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Clinical Characteristics of Anti-Synthetase Syndrome: Analysis From the Classification Criteria for Anti-Synthetase Syndrome Project

Sara Faghihi-Kashani,[1] Akira Yoshida,[2] Francisca Bozan,[3] Giovanni Zanframundo,[4] Davide Rozza,[5] Aravinthan Loganathan,[6] Eduardo Dourado,[7] Gianluca Sambataro,[8] Iazsmin Bauer-Ventura,[9] Sangmee Sharon Bae,[10] Darosa Lim,[11] Daphne Rivero-Gallegos,[12] Yasuhiko Yamano,[13] Albert Selva-O'Callaghan,[14] Andrew L. Mammen,[15] Carlo A. Scirè,[16] Carlomaurizio Montecucco,[4] Chester V. Oddis,[1] David Fiorentino,[17] Francesco Bonella,[18] Frederick W. Miller,[19] Ingrid E. Lundberg,[20] Jens Schmidt,[21] Jorge Rojas-Serrano,[12] Marie Hudson,[22] Masataka Kuwana,[2] Miguel Angel González-Gay,[23] Neil McHugh,[24] Tamera J. Corte,[25] Tracy Jennifer Doyle,[26] Victoria P. Werth,[11] Latika Gupta,[27] Diana Isabel Perez Roman,[12] Lorenzo M. Bianchessi,[28] Phani Kumar Devarasetti,[29] Samuel Katsuyuki Shinjo,[30] Fabrizio Luppi,[31] Ilaria Cavazzana,[32] Siamak Moghadam-Kia,[1] Marco Fornaro,[33] Elizabeth R. Volkmann,[10] Matteo Piga,[34] Jesus Loarce-Martos,[35] Giacomo De Luca,[36] Johannes Knitza,[37] Veronica Wolff-Cecchi,[38] Marco Sebastiani,[39] Adam Schiffenbauer,[40] Lisa G. Rider,[40] Raquel Campanilho-Marques,[41] Lucian Marts,[42] Elena Bravi,[43] Harsha Gunawardena,[44] Rohit Aggarwal,[1] and Lorenzo Cavagna,[4] on behalf of the Classification Criteria for Anti-Synthetase Syndrome Project participating investigators

Objective. Anti-synthetase syndrome (ASSD) is a rare systemic autoimmune rheumatic disease (SARD) with significant heterogeneity and no shared classification criteria. We aimed to identify clinical and serological features associated with ASSD that may be suitable for inclusion in the data-driven classification criteria for ASSD.

Methods. We used a large, international, multicenter "Classification Criteria for Anti-synthetase Syndrome" (CLASS) project database, which includes both patients with ASSD and controls with mimicking conditions, namely, SARDs and/or interstitial lung disease (ILD). The local diagnoses of ASSD and controls were confirmed by project team members. We employed univariable logistic regression and multivariable Ridge regression to evaluate clinical and serological features associated with an ASSD diagnosis in a randomly selected subset of the cohort.

Results. Our analysis included 948 patients with ASSD and 1,077 controls. Joint, muscle, lung, skin, and cardiac involvement were more prevalent in patients with ASSD than in controls. Specific variables associated with ASSD included arthritis, diffuse myalgia, muscle weakness, muscle enzyme elevation, ILD, mechanic's hands, secondary pulmonary hypertension due to ILD, Raynaud phenomenon, and unexplained fever. In terms of serological variables, Jo-1 and non–Jo-1 anti-synthetase autoantibodies, antinuclear antibodies with cytoplasmic pattern, and anti-Ro52 autoantibodies were associated with ASSD. In contrast, isolated arthralgia, dysphagia, electromyography/magnetic resonance imaging/muscle biopsy findings suggestive of myopathy, inflammatory rashes, myocarditis, and pulmonary arterial hypertension did not differentiate between patients with ASSD and controls or were inversely associated with ASSD.

Conclusion. We identified key clinical and serological variables associated with ASSD, which will help clinicians and offer insights into the development of data-driven classification criteria for ASSD.

INTRODUCTION

Anti-synthetase syndrome (ASSD) is a rare systemic autoimmune rheumatic disease (SARD) usually characterized by the presence of autoantibodies against aminoacyl-transfer RNA synthetases (ARSs).[1,2] Until now, eight anti-ARS autoantibodies have been identified, namely, anti–Jo-1, PL-7, PL-12, EJ, OJ, KS, Zo, and Ha autoantibodies,[3] and other possible anti-ARS

autoantibodies have been recently recognized.[4–6] The clinical manifestations of ASSD include the classic "triad" of arthritis, myositis, and interstitial lung disease (ILD), along with other typical clinical features including fever, Raynaud phenomenon, and mechanic's hands/hiker's feet.[7,8]

Although ASSD is commonly categorized as a subtype of idiopathic inflammatory myopathies (IIMs), not all patients with ASSD exhibit myositis. In fact, most studies have shown a higher prevalence of ILD than myositis, particularly among patients with non–Jo-1 anti-ARS autoantibodies.[9,10] Furthermore, a study from the American and European Network of Anti-synthetase Syndrome (AENEAS) cohort reported that 24% of patients with anti–Jo-1–positive ASSD presented with isolated arthritis, and these patients were often classified as having rheumatoid arthritis (RA).[11] In this study, only 20% of patients had the complete "triad" at presentation.[12] For these reasons, patients with ASSD, in particular those presenting with isolated arthritis or ILD and non–Jo-1 anti-ARS autoantibodies, may not meet the 2017 EULAR/American College of Rheumatology (ACR) classification criteria for adult and juvenile IIMs and their major subgroups,[13] in which muscle involvement is weighted heavily, whereas arthritis, ILD, and non–Jo-1 anti-ARS autoantibodies are not included.[14] Moreover, ~20% of patients with ASSD present with inflammatory rashes and can be diagnosed with dermatomyositis (DM).[9] Whether these patients are better characterized as having DM or ASSD needs to be explored further, especially due to differences in the pathophysiologic findings between DM and ASSD.[15,16]

Serological testing of anti-ARS autoantibodies is considered crucial for ASSD diagnosis; however, the availability, methodology, and accuracy of anti-ARS autoantibody detection vary significantly among different centers and countries.[17] Because of the lack of standardized and reliable anti-ARS autoantibody testing,[18] defining ASSD based solely on the positivity of the antibodies may lead to both under- and overclassification. Given these disparities, there is an increasing consensus on the need for specific clinical or clinic-serologic classification criteria for ASSD that are distinct from other forms of IIMs or ILD.[19,20] Although several classification criteria for ASSD have been proposed by different groups,[21–23] they lack a data-driven foundation and have not been validated, nor are they widely accepted. The

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[1]Sara Faghihi-Kashani, MD, MPH, Chester V. Oddis, MD, Siamak Moghadam-Kia, MD, MPH, Rohit Aggarwal, MD, MS: University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; [2]Akira Yoshida, MD, Masataka Kuwana, MD, PhD: Nippon Medical School Graduate School of Medicine, Tokyo, Japan; [3]Francisca Bozan, MD: Hospital Clínico Universidad de Chile, Santiago, Chile; [4]Giovanni Zanframundo, MD, PhD, Carlomaurizio Montecucco, MD, Lorenzo Cavagna, MD: Università di Pavia and Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, Pavia, Italy; [5]Davide Rozza, MSc: Italian Society of Rheumatology, Milan, Italy; [6]Aravinthan Loganathan, MBBS: Royal National Hospital for Rheumatic Diseases and University of Bath, Bath, UK, and Arthritis Australia, Broadway, Glebe, New South Wales, Australia; [7]Eduardo Dourado, MD: Centro Hospitalar do Baixo Vouga and Egas Moniz Health Alliance, Aveiro, and Faculdade de Medicina, Universidade de Lisboa, Lisbon, Portugal; [8]Gianluca Sambataro, MD: Policlinico G. Rodolico-San Marco, University of Catania, Catania, Italy; [9]Iazsmin Bauer Ventura, MD, MSc: University of Chicago, Chicago, Illinois; [10]Sangmee Sharon Bae, ••, Elizabeth R. Volkmann, MD: David Geffen School of Medicine, University of California, Los Angeles, California; [11]Darosa Lim, MD, Victoria P. Werth, MD: Perelman School of Medicine & Corporal Michael J. Crescenz Department of Veterans Affairs Medical Center, Philadelphia, Pennsylvania; [12]Daphne Rivero Gallegos, MD, MS, Jorge Rojas-Serrano, PhD, Diana Isabel Perez Roman, MD: Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City, Mexico; [13]Yasuhiko Yamano, MD, PhD: Tosei General Hospital, Seto, Japan; [14]Albert Selva-O'Callaghan, PhD: Vall d'Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain; [15]Andrew L. Mammen, MD, PhD: National Institute of Arthritis and Musculoskeletal and Skin Diseases, NIH, Bethesda, and Johns Hopkins University School of Medicine, Baltimore, Maryland; [16]Carlo A. Scirè, MD, PhD: University of Milano Bicocca, Milan, and Istituto di Ricovero e Cura a Carattere Scientifico San Gerardo dei Tintori Foundation, Monza, Italy; [17]David Fiorentino, MD, PhD: Stanford University School of Medicine, Redwood City, California; [18]Francesco Bonella, PhD: Ruhrlandklinik University Hospital, University of Duisburg-Essen, Essen, Germany; [19]Frederick W. Miller, MD: National Institute of Environmental Health Sciences, NIH, Durham, North Carolina; [20]Ingrid E. Lundberg, MD, PhD: Karolinska Institutet, Stockholm, Sweden; [21]Jens Schmidt, MD, PhD: University Medical Center Göttingen, Göttingen, Germany, and Immanuel Klinik Rüdersdorf, University Hospital of the Brandenburg Medical School and Faculty of Health Sciences Brandenburg, Brandenburg Medical School Theodor Fontane, Rüdersdorf bei Berlin, Germany; [22]Marie Hudson, MD, MPH: McGill University, Montreal, Quebec, Canada; [23]Miguel Angel González-Gay, MD, PhD : Instituto de Investigación Sanitaria-Fundación Jiménez Díaz, Madrid, and University of Cantabria, Santander, Spain; [24]Neil McHugh, MBChB, MD: University of Bath, Bath, UK; [25]Tamera J. Corte, MD, PhD : Royal Prince Alfred Hospital, University of Sydney, Sydney, New South Wales, Australia; [26]Tracy Jennifer Doyle, MD, MPH: Brigham and Women's Hospital, Boston, Massachusetts; [27]Latika Gupta, MD, MRCP, DM: Royal Wolverhampton Hospitals NHS Trust, Wolverhampton, and The University of Manchester, Manchester, UK; [28]Lorenzo M. Bianchessi, MD: Università di Pavia, Pavia, Italy; [29]Phani Kumar Devarasetti, MD: The University of Manchester, Manchester, UK; [30]Samuel Katsuyuki Shinjo, MD, PhD: Faculdade de Medicina Faculdade de Medicina, Universidade de São Paulo, Universidade de Sao Paulo, Sao Paulo, Brazil; [31]Fabrizio Luppi, MD: University of Milano Bicocca, Monza, Italy; [32]Ilaria Cavazzana, MD: University and Azienda Ospedaliera Spedali Civili, Brescia, Italy; [33]Marco Fornaro, MD: University of Bari, Bari, Italy; [34]Matteo Piga, MD: University of Cagliari and Azienda Ospedaliera Universitaria Cagliari, Cagliari, Italy; [35]Jesus Loarce-Martos, MD: Hospital Universitario Ramón y Cajal, Madrid, Spain; [36]Giacomo De Luca, MD: Vita-Salute San Raffaele University & Istituto di Ricovero e Cura a Carattere Scientifico San Raffaele Hospital, Milan, Italy; [37]Johannes Knitza, MD: University Hospital of Giessen and Marburg, Philipps-University Marburg, Marburg, and Friedrich-Alexander-Universität Erlangen-Nürnberg and Universitätsklinikum Erlangen, Erlangen, Germany; [38]Veronica Wolff-Cecchi, MD: Instituto Nacional del Torax and Universidad de Chile, Santiago, Chile; [39]Marco Sebastiani, MD: Guglielmo da Saliceto Hospital of Piacenza, University of Parma, Parma, Italy; [40]Adam Schiffenbauer, MD, Lisa G. Rider, MD: National Institute of Environmental Health Sciences, NIH, Bethesda, Maryland; [41]Raquel Campanilho-Marques, MD, MSc: Faculdade de Medicina, Universidade de Lisboa and Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal; [42]Lucian Marts, MD: Emory University School of Medicine, Atlanta, Georgia; [43]Elena Bravi, MD: Ospedale Guglielmo da Saliceto, Piacenza, Italy; [44]Harsha Gunawardena, MRCP, PhD: North Bristol NHS Trust, Bristol, UK.

Drs Faghihi-Kashani and Yoshida are co-first authors and contributed equally to this work. Drs Bozan and Zanframundo are co-second authors and contributed equally to this work. Drs Aggarwal and Cavagna are co-senior authors and contributed equally to this work.

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Address correspondence via email to Rohit Aggarwal, MD, MS, at aggarwalr@upmc.edu; or to Lorenzo Cavagna, MD, at lorenzo.cavagna@unipv.it.

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lack of data- and consensus-driven classification criteria for ASSD has hindered the development of international, multicenter studies and clinical trials for this rare and potentially life-threatening condition.

The Classification Criteria for Anti-synthetase Syndrome (CLASS) project is an international collaborative study funded by EULAR/ACR to develop and validate data and consensus-driven classification criteria for ASSD. For the data-driven process, the CLASS database, comprising 2,035 ASSD cases and 2,140 control diseases from 92 centers across 30 countries worldwide, has been developed. In this manuscript, we report the results of univariable and multivariable analysis in the CLASS database to identify clinical and serological variables associated with ASSD. The identified variables will be incorporated into the process leading to data-driven classification criteria for ASSD.

PATIENTS AND METHODS

The CLASS project. The CLASS project is an international, multicenter, retrospective observational study funded by EULAR/ACR to develop and validate classification criteria for ASSD (co–principal investigators [PIs]: RA and LC). The complete list of the CLASS project investigators is provided in Appendix A as well as in Supplementary Table S1. We recruited centers with databases or registries of patients with ASSD, IIMs, SARDs, or ILD. A total of 350 investigators from 92 centers worldwide participated in the CLASS project (Supplementary Table S1). We also invited international experts on ASSD, IIMs, and ILD to join the project as members of the steering committee, which included 12 rheumatologists, 4 pulmonologists, 2 dermatologists, and 2 neurologists from North America, South America, Europe, Asia, and Australia (Supplementary Table S2). The project was approved by the Ethical Committee of the IRCCS Policlinico S. Matteo Foundation of Pavia, Pavia, Italy (P-201190088730; Prot. 20190094533) and the local institutional review boards in each participating center. The complete study process was conducted according to the Declaration of Helsinki. Written informed consent was obtained from all patients at each center.

Data collection. Participating centers were requested to report retrospectively or prospectively collected data from patients with ASSD (cases) or other conditions mimicking ASSD (controls), according to their clinical diagnosis. For controls, we considered all conditions for which clinicians may consider ASSD in the differential diagnosis or those that have overlapping clinical features with ASSD. A comprehensive list of variables potentially associated with ASSD covering clinical manifestations, laboratory data, imaging studies, and autoantibody testing was provided to each center on REDCap, a secure, web-based data capture platform hosted at the University Hospital of Ferrara (https://redcap.ospfe.it/). The list of variables was developed based on the systematic literature review that we performed previously,[24] as well as expert opinions from the steering committee members, which included multiple clinical (joint, muscle, lung, skin, cardiac, and others) and serological domains (Figure 1 and Supplementary Table S3). The data collection process began in August 2020 and ended in April 2021.

Data reviewing process. All imputed patient data underwent quality control, and the diagnoses of both ASSD and other SARD were verified by the CLASS project working group. Each record was assessed by a minimum of two reviewers: one working group member and one of the two PIs (RA and LC). We sent queries to the participating centers regarding missing data or reports with discrepancies. The participating centers were allowed to revise or enter new data if needed to confirm the variables or diagnoses. Equivocal cases were reviewed by the two PIs, and the final decision to include the patients as an ASSD case or control SARD was based on the consensus of both PIs. Because the disease concept of ASSD has not been established yet, patients diagnosed with both ASSD and other SARDs were classified as ASSD (cases), especially given the positivity of anti-ARS autoantibodies and treating physicians' diagnoses. Inconsistent patient records were excluded from the analysis (Supplementary Figure S1).

Statistical analyses. 50% of the verified cases and controls were randomly selected using the *sample* function provided in the base R package; the remaining 50% were used for the validation analyses. First, we performed univariable logistic regression analyses to investigate the association between each clinical or serological variable and the diagnosis of ASSD. For each variable (e.g., arthritis), the comparator was those lacking the specific item analyzed (e.g., no arthritis). We also performed sensitivity analyses using another comparator definition: those completely lacking the corresponding organ involvement (e.g., no joint involvement) (see Supplementary Table S4 for detailed definitions of comparators). We generated several macro variables in some clinical domains based on input from the steering committee members. For instance, a macro variable "inflammatory rashes" was composed of Gottron signs/papules, heliotrope rash, V-sign, shawl sign, and malar rash, and "Other myositis-specific autoantibodies (MSAs)/myositis-associated autoantibodies (MAAs)" included anti–Mi-2, anti–transcription intermediary factor 1-γ, anti–melanoma differentiation–associated gene 5, anti–small ubiquitin-like modifier-1 activating enzyme, anti–nuclear matrix protein 2/MJ, anti–signal recognition peptide, anti–3-hydroxy-3-methylglutaryl-CoA reductase, anti–PM-Scl, anti-U1-RNP, and anti-Ku autoantibodies. Detailed definitions of the macro variables are presented in Supplementary Table S5.

Additionally, we performed subgroup analyses in four distinct subcohorts that included all cases and controls with specific

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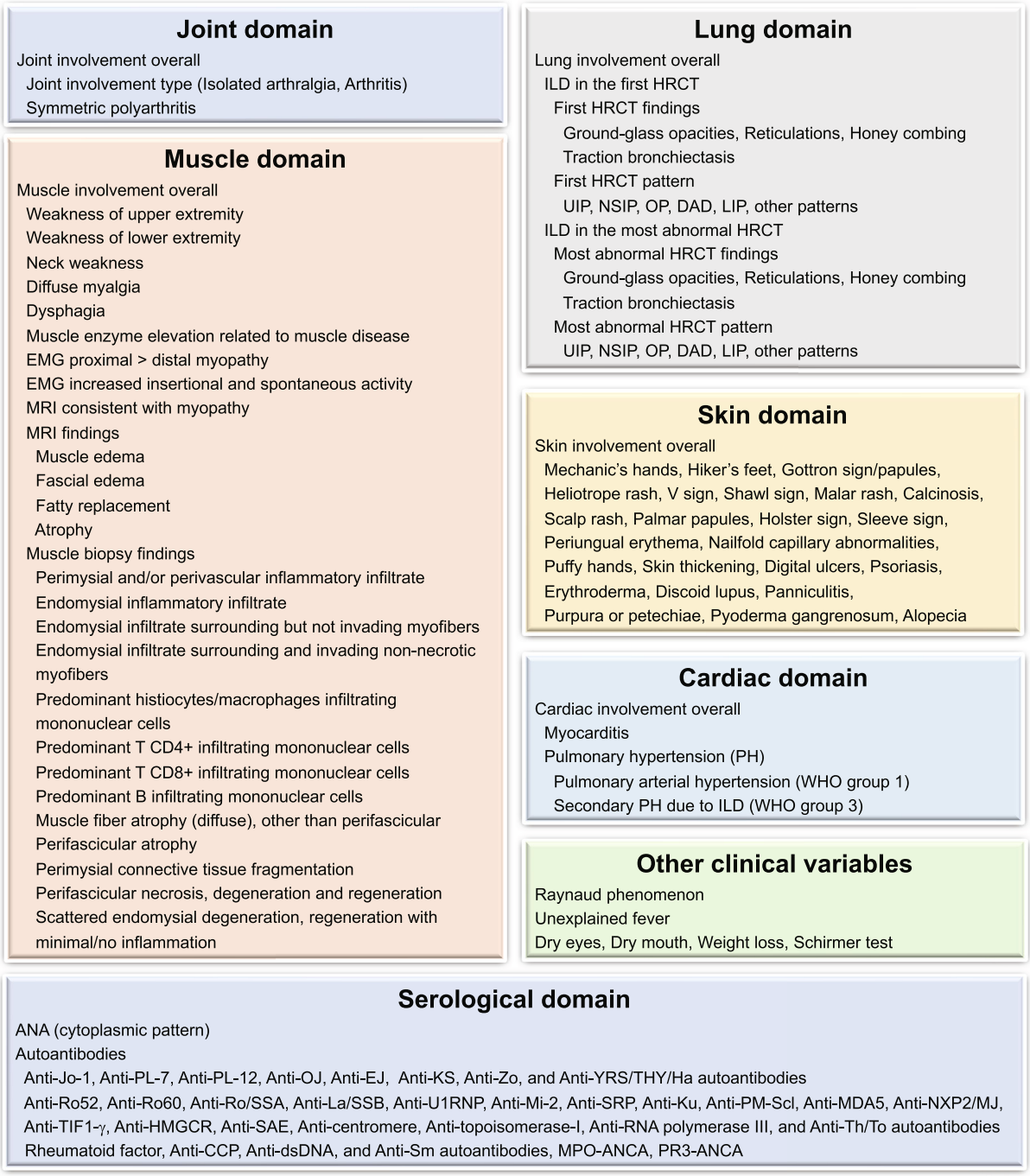

Figure 1. Clinical and serological variables included in each domain. ANA, antinuclear autoantibody; ANCA, anti–neutrophil cytoplasmic antibody; CCP, cyclic citrullinated peptide; DAD, diffuse alveolar damage; dsDNA, double-stranded DNA; EMG, electromyography; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; LIP, lymphoid interstitial pneumonia; MDA5, melanoma differentiation–associated gene 5; MPO, myeloperoxidase; MRI, magnetic resonance imaging; NSIP, nonspecific interstitial pneumonia; NXP2, nuclear matrix protein 2; OP, organizing pneumonia; PH, pulmonary hypertension; PR3, proteinase 3; SAE, small ubiquitin-like modifier-1 activating enzyme; SRP, signal recognition peptide; TIF1-γ, transcription intermediary factor 1-γ; UIP, usual interstitial pneumonia; WHO, World Health Organization.

organ involvement, namely, joint, muscle, lung, or skin involvement, which we refer to as the joint, muscle, lung, or skin cohort, respectively, to better understand the association between certain variables and the diagnosis of ASSD in patients with a specific organ involvement (e.g., the joint cohort included all patients with ASSD and controls who had joint involvement). Specifically, we repeated univariable logistic regression analyses in these four cohorts. For example, to evaluate the performance of

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inflammatory rashes in discriminating ASSD among patients with ILD, we analyzed the association of inflammatory rashes with ASSD in the lung cohort, which was composed of cases and controls with lung involvement.

Finally, we employed multivariable Ridge regression to estimate each variable's weight for ASSD diagnosis prediction. Ridge regression is a regularization method employed in classification tasks, which is able to regularize coefficient magnitude in the presence of multicollinearity. We selected variables incorporated into the multivariable models based on the results of 1) univariable analysis and 2) multivariable penalized regression models run within each domain, as well as 3) clinical input from steering committee members. Linear coefficients obtained were scaled into 0% to 100% to calculate the weights. Ninety-five percent bootstrap confidence intervals (95% CIs) for the weights were built on 1,000 samples from the data set using the bias-corrected and accelerated method. We ran two separate multivariable models with and without anti-ARS autoantibodies, considering that their strong association with ASSD diagnosis could overshadow the effect of other variables.

In the univariable analysis, cases or controls with missing data for each variable were excluded from the analysis for the variable. As for the multivariable regression, we imputed missing data employing random forest models. For this purpose, we used the *rfImpute* function belonging to the randomForest R package. Results are shown as odds ratios (ORs) or 100% weights with 95% CIs. A two-sided *P* value of less than 0.05 was considered statistically significant. All statistical analyses were conducted by a statistician (DR) using R version 4.2.2. (R Foundation for Statistical Computing). The data underlying the findings reported herein are available on a reasonable request from the corresponding author.

RESULTS

The CLASS database. A total of 2,035 ASSD cases and 2,140 controls were submitted by the local investigators. The diagnosis of ASSD and control SARDs/ILD was confirmed in 1,952 and 2,097 records, respectively. For the present study, 948 ASSD cases and 1,077 controls were randomly selected from the list of verified reports (Supplementary Figure S1). The mean age at diagnosis, sex distribution, and disease duration were comparable between patients with ASSD and controls (Table 1). The predominant diagnoses among the controls were DM (28.3%), RA (11.7%), systemic sclerosis (10.8%), polymyositis (8.4%), and interstitial pneumonia with autoimmune features (without anti-ARS autoantibodies) (7.6%).

Joint domain. We observed a significant association between joint involvement overall and ASSD diagnosis. Specifically, 57.3% of patients with ASSD had joint involvement compared with 44.0% of controls (OR 1.71 [95% CI 1.43–2.05], $P < 0.001$) (Figure 2 and Supplementary Table S6). Breaking down the types of joint involvement, isolated arthralgia was not a distinguishing feature for ASSD (11.8% cases vs 12.8% controls, OR 0.91 [95% CI 0.70–1.19], $P = 0.508$). In contrast, arthritis was significantly associated with ASSD diagnosis (45.2% cases vs 31.0% controls, OR 1.84 [95% CI 1.53–2.21], $P < 0.001$). Symmetric polyarthritis was also significantly associated with ASSD, whereas the OR was numerically lower than that for arthritis (34.9% cases vs 28.1% controls, OR 1.38 [95% CI 1.13–1.67], $P = 0.001$).

Table 1. Demographics and clinical characteristics of patients with ASSD and controls included in the univariable analysis*

Characteristics	Patients (n = 948)	Controls (n = 1,077)
Age at diagnosis, mean ± SD, y	60 ± 14	58 ± 17
Female, n (%)	666 (70.3)	762 (70.8)
Ethnicity, n (%)		
Hispanic or Latino	272 (28.7)	324 (30.1)
Not Hispanic or Latino	615 (64.9)	696 (64.6)
Unknown/not reported	61 (6.4)	57 (5.3)
Race, n (%)		
American Indian/Alaska Native	58 (6.1)	46 (4.3)
Asian	150 (15.8)	189 (17.5)
Native Hawaiian or other Pacific Islanders	2 (0.2)	0
Black or African American	78 (8.2)	36 (3.3)
White	562 (59.3)	712 (66.1)
Others	15 (1.6)	16 (1.5)
Unknown/not reported	83 (8.8)	78 (7.2)
Disease duration, median (IQR), y	0.5 (0.2–2.2)	0.5 (0.1–1.8)
Clinical diagnosis of controls, n (%)		
Dermatomyositis	–	305 (28.3)
Rheumatoid arthritis	–	126 (11.7)
Systemic sclerosis	–	116 (10.8)
Polymyositis	–	91 (8.4)
Interstitial pneumonia with autoimmune features[a]	–	82 (7.6)
Sjögren disease	–	61 (5.7)
Systemic lupus erythematosus	–	57 (5.3)
Inclusion body myositis	–	40 (3.7)
Scleromyositis	–	40 (3.7)
Immune-mediated necrotizing myopathy	–	39 (3.6)

* ASSD, anti-synthetase syndrome; IQR, interquartile range.
[a] Not with anti-synthetase antibodies.

Muscle domain. Muscle involvement overall was significantly associated with the diagnosis of ASSD (69.5% cases vs 55.2% controls, OR 1.85 [95% CI 1.54–2.22], $P < 0.001$) (Figure 2 and Supplementary Table S7). Among the different items related to muscle involvement, a significant association with ASSD diagnosis was observed for diffuse myalgia (43.9% cases vs 36.4% controls, OR 1.37 [95% CI 1.14–1.65], $P = 0.001$) and muscle enzyme elevation (54.5% cases vs 44.0% controls, OR 1.52 [95% CI 1.27–1.82], $P < 0.001$), whereas neither muscle weakness (49.1% cases vs 48.3% controls) nor dysphagia (14.9% cases vs 21.9% controls) was associated with ASSD.

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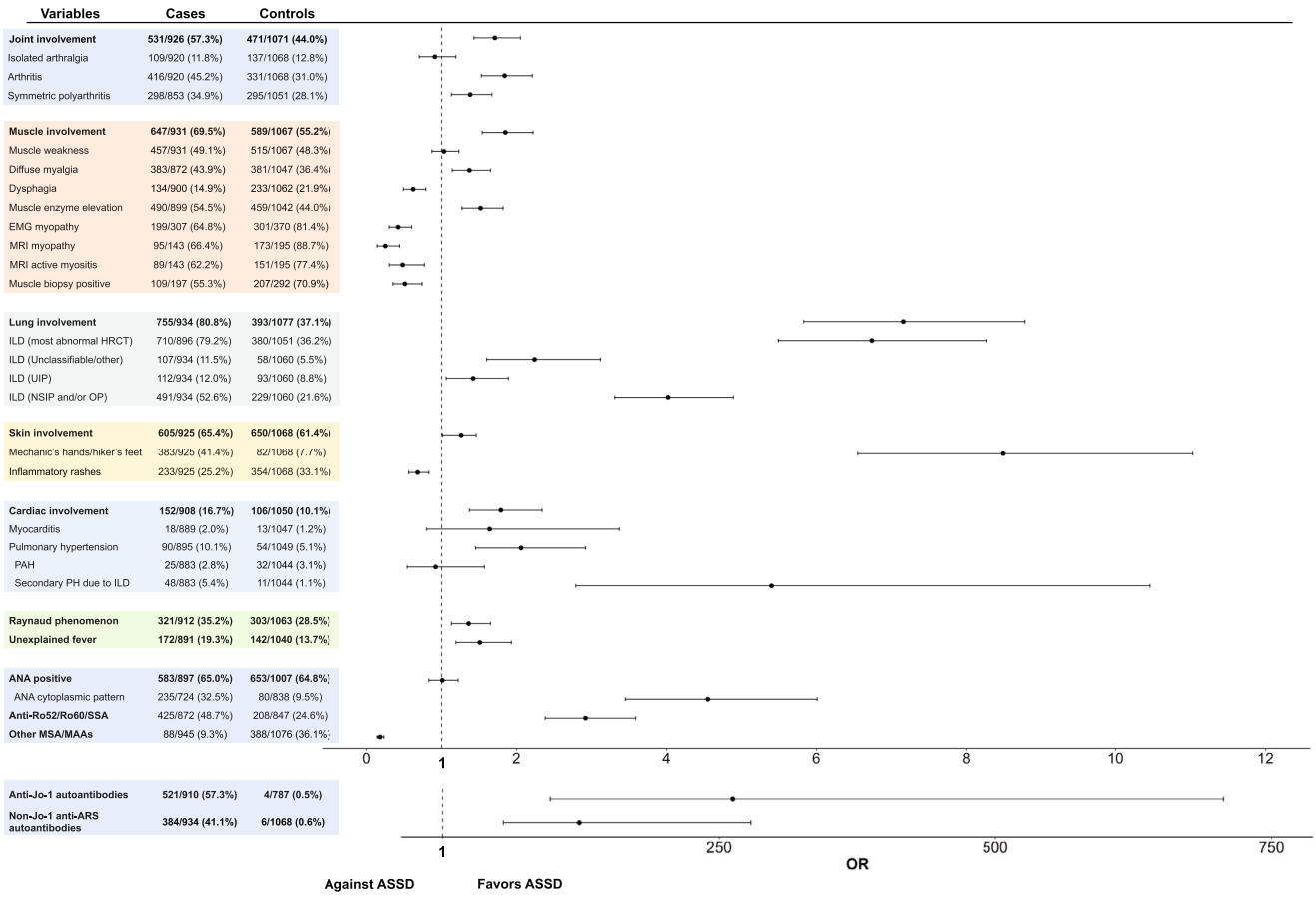

Figure 2. Prevalence of variables in cases and controls and the association of each variable with ASSD diagnosis. ANA, antinuclear autoantibody; ARS, aminoacyl-transfer RNA synthetase; ASSD, anti-synthetase syndrome; EMG, electromyography; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; MAA, myositis-associated autoantibody; MRI, magnetic resonance imaging; MSA, myositis-specific autoantibody; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; OR, odds ratio; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; UIP, usual interstitial pneumonia. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/art.43038/abstract.

Electromyography (EMG) was performed in 54.8% of patients and 68.1% of controls. EMG findings consistent with myopathy were negatively associated with ASSD (64.8% cases vs 81.4% controls of EMG performed, OR 0.42 [95% CI 0.30–0.60], $P < 0.001$). Only 24.2% of patients and 34.5% of controls underwent muscle magnetic resonance imaging (MRI). Interestingly, MRI findings consistent with myopathy were also negatively associated with ASSD diagnosis (66.4% cases vs 88.7% controls of MRI performed, OR 0.25 [95% CI 0.14–0.44], $P < 0.001$). None of the individual MRI findings, including muscle edema (76.9% cases vs 71.8% controls of MRI performed) and fascial edema (21.7% cases vs 19.5% controls of MRI performed), were associated with ASSD. Muscle biopsy was performed in 22.3% and 27.7% of patients and controls, respectively. Muscle biopsy findings suggestive of myopathy overall were negatively associated with ASSD (55.3% cases vs 70.9% controls of muscle biopsy performed, OR 0.51 [95% CI 0.35–0.74], $P = 0.001$). Individual muscle biopsy findings were not significantly associated or negatively associated with ASSD.

Lung domain. Lung involvement was strongly associated with the diagnosis of ASSD (80.8% cases vs 37.1% controls, OR 7.16 [95% CI 5.84–8.81], $P < 0.001$) (Figure 2 and Supplementary Table S8). Nearly all patients (97.2%) and controls (97.7%) with lung involvement underwent high-resolution computed tomography (HRCT). HRCT findings compatible with ILD were significantly associated with ASSD (79.2% cases vs 36.2% controls, OR 6.74 [95% CI 5.49–8.27], $P < 0.001$).

Regarding distinct HRCT ILD patterns, predominant nonspecific interstitial pneumonia (NSIP) and/or organizing pneumonia (OP) pattern was the most prevalent and associated with ASSD diagnosis (52.6% cases vs 21.6% controls, OR 4.02 [95% CI 3.31–4.89], $P < 0.001$). Of note, predominant usual interstitial pneumonia (UIP) pattern (12.0% cases vs 8.8% controls, OR 1.42 [95% CI 1.06–1.89], $P < 0.001$) and unknown/unclassifiable/other patterns (11.5% cases vs 5.5% controls, OR 2.24 [95% CI 1.60–3.12], $P < 0.001$) were less frequent but still significantly associated with ASSD diagnosis. The results remained consistent between the first and the most abnormal HRCT except

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for predominant UIP pattern, which was associated with ASSD only in the most abnormal HRCT.

Skin domain. Overall, skin involvement was slightly associated with ASSD diagnosis (65.4% cases vs 60.9% controls, OR 1.26 [95% CI 1.01–1.46], $P = 0.036$) (Figure 2 and Supplementary Table S9). We observed a robust association of mechanic's hands/hiker's feet with ASSD (41.4% cases vs 7.7% controls, OR 8.50 [95% CI 6.55–11.03], $P < 0.001$), whereas the prevalence of hiker's feet was low in both groups (1.6% cases vs 0.8% controls). In contrast, inflammatory rashes were negatively associated with ASSD (25.2% cases vs 33.1% controls, OR 0.68 [95% CI 0.56–0.83], $P < 0.001$). Individual rashes and other skin manifestations either showed a negative association with ASSD or did not provide a clear distinction between ASSD and controls. Skin biopsy was performed only in 56/605 (9.3%) of patients with ASSD and 102/650 (15.7%) of controls with skin involvement.

Cardiac domain. Cardiac involvement overall was associated with the diagnosis of ASSD (16.7% cases vs 10.1% controls, OR 1.79 [95% CI 1.37–2.34], $P < 0.001$) (Figure 2 and Supplementary Table S10). Both patients and controls exhibited a low prevalence of myocarditis (2.0% cases vs 1.2% controls), hindering comparative analysis between patients with ASSD and controls. Pulmonary hypertension (PH) overall was associated with ASSD (10.1% cases vs 5.1% controls, OR 2.06 [95% CI 1.45–2.92], $P < 0.001$). Breaking down the types of PH, secondary PH due to ILD (World Health Organization [WHO] group 3) was associated with ASSD (5.4% cases vs 1.1% controls, OR 5.40 [95% CI 2.79–10.46], $P < 0.001$), whereas pulmonary arterial hypertension (PAH) (WHO group 1) was not (2.8% cases vs 3.1% controls, OR 0.92 [95% CI 0.54–1.57], $P = 0.763$).

Other clinical variables. For the remaining clinical manifestations, Raynaud phenomenon (35.2% cases vs 28.5% controls, OR 1.36 [95% CI 1.13–1.65], $P = 0.001$) and unexplained fever (19.3% cases vs 13.7% controls, OR 1.51 [95% CI 1.19–1.93], $P = 0.001$) were significantly associated with ASSD (Figure 2 and Supplementary Table S11). Dry eyes were slightly associated with ASSD (17.1% cases vs 13.7% controls, OR 1.30 [95% CI 1.01–1.67], $P = 0.038$), but dry mouth was not (17.3% cases vs 14.1% controls, OR 1.27 [95% CI 0.99–1.63], $P = 0.054$).

Serological domain. Antinuclear antibody (ANA) positivity overall did not differentiate ASSD from controls (65.0% cases vs 64.8% controls, OR 1.01 [95% CI 0.83–1.22], $P = 0.946$) (Figure 2 and Supplementary Table S12). ANAs with cytoplasmic pattern were significantly associated with ASSD diagnosis (32.5% cases vs 9.5% controls, OR 4.55 [95% CI 3.45–6.01], $P < 0.001$). As expected, the presence of anti–Jo-1 autoantibodies (57.3% cases vs 0.5% controls), as well as non–Jo-1 anti-ARS autoantibodies (41.1% cases vs 0.6% controls), was strongly associated with ASSD diagnosis (OR 262.17 [95% CI 97.30–706.45], $P < 0.001$ for Jo-1; OR 123.58 [95% CI 54.81–278.61], $P < 0.001$ for non–Jo-1). For non–Jo-1 anti-ARS autoantibodies, the results were consistent regardless of whether the testing method was immunoprecipitation (IP) or not (Supplementary Table S13).

The presence of either anti-Ro52/Ro60 or anti-Sjögren's-syndrome-related antigen A (anti-Ro/SSA) autoantibodies demonstrated a significant association with ASSD (48.7% cases vs 24.6% controls, OR 2.92 [95% CI 2.38–3.59], $P < 0.001$). Analyzing each autoantibody individually upheld the significant relationship between anti-Ro52 autoantibodies and ASSD (51.1% cases vs 23.1% controls, OR 3.48 [95% CI 2.78–4.35], $P < 0.001$), whereas anti-Ro60 autoantibodies (15.3% cases vs 12.2% controls, OR 1.30 [95% CI 0.96–1.77], $P = 0.095$) and anti-Ro/SSA autoantibodies (34.2% cases vs 31.6% controls, OR 1.13 [95% CI 0.49–2.61], $P = 0.777$) were not associated with the diagnosis of ASSD. In contrast, the presence of any other MSAs/MAAs was negatively associated with ASSD diagnosis (9.3% cases vs 36.1% controls, OR 0.18 [95% CI 0.14–0.23], $P < 0.001$). The presence of individual MSAs/MAAs or other autoantibodies such as rheumatoid factor, anti–cyclic citrullinated peptide, anti–double-stranded DNA, anti-Sm autoantibodies, myeloperoxidase–antineutrophil cytoplasmic antibodies (ANCAs), and proteinase 3–ANCAs either did not show a significant association with ASSD diagnosis or had a negative correlation.

Subgroup analyses in cohorts including patients and controls with specific organ involvement. We conducted subgroup analyses in four cohorts focusing on patients and controls having specific organ involvement, ie, joint, muscle, lung, or skin involvement. Clinical diagnoses of controls included in each cohort are presented in Supplementary Table S14.

In all cohorts, arthritis was correlated with ASSD diagnosis, whereas isolated arthralgia was not (Table 2). Muscle weakness, which did not have an association with ASSD in the entire cohort, was associated with ASSD in the subgroups focusing on joint (OR 2.02 [95% CI 1.57–2.61], $P < 0.001$) or lung involvement (OR 2.30 [95% CI 1.77–2.99], $P < 0.001$), whereas it was inversely associated with ASSD in the muscle cohort (OR 0.35 [95% CI 0.26–0.46], $P < 0.001$).

ILD with predominant NSIP and/or OP pattern maintained its strong association with ASSD across all subgroups. Meanwhile, predominant UIP pattern was not associated with ASSD in the joint cohort (OR 1.26 [95% CI 0.85–1.89], $P = 0.253$) and was negatively associated with ASSD in the lung cohort (OR 0.56 [95% CI 0.41–0.76], $P < 0.001$). Inflammatory rashes did not show a significant association with ASSD even in the joint (OR 0.86 [95% CI 0.65–1.14], $P = 0.296$) or the lung cohort (OR 1.04 [95% CI 0.78–1.38], $P = 0.797$), and they were inversely associated with ASSD in the muscle cohort (OR 0.42 [95% CI

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Table 2. Subgroup analyses in cohorts including patients with ASSD and controls with specific organ involvement*

	All cohort: case, n = 948; control, n = 1,077		Joint cohort: case, n = 531; control, n = 471		Muscle cohort: case, n = 647; control: n = 589		Lung cohort: case, n = 755; control, n = 393		Skin cohort: case, n = 605; control, n = 650	
	OR[a] (95% CI)	*P*	OR[a] (95% CI)	*P*	OR[a] (95% CI)	*P*	OR[a] (95% CI)	*P*	OR[a] (95% CI)	*P*
Joint domain	1.71 (1.43–2.05)	<0.001	–	–	3.25 (2.57–4.11)	<0.001	1.26 (0.98–1.61)	0.066	2.05 (1.63–2.57)	<0.001
Isolated arthralgia	0.91 (0.70–1.19)	0.508	0.63 (0.47–0.85)	0.002	1.16 (0.83–1.62)	0.380	0.94 (0.65–1.38)	0.765	0.99 (0.72–1.37)	0.959
Arthritis	1.84 (1.53–2.21)	<0.001	1.58 (1.18–2.11)	0.002	3.30 (2.58–4.22)	<0.001	1.30 (1.01–1.68)	0.040	1.53 (1.20–1.95)	0.001
Symmetric polyarthritis	1.38 (1.13–1.67)	0.001	0.98 (0.75–1.29)	0.913	2.30 (1.78–2.98)	<0.001	0.98 (0.75–1.27)	0.858	1.65 (1.29–2.12)	<0.001
Muscle domain	1.85 (1.54–2.22)	<0.001	4.31 (3.27–5.69)	<0.001	–	–	3.62 (2.80–4.69)	<0.001	1.56 (1.22–1.98)	<0.001
Muscle weakness	1.03 (0.87–1.23)	0.714	2.02 (1.57–2.61)	<0.001	0.35 (0.26–0.46)	<0.001	2.30 (1.77–2.99)	<0.001	0.93 (0.74–1.16)	0.535
Diffuse myalgia	1.37 (1.14–1.65)	0.001	2.08 (1.60–2.71)	<0.001	0.92 (0.72–1.18)	0.513	2.61 (1.95–3.50)	<0.001	1.03 (0.82–1.29)	0.807
Muscle enzyme elevation related to myositis	1.52 (1.27–1.82)	<0.001	3.71 (2.84–4.86)	<0.001	0.90 (0.67–1.20)	0.460	3.02 (2.30–3.97)	<0.001	1.40 (1.12–1.76)	0.004
EMG findings suggestive of myopathy	0.42 (0.30–0.60)	<0.001	0.72 (0.43–1.20)	0.213	0.42 (0.30–0.60)	<0.001	0.52 (0.28–0.99)	0.046	0.43 (0.28–0.66)	<0.001
Muscle MRI findings consistent with myopathy	0.25 (0.14–0.44)	<0.001	0.46 (0.19–1.13)	0.091	0.25 (0.14–0.44)	<0.001	0.30 (0.12–0.76)	0.012	0.29 (0.15–0.57)	<0.001
Muscle biopsy findings suggestive of myopathy	0.51 (0.35–0.74)	0.001	0.96 (0.53–1.72)	0.884	0.51 (0.35–0.74)	0.001	0.64 (0.33–1.23)	0.178	0.62 (0.39–0.99)	0.046
Lung domain	7.15 (5.84, 8.81)	<0.001	4.63 (3.56, 6.19)	<0.001	10.77 (8.28–14.10)	<0.001	–	–	7.61 (5.88–9.89)	<0.001
Unknown/ unclassifiable/ other ILD patterns alone[b]	2.24 (1.60–3.12)	<0.001	2.71 (1.66–4.44)	<0.001	3.83 (2.34–6.28)	<0.001	0.95 (0.68–1.35)	0.788	2.36 (1.53–3.66)	<0.001
Predominant UIP pattern[b]	1.42 (1.06–1.89)	0.019	1.26 (0.85–1.89)	0.253	3.90 (2.26–6.72)	<0.001	0.56 (0.41–0.76)	<0.001	2.93 (1.89–4.54)	<0.001
Predominant NSIP and/or OP pattern[b]	4.02 (3.31–4.89)	<0.001	2.76 (2.11–3.61)	<0.001	5.51 (4.20–7.25)	<0.001	1.33 (1.04–1.71)	0.025	3.57 (2.80–4.54)	<0.001
Skin domain	1.26 (1.01–1.46)	0.036	1.50 (1.15–1.95)	0.003	0.96 (0.75–1.22)	0.744	1.36 (1.06–1.75)	0.016	–	–
Mechanic's hands/ hiker's feet	8.50 (6.55–11.03)	<0.001	8.46 (5.90–12.14)	<0.001	7.70 (5.58–10.64)	<0.001	6.26 (4.42–8.87)	<0.001	11.95 (8.99–15.88)	<0.001
Inflammatory rashes[c]	0.68 (0.56–0.83)	<0.001	0.86 (0.65–1.14)	0.296	0.42 (0.33–0.54)	<0.001	1.04 (0.78–1.38)	0.797	0.52 (0.42–0.66)	<0.001
Cardiac domain	1.79 (1.37–2.34)	<0.001	2.10 (1.44–3.07)	<0.001	1.95 (1.40–2.72)	<0.001	1.38 (0.97–1.97)	0.074	1.87 (1.35–2.60)	<0.001
Myocarditis	1.64 (0.80–3.37)	0.176	3.02 (0.98–9.34)	0.055	1.18 (0.55–2.55)	0.669	2.18 (0.61–7.79)	0.228	0.88 (0.34–2.25)	0.791
PH	2.06 (1.45–2.92)	<0.001	1.94 (1.19–3.16)	0.008	2.55 (1.59–4.07)	<0.001	1.42 (0.92–2.17)	0.112	2.08 (1.36–3.18)	0.001
Pulmonary arterial hypertension (group 1)	0.92 (0.54–1.57)	0.763	0.72 (0.34–1.50)	0.377	0.90 (0.46–1.76)	0.757	0.91 (0.45–1.82)	0.783	0.72 (0.39–1.35)	0.311

(Continued)

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Table 2. (*Cont'd*)

	All cohort: case, n = 948; control, n = 1,077		Joint cohort: case, n = 531; control, n = 471		Muscle cohort: case, n = 647; control: n = 589		Lung cohort: case, n = 755; control, n = 393		Skin cohort: case, n = 605; control, n = 650	
	OR[a] (95% CI)	*P*	OR[a] (95% CI)	*P*	OR[a] (95% CI)	*P*	OR[a] (95% CI)	*P*	OR[a] (95% CI)	*P*
Secondary PH due to ILD (group 3)	5.40 (2.79–10.46)	<0.001	5.39 (2.06–14.12)	0.001	12.18 (3.73–39.81)	<0.001	2.39 (1.23–4.67)	0.011	14.36 (4.40–46.92)	<0.001
Other clinical variables										
Raynaud phenomenon	1.36 (1.13–1.65)	0.001	1.35 (1.04–1.75)	0.025	1.72 (1.34–2.19)	<0.001	1.03 (0.80–1.33)	0.820	1.34 (1.07–1.67)	0.011
Unexplained fever	1.51 (1.19–1.93)	0.001	1.52 (1.11–2.08)	0.009	1.18 (0.88–1.57)	0.274	1.83 (1.29–2.60)	0.001	1.25 (0.94–1.65)	0.123
Serological domain										
ANAs with cytoplasmic pattern	4.55 (3.45–6.01)	<0.001	4.43 (3.01, 6.53)	<0.001	4.49 (3.12, 6.47)	<0.001	4.44 (2.97, 6.65)	<0.001	4.44 (3.10, 6.35)	<0.001
Anti–Jo-1 autoantibodies	262.17 (97.30–706.45)	<0.001	698.77 (97.26–5,020.35)	<0.001	315.87 (100.34–994.35)	<0.001	NA[d]	NA[d]	172.02 (63.46–466.28)	<0.001
Non–Jo-1 anti-ARS autoantibodies	123.58 (54.81–278.61)	<0.001	203.64 (28.39–1,460.87)	<0.001	96.13 (30.56–302.33)	<0.001	91.62 (29.15–288.00)	<0.001	142.79 (45.40–449.09)	<0.001
Anti-Ro52/Ro60 or anti-Ro/SSA autoantibodies	2.92 (2.38–3.59)	<0.001	3.28 (2.43–4.43)	<0.001	3.71 (2.85–4.84)	<0.001	2.79 (2.09–3.73)	<0.001	3.07 (2.38–3.95)	<0.001
Other MSAs/MAAs[e]	0.18 (0.14–0.23)	<0.001	0.21 (0.15–0.30)	<0.001	0.10 (0.07–0.13)	<0.001	0.24 (0.17–0.32)	<0.001	0.12 (0.09–0.16)	<0.001

* ANA, antinuclear antibody; ARS, aminoacyl-transfer RNA synthetase; ASSD, anti-synthetase syndrome; EMG, electromyography; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; MAA, myositis-associated autoantibody; MRI, magnetic resonance imaging; MSA, myositis-specific autoantibody; NA, not applicable; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; OR, odds ratio; PH, pulmonary hypertension; UIP, usual interstitial pneumonia; 95% CI, 95% confidence interval.

[a] Comparators were those without each specific variable analyzed.

[b] Most abnormal HRCT pattern.

[c] Gottron signs/papules, heliotrope rash, V-sign, Shawl sign, and malar rash.

[d] OR and *P* value could not be calculated because the prevalence in controls was zero.

[e] Anti–Mi-2, anti-TIF1-γ, anti-MDA5, anti-SAE, anti-NXP2/MJ, anti-SRP, anti-HMGCR, anti-PM-Scl, anti-U1RNP, and anti-Ku autoantibodies.

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0.33–0.54], $P < 0.001$). The presence of ANAs with cytoplasmic pattern, anti-ARS autoantibodies, anti-Ro52/60 or anti-Ro/SSA autoantibodies, and other MSAs/MAAs showed uniform performance across all subgroups, in line with the results obtained in the entire cohort.

Multivariable analysis. We performed multivariable Ridge regression to estimate the weight of each clinical or serological variable for ASSD diagnosis prediction, incorporating covariates based on the results of univariable analysis and intradomain penalized multivariable regression, as well as clinical judgment (Table 3). According to the input from the steering committee, diffuse myalgia was considered positive only in the presence of muscle enzyme elevation. As for ILD, we analyzed whether predominant NSIP and/or OP patterns had additional weight. We did not incorporate secondary PH due to ILD into the multivariable model because it would cause significant multicollinearity with ILD.

In the multivariable model with anti-ARS autoantibodies, the highest estimated weights were for anti-ARS autoantibodies (% weight 39.3 [95% CI 35.2–46.5] for anti–Jo-1 positive by any methods or non–Jo-1 anti-ARS positive by IP; %weight 38.7 [95% CI 34.6–44.8] for non–Jo-1 anti-ARS positive by non-IP methods), followed by mechanic's hands/hiker's feet (%weight 11.8 [95% CI 10.0–13.6]), ILD (%weight 11.1 [95% CI 9.9–13.0]; additional %weight 4.1 [95% CI 2.2–5.2] for predominant NSIP and/or OP patterns), ANAs with cytoplasmic pattern (%weight 7.2 [95% CI 5.4–8.6]), muscle enzyme elevation (%weight 7.2 [95% CI 5.7–8.3]), anti-Ro52/60 or anti-Ro/SSA autoantibodies (%weight 6.7 [95% CI 5.1–7.8]), arthritis (%weight 4.2 [95% CI 2.6–5.3]), and unexplained fever (%weight 3.4 [95% CI 1.2–4.9]). Of note, muscle weakness had a significant weight for ASSD diagnosis prediction (%weight 2.9 [95% CI 0.6–4.2]), whereas diffuse myalgia did not provide significant additional weight to muscle enzyme elevation (additional %weight 1.2 [95% CI 0.0–2.6]). In the model without anti-ARS autoantibodies, the weight for each variable increased substantially, which also identified Raynaud phenomenon as another variable with a significant weight (% weight 2.8 [95% CI 0.1–4.5]).

Table 3. The estimated weights of clinical and serological variables for ASSD diagnosis prediction by multivariable Ridge regression*

Variables	Before imputation		After imputation		%Weight (95% CI)	
	Cases, n = 948	Controls, n = 1,077	Cases, n = 948	Controls, n = 1,077	Model with anti-ARS	Model without anti-ARS
Isolated arthralgia	109/920 (11.8)	137/1,068 (12.8)	109/948 (11.5)	137/1,077 (12.7)	1.0 (0.0–3.0)	2.4 (0.0–4.6)
Arthritis	416/920 (45.2)	331/1,068 (31.0)	431/948 (45.5)	331/1,077 (30.7)	4.2 (2.6–5.3)	7.1 (5.4–8.8)
Muscle weakness	457/931 (49.1)	515/1,067 (48.3)	463/948 (48.8)	515/1,077 (47.8)	2.9 (0.6–4.2)	3.1 (0.7–4.8)
Muscle enzyme elevation related to muscle disease	490/899 (54.5)	459/1,042 (44.0)	520/948 (54.9)	464/1,077 (43.1)	7.2 (5.7–8.3)	11.2 (9.3–13.2)
Diffuse myalgia (additional)	312/445 (70.1)	312/449 (69.5)	343/520 (66.0)	329/464 (70.9)	1.2 (0.0–2.6)	0.0 (0.0–0.0)
EMG or MRI findings consistent with myopathy	282/948 (29.8)	406/1,077 (37.7)	284/948 (30.0)	406/1,077 (37.7)	0.4 (0.0–2.2)	1.5 (0.0–3.5)
Muscle biopsy findings suggestive of myositis	101/882 (11.5)	169/1,054 (16.0)	102/948 (10.8)	169/1,077 (15.7)	0.0 (0.0–0.0)	0.6 (0.0–3.0)
ILD confirmed by HRCT	755/934 (80.1)	393/1,060 (37.1)	769/948 (81.1)	403/1,077 (37.4)	11.1 (9.9–13.0)	16.3 (14.5–19.5)
Predominant NSIP and/or OP patterns (additional)	504/755 (66.8)	244/393 (62.1)	517/769 (67.2)	246/403 (61.0)	4.1 (2.2–5.2)	6.8 (4.7–8.4)
Mechanic's hands or hiker's feet	383/925 (41.4)	82/1,068 (7.7)	400/948 (42.2)	82/1,077 (7.6)	11.8 (10.0–13.6)	18.2 (16.3–21.3)
Raynaud phenomenon	321/912 (35.2)	303/1,063 (28.5)	338/948 (35.7)	303/1,077 (28.1)	1.9 (0.0–3.1)	2.8 (0.1–4.5)
Unexplained fever	172/891 (19.3)	142/1,040 (13.7)	212/948 (22.4)	142/1,077 (13.2)	3.4 (1.2–4.9)	5.6 (3.2–7.5)
Anti–Jo-1 positive by any methods or non–Jo-1 anti-ARS positive by IP	602/945 (63.7)	4/1,076 (0.4)	602/948 (63.5)	4/1,077 (0.4)	39.3 (35.2–45.6)	–
Non–Jo-1 anti-ARS positive by non-IP methods	284/945 (30.1)	6/1,076 (0.6)	284/948 (30.0)	6/1,077 (0.6)	38.7 (34.6–44.8)	–
ANAs with cytoplasmic pattern	235/724 (32.5)	80/838 (9.5)	272/948 (28.7)	80/1,077 (7.4)	7.2 (5.4–8.6)	14.1 (12.3–17.1)
Anti-Ro52/Ro60 or anti-Ro/SSA autoantibodies	425/872 (48.7)	208/847 (24.6)	473/948 (49.9)	208/1,077 (19.3)	6.7 (5.1–7.8)	12.7 (11.1–14.8)

* Values are the number/total number (%) unless otherwise specified. ANA, antinuclear antibody; ARS, aminoacyl-transfer RNA synthetases; ASSD, anti-synthetase syndrome; EMG, electromyography; HRCT, high-resolution computed tomography; ILD, interstitial lung disease; IP, immunoprecipitation; MRI, magnetic resonance imaging; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; 95% CI, 95% confidence interval.

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DISCUSSION

The current study used a large, multicenter database including patients with ASSD and mimicking conditions. We identified several clinical and serological factors associated with ASSD diagnosis based on univariable and multivariable analysis, including arthritis, muscle involvement including muscle weakness and muscle enzyme elevation, ILD, mechanic's hands, secondary PH due to ILD, Raynaud phenomenon, unexplained fever, ANAs with cytoplasmic pattern, anti-Ro52 autoantibodies, and as expected, Jo-1 or non–Jo-1 anti-ARS autoantibodies. In contrast, dysphagia, EMG/MRI/muscle biopsy findings suggestive of myopathy, inflammatory rashes, myocarditis, and PAH were not associated with ASSD diagnosis. In some cases, these variables were even inversely associated with ASSD, likely due to the higher frequency of those findings in the control group. Our findings offer a comprehensive set of variables as well as their weights, aimed at establishing data-driven classification criteria for ASSD.

Regarding joint involvement, isolated arthralgia was not a defining feature of ASSD. Notably, the OR for symmetric polyarthritis was numerically lower compared with that for arthritis overall, underscoring the phenotypic heterogeneity of arthritis in ASSD. This heterogeneity appears to be affected by the timing of joint involvement onset during the disease course. Patients who present with arthritis at the initial stages of ASSD commonly have symmetric polyarthritis (70%),[11] whereas patients who develop "de novo" arthritis during their clinical course are more likely to exhibit asymmetric oligoarthritis.[25] Our analysis is limited here because we did not collect specific data for oligoarthritis; however, given this heterogeneity, it becomes evident that the variable "arthritis" should not be restricted to symmetric polyarthritis.

Univariable analyses demonstrated that, within the muscle domain, a particular focus was not on muscle weakness, but rather on diffuse myalgia and muscle enzyme elevation as factors significantly associated with an ASSD diagnosis. Although ASSD is traditionally classified under the umbrella of IIMs, it is important to recognize that muscle weakness is not ubiquitously reported in this patient group. For instance, 25% in the Pittsburgh cohort[9] and 20% in the AENEAS cohort[7] were amyopathic and remained so even after the median follow-up periods of longer than three years. Moreover, patients with specific anti-ARS autoantibodies, including anti-PL-12, OJ, and KS autoantibodies, were reported to maintain an amyopathic profile through their disease trajectory.[26] Our findings thus corroborate that muscle involvement is not universally prevalent in ASSD and, if present, may exhibit a milder phenotype with myalgia and/or muscle enzyme elevation. With that said, subgroup analyses within the joint or ILD cohort revealed an association between muscle weakness and ASSD diagnosis, and importantly, the multivariable regression identified muscle weakness as a variable with a significant weight for ASSD diagnosis prediction; therefore, muscle weakness should be considered as a variable in future classification criteria.

Only 20% to 60% of patients or controls in our database underwent EMG, muscle MRI, or muscle biopsy, restricting our ability to comprehensively evaluate their diagnostic utility in distinguishing ASSD from its mimickers. Nonetheless, findings suggestive of myopathy from these modalities either failed to differentiate ASSD from controls or, paradoxically, were inversely correlated with the diagnosis of ASSD, even in subgroup analyses focusing on joint or lung involvement. The high prevalence of DM in the control groups (17.6%–45.7%) could explain these counterintuitive associations. The limited number of patients who underwent EMG/muscle MRI/muscle biopsy demonstrates that these modalities are not commonly assessed in patients with ASSD in daily practice and warrants further efforts to unravel the characteristics and diagnostic utility of EMG/muscle MRI/muscle biopsy findings in ASSD.

In our cohort, ~80% of patients with ASSD had ILD diagnosed via HRCT. In patients with ASSD, ILD typically shows a unique HRCT pattern with overlapping NSIP and OP.[27] In the present study, predominant NSIP/OP pattern accounted for 69.2% of ILD in ASSD and was in a robust association with ASSD, which provided a significant additional weight in the multivariable regression model. Meanwhile, UIP pattern was associated with ASSD only in the worst HRCT available, but not in the first HRCT. Interestingly, we also observed a significant association of unclassifiable/unknown/other patterns with ASSD. These findings underline the phenotypic heterogeneity of ILD within the ASSD cohort, suggesting that various ILD patterns, including UIP and other unclassifiable patterns, should be considered when constructing future ASSD classification criteria.

Regarding cutaneous involvement, mechanic's hands showed a strong association with ASSD. Although inflammatory rashes were either not useful or negatively associated with ASSD even in the joint, muscle, or lung cohort, the prominence of mechanic's hands accentuates its potential for specificity in ASSD classification. As for other skin features, such as hiker's feet, their low occurrence in our data set merits further investigation given their recent recognition.[28] The lack of association of inflammatory rashes with ASSD could be partly attributed to the fact that DM diagnosis accounted for 28.3% of all controls used in the analysis. Around 20% of patients with ASSD present with inflammatory rashes, which are well-recognized clinical features of ASSD.[9] It remains controversial whether those cases should be classified as 1) ASSD-DM overlap, 2) ASSD with inflammatory rashes, or 3) DM with anti-ARS antibodies.[29,30] Although a recent study reported a significant overlap in the pathophysiology of DM-like skin lesions in ASSD and DM,[31] further studies are necessary to elucidate the potential pathophysiologic differences in patients with "pure" ASSD—ie, those without inflammatory rashes—and patients with ASSD with inflammatory rashes.

Additional clinical manifestations associated with ASSD included Raynaud phenomenon and unexplained fever, consistent with previous publications.[7,12] PH overall was associated

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with ASSD; however, this merits cautious interpretation because the relationship appears primarily driven by secondary PH due to ILD (WHO group 3), rather than PAH (WHO group 1). In a multicenter cohort in France, only 8% of patients with ASSD were diagnosed with precapillary PH by right heart catheterization.[32] Recently, a new definition of PH has been proposed and is widely accepted.[33,34] Lowering mean pulmonary arterial pressure and pulmonary vascular resistance threshold for defining precapillary PH should increase the prevalence of both group 1 and group 3 PH in ASSD. With that said, considering the low prevalence and the negative result from the present analysis, PAH may not be considered in future classification criteria.

Our analysis revealed a high level of association for both Jo-1 and non–Jo-1 anti-ARS autoantibodies, indicating that local diagnostic practices may rely heavily on these markers. The extremely high ORs for anti-ARS autoantibodies might have been affected by selection bias; local investigators were unlikely to submit ASSD cases without anti-ARS autoantibodies or controls with anti-ARS autoantibodies because ASSD is commonly recognized as a serological subset of IIMs. This strong association could overshadow the impact of other variables as observed in the two multivariable models with and without anti-ARS autoantibodies. Other autoantibodies, such as ANAs with cytoplasmic pattern and anti-Ro52 autoantibodies, were significantly associated with the diagnosis of ASSD. This highlights the potential utility of these autoantibodies in the classification criteria, particularly in settings where access to non–Jo-1 anti-ARS autoantibody detection may be limited and when the precision of alternative detection methods, such as line immunoassay (LIA), remains uncertain.[18,35,36]

The strengths of this study lie in its expansive, international scope of real-world data, allowing us to mitigate selection bias that is common in smaller cohort studies. However, we must acknowledge several limitations. First, the reliability of autoantibody data may be compromised because of variations in assay methods across participating centers, most of which employed non-IP techniques. To mitigate this, we are conducting central IP, enzyme-linked immunosorbent assay, and/or LIA on the majority of both case and control patient sera.[36] Second, ASSD or non-ASSD (controls) was defined solely on the clinical diagnosis of participating physicians. Since the disease concept of ASSD has not been established yet, the clinical diagnosis of ASSD or non-ASSD could differ depending on the investigators, specialties, or regions. Also, any case-control study or criteria development is heavily dependent on the mix of controls used for comparison, where any single control type may lead to skewed results. We believe that our data ascertained from 92 centers across five continents likely represent real-world data.

In conclusion, univariable and multivariable analyses of the CLASS database identified several key variables associated with ASSD diagnosis. Our results provide insights into the key clinical features of ASSD, which can help clinicians as well as lay the groundwork for the development of data-driven classification criteria for ASSD. The CLASS project team is planning to simplify and/or provide minor modifications of the weights or variables based on feedback from the steering committee to propose candidate classification criteria. The steering committee will discuss the criteria in terms of face validity, feasibility, ease of use, etc, to reach the final consensus, and the final classification criteria will be tested on the validation data set.

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AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Drs Aggarwal and Cavagna confirm that all authors have provided the final approval of the version to be published, and take responsibility for the affirmations regarding article submission (e.g., not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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APPENDIX A: CLASS PROJECT INVESTIGATORS

Participating CLASS project investigators are as follows: Upendra Rathore, Anamika Anuja, Domenico Sambataro, Michele Colaci, Carlo Vancheri, Mayra Mejia, Pedro Abisay Rivera Matias, Francesca Bottazzi, Claudia Alpini, Liza Rajasekhar, Vikas Agarwal, Fernando Henrique Carlos De Souza, Renata Miossi, Maria Rosa Pozzi, Paola Faverio, Giovanni Franco, Giulia Dei, Franco Franceschini, David Lacomis, Florenzo Iannone, Francesco Girolamo, Ernesto Trallero-Araguás, Albert Gil-Vila, Ana Villar, Christina Charles-Schoeman, Heather Bukiri, Chiara Murru, Alberto Cauli, Javier Bachiller-Corral, Lorenzo Dagna, Corrado Campochiaro, Jorg Distler, George Schett, Matias Florenzano, Felipe Reyes, Antony Amato, Paul Dellaripa, Silvana Saavedra, Karen Vergara, Andreina Manfredi, Caterina Vacchi, Teresa Melo, Prateek Gandiga, Dhruv Amratia, Eugenio Arrigoni, Yuko Kaneko, Konstantinos Triantafyllias, Anna Mandel, Santos Castañeda, Esther Francisca Vicente-Rabaneda, Océane Landon-Cardinal, María Laura Alberti, Fabian Caro, Martín Gerardo Greco Merino, Iñigo Rua-Figueroa, Christoph Fiehn, Jutta Bauhammer, Yair Molad, Osnat Klein, Marcello Govoni, Ran Nakashima, Erkan Alpsoy, Alain Meyer, Margherita Giannini, Hector Chinoy, James Lilleker, Laure Gallay, Vincent Cottin, Philippe Dieudè, Julien Campagne, André Pinto Saraiva, Edoardo Conticini, Giandomenco Sebastiani, Laura Nuno, Salvatore Scarpato, Elena Schiopu, Pier Paolo Sainaghi, Vega Jovani, Simone Barsotti, Natsuka Umezawa, Merrilee Needham, Giovanni Cagnotto, Maria Giovanna Danieli, Paola Tomietto, Nair Perez Gomez, Massimiliano Limonta, Giovanni Barausse, Yasuhiro Kondo, Daniela Ghetie, Farah Tamirou, Pari Basharat, Stylianos Tomaras, Reinhard Edmund Voll, Helena Andersson, Julia Martinez Barrio, Matthias Schneider, Paola Parronchi, Antonella Notarnicola, and Jose Cifrian.

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