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Original Article

New Provisional Classification of Juvenile Idiopathic Arthritis Applying Rheumatoid Factor and Antinuclear Antibody

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Objective. Previous classification systems for juvenile idiopathic arthritis (JIA) were based on the number of joints involved and did not categorize homogenous disease entities. Therefore, JIA patients were reclassified retrospectively by applying rheumatoid factor (RF) and antinuclear antibody (ANA), which have been proven to constitute a homogenous disease entity. **Methods.** The medical records of JIA patients were investigated retrospectively and reclassified into six categories using the new provisional classification. The nomenclature was based on Dr. Martini's proposal in the 23rd European Paediatric Rheumatology Congress (2016) at Genoa, Italy. New categories included systemic JIA (sJIA), RF-positive JIA (RF-JIA), early-onset ANA-positive JIA (eoANA-JIA), enthesitis/spondylitis-related JIA (ESR-JIA), "other JIA", and "unclassified JIA". **Results.** Of a total of 262 JIA patients, 71 (27.1%) were reclassified as sJIA, 31 (11.8%) as RF-JIA, 22 (8.4%) as eoANA-JIA, 63 (24.0%) as ESR-JIA, 65 (24.8%) as "other JIA", and 10 (3.8%) as "unclassified JIA". A comparison of RF-JIA, eoANA-JIA, and ESR-JIA revealed significant differences in the gender ratio, age of disease onset, and the cumulative number and type of joints involved among the three groups. "Other JIA" comprised a significant proportion (24.8%) and warrants the need for further classification. The characteristics of the RF-positive patients were comparable to those of the anti-cyclic citrullinated peptide antibody-positive patients. The ANA positivity was lower (28.2%) than that in Western studies but showed similar clinical features. **Conclusion.** This is the first study applying RF and ANA to classify JIA without considering the joint counts. The six new categories include sJIA, RF-JIA, eoANA-JIA, ESR-JIA, "other JIA," and "unclassified JIA". **(J Rheum Dis 2018;25:34-46)**

Key Words. Juvenile idiopathic arthritis, Classification, Rheumatoid factor, Antinuclear antibody

INTRODUCTION

The term "juvenile idiopathic arthritis (JIA)" was first proposed by the International League of Associations for Rheumatology (ILAR) in Santiago (1994) and was revised twice in Durban (1997) and in Edmonton (2001) [1-3]. It encompasses all forms of arthritis that begin before the age of 16, persist for more than 6 weeks, and are of unknown origins [4]. Before the ILAR classification, the American College of Rheumatology (ACR) had developed classification criteria (1972) for chronic childhood arthritis and revised it (1977) [5,6], and the European League against Rheumatism (EULAR) also proposed their classification system in Basel (1977) [7]. The ACR and EULAR classifications used the terms juvenile rheumatoid arthritis (JRA) and juvenile chronic arthritis (JCA), respectively, and there were some differences in contents as well. ILAR classification resolved this disparity of terminology between the European and North American versions and aimed at identifying more homogenous and mutually exclusive disease groups [8].

However, ILAR classification for JIA had a limitation of being an incomplete system as it was based on the consensus of experts rather than being data-driven [8]. In other words, the ILAR classification was part of "work in progress" to create more precise classification criteria in the future. As a result, numerous suggestions for revising the ILAR classification have been proposed until now

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[8-19].

First, patients with a distinct set of features, including antinuclear antibody (ANA) positivity, young age at disease onset, female predilection, asymmetric arthritis, and high risk for chronic uveitis, represent a homogenous group [8,10]. Second, the ILAR classification includes less well-characterized categories, such as rheumatoid factor (RF)-negative polyarthritis and psoriatic arthritis [20]. Multiple studies have reported that these subtypes comprise heterogeneous disease entities [11,16]. Third, the number of joints involved or presence of psoriasis no longer represent useful markers for defining a homogenous disease group [9,11,17]. In addition, these findings were supported by various genetic studies [16,19,21]. With the accumulation of these diverse evidences, experts in pediatric rheumatology became more enthusiastic to revise the JIA classification system. As part of this process, Dr. Martini proposed and issued a prospective research plan on establishing a new provisional classification system for JIA in the 23rd European Paediatric Rheumatology Congress (2016) at Genoa, Italy [12].

This newly proposed classification for JIA applied RF and ANA, which are the most frequently tested and useful autoantibodies for analyzing JIA [22]. Conversely, the number of joints involved and the presence of psoriasis, which were included criteria in previous classification systems, were excluded. As a result, the concepts of oligoarthritis, polyarthritis, and psoriatic arthritis based on the old criteria were replaced by new categories that considered the presence of RF and ANA. Conversely, systemic arthritis remained untouched because it has prominent extra-articular manifestations, such as quotidian fever and evanescent rash.

As mentioned above, autoantibodies have a pivotal role in the new provisional classification for JIA [22]. In particular, RF has been extensively studied in connection with anti-cyclic citrullinated peptide antibody (anti-CCP Ab). In adult rheumatoid arthritis (RA), RF and anti-CCP Ab have high specificity for RA and are a part of the diagnostic criteria [23]. Anti-CCP Ab is also considered a strong predictive factor of RA [24]. In the pediatric population, anti-CCP Ab is associated with RF-positive polyarthritis, and more erosive disease [25,26]. It was also found to be increased in human leukocyte antigen (HLA)-DR4-positive polyarthritis in a Western study [27]. In this study, we included anti-CCP Ab in the diagnostic criteria of RF-positive JIA as recommended in Dr. Martini's proposal.

To establish a more precise classification for JIA, further large-scaled, multi-center studies should be conducted. The aim of this study is to reclassify JIA patients in a relatively simple way based on tests for RF and ANA.

MATERIALS AND METHODS

Patients

We conducted a retrospective, single-center study of 262 patients with JIA by reviewing their medical records between February 2002 and April 2016. The inclusion criterion was a diagnosis of JIA based on the 2nd revision of ILAR classification for JIA in Edmonton (2001) [3]. Patients were categorized into seven disease subtypes on the basis of features presented in the first 6 months of illness: systemic arthritis, oligoarthritis (persistent type and extended type), RF-negative polyarthritis, RF-positive polyarthritis, psoriatic arthritis (PsA), enthesitis-related arthritis (ERA), and undifferentiated arthritis.

Then, we reclassified the patients based on the new provisional classification that considers RF and ANA modified from the proposal by Dr. Martini in the 23rd European Paediatric Rheumatology Congress (2016) at Genoa, Italy. The subtypes of the new classification included systemic JIA (sJIA), RF-positive JIA (RF-JIA), early-onset ANA-positive JIA (eoANA-JIA), enthesitis/spondylitis-related JIA (ESR-JIA), "other JIA" and "unclassified JIA." The inclusion criteria for each subtype are as follows.

1. sJIA remained unchanged from the ILAR classification, because it is a well-defined disease category by its prominent systemic, extra-articular features.
2. RF-JIA comprised patients with positive RF, irrespective of the number of joints involved. It also included patients with positive Anti-CCP Ab.
3. ESR-JIA comprised patients presenting with the features of spondyloarthritis (SpA). In this study, we simply combined ERA patients and PsA patients (with ANA-negative) in the ILAR classification.
4. eoANA-JIA comprised ANA-positive patients (aged $\leq$6 years) who are not included in the above three groups.
5. "Other JIA" comprised patients not included in the above four groups.
6. "Unclassified JIA" comprised patients having features of more than two of the first four subtypes in this list.

A comparison of subtypes between the ILAR classification and the new provisional classification for JIA is

shown in Figure 1. We also applied the Assessment of the SpondyloArthritis International Society (ASAS) criteria for adult SpA to JIA patients [28]. Patients were diagnosed and classified by a skilled pediatric rheumatologist, and excluded if they were followed up for less than 6 months. This study was approved by the Institutional Review Board at Hallym University Sacred Heart Hospital (2017-I072).

Data collection

Medical charts were reviewed for the following information: sex, age at disease onset, cumulative number and type of joints involved, joint symmetricity, uveitis, enthesitis, back pain, psoriasis, dactylitis, nail pitting, and familial history of SpA. Associated laboratory findings included RF, ANA, Anti-CCP Ab, and HLA-B27.

Definition

ANA, RF, and Anti-CCP Ab were all tested by enzyme-linked immunosorbent assay. The patients were considered ANA-positive if they had at least two positive results on indirect immunofluorescence assay performed over 3 months apart. HEp-2 cells were the substrate used for ANA determination. The patients were considered RF-positive if they had at least two positive results ($\geq$20 IU/mL) for over 3 months apart. The patients were considered anti-CCP Ab-positive if there was at least one positive test ($\geq$20 arbitrary unit/mL).

Upper large joints included elbows and wrists, and lower large joint included knees and ankles. Upper small joints were metacarpophalangeal (MCP) and interphalangeal joints, and lower small joints were metatarsophalangeal and interphalangeal joints. Axial joints included temporomandibular joint, sacroiliac joints, and the joints of shoulders, cervical or lumbar spine, and hips.

Arthritis was defined as symmetric if >50% of the joints involved during the first 6 months of the disease were symmetric pairs. This definition of joint symmetricity was previously adopted by Ravelli et al. [8], which was used in adults with rheumatoid and psoriatic arthritis [29].

Statistical analysis

All statistical analyses were conducted with IBM SPSS statistics ver. 24.0 (IBM Co., Armonk, NY, USA). Quantitative variables were compared among patient groups using the Mann-Whitney U test. Qualitative data were compared using the chi-square test or Fisher's exact test. Bonferroni's adjustment was applied as a correction method for multiple comparisons to explore the post-hoc differences between pairs of patient groups. Univariate logistic regression analysis was performed to evaluate which parameters had significant results on the presence of RF and anti-CCP Ab. All statistical tests were two-sided, and p-values <0.05 were considered significant.

RESULTS

A total 262 JIA patients (132 male, 130 female) were included in this study. The median age of disease onset was 7.3 years, being 8.4 years for males, and 5.8 years for females. All patients were categorized into subtypes by ILAR classification, and the characteristics of each subtype are shown in Table 1.

Table 2 shows the characteristics of the subtypes of the new provisional classification and how each subtype was reclassified from the ILAR categories. We summarized the relation of subtypes between the ILAR classification and the new provisional classification with an organization chart represented in Figure 1. The solid line in

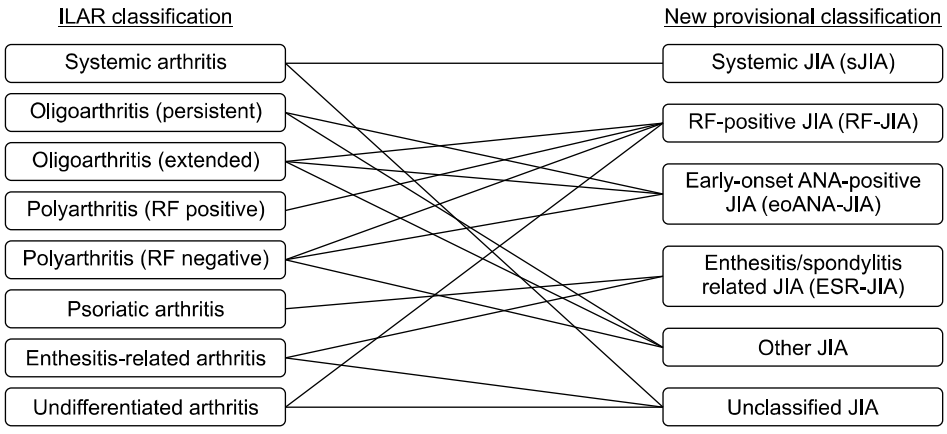

Figure 1. Comparison of subtypes between the ILAR classification and the new provisional classification. ILAR: International League of Associations for Rheumatology, RF: rheumatoid factor, ESR: enthesitis/spondylitis-related, JIA: juvenile idiopathic arthritis, ANA: antinuclear antibody.

Table 1. Demographic and patient characteristics of JIA patients classified by the ILAR classification

Variable	Systemic arthritis	Oligoarthritis		RF-negative polyarthritis	RF-positive polyarthritis	Psoriatic arthritis	ERA	Undifferentiated arthritis	Total
		PE	EX						
Patient	73 (27.9)	39 (14.9)	16 (6.1)	37 (14.1)	15 (5.7)	1 (0.4)	63 (24.0)	18 (6.9)	262 (100)
Male:Female (female, %)	38:35 (47.9)	11:28 (71.8)	5:11 (68.8)	11:26 (70.3)	4:11 (73.3)	0:1 (100)	57:6 (9.5)	6:12 (66.7)	132:130 (49.6)
Disease onset, median (IQR) (yr)	6.0 (3.8～9.4)	3.5 (2.3～5.4)	3.5 (2.1～11.3)	7.3 (3.3～10.9)	7.7 (5.9～11.9)	11.8	9.8 (7.8～11.8)	6.7 (4.5～9.5)	7.3 (3.9～10.5)
RF	0 (0)	0 (0)	0 (0)	0 (0)	15 (100)	0 (0)	0 (0)	14 (77.8)	29 (11.1)
Anti-CCP Ab	2 (2.7)	0 (0)	2 (12.5)	3 (8.1)	13 (86.7)	0 (0)	1 (1.6)	10 (55.6)	31 (11.8)
ANA	12 (16.4)	15 (38.5)	4 (25.0)	15 (40.5)	11 (73.3)	0 (0)	8 (12.7)	9 (50.0)	74 (28.2)
HLA-B27	5 (6.8)	4 (10.3)	2 (12.5)	8 (21.6)	1 (6.7)	0 (0)	58 (92.1)	6 (33.3)	84 (32.1)
Uveitis	7 (9.6)	8 (20.5)	4 (25.0)	2 (5.4)	1 (6.7)	0 (0)	9 (14.3)	1 (5.6)	32 (12.2)
Enthesitis	1 (1.4)	1 (2.6)	0 (0)	2 (5.4)	0 (0)	0 (0)	32 (50.8)	1 (5.6)	37 (14.1)
Symmetricity	35 (47.9)	7 (17.9)	8 (50.0)	30 (81.1)	13 (86.7)	0 (0)	15 (23.8)	9 (50.0)	117 (44.7)
Cumulative number of joints involved, mean±SD	7.3±9.2	2.1±1.1	9.4±3.9	13.4±7.4	15.5±8.4	4	6.0±6.2	11.4±8.9	8.0±8.0
Upper large joint	36 (49.3)	7 (17.9)	15 (93.8)	29 (78.4)	14 (93.3)	0 (0)	17 (27.0)	16 (88.9)	134 (51.1)
Upper small joint	21 (28.8)	3 (7.7)	7 (43.8)	29 (78.4)	15 (100.0)	1 (100)	17 (27.0)	9 (50.0)	102 (38.9)
Lower large joint	60 (82.2)	35 (89.7)	15 (93.8)	33 (89.2)	11 (73.3)	0 (0)	59 (93.7)	17 (94.4)	230 (87.8)
Lower small joint	13 (17.8)	2 (5.1)	3 (18.8)	18 (48.6)	11 (73.3)	0 (0)	26 (41.3)	5 (27.8)	78 (29.8)
Axial joint	20 (27.4)	4 (10.3)	8 (50.0)	21 (56.8)	9 (60.0)	1 (100)	34 (54.0)	8 (44.4)	105 (40.1)

Except where indicated otherwise, values are the number (%). JIA: juvenile idiopathic arthritis, ILAR: International League of Associations for Rheumatology, PE: persistent, EX: extended, RF: rheumatoid factor, ERA: enthesitis-related arthritis, IQR: interquartile range, Anti-CCP Ab: anti-cyclic citrullinated peptide antibody, ANA: antinuclear antibody, HLA: human leukocyte antigen, SD: standard deviation.

Table 2. Demographic and patient characteristics of subtypes in new provisional classification

Variable	sJIA	RF-JIA	eoANA-JIA	ESR-JIA	Other JIA	Unclassified JIA	Total	p-value*	Comparisons significant on *post-hoc* tests†
Patient	71 (27.1)	31 (11.8)	22 (8.4)	63 (24.0)	65 (24.8)	10 (3.8)	262 (100)		
ILAR subtypes (n)									
Systemic arthritis	71	0	0	0	0	2	73		
Oligoarthritis PE	0	0	12	0	27	0	39		
Oligoarthritis EX	0	2	3	0	11	0	16		
Polyarthritis RF (−)	0	3	7	0	27	0	37		
Polyarthritis RF (+)	0	15	0	0	0	0	15		
Psoriatic arthritis	0	0	0	1	0	0	1		
ERA	0	0	0	62	0	1	63		
Undifferentiated	0	11	0	0	0	7	18		
Male:Female (female, %)	38:33 (46.5)	7:24 (77.4)	5:17 (77.3)	56:7 (11.1)	20:45 (69.2)	6:4 (40.0)	132:130 (49.6)	<0.00001	RF vs. ESR ANA vs. ESR
Disease onset, median (IQR) (yr)	6.0 (3.8∼9.3)	7.0 (4.0∼9.6)	2.4 (2.1∼4.2)	9.8 (7.8∼11.8)	5.6 (3.0∼10.9)	9.0 (5.2∼12.2)	7.3 (3.9∼10.5)	<0.00001	ANA vs. RF RF vs. ESR ANA vs. ESR
RF	0 (0)	26 (83.9)	0 (0)	0 (0)	0 (0)	3 (30.0)	29 (11.1)		
Anti-CCP Ab	0 (0)	27 (87.1)	0 (0)	0 (0)	0 (0)	4 (40.0)	31 (12.7)		
ANA	12 (16.9)	19 (61.3)	22 (100)	8 (12.7)	11 (16.9)	2 (20.0)	74 (28.2)		
HLA-B27	5 (7.4)	5 (17.2)	4 (20.0)	57 (90.5)	7 (10.8)	6 (60.0)	84 (32.9)	<0.00001	RF vs. ESR ANA vs. ESR
Uveitis	7 (9.9)	2 (6.5)	7 (31.8)	9 (14.3)	7 (10.8)	0 (0)	32 (12.2)	0.039	
Enthesitis	1 (1.4)	0 (0)	0 (0)	31 (49.2)	3 (4.6)	2 (20.0)	37 (14.1)	<0.00001	RF vs. ESR ANA vs. ERA
Symmetricity	34 (47.9)	19 (61.3)	5 (22.7)	14 (22.2)	38 (58.5)	7 (70.0)	117 (44.7)	0.0004	RF vs. ESR ANA vs. RF
Cumulative no. of joints involved, mean±SD	7.4±9.3	14.2±7.9	6.0±6.3	6.1±6.2	8.0±7.2	8.8±9.4	8.0±8.0	<0.00001	ANA vs. RF RF vs. ERA
Upper large joint	35 (49.3)	29 (93.5)	12 (54.5)	17 (27.0)	35 (53.8)	6 (60.0)	134 (51.1)	<0.00001	RF vs. ESR ANA vs. RF
Upper small joint	20 (28.2)	25 (80.6)	9 (40.9)	18 (28.6)	26 (40.0)	4 (40.0)	102 (38.9)	0.00001	RF vs. ESR ANA vs. RF
Lower large joint	59 (83.1)	27 (87.1)	19 (86.4)	58 (92.1)	59 (90.8)	8 (80.0)	230 (87.8)	0.647	
Lower small joint	12 (16.9)	16 (51.6)	9 (27.3)	26 (41.3)	15 (23.1)	3 (30.0)	78 (29.8)	0.208	
Axial joint	20 (28.2)	16 (51.6)	3 (13.6)	35 (55.6)	27 (41.5)	4 (40.0)	105 (40.1)	0.003	ANA vs. ESR ANA vs. RF

Table 2. Continued

Variable	sJIA	RF-JIA	eoANA-JIA	ESR-JIA	Other JIA	Unclassified JIA	Total	p-value*	Comparisons significant on *post-hoc* tests†
ASAS criteria	9 (12.7)	6 (19.4)	10 (45.5)	62 (98.4)	14 (21.5)	6 (60.0)	107 (40.8)	<0.00001	RF vs. ESR ANA vs. ESR
Axial SpA (n)	0	0	0	9	1	1	11		
Peripheral SpA (n)	9	6	10	53	13	5	96		

Except where indicated otherwise, values are the number (%). JIA: juvenile idiopathic arthritis, sJIA: systemic JIA, RF-JIA: Rheumatoid factor-positive JIA, eoANA-JIA: early-onset antinuclear antibody-positive JIA, ESR-JIA: enthesitis/spondylitis-related JIA, ILAR: International League of Associations for Rheumatology, PE: persistent, EX: extended, ERA: enthesitis-related arthritis, IQR: interquartile range, Anti-CCP Ab: anti-cyclic citrullinated peptide antibody, ANA: antinuclear antibody, HLA: human leukocyte antigen, SD: standard deviation, ASAS: Assessment of SpondyloArthritis International Society, SpA: spondyloarthritis. *For overall comparisons. Following three subtypes were compared statistically—RF positive arthritis, ANA positive arthritis, and ERA/SpA. Comparisons of quantitative data were made by Mann-Whitney U test; comparisons of frequencies were made by chi-square test (or by Fisher's exact test if expected frequencies were <5). †Pairs of comparisons that were statistically significant on post-hoc tests (Bonferroni adjustment). RF: RF-JIA, ANA: eoANA-JIA, ESR: ESR-JIA.

Figure 1 indicates how patients were actually reclassified within this study.

In the new provisional classification, classification remained unchanged for 71/73 classified as having systemic arthritis as per the ILAR classification, except for two patients who were categorized as having "unclassified JIA" due to the presence of anti-CCP Ab. Thirty-one (11.8%) patients of RF-JIA comprised patients from various ILAR subtypes who had RF or Anti-CCP Ab. Twenty-two (8.4%) eoANA-JIA patients were reclassified from persistent oligoarthritis, extended oligoarthritis, and RF-negative polyarthritis. ESR-JIA was composed of 63 (24.0%) patients. This was the result of combining 62/63 patients of ERA and 1/1 patient of psoriatic arthritis. One patient of ERA was re-categorized into "unclassified JIA" because of the presence of anti-CCP Ab. Sixty-five (24.8%) patients were classified under "other JIA" which comprised oligoarthritis and RF-negative polyarthritis patients negative for ANA and anti-CCP Ab, or positive for ANA at age (>6 years). Ten (3.8%) "unclassified JIA" patients were composed of 7 undifferentiated arthritis, 2 systemic arthritis, and 1 ERA.

RF-JIA included patients positive for RF or anti-CCP Ab. They may be divided into two groups: 26 patients with positive RF and/or anti-CCP Ab and five patients with anti-CCP Ab alone and no RF. The former were 15 RF-positive polyarthritis and 11 undifferentiated arthritis patients, and the latter were two extended oligoarthritis and three RF-negative polyarthritis patients.

Further, eoANA-JIA patients comprised patients from both persistent (n=12) and extended (n=3) types of oligoarthritis and RF-negative polyarthritis (n=7) from the ILAR classification. Eleven patients were not included in this group because their age of disease onset was over 6 years, and they were reclassified under "other JIA."

When comparing these 11 patients (aged >6 years) with eoANA-J patients (aged ≤6 years), the eoANA-JIA patients had lower cumulative number of joints (p=0.040) and lower axial joints involved (p=0.006). Sixty-three ESR-JIA patients included one psoriatic arthritis and all ERA patients, except for one patient with positive anti-CCP Ab. Sixty-five patients classified under "other JIA" comprised 27/39 persistent oligoarthritis, 11/16 extended oligoarthritis, and 27/37 RF-negative polyarthritis. Ten "unclassified arthritis" patients as per the new provisional classification included 7/18 undifferentiated arthritis, 1/63 ERA, and 2/73 systemic arthritis as per the

ILAR classification.

We compared the three groups, RF-JIA, eoANA-JIA, and ESR-JIA, and the results are shown in Tables 2 and 3. Overall p-values were obtained first, and *post-hoc* test was performed to compare the groups. The proportion of females was lower in ESR-JIA than in RF-JIA and eoANA-JIA. There was a significant difference in the age of onset among the three groups. Regarding the age of disease onset, ESR-JIA was the oldest, and eoANA-JIA was the youngest. Enthesitis was found more frequently in ESR/JIA than in the other two groups. Joint symmetricity and the cumulative number of joints involved were higher in RF-JIA than in the other two groups. Upper large joints and upper small joints were found to be involved more in RF-JIA; however, lower joint involvement was comparable among the three groups. The involvement of axial joints was comparable for RF-JIA and ESR-JIA groups and was much higher than in the eoANA-JIA group.

Comparisons of each joint between RF-JIA, eoANA-JIA, and ESR-JIA are shown in Table 3. In lower limbs, ankles and MTP joint involvement showed overall variance, but no pair of groups showed significant difference after the *post-hoc* tests. Ankles were the most involved in RF-JIA (80.5%), followed by involvement in ESR-JIA (58.7%) and eoANA-JIA (50.0%). MTP joints were involved lesser in eoANA-JIA (18.2%) than RF-JIA (48.4%) and ESR-JIA (28.6%). In upper limbs, elbows were more involved in RF-JIA (45.2%) than ESR-JIA (11.1%), and wrists were markedly more involved in RF-JIA (93.3%) than in the other two groups (31.8% in eoANA-JIA, and 20.6% in ESR-JIA). MCP joints were involved more in RF-JIA (45.2%) than in ESR-JIA (20.6%). Finger joints were also involved more in RF-JIA (67.7%) than in ESR-JIA (12.7%). In axial joints, involvement of shoulders was more frequent in RF-JIA (35.5%) than in eoANA-JIA

Table 3. Joint involvement of RF-positive juvenile idiopathic arthritis (RF-JIA), early-onset ANA-positive JIA (eoANA-JIA) and Enthesitis/spondylitis related JIA (ESR-JIA)

Variable	RF-JIA	eoANA-JIA	ESR-JIA	p-value*	Comparisons significant on post-hoc test†
Lower limbs					
Knee	23 (74.2)	18 (81.8)	51 (81.0)	0.711	
Ankle	25 (80.6)	11 (50.0)	37 (58.7)	0.045	
MTP joint	15 (48.4)	4 (18.2)	18 (28.6)	0.047	
Toe	8 (25.8)	3 (13.6)	16 (25.4)	0.493	
Upper limbs					
Elbow	14 (45.2)	8 (36.4)	7 (11.1)	0.001	RF vs. ESR
Wrist	28 (93.3)	7 (31.8)	13 (20.6)	<0.00001	ANA vs. RF RF vs. ESR
MCP joint	14 (45.2)	5 (22.7)	13 (20.6)	0.037	RF vs. ESR
Finger	21 (67.7)	8 (36.4)	8 (12.7)	<0.00001	RF vs. ESR
Axial joints					
TMJ	4 (12.9)	2 (9.1)	4 (6.3)	0.565	
Neck	1 (3.2)	1 (3.0)	8 (12.7)	0.087	
Shoulder	11 (35.5)	0 (0)	11 (17.5)	0.005	ANA vs. RF
Back	0 (0)	0 (0)	10 (15.9)	0.010	
Sacroiliac joint	1 (3.2)	0 (0)	9 (14.3)	0.055	
Hip	12 (38.7)	2 (9.1)	26 (41.3)	0.020	ANA vs. RF ANA vs. ESR

Except where indicated otherwise, values are the number (%). Comparisons of frequencies were made by chi-square test (or by Fisher's exact test if expected frequencies were <5). RF: rheumatoid factor, ANA: antinuclear antibody, MTP: metatarsophalangeal, MCP: metacarpophalangeal, TMJ: temporomandibular joint, ERA: enthesitis-related arthritis, SpA: spondyloarthritis. *For overall comparisons. Following three subtypes were compared statistically—RF positive arthritis, ANA positive arthritis, and ERA/SpA. Comparisons of quantitative data were made by Mann-Whitney U test; comparisons of frequencies were made by chi-square test (or by Fisher's exact test if expected frequencies were <5). †Pairs of comparisons that were statistically significant on post-hoc tests (Bonferroni adjustment). RF: RF-JIA, ANA: eoANA-JIA, ESR: ESR-JIA

(0%). Involvement of hip joints was higher in RF-JIA (38.7%) and ESR-JIA (41.3%) than in eoANA-JIA (9.1%).

The ASAS criteria for adult SpA were applied to JIA patients, and the results were also shown in Table 2. Overall, SpA was diagnosed in 40.8% (107/262) of total JIA patients by the ASAS criteria (axial SpA, 11; peripheral SpA, 96). They included as many as 98.4% (62/63) of ESR-JIA, 60% (6/10) of "unclassified JIA," and 45.5% (10/22) of eoANA-JIA.

We performed univariate logistic regression analysis by setting the positivity of RF and anti-CCP Ab as independent variables (Table 4). Each variable showed almost consistent results between RF-positive patients and anti-CCP Ab-positive patients. In both groups, female gender, ANA positivity, and the number of joints involved ($\geq$5) were statistically significant, while age of disease onset ($>$6 years), uveitis, and enthesitis were not. Joint symmetricity was not statistically significant in Anti-CCP Ab-positive patients (p=0.051).

We analyzed whether there were significant differences between ANA-positive patients and ANA-negative patients (Table 5). sJIA, RF-JIA, and ESR-JIA were excluded from this comparison because these subtypes were presumed to have prominent features regardless of ANA-positivity [8]. Thus, the remaining 95 patients were investigated. The female proportion and the risk of uveitis were both significantly higher in ANA-positive patients (p=0.045 and p=0.021, respectively). The ANA-positive group showed younger age of disease onset and lower joint symmetricity, although these were not statistically significant. Enthesitis, HLA-B27, and the cumulative number and types of joints involved did not significantly differ between the two groups.

We divided 35 ANA-positive patients in Table 5 by age of disease onset (6 years) and compared each other (not shown in table). Patients with disease onset at an age of $\leq$6 years had fewer occurrences of enthesitis (p=0.046), frequent involvement of lower large joints (p=0.045), and lesser involvement of axial joints (p=0.022). Although not statistically significant, there was some tendency of higher female predilection, higher risk for uveitis, lesser risk for HLA-B27 positivity, lower joint symmetricity, and small cumulative number of joints involved in patients with disease onset at an age of $\leq$6 years.

DISCUSSION

The most important point in the new provisional classification for JIA is that the previous diagnostic criteria based on the number of joints were substituted by the positivity for RF and ANA. Thus, in the new provisional classification, we discontinued the use of the term pauci/oligoarthritis and polyarthritis which have been used in the pediatric field for over 4 decades. The category of PsA excluded as well. Instead, patients who once belonged to these groups were re-categorized to RF-JIA, eoANA-JIA, ESR-JIA, "other JIA," and "unclassified JIA." sJIA remained unchanged from the ILAR classification.

As mentioned earlier, this nomenclature was originated from the new provisional classification for JIA proposed by Dr. Martini in 2016. The Paediatric Rheumatology European society (PReS) is currently conducting a large-scale prospective study in Europe with this new provisional classification. The aim of our current study was to retrospectively apply the concept of the new classification to JIA patients.

Table 4. Univariate logistic regression analysis on rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (anti-CCP Ab)

Variable	RF		Anti-CCP Ab	
	p-value	Exp(β) (95% CI)	p-value	Exp(β) (95% CI)
Female	0.002	4.514 (1.773~11.495)	0.005	3.332 (1.431~7.757)
Age ($>$6 yr)	0.743	0.879 (0.406~1.903)	0.662	1.183 (0.557~2.512)
Uveitis	0.363	0.501 (0.113~2.216)	0.137	0.215 (0.028~1.634)
Enthesitis	0.998	0.000 (not available)	0.104	0.187 (0.025~1.414)
ANA	0.000	7.366 (3.169~17.123)	0.000	4.327 (1.995~9.385)
HLA-B27	0.018	0.227 (0.066~0.776)	0.238	0.585 (0.240~1.424)
Number of Joints involved ($\geq$5)	0.001	5.885 (1.986~17.440)	0.001	6.464 (2.192~19.059)
Symmetricity	0.020	2.617 (1.166~5.876)	0.051	2.149 (0.997~4.633)

CI: confidence interval, ANA: antinuclear antibody, HLA: human leukocyte antigen.

Table 5. Comparison of ANA-positive patients and ANA-negative patients

Variable	ANA-positive patients	ANA-negative patients	p-value
Patient	35 (36.8)	60 (63.2)	
Male:Female (female, %)	7:28 (80.0)	24:36 (60.0)	0.045
Disease onset, median (IQR) (yr)	4.1 (2.3～8.0)	5.1 (2.8～11.3)	0.104
Uveitis	9 (25.7)	5 (8.3)	0.021
Enthesitis	1 (2.9)	4 (6.7)	0.649
HLA-B27	5 (15.2)	12 (20.0)	0.563
Symmetricity	14 (40.0)	35 (58.3)	0.085
Cumulative number of joints involved, mean±SD	8.9±9.1	7.0±5.9	0.623
Upper large joint	21 (60.0)	31 (51.7)	0.431
Upper small joint	18 (51.4)	20 (33.3)	0.082
Lower large joint	30 (85.7)	55 (91.7)	0.490
Lower small joint	10 (28.6)	13 (21.7)	0.449
Axial joint	11 (31.4)	23 (38.3)	0.498

Except where indicated otherwise, values are the number (%). Comparisons of quantitative data were made by Mann-Whitney U test; comparisons of frequencies were made by chi-square test (or by Fisher's exact test if expected frequencies were <5). ANA: antinuclear antibody, IQR: interquartile range, HLA: human leukocyte antigen, SD: standard deviation.

As shown in Tables 2 and 3, RF-JIA, eoANA-JIA, and ESR-JIA represent significant difference. First, the female predilection is much higher in RF-JIA (77.4%) and eoANA-JIA (77.3%) than in ESR-JIA (11.1%). It is well known that ANA and RF positivity patients shows female predominance, and that ERA patients have male predominance in Western studies [4]. The age of disease onset was the highest in ESR-JIA and lowest in eoANA-JIA. The risk of uveitis was higher in eoANA-J (31.8%) than in other categories, albeit not statistically significantly so. The cumulative number of joints involved also significantly differed between groups in that RF-JIA included much more joints than eoANA-JIA or ESR-JIA. eoANA-JIA included RF-negative polyarthritis patients, and RF-JIA included oligoarticular-onset patients; nevertheless eoANA-JIA had a lower average number of joints involved than RF-JIA.

It is well known that patients with a distinct set of features, including ANA positivity, early-onset of disease, female predilection, asymmetric arthritis, and high risk of uveitis, represent a homogenous disease entity in JIA [8-10]. To group them into a single homogenous category in the new classification, we excluded patients with positive ANA in sJIA, RF-JIA and ESR-JIA in the new provisional classification in recruiting eoANA-JIA, because these categories represent well-defined and separate disease entities. Ravelli et al. [8] also excluded systemic arthritis, RF-positive polyarthritis, and ERA in their study about ANA. In addition, in that ANA positivity and young age were both important in defining the homogenous disease entity[8], and JIA patients with early-onset arthritis (aged ≤6 years) were characterized by genetic features [12,19,21]; we defined eoANA-JIA as occurring at ≤6 years of age in this new classification.

The number of patients (n=22, 8.4%) in the eoANA-JIA was relatively small as shown in Table 2. The fact that the overall positive rate of ANA (74/262, 28.2%) was low in this study may be a contributable factor. This was comparable with the statistics presented in two studies of Korean JIA patients [30,31], wherein ANA was positive in 18% and 33% of total JIA patients. For Caucasian populations, ANA positivity was reportedly 38%～85% in pauci/oligoarthritis, 30%～50% in polyarthritis, and 0%～17% in systemic JIA [22]. Notably, in one multiethnic cohort study, young-onset ANA-positive patients were found significantly more in the European population than in the Asian population [32]. In addition, ANA positivity rate was extremely low in India and Costa Rica (1.1% and 6.3%, respectively) [33,34]. Owing to these differences in ANA positivity, the patient fraction of eoANA-JIA could vary with the countries and ethnic groups being studied.

As shown in Table 2, 65 patients (24.8%) newly classified under "other JIA" comprise of 27 of 39 persistent oligoarthritis, 11 of 16 extended oligoarthritis, and 27 of 37

RF-negative polyarthritis from the ILAR classification. In other words, 70.7% (65/92) of these three ILAR subtypes were recruited to "other JIA," while the remaining 29.3% (27/92) were reclassified into eoANA-JIA and RF-JIA because of the presence of Anti-CCP Ab. Although "other JIA" does not represent a homogenous disease group by definition, it accounts for as many as one fourth of total JIA patients. One of the reasons for this significant proportion of "other JIA" is thought to be relatively low positive rate of ANA than in Western studies as mentioned above. Patients of oligoarthritis and RF-negative polyarthritis without ANA positivity are most likely to be reclassified as "other JIA" in the new provisional classification. That is, lower positive rate of ANA might result in higher proportion of "other JIA." This high proportion of "other JIA" is far from the original intent to specifically classify most types and identify homogenous disease groups; thus there is a need to reform this group in the future. As part of this attempt, we used the ASAS criteria to identify patients who have features of spondyloarthritis among those classified under "other JIA."

Table 2 shows the results of applying the ASAS criteria to JIA patients. A total 107 patients (40.8%) were diagnosed as SpA (axial SpA: 11 patients, peripheral SpA: 96 patients). In "other JIA," a total 14 patients were diagnosed as SpA (axial SpA: 1 patient, peripheral SpA: 13 patients). However, we should be careful when applying the ASAS criteria to JIA patients. In the ASAS criteria, peripheral SpA can be diagnosed if the patients have both arthritis and uveitis. However, uveitis is a common manifestation in early-onset ANA-positive JIA group, which is known not to be relevant with SpA. For example, 10 of 22 patients (45.5%) of eoANA-JIA were diagnosed as SpA by the ASAS criteria (Table 2). They were all peripheral SpA, with eight of them being "arthritis+uveitis" and two being "arthritis+HLA-B27." It is unlikely that all these eoANA-JIA patients are at high risk of SpA in the future. Therefore, it is necessary to modify the ASAS criteria to resolve this controversy before applying it to JIA patients. Thus, Dr. Martini proposed to combine the existing ERA and ASAS criteria in the new provisional classification.

In Table 2, the overall positive rate of HLA-B27 was 32.9% (84/262) which was similar to the multiethnic cohort study on JIA [32]. This significant rate of HLA-B27 positivity in JIA might be due to the considerable inclusion of juvenile SpA patients in some JIA subtypes. Especially, ESR-JIA is intended to categorize juvenile SpA patients, and it is the subtype most associated with HLA-B27 that 57 of 63 ESR-JIA patients (90.5%) are HLA-B27 positive. In "unclassified JIA", HLA-B27 positive rate was as high as 60% (6/10), but those of the other subtypes were relatively low (7.4%～20.0%). "Unclassified JIA" included patients who had features belonging to more than 2 subtypes except for "other JIA," and 6 of 10 "unclassified JIA" patients had the features of ESR-JIA with the positivity of HLA-B27. In addition, peripheral SpA by the ASAS criteria can be diagnosed when patients both have arthritis and HLA-B27. So JIA patients, who already have arthritis by definition, can be diagnosed as peripheral SpA if they are positive for HLA-B27. Thus, when applying the ASAS criteria to JIA patients, it is highly correlated with HLA-B27 positivity.

The presentation of SpA differs in children and adults; most notably, spinal involvement is uncommon and hip arthritis and enthesitis are frequently seen in juvenile SpA [35]. Although most juvenile SpA is classified as ERA by the ILAR classification, the ILAR system does not specifically acknowledge the presence of axial disease in juvenile SpA [35]. In addition, unlike adult SpA classification, psoriatic features comprise a separate category in JIA [35]. Further, it is now known that psoriatic arthritis in the ILAR classification is another heterogeneous category that has two identifiable populations: a) one that belongs to ERA and thus represents a form of undifferentiated SpA and b) another that has the same features as those of early-onset ANA-positive JIA patients [9,12,18]. These differences are making difficult to communicate between pediatric and adult rheumatologists, when JIA patients transit to adult clinic. It is important to understand that all the different forms of adult SpA can be found in children and that there is much higher proportion of undifferentiated SpA in childhood [12]. Currently, these pediatric patients with juvenile SpA or SpA features are sorted into ERA, PsA, or undifferentiated arthritis as per the ILAR classification, or diagnosed as juvenile ankylosing spondylitis (JAS) or juvenile SpA. Thus, by eliminating the concept of the subtype psoriatic arthritis and by reforming the ERA criteria to better recruit SpA patients, we could more reliably classify juvenile SpA in the new provisional classification.

RF-positive polyarthritis in the ILAR classification is considered the same as adult RF-positive RA, and it is the only category wherein anti-CCP Abs are found [4,36]. However, there has been controversy over applying RF to only polyarthritis, and not oligoarthritis in the proposal of the ILAR classification [13,14]. Patients with oli-

goarticular onset and positive RF have been classified under "undifferentiated arthritis" in the ILAR classification. It is now considered that the number of joints involved simply reflects a more rapid spread of arthritis within the same disease and thus may not represent a suitable marker defining a homogeneous JIA subgroup [8,9]. Moreover, imaging techniques, such as ultrasonography, which are useful in detecting subclinical synovitis in JIA make physical examination seem unreliable in assessing the number of joints involved [12,17,37]. In the new classification, therefore, the number of joints is no longer used as a criterion in defining the subtype.

Anti-CCP Ab, together with RF, has higher specificity in diagnosing RA, and is involved in diagnostic criteria of adult RA [23]. RF and anti-CCP are known to precede the RA symptoms and present at the early process of RA [24,38]. In addition, a study reported the development of more severe radiological damage in anti-CCP Ab-positive patients than in anti-CCP Ab-negative patients [39]. In pediatric population, numerous studies have been conducted on the Anti-CCP Ab recently [25,26,36]. Overall, RF is approximately found between 2% and 12% of JIA patients and was 11.1% in this study [22]. Anti-CCP Ab is known to be detected almost exclusively in RF-positive polyarthritis (57%～73%) and only seldom in other subtypes (2%～3%) [22,36].

Although anti-CCP Ab is not yet used as a diagnostic criterion in JIA, there is an ongoing attempt by Dr. Martini to apply it as a criterion for RF-positive JIA. We also recruited anti-CCP Ab-positive patients to RF-JIA in this study. In Table 2, positivity of RF and Anti-CCP Ab are not 100% in RF-JIA because RF-JIA included patients with only RF-positive or Anti-CCP Ab-positive. As shown in Table 4, most of the variables in RF-positive patients and anti-CCP Ab-positive patients show consistent results in univariate logistic regression analysis. These results provide some evidence that these two factors represent the same disease entity—RF-positive JIA—in the new provisional classification.

We did not make any changes in the sJIA classification in this study except for the two patients who were re-categorized to "unclassified arthritis" due to the presence of anti-CCP Ab. sJIA is characterized by prominent systemic features, marked activation of the innate immune system, and important pathogenic roles played by interleukin 1 (IL-1), IL-6, and interferon-γ [12,40]. Adult-onset Still's disease is considered similar to sJIA, but the former is different in terms of arthritis not being an essential diagnostic criterion [12]. Among the pediatric patients, there are cases that cannot be diagnosed as sJIA because arthritis does not develop during the extra-articular manifestation period. Thus, Martini [12] suggested that these patients with systemic features and no arthritis should be included in the sJIA category. However, given the absence of arthritis, Dr. Martini also suggested that the term sJIA should also be revised to a new name, such as Still's disease, owing to analogy with the adult counterpart—adult-onset Still's disease.

We acknowledge the limitations that this is a retrospective study with a relatively small number of patients in a single center. Furthermore, we used a relatively simple classification system that is modified from the proposal of Dr. Martini from 2016 PReS annual meeting.

However, it is meaningful that this is the first study implementing the new JIA classification system that uses laboratory factors such as RF and ANA rather than the number of joints involved or the presence of psoriatic feature as key identifiers. In the new provisional classification, eoANA JIA, RF-JIA, and ESR-JIA showed significantly distinct features such as age of disease onset, male-to-female ratio, risk of uveitis, and cumulative number and type of joints involved. In other words, JIA patients who were previously classified into subtypes with heterogeneous nature were re-categorized into homogenous categories based on the new evidence-based classification. RF-positive patients were comparable to anti-CCP Ab-positive patients, and they could be categorized together. The number of ANA-positive patients was lower (28.2%) than that reported in Western studies (30%～50%), but ANA positivity showed clear difference in terms of lower age of onset and higher risk of uveitis. Ethnic differences such as rate of ANA positivity should be taken into consideration when developing a new classification system for JIA in the future.

CONCLUSION

Previous classification systems for JIA including the ILAR classification do not categorize homogenous disease entities. The number of joints involved and the psoriatic features are no longer valid criteria for dividing subtypes in the new classification and the concepts of oligoarthritis, polyarthritis, and psoriatic arthritis should be excluded. Herein, we reclassified the JIA patients by new provisional classification applying RF and ANA which have been proven to constitute homogenous disease

entities.

The new provisional classification for JIA includes six subtypes; sJIA, RF-JIA, early-onset eoANA-JIA, ESR-JIA, "other JIA," and "unclassified JIA". RF-JIA, eoANA-JIA, and ESR-JIA were well distinguished by female ratio, age of disease onset, HLA-B27, enthesitis, joint symmetricity, and cumulative number and type of joints involved. Criteria for RF-JIA included anti-CCP Ab positivity in this study, which was proven to have almost same features as RF. ANA positivity ratio differed among ethnicities, but the features of ANA positivity seemed to be shared, such as lower age of onset and higher risk of uveitis. A significant proportion (24.8%) of the "other JIA" in this study warrant the need for further reforming the classification in the future. sJIA was not changed from the ILAR classification in this study.

To establish a more precise and globally accepted classification system for JIA, further large-scale, prospective, and multiethnic studies are needed.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Fink CW. Proposal for the development of classification criteria for idiopathic arthritides of childhood. J Rheumatol 1995;22:1566-9.
2. Petty RE, Southwood TR, Baum J, Bhettay E, Glass DN, Manners P, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. J Rheumatol 1998;25:1991-4.
3. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31: 390-2.
4. Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet 2007;369:767-78.
5. Criteria for the classification of juvenile rheumatoid arthritis. Bull Rheum Dis 1972;23:712-9.
6. Brewer EJ Jr, Bass J, Baum J, Cassidy JT, Fink C, Jacobs J, et al. Current proposed revision of JRA Criteria. JRA Criteria subcommittee of the diagnostic and therapeutic criteria committee of the American rheumatism section of the arthritis foundation. Arthritis Rheum 1977;20(2 Suppl):195-9.
7. European League Against Rheumatism. EULAR Bulletin No. 4: Nomenclature and classification of arthritis in children. Basel, National Zeitung AG, 1977.
8. Ravelli A, Varnier GC, Oliveira S, Castell E, Arguedas O, Magnani A, et al. Antinuclear antibody-positive patients should be grouped as a separate category in the classification of juvenile idiopathic arthritis. Arthritis Rheum 2011;63:267-75.
9. Martini A. Are the number of joints involved or the presence of psoriasis still useful tools to identify homogeneous disease entities in juvenile idiopathic arthritis? J Rheumatol 2003;30:1900-3.
10. Ravelli A, Felici E, Magni-Manzoni S, Pistorio A, Novarini C, Bozzola E, et al. Patients with antinuclear antibody- positive juvenile idiopathic arthritis constitute a homogeneous subgroup irrespective of the course of joint disease. Arthritis Rheum 2005;52:826-32.
11. Stoll ML, Zurakowski D, Nigrovic LE, Nichols DP, Sundel RP, Nigrovic PA. Patients with juvenile psoriatic arthritis comprise two distinct populations. Arthritis Rheum 2006;54:3564-72.
12. Martini A. It is time to rethink juvenile idiopathic arthritis classification and nomenclature. Ann Rheum Dis 2012;71: 1437-9.
13. Hofer MF, Mouy R, Prieur AM. Juvenile idiopathic arthritides evaluated prospectively in a single center according to the Durban criteria. J Rheumatol 2001;28:1083-90.
14. Petty RE. Growing pains: the ILAR classification of juvenile idiopathic arthritis. J Rheumatol 2001;28:927-8.
15. Tsitsami E, Bozzola E, Magni-Manzoni S, Viola S, Pistorio A, Ruperto N, et al. Positive family history of psoriasis does not affect the clinical expression and course of juvenile idiopathic arthritis patients with oligoarthritis. Arthritis Rheum 2003;49:488-93.
16. Griffin TA, Barnes MG, Ilowite NT, Olson JC, Sherry DD, Gottlieb BS, et al. Gene expression signatures in polyarticular juvenile idiopathic arthritis demonstrate disease heterogeneity and offer a molecular classification of disease subsets. Arthritis Rheum 2009;60:2113-23.
17. Magni-Manzoni S, Epis O, Ravelli A, Klersy C, Veisconti C, Lanni S, et al. Comparison of clinical versus ultrasound- determined synovitis in juvenile idiopathic arthritis. Arthritis Rheum 2009;61:1497-504.
18. Stoll ML, Lio P, Sundel RP, Nigrovic PA. Comparison of Vancouver and international league of associations for rheumatology classification criteria for juvenile psoriatic arthritis. Arthritis Rheum 2008;59:51-8.
19. Barnes MG, Thompson SD, Griffin TA, Grom AA, Glass DN, Colbert RA. B-cell signature in patients with JIA is associated with age of onset suggesting biologically relevant classification criteria. Arthritis Rheum 2009;60 Suppl 10: 620.
20. Prakken B, Albani S, Martini A. Juvenile idiopathic arthritis. Lancet 2011;377:2138-49.
21. Barnes MG, Grom AA, Thompson SD, Griffin TA, Luyrink LK, Colbert RA, et al. Biologic similarities based on age at onset in oligoarticular and polyarticular subtypes of juvenile idiopathic arthritis. Arthritis Rheum 2010;62:3249-58.
22. Borchers AT, Selmi C, Cheema G, Keen CL, Shoenfeld Y, Gershwin ME. Juvenile idiopathic arthritis. Autoimmun Rev 2006;5:279-98.
23. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/ European League Against Rheumatism collaborative initiative. Arthritis Rheum 2010;62:2569-81.

24. Rantapää-Dahlqvist S, de Jong BA, Berglin E, Hallmans G, Wadell G, Stenlund H, et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. Arthritis Rheum 2003; 48:2741-9.
25. Kang M, Sohn TY, Kim SH, Lee HR, Kang HJ, Kim KN. The clinical significance of anti-cyclic citrullinated peptide antibodies in juvenile rheumatoid arthritis. J Rheum Dis 2014;21:236-40.
26. Omar A, Abo-Elyoun I, Hussein H, Nabih M, Atwa H, Gad S, et al. Anti-cyclic citrullinated peptide (anti-CCP) antibody in juvenile idiopathic arthritis (JIA): correlations with disease activity and severity of joint damage (a multicenter trial). Joint Bone Spine 2013;80:38-43.
27. Ferucci ED, Majka DS, Parrish LA, Moroldo MB, Ryan M, Passo M, et al. Antibodies against cyclic citrullinated peptide are associated with HLA-DR4 in simplex and multiplex polyarticular-onset juvenile rheumatoid arthritis. Arthritis Rheum 2005;52:239-46.
28. Burgos-Vargas R. The assessment of the spondyloarthritis international society concept and criteria for the classification of axial spondyloarthritis and peripheral spondyloarthritis: A critical appraisal for the pediatric rheumatologist. Pediatr Rheumatol Online J 2012;10:14.
29. Helliwell PS, Hetthen J, Sokoll K, Green M, Marchesoni A, Lubrano E, et al. Joint symmetry in early and late rheumatoid and psoriatic arthritis: comparison with a mathematical model. Arthritis Rheum 2000;43:865-71.
30. Shin JI, Kim KH, Chun JK, Lee TJ, Kim KJ, Kim HS, et al. Prevalence and patterns of anti-nuclear antibodies in Korean children with juvenile idiopathic arthritis according to ILAR criteria. Scand J Rheumatol 2008;37:348-51.
31. Lee JH, Ryu JM, Park YS. Clinical observations of juvenile rheumatoid arthritis. Korean J Pediatr 2006;49:424-30.
32. Saurenmann RK, Rose JB, Tyrrell P, Feldman BM, Laxer RM, Schneider R, et al. Epidemiology of juvenile idiopathic arthritis in a multiethnic cohort: ethnicity as a risk factor. Arthritis Rheum 2007;56:1974-84.
33. Arguedas O, Fasth A, Andersson-Gäre B, Porras O. Juvenile chronic arthritis in urban San José, Costa Rica: a 2 year prospective study. J Rheumatol 1998;25:1844-50.
34. Aggarwal A, Misra R. Juvenile chronic arthritis in India: is it different from that seen in Western countries? Rheumatol Int 1994;14:53-6.
35. Colbert RA. Classification of juvenile spondyloarthritis: Enthesitis-related arthritis and beyond. Nat Rev Rheumatol 2010;6:477-85.
36. van Rossum M, van Soesbergen R, de Kort S, ten Cate R, Zwinderman AH, de Jong B, et al. Anti-cyclic citrullinated peptide (anti-CCP) antibodies in children with juvenile idiopathic arthritis. J Rheumatol 2003;30:825-8.
37. Guzmán J, Burgos-Vargas R, Duarte-Salazar C, Gómez-Mora P. Reliability of the articular examination in children with juvenile rheumatoid arthritis: interobserver agreement and sources of disagreement. J Rheumatol 1995;22:2331-6.
38. Nielen MM, van Schaardenburg D, Reesink HW, van de Stadt RJ, van der Horst-Bruinsma IE, de Koning MH, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. Arthritis Rheum 2004;50:380-6.
39. Kroot EJ, de Jong BA, van Leeuwen MA, Swinkels H, van den Hoogen FH, van't Hof M, et al. The prognostic value of anti-cyclic citrullinated peptide antibody in patients with recent-onset rheumatoid arthritis. Arthritis Rheum 2000;43: 1831-5.
40. Bracaglia C, de Graaf K, Pires Marafon D, et al. Elevated circulating levels of interferon-γ and interferon-γ-induced chemokines characterise patients with macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. Ann Rheum Dis 2017;76:166-72.