Demographic, clinical, laboratory data, prognostic, and treatment features of patients with antisynthetase syndrome: An international, two-center cohort study

Lila Morena Bueno Da Silva, Upendra Rathore, Vikas Agarwal, Latika Gupta, Samuel Katsuyuki Shinjo

ABSTRACT

Objectives: To compare clinical, demographic, laboratory data, prognostic and treatment characteristics of patients with antisynthetase syndrome (ASSD) treated in two different centers of India and Brazil.

Patients and methods: This international, two-center, retro-prospective cohort study which was conducted at two tertiary rheumatology centers (one in Brazil and one in India) between January 2000 to January 2020 included a total of 115 patients with ASSD (21 males, 94 females; mean age; at disease diagnosis at 40.3; range, 18 to 80 years). Demographic, clinical and laboratory data of the patients were recorded. Clinical involvement was evaluated.

Results: Of the patients, 81 were Brazilians and 34 were of Indian origin. The Indian group exhibited a greater delay in diagnosis after the onset of symptoms compared to Brazilian patients (12 vs. 6 months, respectively; p=0.026). Brazilian patients exhibited a significantly higher prevalence of joint and lung involvement, mechanic's hands, and Raynaud's phenomenon. Anti-Jo-1 was the most common autoantibodies in both groups. Systemic arterial hypertension, followed by diabetes mellitus were the most prevalent comorbidities. Concerning previously used drugs, the Indian patients had a larger group of patients treated with antimalarials, whereas the Brazilian group used more azathioprine and intravenous immunoglobulin. A higher proportion of Indian patients was treated with one immunosuppressive drug (70.6%), while the Brazilian group were often treated using two immunosuppressive drugs (33%). Comparison between the severity and prognosis showed that Brazilian group had a higher number of relapses, and during follow-up, the global mortality rates were similar in both groups (6.2% for Brazilian vs. 8.8% for Indian).

Conclusion: Brazilian and Indian patients with ASSD have comparable epidemiological characteristics such as age at the time of disease diagnosis, and sex distribution, and autoantibodies. Diagnostic delay is seen in Indian patients, and Brazilians exhibit a higher prevalence of joint and lung involvement, mechanic's hands, Raynaud's phenomenon with a higher number of relapses, although the mortality rate seems to be similar in both groups.

Keywords: Antisynthetase syndrome; dermatomyositis; myositis; outcomes.

Antisynthetase syndrome (ASSD) is a systemic autoimmune myopathy characterized by myositis, arthritis, and interstitial pneumopathy. Moreover, other symptoms such as fever, Raynaud’s phenomenon and “mechanic’s hands” may also be present. In the laboratory, ASSD is characterized by the presence of anti-aminoacyl-tRNA synthetase (anti-ARS) autoantibodies (e.g., anti-Jo-1, anti-PL-7, anti-PL-12, anti-OJ, anti-EJ, anti-KS, anti-Zo, or anti-Ha).
The clinical presentation of ASSD is highly variable with a substantial heterogeneity in disease phenotype and severity.\(^4\) The positivity of anti-ARS autoantibodies can partially determine the profile of clinical manifestations and the severity of ASSD.\(^1,5,7\) Anti-Jo-1, the most studied autoantibody in ASSD, is related to a higher frequency of joint and muscle involvement and a lower frequency of pulmonary involvement and systemic manifestations (asthenia, weight loss), compared to negative anti-Jo-1 autoantibodies.\(^8,9\) In addition to clinical manifestations, they seem to be related to early diagnosis and better survival compared to negative anti-Jo-1 patients.\(^8\) Another promising feature of anti-Jo-1 is the growing evidence related to the activity of the disease and response to treatment, particularly in muscle involvement.\(^10\)

In contrast, patients with positive anti-PL-7 and anti-PL-12 autoantibodies, compared to patients with positive anti-Jo-1 autoantibodies, have a higher incidence of interstitial pneumopathy (and possibly greater severity of the disease), mortality, and systemic manifestations, and a lower incidence of myositis and joint involvement.\(^6,8,9\)

Due to the rarity of the disease, most of the studies concerning ASSD patients involve small samples of patients.\(^11\) In addition, ASSD has a polymorphic clinical presentation and can be influenced by geographic distribution.\(^12\) Type specificity of autoantibodies, conformational epitopes, and clinical presentation associated with myositis specific autoantibodies are known to vary in different ethnic groups. Moreover, delay in diagnosis may translate into varied opportunities for treatment, and consequently different long-term outcomes. The specific patterns of presentation, prevalent treatment practices, and outcomes are less explored in the Asian and Hispanic population. Therefore, in the present study, we aimed to enrich the still scarce knowledge of patients with ASSD, comparing two geographically disparate and ethnically distinct cohorts to compare and contrast the demographic, clinical, and laboratory features, comorbidities, treatment and short-term outcomes of ASSD. We believe that this study would provide preliminary understanding of the differences, paving the way for larger prospective studies to improve the management of the disease in the region.

**PATIENTS AND METHODS**

This international, two-center, retro-prospective cohort study was conducted at two tertiary rheumatology centers (one in Brazil and one in India) between January 2000 to January 2020. A total of 115 patients with ASSD (21 males, 94 females; mean age; at disease diagnosis at 40.3, range, 18 to 80 years) were included in the study. The medical data were retrieved from the electronic medical records for Brazilian patients, with pre-standardized and parameterized information. The MyoCite cohort is an established retro-prospective cohort with data collection in a prespecified detailed case record form replete with biorepository and regular follow-up.\(^13,15\) Data for eligible candidates were retrieved from the database.

Patients with ASSD who were 18 years or older and fulfilled the criteria of Behrens Pinto et al.\(^16\) and Cavagna et al.\(^17\) were included in the study. These criteria included the presence of an anti-ARS autoantibody associated with the presence of at least two of the following parameters: pulmonary or articular involvement; the presence of fever, mechanic’s hands, and/or Raynaud’s phenomenon. Patients having other systemic diseases (overlap syndrome), malignancy, dermatomyositis, polymyositis or inclusion body myositis were excluded from the study. Of a total of 115 patients with ASSD, 81 were Brazilians and 34 were Indian.

To define clinical involvement, the following data were evaluated:

a. Joint involvement was defined by the presence of arthritis (joint pain or edema required)

b. Muscle involvement was defined by the elevation of muscle enzymes (creatine phosphokinase and/or an aldolase increase >50%, compared to the upper normal values), and muscle weakness (verified by a rheumatologist and classified by a muscle strength score - Manual Muscle Testing - MMT-8\(^18,19\) or Medical Research Council - MRC\(^20\) and/or the presence of an electromyographic finding typical of myositis and/or muscle biopsy compatible with muscle involvement
c. Pulmonary involvement was defined by the presence of dyspnea, exercise intolerance or cough. It was confirmed by the pulmonary function test pattern (forced vital capacity [FVC] <80%, forced expiratory volume in 1 sec [FEV1]/FVC <70%, decreased or normal FEV1 and/or <20% reduction in diffusing capacity of the lung for carbon monoxide), and or image with signs of alveolitis/fibrosis, incipient pneumopathy, ground-glass opacities with or without bronchiectasis or pulmonary fibrosis and honeycombing areas on high-resolution computed tomography (HRCT).\textsuperscript{17,21,22} The MyoCite cohort protocol involves subjecting symptomatic individuals to HRCT screening.

d. The presence of constitutional symptoms such as fever (axillary temperature $>37.8^\circ$C objectively measured) and/or involuntary weight loss of $>10\%$ of weight in the last six months of the inclusion of patients in the study was also evaluated.

e. Skin symptoms were defined by mechanic’s hands or Raynaud’s phenomenon.

f. The comorbidities and habits assessed were systemic arterial hypertension defined by arterial blood pressure $\geq140\times90$ mmHg,\textsuperscript{23} diabetes mellitus,\textsuperscript{24} a history of myocardial infarction, brain stroke and smoking habits.

The following parameters were also evaluated: age at the disease’s onset, age at the symptoms’ onset, clinical manifestations, comorbidities, treatment (current and previous), disease status, and evaluation (e.g., infections and death). Additionally, disease status was classified as remission or activity. Active disease was defined either a new or worse symptoms as per the Myositis Disease Activity Assessment (MDAAT)\textsuperscript{25} in any of the involved domains, or the followings:

a. Muscle disease activity was defined by new or worsening muscular impairment, characterized by the elevation of creatine phosphokinase and/or an aldolase increase $>50\%$ (compared to the upper normal values or patient’s baseline value); worsening of muscle weakness verified by a rheumatologist and classified by MMT-8\textsuperscript{18,19} or MRC;\textsuperscript{20} the presence of an electromyographic with new typical finding of myositis and/or compatible muscle biopsy demonstrating muscle inflammation.

b. Pulmonary activity was assessed by new or worsening symptoms (as cough, dyspnea, exercise intolerance) associated with compatible physical examination; HRCT with new signs of lung impairment (alveolitis, ground-grass opacities, pulmonary fibrosis or honeycombing areas); or committed pulmonary function test pattern

c. Presence of active inflammatory arthritis in one or more joints

d. New-onset or relapse of fever (axillary temperature $>37.8^\circ$C objectively measured) and/or involuntary weight loss of $>10\%$ of weight in the last six months of the clinical consultation

e. The presence of Raynaud’s phenomenon was not considered as disease activity.

Infection was defined as the presence of current or previous serious infections, while severe infection was assessed by the need for hospitalization or death or clinically compatible picture that improved with antibiotics.

**Laboratory data**

Laboratory data were evaluated from electronic medical records. A routine laboratory test was performed before outpatient consultation to evaluate the following parameters: creatine phosphokinase, with a normal range between 32 and 294 U/L; alanine aminotransferase (ALT) with a normal range between 7 and 56 U/L; aspartate aminotransferase (AST), 5 and 40 U/L; lactic dehydrogenase (LDH), 120 and 246 UI/L; antinuclear antibodies (ANA), anti-Ro-52; and -aminoacyl-tRNA synthetases autoantibodies. The myositis specific/antisynthetase antibodies (MSA) were identified using the Euroimmun immunoblot strips (Euroimmun AG, Lübeck, Germany) according to the manufacturer’s instructions, including the anti-Jo1, anti-PL7, anti-PL12, anti-EJ, and anti-OJ antibodies. The results were considered positive, if the bands showed moderate or strong reactions.\textsuperscript{26}
### Table 1. Baseline features of Brazilian and Indian patients with antisynthetase syndrome

| Variables                             | Total (n=115) | Brazil (n=81) | India (n=34) | p     |
|---------------------------------------|---------------|---------------|--------------|-------|
| Age at disease diagnosis (year)       | 40.3±12.8     | 40.0±13.1     | 41.1±12.3    | 0.677 |
| Sex                                   |               |               |              | >0.999|
| Female                                | 94 (81.7%)    | 66 (81.5%)    | 28 (82.4%)   |       |
| Diagnosis-symptoms' onset (month)     | 7 (6.1%)      | 6 (7.4%)      | 12 (35.3%)   | 0.026 |
| Clinical and laboratory manifestations|               |               |              |       |
| Fever                                 | 92 (80.0%)    | 68 (84.0%)    | 24 (70.6%)   | 0.127 |
| Muscle involvement                    | 108 (93.9%)   | 76 (93.8%)    | 32 (94.1%)   | >0.999|
| Creatine phosphokinase (U/L)          | 2,317 (20.4%) | 3,346 (550-7,950) | 1,369 (287-3,718) | 0.068 |
| Joint involvement                     | 95 (82.6%)    | 74 (91.4%)    | 21 (61.8%)   | <0.001|
| Lung involvement                      | 98 (85.2%)    | 74 (91.4%)    | 24 (70.6%)   | 0.008 |
| “Mechanics’ hands”                    | 81 (70.4%)    | 64 (79.0%)    | 17 (50.0%)   | 0.003 |
| Raynaud’s phenomenon                  | 64 (55.7%)    | 57 (70.4%)    | 7 (20.6%)    | <0.001|
| Autoantibodies                        |               |               |              |       |
| Anti-Jo-1                             | 92 (80.0%)    | 68 (84.0%)    | 24 (70.6%)   | 0.127 |
| Anti-PL-7                             | 7 (6.1%)      | 4 (4.9%)      | 3 (8.8%)     | 0.420 |
| Anti-PL-12                            | 11 (9.6%)     | 5 (6.2%)      | 6 (17.6%)    | 0.080 |
| Anti-EJ                               | 5 (4.3%)      | 4 (4.9%)      | 1 (2.9%)     | >0.999|
| Anti-OJ                               | 1 (0.9%)      | 0 (0%)        | 1 (2.9%)     |     |
| Antinuclear antibody                  | 86 (74.8%)    | 64 (79.0%)    | 22 (64.7%)   | 0.320 |
| Anti-Ro-52                            | 64 (55.7%)    | 241 (50.6%)   | 23 (67.6%)   | 0.104 |

SD: Standard deviation.
Statistical analysis

Statistical analysis was performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were presented in mean ± standard deviation (SD), median (interquartile 25th to 75th) for continuous variables, and in number and frequency (%) for categorical variables. Comparison of continuous variables between the two groups was performed using the t-test and Mann-Whitney U test. Categorical variables were compared using the chi-square and Fisher exact test. A p value of <0.05 was considered statistically significant.

RESULTS

Disease characteristics

Of a total of 115 patients with ASSD, the mean age at the time of disease diagnosis was similar in both groups, with a predominance of female patients (Table 1). Brazilian patients had a follow-up significantly longer with 70 vs. 33 months. The Indian group exhibited a greater delay in diagnosis after the onset of symptoms compared to the Brazilian patients 12 vs. 6 months.

Clinical and laboratory features were largely comparable between the groups. Brazilian patients exhibited a higher prevalence of joint and lung involvement, mechanic’s hands, and Raynaud’s phenomenon. Anti-Jo-1 autoantibodies were the most common MSA in both groups, positive in 92 (80%) patients. Although there were no significant laboratory differences between the groups, extra-muscular manifestations were more common in Brazilian patients.

Comorbidities and habits

Systemic arterial hypertension, followed by diabetes mellitus were the most common comorbidities in both groups (Table 2). However, myocardial infarction was observed only in Brazilian patients. Ex-smoking is equally prevalent in the two cohorts, although current smoking was reported only among Brazilian patients.

Comparison between severity and prognosis

The disease activity states (remission or activity) were comparable between both groups. Nearly four quarters of patients (n=87, 75.7%) had a relapse during follow-up (Table 3). The Brazilian group appeared to have a higher number of relapses with a median of 2 vs. 1 among Indian patients respectively. However, the mortality rate was similar in both groups with 6.2% in Brazil vs. 8.8% in India.

Treatment differences

Analyzing the drugs previously used, in the Brazilian group, azathioprine was the most used drug, followed by methotrexate and mycophenolate mofetil, whereas in Indian patients, mycophenolate mofetil was the most used, followed by methotrexate and azathioprine (Table 4). Indian patients were more often prescribed antimalarials (41% vs. 21%), while the Brazilian group was often treated with azathioprine (93.8% vs. 44.1%) and intravenous immunoglobulin (40.7% vs. 2.9%).

Regarding the ongoing treatment, nearly a quarter (29 patients, 25.2%) were not on any immunosuppressants and 36.5% were on glucocorticoids (Table 4). The Indian group had a higher number of patients using only one immunosuppressive drug (70.6%), while the
| Variables                      | Total (n=115) | Brazil (n=81) | India (n=34) | p   |
|--------------------------------|---------------|---------------|--------------|-----|
|                                | n  | %  | Mean±SD | Median | 25th-75th percentiles | n  | %  | Mean±SD | Median | 25th-75th percentiles | n  | %  | Mean±SD | Median | 25th-75th percentiles |       |
| Current age (year)             | 52.9±37.0     | 52.0±11.0     | 55.1±66.6    | 0.785 |
| Duration of following up (month) | 52-110       | 36-115       | 15-76        | 0.003 |
| Current following up (%)       | 82  | 71.3 | 59  | 72.8 | 23  | 67.6 | 33  | 67.6 | 0.653 |
| Death (%)                      | 8  | 7.0  | 5  | 6.2  | 3  | 8.8  | 0.399 |
| Current status                 | Disease remission | 69  | 60.0 | 50  | 61.7 | 19  | 55.9 | 0.352 |
|                               | Disease activity | 37  | 32.2 | 31  | 38.3 | 6  | 17.6 | 0.235 |
|                               | MMT8 (0-80) | 80  | 78-80 | 80  | 78-80 | 80  | 80-80 | 0.227 |
|                               | Physician’s VAS (0-10) | 0  | 0-2  | 0  | 0-3  | 0  | 0-1 | 0.164 |
|                               | Patients’ VAS (0-10) | 0  | 0-2  | 0  | 0-3  | 0  | 0-1.3 | 0.106 |
|                               | Creatine phosphokinase (U/L) | 124  | 86-224 | 124  | 86-203 | 113  | 59-362 | 0.805 |
| Disease relapse                | 87  | 75.7 | 65  | 80.2 | 22  | 64.7 | 0.317 |
| Number of disease relapse      | 2  | 1-3  | 2  | 1-3  | 1  | 0-2 | 0.004 |
| Infections                     | Tuberculosis | 5  | 4.3  | 3  | 3.7  | 2  | 5.9  | 0.631 |
|                               | Severe infections | 33  | 30.4 | 22  | 27.2 | 13  | 38.2 | 0.271 |

SD: Standard deviation; VAS: Visual Analogue Scale; MMT-8: Manual Muscle Testing-8 score.
Brazilian group had a higher number of patients using two immunosuppressive drugs (33%). Despite that, severe infections requiring hospitalization or led to death occurred in approximately one-third of both groups, with no significant difference between the groups (Table 3).

Table 4. Treatments applied

| Variables                  | Total (n=115) | Brazil (n=81) | Indian (n=34) | p  |
|----------------------------|---------------|---------------|---------------|----|
| Current treatment          |               |               |               |    |
| Glucocorticoid             | 42 (36.5%)    | 29 (35.8%)    | 13 (38.2%)    | 0.140 |
| Using Dose (mg/day)        |               |               |               |    |
| None                       | 29 (25.2%)    | 21 (25.9%)    | 8 (23.5%)     | >0.999 |
| One                        | 57 (49.6%)    | 33 (40.7%)    | 24 (70.6%)    | 0.004 |
| Two                        | 29 (25.2%)    | 27 (33.3%)    | 2 (5.9%)      | 0.002 |
| Rituximab                  | 19 (16.5%)    | 14 (17.3%)    | 5 (14.7%)     | >0.999 |
| Immunosuppressive drugs    |               |               |               |    |
| None                       | 91 (79.1%)    | 76 (93.8%)    | 15 (44.1%)    | <0.01 |
| Methotrexate               | 68 (59.1%)    | 52 (64.2%)    | 16 (47.1%)    | 0.08 |
| Intravenous immunoglobulin| 34 (29.6%)    | 33 (40.7%)    | 1 (2.9%)      | <0.01 |
| Mycophenolate mofetil      | 55 (47.8%)    | 35 (43.2%)    | 20 (58.8%)    | 0.12 |
| Rituximab                  | 35 (30.4%)    | 28 (34.6%)    | 7 (20.6%)     | 0.137 |
| Cyclophosphamide           | 29 (25.2%)    | 24 (29.6%)    | 5 (14.7%)     | 0.09 |
| Antimalarial               | 31 (27%)      | 17 (21%)      | 14 (41.2%)    | 0.02 |

DISCUSSION

Since ASSD was first described, substantial heterogeneity has been observed, both in phenotype and in the severity of disease.4 This bicentric retro-prospective cohort study highlights differences in clinical phenotype between the studied populations which merits further exploration. Anti-Jo-1 autoantibodies were the most common anti-ARS autoantibody, consistent with the literature, seen in 60 to 80% of patients on an average.12 Although classically patients with anti-Jo-1 autoantibodies have a higher prevalence of muscle involvement,8,9 interestingly, the Brazilian group presented a higher prevalence of extra-muscular manifestations, unlike the Indian population in this study. This may also account for earlier diagnosis than in the Indian cohort with ASSD. No significant difference between other anti-ARS autoantibodies was found between the groups.

Notably, there were certain differences in the treatment practices in the two regions. While the Indian patients were often managed with one immunosuppressive drug (70.6%), the Brazilian group had a higher number of patients using two immunosuppressive drugs (33%), although this could be accounted for by a longer follow-up duration of those refractory to treatment. The drug preference also varied, with mycophenolate mofetil being the most common in Indians, whereas the azathioprine was preferred in the Brazilian population, suggesting lack of consensus for first choice among rheumatologists in this domain.

Due to its rarity, until now, there is no validated guideline about ASSD treatment. Glucocorticoids have long been first-line drug for managing idiopathic inflammatory myopathy,27,28 although due to their known adverse effects - hyperglycemia, glucocorticoid-induced osteoporosis, dyslipidemia, and others,29 the long-term use is not recommended. In the present study, both groups, nearly one-thirds, were using glucocorticoids. There is a high rate of recurrence of the disease when used as monotherapy in ASSD, during corticosteroid tapering,27 the use of a non-corticosteroid immunosuppressive drug is frequently recommended from the onset of the disease28 as sparing glucocorticoids and also for some refractory cases.27

In patients with interstitial lung disease (ILD), mycophenolate, cyclophosphamide and azathioprine have demonstrated similar utility
Evaluation of patients with antisynthetase syndrome: An international bicenter cohort study

in stabilizing the disease. However, several experts have advocated the use of mycophenolate as the first-line for ILD in ASSD patients in recent years. Despite its frequent use, due to toxicity, cyclophosphamide is often reserved for severe or refractory ILD, with demonstrated improvement in diffusing capacity of the lung for carbon monoxide (DLCO) and FVC in meta-analyses. However, drug toxicity is a major deterrent in developing countries, where infection burden is high. Cyclophosphamide was used in only a subset in both groups in the current study as well, suggesting a shift toward recent expert guidance in drug prescription.

Managing patients with ASSD who manifest with predominant arthritis is another ball game altogether, with methotrexate being considered the first-line agent. Also, ASSD is known to be confused with rheumatoid and go undiagnosed for years. However, ILD lurking in the background can be a major impediment for the rheumatologist to prescribe methotrexate which works well for arthritis unlike mycophenolate mofetil. Although recent work suggests that methotrexate is beneficial in rheumatoid arthritis-ILD, such evidence is yet to be explored in ASSD and a need of the hour. Recent reports have shown promise in the use of rituximab in refractory cases as well, with a positive effect on ILD as well as arthritis. Unfortunately, the lack of clear guidelines and comparative evidence base between drugs are a deterrent to uniformity in drug selection across centers. Moreover, prescription patterns may also be reflective of socioeconomic strata, age group of disease (which have a bearing on conception choices), and reimbursement policies, more so in developing countries where state coverage of health insurance is dismal.

The current knowledge about comorbidities associated with ASSD is limited in the literature. Only one study showed that patients with ASSD have a higher prevalence of metabolic syndrome and insulin resistance, compared to the control group (42.9% vs. 13.1%, respectively). Systemic arterial hypertension, followed by diabetes mellitus were the most common comorbidities in both groups. The prevalence of diabetes in the general population of adults aged 20 to 79 years in India is reported to be 8.7%; in Brazilian general population the prevalence is 10.2%. Also, the worldwide prevalence in the adult population of diabetes mellitus is 5.1%. Although not directly comparable, our study depicts three-fold higher prevalence than average population estimates. These may be contributed by glucocorticoid usage, immobility, and potentially by disease specific effects which remain largely unknown so far. Interestingly, only Brazilian patients reported myocardial infarction, despite similar age and sex profile. Systematic population-based studies may throw a greater light on the differences between patients with ASSD in the two ethnic groups.

Mortality in ASSD commonly relates to pulmonary involvement, particularly ILD, infections, and cardiovascular events. Interstitial lung disease is a very prevalent manifestation in ASSD, its prevalence varies among the different populations studied as demonstrated in Chinese population (94.4%) and South Australian cohort (69%). In the studied group, the Brazilian group appeared to have a higher number of relapses, despite that it does not seem to influence the mortality rate, which was similar in both groups. It was considered only death, without discriminating the cause, and it was a limitation of the current study. Patients with ASSD have a poor prognosis compared to non-anti-ARS autoantibodies-related inflammatory myositis owing to the increased frequency and severity of glucocorticoid-resistant ILD.

We fully acknowledge limitations arising out of sampling biases and small sample size in the current study. Besides, the presence of ILD may be underrepresented due to HRCT being limited to symptomatic individuals. However, this being a pilot study comparing data from the two regions, we believe that it paves the way for further global multi-center collaborative studies with inclusion of dermatologists, pulmonologists and neurologists to account for referral biases and varied patient profiles.

In conclusion, ASSD is a rare autoimmune disease, with a polymorphic clinical presentation with a challenging diagnosis. The severity may be influenced by different factors (e.g., presence of a specific autoantibody) and, although some manifestations seem to be influenced by geographic distribution (as evidenced in Brazilian group), the prognosis of the disease and mortality
rate were similar in both groups. Brazilian and Indian patients with ASSD have comparable epidemiological characteristics such as age at the time of disease diagnosis, prevalence of female patients, and MSA panel; also, prevalence of comorbidities was similar in both groups, with a higher prevalence of diabetes mellitus than general population. In our study, Brazilian patients exhibited a higher prevalence of joint and lung involvement, mechanic’s hands and Raynaud’s phenomenon; and also, a higher number of relapses. Due to the lack of a validated consensus in the literature, different centers may differ in the choice of treatment for ASSD, as evidenced in this study. Despite that, mortality was similar between the groups. To improve patient care and allow the development of individualized treatments, it is of utmost importance to have a better comprehension of the disease, aiming to understand whether there are demographic differences in many aspects of the disease, sharing knowledge and experience between centers.

Acknowledgment: Nacional de Desenvolvimento Científico e Tecnológico (CNPq) #303379/2018-9, and Faculdade de Medicina da USP to S.K.S.

Ethics Committee Approval: The study protocol was approved by the CAPPEsq Ethics Committee (Date/no: July 23rd 2020/CAAE 349854620.5.0000.0068). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: All authors contributed equally to the article.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

REFERENCES
1. Shinjo SK, Levy-Neto M. Anti-Jo-1 antisynthetase syndrome. Rev Bras Reumatol 2010;50:492-500.
2. Cavagna L, Castañeda S, Sicrè C, Gonzalez-Gay MA; AENEAS Collaborative Group Members. Antisynthetase syndrome or what else? Different perspectives indicate the need for new classification criteria. Ann Rheum Dis 2018;77:e50.
3. Katzap E, Barilla-LaBarca ML, Marder G. Antisynthetase syndrome. Curr Rheumatol Rep 2011;13:175-81.
4. Hervier B, Benveniste O. Clinical heterogeneity and outcomes of antisynthetase syndrome. Curr Rheumatol Rep 2013;15:349.
5. Mahler M, Miller FW, Fritzler MJ. Idiopathic inflammatory myopathies and the anti-synthetase syndrome: A comprehensive review. Autoimmun Rev 2014;13:367-71.
6. Souza FH, Cruellas MG, Levy-Neto M, Shinjo SK. Anti-synthetase syndrome: Anti-PL-7, anti-PL-12 and anti-EJ. Rev Bras Reumatol 2013;53:352-7.
7. Cojocaru M, Cojocaru IM, Chicos B. New insights into antisynthetase syndrome. Maedica (Bucur) 2016;11:130-5.
8. Rojas-Serrano J, Herrera-Bringas D, Mejía M, Rivero H, Mateos-Toledo H, Figueroa JE. Prognostic factors in a cohort of antisynthetase syndrome (ASS): Serologic profile is associated with mortality in patients with interstitial lung disease (ILD). Clin Rheumatol 2015;34:1563-9.
9. Hervier B, Devilliers H, Stanciu R, Meyer A, Uzunhan Y, Masseau A, et al. Hierarchical cluster and survival analyses of antisynthetase syndrome: Phenotype and outcome are correlated with anti-tRNA synthetase antibody specificity. Autoimmun Rev 2012;12:210-7.
10. Monti S, Montecucco C, Cavagna L. Clinical spectrum of anti-Jo-1-associated disease. Curr Opin Rheumatol 2017;29:612-7.
11. Opinc AH, Makowska JS. Antisynthetase syndrome - much more than just a myopathy. Semin Arthritis Rheum 2021;51:72-83.
12. Shi J, Li S, Yang H, Zhang Y, Peng Q, Lu X, et al. Clinical profiles and prognosis of patients with distinct antisynthetase autoantibodies. J Rheumatol 2017;44:1051-7.
13. Gupta L, Appani SK, Janardana R, Muhammed H, Lawrence A, Amin S, et al. Meeting report: MyoIN – Pan-India collaborative network for myositis research. Indian J Rheumatol 2019;14:136-42.
14. Naveen R, Anuja AK, Rai MK, Agarwal V, Gupta L. Development of the MyoCite biobank: Cost-efficient model of public sector investigator-driven biobank for idiopathic inflammatory myositis. Indian J Rheumatol 2020;15:194-9.
15. Mehta P, Gupta L. Combined case record forms for collaborative datasets of patients and controls of idiopathic inflammatory myopathies. Indian J Rheumatol 2020;15:191-3.
16. Behrens Pinto GL, Carboni RCS, de Souza FHC, Shinjo SK. A prospective cross-sectional study of...
Evaluation of patients with antisynthetase syndrome: An international bicenter cohort study

28. Zanframundo G, Marasco E, Carrubba C, Stefano LD, Volpiano L, Tirelli C, et al. Update on treatment of antisynthetase syndrome: A brief review. Current Treatment Options in Rheumatology 2020;6:18-28.

29. Oray M, Abu Samra K, Ebrahimiadib N, Meese H, Foster CS. Long-term side effects of glucocorticoids. Expert Opin Drug Saf 2016;15:457-65.

30. Mira-Avendano IC, Parambl JG, Yadav R, Arrossi V, Xu M, Chapman JT, et al. A retrospective review of clinical features and treatment outcomes in steroid-resistant interstitial lung disease from polymyositis/dermatomyositis. Respir Med 2013;107:890-6.

31. Marco JL, Collins BF. Clinical manifestations and treatment of antisynthetase syndrome. Best Pract Res Clin Rheumatol 2020;34:101503.

32. Ge Y, Peng Q, Zhang S, Zhou H, Lu X, Wang G. Cyclophosphamide treatment for idiopathic inflammatory myopathies and related interstitial lung disease: A systematic review. Clin Rheumatol 2015;34:99-105.

33. Chatterjee R, Mehta P, Agarwal V, Gupta L. High burden of infections in Indian patients with Idiopathic Inflammatory Myopathy: Validation of observations from the MyoCite dataset. Rheumatology (Oxford) 2021;60:4315-26.

34. Mehta P, Agarwal V, Gupta L. High early mortality in idiopathic inflammatory myopathies: Results from the inception cohort at a tertiary care centre in Northern India. Rheumatology (Oxford) 2021;60:4281-90.

35. Muhammed H, Gupta L, Zanwar AA, Misra DP, Lawrence A, Agarwal V, et al. Infections are leading cause of in-hospital mortality in Indian patients with idiopathic myopathy. J Clin Rheumatol 2021;27:114-9.

36. Kumar RR, Jha S, Dhoria A, Naidu GSRSNK, Minz RW, Kumar S, et al. Anti-Jo-1 syndrome often misdiagnosed as rheumatoid arthritis (for many years): A single-center experience. J Clin Rheumatol 2021;27:150-5.

37. Brulhart L, Waldburger JM, Gabay C. Rituximab in the treatment of antisynthetase syndrome. Ann Rheum Dis 2006;65:974-5.

38. Dugar M, Cox S, Limaye V, Blumbergs P, Roberts-Thomson PJ. Clinical heterogeneity and prognostic features of South Australian patients with anti-synthetase autoantibodies. Intern Med J 2011;41:674-9.

39. Doyle TJ, Dhillon N, Madan R, Cabral F, Fletcher EA, Koonitz DC, et al. Rituximab in the treatment of interstitial lung disease associated with antisynthetase syndrome: A multicenter retrospective case review. J Rheumatol 2018;45:841-50.

40. Arafou PAO, Silva MG, Borba EF, Shinjo SK. High prevalence of metabolic syndrome in antisynthetase syndrome. Clin Exp Rheumatol 2018;36:2417.

41. IDF Diabetes Atlas. International Diabetes Federation. 7th ed. Brussels: Karakas Print; 2015.

42. Imbert-Masseau A, Hamidou M, Agard C, Grollois JY, Chérin P. Antisynthetase syndrome. Joint Bone Spine 2003;70:161-8.
43. Sultan SM, Ioannou Y, Moss K, Isenberg DA. Outcome in patients with idiopathic inflammatory myositis: Morbidity and mortality. Rheumatology (Oxford) 2002;41:22-6.

44. Triantafyllias K, Cavagna L, Klonowski A, Drott U, Fiehn C, Wendel S, et al. Possible misclassification of cardiovascular risk by SCORE in antisynthetase syndrome: Results of the pilot multicenter study RI.CAR.D.A. Rheumatology (Oxford) 2021;60:1300-12.