Different phenotypic manifestations between Brazilian and Japanese anti-MDA5 antibody-positive dermatomyositis: an international tricentric longitudinal study

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Abstract

Objective

Anti-MDA5 autoantibodies are strongly associated with interstitial lung disease (ILD) and rapidly progressive ILD (RP-ILD) in Asian patients with dermatomyositis (DM) or amyopathic DM (ADM). However, this association has not yet been established in Brazilian patients with anti-MDA5(+) DM/ADM. This study aimed to investigate the phenotypic differences between Brazilian and Japanese patients with anti-MDA5(+) DM/ADM, with a particular focus on ILD.

Methods

This was an international, tricentric, retrospective cohort study conducted in one Brazilian and two Japanese tertiary centres. Patients diagnosed with anti-MDA5(+) DM/ADM at the three centres were enrolled. Clinical characteristics and outcomes were collected using a pre-standardised protocol and compared between Brazilian and Japanese patients.

Results

Thirty-four Brazilian and 65 Japanese patients were analysed. Brazilian patients were younger at the time of diagnosis than Japanese patients. The prevalence of muscle weakness, myalgia, dysphagia, heliotrope rash, V-sign, calcinosis, Raynaud's phenomenon, and digital ulcers was higher in Brazilian patients, whereas mechanic's hands were more prevalent in Japanese patients. The prevalence of ILD was significantly lower in Brazilian patients than in Japanese patients (50.0% vs. 98.5%, $p<0.001$). RP-ILD was observed in 34 (52.3%) Japanese patients and in only one (3.3%) Brazilian patient ($p<0.001$). Outcomes including overall survival and the frequency of relapses and complications, such as severe infection and malignancy, were comparable between the two populations.

Conclusion

Brazilian patients with anti-MDA5(+) DM/ADM had a higher prevalence of skin and muscle involvement, whereas the prevalence of ILD and RP-ILD was significantly lower than in Japanese patients.

Key-words

anti-MDA5 antibody, dermatomyositis, interstitial lung disease, ethnic differences

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Introduction

Dermatomyositis (DM) is a major subtype of idiopathic inflammatory myopathy (IIM) or systemic autoimmune myopathy, characterised by the involvement of skeletal muscles with proximal limbs predominantly affected and distinctive skin conditions such as heliotrope rash and Gottron's papules. Other cutaneous manifestations may be present, such as facial erythema, V-sign, shawl sign, holster sign, skin ulcers, cuticular hypertrophy, periungual telangiectasias, and calcinosis. Furthermore, other organs, including the heart, lungs, joints, and gastrointestinal tract, can also be involved in extramuscular manifestations (1-3).

In the last few decades, different myositis-specific autoantibodies (MSAs) and myositis-associated autoantibodies (MAAs) have been described, which are extremely useful for disease subclassification as well as for predicting treatment response and prognosis (4-6). MSAs include anti-aminoacyl-tRNA synthetase (anti-synthetase), anti-SRP, anti-HMGCR, anti-Mi-2, anti-TIF-1g, anti-NXP-2, anti-SAE, and anti-melanoma differentiation-associated gene 5 (anti-MDA5) autoantibodies, whereas MAAs include anti-PM/Scl, anti-U1-snRNP, anti-Ku, and anti-Ro52 autoantibodies (4, 7).

Anti-MDA5 antibodies, which target a cytosolic pattern recognition receptor responsible for the antiviral immune response through the detection of double-stranded RNA virus, were first described in 2005 in Japanese patients with amyopathic DM (ADM) (8, 9). In East Asian cohorts, patients with anti-MDA5 antibodies often present with interstitial lung disease (ILD), particularly rapidly progressive ILD (RP-ILD), which is defined as progressive dyspnoea, hypoxemia, and a worsening of interstitial changes on chest radiograph or high-resolution computed tomography (HRCT) within 1-3 months of the onset of respiratory symptoms (8). RP-ILD in anti-MDA5(+) DM/ADM is associated with high mortality rates, especially in the ADM group (10-14).

Chen *et al*. (11) reported the prevalence of ILD and RP-ILD as 100% and 38.5% in Chinese patients with anti-MDA5 antibodies. Nakashima *et al*. (15) reported that 46% of patients with anti-MDA5 antibodies died due to respiratory failure within six months of disease onset. In Western cohorts, data on the association between anti-MDA5 antibodies and RP-ILD are inconsistent (16-22). For example, Fiorentino *et al*. (23) and Moghadam-Kia *et al*. (21) reported the prevalence of RP-ILD in patients with anti-MDA5 antibodies as 22% and 44%, respectively, while Hall *et al*. (16) did not find a significant association between anti-MDA5 antibodies and RP-ILD. Regarding the Latin American population, previously published data suggested a lower prevalence of ILD and RP-ILD (24, 25). The discrepancy in the prevalence of RP-ILD in patients with anti-MDA5(+) DM/ADM between studies could be attributed to selection bias inherent to single-centre retrospective studies, or differences in genetic or environmental factors between ethnicities. These observations lead to the hypothesis that phenotypic diversity, including the prevalence of ILD and RP-ILD, in patients with anti-MDA5(+) DM/ADM depends on the race, ethnicity, and/or geographic regions studied (26-28).

The phenotypic diversity of patients with anti-MDA5(+) DM/ADM has recently been addressed using cluster analysis by different authors who sought to classify patients into distinct subgroups with homogenous characteristics (29-33). For instance, Xu *et al*. (29) identified three distinct clusters in their cohort of patients with anti-MDA5(+) DM/ADM; Cluster 1 included patients presenting with typical DM rash, muscle weakness, and mild risk of RP-ILD; Cluster 2 comprised patients with DM rash, arthritis, and moderate risk of RP-ILD; Cluster 3 included patients with the highest risk of RP-ILD but with mild rash and muscle weakness. Yang *et al*. (30) and Allenbach *et al*. (31) also reported three clusters with different risk of RP-ILD and mortality in their cohorts of anti-MDA5(+) DM/ADM. The reproducibility of these clusters remains to be elucidated in a geographically and ethnically diverse cohort of anti-MDA5(+) DM/ADM.

In this context, the present study aimed to investigate the differences in demographic and clinical characteristics as well as the outcomes of Brazilian and Japanese patients with anti-MDA5(+) DM/ADM. To mitigate selection bias, we assessed patients included in an international tricentric cohort comprising one Brazilian and two Japanese tertiary centres, employing a pre-standardised protocol for data collection.

Patients and methods

Study design

This was an international, tricentric, retrospective cohort study that included incident cases of anti-MDA5(+) DM/ADM from a Brazilian tertiary centre (Rheumatology) and two Japanese tertiary centres (Rheumatology and Dermatology) that underwent outpatient follow-up between 2005 and 2023. The study was approved by the local ethics committees of each centre: Brazil (no. CAAE 67992323.4.0000.0068) and Japan (no. 1142601-1 and no. B-2020-127).

Inclusion and exclusion criteria

Adult patients aged >18 years at diagnosis with definite or probable DM or ADM, according to the 2017 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for IIMs (34), were included. All patients were tested positive for anti-MDA5 autoantibodies.

Patients with a follow-up period of less than 12 months were excluded, except for those who deceased within 12 months from the initial visit. Those with cancer-associated myositis, overlap syndrome with other systemic autoimmune rheumatic diseases, MSAs other than anti-MDA5 antibodies, and a history of infectious lung diseases including tuberculosis and aspergillosis were also excluded.

Clinical assessments

Patient information was obtained from the medical records of each centre using a pre-standardised protocol for data collection. The following clinical data were collected: age at diagnosis, sex, ethnicity, time intervals between the onset of symptoms and diagnosis of the disease, clinical diagnosis (DM or ADM), and duration of follow-up; clinical manifestations at presentation, including constitutional symptoms (fever, weight loss), skin involvement (facial erythema, heliotrope rash, Gottron's signs/papules, V-sign, shawl sign, digital ulcers, skin ulcers, calcinosis, mechanic's hands, and Raynaud's phenomenon), muscle involvement [myalgia, muscle weakness in the limbs according to the Medical Research Council (MRC) scale (35)], dysphagia, and joint involvement (isolated arthralgia or arthritis). Serum concentrations of muscle enzymes, including creatine phosphokinase (CPK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactic dehydrogenase (LDH), as well as C-reactive protein (CRP) were collected at diagnosis.

For lung involvement, the following information was collected: the presence of objective dyspnoea (presence or absent); the presence of ILD confirmed by high-resolution computed tomography (HRCT) (36); the mode of ILD onset was classified as acute (<1 month), subacute (1 to 3 months), chronic (>3 months), or asymptomatic; RP-ILD, defined as ILD with all three of the following within three months from the onset of respiratory symptoms: a) progressive dyspnoea, b) progressive hypoxemia, and c) worsening on chest radiography or HRCT (8); and the morphological patterns of ILD on HRCT evaluated by a radiologist and/or rheumatologist, including lower lobe consolidation and/or ground-glass opacities (GGOs), lower lobe reticulations, and random GGOs (37).

Initial treatment regimens, defined as those introduced within six months of treatment initiation, including pulse methylprednisolone, immunosuppressive or immunomodulatory agents, intravenous immunoglobulin (IVIG), rituximab, and Janus kinase (JAK) inhibitors, were collected. Treatment at the last clinical visit was also assessed.

The clinical outcomes investigated were all-cause mortality and relapse of the disease (defined as the re-emergence of any symptoms or clinical signs related to DM and/or ILD following a complete clinical response). Current disease status at the last visit was categorised as active disease (defined as the presence of any symptoms or clinical signs related to DM and/or ILD, without other apparent causes); complete clinical response (defined as the absence of disease activity for a continuous period of more than six months, while still receiving glucocorticoids and/or immunosuppressants for DM and/or ILD); and remission (defined as the absence of disease activity for a continuous period of more than six months, without receiving any medications for DM and/or ILD). Information on the history of disease/treatment-related complications, including serious infections requiring hospitalisation and the emergence of any malignancy after the diagnosis of DM/ADM, was also collected.

Analysis of anti-MDA5 autoantibodies

Serum samples were collected from each patient at the initial visit and stored at -20°C until use. At the Brazilian centre, a commercial line immunoassay EUROLINE Autoimmune Inflammatory Myopathies 16 Ag (IgG) (Euroimmun, Lübeck, Germany) was used to identify anti-MDA5 autoantibodies, in which only strong reactions (+++) assessed by two independent readers were considered positive according to a previous study (38). At Japanese centres, anti-MDA5 autoantibodies were identified using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (MESACUP™, Medical and Biological Laboratories, Tokyo, Japan), in which an anti-MDA5 antibody level >32 U/mL was considered positive (internal validated with high sensibility and specificity) (39, 40).

Statistical analysis

The Kolmogorov-Smirnov test was used to evaluate the distribution of each continuous variable. The results were presented as mean ± standard deviation (SD) or median with interquartile range (IQR) for continuous variables and frequency (%) for categorical variables. The demographic and clinical data of Brazilian and Japanese patients with anti-MDA5(+) DM/ADM were compared. Additionally, we stratified each

cohort according to the presence of RP-ILD. We also performed an analysis stratified by the year of diagnosis: before 2018 and after 2019, considering the potential efficacy of JAK inhibitors (41) and the trial of triple combination therapy, comprising glucocorticoids, tacrolimus, and intravenous cyclophosphamide (IVCYC) (42), were reported in 2018 and 2020, respectively.

Continuous variables were compared using the Student's t-test or Mann-Whitney U-test. Chi-square or Fisher's exact test was used to compare categorical variables as appropriate. Survival analysis was performed using Kaplan-Meier curves, and differences between groups were tested using the log-rank test. Statistical significance was defined as two-sided $p<0.05$. IBM SPSS Statistics v. 21 (IBM Corp., Armonk, NY, USA) was used for data analysis.

Results

Demographics

Brazilian and Japanese cohorts comprised 121 and 360 patients diagnosed with DM/ADM, respectively, according to the 2017 EULAR/ACR classification criteria for IIMs. Of these, 47 (38.8%) and 72 (20.0%) were positive for anti-MDA5 autoantibodies. For the present study, 13 and 7 were excluded and 34 (34.3%) and 65 (65.7%) patients with anti-MDA5(+) DM/ADM from the Brazilian and Japanese centres were included in the analysis (Fig. 1).

Brazilian patients were younger at diagnosis compared to Japanese patients (41.6 [35.4–50.0] *vs*. 50.0 [42.3–62.3] years old, respectively; $p=0.001$) (Table I). The majority of patients in both groups were female. The median time interval between the onset of symptoms and the diagnosis of the disease was significantly longer in Brazilian patients than in Japanese patients (4.3 [1.0–13.0] *vs*. 2.1 [1.3–3.5] months, $p=0.006$). In the Brazilian centre, only one patient was of Asian ethnicity, whereas the other patients were South American. All patients in the Japanese centres were of Asian ethnicity.

Clinical characteristics

Brazilian patients were more likely to be classified as having DM than

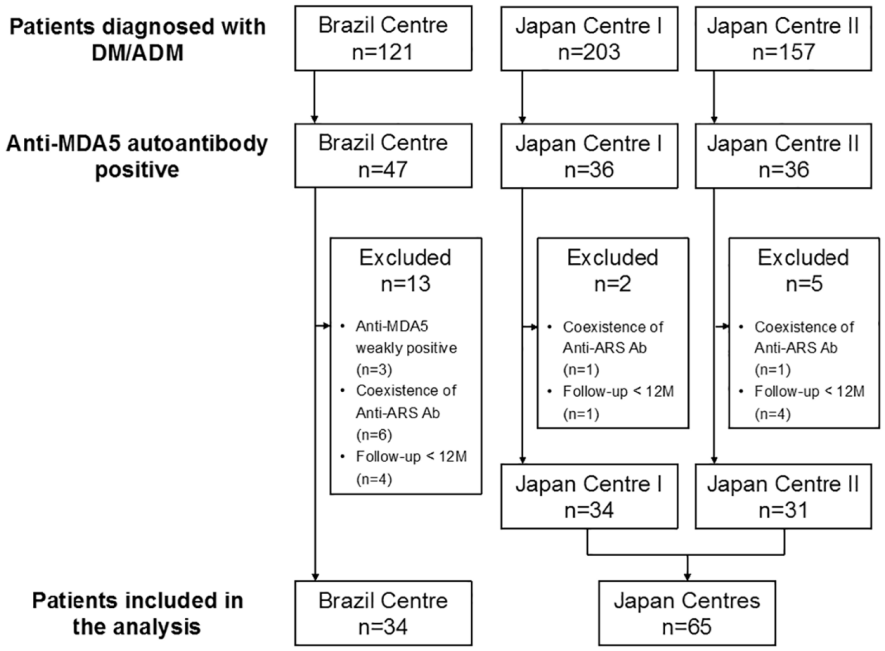

Fig. 1. Screening flowchart of patients with anti-MDA5(+) DM/ADM in the Brazilian and Japanese centres.
Anti-ARS Ab: anti-aminoacyl-tRNA synthetase autoantibodies; JDM: juvenile dermatomyositis; IPAF: interstitial pneumonia with autoimmune features.

Table I. Baseline characteristics and initial treatment regimens of Brazilian and Japanese patients with anti-MDA5(+) dermatomyositis.

Variables	Brazil (n=34)	Japan (n=65)	*p*
Demographics			
Mean age at diagnosis (years)	41.6 (35.4-50.0)	50.0 (42.3-62.3)	0.001
Female, n (%)	20 (58.8)	44 (67.7)	0.387
Ethnicity, n (%)			
Asia	1 (2.9)	65 (100)	<0.001
Africa	0	0	
Europe	0	0	
North-America	0	0	
South-America	33 (97.1)	0	
Oceania	0	0	
Clinical diagnosis, n (%)			
DM	19 (55.9)	12 (18.5)	<0.001
ADM	15 (44.1)	53 (81.5)	
Time intervals between the symptom onset and the disease diagnosis (months)	4.3 (1.0-13.0)	2.1 (1.3-3.5)	0.006
Clinical manifestations, n (%)			
Fever	10 (29.4)	26 (40.0)	0.380
Weight loss	20 (58.8)	23 (35.4)	0.033
Gottron's papules	32 (94.1)	54 (83.1)	0.209
Gottron's sign	32 (94.1)	62 (95.4)	>0.999
Heliotrope rash	30 (88.2)	19 (29.3)	<0.001
Facial erythema	20 (58.8)	43 (66.2)	0.514
V-sign	15 (44.1)	15 (23.1)	0.039
Shawl sign	10 (29.4)	15 (23.1)	0.627
Scratch dermatitis	2 (5.9)	12 (18.5)	0.129
Raynaud's phenomenon	16 (47.1)	1 (1.5)	<0.001
Digital ulcers	8 (23.5)	2 (3.1)	0.003
Skin ulcers	7 (20.6)	9 (13.9)	0.402
Holster's sign	0	4 (6.2)	0.296
Calcinosis	9 (26.5)	0	<0.001
Mechanic's hands	8 (23.5)	45 (69.2)	<0.001

Variables	Brazil (n=34)	Japan (n=65)	*p*
Joint involvement			
Isolated arthralgia	10 (29.4)	20 (30.8)	>0.999
Arthritis	14 (41.2)	19 (29.3)	0.266
Myalgia	18 (52.9)	18 (27.7)	0.016
Muscle weakness			
Upper limbs			
Grade V	8 (23.5)	44 (67.7)	<0.001
Grade IV	24 (70.6)	19 (29.3)	
Grade III	2 (5.9)	1 (1.5)	
Grade II	0	1 (1.5)	
Grade I	0	0	
Lower limbs			
Grade V	9 (26.5)	41 (63.1)	0.004
Grade IV	22 (64.7)	20 (30.8)	
Grade III	3 (8.8)	3 (4.6)	
Grade II	0	1 (1.5)	
Grade I	0	0	
Dysphagia, n (%)	11 (32.4)	4 (6.2)	0.001
Lung involvement, n (%)			
Dyspnoea	13 (38.2)	30 (46.2)	0.525
ILD confirmed by HRCT	15/30 (50.0)	64 (98.5)	<0.001
Onset of ILD			
Acute onset (< 1 months)	4/30 (13.3)	30 (46.2)	<0.001
Subacute onset (1–3 months)	5/30 (16.7)	16 (24.6)	
Chronic onset (> 3 months)	3/30 (10.0)	7 (10.8)	
Asymptomatic	3/30 (10.0)	11 (16.9)	
RP-ILD	1/30 (3.3)	34 (52.3)	<0.001
HRCT findings of ILD			
Lower lobe consolidation	3/30 (10.0)	41 (63.1)	<0.001
Lower lobe reticulation	5/30 (16.7)	38 (58.5)	0.001
Random GGO	9/30 (30.0)	26 (40.0)	0.348
Laboratory data			
CPK (U/L)	79 (49-487)	126 (73-189)	0.409
AST (U/L)	46 (24-86)	50 (36-80)	0.440
ALT (U/L)	39 (24-63)	39 (24-70)	0.917
LDH (U/L)	421 (267-755)	332 (280-440)	0.046
C-reactive protein (CRP)	3.9 (0.9-9.4)	0.4 (0.2-0.8)	<0.001
Treatment, n (%)			
MP pulse therapy	18 (52.9)	40 (61.5)	0.292
IVIG	14 (41.2)	23 (35.4)	0.828
Drugs used up to 6 months after diagnosis			
(Hydroxy)chloroquine	18 (52.9)	0	-
Methotrexate	12 (35.3)	1 (1.5)	<0.001
Azathioprine	20 (58.8)	0	-
Cyclosporine	8 (23.5)	5 (7.7)	0.037
Leflunomide	3 (8.8)	0	-
Tacrolimus	0	59 (90.8)	-
Cyclophosphamide	2 (5.9)	56 (86.2)	<0.001
Mycophenolate mofetil	4 (11.8)	1 (1.5)	0.027
Rituximab	0	0	-
JAK inhibitors	0	4 (6.2)	-

Data are presented as mean ± standard deviation, median (25%-75%), or frequency (%).
ALT: alanine aminotransferase; AST: aspartate aminotransferase; ADM: amyopathic dermatomyositis; CPK: creatine phosphokinase; DM: dermatomyositis; GGO: ground-glass opacities; HRCT: high-resolution computed tomography; ILD: interstitial lung disease; IVIG: intravenous immunoglobulin; JAK: Janus kinase; LDH: lactic dehydrogenase; mo: months; MP: methylprednisolone; RP-ILD: rapidly progressive interstitial lung disease.

Japanese patients (55.9% *vs*. 18.5%, respectively; $p<0.001$) (Table I). Brazilian patients had a higher prevalence of skin rashes, including heliotrope rash (88.2% *vs*. 29.3%, $p<0.001$) and V-sign (44.1% *vs*. 23.1%, $p=0.039$). Calcinosis was present in 26.5% of Brazilian patients, whereas no patients in the Japanese group presented with this finding. Digital ulcers (23.5% *vs*. 3.1%, $p=0.003$), Raynaud's phenomenon (47.1% *vs*. 1.5%, $p<0.001$), myalgia (52.9% *vs*. 27.7%, $p=0.016$), and dysphagia (32.4% *vs*. 6.2%, $p=0.001$) were also more common in Brazilian patients. In contrast, Japanese patients had a higher prevalence of mechanic's hands (23.5% *vs*. 69.2%, $p<0.001$). The prevalence of joint involvement was comparable between the two groups. Laboratory data, including the median levels of muscle enzymes, were also comparable between the groups except for the serum levels of LDH (421 [267–755] *vs*. 332 [280–440] U/L, $p=0.046$) and CRP (3.9 [0.9–9.4] *vs*. 0.4 [0.2–0.8] mg/L, $p<0.001$), which were higher in the Brazilian group.

All but four Brazilian and all the Japanese patients underwent chest HRCT for ILD assessment. Notably, the prevalence of ILD was significantly lower in Brazilian patients than in those Japanese patients (50.0% *vs*. 98.5%, $p<0.001$). The proportion of patients who reported dyspnoea was comparable between the two groups (38.2% *vs*. 46.2%, $p=0.525$); however, more patients presented with acute ILD in the Japanese population (13.3% *vs*. 46.2%, $p<0.001$), and the prevalence of RP-ILD was significantly higher in Japanese patients (3.3% *vs*. 52.3%, $p<0.001$). Moreover, the results remained consistent even when the prevalence of ILD or RP-ILD was stratified according to time intervals between the disease diagnosis and symptoms' onset (Supplementary Table S1). The only Brazilian patient who developed RP-ILD was of Asian (Japanese) descent.

Regarding the HRCT findings of ILD, the prevalence of lower lobe consolidation (10.0% *vs*. 63.1%, $p<0.001$) and lower lobe reticulation (16.7% *vs*. 58.5%, $p=0.001$) was higher in Japanese patients than in Brazilian patients, whereas the prevalence of random GGO was comparable between the two groups (30.0% *vs*. 40.0%, $p=0.348$).

Regarding the initial treatment regimens, the proportion of patients who received a pulse dose of methylprednisolone (52.9% *vs*. 61.5%, $p=0.292$) or IVIG (41.2% *vs*. 35.4%, $p=0.828$) was comparable between the two groups. Chloroquine or hydroxychloroquine

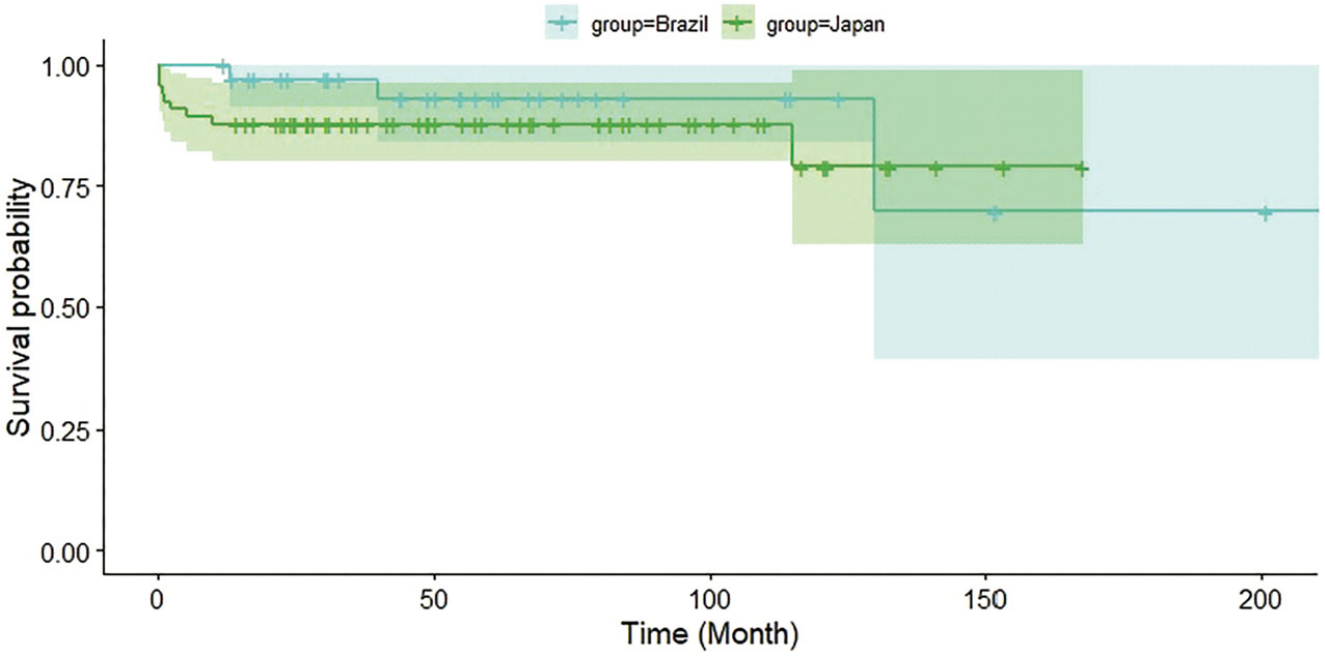

Fig. 2. Overall survival of patients with anti-MDA5(+) DM/ADM in the Brazilian and Japanese cohorts. Difference between the Brazilian and Japanese groups (log-rank test): p=0.410.

(52.9% *vs*. 0%), methotrexate (35.3% *vs*. 1.5%, p<0.001), azathioprine (58.8% *vs*. 0%), cyclosporine (23.5% *vs*. 7.7%, p=0.037), leflunomide (8.8% *vs*. 0%), and mycophenolate mofetil (11.8% *vs*. 1.5%, p=0.027) were used more frequently in Brazilian patients, whereas tacrolimus (0% *vs*. 90.8%) and IVCYC (5.9% *vs*. 86.2%, p<0.001) were used more frequently in Japanese patients.

Outcomes

The median follow-up period was comparable between the two groups (56 [31–81] *vs*. 52 [29–98] months, p=0.669). Three Brazilian patients died due to infectious complications during follow-up, whereas nine Japanese patients deceased mostly due to RP-ILD; only one patient from the Japanese centre in Tokyo died of malignancy. The Kaplan-Meier curves demonstrated early mortality in Japanese patients (Fig. 2); however, there was no statistically significant difference in the overall survival between the Brazilian and Japanese patients (p=0.410). Also, there was no significant difference in the proportion of patients who experienced relapse or those who were complicated with severe infection or malignancy between the two populations (Table II).

Table II. Clinical outcomes, follow-up duration, complications, current disease status, and medications in use at the last clinical assessment.

Variables	Brazil (n=34)	Japan (n=65)	p
Follow-up duration (months)	56 (31-81)	52 (29-98)	0.669
Outcomes, n (%)			
Relapse	11 (32.4)	13 (20.0)	0.218
Death	3 (8.8)	9 (13.8)	0.537
Complications, n (%)			
Severe infection	4 (11.8)	5 (7.7)	0.489
Malignancy	3 (8.8)	5 (7.7)	>0.999
Current disease status, n (%)			
Active disease	3 (8.8)	4/56 (7.1)	0.831
Complete clinical response	18 (52.9)	38/56 (67.9)	
Remission	13 (38.2)	15/56 (26.8)	
Current medications, n (%)			
Systemic glucocorticoids			
In use	7 (20.6)	48/56 (85.5)	<0.001
Dose (mg/day)	0 (0.0-0.0)	4.0 (1.0-6.0)	<0.001
IVIG	0	2 (3.1)	-
(Hydroxy)chloroquine	1 (2.9)	0	-
Methotrexate	6 (17.7)	1 (1.4)	0.002
Azathioprine	6 (17.7)	0	
Cyclosporine	4 (11.8)	4 (6.3)	0.377
Leflunomide	3 (8.8)	0	-
Tacrolimus	0	44 (67.7)	-
Cyclophosphamide	0	0	-
Mycophenolate mofetil	6 (17.7)	7 (10.8)	0.336
Rituximab	3 (8.8)	0	-
JAK inhibitors	0	2 (3.1)	-

Data are presented as the mean ± standard deviation, median (25%-75%), or frequency (%).
ILD: interstitial lung disease; IVIG: intravenous immunoglobulin; JAK: Janus kinase; MP: methylprednisolone; RP-ILD: rapidly progressive interstitial lung disease.

At the last clinical evaluation, the proportion of patients with active disease was comparable between Brazilian and Japanese populations (8.8% *vs*. 7.1%, p=0.831). The proportion of patients who achieved a complete clinical res-

ponse or remission was also comparable. Meanwhile, the proportion of patients receiving glucocorticoids (20.6% *vs*. 85.5%, $p<0.001$) and the median dose of glucocorticoids (0.0 mg/day *vs*. 4.0 mg/day, $p<0.001$; prednisolone/prednisone-equivalent dose) were significantly lower in Brazilian patients than in Japanese patients. Regarding immunosuppressive or immunomodulatory agents, methotrexate (17.7% *vs*. 1.4%, $p=0.002$) and azathioprine (17.7% *vs*. 0%) were used more frequently in Brazilian patients, whereas tacrolimus (0% *vs*. 67.7%) was favourably used in Japanese patients (Table II).

Stratified analyses

We stratified the Brazilian and Japanese cohorts according to the presence of RP-ILD. Given there was only one patient who presented with RP-ILD in the Brazilian cohort, we made two types of comparisons: i. Brazilian patients without RP-ILD *vs*. Japanese patients without RP-ILD, and ii. Brazilian patients without RP-ILD *vs*. Japanese patients with RP-ILD (Suppl. Table S2). The results of two comparisons were largely consistent with the primary analysis.

We also stratified each cohort according to the year of diagnosis: before 2018 and after 2019 (Suppl. Table S3). The results were again consistent with the primary analysis, regardless of the year of diagnosis.

Discussion

To the best of our knowledge, this is the first study to investigate the differences in clinical characteristics and outcomes of Brazilian and Japanese patients with anti-MDA5(+) DM/ADM using a standardised protocol for data collection. Compared with Japanese patients, Brazilian patients were younger at diagnosis and were more likely to be classified as having DM than ADM. Furthermore, Brazilian patients had a lower prevalence of ILD and a lower frequency of RP-ILD. The Japanese sample was highlighted by the more frequent use of tacrolimus and IVCYC, mirroring the severity of the lung involvement. The survival analysis demonstrated early mortality in Japanese patients; however, there was no significant difference in the overall survival between Brazilian and Japanese patients. The frequency of relapse and disease/treatment-related complications, such as severe infection and malignancy, were comparable between the two samples. Our results reinforce the idea that anti-MDA5(+) DM/ADM is not a homogenous disease entity with severe lung involvement, and clinicians should choose treatment regimens carefully according to mortality or RP-ILD risk stratification to avoid overtreatment. Furthermore, the phenotypic diversity among different regions suggests that genetic and/or environmental factors may play a role in the pathogenesis of anti-MDA5(+) DM/ADM.

Our study is pioneering in directly comparing patients with anti-MDA5(+) DM/ADM from different ethnic backgrounds. Although this was a retrospective study, we included only incident cases and the protocol for data collection was pre-parameterised and standardised between the participating centres. Anti-MDA5 autoantibodies were tested using different methods between the centres; therefore, only strong reactions were considered positive to increase the specificity of anti-MDA5 antibody positivity in the Brazilian centre, which utilised a line immunoassay, although false-positivity is reported to be relatively rare in line immunoassays for anti-MDA5 autoantibodies (43). As tuberculosis is an endemic disease in Brazil, the Brazilian centre carefully evaluated the patients before their inclusion in the study, avoiding the possibility that the underlying lung infection could be misclassified as lung involvement.

Recently reported cluster analyses in anti-MDA5(+) DM/ADM enabled us to better understand the heterogeneity of clinical phenotypes and predict the outcomes of each patient at an early stage of the disease according to the clinical characteristics at presentation. In the present study, our Brazilian patients resembled those included in cluster 1 described by Xu *et al*. (29), which corresponds to a profile of classic DM, presenting with skin lesions typical of DM (95.4%), muscle weakness (68.5%), skin ulcers (16.7%), and ILD (72.2%) with a low rate of progression to RP-ILD (14.8%), leading to low mortality (3.7%). This cluster was also associated with a higher prevalence of cutaneous vasculopathy and lower levels of acute-phase reactants and muscle enzymes. The characteristics of our Brazilian patients also corresponded to those included in cluster 2 described by Yang *et al*. (30), which comprised younger patients classified as having classic DM, with a higher prevalence of V-sign (69.2%), myalgia (69.2%), muscle weakness (92.3%), and a lower frequency of RP-ILD (7.7%), in whom no deaths were reported. In contrast, our Japanese patients had a clinical profile similar to that of cluster 1 described by Allenbach *et al*. (31), which included patients with a high rate of ILD (100%), RP-ILD (93.3%), and mechanic's hands (73.3%), associated with high mortality (80% died within three months from the diagnosis). However, the clinical characteristics of Japanese patients in the present study did not correspond perfectly to those of any clusters in Chinese study (29, 43), suggesting a potential modification effect of race, ethnicity, and geographics on the clinical phenotype of anti-MDA5(+) DM/ADM.

Meanwhile, the results of cluster analyses indicate that there is a subgroup of anti-MDA5(+) DM/ADM patients with less frequent ILD or RP-ILD and low mortality in different cohorts across regions, such as cluster 1 (classic DM profile) described by Xu *et al*. (29), clusters 1 (rheumatological profile with favourable prognosis) and 2 (classic DM profile and favourable prognosis) described by Yang *et al*. (30), clusters 2 (dermato-rheumatological profile) and 3 (male patients with muscle weakness and vasculopathy) described by Allenbach *et al*. (31). Along with previously published data on the Latin American population (24, 25), these observations support an idea that anti-MDA5(+) DM/ADM is not a homogeneous clinical entity with severe pulmonary involvement. Even in our Brazilian institution, which is a national referral centre for patients with IIMs, there was only one anti-MDA5(+) patient with RP-ILD, who was of Asian (Japanese) descent. This reinforces our attention to the potential

modifying effects of race and ethnicity on the clinical phenotypes of patients with anti-MDA5(+) DM/ADM.

Pulmonary involvement in Brazilian patients contrasts with that of the Japanese sample in our study, with the prevalence of ILD being significantly lower in Brazilian patients than in Japanese patients. The prevalence of acute ILD and RP-ILD was also significantly lower in Brazilian patients. Furthermore, lower lobe consolidation and lower lobe reticulation on HRCT, which have been reported to be associated with RP-ILD in anti-MDA5(+) DM/ADM (32), were more frequently noted in our Japanese patients. This result is consistent with the higher prevalence of RP-ILD in the Japanese group in the present study. Patients with RP-ILD require upfront combination therapy. Triple combination therapy with high-dose glucocorticoids, calcineurin inhibitors, and IV-CYC improved the survival of patients with anti-MDA5(+) DM/ADM, as described by Tsuji *et al*. (43). In our study, in line with the high prevalence of RP-ILD, Japanese patients were more likely to receive combination therapies comprising tacrolimus and IVCYC and some even received JAK inhibitors, which have been reported to be effective in refractory cases (44, 45). As a result, although early mortality due to RP-ILD was still observed, the overall survival rate was 86.2% in our Japanese patients, which was comparable to that of our Brazilian patients. In contrast, in line with the classic DM subtype as well as the low prevalence and attenuated severity of ILD, methotrexate, azathioprine, and mycophenolate mofetil were more frequently used as initial treatments in Brazilian patients.

The present study had some limitations. First, we included patients with anti-MDA5(+) DM/ADM who were treated only in the rheumatology and dermatology departments. Patients with severe ILD might have been seen only in pulmonology services and were therefore not referred to us. Second, all three institutions were tertiary care centres, which limits the generalisability of our results. Importantly, the median time interval between the onset and diagnosis of the disease was significantly longer in the Brazilian centre than in the Japanese centres; therefore, we cannot exclude the possibility that some Brazilian patients who developed RP-ILD died prematurely and were missed in our study. Nonetheless, our Brazilian centre is a national referral centre, and it is unlikely that the majority of patients with anti-MDA5 antibodies and RP-ILD were not captured. In fact, the prevalence of ILD and RP-ILD was consistently lower in Brazilian patients regardless of time intervals between the onset of symptoms and the diagnosis of the disease.

In conclusion, Brazilian patients with anti-MDA5(+) autoantibodies demonstrated a clinical phenotype compatible with that of classic DM, and the prevalence of ILD and RP-ILD was significantly lower than that of Japanese patients. Our study highlights the potential modifying effects of race, ethnicity, and geographic background on the phenotypic heterogeneity observed in patients with anti-MDA5(+) DM/ADM.

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