.95%) Specificity 85.71% 95%CI (74.61-93.25%) PPV 62.50% 95%CI (46.58-76.11%) NPV 93.10% 95%CI (84.89-97.01%) DOR 22.5 95%CI (6.0747-83.34) p<0.0001 LR+ 5.53 95%CI (2.89-10.56)

Study	Number of pts	Population	Controls	Study design	Reference standard	Index test (variables)	Diagnostic performance
							LR- 0.25 95%CI (0.10-0.59) myofiber atrophy Sensitivity 84.21% 95%CI (60.42-96.62%) Specificity 3.17% 95%CI (0.39-11%) PPV 20.78% 95%CI (17.68-24.26%) NPV 40% 95%CI (10.72-78.73%) DOR 0.175 95%CI (0.027-1.137) p=0.0679 LR+ 0.87 95%CI (0.71-1.06) LR- 4.97 95%CI (0.9-27.61) perifascicular atrophy Sensitivity 63.16% 95%CI (38.36-83.71%) Specificity 71.43% 95%CI (58.65-82.11%) PPV 40.00% 95%CI (28.38-52.86%) NPV 86.54% 95%CI (77.76-92.20%) DOR 4.29 95%CI (1.45-12.63) p=0.0083 LR+ 2.21 95%CI (1.31-3.72) LR- 0.52 95%CI (0.28-0.95) perimysial fragmentation Sensitivity 73.68% 95%CI (48.80-90.85%) Specificity 73.02% 95%CI (60.35-83.43%) PPV 45.16% 95%CI (33.60-57.27%) NPV 90.20% 95%CI (81.30-95.20%) DOR 7.58 95%CI (2.37-24.24) p=0.0006 LR+ 2.73 95%CI (1.68-4.44) LR- 0.36 95%CI (0.17-0.78) perimysial inflammation Sensitivity 100% 95%CI (82.35-100%) Specificity 38.10% 95%CI (26.15-51.20%) PPV 32.76% 95%CI (28.64-37.16%) NPV 100%

Study	Number of pts	Population	Controls	Study design	Reference standard	Index test (variables)	Diagnostic performance
						<ul style="list-style-type: none"> • perimysial inflammation with extension to endomysium • MHC I diffuse positivity • MHC CLASS I in perifascicular regions 	<p>DOR 24.19 95%CI (1.4-419.04) p=0.0286 LR+ 1.62 95%CI (1.33-1.96) LR- 0</p> <p>perimysial inflammation with extension to endomysium Sensitivity 73.68% 95%CI (48.80-90.85%) Specificity 33.33% 95%CI (21.95-46.34%) PPV 25.00% 95%CI (19.48-31.47%) NPV 80.77% 95%CI (64.69-90.59%) DOR 1.4 95%CI (0.44-4.41) p=0.5655 LR+ 1.11 95%CI (0.80-1.52) LR- 0.79 95%CI (0.34-1.81)</p> <p>MHC I diffuse positivity Sensitivity 94.74% 95%CI (73.97-99.87%) Specificity 25.40% 95%CI (15.27-37.94%) PPV 27.69% 95%CI (24.26-31.41%) NPV 94.12% 95%CI (69.39-99.12%) DOR 6.13 95%CI (0.76-49.64) p=0.0894 LR+ 1.27 95%CI (1.06-1.52) LR- 0.21 95%CI (0.03-1.46)</p> <p>MHC CLASS I in perifascicular regions Sensitivity 78.95% 95%CI (54.43-93.95%) Specificity 71.43% 95%CI (58.65-82.11%) PPV 45.45% 95%CI (34.60-56.76%) NPV 91.84% 95%CI (82.28-96.46%) DOR 9.375 95%CI (2.74-32.11) p=0.0004 LR+ 2.76 95%CI (1.75-4.35) LR- 0.29 95%CI (0.12-0.71)</p> <p>C5b-9 sarcolemmal immunoreactivity</p>

Study	Number of pts	Population	Controls	Study design	Reference standard	Index test (variables)	Diagnostic performance
						<ul style="list-style-type: none"> C5b-9 sarcolemmal immunoreactivity C5b-9 perifascicular 	<p>Sensitivity 84.21% 95%CI (60.42-96.62%) Specificity 25.40% 95%CI (15.27-37.94%) PPV 25.40% 95%CI (21.09-30.25%) NPV 84.21% 95%CI (63.47-94.24%) DOR 1.82 95%CI (0.47-7.05) p= 0.39 LR+ 1.13 95%CI (0.89-1.44) LR- 0.62 95%CI (0.20-1.91)</p> <p>C5b-9 perifascicular Sensitivity 26.32% 95%CI (9.15-51.20%) Specificity 19.05% 95%CI (10.25-30.91%) PPV 8.93% 95%CI (4.38-17.36%) NPV 46.15% 95%CI (32.52-60.38%) DOR 0.084 95%CI (0.025-0.28) p= 0.0001 LR+ 0.33 95%CI (0.15-0.70) LR- 3.87 95%CI (2.18-6.88)</p>
Uruha 2018 (79)	30 ASSD 78 controls	Patients with myositis and ARS positivity	10 anti TIF1-gamma 13 anti NXP2 6 anti Mi-2 10 anti MDA5 1 anti SAE 17 antibody negative DM	Case-control study	Expert opinion (ARS and myositis)	<ul style="list-style-type: none"> sarcolemmal myxovirus resistance protein A (MxA) expression RIG-1 expression perifascicular atrophy 	<p>sarcolemmal myxovirus resistance protein A (MxA) expression Sensitivity 0 Specificity 43.6% 95%CI(32.39% to 55.30%) PPV 0 NPV 53.12% 95%CI(46.82-59.33%) DOR 0.0127 95%CI(0.0008 to 0.2153) LR+ 0 LR- 2.29 95%CI(1.78-2.95)</p> <p>RIG-1 expression Sensitivity 0 Specificity 89.74% 95%CI(80.79% to 95.47%) PPV 0 NPV 70% 95%CI(68.40% to 71.55%) DOR 0.136 95%CI(0.0076 to 2.4311) LR+ 0 LR- 1.11 95%CI(1.03 to 1.20)</p> <p>perifascicular atrophy</p>

Study	Number of pts	Population	Controls	Study design	Reference standard	Index test (variables)	Diagnostic performance
							Sensitivity 20% 95%CI(7.71% to 38.57) Specificity 57.69% 95%CI(45.98% to 68.81%) PPV 15.38% 95%CI(7.83% to 28.02%) NPV 65.22% 95%CI(59.09% to 70.88%) DOR 0.34 95%CI(0.1253 to 0.9277)(1) LR+ 0.47 95%CI(0.22 to 1.01) LR- 1.39 95%CI(1.07 to 1.80)
Andersson 2017 (80)	66 ASSD 67 controls	Patients with ARS positivity, ILD or myositis	Healthy matched control	Case control	Expert opinion (ARS positivity + ILD and/or PM/DM diagnosis)	<ul style="list-style-type: none"> MRI Muscle edema MRI Fascial edema MRI Fatty replacement MRI Muscle volume reduction 	Muscle edema Sensitivity 37.88% 95%CI(26.22 to 50.66%) Specificity 88.06% 95%CI(77.82% to 94.70%) PPV 75.76% 95%CI(60.34% to 86.52%) NPV 59% 95%CI(53.89% to 63.92%) DOR 4.4970 95%CI(1.8461 to 10.9542) LR+ 3.17 95%CI(1.54 to 6.52) LR- 0.71 95%CI(0.57 to 0.87) Fascial edema Sensitivity 28.79% 95%CI(18.30% to 41.25%) Specificity 92.54% 95%CI(83.44% to 97.53%) PPV 79.17% 95%CI(60.12% to 90.55%) NPV 56.88% 95%CI(52.73% to 60.94%) DOR 5.0128 95%CI(1.7444 to 14.4046) LR+ 3.86 95%CI(1.53 to 9.72) LR- 0.77 95%CI(0.65 to 0.91) Fatty replacement Sensitivity 42.42% 95%CI(30.34% to 55.21%) Specificity 95.52% 95%CI(87.47% to 99.07%) PPV 90.32% 95%CI(74.88% to 96.69%)

Study	Number of pts	Population	Controls	Study design	Reference standard	Index test (variables)	Diagnostic performance
							NPV 62.75% 95%CI(57.64% to 67.59%) DOR 16.46 95%CI(4.6891 to 57.7517) LR+ 9.47 95%CI(3.03 to 29.66) LR- 0.6 95%CI(0.49 to 0.75) Muscle volume reduction Sensitivity 13.64% 95%CI(6.43% to 24.31%) Specificity 92.54% 95%CI(83.44% to 97.53%) PPV 64.29% 95%CI(38.91% to 83.57%) NPV 52.1% 95%CI(49.16% to 55.02%) DOR 1.958 95%CI(0.6194 to 6.1888) LR+ 1.83 95%CI(0.65 to 5.16) LR- 0.93 95%CI(0.83 to 1.05)
Watanabe 2011 (81)	13 ASSD 185 controls	Patients with ILD and ARS positivity	Patients with ILD without ARS	Retrospective longitudinal	Expert opinion (IIP + ARS positivity)	<ul style="list-style-type: none"> • Fever (>38 °C) • Body weight loss • Dyspnea • Cough • Other respiratory symptoms • Fine crackles • Clubbed fingers • Arthralgia or joint deformity • Raynaud’s phenomenon • Cutaneous symptoms 	Fever Sensitivity 15.38% 95%CI(1.92% to 45.45%) Specificity 94.87 % 95%CI(90.77% to 97.51%) PPV 16.67% 95%CI(4.65% to 45.05%) NPV 94.39 % 95%CI(93.01% to 95.51%) DOR 3.1818 95%CI(0.6197 to 16.3356) LR+ 3 95%CI(0.73 to 12.30) LR- 0.89 95%CI(0.71 to 1.13) Body weight loss Sensitivity 7.69% 95%CI(0.19% to 36.03%) Specificity 95.14 % 95%CI(90.97% to 97.75%) PPV 10% 95%CI(1.50% to 44.79%) NPV 93.62 % 95%CI(92.59% to 94.51%)

Study	Number of pts	Population	Controls	Study design	Reference standard	Index test (variables)	Diagnostic performance
							<p>DOR 1.6296 95%CI(0.1904 to 13.9508)</p> <p>LR+ 1.58 95%CI(0.22 to 11.54)</p> <p>LR- 0.97 95%CI(0.83 to 1.14)</p> <p>Dyspnea</p> <p>Sensitivity 92.31% 95%CI(63.97% to 99.81%)</p> <p>Specificity 16.76 % 95%CI(11.68% to 22.93%)</p> <p>PPV 7.23% 95%CI(6.17% to 8.45%)</p> <p>NPV 96.88 % 95%CI(82.11% to 99.52%)</p> <p>DOR 2.4156 95%CI(0.3029 to 19.2621)</p> <p>LR+ 1.11 95%CI(0.94 to 1.31)</p> <p>LR- 0.46 95%CI(0.07 to 3.10)</p> <p>Cough</p> <p>Sensitivity 38.46% 95%CI(13.86% to 68.42%)</p> <p>Specificity 61.62% 95%CI(54.20% to 68.66%)</p> <p>PPV 6.58% 95%CI(3.34% to 12.55%)</p> <p>NPV 3.44 % 95%CI(90.13% to 95.69%)</p> <p>DOR 1.0035 95%CI(0.3159 to 3.1884)</p> <p>LR+ 1 95%CI(0.49 to 2.04)</p> <p>LR- 1 95%CI(0.64 to 1.56)</p> <p>Other respiratory symptoms</p> <p>Sensitivity 7.69% 95%CI(0.19% to 36.03%)</p> <p>Specificity 95.14 % 95%CI(90.97% to 97.75%)</p> <p>PPV 10% 95%CI(1.50% to 44.79%)</p>

Study	Number of pts	Population	Controls	Study design	Reference standard	Index test (variables)	Diagnostic performance
							<p>NPV 93.62% 95%CI(92.59% to 94.51%)</p> <p>DOR 1.6296 95%CI(0.1904 to 13.9508)</p> <p>LR+ 1.58 95%CI(0.22 to 11.54)</p> <p>LR- 0.97 95%CI(0.83 to 1.14)</p> <p> Fine crackles</p> <p>Sensitivity 92.31% 95%CI(63.97% to 99.81%)</p> <p>Specificity 9.73 % 95%CI(5.87% to 14.94%)</p> <p>PPV 6.70% 95%CI(5.75% to 7.80%)</p> <p>NPV 94.74 % 95%CI(72.25% to 99.20%)</p> <p>DOR 1.2934 95%CI(0.1588 to 10.5325)</p> <p>LR+ 1.02 95%CI(0.87 to 1.20)</p> <p>LR- 0.79 95%CI(0.11 to 5.47)</p> <p> Clubbed fingers</p> <p>Sensitivity 7.69% 95%CI(0.19% to 36.03%)</p> <p>Specificity 81.62 % 95%CI(75.28% to 86.92%)</p> <p>PPV 2.86% 95%CI(0.43% to 16.54%)</p> <p>NPV 92.64 % 95%CI(91.38% to 93.72%)</p> <p>DOR 0.3701 95%CI(0.0465 to 2.9438)</p> <p>LR+ 0.42 95%CI(0.06 to 2.82)</p> <p>LR- 1.13 95%CI(0.95 to 1.34)</p> <p> Arthralgia or joint deformity</p> <p>Sensitivity 15.38% 95%CI(1.92% to 45.45%)</p>

Study	Number of pts	Population	Controls	Study design	Reference standard	Index test (variables)	Diagnostic performance
							<p>Specificity 97.84 % 95%CI(94.56% to 99.41%)</p> <p>PPV 33.33% 95%CI(9.16% to 71.27%)</p> <p>NPV 94.27 % 95%CI(92.88% to 95.41%)</p> <p>DOR 8.2273 95%CI(1.3556 to 49.9334)</p> <p>LR+ 7.12 95%CI(1.43 to 35.30)</p> <p>LR- 0.86 95%CI(0.69 to 1.09)</p> <p>Raynaud’s Phenomenon</p> <p>Sensitivity 7.69% 95%CI(0.19% to 36.03%)</p> <p>Specificity 97.84 % 95%CI(94.56% to 99.41%)</p> <p>PPV 20.00% 95%CI(2.92% to 67.52%)</p> <p>NPV 93.78 % 95%CI(92.79% to 94.64%)</p> <p>DOR 3.7708 95%CI(0.3904 to 36.4227)</p> <p>LR+ 3.56 95%CI(0.43 to 29.58)</p> <p>LR- 0.94 95%CI(0.81 to 1.11)</p> <p>CUTANEOUS SYMPTOMS</p> <p>Sensitivity 30.77% 95%CI(9.09% to 61.43%)</p> <p>Specificity 98.38 % 95%CI(95.33% to 99.66%)</p> <p>PPV 57.14% 95%CI(24.98% to 84.22%)</p> <p>NPV 95.29 % 95%CI(93.36% to 96.67%)</p> <p>DOR 26.963 95%CI(5.2314 to 138.9684)</p> <p>LR+ 18.97 95%CI(4.74 to 75.98)</p>

Study	Number of pts	Population	Controls	Study design	Reference standard	Index test (variables)	Diagnostic performance
							LR- 95.29 95%CI(93.36% to 96.67%)
Cerbelli 2018 (50)	18	Consecutive patients with anti ARS antibodies and suspected myositis referred for histological evaluation.	DM according to the ENMC criteria	Case-control	Expert opinion + antiJo1 or PL7	<ul style="list-style-type: none"> • Perifascicular Necrosis • Perifascicular Regeneration • Perifascicular Atrophy • Endomysial infiltrates (inflammation) 	<p>Sensitivity 66% 95%CI (34% to 90%) Specificity 57% 95%CI (18% to 90%) PPV 72% 95%CI (50% to 87%) NPV 50% 95%CI (26% to 73%) LR+ 0.61 95%CI (0.61 to 4) LR- 0.58 95%CI (0.21 to 1.63)</p> <p>Sensitivity 66% 95% CI (34% to 90%) Specificity 28% 95% CI (3% to 70%) PPV 61% 95% CI (46% to 74%) NPV 33% 95% CI (10% to 67%) LR+ 0.93 95% CI (0.46 to 0.74) LR- 1.17 95% CI (0.28 to 4.82)</p> <p>Sensitivity 36% 95% CI (10% to 69%) Specificity 0% 95% CI (0% to 40%) PPV 36% 95% CI (20% to 55%) LR+ 0.36 (0.17 to 0.79)</p> <p>Sensitivity 72% 95% CI (39% to 93%) Specificity 28% 95% CI (3% to 70%) PPV 61% 95% CI (35% to 82%) NPV 40 % 95% CI (12% to 75%) LR+ 1.02 95% CI (0.56 to 1.84) LR- 0.95 95% CI (0.21 to 4.35)</p>

Study	Number of pts	Population	Controls	Study design	Reference standard	Index test (variables)	Diagnostic performance
						<ul style="list-style-type: none"> <li data-bbox="1323 240 1507 309">• Perimysial inflammation <li data-bbox="1323 552 1516 620">• Perimysial fragmentation <li data-bbox="1323 863 1574 884">• MHC I enhancement <li data-bbox="1323 1174 1554 1243">• C5B9 sarcolemmal positivity 	<p data-bbox="1608 197 1966 218">Sensitivity 54% 95% CI (23% to 83%)</p> <p data-bbox="1608 240 1973 261">Specificity 14% 95% CI (0.3% to 57%)</p> <p data-bbox="1608 284 1890 304">PPV 5% 95% CI (35% to 82%)</p> <p data-bbox="1608 327 1899 347">NPV 16% 95% CI (2% to 57%)</p> <p data-bbox="1608 370 1912 391">LR+ 0.64 95 % CI (0.34 to 1.18)</p> <p data-bbox="1608 413 1910 434">LR- 3.18 95% CI (0.46 to 21.85)</p> <p data-bbox="1608 504 1968 525">Sensitivity 81% 95% CI (48% to 97%)</p> <p data-bbox="1608 547 1955 568">Specificity 28% 95% CI (3% to 70%)</p> <p data-bbox="1608 590 1908 611">PPV 64% 95% CI (51% to 75%)</p> <p data-bbox="1608 633 1910 654">NPV 50% 95% CI (15% to 84%)</p> <p data-bbox="1608 676 1901 697">LR+ 1.15 95% CI (0.66 to 1.98)</p> <p data-bbox="1608 719 1901 740">LR- 0.64 95 % CI (0.11 to 3.54)</p> <p data-bbox="1608 810 1966 831">Sensitivity 54% 95% CI (23% to 83%)</p> <p data-bbox="1608 853 1973 874">Specificity 14% 95% CI (0.3% to 57%)</p> <p data-bbox="1608 896 1912 917">PPV 050% 95% CI (35% to 64%)</p> <p data-bbox="1608 940 1892 960">NPV 16% 95% CI (2% to 57%)</p> <p data-bbox="1608 983 1883 1003">LR+ 0.64 95% CI (0.34,1.18)</p> <p data-bbox="1608 1026 1883 1046">LR- 3.18 95% CI (0.46,21.85)</p> <p data-bbox="1608 1117 1968 1137">Sensitivity 72% 95% CI (39% to 93%)</p> <p data-bbox="1608 1160 1973 1181">Specificity 14% 95% CI (3.6% to 57%)</p> <p data-bbox="1608 1203 1908 1224">PPV 57% 95% CI (45% to 68%)</p> <p data-bbox="1608 1246 1899 1267">NPV 25% 95% CI (4% to 72%)</p> <p data-bbox="1608 1289 1906 1310">LR+ 0.85 95% CI (0.53 to 1.36)</p> <p data-bbox="1608 1332 1915 1353">LR- 1.91 95% CI (0.24 to 14.91)</p>

Study	Number of pts	Population	Controls	Study design	Reference standard	Index test (variables)	Diagnostic performance
						<ul style="list-style-type: none"> COX deficient fibers 	Sensitivity 0% 95% CI (0% to 28%) Specificity 0% 95% CI (0% to 40%)
Mozaffar 2000 (82)	11	Patients who underwent muscle biopsy for myositis	26 DM 27 PM 8 IBM 5 fasciitis	Case-control	Myositis + anti Jo1	<ul style="list-style-type: none"> Perifascicular atrophy Perifascicular necrosis/regeneration Perimysial Inflammation 	Perifascicular atrophy Sensitivity 100% (CI 71.5%-100%) Specificity 59% (CI 46.3-71%) PPV 28.95% (CI 23.36-35.25%) NPV 100% AUC DOR LR+ 2.44 (CI 1.83-3.27) LR- 100 Perifascicular necrosis/regeneration Sensitivity 90.91% (CI 58.72-99.77%) Specificity 71.21% (CI 58.75-81.7%) PPV 34.48% (CI 25.64-44.55%) NPV 97.92% (CI 87.82-99.67%) AUC DOR LR+ 3.16 (2.07-4.82) LR- 0.13 (0.02-0.83) Perimysial Inflammation Sensitivity 100% (CI 71.51-100%) Specificity 71.21% (CI 58.75-81.7%) PPV 36.67% (CI 28.37-45.83%) NPV 100% AUC DOR LR+ 3.47 (CI 2.38-5.08) LR- 0 Endomysial inflammation Sensitivity 18.18% (CI 2.28-51.78%)

Study	Number of pts	Population	Controls	Study design	Reference standard	Index test (variables)	Diagnostic performance
						<ul style="list-style-type: none"> ○ Endomysial Inflammation ○ Perivascular inflammation ○ Perimysial fragmentation ○ ALP Perimysial staining 	<p>Specificity 48.48% (CI 35.99-61.12%) PPV 5.56% (CI 1.62-17.39%) NPV 78.05% (CI 70.99-83.78%) AUC DOR LR+ 0.35 (CI 0.1-1.26) LR- 1.69 (CI 1.16-2.45)</p> <p>Perivascular inflammation Sensitivity 9.09% (CI 0.23-41.28%) Specificity 39.39% (CI 27.58-52.19%) PPV 2.44% (CI 0.38-14.06%) NPV 72.22% (CI 64.63-78.72%) AUC DOR LR+ 0.15 (CI 0.02-0.98) LR- 2.31 (CI 1.62-3.28)</p> <p>Perimysial fragmentation Sensitivity 100% (CI 71.51-100%) Specificity 84.84% (CI 73.9-92.49%) PPV 52.38% (CI 38.33-66.07%) NPV 100% AUC DOR LR+ 6.6 (CI 3.73-11.68) LR- 0</p> <p>ALP perimysial staining Sensitivity 90.91% (CI 58.72-99.77%) Specificity 59.09% (CI 46.29-71.05%) PPV 27.01% (CI 20.78-34.34%) NPV 97.5% (CI 85.62-99.61%) AUC DOR LR+ 2.22 (CI 1.57-3.14) LR- 0.15 (CI 0.02-1.01)</p>

Study	Number of pts	Population	Controls	Study design	Reference standard	Index test (variables)	Diagnostic performance
						<ul style="list-style-type: none"> <li data-bbox="1323 284 1532 352">○ ALP Small vessel staining <li data-bbox="1323 592 1554 751">○ Perifascicular COX deficiency (mitochondrial dysfunction) <li data-bbox="1323 991 1518 1059">○ Scattered COX deficiency 	<p>ALP small vessels staining Sensitivity 9.09% (CI 0.23-41.28%) Specificity 60.61% (CI 47.81-72.42%) PPV 3.7% (CI 0.58-20.33%) NPV 80% (CI 75.33-83.97%) AUC DOR LR+ 0.23 (CI 0.03-1.53) LR- 1.5 (1.15-1.96)</p> <p>Perifascicular COX deficiency Sensitivity 0% (CI 0-28.49%) Specificity 75.76% (CI 63.64-85.46%) PPV 0 NPV 81.97% (CI 79.86-83.9%) AUC DOR LR+ 0 LR- 1.32 (CI 1.15-1.51)</p> <p>Scattered COX deficiency Sensitivity 0% (CI 0-28.49%) Specificity 78.79% (CI 66.98-87.89%) PPV 0 NPV 82.54% (CI 80.66-84.27%) AUC DOR LR+ 0 LR- 1.27 (1.12-1.44)</p>

Figure S2. Risk of Bias for studies included in Q2, assessed by QUADAS -2.

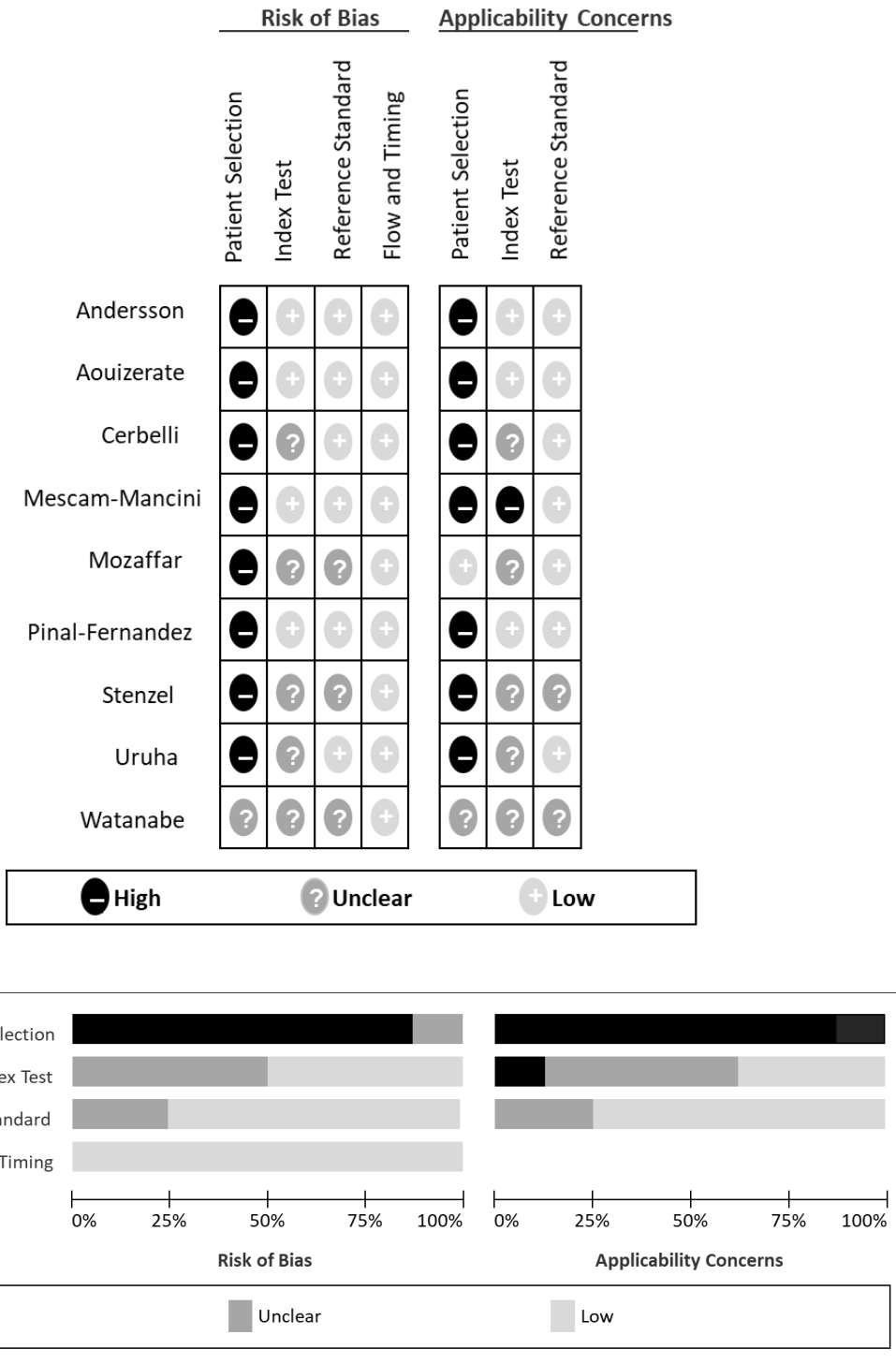
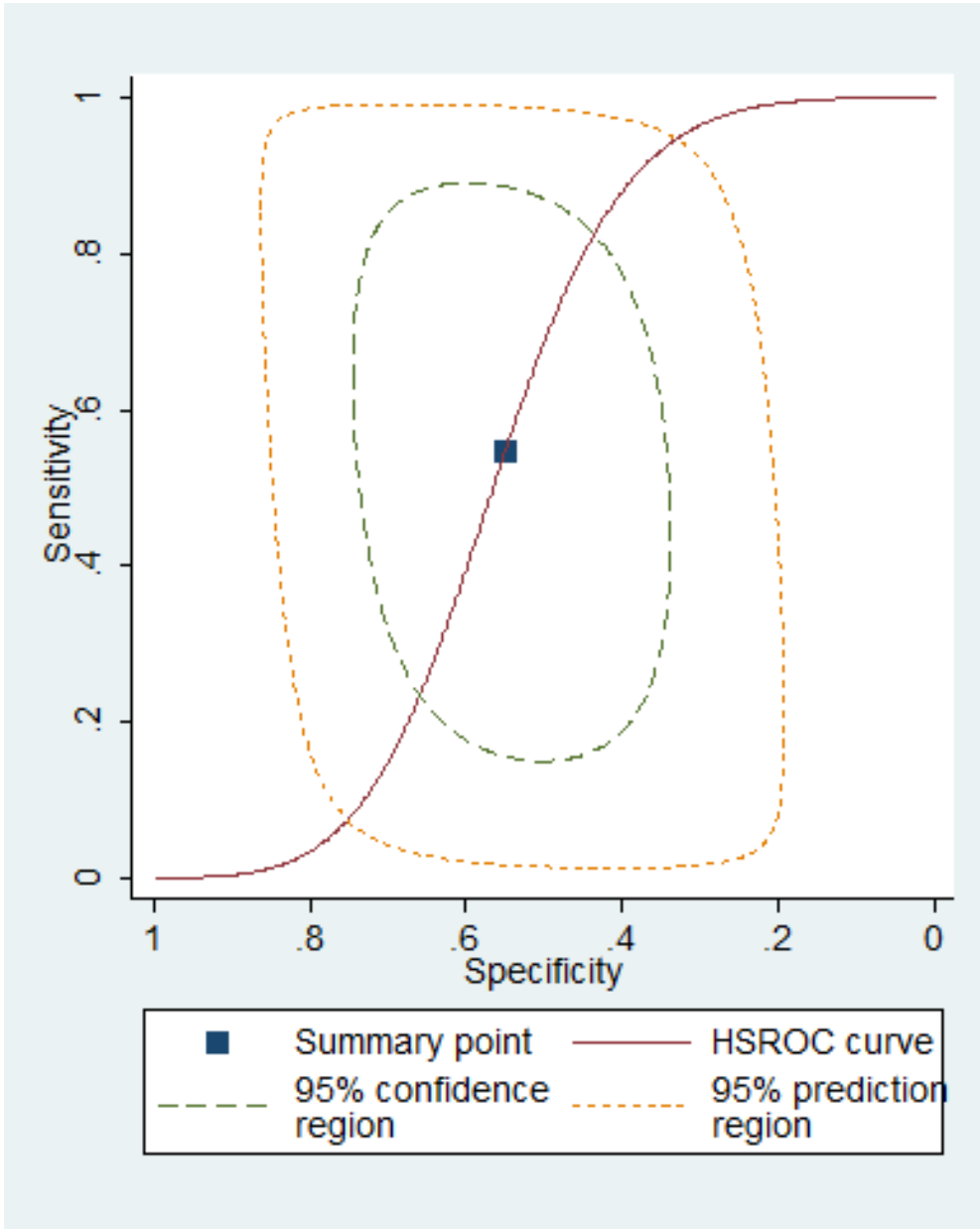


Figure S3. Hierarchical summary ROC for perifascicular necrosis/atrophy.



- Pooled sensitivity (95% CI) 0.55 (0.3,0.77)
- Pooled specificity (95% CI) 0.55 (0.44,0.65)
- Pooled LR + (95%CI) 1.21 (0.68,2.14)
- Pooled LR- (95% CI) 0.82 (0.44,1.54)