Arthritis Care & Research
Vol. 0, No. 0, Month 2024, pp 1–10
DOI 10.1002/acr.25296

American College of Rheumatology
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Overlap of International League of Associations for Rheumatology and Preliminary Pediatric Rheumatology International Trials Organization Classification Criteria for Nonsystemic Juvenile Idiopathic Arthritis in an Established UK Multicentre Inception Cohort

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Objective. The goal was to assess the degree of overlap between existing International League of Associations for Rheumatology (ILAR) and preliminary Paediatric Rheumatology International Trials Organisation (PRINTO) classification criteria for juvenile idiopathic arthritis (JIA).

Methods. Participants from the Childhood Arthritis Prospective Study, a multicenter UK JIA inception cohort, were classified using the PRINTO and ILAR classification criteria into distinct categories. Systemic JIA was excluded because several classification items were not collected in this cohort. Adaptations to PRINTO criteria were required to apply to a UK health care setting, including limiting the number of blood biomarker tests required. The overlap between categories under the two systems was determined, and any differences in characteristics between groups were described.

Results. A total of 1,223 children and young people with a physician's diagnosis of JIA were included. Using PRINTO criteria, the majority of the patients had "other JIA" (69.5%). There was a high degree of overlap (91%) between the PRINTO enthesitis/spondylitis- and ILAR enthesitis-related JIA categories. The PRINTO rheumatoid factor (RF)–positive category was composed of 48% ILAR RF-positive polyarthritis and 52% undifferentiated JIA. The early-onset antinuclear antibodies–positive PRINTO category was largely composed of ILAR oligoarthritis (50%), RF-negative polyarthritis (24%), and undifferentiated JIA (23%). A few patients were unclassified under PRINTO (n = 3) and would previously have been classified as enthesitis-related JIA (n = 1) and undifferentiated JIA (n = 2) under ILAR.

Conclusion. Under the preliminary PRINTO classification criteria for childhood arthritis, most children are not yet classified into a named category. These data can help support further delineation of the PRINTO criteria to ensure homogenous groups of children can be identified.

The views expressed herein are those of the authors and do not necessarily represent those of the NHS, the National Institute of Health Research (NIHR), or the Department of Health.

Supported by Versus Arthritis (UK grant 20542). Dr Shoop-Worrall's work was supported by the Medical Research Council (grant MR/W027151/1). Drs Ciurtin and Wedderburn's work was supported by the Centre for Adolescent Rheumatology Versus Arthritis at University College London, University College London Hospital, and Great Ormond Street Hospital (GOSH) (UK grant 20164, 21593). Dr Wedderburn's work was supported by the NIHR Biomedical Research Centre at GOSH and for the Childhood arthritis and its associated Uveitis: Stratification through Endotypes and mechanism to deliver benefit consortium, by the Medical Research Council (grant MR/R013926/1), Versus Arthritis (UK grant 22084), Great Ormond Street Hospital Children's Charity (grant VS0518) and Olivia's Vision. Dr Hyrich's work was supported by Versus Arthritis Centre for Epidemiology (UK grant 21755) and by the NIHR Manchester Biomedical Research Centre. This report includes independent research funded by the NIHR Biomedical Research Centre Funding Scheme.

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Author disclosures are available at https://onlinelibrary.wiley.com/doi/10.1002/acr.25296.

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Submitted for publication September 21, 2023; accepted in revised form January 9, 2024.

SIGNIFICANCE & INNOVATIONS

- A direct comparison of International League of Associations for Rheumatology and new provisional Pediatric Rheumatology International Trials Organization (PRINTO) classification criteria for juvenile idiopathic arthritis (JIA) was performed.
- More than two-thirds of children were classified as "Other JIA" under PRINTO.
- New early-onset antinuclear antibodies–positive JIA category represented almost 20% of children with JIA.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a group of chronic inflammatory childhood-onset diseases.[1] These conditions are heterogeneous; therefore, to facilitate research, in 1995 the International League of Associations for Rheumatology (ILAR) classification criteria were proposed in order to group patients with the disease into distinct categories[2] based on predominant clinical and laboratory features. These criteria aimed to ensure homogenous groups of children are enrolled in research, including drug trials, to help better understand disease pathogenesis and outcomes and to facilitate comparability across research studies while also being of value in everyday clinical settings.[2,3]

The ILAR categories, which have become standard in JIA research, were largely derived using expert opinion to represent the most common presentations of disease; however, as treatments advance and our understanding of the disease continues, new preliminary criteria, under the auspices of the Paediatric Rheumatology International Trials Organisations (PRINTO) have been proposed.[4]

Unlike ILAR criteria, the PRINTO criteria aim to both capture childhood counterparts of adult diseases, alongside distinguishing forms of arthritis unique to children. In addition, it has been suggested that several of the existing ILAR categories do not adequately describe homogenous subgroups of disease.[4,5] In particular, the clinical, genetic, and demographic overlap between children with ILAR rheumatoid factor (RF)–negative polyarthritis and ILAR oligoarthritis is suggestive of different levels of severity within the same disease subtype.[6,7] Conversely, there is increasing evidence for distinct subgroups within existing categories, with three different gene expression signatures identified in ILAR RF-negative polyarthritis,[8,9] and two distinct phenotypic subgroups of ILAR psoriatic arthritis (PsA) reported.[9–12] Lastly, certain features of JIA, such as the presence of antinuclear antibodies (ANA), are not currently included in the ILAR criteria but may be relevant in predicting outcomes, such as uveitis,[13] and influencing treatment decisions.[4,9,10,14] The preliminary PRINTO criteria aim to address these limitations in their reclassification of JIA.[4]

The existing ILAR criteria have been in use for almost 25 years, with many clinical trials and observational research studies embedded within this classification system. Therefore, as new criteria are proposed, it is critical to understand how these criteria map to existing criteria such that existing evidence can be interpreted and applied going forward. Previous studies have compared PRINTO and ILAR criteria for individual subsets of JIA[15,16] and across all categories in a Canadian inception cohort.[17] Understanding how these new criteria perform in different populations with different health care systems may also provide further insight into applicability and feasibility of these proposed classification criteria internationally, as well as increasing delineation of the currently proposed other or unclassified categories. Therefore, this analysis, using data from a large UK JIA inception cohort, aims to apply (retrospectively) both the ILAR and preliminary PRINTO criteria to all participants with JIA to understand the distribution of the PRINTO categories, to understand overlap between the two sets of criteria, and to better characterize children classified as other or unclassified JIA.

METHODS

Study population. Children with a physician's diagnosis of JIA were selected from those recruited to the Childhood Arthritis Prospective Study (CAPS; for a list of principal investigators, see Appendix A), a UK multicenter prospective inception cohort of childhood-onset inflammatory arthritis. The methods of this study have been published elsewhere.[18] For the current study, children were included if they had been recruited to CAPS between 2001 and 2016. All participants were <16 years old at symptom onset as per the current ILAR criteria. Although CAPS recruited further children after 2016, certain variables that were relevant to classification, such as family history, were only collected before this time point.

Data collection in CAPS. Data for CAPS were extracted from the clinical case notes by pediatric rheumatologists and study nurses. Participants are followed annually from first pediatric rheumatology appointment for a total of 10 years or until discharge (either in remission back to primary care or transition to adult rheumatology), whichever comes first. For those recruited up to 2010, an additional data extraction point at six months also occurred. In brief, at each time point, data collected included demographics; family history of related diseases; JIA disease features, including disease duration at first presentation to pediatric rheumatology, active and limited joint count, locations of involved joints, extra-articular manifestations such as serositis, nail pitting, and uveitis (all binary yes/no); and treatment.[18–20] The results of laboratory tests, if they were performed as part of pediatric rheumatology care, were also extracted at each study follow-up time point and included ANA, RF and HLA-B27 (positive or negative).[20]

Application of classification criteria to CAPS data. All included children were classified according to both the 2019

preliminary PRINTO[4] and the 2001 second revision ILAR criteria[21] into distinct categories. Each child was assigned to a single category in each system according to operationalization rules in Tables 1 and 2. Operationalization was automated through statistical programming once the rules were set. Adaptations to PRINTO classification criteria were made a priori through examination of classification requirements and data dictionaries by the study team. Given the follow-up schedule of the cohort and the nature of blood biomarker testing under the NHS, secondary a priori analyses assessed how many RF and ANA tests were actually taken within a time frame that could be used within PRINTO classification criteria. Data from baseline (first pediatric rheumatology visit), six months (where available), and one year were used for this analysis because all the initial baseline tests, including relevant blood tests, are usually completed within one year of follow-up.

Table 1. PRINTO classification criteria*

PRINTO classification	Criteria	Operationalization of the criteria using CAPS data (within the first year from initial presentation to rheumatology)
A. sJIA	Fever of unknown origin (excluding infectious, neoplastic, autoimmune, or monogenic autoinflammatory diseases) that is documented to be daily (quotidian; fever that rises to ≥39°C once a day and returns to ≤37°C between fever peaks) for at least 3 consecutive days and reoccurring over a duration of at least 2 weeks and accompanied by 2 major criteria OR 1 major criterion and 2 minor criteria. Major criteria are (1) evanescent (nonfixed) erythematous rash; and (2) arthritis. Minor criteria are (1) generalized lymph node enlargement and/or hepatomegaly and/or splenomegaly; (2) serositis; (3) arthralgia lasting 2 weeks or longer (in the absence of arthritis); and (4) leucocytosis (≥15,000/mm^3) with neutrophilia.	Physician's classification was sJIA.
B. RF-positive JIA	Arthritis for ≥6 weeks (number of active joints not specified) Association with 2 positive tests for RF at least 3 months apart or at least 1 positive test for anti-CCP	Active joint count ≥1 at initial presentation At least one positive test for RF recorded in CAPS database
C. Enthesitis/ spondylitis-related arthritis	Peripheral arthritis and enthesitis or arthritis or enthesitis plus ≥3 months of inflammatory back pain and sacroiliitis on imaging or arthritis or enthesitis plus 2 of the following: 1. sacroiliac joint tenderness or 2. inflammatory back pain 3. presence of HLA-B27 antigen 4. acute (symptomatic) anterior uveitis 5. history of an SpA in a first-degree relative	Active joint count ≥1 and enthesitis Active joint count ≥1 or enthesitis Sacroiliac tenderness and/or inflammatory spinal pain AND radiological sacroiliitis Active joint count ≥1 or enthesitis, plus 2 or more of the following: 1. Sacroiliac tenderness and/or inflammatory spinal pain 2. Presence of HLA-B27 antigen 3. Presence of anterior uveitis (acute or chronic) 4. Family history of ankylosing spondylitis in a first-degree relative
D. Early-onset ANA-positive JIA	Arthritis for ≥6 weeks (number of active joints not specified) Early-onset (≤6 y) Presence of 2 positive ANA tests with a titer ≥1/160 (tested by immunofluorescence) at least 3 months apart Exclusions are systemic JIA, RF-positive arthritis, and enthesitis/ spondylitis-related JIA	Active joint count ≥1 Coded as early-onset if the time between date of birth and date of symptom onset is ≤6 y One positive test for ANA. When data on titer level was available, tests were counted as positive if titer ≥1/160. When this information was missing, tests were considered positive if the test result was coded as positive[a] Participants fits criteria for RF-positive arthritis or enthesitis/spondylitis-related JIA or had been classified as having systemic arthritis by a physician.
E. Other JIA	Arthritis for ≥6 weeks (number of active joints not specified) Does not fit criteria for disorders A–D	Active joint count ≥1 Not already classified into other PRINTO categories
F. Unclassified JIA	Arthritis for ≥6 weeks (number of active joints not specified) Fits >1 disorder A–D	Active joint count ≥1 Classified into more than one PRINTO category. (children who fit this criterion will be removed from other categories and classified as Unclassified JIA)

* ANA, antinuclear antibodies; anti-CCP, anti–cyclic citrullinated peptide; CAPS, Childhood Arthritis Prospective Study; JIA, juvenile idiopathic arthritis; PRINTO, Paediatric Rheumatology International Trials Organisation; RF, rheumatoid factor; sJIA, systemic juvenile idiopathic arthritis; SpA, spondyloarthritis.
[a] Not all NHS labs provide ANA titer as part of routine testing.

Table 2. ILAR classification criteria*

ILAR classification	Criteria	Operationalization of the criteria using CAPS data (using all recorded within the first year from initial presentation to rheumatology)
1. Systemic arthritis	Arthritis in one or more joints with or preceded by fever of at least 2 wk duration that is documented to be daily ("quotidian") for at least 3 days, and accompanied by one or more of the following: 1. Evanescent (nonfixed) erythematous rash 2. Generalized lymph node enlargement 3. Hepatomegaly and/or splenomegaly 4. Serositis Exclusions: a, b, c, d.	Physician's classification is sJIA.
2. Oligoarthritis	Persistent: Affecting ≤4 joints throughout the disease course Extended: Affecting a total of >4 joints after the first 6 mo of disease Exclusions: a, b, c, d, e	Between 1 and 4 active joints only in the first year following first PRh visit Between 1 and 4 active joints at first PRh visit and the total number of joint affected including those recorded at 1 y (±6 mo) is >4
3. Polyarthritis (RF negative)	Arthritis affecting ≥5 joints during the first 6 mo of disease A test for RF is negative. Exclusions: a, b, c, d, e	>4 active joints at first PRh visit At least one negative test for RF, with no positive test for RF recorded.
4. Polyarthritis (RF positive)	Arthritis affecting ≥5 joints during the first 6 mo of disease One positive test for RF Exclusions: a, b, c, e	>4 active joints at first PRh visit One positive test for RF
5. Psoriatic arthritis	Arthritis and psoriasis or arthritis and at least 2 of the following: 1. Dactylitis 2. Nail pitting or onycholysis 3. Psoriasis in a first-degree relative Exclusions: b, c, d, e	Active joint count ≥1 and psoriasis Active joint count ≥1 Dactylitis Nail pitting or onycholysis Psoriasis in a first-degree relative
6. Enthesitis-related arthritis	Arthritis and enthesitis or arthritis or enthesitis with at least 2 of the following: 1. The presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain 2. The presence of HLA-B27 antigen 3. Onset of arthritis in a boy >6 y of age 4. Acute (symptomatic) anterior uveitis 5. History of ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with IBD, reactive syndrome[a], or acute anterior uveitis in a first-degree relative Exclusions: a, d, e	Active joint count ≥1 and enthesitis Active joint count ≥1 or enthesitis The presence of or a history of sacroiliac tenderness and/or inflammatory spinal pain Presence of HLA-B27 antigen Male sex and the time between date of birth and date of symptom onset is >6 y Presence of anterior uveitis (acute or chronic) Arthritis (inflammatory–ankylosing spondylitis), acute uveitis, IBD, or arthritis (inflammatory–reactive[a]) in at least one first-degree relative
7. Undifferentiated arthritis	Arthritis that fulfills criteria in no category or in ≥2 of the above categories.	Not classified into other ILAR categories or classified into ≥2 ILAR categories. Children who fit this latter criterion will be removed from other categories and classified as unclassified JIA.
Exclusions		Operationalization of exclusion criteria in CAPS
a. Psoriasis or a history of psoriasis in the patient or first-degree relative.		Psoriasis recorded or family history of psoriasis in at least one first-degree relative
b. Arthritis in an HLA-B27 positive boy beginning after the sixth birthday.		Presence of HLA-B27 antigen, male sex, and >6 y between their date of birth and date of onset
c. Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with IBD, reactive syndrome[a], or acute anterior uveitis, or a history of one of these disorders in a first-degree relative.		Sacroiliitis or enthesitis or acute uveitis, or arthritis (inflammatory–ankylosing spondylitis) acute uveitis in the patient, or IBD or arthritis (inflammatory–reactive syndrome[a]) in at least one first-degree relative
d. The presence of IgM RF		One positive test for RF
e. The presence of systemic JIA in the patient.		Physician's classification is sJIA

* CAPS, Childhood Arthritis Prospective Study; IBD, inflammatory bowel disease; ILAR, International League of Associations for Rheumatology; JIA, juvenile idiopathic arthritis; PRh, Paediatric rheumatology; RF, rheumatoid factor; sJIA, systemic juvenile idiopathic arthritis.
[a] Reactive syndrome was formally known as "Reiter's syndrome."

Two positive ANA (PRINTO) or RF (PRINTO and ILAR) tests are required under the classification criteria for consideration of a true positive; however, pediatric rheumatologists in the United Kingdom often do not conduct more than one blood test for ANA or RF if the first is strongly positive or negative. Therefore, participants were considered positive for ANA and RF is they had one positive result. Additionally, because participants were not tested routinely for antibodies to cyclic citrullinated peptide

(anti-CCP) over the years that CAPS was recruiting, this criterion was not used for the PRINTO classification.

Unfortunately, the elements required to classify systemic arthritis under either system, particularly the specific nature of the fever and rash, results of white blood cell analyses, and presence of arthralgia, were not recorded in CAPS. Therefore, a pragmatic decision to accept the rheumatologist's reported classification in only this case, given the distinct features of this category, and to exclude these children from further classification, was made. Participants were also excluded from the analysis if their active joint count was missing or recorded as 0 without presence of enthesitis at all of the time points up to one year, because PRINTO and ILAR classification require confirmation of an active joint count for classification in the absence of enthesitis.

The overlap between participants in PRINTO and ILAR categories was analyzed descriptively, including using a chord diagram to visualize where children categorized by ILAR are categorized under PRINTO criteria. Those in similar categories (eg, PRINTO RF-positive JIA and ILAR RF-positive polyarthritis) were examined further to understand characteristics of children who did not fulfill both criteria.

Uveitis in the following two years. Those classified within the current study who had data for at least three years of follow-up were included in a secondary analysis to determine uveitis development between one and three years following initial presentation to pediatric rheumatology, which was described using descriptive analyses.

Missing data. This analysis took a complete case approach (every item required within the first year following initial presentation in order to classify) in order to (i) understand overlap in classification criteria in data that are currently collected and (ii) determine where missing data limit the feasibility of classification criteria application to observational data. Two exceptions to this rule were included: extra-articular features and family history data, in which missing data were treated as "not present," because the criteria call for "the presence of" certain features. This assumption was discussed with health care professionals, confirming that positive features are likely always noted in the clinical record, and absent features may either be noted as absent or more commonly not noted in the clinical record at all. All analyses were conducted using Stata version 14.0 (StataCorp),[22] and figures were created in RStudio version 3.5.1.[23]

RESULTS

Patient cohort. By 2016, 1,571 children with inflammatory arthritis had been recruited to CAPS. Of these participants, 73 were excluded because they did not have a physician's diagnosis of JIA, and 173 participants were excluded due to no arthritis or enthesitis recorded at any point over the first year (either recorded as 0 or missing). Lastly, 102 (5.6%) participants were removed from the overlap analysis because they had been classified by their rheumatologist as having systemic JIA. The final cohort of 1,223 participants who had data on any of the classification criteria were majority female (807, 66%), had a median age of 7.6 years (interquartile range [IQR] 3.4–11.8 years), and a median disease duration of 5.5 months to first pediatric rheumatology appointment (IQR 3.0–12.0 months).

ANA available data and results. Eight hundred and ninety-two participants had tests for ANA within the year following initial presentation to pediatric rheumatology (one test 658, two tests 198, three tests 29, four tests 3). Of these, 519 had at least one positive ANA measurement and were therefore considered for the ANA-positive JIA PRINTO subgroup. For RF, 60 participants had one positive measurement.

Classification and overlap between PRINTO and ILAR. The number of participants who were classified into each PRINTO and ILAR category, including the overlap are shown in Table 3 and Figure 1.

Table 3. Overlap between participants in each PRINTO and ILAR category*

	ILAR						
PRINTO	Oligoarthritis[a]	RF-negative polyarthritis	RF-positive polyarthritis	Psoriatic JIA	Enthesitis-related JIA	Undifferentiated	Total
RF-positive JIA	0 (0%)	0 (0%)	31 (48%)	0 (0%)	0 (0%)	34 (52%)	65
Enthesitis/ spondylitis-related JIA	0 (0%)	0 (0%)	0 (0%)	0 (0%)	59 (91%)	6 (9%)	65
Early-onset ANA-positive JIA	119 (50%)	58 (24%)	0 (0%)	6 (3%)	3 (1%)	54 (23%)	240
Other	447 (53%)	165 (19%)	0 (0%)	41 (5%)	32 (4%)	165 (19%)	850
Unclassified	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (33%)	2 (67%)	3
Total	566	223	31	47	95	261	1223

* ANA, antinuclear antibodies; ILAR, International League of Associations for Rheumatology; JIA, juvenile idiopathic arthritis; PRINTO, Paediatric Rheumatology International Trials Organisation; RF, rheumatoid factor.
[a] By one year, 536 patients were recorded as still having persistent oligoarthritis, and 32 were recorded as having extended oligoarthritis. Of those with extended oligoarthritis (n = 32), 26 had at least one test for RF, and none were positive.

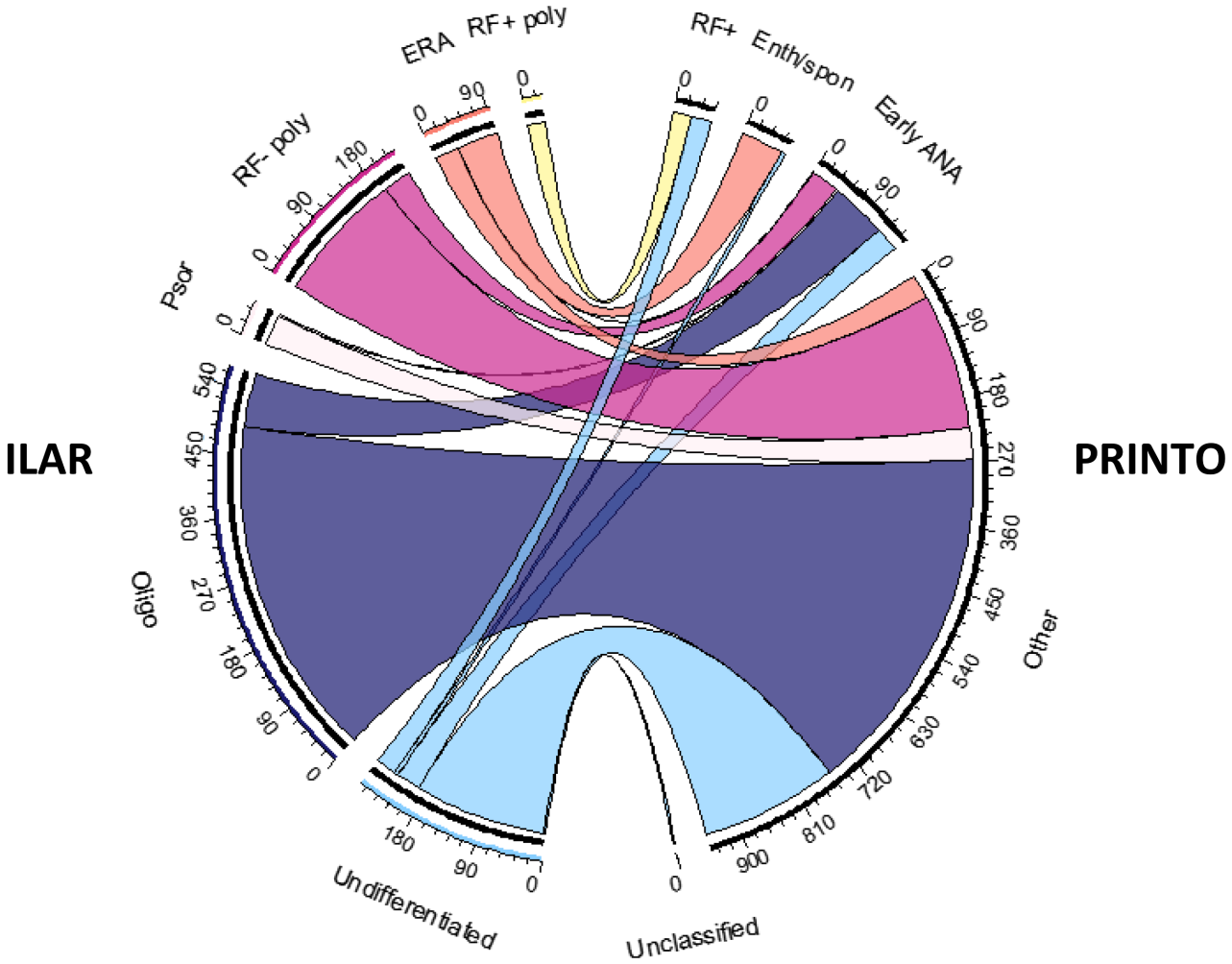

Figure 1. Overlap of classification using ILAR and PRINTO criteria in a UK inception cohort. Early ANA, early-onset antinuclear antibody-positive JIA; Enth/spon, enthesitis/spondylitis-related JIA; ERA, enthesitis-related JIA; ILAR, International League of Associations for Rheumatology; JIA, juvenile idiopathic arthritis; Oligo, oligoarticular JIA; PRINTO, Paediatric Rheumatology International Trials Organisation; Psor, psoriatic JIA; RF-poly, rheumatoid factor–negative polyarticular JIA; RF+, rheumatoid factor positive JIA; RF+ poly, rheumatoid factor–positive polyarticular JIA.

PRINTO early-onset ANA-positive JIA. Overall, 240 (19.6%) participants were classified as having PRINTO early-onset ANA-positive JIA. According to the ILAR criteria, 119 (49.6%) within this PRINTO category were classified as having oligoarthritis, 58 (24.2%) as RF-negative polyarthritis, 6 (2.5%) as PsA, 3 (1.3%) as enthesitis-related arthritis, and 54 (22.5%) were classified as undifferentiated arthritis. None were classified as RF-positive polyarthritis. Of those who had PRINTO early-onset ANA-positive JIA, 186 (77.5%) were female. The majority (168, 70.0%) had <5 active joints at presentation with a median of 2 active joints (IQR 1–5 active joints). In the following two years, 47 of 150 (31.3%) participants within this category with follow-up data developed uveitis.

PRINTO RF-positive JIA. Sixty-five (5.3%) participants were classified as PRINTO RF-positive JIA. Of these, 31 (47.7%) were also classified as having ILAR RF-positive polyarthritis, with the rest classified as having ILAR undifferentiated arthritis (34, 52.3%). The majority (79%) who did not fulfill the ILAR RF-positive polyarthritis criteria had a positive RF but <5 active joints within the first six months following diagnosis.

Of those with PRINTO RF-Positive JIA, the majority were female (52, 80.0%), and most (69.2%) were >6 years old (median age 11 years, IQR 5–13 years). There was an equal distribution between patients with <5 (49.2%) and >5 (50.7%) active joints at presentation.

In the following two years, 5 of 47 (10.6%) participants within this category with follow-up data developed uveitis. None of these were categorized as RF-positive polyarthritis under ILAR.

PRINTO enthesitis/spondylitis-related JIA. Sixty-five participants (5.3%) were classified as PRINTO enthesitis/spondylitis-related JIA (ERA). The majority (59, 90.8%) also met the ILAR enthesitis-related JIA criteria with the remaining having ILAR undifferentiated JIA (6, 9.2%).

The children with ILAR ERA who did not fulfill the PRINTO ERA criteria were all male and over the age of 6 years. They did not fulfill the PRINTO criteria because they had enthesitis or arthritis but only met one of the following criteria: HLA-B27 positivity, had uveitis, had reported spinal pain, and/or had a relevant family history. One of these participants had been classified as having PRINTO ERA but was moved into the Unclassified JIA category because they also fulfilled criteria for PRINTO RF-positive JIA. The range of diseases within family history that could be included was wider with ILAR, and these children had a family history of uveitis or inflammatory bowel disease in a first-degree relative rather than only ankylosing spondylitis as per the PRINTO criteria.

The majority of those with PRINTO ERA were male (48, 73.9%), and 60 (92.3%) had an onset after their sixth birthday. Most (44, 67.7%) had <5 active joints (median 3 active joints, IQR 2–5 active joints), and one participant was recorded as having enthesitis without arthritis. In the following two years, 9 of 59 (15.3%) participants within this category with follow-up data developed uveitis.

PRINTO other JIA. Most children in the CAPS cohort were classified as having PRINTO other JIA (850, 69.5%). Using ILAR criteria, 447 (52.6%) of these were classified as having oligoarthritis, 165 (19.4%) had RF-negative polyarthritis, 32 (3.8%) ERA, 41 (4.8%) PsA, and 165 (19.4%) undifferentiated arthritis.

Of those with PRINTO other JIA, 546 (64.2%) were female, and 553 (64.9%) were over 6 years old at symptom onset. At presentation, the majority in this category (641, 75.4%) had <5 active joints with a median of 2 active joints (IQR 1–5 active joints). Within this group, 208 (26.4%) also tested positive for ANA (43.8% ILAR oligo, 23.1% RF-poly, 9.6 % ERA, 5.8% PsA, and 17.8% undifferentiated), but all who tested ANA positive had a disease onset after their sixth birthday. In the following two years, 102 of 824 (12.4%) participants within this category with follow-up data developed uveitis.

PRINTO unclassified JIA. Finally, the PRINTO unclassified JIA only contained three participants (all male, >6 years old) who met criteria for both RF-positive (PRINTO) and ERA (PRINTO) and as a result could not be classified into either category. Under ILAR, one participant (33%) was classified as having ERA, and the other two (67%) had undifferentiated arthritis. The two participants who had undifferentiated arthritis (ILAR) were RF positive, but both met exclusion criteria for ILAR RF-positive polyarthritis. Neither of the two participants (0.0%) within this category with follow-up data developed uveitis.

DISCUSSION

This analysis has assessed the overlap of the preliminary 2019 PRINTO Classification Criteria with the 2001 second revision ILAR criteria in an existing cohort of patients with JIA. Although the PRINTO criteria are provisional and currently under evaluation, the results of this analysis in a UK cohort found that a majority of children across a number of ILAR categories are not yet classified under the preliminary PRINTO criteria, confirming that further consideration is needed before these can be used more widely, particularly among observational research studies. Around 20% of children included in this analysis were classified into the new early-onset ANA-positive category, largely from ILAR oligoarthritis, RF-positive polyarthritis, and undifferentiated JIA.

There was considerable overlap between the PRINTO RF-positive JIA and ILAR RF-positive polyarthritis categories. There were a larger proportion of children classified as having PRINTO RF-positive arthritis than ILAR RF-positive polyarthritis due to the removal of the requirement for a minimum joint count. This highlights a group of children with RF-positive oligoarthritis. This group should be investigated for similar disease mechanisms and course to rheumatoid arthritis (RA), which more commonly presents with RF-positive disease, so much so that it is a component in the current EULAR/American College of Rheumatology Classification Criteria.[24] For RA, no exclusions or distinctions are made based on the number of active joints in regard to disease classification. Therefore, new PRINTO criteria make a step toward harmonized classification of potentially similar diseases across the life course. However, the grouping of oligoarthritis and polyarthritis together presents challenges for understanding existing evidence across this combined group. Less is known about outcomes of oligoarthritis compared with polyarthritis, including whether treatments, such as earlier introduction of systemic therapies, should differ between these groups. Further longer-term studies are particularly needed to understand the significance of a positive RF test in children with oligoarthritis in terms of both treatment and disease outcomes.

There was also a considerable overlap between PRINTO ERA and ILAR enthesitis-related JIA categories. The main differences between the criteria for these categories were the list of "allowed" diagnoses in first-degree relatives (being more restrictive in PRINTO than ILAR) and the new requirement for inflammatory back pain and sacroiliitis on imaging in the PRINTO criteria, adopted from the adult criteria for spondyloarthritis (SpA).[25,26] In our cohort, this limited assignment to PRINTO ERA; sacroiliitis was rarely reported as present (n = 30 patients). Unfortunately, we cannot confirm whether "no sacroiliitis" is indicative of imaging not undertaken or that it was but was negative. It is also not known for those who did have sacroiliitis on imaging whether this was x-ray or magnetic resonance (MR) scanning. Because x-ray is less sensitive than MR scanning for the detection of sacroiliitis in juvenile-onset SpA,[27–29] more children may have been recorded as having sacroiliitis on imaging if more MR scans had been used instead of x-ray. However, MR scans may be less appropriate for the detection of sacroiliitis in children due to (i) difficulties distinguishing active versus inactive inflammation because of perfusion in joint tissue due to growth in children with active growth plates[30] and (ii) challenges around anxiety or

remaining still in the MR scanner, which can result in difficulties in conducting the scan without the use of sedation.[31–33] Therefore, these limitations may limit the application of PRINTO ERA criteria for research purposes for this category.

Those with PRINTO early-onset ANA-positive JIA fulfilled many different ILAR categories, including oligoarthritis, RF-negative polyarthritis (found previously to be genetically homogenous[34]), and PsA, corroborating previous findings.[4,6,9,14,35] Children with PsA have not been defined currently as a separate disease category under the provisional PRINTO criteria. Although 13% of those classified as ILAR PsA fell into this early-onset ANA-positive group, the vast majority fell within the "other JIA" category, largely due to having an older age at disease onset (>6 years). This finding validates the need for further consideration of definitive criteria for PsA in children. This is particularly pertinent given the often-delayed onset of psoriatic features in children previously classified as oligo or polyarticular JIA.[36] That younger age of disease onset is generally associated with better outcomes, in terms of disease activity including treatment response,[37–39] is readily corroborated. However, the association is not as clear after adjustment for ILAR category, because those with oligoarthritis tend to both be younger and have milder disease.[40] In addition, older age has been associated with delays in reaching pediatric rheumatology and therefore longer periods to effective treatment initiation,[41] potentially affecting treatment outcomes. Although the bimodal onset age of JIA has prompted several subgrouping studies to consider early- and late-onset disease, such as within psoriatic JIA,[42] the differences in disease features themselves, which are not entirely distinct between age groups, may drive outcome, rather than age specifically. Therefore, the evidence is not yet clear that age groups themselves represent distinct subtypes of JIA with different outcome or treatment needs. In addition, ANA positivity has not consistently associated with arthritis outcome in JIA[43] and is largely used as a biomarker for risk of uveitis onset.[44,45] Any potential interaction between ANA status and age on disease outcomes or treatment requirements must, therefore, be explored further.

The current study mirrored proportions of early-onset ANA-positive JIA and other JIA in a similarly large Canadian inception cohort.[17] In contrast, the current UK cohort identified a smaller proportion of children with ERA (5.3% vs 12.8%) and a greater proportion with RF-positive JIA (5.3% vs 0.8%) compared with the Canadian cohort. These differences may relate to differences in data availability, with the current study collecting data on sacroiliac joint tenderness, the absence of which may have excluded participants otherwise classified within the Canadian cohort. The higher proportion of RF-positive JIA may be due to our requirement for one positive RF test, and the Canadian requirement for two, as in the criteria set. The lack of children classified in the Canadian cohort alongside our results demonstrates that requiring two RF test results may not readily occur in clinical practice and may not be feasible for larger cohort studies of JIA. It is also possible that underlying population heritage drives some of the differences between populations. Of note, neither the current UK or Canadian cohorts had information on fever pattern, temperature, or duration available to classify systemic JIA, showing an additional limited feasibility of application of the proposed provisional PRINTO systemic JIA criteria to data in existing observational research studies. This is particularly important because the new PRINTO criteria allow for a diagnosis of systemic JIA in those without arthritis, which could accelerate effective treatment access in this subgroup of children.

Strengths of the current study include the recruitment and inclusion of a large sample of participants from a national multicenter inception study on JIA with a generalizable population. Although this study sought to classify JIA in early disease, because CAPS is a longitudinal study with serial data collection points, we were able to capture further data beyond presentation and how they evolved, such as joint involvement over time and blood tests taken after the first pediatric rheumatology visit. Although the classification criteria are designed to be applied at a single time point looking at concomitant features, or classify based on features that have become apparent over six months (persistent vs extended oligoarthritis), in many children with JIA, disease features unfold sequentially over time. This phenomenon often leads to reclassification of children within oligo or polyarticular JIA as psoriatic or enthesitis-related categories in practice. Further development of classification criteria needs to account for this sequential disease progression, because underlying mechanisms of disease, and therefore effective treatment strategies, may rely on latent disease type rather than initial presenting features.

There were also some limitations. Due to a change in the study protocol, autoimmune and rheumatic conditions in relatives were not captured after 2015, limiting the analysis to children recruited before 2016. However, it is unlikely that the disease evolved meaningfully between 2016 and the study conclusion in 2019. The study did not collect anti-CCP status, and so this could not be analyzed. However, there are potential clinical implications for treatment in children who test negative for RF but positive for anti-CCP if they received a test. Anti-CCP positivity may be a better predictor of disease severity in adults with RA than RF positivity,[46] and double positivity for both antibodies is a strong predictor of mortality in adults with RA.[47] Therefore, further research is needed on the predictive value of anti-CCP in terms of disease severity in children with JIA. Further development of classification criteria based on immunological or genetic characteristics is also for consideration in the future. A further limitation is that the PRINTO criteria apply to children up to the age of 18 years. Because CAPS was designed and recruited in the era of ILAR criteria, which has a lower age limit of <16 years, no patients with a disease onset at >16 years old was recruited. Therefore, it is not known how these criteria would perform in this older-onset age group.

The current study has evaluated the overlap between the preliminary PRINTO JIA criteria and existing ILAR classification criteria using data collected over the first year of disease, informing the revision of the JIA classification criteria. The proportion of children with early onset ANA-positive JIA is high, representing almost 20% of our cohort under study. There was marked comparability between the ILAR enthesitis-related and PRINTO enthesitis/spondylitis-related categories, as well as ILAR RF-positive polyarthritis and PRINTO RF-positive JIA, although more children with oligoarthritis also fit into this PRINTO category. A combined 70% of children could not currently be classified using PRINTO criteria, indicating that further refinement and consideration of these criteria are needed, which is work that is underway currently. Understanding how these new criteria differ from the existing ILAR criteria in terms of investigating longer-term outcome and best treatments for children with JIA remains unknown, although new criteria based on clinically homogenous groups have the potential to improve clinical care and outcome prediction research in this field.

ACKNOWLEDGMENTS

We thank the children and their families involved in CAPS, as well as clinical staff and administrators. We are most grateful to Professor Wendy Thomson who led CAPS from its inception until her retirement in August 2020. We also thank the data management team at the University of Manchester (UK).

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr Shoop-Worrall had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Shoop-Worrall, Macintyre, Hyrich.
Acquisition of data. Ciurtin, Cleary, McErlane, Wedderburn, Hyrich.
Analysis and interpretation of data. Shoop-Worrall, Macintyre, Hyrich.

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