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Original article

Clinical profile and treatment outcomes in antisynthetase syndrome: a tertiary centre experience

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Abstract

Objectives The aim was to describe the clinical profile and outcomes in patients with antisynthetase syndrome (ASS) from a tertiary care centre.

Methods The clinical data and investigations of all patients classified as ASS by Connors criteria over 5 years were recorded, and they were followed up prospectively. The median (interquartile range) was used for descriptive statistics. Clinical variables between the Jo-1 and non-Jo-1 groups and between patients with and without anti-Ro52 antibodies were compared using the χ^2 test. Survival analysis was done using the log rank test.

Results The 28 patients (23 females) had a median age of 42.5 (34.8–52.3) years, with a disease duration of 1.75 (0.6–3.8) years at diagnosis, and had a follow-up of 2 (0.25–4.25) years. Seronegative arthritis was seen in 23 of 28 patients. Non-specific interstitial pneumonia was seen in 19 patients with interstitial lung disease (ILD). Antibodies to Jo-1 ($n = 17$) were more frequent than non-Jo-1 antibodies ($n = 11$; five anti-PL-12, four anti-PL-7 and two anti-EJ). There was no significant difference in the prevalence of myositis ($P = 0.07$) or ILD ($P = 0.11$) between groups. Anti-Ro52 antibodies were more frequently found in the non-Jo-1 group ($P = 0.006$, $\phi = 0.51$). A partial or complete improvement with treatment was seen in three-quarters of the patients. Five patients succumbed to the illness. Better survival was seen in the Jo-1 group ($P = 0.05$).

Conclusion The most typical presenting manifestation of ASS in our cohort was isolated seronegative arthritis. Non-specific interstitial pneumonia was the commonest ILD pattern. Patients with antibodies to Jo-1 had better survival compared with non-Jo-1. The non-Jo-1 aminoacyl-transfer RNA synthetases had a strong association with anti-Ro52 antibodies.

Key words: antisynthetase, anti-Jo-1, interstitial lung disease, myositis, seronegative arthritis

CLINICAL SCIENCE

Key messages

- Antisynthetase syndrome should be considered in isolated seronegative arthritis, myositis or interstitial lung disease in middle-aged females.
- There is better survival associated with antibodies to Jo-1.
- The non-Jo-1 aminoacyl-transfer RNA synthetases have a strong association with anti-Ro52 antibodies.

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Introduction

Antisynthetase syndrome (ASS) is an autoimmune disease with multisystem involvement characterized by antibodies against different aminoacyl-transfer RNA synthetases (ARS) [1]. Anti-ARS autoantibodies are the hallmarks of the syndrome, which has clinical features of interstitial lung disease (ILD), often accompanied by myositis, non-erosive arthritis, Raynauds phenomenon (RP), mechanic's hands and fever. The most frequently reported ARS in ASS is anti-Jo-1, directed against the histidyl-transfer RNA (tRNA) synthetase. In contrast, other antisynthetase specificities are less frequently identified and include anti-PL-7 (antithreonyl), anti-PL-12 (anti-alanyl), anti-EJ (anti-glycyl), anti-OJ (anti-isoleucyl), anti-KS (anti-asparaginyl), anti-YRS (anti-tyrosyl) and anti-Zo (antiphenylalanyl) autoantibodies [2]. There is heterogeneity in disease expression, leading to delayed diagnosis and morbidity. The underlying ARS antibody can determine the clinical phenotype; hence, the prognosis [3]. The patients with anti-Jo-1 have a significantly better cumulative survival. Patients with anti-non-Jo-1 ASS who have atypical presentations, such as isolated ILD, are often diagnosed late and have worse clinical outcomes. The treatment of ASS includes glucocorticoids in combination with one or more immunosuppressive drugs. There is no consensus or guidelines regarding the choice of additional immunosuppressive drugs. AZA, MMF, tacrolimus, rituximab (RTX) and CYC are the most frequently used agents [4]. Pulmonary involvement is a major cause of morbidity and mortality in ASS and is encountered in 70–100% of the patients [5]. ILD in ASS can be the initial or sole manifestation.

There are limited data from Indian cohorts reporting on ASS patients and their outcomes. We present our data from a tertiary care centre in India on ASS patients with their outcomes.

Methods

Patients with ASS fulfilling Connor's criteria [6] [the presence of an ARS antibody (required criterion) and one or more of the following clinical features: RP, arthritis, ILD, fever (not attributable to another cause), mechanic's hands (thickened and cracked skin on hands, particularly at the fingertips)] were identified from the medical records of outpatients, inpatients of Nizam's Institute of Medical Sciences and patients included in the MYOIN registry. MYOIN is a prospective, multicentre registry from India to study risk factors for susceptibility, severity and prognosis of inflammatory myopathies and maintains follow-up data and bio-repository of myositis patients [7]. Patients of ASS with $\geq$6 months of follow-up were enrolled as cases. Written informed consent was obtained from all participants. Demographic and clinical data were entered into case record forms.

Objective muscle testing was done by Manual Muscle Testing 8 score (MMT8), and severity was assessed by determining the functional class. Functional class 3 or 4 at presentation was considered as severe myositis. All patients had a baseline high-resolution CT of the chest, and pulmonary function tests (PFT) were done wherever the condition of the patient permitted. Forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) were recorded. A baseline two-dimensional echocardiogram was done in all patients, and pulmonary arterial hypertension was defined on the basis of the right ventricular systolic pressure [mild: 30–40 mmHg; moderate: 40–60 mmHg; severe: $>$60 mmHg].

Muscle enzymes [creatine phosphokinase, aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], ANA and IgM RF were measured. Myositis-specific and -associated antibodies were measured using the EUROIMMUN EUROLINE kit (Medizinische Labordiagnostika AG,Lubeck,Germany) which provides qualitative determination of autoantibodies of the immunoglobulin class IgG to 16 different antigens [8]. Titres of 1+ and above were taken as positive. ANA was measured using indirect immunofluorescence at 1:100 dilution. The pattern was described as homogeneous, speckled, nucleolar, cytoplasmic, mixed or others, with an intensity of ANA above 2+ taken as significant. IgM RF was measured by ELISA.

For this study, response criteria based on clinical discretion and experience were used to assess response. Complete response (CR) in the ILD domain was defined as the absence of clinical symptoms or signs and/or an increase in FVC by $\geq$10% on follow-up. CR in the myositis domain was defined as an achievement of functional class 1, with normalization of muscle power assessed by MMT8 and normal muscle enzyme concentrations. CR in arthritis and cutaneous domains was defined as absent tender and swollen joints and healed old lesions, or no new or worsening skin rash. Partial response (PR) was an improvement in any of these domains, which did not meet the criteria for CR. Disease worsening in the ILD domain was characterized by increasing breathlessness and/or decline in FVC $\geq$10% on follow-up and new or worsening ground-glass opacities, fibrosis or traction bronchiectasis. Rapidly progressing ILD (RP-ILD) was defined as a worsening of radiological interstitial changes with progressive dyspnoea and hypoxaemia within 3 months after the onset of respiratory symptoms [9]. Disease worsening in the myositis domain meant decreased muscle power (worsening functional class, decreased MMT8 scores and elevated creatine phosphokinase). This study complies with the Declaration of Helsinki and was approved by the Nizam's Institute of Medical Sciences (NIMS) Institutional Ethics Committee (PBAC no. 1226/2018).

Statistics

Categorical variables were described as percentages and continuous variables as the median (interquartile range). The χ^2 test was used to make comparisons between groups, and the correlation between dichotomous variables was determined using the ϕ coefficient. Survival analysis between groups was done using log

rank test. The Statistical Package of Social Sciences (SPSS) v.19 (IBM SPSS, Chicago, IL, USA) was used, and a *P*-value of $\leq$0.05 was considered significant.

Results

The study included 28 patients. The clinical characteristics and investigations are described in Table 1. The complete ASS triad (arthritis, ILD and myositis) was present in seven patients at presentation. During follow-up, 14 patients fulfilled the triad. The most common presenting complaint was symmetrical non-deforming polyarthritis (22 of 28). A deforming, subluxing arthritis of the DIP joints was seen in one patient. Myositis was seen in 17 patients, with 5 having severe myositis at presentation.

TABLE 1 Clinical characteristics and investigations of study population

Baseline characteristics	Value
Number of patients, *n*	28
Age, median (IQR), years	42.5 (34.75–52.25)
Females, *n* (%)	23 (82.1)
Duration at diagnosis, median (IQR), years	1.75 (0.62–3.75)
Duration of follow-up, median (IQR), years	2 (0.25–4.25)
MMT 8 at baseline, median (IQR)	72 (40–76)
CPK, median (IQR)	618 (70–2128)
FEV1, median (IQR), %	62.5 (58.5–67.7)
FVC, median (IQR), %	61.5 (56.7–66)
Frequency of clinical features ($n = 28$)	
Arthritis	23
Interstitial lung disease	21
Constitutional (fever/ loss of weight)	19
Myositis	17
RP	6
Mechanic's hands	14
Hiker's foot	1
Pulmonary artery hypertension	4
Gottron's sign	3
Serological parameters, *n* (%)	
ANA (IF)	18 (64.2)
Cytoplasmic	7 (38.8)
Mixed (H + C, S + C)	5 (27.7)
Speckled	2 (11.1)
Diffuse fine speckled	2 (11.1)
Nucleolar/nuclear dots	1/1 (5.5)
IgM RF	3 (10.7)
Myositis-specific antibody, *n* (%)	
Anti-Jo-1	17 (60.7)
Anti-PL-7	4 (14.3)
Anti-PL-12	5 (17.8)
Anti-EJ	2 (7.1)
Myositis-associated antibody, *n* (%)	
Anti-Ro52	14 (50)
PFT at follow-up, median (IQR)	
FEV1	70 (57–75)
FVC	65 (51.5–72.5)

CPK: creatine phosphokinase; FEV1: forced expiratory volume in 1s; FVC: forced vital capacity; IQR: interquartile range; MMT: manual muscle testing; PFT: pulmonary function tests.

Interstitial lung disease was present in 21 patients (16 females) and was the isolated presenting complaint in 5 patients. Arthritis preceded ILD in three patients. Cough and dyspnoea were present in 11 and 19 patients. Spirometry was available at both presentation and follow-up in 10 patients. All patients who had spirometry data available at baseline had a restrictive abnormality, with the median FVC 61.5% of predicted (56.7–66%), improving to 65% of predicted (51.5–72.5%) at follow-up. Asymptomatic ILD was detected by imaging in two patients. Two in the Jo-1 group developed RP-ILD. The most common pattern on high-resolution CT was non-specific interstitial pneumonia (90%). The demographics, clinical features, antibody profile and outcomes of ASS patients with ILD are shown in Table 2.

Anti-Jo-1 antibodies were the commonest ARS ($n = 17$), and patients positive for them constituted the Jo-1 group. The other ARS ($n = 11$) were anti-PL-12 ($n = 5$), anti- PL-7 ($n = 4$) and anti-EJ ($n = 2$), and patients positive for them were collectively termed the non-Jo-1 group. The median time to diagnosis of ASS was similar in both Jo-1 and non-Jo-1 groups (1.75 years). The Jo-1 group of patients had a higher proportion of myositis, but the difference was not significant ($P = 0.07$). There was no significant difference in the prevalence of mechanic's hands ($P = 0.69$) or ILD ($P = 0.11$) between the two groups. The other antibodies explored were ANA, anti-Ro52 and IgM RF. ANA was positive in 18 sera, with cytoplasmic pattern being the commonest ($n = 12$). Antibodies to Ro52 were more frequent in the non-Jo-1group (9 of 11; $P = 0.006$, $\phi = 0.51$). IgM RF was found in only three patients and was not more frequent in those with arthritis. Twenty of 23 patients with arthritis were IgM RF negative. Echocardiography revealed the presence of pulmonary arterial hypertension with mild to moderate severity in four patients (Jo-1, EJ, PL-12 and PL-17: $n = 1$ each). All four were positive for anti-Ro52.

Treatment and clinical outcomes

Treatment was initiated with CSs and immunosuppression according to the physician's discretion. The predominant clinical manifestation dictated the physician's choice of initial immunosuppressive drug, with CYC (500–750 mg/m^2 i.v. every month for six doses) used if there was predominant ILD, and MTX (15–25 mg/week) or AZA (50–125 mg/day) used for arthritis and myositis, respectively. CYC was used in 11, MTX in 10, MMF (1.5–2.0 g/day) in 3, and AZA in 2 patients. Ten patients became clinically asymptomatic during follow-up and remained on stable immunosuppression and low-dose CSs (5–7.5 mg/day), including six patients with predominant ILD and two with arthritis and myositis each.

Table 2 Demographics, clinical features and treatment outcomes of antisynthetase syndrome-associated interstitial lung disease

Number	Age/sex	Pulmonary manifestations (clinical history)	Imaging (high-resolution CT pattern)	PFT (FVC, %)		Serology	Other manifestations (ASS related)	Treatment	Follow-up (months)	Outcome
				BL	FU					
1	41/F	Cough, SOB	NSIP	NA		ANA, PL-12, Ro52	Fever, RP, LOW	MMF	7	Death
2	39/F	Cough, SOB	NSIP	43	51	ANA, Jo-1, Ro52	Fever, arthritis, RP, myositis	GC, MTX	24	PR
3	50/F	Cough, SOB	NSIP	NA		ANA, PL-7	Fever, arthritis, MH, myositis	GC	6	Death
4	50/F	Cough, SOB	AIP to NSIP	NA		ANA, Jo-1	Fever, myositis	GC, i.v. CYC	12	PR
5	37/M	AP	NSIP	59	NA	ANA, EJ	Fever, arthritis MH, rash	GC, AZA	18	CR
6	53/F	Cough, SOB	NSIP	NA		ANA, Jo-1	Arthritis, myositis, RP, MH	GC, i.v. CYC	24	CR
7	40/F	SOB	NSIP	56	66	ANA, Jo-1	Fever, arthritis, myositis, MH	GC, i.v. CYC, AZA, MMF, RTX	24	CR
8	54/F	Cough, SOB	NSIP	56	88	ANA, IgM RF, Ro52, PL-12	Arthritis, MH	GC, AZA, i.v. CYC	36	CR
9	55/F	SOB	NSIP	65	84	ANA, IgM RF, RO52, PL-12	Fever, arthritis	GC, i.v. CYC, AZA	48	PR
10	40/F	SOB, cough	NSIP	39	52	ANA, PL-7, Ro52	Fever, arthritis	GC, i.v. CYC, AZA	12	PR, moderate PAH
11	45/F	SOB, cough	NSIP	NA		ANA, PL-7, Ro52	Fever, arthritis, myositis, RP, rash	GC, MTX	3	Death
12	56/F	SOB, cough	NSIP, DAH	60	65	ANA, Jo-1	Arthritis, MH	GC, MMF, MTX	6	Death
13	34/F	SOB	NSIP	67	57	ANA, Jo-1, Ro52	Fever, arthritis, myositis, MH	GC, MTX, MMF, i.v. CYC	24	RP-ILD, mild PAH
14	53/M	SOB	NSIP	NA		ANA, Jo-1, Ro52	Fever, arthritis, myositis,	GC, MMF, RTX	12	PR
15	40/F	SOB, cough	NSIP	NA		ANA, Jo-1	Arthritis, myositis, MH	GC, i.v. CYC, AZA	12	PR
16	55/M	SOB	UIP	NA	67	Jo-1	Fever, arthritis,	MTX, MMF	72	PR
17	55/M	SOB	NSIP	63	51	EJ, Ro52	Arthritis	GC, i.v. CYC, MMF	72	PR
18	50/F	SOB, cough	NSIP	57	40	PL-12, Ro52	MH, LOW	GC, MMF	36	PR
19	30/F	AP	NSIP	66	NA	PL-12, Ro52	Fever, arthritis, RP, MH, LOW	MTX	36	CR
20	38/F	SOB	NSIP	69	NA	Jo-1	Arthritis, myositis, MH, RP	GC, i.v. CYC, MTX, RTX	24	CR
21	50/M	SOB	NSIP	77	78	Jo-1	Arthritis, MH	GC, i.v. CYC, MMF, MTX	72	CR

AIP: acute interstitial pneumonia; AKI: acute kidney injury; AP: asymptomatic at presentation; ASS: antisynthetase syndrome; BL: baseline; CR: complete remission; DAH: diffuse alveolar haemorrhage; F: female; FU: follow-up; FVC: forced vital capacity; GC: glucocorticoids; LOW: loss of weight; M: male; MH, mechanic's hands; NA: not available (unable to perform); NSIP: non-specific interstitial pneumonia; PAH: pulmonary arterial hypertension; PFT: pulmonary function tests; PR: partial remission; RP-ILD: rapidly progressive interstitial lung disease; RTX: rituximab; SOB: shortness of breath; UIP: usual interstitial pneumonia.

Table 3 Comparison of demographic data, clinical features and outcomes between Jo-1 and anti-Jo-1 groups

Parameter	Jo-1 group ($n = 17$)	Non-Jo-1 group ($n = 11$)	*P*-value
Females, *n*	14	9	–
Duration of disease at diagnosis, median (IQR), years	1.75 (0.62–3.75)	1.75 (0.6–3.7)	_
Clinical and laboratory parameters			
Arthritis, *n*	14	9	0.97
Myositis, *n*	13	4	0.07
Interstitial lung disease, *n*	11	10	0.11
Fever, *n*	11	7	0.5
RP, *n*	3	3	0.9
Mechanic's hands, *n*	9	5	0.69
ANA positivity, *n*	11	7	0.95
Ro52 positivity, *n*	5	9	**0.006**
Outcomes			
Arthritis			
Complete response	9	3	
Partial response	4	3	0.24
Worsening/death	1	3	
Myositis			
Complete response	9	0	
Partial response	3	1	**0.01**
Worsening/death	1	3	
Interstitial lung disease			
Complete response	4	3	
Partial response	5	4	0.87
Worsening/death	2	3	
Number of deaths (total), *n*	1	4	**0.03**

The bold text indicates significant *P*-values ($P < 0.05$). IQR: interquartile range.

Complete response in the ILD domain was seen in seven patients, partial response in nine, and worsening in five. The outcomes in ILD compared between Jo-1 and non-Jo-1 groups were not statistically significant ($P = 0.81$). Of the two patients with RP-ILD (both from the Jo-1 group), one experienced fatal diffuse alveolar haemorrhage, and the other is currently on CYC with a good response to treatment.

Complete response in the myositis domain was seen in nine patients, while partial response and worsening were seen in four. There was a better outcome in myositis in the Jo-1 group ($P = 0.01$). The clinical responses in the Jo-1 and non-Jo-1 groups are given in Table 3.

Change in therapy to alternative drugs was required in six patients owing to persistent disease activity. There was a switch from MTX to MMF for myositis in one, from AZA and MMF to CYC and RTX in one each for ILD progression, from MMF to MTX in one for arthritis, and from MMF and MTX to RTX in two for myositis.

One patient developed follicular adenoma of the thyroid, and no other malignancies were noted during the follow-up period. Of the five patients who died owing to disease, four had ILD, and one had severe myositis (Table 4). Survival was better in the Jo-1 group compared with the non-Jo-1 group ($P = 0.05$).

Discussion

Here, we describe a group of patients with ASS and provide data on follow-up outcomes from India, for the first time. Seronegative arthritis was the most common presentation, followed by ILD and myositis. Our study showed immunosuppression to be effective in ILD irrespective of the ARS antibody subtype. We found a strong association of anti-Ro52 antibodies with non-Jo-1 antisynthetase antibodies. Survival was better in the Jo-1 group.

The largest and oldest ASS cohort was the Pittsburgh cohort, with 202 patients and 24 years of follow-up [10]. The cohort from Johns Hopkins followed 169 Black patients for 13 years [11]. Rojas-Serrano *et al.* [12] reported 43 Mexican ASS patients, and Shi *et al.* [9] described 124 Chinese patients with 18 and 22 years of follow-up, respectively. The cohorts that focused on anti-Jo-1-positive patients were the European American AENEAS group (58 patients), the cohort described by Kumar *et al.* from India (27 patients), and the Spanish group by Trallero-Araguás *et al.* (148 patients) [1, 13, 14]. The study by Srivastava *et al.* [15] on the prevalence of myositis-specific and -associated antibodies in a North Indian population reported 29 ASS patients, of whom 14 were Jo-1 positive.

The prevalence of ILD in most cohorts, including ours, was ~75% [10, 11, 16]. Non-specific interstitial

Table 4 Clinical details and antibody status of the non-survivors

Number	Age	Sex	ILD	Serology	ASS manifestations	Treatment	Delay in diagnosis (months)	Time to death after diagnosis (months)	Cause of death
1	41	F	NSIP	PL-12, Ro52	Fever, RP	MMF	24	7	Progression of ILD, CAD
2	50	F	NSIP	PL-7	Fever, arthritis, MH, myositis	GC	12	24	Pneumonia with respiratory failure
3	45	F	NSIP	PL-7, Ro52	Fever, arthritis, myositis, RP, rash	GC, MTX	18	3	Sepsis, ARDS, MODS, respiratory failure
4	56	F	NSIP	Jo-1	Arthritis, MH	GC, MMF, MTX	60	6	Rapidly progressive ILD, DAH, respiratory failure
5	44	F	–	PL-7	Myositis, hand fissuring, rash, arthritis, fever	AZA	3	18	Pneumonia with respiratory failure

ASS: antisynthetase syndrome; CAD: Coronary artery disease; DAH: diffuse alveolar haemorrhage; F: female; GC: glucocorticoids; ILD: interstitial lung disease; M: male; MH: mechanic's hands; NSIP: non-specific interstitial pneumonia.

pneumonia, as in other studies, was the commonest pattern present on high-resolution CT in our study [9, 13, 16, 17]. Although the two RP-ILD cases in our cohort were anti-Jo-1 positive, Shi *et al.* [9] reported a significant association with anti-PL-7 antibodies and mortality of ∼9%.

Antisynthetase syndrome may present as arthritis [13, 18]. We reported a very high incidence of isolated arthritis at presentation (42%) compared with three previous reports (21, 25 and 21%) [10, 12, 18]. A very high percentage of seronegative arthritis was reported by Lefevre *et al.* [18], the AENEAS cohort [19], and our study (87, 73 and 86%, respectively). Kumar *et al.* [13], however, found a much higher (71.4%) seropositivity, probably because they had focused on patients misdiagnosed as RA. The distal subluxating arthropathy of the hand seen in one of our patients had been described in case reports of ASS [20, 21].

The prevalence of myositis in our cohort was comparable to that in other cohorts [1, 9–14, 17]. There were no data on the severity of myositis at presentation available from other cohorts. Although ASS is classified as a subset of idiopathic inflammatory myositis, almost 40% of our patients never developed myositis. A lower prevalence of myositis has been reported in non-Jo-1 ARS antibodies.

Anti-Jo-1 antibodies were the more frequent ARS antibodies in our cohort. The prevalence of Jo-1 ARS in other cohorts varied from 50 to 81% [9–12, 17]. This wide variability could be explained by the different methods used for detection of anti-Jo-1. Immunoprecipitation was used by Aggarwal *et al.* [10], and immunodiffusion with subsequent confirmation by ELISA used by Marie *et al.* for detecting anti-Jo-1 [17]. The rest of the studies described here have used the 16-antigen EUROIMMUN line blot assay. Although immunoprecipitation remained the gold standard technique for detecting most of the myositis-specific antibodies, the thin band of the 50 kDa Jo-1 antigen was difficult to observe, and the histidyl tRNA was difficult to characterize in immunoprecipitation [22]. In a study comparing different methods for detecting myositis-specific antibodies, agreement between line blot and immunoprecipitation for detecting anti-Jo-1 antibodies was 0.69, much less than that for anti-SRP, Ku and SAE-1. Furthermore, commercial ELISA for anti-Jo-1 antibodies failed to detect the antibody unequivocally in two of five sera that were line blot positive and immunoprecipitation negative [23]. The prevalence of anti-Jo-1 antibodies in our cohort (60%) was higher than that reported by Srivastava *et al.* [15] (48.2%) using the line blot assay. It has been well documented that the association of clinical features and prognosis of Jo-1-positive *vs* Jo-1-negative patients are different. Jo-1-positive patients were more likely to have myositis and arthritis, whereas non-Jo-1 patients were likely to have greater ILD [6, 10–12, 17]. We also reported more frequent myositis in the Jo-1 group and a higher prevalence of ILD in the non-Jo-1 group, although the differences were found not to be significant. Srivastava *et al.* [15], however, reported an association of ILD with the Jo-1 group. A longer time to diagnosis had been reported in non-Jo-1 ASS patients [10, 12]; however, non-Jo-1 patients in our cohort with ILD or skin involvement did not have any delay in diagnosis.

The better survival seen in the Jo-1 group in the present study was in concordance with outcomes of Jo-1-positive patients reported from other cohorts [9, 10, 12, 17]. We reported good improvement in muscle power with treatment and no relapses at follow-up in the Jo-1 group, whereas Marie *et al.* [17] described less improvement of muscle power and frequent relapse in myositis. The coexistence of ILD led to poor survival of a majority (75%) of our non-Jo-1 patients with myositis.

In cohorts with inflammatory myositis, anti-Ro52 antibodies had been strongly associated with anti-Jo-1 antibodies and ILD [15, 24–26]. In our study, we found a

Table 5 Comparison of data between present study and other published ASS cohorts

Parameter	Aggarwal *et al.* [10] (2012)	Marie *et al.* [17] (2012)	Rojas-Serrano *et al.* [12] (2015)	GEAS Trallero-Araguás *et al.* [14] (2016)	AENEAS Cavagna *et al.* [1] (2016)	Pinal-Fernandez *et al.* [11] (2017)	Shi *et al.* [9] (2017)	Kumar *et al.* [13] (2019)	Present study (2020)
Number	202	95	43	148	58	169	124	27	28
Female, %	68	60	79	60	–	73	76	80	82.1
Age, mean, years	47.5	53.3	47	50.8	54	47.4	50	40	42.5
Time to diagnosis, years	0.5	–	0.25	–	1	–	1.07	–	1.75
Criteria used	Positive ARS antibody	Positive ARS antibody	Positive ARS antibody + ILD + 2 of F, A, MH	Positive anti-Jo-1 in two samples	Positive ARS antibody with presentation as A	Positive ARS antibody	Solomon	Connors	Connors
Fever, %	2.5	21	81	33	8	20	–	59.2	64.2
Arthritis, %	21	57.8	79	70.1	100	50	54	66.6	82.1
Arthritis at onset, %	63.3	–	–	17.9	100	19	–	25.9	46
Myositis, %	75.2	63.1	80.4	83.1	65.5	82	63.7	88.8	60.7
ILD, %	76.4	72.6	100	81.8	58.6	74	94.4	81.4	75
Predominant ILD type, %	–	NSIP (60)	OP (58)	–	–	–	NSIP (72.5)	NSIP (81)	NSIP (90)
RP, %	14	45.2	21	34.5	25.8	35	9.7	33	21.4
Mechanic's hands, %	–	29.4	68	44.9	13.7	53	53	37	50
Jo-1, %	60	78.9	81.4	100	100	73	50	100	60.7
Non-Jo-1, %	40	21.1	33	–	–	25	50	–	39.2
ANA, %	50.2	–	–	–	–	–	55.6	60	64.2
Ro52, %	–	–	68	–	47	66	29	70	50
Treatment	CSs, MTX, tacrolimus, lung transplant	IS, IVIG	CSs, Cyc, AZA, MTX, LEF, RTX	NA	NA	CSs, AZA, MTX, IVIG, RTX	CSs CYC, IVIG	CSs, MTX, AZA, CYC, RTX	CSs, MTX, CYC, MMF, AZA, RTX
Mortality, %	33	14.4	14	25	22.4	8	6.8	3	17.8

A: arthritis, ARS: anti-aminoacyl transfer RNA synthetases; ASS: antisynthetase syndrome; F: fever; ILD: interstitial lung disease; IS: immunosuppressants; MH: mechanic's hands; NSIP: non-specific interstitial pneumonia; OP: organizing pneumonia; RTX: rituximab.

higher prevalence of anti-Ro52 in the non-Jo-1 group (81.9% *vs* 29.4%). This observation could be explained, in part, by the fact that our cohort was collected based on the presence of ARS antibody rather than a particular clinical feature. Yamasaki *et al.* [26] had reported a higher frequency of anti-Ro52 in patients with anti-PL-7 (67%) compared with the anti-Jo-1 (57%) and non-ARS population (22%). Similar findings were reported by Shi *et al.* [9], with a more frequent presence of anti-Ro52 in patients with anti-PL-7, anti-PL-12 and anti-EJ compared with the anti-Jo-1group of patients (48.3% *vs* 9.7%). The Southeast Asian ethnicity of these cohorts could explain these differences in the association, because most of the other described cohorts were Caucasian. In addition, a high frequency of non-Jo-1 ARS was seen in the cohort described by Shi *et al.* [9].

There was no difference in the prevalence of ILD between anti-Ro52-positive and -negative patients in the present study. Shi *et al.* [9] had reported an increased incidence of RP-ILD in Ro52-positive patients, especially in those who were also PL-7 positive. Given that only two patients in our cohort had RP-ILD, no conclusions could be drawn on its occurrence in only the Jo-1 group.

The few studies on the association and pattern of ANA in ASS reported a prevalence from 56 to 70% [9, 13, 18]. In 62% of patients with ANA positivity, in contrast to the higher prevalence of speckled pattern described in the above studies, the cytoplasmic pattern (68%) predominated in our cohort.

The overall outcomes in our cohort at follow-up with respect to complete response, partial response and worsening (52.9, 23.5 and 23.5% for myositis and 33.3, 42.8 and 23.8% for ILD, respectively) were comparable to responses reported by Marie *et al.* [17] (27.4, 60 and 10.5% for myositis and 23.9%, 57%, 17.2% for ILD, respectively). The outcomes of ILD in the present study did not vary significantly between Jo-1 and non-Jo-1 groups.

In our series, at 17.8%, mortality was lower than the 33% reported by Aggarwal *et al.* [10] from the Pittsburgh cohort. However, lower mortality has also been reported from other cohorts [9, 11, 13]. As in the other studies, respiratory involvement was the leading cause of death. The differences in mortality might be attributable to differences in the time taken to diagnosis and lack of uniformity in treatment protocols. A comparison of the published ASS cohorts is given in Table 5.

In this study, to the best of our knowledge, we describe the largest series of patients with ASS with outcomes reported from India. A diagnosis of ASS should be considered, especially in middle-aged females with seronegative arthritis, isolated ILD or myositis, and facilities should be made available to test the less common non-Jo-1 antibodies.

The limitations of this study were that comparison of treatment effects between groups was not possible owing to the small numbers in our cohort. PFT at baseline was not possible in all patients.

There is a need for collaborative research, with more studies from different large cohorts, to understand this heterogeneous disease entity better and improve prognosis. This should result in the derivation of improved diagnostic criteria, uniformity in testing myositis antibodies, and randomized trials to prove the efficacy of immunosuppressive drugs.

Conclusion

This study on ASS showed a higher female prevalence and high rates of isolated seronegative arthritis at presentation. ILD was more frequent than myositis in our cohort. Anti-Ro52 antibodies were significantly associated with non-Jo-1 ARS, contrary to most previous reports. Patients with anti-PL-7/PL-12 antibodies had a lower survival rate compared with those with anti-Jo-1.

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Data availability statement

The datasets generated during and analysed during the current study are available from the corresponding author on reasonable request.

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