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Comparison of the 2017 EULAR/ACR Criteria with Clinicoserologic Criteria for the Classification of Idiopathic Inflammatory Myopathies in Korean Patients

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Purpose: To investigate correlations between myositis-specific autoantibodies (MSA) or myositis-associated antibodies (MAA) and clinical features, thereby demonstrating the utility of clinicoserologic classification in idiopathic inflammatory myopathies (IIM) patients.

Materials and Methods: We conducted a multicenter study of 108 adult patients (age ≥18 years) who were diagnosed with IIM by Peter and Bohan criteria or 2004 European Neuromuscular Centre (ENMC) criteria. Clinical data were obtained by medical record review. Immunoblot assay with Euroline strip (EUROIMMUN, Germany) was performed using the sera of dermatomyositis (DM, n=56), polymyositis (PM, n=45), amyopathic DM (n=5), DM sine dermatitis (n=1), and immune mediated necrotizing myopathy (n=1) patients. Patients were classified based on two classifications: 2017 EULAR/ACR and novel clinicoserologic classification.

Results: According to 2017 EULAR/ACR criteria, DM and PM were the most and the second most frequent entities. Overlap myositis was the major entity of IIM, and the frequency of PM was significantly lower when applying clinicoserologic classification criteria. Sixty-nine (63.9%) patients had one or more MSA, and 61 (56.5%) patients had one or more MAA. Interstitial lung disease was closely associated with anti-MDA5 and anti-ARS, and DM-specific skin lesions were frequently observed in patients with anti-TIF1γ, anti-SRP, and anti-MDA5.

Conclusion: The clinicoserologic criteria based on MSA/MAA positivity could reflect more precise clinical features of IIM. Establishment of a laboratory system routinely available to screen for MSA/MAA status will be beneficial to provide precise diagnosis and proper management of IIM patients.

Key Words: Idiopathic inflammatory myositis, novel classification criteria, overlap myositis, myositis specific autoantibody

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INTRODUCTION

Idiopathic inflammatory myopathies (IIM) are systemic autoimmune diseases characterized by muscular inflammation that leads to muscle weakness. Extra-muscular complications can involve the skin, joints, gastrointestinal tract, heart, and lungs,[1] all of which have impact on morbidity and mortality. In 1975, Bohan and Peter proposed the original classification for both diagnosis and classification of IIM,[2,3] and since then, remarkable progress has been toward understanding the vary-

ing features and pathogenesis of IIM, leading to the development of several classification criteria for IIM. By the European Neuromuscular Centre (ENMC) criteria in 2004, IIMs are subclassified into polymyositis (PM), dermatomyositis (DM), inclusion body myositis (IBM), and immune-mediated necrotizing myopathy (IMNM).[4] In 2017, the EULAR/ACR classification criteria for adult and juvenile IIMs and their major subgroups were developed.[5] However, these classification criteria have limitations as these subgroups often have overlapping clinical and histopathological features. Thus, new classification criteria have been proposed for not only the diagnosis of IIM, but also for distinguishing patients with extra-muscular complications as the predominant manifestations of IIM.

As understanding of the etiology of IIM increases, a number of myositis-specific antibodies (MSA) and myositis-associated antibodies (MAA) have been discovered in sera of patients with IIM. These autoantibodies are associated with distinct clinical features, including malignancy, skin manifestations, arthritis, or interstitial lung disease (ILD).[6] Moreover, they can help in classifying IIM into several subtypes and in predicting the disease course with better precision. The discovery of MSA and MAA led to the proposal of a serologic approach complementary to the Bohan and Peter IIM classification. In 2017, Senécal, et al.[7] proposed a new clinicoserologic classification criteria of adult autoimmune myositis .

Integrating MSA and MAA results to the modified classification has facilitated separation of classic PM and DM into new subsets with distinct clinical features, courses, prognoses, associations with cancer, and even therapeutic responses. Under these new criteria, the concept of overlap myositis (OM) was proposed and defined as the association of myositis with overlap features, such as Raynaud's phenomenon, arthritis and ILD, as well as features of other connective tissue diseases (CTD): IIM patients presenting with several autoantibodies (e.g., targeting Jo-1, non-Jo-1 synthetases, MDA5, U1 RNP, U3 RNP, U5 RNP, U11-12 RNP, PM-Scl, Ku, nup, CENP-B, Th/To, RuvB-like 1/2, DNA polymerase III, RNA polymerase III, SMN, native DNA) are also classified as OM.

Our objectives were to determine the prevalence of MSA and MAA in Korean adult patients with IIM and to investigate correlations between myositis autoantibodies and their frequencies and clinical features across different IIM subgroups, collectively demonstrating the utility of the new clinicoserologic classification in Korean adult patients with IIM.

MATERIALS AND METHODS

Patients

We conducted a multicenter study of 108 adult IIM patients seen at tertiary care centers of six university hospitals (Kyung Hee University Hospital, Chungbuk National University Hospital, Chungnam National University Hospital, Konyang University Hospital, Soonchunhyang University Hospital, and Dankook University Hospital) from March 2016 to July 2019. Adult patients older than age 18 years old diagnosed with IIM according to Peter and Bohan criteria or 2004 ENMC criteria were enrolled.[4] Clinical information regarding disease manifestations, laboratory data, radiographic data, and the presence of internal malignancies was obtained retrospectively by medical record review. Steroid dosage was defined as the highest dose of steroid used in the first treatment. Both muscle biopsy and electromyography were performed in 79 patients. Data on target organ involvement, including Raynaud phenomenon, arthritis, esophageal dysfunction, and lung involvement, were obtained. DM-specific skin lesions included Gottron's papules, heliotrope rash, photo-distributed poikiloderma, such as shawl and V signs, and mechanic hands. This study was approved by the Institutional Review Boards of each hospital, and informed consent was obtained from all study participants (IRB 2018-08-189).

Myositis classifications

Patients were reclassified based on two classifications: 1) 2017 EULAR/ACR classification criteria[5] and 2) clinicoserologic classification suggested by Senécal, et al.[7]

Immunoprecipitation assay

Samples were collected at the time of study enrollment, and immunoprecipitation assay tests were performed simultaneously. The presence of myositis antibodies was assessed using the immunoblot assay Euroline: Autoimmune Inflammatory Myopathies 16Ag (Euroimmun, Bussy-Saint-Martin, France). This assay utilizes membrane strips with antigens to detect the presence of myositis-related antibodies in patient sera. The immunoblot detects antibodies to the following antigens: Ku, PM/Scl100, PM/Scl75, Jo-1, SRP, PL-7, PL-12, EJ, OJ, Ro-52, Mi-2 α/β, TIF1γ, MDA5, NXP2, and SAE1. Because both anti-Mi-2α and Mi-2β target two closely related isoforms of the same protein, they were considered together as anti-Mi-2.[8] Similarly, anti-PM/Scl100 and anti-PM/Scl75 were both considered as anti-PM/Scl. All immunoblot strips were analyzed with Euroline Scan (Euroimmun), which provides semi-quantitative results based on signal intensities measured for each Ab. We chose to exclude borderline positivity from our study. The analysis of the results was performed semi-quantitatively based on the signal intensity of each antibody, following the manufacturer's recommendations. Anti-nuclear antibodies (ANA) were assessed by indirect immunofluorescence on HEp-2 cells. The assay was performed according to the manufacturer's recommendations using a screening dilution of 1:80.

Statistical analysis

Continuous values are represented as means±standard deviation. Statistical analysis was performed using the Mann Whitney U test and the chi-square test (or Fisher's exact test if ap-

propriate) to compare continuous and categorical variables, respectively. SPSS ver. 21 (IBM Corp., Armonk, NY, USA) was used throughout, and two-sided *p* values of <0.05 were considered statistically significant.

RESULTS

Demographics and clinical characteristics of the patients

The mean age at diagnosis of IIM was 50.6±13.9 years; 79 (73.1%) patients were female. The mean interval between clinical onset and myositis diagnosis was 16.3 months. The mean duration of follow-up after myositis diagnosis was 5.7 years. Eighty (74.1%) patients had proximal muscle weakness. The elevation of muscle enzyme was noted in 96 (88.9%) patients, and the mean CK level was 3459.6±4511.1 U/L. The clinical characteristics of the patients are summarized in Table 1. ILD was recorded in 57 patients, comprising 52.8% of all patients, 52.2% of the PM group, and 52.6% of the DM group. Fourteen (13%) malignancies were diagnosed

Classification of idiopathic IIM

Of all 108 patients, only 79 patients who had undergone biopsy were reclassified. The distribution of subgroups of IIM using the 2017 EULAR/ACR criteria differed strikingly from those us-

Table 1. Clinical and Demographic Characteristics of the Study Patients

	PM (n=46, Including 1 IMNM)	DM (n=57, Including 1 DM sine dermatitis)	ADM (n=5)	Total (n=108)	*p* value
Age at diagnosis (yr)	52.9±12.9	47.8±14.1	61.8±15.9	50.6±13.9	0.034
Sex (F:M)	29:17	45:12	5:0	79:29	0.074
Disease duration (yr)	6.19±4.19	5.47±4.66	3.40±2.51	5.69±4.40	0.354
Immunosuppressant user	40 (87.0)	47 (82.5)	5 (100.0)	92 (85.2)	0.525
Steroid dosage* (mg)	246.1±420.9	217.4±384.4	285.0±539.9	230.9±402.4	0.973
Clinical manifestation					
Arthritis	10 (21.7)	16 (28.1)	1 (20.0)	27 (25.0)	0.799
Raynaud phenomenon	6 (13.0)	7 (12.3)	1 (20.0)	14 (13.0)	<0.999
Dysphagia	5 (10.9)	11 (19.3)	0 (0.0)	16 (14.8)	0.349
ILD	24 (52.2)	30 (52.6)	3 (60.0)	57 (52.8)	<0.999
Malignancy	3 (6.5)	11 (19.3)	0 (0.0)	14 (13.0)	0.301

PM, polymyositis; IMNM, immune mediated necrotizing myositis; DM, dermatomyositis; ADM, amyopathic dermatomyositis; ILD, interstitial lung disease.
Values are presented as a mean±standard deviation or total n (%).
*The highest dose of steroid used in the first treatment.

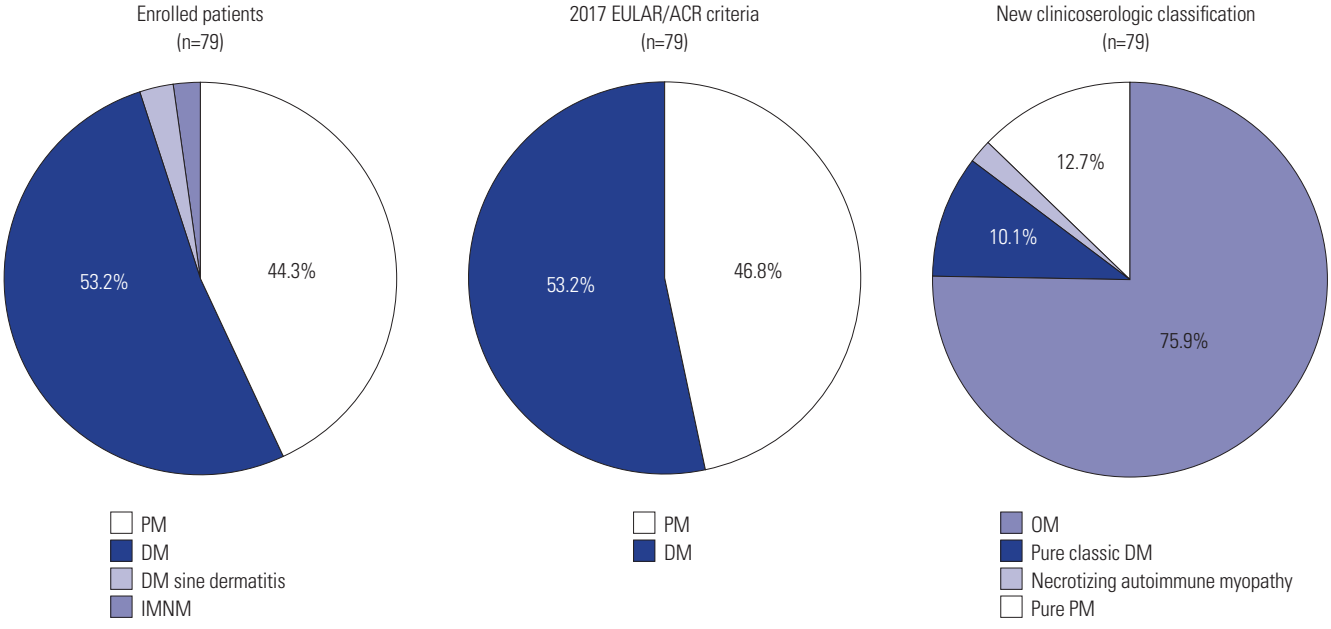

Fig. 1. Distribution of 79 patients with myositis at diagnosis according to three classifications for idiopathic inflammatory myopathies. PM, polymyositis; DM, dermatomyositis; IMNM, immune mediated necrotizing myositis; OM, overlap myositis.

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ing the novel clinicoserologic criteria (Fig. 1). At myositis diagnosis, according to 2004 ENMC criteria, 35 definite PM, one IMNM, 42 definite DM, and one DM sine dermatitis were seen. According to the ENMC criteria and 2017 EULAR/ACR criteria, DM was the most frequent entity (n=42, 53.2%). In striking contrast, using the new clinicoserologic classification criteria, OM was the most common entity (n=60, 75.9%), and only 8 of 42 patients diagnosed with DM by the ENMC classification criteria were still classified as pure classic DM (n=8, 10.1%). Also, 10 cases (12.7%) were reclassified as pure PM by new classification criteria. This demonstrated that previous criteria could not reflect the overlap clinical features of IIM.

Autoantibody profiles of reclassified groups by novel clinicoserologic criteria

Sixty-nine (63.9%) patients had one or more MSA, and 61 (56.5%) patients had one or more MAA among all 108 patients. The frequency of autoantibodies in the reclassified groups according to new clinicoserologic criteria are shown in Table 2. In 79 patients, ANA was positive in 45 (57.0%) patients. Forty-four (55.7%) patients had one or more MSA (including Anti-Jo-1, OJ, EJ, PL7, PL12, SRP, MDA5, Mi2, TIF1-r, SAE), and 42 (53.2%) patients had one or more MAA (including Anti-Ro52, Ku, PM-Scl). Anti-Ro52, one of the MAAs, was most frequently observed (34, 43.0%). After that, the frequencies of antibodies were as follows: anti-ARS (17, 21.5%), anti-MDA5 (13, 16.5%), anti-TIF1γ (8, 10.1%), anti-SRP (12, 15.2%), anti-Mi2 (7, 8.9%), anti-PM/Scl (7, 8.9%), and anti-Ku (4, 5.1%). In the OM group, among MSAs, anti-ARS was seen most frequently (17/60, 28.3%). Anti-MDA5 and anti-SRP were noted in 21.7% and 11.7%, respectively. Of the MAAs, anti-Ro52 was the most frequent antibody (29/60, 48.3%), followed by anti-PM/Scl at 11.7%. In the pure classic DM group, anti-TIF1γ was seen most frequently (4/8, 50.0%); anti-Mi2 was noted in 37.5%. Of the MAAs, anti-Ro52 was positive in 37.5%. In the pure PM group, anti-SRP was the most frequent antibody (5/10, 50.0%).

Table 2. Clinical Characteristics and Autoantibody Profiles of Reclassified Groups by Novel Clinicoserologic Criteria

	OM n=60	Pure classic DM n=8	Pure PM n=10	Necrotizing autoimmune myositis n=1	Total n=79
ANA	34 (56.7)	7 (87.5)	4 (40.0)	0	45 (57.0)
MSA					44 (55.7)
Anti-ARS*	17 (28.3)	0	0	0	17 (21.5)
Anti-Jo-1	9 (15.0)	0	0	0	9 (11.4)
Anti-OJ, EJ, PL7, PL12	7 (11.7)	0	0	0	7 (8.9)
Anti-SRP*	7 (11.7)	0	5 (50.0)	0	12 (15.2)
Anti-MDA5	13 (21.7)	0	0	0	13 (16.5)
Anti-Mi2*	3 (5.0)	3 (37.5)	1 (10.0)	0	7 (8.9)
Anti TIF1-r*	4 (6.6)	4 (50.0)	0	0	8 (10.1)
Anti-SAE	0	0	0	0	0
MAA					
Anti-Ro52*	29 (48.3)	3 (37.5)	2 (20.0)	0	34 (43.0)
Anti-Ku	3 (5.0)	0	1 (10.0)	0	4 (5.1)
Anti-PM-Scl	7 (11.7)	0	0	0	7 (8.9)

OM, overlap myositis; DM, dermatomyositis; PM, polymyositis; ANA, anti-nuclear antibody; MSA, myositis-specific autoantibodies; MAA, myositis-associated antibodies.
Data are presented as n (%).
*$p<0.05$.

Table 3. Associations between Autoantibodies and Clinical Features in IIM

	Anti-ARS n=24	Anti-SRP n=13	Anti-MDA5 n=16	Anti-TIF1γ n=13	Anti-Mi2 n=9	Anti-SAE n=2	Anti-Ro52 n=51	Anti-PM/Scl n=9	Anti-Ku n=6	Total n=108
ILD	21†	4	14*	1†	2	1	35*	7	2	57
Malignancy	2	1	1	7†	0	0	7	0	2	14
DM specific skin lesion	9*	3*	15*	12*	6	1	29	5	2	62
Gottron' papule	3	1	12	11	6	1	15	3	2	37
V sign or shawl sign	4	2	1	7	4	1	11	1	0	21
Dysphagia	3	2	0	1	1	1	6	3	0	16

IIM, inflammatory myopathies; ILD, interstitial lung disease; DM, dermatomyositis.
Values are presented as total numbers.
*$p<0.05$, †$p<0.001$.

Associations between autoantibodies and clinical features of myositis

We analyzed the associations between myositis autoantibodies and clinical features, including ILD, malignancy, DM-specific skin lesion, and dysphagia (Table 3). Anti-ARS positive patients and anti-MDA5 positive patients had higher frequencies of ILD than negative patients (87.5% vs. 42.9%, $p<0.001$; 87.5% vs. 46.7%, $p=0.003$, respectively). Otherwise, anti-TIF1γ positive patients had a significantly lower frequency of ILD than negative patients (7.7% vs. 58.9%, $p<0.001$). Anti-Ro52 positive patients had a higher frequency of ILD than negative patients (68.6% vs. 41.5%, $p=0.002$). Regarding malignancy, there was only a significant difference in anti-TIF1γ positivity (53.8% vs. 7.4%, $p<0.001$). Anti-ARS, anti-MDA5, and anti-TIF1γ positive patients had higher frequencies of DM-specific skin lesions. Otherwise, anti-SRP positive patients had a lower frequency of skin lesions. Cancer was present in 14 patients. Table 4 presents the clinical characteristics and autoantibody profiles of 14 patients. According to ENMC criteria, DM including amyopathic dermatomyositis was most frequent in patients with malignancy (11/14, 78.6%). However, when reclassified by new clinicoserologic criteria, OM was most frequent among patients with malignancy (8/14, 57.1%). Anti-TIF1γ was most frequently observed among them (7/14, 50%).

Autoantibody profiles of ANA and anti-Jo-1 negative patients

ANA and anti Jo-1 negative patients were 39 (36%) in 108 total IIM patients. In these 39 patients, 36 (84.6%) had one or more autoantibodies, except ANA and anti Jo-1. In MSA, anti-MDA5 was most frequently observed (12/39, 30.8%), and in MAA, anti-Ro52 was most frequently observed (18/39, 46.2%).

DISCUSSION

With the discovery of variable MSAs and MAAs, understanding of the heterogeneity of IIM has grown to include IIM with multi-organ involvement or IIM without muscular involvement. These broad spectrums need novel classification criteria. In 2017, the new EULAR/ACR classification criteria for IIM, however, did not include criteria reflective of the latest trends in autoantibodies. Senécal, et al.[7] proposed a novel classification of IIMs that reflects emerging concepts in the nosology of PM and DM brought forward by new autoantibodies. They classified IIM as five major entities: OM,[9] pure (classic) DM, necrotizing autoimmune myositis,[10] PM, and IBM. The term OM was proposed in 2005 first, defined as myositis with one or more overlapping CTD feature, including Raynaud's phenomenon, arthritis, and ILD, or certain overlap autoantibodies, including anti-ARS, MDA-5, RNP, Ku, and PM-Scl. Other studies have defined OM more strictly as patients who fulfill both IIM and other CTD criteria. OM is the most common form of IIM, accounting for about 50% of IIM patients.[7] Among the five entities classified by Bohan and Peter, OM (IIM with other CTD features) has a better prognosis than primary PM, primary DM, and cancer-associated myositis due to the mild course of the myositis and the good response to low-dose corticosteroids.[3,11] However, in other studies, OM has a worse prognosis and more severe infections than other myositis subsets.[12-14] These differences are due to the lack of a correct definition of OM.

A new way of subgrouping patients could be on the basis of the presence of MSA. Recent studies have studied the associations of myositis-related autoantibodies, along with clinical outcomes, to develop appropriate management strategies.[15-17] Traditionally, myositis-related autoantibodies have been described into two categories, MSAs and MAAs, depending on

Table 4. Clinical Data of 14 Patients with Malignancy

	Sex/age	Diagnosis	Diagnosis by clinicoserologic criteria	Time of detections* (month)	Primary site	Detected autoantibodies
1	F/34	DM	OM	-60	Colon, uterus	Anti-Ro52
2	F/48	DM	OM	-9	Breast	Anti-TIF1γ
3	F/50	DM	OM	0	Breast	(-)
4	F/52	DM	OM	-24	Tongue	Anti-EJ, Anti-Ro52
5	F/53	PM	Pure PM	34	Stomach	Anti-SRP
6	M/55	DM	Pure classic DM	NA	NA	Ani-Ro52
7	M/66	DM	Pure classic DM	0	Lung	Anti-TIF1γ, Anti-Ku
8	F/70	ADM	OM	-96	Breast	Anti-MDA5, Anti-Ro52
9	M/74	DM	Pure classic DM	0	Stomach	Anti-Ro52, Anti-TIF1γ
10	F/74	ADM	Pure classic DM	-2	Breast	Anti-TIF1γ
11	F/77	DM	OM	-2	Gall bladder	Anti-Ro52, Anti-TIF1γ
12	F/78	PM	OM	0	Tongue	Anti-Jo1, Anti-PL7, Anti-Ro52
13	F/78	DM	OM	-18	Lung	Anti-TIF1γ, Anti-Ku
14	M/86	PM	Pure PM	2	Lung	Anti-TIF1γ

F, female; M, male; DM, dermatomyositis; OM, overlap myositis; PM, polymyositis; NA, not available; ADM, amyopathic dermatomyositis.
*Relative to time of myositis diagnosis.

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their frequencies in related conditions.[17,18] MSAs include anti-ARS (targeting Jo1, PL7, PL12, EJ, OJ, KS, Zo, YRS/HS), anti-Mi2, anti-SAE, anti-MDA5, anti-TIF1γ/α, anti-NXP2, anti-SRP, and anti-HMGCR.[19] MSAs show high specificity for IIM and are rarely found in other related conditions. Each MSA is associated with a distinctive pattern of disease or phenotype. Anti-ARS are found in patients with ILD, particularly in association with anti-synthetase syndrome characterized by myositis, ILD, arthritis, Raynaud's phenomenon, fever, and mechanic's hands.[20,21] Anti TIF1γ antibodies are associated with myositis-associated cancer[15] and anti-HMGCR antibodies with statin-induced myositis.[22] The presence of anti MDA5 antibodies is a risk factor for rapidly progressive ILD, particularly in Eastern Asian populations.[23] MAAs are associated with myositis; however, they are also found in other related conditions, including systemic sclerosis, systemic lupus erythematosus, and Sjögren syndrome. MAAs include anti-PM/Scl, anti-U1/U2 RNP, anti-Ku, and anti-Ro52.[24]

In this study, OM was defined as myositis with an extra-muscular CTD feature or one overlap of autoantibodies according to the novel classification by Senécal, et al.[7] The distribution of the various IIMs differed strikingly from those using each classification. OM was the most common entity when reclassified by a novel clinicoserologic classification, 74% of total patients. The presence of any autoantibody was noted in 64% of all patients. This is consistent with previous studies. Approximately 60–70% of patients with IIM carry an identifiable myositis autoantibody.[6,25] In sub-analysis about associations between myositis autoantibodies and clinical features, anti-ARS and anti-MDA5 had correlations with ILD, and patients with anti-TIF1γ rarely developed ILD. These findings are consistent with previous studies. Fiorentino, et al.[26] reported that systemic features associated with anti-TIF1γ in adults with DM. Among MAAs, anti-Ro52 had a correlation with ILD. Anti-Ro52 was frequently detected with anti-ARS. Furthermore Marie, et al.[27] reported that anti-Jo1/anti-Ro52 positive IIM patients had more ILD than anti-Jo1/anti Ro-52 negative patients. In our study, anti MDA5 and anti TIF1γ antibodies were associated with DM-specific skin lesions, and patients with anti-SRP rarely developed skin lesion. In previous research, patients with anti-TIF1γ/α antibody presented with classic DM skin lesions, such as heliotrope rash, Gottron's papules, V-sign, and shawl sign.[26] In anti-MDA5 positive patients, the cutaneous phenotype is often particularly severe.[28] Anti-SRP is detected in almost all patients with PM.[29] This may explain the negative correlation with anti-SRP and DM-specific skin lesions in our study. In addition, both ANA and anti Jo-1 negative patients were 36% of all IIM patients in this study. In these patients, 84.6% had one or more MSA or MAA. Currently, the only MSA that can be commercially tested in Korea is anti-Jo 1. Therefore, an additional test for MSA and MAA that can accurately classify these patients would help with predicting clinical aspects and progress.

This study has several limitations. First, the sample size was not large. Second, the antibody panel lacked cN1A and HMGCR, two important antibodies associated with IBM and IMNM, respectively. Thus, further studies with large sample sizes are warranted for making the subgroup analysis according to autoantibody profile. Third, we did not analyze outcomes of death, respiratory failure, or functional status. Despite these limitations, the strength of our study is that it is the first study to reclassify Korean IIM patients by novel clinicoserologic criteria and to examine correlations between novel myositis autoantibodies and clinical subsets.

Novel clinicoserologic classification criteria could reflect autoantibodies and distinctive clinical features of IIM, and these autoantibodies have considerable implications for the diagnosis and management of myositis. These findings may help lead to early diagnosis and a more personalized approach to management. The recognition that phenotypes with specific organ involvement other than the muscles is important for identifying patients with early disease.

AUTHOR CONTRIBUTIONS

Conceptualization: Jinhyun Kim and Yeon-Ah Lee. Data curation: Sang Wan Chung, In Ah Choi, Sung Hae Chang, and Mi Il Kang. Formal analysis: Sang Wan Chung. Investigation: Sang Wan Chung and In Seol Yoo. Methodology: Jinhyun Kim and Seung-Jae Hong. Project administration: Jinhyun Kim. Resources: Jinhyun Kim. Supervision: Seong Wook Kang, Jinhyun Kim, Yeon-Ah Lee, and Seung-Jae Hong. Validation: Sang Wan Chung. Writing—original draft: Sang Wan Chung. Writing—review & editing: Mihye Kwon and Chung-Il Joung. Approval of final manuscript: all authors.

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