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Original Article

Performance of recent PRINTO criteria versus current ILAR criteria for systemic juvenile idiopathic arthritis: A single-centre experience

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ABSTRACT

Objectives: The purpose of this study is to evaluate the performances of recently proposed Pediatric Rheumatology International Trials Organization criteria versus current International League of Associations for Rheumatology criteria for systemic juvenile idiopathic arthritis (sJIA).

Methods: The study was performed at the Department of Pediatric Rheumatology in Istanbul Faculty of Medicine with a retrospective design, covering the date range 2010–2021. Patients diagnosed with sJIA, Kawasaki disease and common autoinflammatory diseases were included. Both the International League of Associations for Rheumatology and Pediatric Rheumatology International Trials Organization classification criteria were applied to each patient and cross-checked with expert rheumatologist diagnosis.

Results: Eighty-two patients with sJIA were compared against 189 (*74 Kawasaki disease, 83 familial Mediterranean fever, 16 mevalonate kinase deficiency, 10 cryopyrin-associated periodic syndromes, and 6 tumour necrosis factor receptor-associated periodic syndrome*) patients. The Pediatric Rheumatology International Trials Organization criteria demonstrated higher sensitivity (62.2% vs 80.5%, $P = .003$) but comparable specificity (90.5% vs 91%) as regards the International League of Associations for Rheumatology criteria.

Conclusions: The revised criteria appear to enhance the ability to provide early recognition and pertinent classification of sJIA. No superiority was observed in segregating sJIA from common autoinflammatory diseases and Kawasaki disease, namely in terms of specificity.

KEYWORDS: Classification criteria; ILAR criteria; PRINTO criteria; systemic juvenile idiopathic arthritis

Introduction

Systemic juvenile idiopathic arthritis (sJIA) is the most exceptional subtype of the disease complex known as juvenile idiopathic arthritis (JIA) with its heterogeneous clinical course, the predominance of extraarticular manifestations, and underlying pathophysiological features [1]. Furthermore, sJIA is widely considered as one of the most challenging childhood diseases that requires a rigorous diagnostic approach and a cautious distinction from differential diagnoses such as infections, malignancies, autoimmune, and other systemic diseases [2].

In the pathogenesis, the disease appears to be a syndrome that evokes polygenic autoinflammatory diseases associated with persistent innate immune system activation rather than an autoimmune disease with chronic arthritis in the foreground [3, 4]. On the other hand, the correlation between the subsequent polyarthritis phase and adaptive immune system, as part of the inconsistency of the disease, creates a paradox. sJIA has been referred to as a part of adult-onset Still's disease (AOSD) for many years, on the basis of their close intercourse and commonalities. The first modification in terminology has been made according to the 1977 American College of Rheumatology classification and named *systemic-onset juvenile rheumatoid arthritis* [5]. Eventually, the disease has been defined as *systemic arthritis* and categorized as a subtype of JIA by the International League of Associations for Rheumatology (ILAR) classification criteria [6].

The heterogeneous nature of the disease with unpredictable clinical course and complicated differential diagnosis, nonspecific symptoms, and the lack of serological biomarkers are challenging factors in the diagnostic approach. Variations in the course of fever and arthritis, the presence of which are mandatory in the current criteria, may lead to misclassification in clinical practice. The lack of coherence is worrisome given the complications of the disease, which is associated with high morbidity and mortality. Therefore, accurate diagnosis and convenient treatment approach require a solid prediction drawn from clinical experiences.

The determination of criteria that can guide the diagnostic approach of the disease and ensuring standardization in terms of patient selection in clinical studies and treatment management are agenda concerns [7–9]. Pediatric Rheumatology International Trials Organization (PRINTO) has recently addressed the issue and proposed revision of the current criteria with an evidence-based approach [10]. The newly proposed criteria for sJIA have been inspired by the Yamaguchi criteria, based on conspicuous similarities between sJIA and AOSD [11]. The requirement of arthritis has been removed

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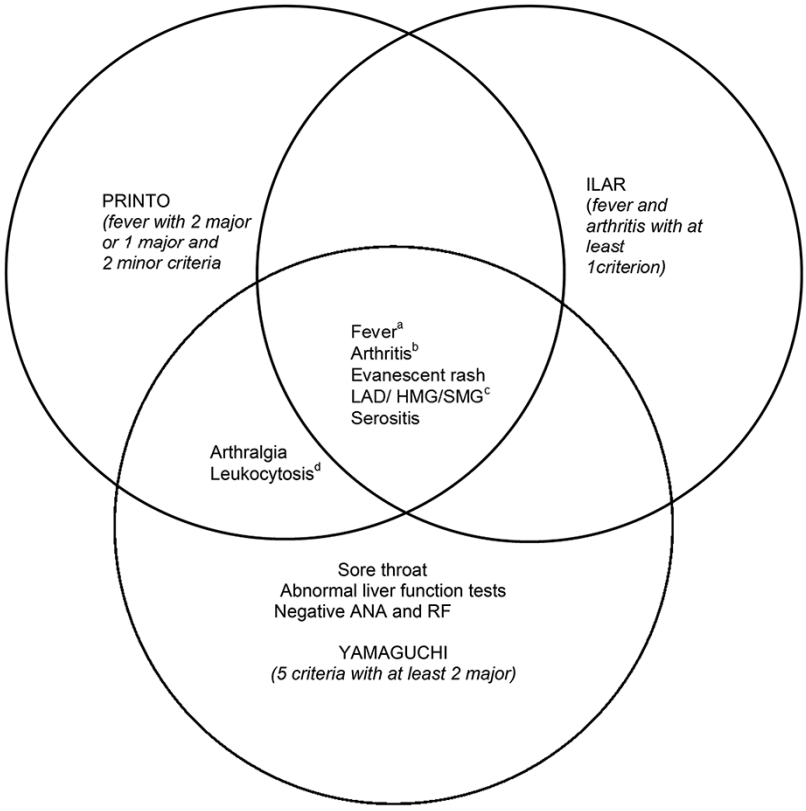


Figure 1. Comparative representation of classification sets proposed for systemic juvenile idiopathic arthritis and AOSD on the Venn diagram.

[a]Duration of fever is at least 2 weeks for PRINTO and ILAR, whereas 1 week for Yamaguchi criteria. [b]Arthritis is a mandatory criterion for ILAR, alternative to arthralgia for PRINTO and Yamaguchi. [c] HMG (hepatomegaly) and SMG (splenomegaly) meet a single criterion, alternative to lymphadenopathy (LAD) in PRINTO. [d]The leukocytosis cut-off value is 10,000/mm^3 in Yamaguchi, 15,000/mm^3 in PRINTO.

from being a mandatory criterion since it may not be a part of the initial picture of the disease and, likewise, as a laboratory criterion, leukocytosis has taken its place among the minor criteria. Figure 1 represents the items and prerequisites for the aforementioned classification criteria.

The primary aim of the study was to evaluate the performance of the classification criteria put forward by PRINTO for sJIA by comparing with the existing ILAR criteria. A secondary aim was to assess the manifestation of arthritis in sJIA, which is a controversial aspect of the disease.

Materials and methods

Patient selection

The study was performed with the patients being followed-up with a diagnosis of sJIA at the Pediatric Rheumatology Department in Istanbul Faculty of Medicine. The sJIA cohort enrolled in the study has been determined as follows: patients who met the ILAR criteria and were evaluated as sJIA by paediatric rheumatologists working in the tertiary centre where the study was conducted, as well as patients who presented with disease features despite not fulfilling the ILAR criteria and were eventually diagnosed as sJIA after being completely eliminated from other possible etiologies with a multidisciplinary approach. The precision of diagnoses has been confirmed by an expert rheumatologist (N.A.A), regardless of the criteria expected to be met for the disease.

According to the current ILAR classification criteria [6], the presence of fever rising to 39°C for at least 2 weeks, a minimum of 6 weeks of arthritis, and accompanying: evanescent erythematous rash, generalized lymphadenopathy, serositis, hepatomegaly, and/or splenomegaly were sought.

PRINTO criteria [10] were performed on the study group and the following items were investigated: quotidian fever; rising to $\geq$39°C once a day and returning to $\leq$37°C between fever peaks for a minimum of 3 consecutive days and reoccurring over a duration of at least 2 weeks and accompanied by two major criteria (evanescent erythematous rash; arthritis) or one major criterion and two minor criteria [generalized lymphadenopathy and/or hepatomegaly and/or splenomegaly; serositis; arthralgia lasting at least 2 weeks (in the absence of arthritis); and leukocytosis ($\geq$15,000/mm^3) with neutrophilia].

Kawasaki disease and common autoinflammatory diseases which are among the other cardinal rheumatic causes of fever, a mandatory criterion of both ILAR and PRINTO, were selected as the comparison group. In the definition of the patients, American Heart Association guidelines [12] have been used for Kawasaki disease while genotype, clinical manifestations, and expert opinion were used for the autoinflammatory diseases in the light of recommended classification criteria [13, 14]. Special attention has been given to include patients who were diagnosed after excluding all existing causes and who did not have any signs that would raise

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diagnostic suspicion during the follow-up and treatment process. Since the diagnoses mentioned above may demonstrate a wide age distribution, patients between the ages of 0–18 years were included in the study.

Data collection

Medical records covering the date range 1 January 2010–1 January 2021, were retrospectively reviewed. Inclusion and exclusion criteria were set to establish standardization. Patients who have been diagnosed at our centre and followed-up regularly were selected. The patients with insufficient medical data or without regular follow-up were excluded. Each participant and his/her legal representative have approved the use of their information and informed consent was obtained from the legally authorized representatives of our patients prior to their inclusion in the study. Approval was obtained from the Ethics Committee of İstanbul Faculty of Medicine (approval: 31.03.2021-149061) for the study.

The details of clinical and laboratory characteristics were recorded by using a standardized form for all subjects. Demographic (age and gender) and disease-related data (age at diagnosis, duration of symptoms before the diagnosis, disease duration from the diagnosis to the time of the study, disease pattern, detailed history of symptoms, and current medication) were assessed. It was verified whether the physical signs within the criteria have been accurately and consistently documented at the time of the diagnosis. Baseline laboratory data, including leukocyte count, neutrophil percentage, platelet count, C-reactive protein, erythrocyte sedimentation rate, ferritin, and serum amyloid A, was investigated both from their own records and from the hospital database. The patients with missing or insufficient data were excluded from the study. The two criteria, ILAR and PRINTO, were applied to each patient according to the obtained diagnostic data.

Statistical analysis

Statistical analyses were performed by using IBM SPSS Statistics for Windows 21.0 software (IBM) and Microsoft Excel. The visual (histograms and probability plots) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk's test) were performed to analyze the distribution of the variables. The demographic and clinical data were evaluated using descriptive analysis, and the data are presented as percentage (%) and median with minimum and maximum values. In the comparison of the study groups, one-way ANOVA for variables with normal distribution and Kruskal–Wallis test for variables without normal distribution were performed.

The analysis of binary classification tests was used to verify the performances of the criteria. The specificity, sensitivity, overall accuracy, positive and negative predictive values, and positive likelihood ratio were figured. McNemar's test was used to compare the performance of each of the sets of criteria. Statistical significance was defined as $P < .05$.

Results

Sample description

Nine patients were excluded from the study because of missing or insufficient data, while 82 patients with a diagnosis of sJIA fulfilled the inclusion criteria. Table 1 details the demographic and clinical characteristics of the patients in the sJIA cohort.

Table 1. Demographic and clinical manifestations of the systemic juvenile idiopathic arthritis cohort.

Characteristics Med (min–max)/*n* (%)	sJIA ($n = 82$)
Demographic data	
Gender	
Female	42 (51.2)
Male	40 (48.8)
Age at the study (mo)	172 (29–229)
Medical history	
Comorbidity	13 (15.9)
Respiratory diseases[a]	4 (4.9)
Epilepsy	3 (3.7)
Urinary system disorders[b]	3 (3.7)
Congenital heart disease	2 (2.4)
Biliary tract disease	1 (1.2)
Concomitant drug	10 (12.2)
Antihistamine or bronchodilator	4 (4.9)
Anti-epileptic drug	3 (3.7)
ACE inhibitor	3 (3.7)
Family history of rheumatic diseases	13 (15.9)
Initial symptoms and signs	
Interval between the first symptom and diagnosis (days)	20 (5–180)
Age at diagnosis (mo)	73.5 (6–180)
Quotidian fever	82 (100)
Evanescent erythematous rash	56 (68.3)
Arthralgia (≥2 weeks)	78 (95.1)
Arthritis at diagnosis	63 (76.8)
Persistent arthritis (>6 mo)	42 (51.2)
The manifestation of arthritis (days)	8 (1–180)
Type of arthritis	
Monoarthritis	14 (17.1)
Oligoarthritis	28 (34.1)
Polyarthritis	28 (34.1)
Major joint involvement	67 (81.7)
Minor joint involvement	16 (19.5)
Axial involvement	18 (22)
Sacroiliitis	4 (4.9)
Generalized lymphadenopathy	24 (29.3)
Hepatomegaly and/or splenomegaly	32 (39)
Serositis	23 (28)
Baseline laboratory data	
WBC ($\times 10^9$/L)	17.6 (3.4–29.1)
Neutrophils (%)	81 (40–90)
Platelet Count ($\times 10^9$/L)	479.5 (110–962)
CRP (mg/L)	130.5 (28–388)
ESR (mm/h)	76.5 (12–140)
Ferritin (μg/L)	1232 (118–67,873)
Clinical progress	
Disease duration (mo)	65.5 (6–190)
Disease course	
Monophasic	25 (30.5)
Polycyclic	22 (26.8)
Persistent	35 (42.7)
MAS	32 (39)
Recurrent MAS	11 (13.4)
Additional organ involvement	11 (13.4)
CNS	6 (7.3)
Liver	2 (2.4)
Coronary	2 (2.4)
Kidney	1 (1.2)
Intensive care unit follow-up	20 (24.4)
Mortality rate	1 (1.2)
Medication history [type, duration (mo)]	
High dose corticosteroid therapy	78 (95.1)
Methotrexate	54 (65.9), 17.5 (4–180)
Leflunomide	2 (2.4), 16 (12–20)

(continued)

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Table 1. (Continued)

Characteristics Med (min–max)/*n* (%)	sJIA (*n* = 82)
Cyclosporine	32 (39), 3 (1–30)
Anakinra	37 (45.1), 4 (1–19)
Canakinumab	18 (22), 14.5 (3–56)
Tocilizumab	30 (36.6), 20 (1–70)
Etanercept	11 (13.4), 12 (3–36)
Adalimumab	3 (3.7), 6 (6–36)
Abatacept	1 (1.2), 11 (2–20)
Current treatment	
Methotrexate	4 (4.9)
Canakinumab	10 (12.2)
Tocilizumab	19 (23.2)
Etanercept	3 (3.7)
Abatacept	2 (2.4)
Oral corticosteroid	2 (2.4)
Medication-free	44 (53.7)

[a]Asthma, chronic sinusitis, allergic rhinitis.
[b]Nocturnal enuresis, nephrolithiasis, renal tubular ectasia.
ACE inhibitor: angiotensin-converting enzyme inhibitor; WBC: white blood cell; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; CNS: central nervous system.

Seventy-four patients with Kawasaki disease and 115 patients with common autoinflammatory diseases were included as a comparison group. Among the entire control group, 50.3% were female. The median age at diagnosis and at the study were 44 (3–195) and 105 (24–253) months, respectively. The median disease duration was 62 (5–174) months. The current age, age at diagnosis, and disease duration revealed a significant difference among the subgroups ($P < .001$), yet there was no difference in terms of gender distribution ($P = .074$).

The distribution of Kawasaki disease according to their clinical presentations was as follows: classic ($n = 46$, 62.2%) atypical or incomplete ($n = 28$, 37.8%). Intravenous immunoglobulin resistance was in 16.2% of cases. Fifty-two (70.2%) patients had coronary abnormalities with a dispersion of increased echogenicity ($n = 14$, 18.9%), coronary dilatation ($n = 30$, 40.5%), and aneurysm ($n = 8$, 10.8%), whereas the frequency of coronary involvement in the sJIA cohort was 2.4%.

The patients with autoinflammatory diseases demonstrated a distribution as familial Mediterranean fever (FMF) ($n = 83$, 72.2%), mevalonate kinase deficiency ($n = 16$, 13.9%), cryopyrin-associated periodic syndrome ($n = 10$, 8.7%), and tumour necrosis factor receptor-associated periodic fever syndrome ($n = 6$, 5.2%). Table 2 presents initial manifestations of the patients in the control groups.

Comparison of the ILAR and PRINTO criteria performances

Among the study groups, a comparison of each criterion displayed $P < .001$. The study groups differed from each other in terms of meeting the ILAR and PRINTO criteria ($P < .001$). The evaluation of the study groups according to the classification criteria is given in Table 3. When the performances of both criteria were compared for sJIA, a significant difference was observed ($P = .003$). Table 4 illustrates the binary measurements assessing the performances of the criteria.

Discussion

Challenging factors at the diagnostic stage of sJIA and the close link between the disease and macrophage activation syndrome (MAS) require explicit criteria to guide the comprehension and interpretation of the disease. In this article, we assessed and compared the performances of existing ILAR criteria and the recently proposed PRINTO criteria in our patients diagnosed with sJIA.

When the ILAR and PRINTO criteria were appraised in the patients diagnosed with sJIA, there was no remarkable difference in terms of the specificity of the criteria, while the sensitivity was different from each other. This result has further strengthened our conviction that new criteria are more sensitive than the existing criteria. In the comparative evaluation, the common mandatory finding of fever in both criteria is conspicuous. PRINTO has focused on the differential diagnosis of fever, and the definition has been improved by incorporating the word *reoccurring* [10]. Since it is sometimes hard to discriminate sJIA from the other rheumatic and non-rheumatic causes of fever of unknown origin, the emphasis seems substantial. All patients in our sJIA cohort had documented fever for 3 consecutive days, returning to $\leq 37°C$ throughout the day, but on an ongoing basis. However, without waiting for these patients to complete the 2-week febrile period as set out in the criteria, the diagnostic and therapeutic approaches have been launched after all other possible causes were ruled out.

Arthritis is a critical finding in sJIA. Considering that arthritis can emerge at any time over the course of the disease, stipulating the relevant item in the early stage of the process is one of the most challenging points for clinicians in practice [8, 9, 15]. In our cohort of sJIA, 23.2% of the patients have had no arthritis at initial presentation, demonstrating a slightly higher rate compared to the literature [8, 16]. One of the most striking revisions in the recently defined criteria is the displacement of arthritis to the major criteria and the inclusion of prolonged arthralgia as an alternative to minor criteria [10], congruently with Yamaguchi criteria for AOSD diagnosis [11]. To better observe the difference, we evaluated the manifestation of arthritis in our patients with sJIA and determined the range 1–180 days. On the other hand, arthralgia was frequently present in the initial picture of the disease and accompanied fever (95.1%). The disparity in the development of articular complaints seems to be the leading factor in revealing the difference between the sensitivity of the two criteria. Therefore, the newly defined criteria appear to be more capable of ensuring early recognition and pertinent classification of the disease. The likelihood ratio and higher overall accuracy of the PRINTO criteria support this superiority. However, the last-mentioned measurements may create bias as they may be influenced by prevalence.

The diagnostic viewpoint of sJIA often requires meticulous clinical experience with a multidisciplinary approach. The pathogenetic and clinical features have positioned sJIA as the intersection cluster of autoimmune and autoinflammatory diseases. Fever, rash, musculoskeletal symptoms, serositis, and increased acute-phase reactants in the clinical framework of sJIA are reminiscent of the episodes of autoinflammatory disorders. According to the analysis of our dataset, the FMF cohort composing the majority of autoinflammatory diseases seems to have a negative influence on the specificity of the ILAR criteria. The crux of this difference is arthritis. The

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Table 2. Initial manifestations of the patients with Kawasaki disease and autoinflammatory diseases in the control group.

Characteristics Med (min–max)/*n* (%)	Kawasaki ($n=74$)	FMF ($n=83$)	MKD ($n=16$)	CAPS ($n=10$)	TRAPS ($n=6$)
Gender					
Female	29 (39.2)	50 (60.2)	9 (56.3)	6 (60)	1 (16.7)
Male	45 (60.8)	33 (39.8)	7 (43.8)	4 (40)	5 (83.3)
Age at the study (mo)	66 (24–178)	154 (44–253)	96 (34–180)	150 (54–216)	94 (50–160)
Age at diagnosis (mo)	15 (3–84)	67 (21–195)	41.5 (6–120)	84 (3–180)	54 (36–132)
Quotidian fever	74 (100)	49 (59)	16 (100)	7 (70)	6 (100)
Evanescent rash	50 (67.6)	6 (7.2)	3 (18.8)	8 (80)	2 (33.3)
Mucosal involvement[a]	67 (90.5)	7 (8.4)	5 (31.3)	3 (30)	3 (50)
Arthralgia ($\geq$2 weeks)	1 (1.4)	39 (47)	9 (56.3)	8 (80)	4 (66.7)
Arthritis	6 (8.1)	16 (19.3)	2 (12.5)	4 (40)	2 (33.3)
Generalized LAD	16 (21.6)	–	3 (18.8)	1 (10)	–
Organomegaly	2 (2.7)	–	1 (6.3)	–	–
Serositis	8 (10.8)	74 (89.2)	–	1 (10)	–
Neurological manifestations	–	–	3 (18.8)	2 (20)	2 (33.3)
WBC ($\times10^9$/L)	15.4 (6.7–33)	8 (3.4–29.6)	11 (5.9–18)	12.4 (6.8–24)	11 (10.2–14)
Leukocytosis ($\geq$15,000/mm^3)	40 (54.1)	14 (16.9)	3 (18.8)	4 (40)	–
Neutrophils	56.6 (14–88)	56 (27–90)	51.5 (20–80)	57.5 (44–80)	53.5 (25–56)
Platelet count ($\times10^9$/L)	583 (213–1200)	308 (148–667)	298 (108–392)	312 (272–519)	354 (208–402)
CRP (mg/L)	66 (2–360)	7 (0.1–265)	72 (1–222)	14.5 (1–299)	23 (5–61)
ESR (mm/h)	71 (9–127)	12 (1–110)	31 (5–100)	15 (2–140)	37 (18–48)
SAA (mg/L)	–	5.3 (0–1200)	8.5 (0–233)	23.5 (1–349)	1 (0–4)
Ferritin (μg/L)	186 (96–1130)	–	–	–	–
Disease duration (mo)	50 (5–100)	75 (13–171)	81 (31–174)	80 (47–170)	66 (30–98)
Recurrence	3 (4.1)	83 (100)	16 (100)	10 (100)	6 (100)

[a]Conjunctivitis or oral mucosa involvement. LAD: lymphadenopathy; WBC: white blood cell; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; SAA: serum amyloid A; MKD: mevalonate kinase deficiency; CAPS: cryopyrin associated periodic syndromes; TRAPS: tumor necrosis factor receptor-associated periodic fever syndrome.

Table 3. Distribution of the study groups based on the fulfillment of the criteria.

Fulfillment Status n (%)	sJIA ($n=82$)	Kawasaki ($n=74$)	FMF ($n=83$)	MKD ($n=16$)	CAPS ($n=10$)	TRAPS ($n=6$)	All Controls ($n=189$)
PRINTO	66 (80.5)	11 (14.9)	1 (1.2)	2 (12.5)	4 (40)	–	18 (9.5)
ILAR	51 (62.2)	6 (8.1)	7 (8.4)	1 (6.3)	3 (30)	–	17 (9)

MKD: mevalonate kinase deficiency; CAPS: cryopyrin associated periodic syndromes; TRAPS: tumor necrosis factor receptor-associated periodic fever syndrome.

Table 4. Comparative evaluation of the performances of proposed criteria for systemic juvenile idiopathic arthritis.

Criteria for sJIA	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR+	OA (%)
PRINTO	80.5	90.5	78.5	91.4	8.3	87.4
ILAR	62.2	91	75	84.7	6.8	82

PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; OA: overall accuracy.

required item of the ILAR criteria can accompany the presentation or attacks of FMF. Serositis is another communal finding that manifests mostly as peritonitis and rarely as pleuritis or pericarditis in FMF. However, the cutaneous manifestation in FMF is quite distinct from that of other monogenic autoinflammatory diseases and sJIA in terms of morphology and location [17]. Hence, most of the patients in FMF cohort failed to meet that criterion. Although the rash appears non-specific in sJIA, emphasizing the *evanescent* feature as in the PRINTO criteria and recognizing the relationship with fever provide more selectivity, particularly in differentiating from the autoinflammatory diseases. Highlighting the distinguishing characteristics of each item in the criteria may provide an indication in routine clinical practice.

Kawasaki disease and sJIA are presumably the two most puzzling diseases of paediatric rheumatology due to their similar systemic manifestations [18–21]. Moreover, as in our patients, coronary involvement may appear in sJIA, or arthritis may be one of the presenting features of Kawasaki disease [19, 22]. It has been noted that 0.2% of patients diagnosed with Kawasaki disease, particularly non-classical type, were later diagnosed with sJIA [18]. Fever, the *sine qua non* for Kawasaki disease, was the most met classification criterion by our cohort. The sustained course of fever is essential to realize but does not always provide convenience for distinction from sJIA in clinical practice. Likewise, the rash expected in the course of Kawasaki disease is far from being determinant as it is non-specific. In this respect, the patients with Kawasaki disease in our cohort fulfilled the fever criterion, and in more than half, the sJIA-like rash was noted. The mucosal involvement, on the other hand, that has been observed in 90.5% of the patients may aid in the process of achieving an accurate diagnosis.

The extent and location of lymphadenopathy give an insight into the differential diagnosis. Twenty-four (29.3%) patients in the sJIA cohort met this criterion, with a ratio parallel to the literature [16, 23]. Although in Kawasaki disease, it is expected to be localized in the cervical region [12], 21.6% of our cohort had lymph node enlargement in two or

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more regions, meeting the criterion. We must not lose sight of the fact that this sign requires first and foremost exclusion of malignancy.

Leukocytosis, which was not included previously but inspired by the Yamaguchi criteria with a higher cut-off value in the newly defined criteria, is a non-specific finding expected in systemic inflammation-related diseases. However, it may differentiate the disease, particularly from non-rheumatic causes. Recent studies focus on serum IL-18 and interferon-γ in reflecting disease activity, evaluating remission, and anticipating MAS [24, 25]. Besides the favourable developments, there is a need for practical and convenient laboratory tests that will guide the diagnosis and monitorization of the disease.

A limited number of studies exist in the literature that assesses different classification criteria for sJIA. In a study by Kumar *et al.*, the ILAR and Yamaguchi criteria have been compared retrospectively in a small sample size of patients with sJIA [26]. They have concluded that the Yamaguchi criteria were met by a greater number of patients (74% vs 58%) and emphasized the need to revise the ILAR criteria. On the contrary, in a study where the ILAR criteria have been applied to the patients diagnosed with AOSD, it has been concluded that the ILAR criteria can be convenient for determining high risk for relapse, MAS, or intensive care needs [27].

The interval between the disease onset and diagnosis may indirectly influence the sensitivity of the criteria. MAS may appear in the initial picture of the disease, causing diagnostic perplexity with clinical and laboratory alterations [9, 28]. Thus, the heterogeneous nature of the disease and individual disparity should not be neglected.

This study appears to be the first study to compare the performances of existing and newly proposed criteria of sJIA comprehensively. The strengths of the study are an in-depth analysis of the overlapping points in differential diagnosis and the diversity of our comparison group. The insights gained from the study may be of assistance to the comprehension of the challenges in the recognition of the disease. On the other hand, the fact that the study was conducted in a single centre with limited sample size and heterogeneous numerical distribution of the comparison group were the limiting factors. Since the pathogenic variants can display a variable expressivity and the diagnostic performance of the genetic tests is not fully comprehensive in autoinflammatory diseases and, on the other hand, while Kawasaki disease, particularly the incomplete form, can be identified by clinical exclusion without a specific diagnostic test, the compliance with the existing criteria has been necessitated in setting the cohort. Although the retrospective design of the study raises questions, the fact that the data of included patients were recorded with a common systematic approach in the same centre improves the quality of our diagnostic data.

In conclusion, the manifestation of arthritis, as one of the heterogeneous aspects of sJIA may vary individually during the disease process. Therefore, the modification of the criterion relevant to arthritis and introducing prolonged arthralgia as an alternative may prevent sJIA from being unnoticed. Furthermore, a literal and comprehensive description of fever and rash would be worthwhile in distinguishing sJIA, particularly from autoinflammatory diseases. In the discrimination of Kawasaki disease from sJIA, features such as the rare presence of arthritis, the predominance of mucosal and coronary involvement, and a better definition of the overlapping manifestations in the criteria may be determinant. Multinational studies with a larger number of patients are needed to evaluate the validity and reliability of the proposed criteria for the definition and classification of sJIA.

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Conflict of interest

None declared.

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Data availability

Author O.K., Author F.G.D., Author F.C., and Author N.A.A. declare the transparency of the data. The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical standards

Approval was obtained for the study from the Ethics Committee of Istanbul University, İstanbul Faculty of Medicine (approval: 31.03.2021-149061). Each participant and his/her legal representative have approved the use of their information, and informed consent was obtained from the legally authorized representatives of our patients prior to their inclusion in the study. Details that might disclose the identity of the subjects under study have been omitted. All procedures performed in the study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and subsequent amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Originality and plagiarism

This manuscript describes the original work. There is no plagiarism in the study. When referring to someone else's work, it has been duly stated.

Authors' contributions

All the authors contributed to the study conception and design. Oya Koker, Fatma Gul Demirkan, Figen Cakmak, and Nuray Aktay Ayaz were responsible for the acquisition of data, analysis, and interpretation of data. Oya Koker and Nuray Aktay Ayaz participated in drafting the work and all authors contributed to the criticism of the manuscript. All authors read the manuscript and approved the submission. All authors of the study agreed to be accountable for all aspects

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of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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