



A Diagnostic Prediction Model for Separating Juvenile Idiopathic Arthritis and Chronic Musculoskeletal Pain Syndrome

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Objective To develop and validate a diagnostic prediction model that can distinguish between juvenile idiopathic arthritis (JIA) and chronic musculoskeletal pain syndrome (CMPS) based on patient-reported outcomes.

Study design This retrospective cohort study evaluated whether the Juvenile Arthritis Multidimensional Assessment Report (JAMAR) performs well in distinguishing JIA from CMPS. We analyzed JAMARs completed by 287 patients at their first visit to the pediatric rheumatology department of Wilhelmina Children's Hospital in Utrecht, The Netherlands. Relevant JAMAR items for predicting a diagnosis of JIA were selected in a penalized multivariable model suitable for clinical application. The model was subsequently validated with new data from the same center.

Results A total of 196 JAMARs (97 JIA, 99 CMPS) were collected in the model development data, and 91 JAMARs (48 JIA, 43 CMPS) were collected in the validation data. Variables in the prediction model that were strongest associated with a diagnosis of JIA instead of CMPS were asymmetric pain/swelling in the shoulder (OR, 2.34), difficulty with self-care (OR, 2.41), skin rash (OR, 2.07), and asymmetric/pain swelling in the knee (OR, 2.29). Calibration and discrimination (area under the receiver operating characteristic curve, 0.83; 95% CI, 0.74-0.92) of the model in the validation data were good.

Conclusions Several items from the JAMAR questionnaire can potentially distinguish JIA from CMPS in patients with corresponding symptoms. We present an easy-to-use, adjusted, and validated model to separate these 2 diagnoses early at presentation based on patient-reported outcomes to facilitate proper referral and treatment. (*J Pediatr* 2022;251:164-71).

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Juvenile idiopathic arthritis (JIA) and chronic musculoskeletal pain syndrome (CMPS) are 2 common diagnoses made in children referred to a pediatric rheumatologist for a suspected rheumatic disease.¹⁻⁴ JIA is defined as all forms of arthritis of unknown cause persisting for >6 weeks starting before age 16 years.⁵ The International League of Associations for Rheumatology (ILAR) classifies 7 subtypes of JIA with distinct clinical and laboratory characteristics.⁶ CMPS is an idiopathic noninflammatory condition of chronic musculoskeletal pain, defined as ongoing pain in the bones, joints, and soft tissues persisting for at least 3 months.^{1,3,7,8} Several pediatric forms of CMPS can be distinguished, some of which have more specific diagnostic criteria; these include generalized pain syndromes (including juvenile primary fibromyalgia), complex regional pain syndrome, local pain syndromes, and lower back pain.^{1,8}

JIA and CMPS present with heterogeneous and overlapping symptoms.^{1,7,9,10} Patient history and physical examination by experienced physicians are needed to distinguish JIA from CMPS, with a family history of certain autoimmune diseases (eg, psoriasis, uveitis, spondyloarthritis), morning stiffness, and joint swelling or limitation of motion arguably pointing toward a diagnosis of JIA. Because the management and prognosis of JIA and CMPS are very different, it is important to differentiate them early for proper referral. Delay in the treatment of JIA could lead to contractures, overgrowth of the affected bone, and joint damage,^{5,11} and a delay in the management of

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AUC	Area under the receiver operating characteristic curve
CMPS	Chronic musculoskeletal pain syndrome
ILAR	International League of Associations for Rheumatology
JAFS	Juvenile Arthritis Functionality Scale
JAMAR	Juvenile Arthritis Multidimensional Assessment Report
JIA	Juvenile idiopathic arthritis
JQL	Pediatric Rheumatology Quality of Life Scale
LASSO	Least absolute shrinkage and selection operator
VAS	Visual analog scale

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CMPS could result in musculoskeletal disequilibrium (ie tightening and hyperextension of certain muscles and tendons) due to adaptive positioning during the pubertal growth spurt and negatively impact psychological well-being.^{4,12}

The aim of this study was to assess whether a combination of patient-reported items from the Juvenile Arthritis Multidimensional Assessment Report (JAMAR) would perform well in distinguishing JIA from CMPS in patients with corresponding symptoms and could serve as a validated prediction model for separating these 2 diagnoses in clinical practice.

Methods

This was a retrospective cohort study using data from the pediatric rheumatology outpatient clinic of the Wilhelmina Children's Hospital, a tertiary care center in Utrecht, The Netherlands. Since 2012, it has been standard of care for all referred patients to complete an electronic version of the JAMAR shortly before their first visit to the outpatient clinic. This questionnaire was developed in 2011 with the aim of assessing health status in patients with JIA and includes 15 parent- or patient-centered items including well-being, pain, functional status, disease activity, joint disease, and drug adverse effects.¹³ Data about first visits of referred patients were extracted from the electronic medical record and the pediatric rheumatology registry of the Wilhelmina Children's Hospital.

The pediatric rheumatology registry was created in 2011 and has since collected clinical and laboratory data from more than 900 patients. For this study, we used the following inclusion criteria at first visit: age <18 years, no immunosuppressive treatment, and a diagnosis (after follow-up) of either JIA or CMPS after having completed a JAMAR questionnaire (within 3 weeks from the first visit). Patients receiving immunosuppressive treatment were excluded because they likely already had been diagnosed with JIA elsewhere. For developing the diagnostic prediction model, we used data from patients that completed a JAMAR before July 1, 2018. This group included 196 eligible patients, of whom 97 (49.5%) were diagnosed with JIA. The model was subsequently validated using new data collected between July 1, 2018, and May 28, 2020, on 91 eligible patients, of whom 48 (52.7%) were diagnosed with JIA.

This study was classified by the Institutional Review Board of University Medical Center Utrecht as exempt from the Medical Research Involving Human Subjects Act (21/774) and was carried out in compliance with the Declaration of Helsinki. All included patients provided informed consent for the use of their data for scientific purposes.

The dataset analyzed in this study is available from the corresponding author on reasonable request.

Outcome and Predictors

The outcome predicted in this study was a diagnosis of JIA instead of CMPS. JIA was diagnosed according to ILAR

criteria, and CMPS was diagnosed if there was persistent musculoskeletal pain for at least 3 months in the absence of any underlying cause. Owing to the retrospective nature of the data, no specific diagnostic criteria for different forms of CMPS were used. Patients potentially with CMPS were selected from the pediatric rheumatology registry using the following diagnosis codes: "arthralgia," "myalgia," "myofascial pain syndrome/tendinitis," "foot osteochondrosis," "patellofemoral pain syndrome," "low back pain," and "orthopedic condition—not further specified." Two researchers independently reviewed descriptions of diagnoses for correctness. Patients with CMPS were further classified as having "local pain" when a maximum of 1 painful joint group was involved and "generalized pain" when at least 2 painful joint groups were involved.

Predictors included in the study were age at first visit, sex, and separate items of the JAMAR. For patients aged <12 years with available child and parent versions of the JAMAR, we used the parent version. For patients aged ≥12 years, we used the child version. JAMAR items regarding drug therapy and previous visits were irrelevant due to the study design and thus were not analyzed. We hypothesized that asymmetric joint involvement would be associated with JIA rather than with CMPS; therefore, we combined JAMAR items about patient-reported pain or swelling in joints on the left and right sides into variables with 3 categories: no pain or swelling, pain or swelling on the left or right side (ie, asymmetric pain/swelling), and pain or swelling on both the left and right side (ie, symmetric pain/swelling). To avoid fitting an overfit model, individual Juvenile Arthritis Functionality Scale (JAFS) and Pediatric Rheumatology Quality of Life Scale (JQL) items were dichotomized into the following categories: "no difficulty/never" (score 0) versus "some difficulty/sometimes or worse" (score 1-3). Age at first visit, visual analog scale (VAS) well-being, VAS pain, and VAS disease activity were treated as continuous variables, and linearity with the logit outcome was assessed visually.

Model Development and Validation

We performed a univariable logistic regression analysis for each variable in the model development data. Variables with a *P* value <.10 were subsequently fitted in a multivariable penalized logistic regression model for diagnosing JIA. The number of self-reported painful or swollen joints (range, 0-18) was not considered for inclusion into the multivariable model, to preserve the independence of predictor variables. The multivariable model was fitted using least absolute shrinkage and selection operator (LASSO) regression on complete cases. LASSO regression is a statistical technique suitable for data with many variables that adds a penalty to model coefficients by shrinking them toward zero.¹⁴ This technique simultaneously performs regularization by making model coefficients less optimistic and variable selection by setting coefficients of variables that are unimportant in predicting the outcome to exactly 0. As a result, predictions from a LASSO regression will be less extreme owing to overfitting, which might benefit future predictions in new

patients. The degree of shrinking model coefficients toward 0 in LASSO regression is determined by the λ variable, and for this study we used the value of λ that minimized prediction error in 10-fold cross-validation.¹⁴

For each patient in the model development and validation data, a predicted probability for JIA was calculated using the shrunken coefficients from the LASSO model. Performance of the model in the development data and validation data was assessed by the area under the receiver operating characteristic curve (AUC) and a calibration plot of mean predicted probabilities versus frequencies of the outcome within quintiles of the data.

As a secondary analysis, we repeated all model building and validation procedures for patients in the model development and validation datasets with only oligoarthritis and local pain syndrome and polyarthritis and generalized pain syndrome.

All analyses were performed with R version 3.6.3¹⁵ with the glmnet, rms, and pROC packages. We adhered to the

guidelines for Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis.¹⁶

Results

Characteristics of Patients in the Model Development Data

A flowchart of patients included in the model development and validation data is provided in **Figure 1** (available at www.jpeds.com). In the group of patients used for developing the prediction model, patients with JIA were significantly more often male (30.1% vs 17.2%) and reported more skin rash and difficulty with self-care compared with patients diagnosed with CMPS (**Table I**). On the other hand, patients with CMPS were older and more often reported symmetric joint involvement and painful or swollen lower back and neck, with the latter reflected in a higher frequency of reported difficulty looking up and over the shoulder compared with patients

Table I. Patient characteristics with $P < .10$ in the model development data (N = 196)

Characteristics	JIA (N = 97)	CMPS (N = 99)	P value
Demographics			
Age at first visit, y, median (IQR)	11.5 (5.4-14.7)	14.8 (12.2-16.1)	<.01
Female, n (%)	67 (69.1)	82 (82.8)	.03
JAMAR items			
Functional ability during previous 4 wk, n (%)			
Difficulty carrying out activities with fingers (JAFS 6)	27 (28.1) (N = 96)	47 (48.0) (N = 98)	<.01
Difficulty squeezing with hands (JAFS 8)	25 (26.3) (N = 95)	38 (38.4)	.07
Difficulty putting hands behind neck (JAFS 12)	7 (7.6) (N = 92)	18 (18.2)	.04
Difficulty looking over shoulder (JAFS 13)	10 (10.5) (N = 95)	23 (23.2)	.02
Difficulty looking up (JAFS 14)	7 (7.4) (N = 94)	19 (19.4) (N = 98)	.02
VAS pain, median (IQR)	5.0 (2.5-7.0)	6.0 (3.5-7.5)	.09
Number of painful/swollen joints, median (IQR)	2 (1-4)	4 (2-7)	<.01
Pain/swelling in finger(s), n (%)			
No	71 (73.2)	59 (59.6)	Reference
Asymmetric	10 (10.3)	10 (10.1)	.70
Symmetric	16 (16.5)	30 (30.3)	.02
Pain/swelling in shoulder(s), n (%)			
No	85 (87.6)	80 (80.8)	Reference
Asymmetric	8 (8.2)	4 (4.0)	.32
Symmetric	4 (4.1)	15 (15.2)	.02
Pain/swelling in hip(s), n (%)			
No	89 (91.8)	71 (71.7)	Reference
Asymmetric	4 (4.1)	10 (10.1)	.06
Symmetric	4 (4.1)	18 (18.2)	<.01
Pain/swelling in knee(s), n (%)			
No	36 (37.1)	41 (41.4)	Reference
Asymmetric	36 (37.1)	14 (14.1)	<.01
Symmetric	25 (25.8)	44 (44.4)	.20
Pain/swelling in ankle(s), n (%)			
No	72 (74.2)	61 (61.6)	Reference
Asymmetric	11 (11.3)	7 (7.1)	.58
Symmetric	14 (14.4)	31 (31.3)	.01
Pain/swelling in neck, n (%)	15 (15.5)	41 (41.4)	<.01
Pain/swelling in lower back, n (%)	12 (12.4)	27 (27.3)	.01
Skin rash, n (%)	20 (20.6) (N = 96)	7 (7.1)	<.01
VAS disease activity, median (IQR)	4.5 (2.5-6.5)	3.0 (1.5-6.0)	.08
Attending school, n (%)	76 (78.4)	94 (94.9)	<.01
Quality of life during previous 4 wk, n (%)			
Difficulty with self-care (JQL 1)	45 (50.0) (N = 90)	32 (34.4) (N = 93)	.02
Felt sad/depressed (JQL 6)	48 (51.1) (N = 94)	65 (66.3) (N = 98)	.03
Difficulty concentrating (JQL 9)	50 (55.6) (N = 90)	66 (67.3) (N = 98)	.10

with JIA. Furthermore, the median number of self-reported painful or swollen joints was significantly higher in patients with CMPS than in patients with JIA. Overall, both patients with JIA and CMPS in the model development data reported substantial pain, as shown by VAS pain scores (median, 5.5; IQR, 3.0-7.3) and the dichotomized question 5 from the JQL scale (97.4%). Extended characteristics of patients in the model development data are reported in [Table II](#) (available at www.jpeds.com).

Development of the Prediction Model

On univariable logistic regression analysis, a P value $<.10$ was observed in the model development data for the following variables: age at first visit, sex, difficulty carrying out activities with fingers, difficulty squeezing with hands, difficulty putting hands behind neck, difficulty looking over shoulder, difficulty looking up, VAS pain score, pain/swelling in the finger(s), pain/swelling in the shoulder(s), pain/swelling in the hip(s), pain/swelling in the knee(s), pain/swelling in the ankle(s), pain/swelling in the neck, pain/swelling in the lower back, skin rash, VAS disease activity, school attendance, difficulty with self-care, feeling sad/depressed, and difficulty concentrating. These variables were subsequently fitted in a multivariable logistic LASSO regression, which forced exclusion of the following variables: difficulty carrying out activities with fingers, difficulty squeezing with hands, difficulty looking up, VAS pain score, pain/swelling in the lower back, pain/swelling in the fingers, symmetric pain/swelling in the shoulders, asymmetric pain/swelling in the ankle, school attendance, and difficulty concentrating. According to the model, a diagnosis of JIA was most closely associated with asymmetric pain/swelling in the shoulder, asymmetric pain/swelling in the knee, skin rash, and difficulty with self-care ([Table III](#)). A diagnosis of CMPS was most closely associated with female sex, older age at first visit, pain/swelling in the neck, pain/swelling in the hip(s), symmetric pain/swelling in the knees, and symmetric pain/swelling in the ankles. The model was based on 170 patients, owing to missing data for 26 patients. The equation for calculating the probability of JIA for an individual patient following the model has the form of

$$P(\text{JIA}) = \frac{1}{1 + e^{-(\beta_0 + \beta_1 * x_1 + \beta_2 * x_2 + \dots + \beta_n * x_n)}}$$

where β_0 is the model intercept, β_1 - β_n are the model coefficients, and x_1 - x_n are the observed patient values for the variables as displayed in [Table III](#).

The prediction model from the development data demonstrated good discrimination (AUC, 0.89; 95% CI, 0.84-0.93) ([Figure 2](#)). Some miscalibration was observed owing to the shrinkage of coefficients. At a cutoff threshold of 70% for the predicted probability of JIA in the model development data, the model had a negative predictive value of 95% and a positive predictive value of 67%.

Validation of the Prediction Model

Compared with the model development data, similar effects across patients with JIA and CMPS were observed in the

Table III. Coefficients of a multivariable LASSO prediction model for a diagnosis of JIA instead of CMPS

Variables	Coefficients	OR*
Intercept	2.48	11.96
Female sex	-0.77	0.46
Age at first visit, y	-0.17	0.84
Functional ability during previous 4 wk		
Difficulty putting hands behind neck (JAFS 12)	-0.09	0.91
Difficulty looking over shoulder (JAFS 13)	-0.17	0.85
Pain/swelling in neck	-0.71	0.49
Asymmetric pain/swelling in shoulder	0.85	2.34
Asymmetric pain/swelling in hip	-0.70	0.49
Symmetric pain/swelling in hips	-1.00	0.36
Asymmetric pain/swelling in knee	0.83	2.29
Symmetric pain/swelling in knees	-0.44	0.64
Symmetric pain/swelling in ankles	-0.42	0.66
Skin rash	0.73	2.07
VAS disease activity	0.07	1.07
Quality of life during previous 4 weeks, n (%)		
Difficulty with self-care (JQL 1)	0.88	2.41
Felt sad/depressed (JQL 6)	-0.16	0.85

*It is not possible to calculate 95% CIs for LASSO (least absolute shrinkage and selection operator) regression coefficients because these coefficients are adjusted to be less overfit to the data and thus cannot be calculated from the observed data. Therefore, only the coefficients and the corresponding ORs are reported.

model validation group ([Table IV](#); available at www.jpeds.com). For both the validation and model development data, the majority of patients with JIA had oligoarthritis, and the majority of patients with CMPS had generalized pain ([Table V](#); available at www.jpeds.com). Predictions in the validation data were calculated for 83 patients, owing to 8 patients with missing data. Calibration and discrimination (AUC, 0.83; 95% CI, 0.74-0.92) in the validation data were good. At the cutoff threshold of 70% for the predicted probability of JIA, the model had a negative predictive value of 85% and a positive predictive value of 66%.

Secondary Analyses

When restricting our analyses to patients with oligoarthritis and patients with local pain syndrome in the model development and validation data, the following were the best predictor variables for differentiating JIA from CMPS on multivariable analysis: age at first visit, difficulty running on flat ground, difficulty walking up 5 steps, difficulty jumping forward, difficulty squatting, pain/swelling in the knee(s), morning stiffness, VAS disease activity, school attendance, and difficulty with self-care. The prediction model demonstrated excellent discrimination in the model development data (AUC, 0.93; 95% CI, 0.87-0.99) and validation data (AUC, 0.86; 95% CI, 0.75-0.97) and overall acceptable calibration ([Figure 3](#); available at www.jpeds.com). Subsequently, when restricting our analyses to patients with polyarthritis and generalized pain syndrome in the model development and validation data, the following were the best predictor variables for differentiating JIA from CMPS on multivariable analysis: age at first visit, difficulty opening doors, pain/swelling in the toe(s), pain/swelling in the neck,

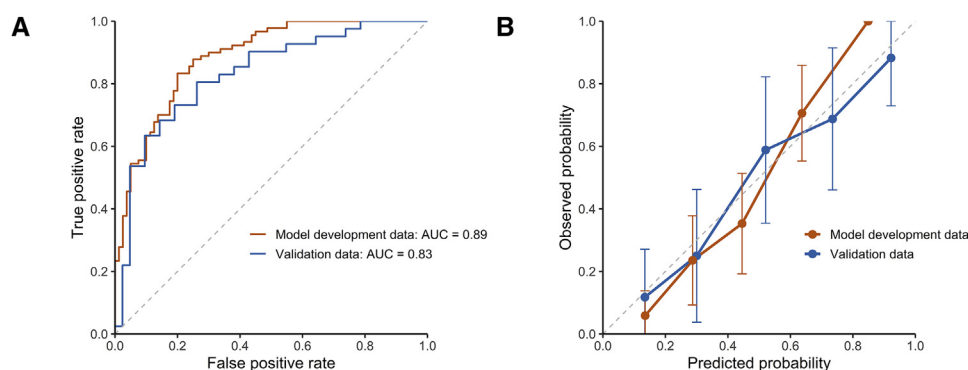


Figure 2. Prediction model performance in development and validation data. **A**, Receiver operating characteristic curves of false-positive and true-positive rates for different thresholds of predicted probabilities. **B**, Calibration plots of mean predicted probabilities versus frequencies of the outcome within quintiles of the data. Vertical bars indicate 95% CIs.

and difficulty with self-care. This prediction model demonstrated good discrimination in the model development data (AUC, 0.87; 95% CI, 0.75-0.98) and validation data (AUC, 0.86; 95% CI, 0.72-1.0) and overall good calibration.

Clinical Application

For clinical practice, predictions from our prediction model can be obtained from a risk calculator ([Appendix](#); available at www.jpeds.com). For nondigital use, a nomogram has been constructed from which predicted risks of JIA can be calculated as a function of the model variables ([Figure 4](#)).

Discussion

In this study, we have shown that the JAMAR questionnaire performs well in separating JIA and CMPS at the first visit to a pediatric rheumatologist. JAMAR items that were strongly associated with a diagnosis of JIA instead of CMPS on multivariable analysis were male sex, young age, patient-reported asymmetric pain/swelling in the shoulder or knee, skin rash, and difficulty with self-care. Patients with CMPS reported more symmetric joint involvement and pain/swelling in the neck and lower back compared with patients with JIA.

We decided to include only patients with a diagnosis of JIA or CMPS because these patients compose the majority of our target domain of patients with signs and symptoms suspicious of JIA. Patients referred to a pediatric rheumatologist with other diseases, such as systemic lupus erythematosus or autoinflammatory conditions, generally present with distinct symptoms. According to our data, a roughly equal number of patients will be diagnosed with CMPS and with JIA at their first visit to a pediatric rheumatologist.

Two previous studies reported that patients with CMPS were older at the onset of symptoms and more often female than patients with JIA¹⁰ and other rheumatic diseases.⁷ It also has been found that patients with CMPS report more pain than patients with JIA.^{10,17} These findings are in line

with the results of the present study, although VAS pain score was not a significant variable in predicting a diagnosis of JIA on multivariable analysis. One previous study presented a tool for predicting the final diagnosis in children with musculoskeletal complaints that identified the pattern of joint swelling over time, duration of morning stiffness, frequency of pain, and precipitating factors as independently correlated with chronic arthritis.¹⁸ However, this tool was based on predictors from a detailed medical history instead of patient-reported outcomes and also included patients with acute and episodic pain.

Several important variables in the prediction model can be explained by the existing literature. A systematic review reported that musculoskeletal pain is more common in girls than in boys and increases with age.¹⁹ Furthermore, asymmetric involvement of large joints, such as the knee and shoulder, is common in oligoarthritis, the largest ILAR category of JIA.^{5,11} Skin rash as a predictor of JIA can be attributed to a diagnosis of systemic or psoriatic JIA.^{6,20} In our model development data, 100% (3 of 3) of patients with systemic JIA and 44% (4 of 9) of patients with psoriatic JIA reported skin rash.

According to our model, difficulty with self-care was another important variable associated with JIA, most often reported by patients with systemic JIA (3 of 3; 100%) and polyarticular JIA (12 of 15; 80%) in the model development data. Examples of self-care activities mentioned in the JAMAR are eating, dressing, and washing, which especially require sufficient functioning of the wrists and hands. In our cohort, patients with polyarticular and systemic JIA most often reported involvement of these joint groups, which is in line with previous literature.^{5,21} We speculate that difficulty with self-care distinguishes children with JIA from children with CMPS because the joints of the latter group are not limited due to increased intra-articular fluid or swollen joint capsules.

Other important predictors for CMPS are pain and swelling in the neck and hip. Although pain in these joints is incorporated in several diagnostic criteria for fibromyalgia,²² data on neck/hip involvement in juvenile CMPS are

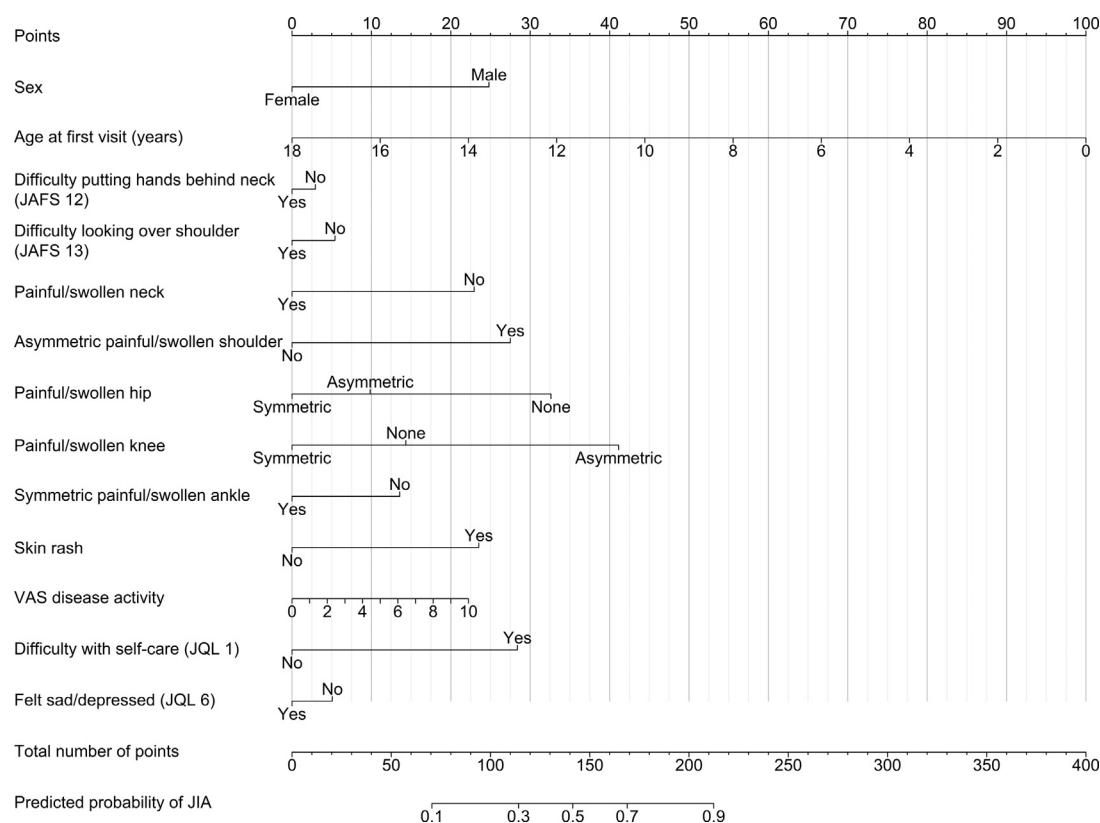


Figure 4. Nomogram of predicted probabilities for JIA instead of CMPS. For every observation of model variables on the left (Sex, ..., JQL 6), read off the corresponding number of points from the top axis. Add up all points to read off the corresponding predicted probability of JIA using the bottom 2 axes. For example, for a 4-year-old female patient with difficulty putting her hands behind her neck but no difficulty looking over her shoulder, no painful/swollen neck, an asymmetric painful/swollen shoulder, no painful/swollen hips, no painful/swollen knees, no painful/swollen ankles, no skin rash, a VAS disease activity of 8, difficulty with self-care, and not feeling sad/depressed, the total number of points would be $0 + 78 + 0 + 6 + 23 + 28 + 33 + 14 + 14 + 0 + 18 + 28 + 5 = 247$, which corresponds to a predicted probability of JIA instead of CMPS of >90%.

scarce.^{1,19} Symmetric pain/swelling in all examined joints was observed more often in patients with CMPS compared with patients with JIA, confirming our prespecified hypothesis that asymmetric joint involvement would be associated with JIA rather than with CMPS. In line with our findings, a study including 33 patients with juvenile fibromyalgia syndrome reported symmetric pain in 79% of patients.²³

As noted earlier, some predictors in our model are likely associated with different subtypes of JIA and CMPS. Indeed, different predictor variables were selected in our secondary analyses restricted to focal or diffuse complaints compared with our main analysis. Nevertheless, the aim of the present study was to present a model able to distinguish between joint pain with inflammatory and noninflammatory causes, not to explain differences between subtypes of JIA and CMPS. Our model can enable physicians to properly refer patients in an early stage for further diagnostics and treatment.

The prediction model performed well in both the development data and the validation data in terms of discrimination and calibration and yielded high negative predictive values and reasonable positive predictive values at a cutoff threshold

of 70% for the predicted probability of JIA. Thus, this threshold seems appropriate for ruling out a diagnosis of JIA, with the risk that some patients with CMPS will be falsely “diagnosed” with JIA by the model. This misclassification is not problematic, because a diagnosis of JIA will subsequently have to be confirmed by the pediatric rheumatologist following a physical examination, which is standard of care. These physicians often face the challenge of distinguishing JIA and CMPS. In fact, we argue that pediatric rheumatologists observe only the tip of the iceberg.

This study has some strengths and limitations. A major strength is that for almost 300 patients, information from the JAMAR was available before a diagnosis of JIA or CMPS, as is standard procedure in our hospital. The final prediction model demonstrated high discriminative power in the validation data, was adjusted for overfitting using LASSO regression, and can be easily applied by physicians using a digital risk calculator. Furthermore, the JAMAR is a commonly used instrument in the care and follow-up (2-4 times annually) of patients with JIA worldwide and has been validated in 54 languages across 52 countries.²⁴ On

the other hand, the JAMAR has not been validated in other diagnoses, and thus its use in patients with CMPS needs further investigation and validation. Another limitation of this study is that we could not differentiate between patients with CMPS with amplified musculoskeletal pain syndromes and those with orthopedic conditions owing to limited descriptions of CMPS diagnoses. In addition, our model has not been validated in a non-Western hospital. It is known that the distribution of ILAR categories varies globally,²⁵ and whether our model performs similarly in other settings is unclear. The clinical relevance of the model also depends on the number of pediatric rheumatologists in the target setting and their availability.

Previous studies have found an average duration of disease of >1 year for patients with CMPS²⁶ as opposed to only several months for patients with JIA.²⁷ For the JAMAR questionnaire to discriminate even better between JIA and CMPS, the items on “joint pain or swelling” might be separated into 2 categories: “joint pain” and “joint swelling.” The latter category is more likely to be associated with JIA than with CMPS as a result of active joint inflammation.

In conclusion, we have shown that several items from the JAMAR questionnaire can help distinguish JIA from CMPS in children with corresponding symptoms. We have presented an easy-to-use, adjusted, and validated model with the aim of differentiating JIA and CMPS early at presentation based on patient-reported outcomes to facilitate proper referral and treatment. Physicians can use the model even without having access to the full JAMAR questionnaire. ■

We thank all patients and their parents or guardians for consenting to this research, as well as the pediatric rheumatologists and research nurses from the Wilhelmina Children's Hospital for the acquisition of patient data.

Permission for use of JAMAR and its translations must be obtained in writing from PRINTO, Genoa, Italy. All JAMAR-related inquiries should be directed to printo@gaslini.org. Permission for use of Childhood Health Assessment Questionnaire (CHAQ) and Child Health Questionnaire (CHQ) derived material is granted through the scientific cooperation of the copyright holder, ICORE, Woodside, California and HealthActCHQ, Boston, Massachusetts. All CHQ-related inquiries should be directed to licensing@healthactchq.com. All CHAQ-related inquiries should be directed to g.singh@stanford.edu.

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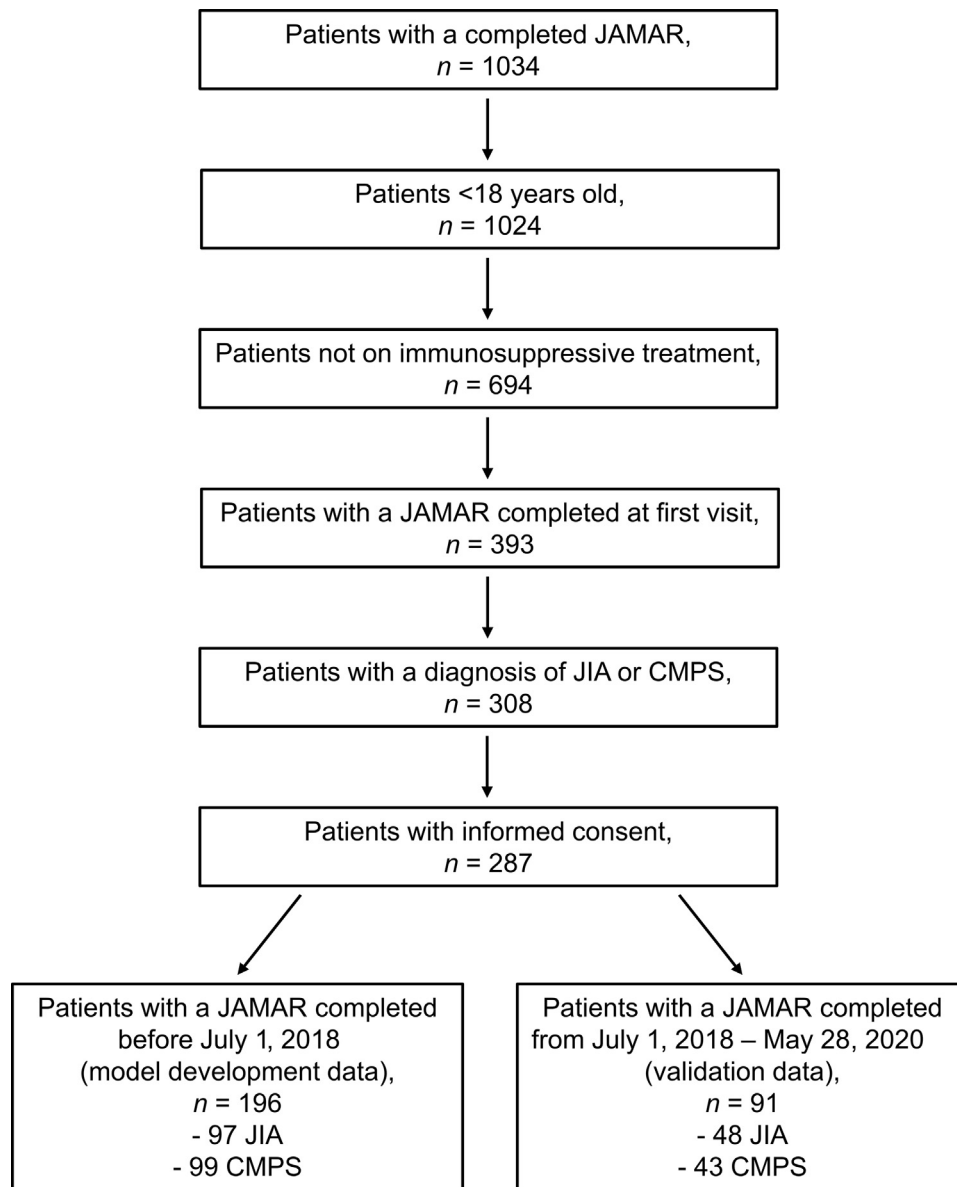


Figure 1. Flowchart of patients included in the model development and validation data.

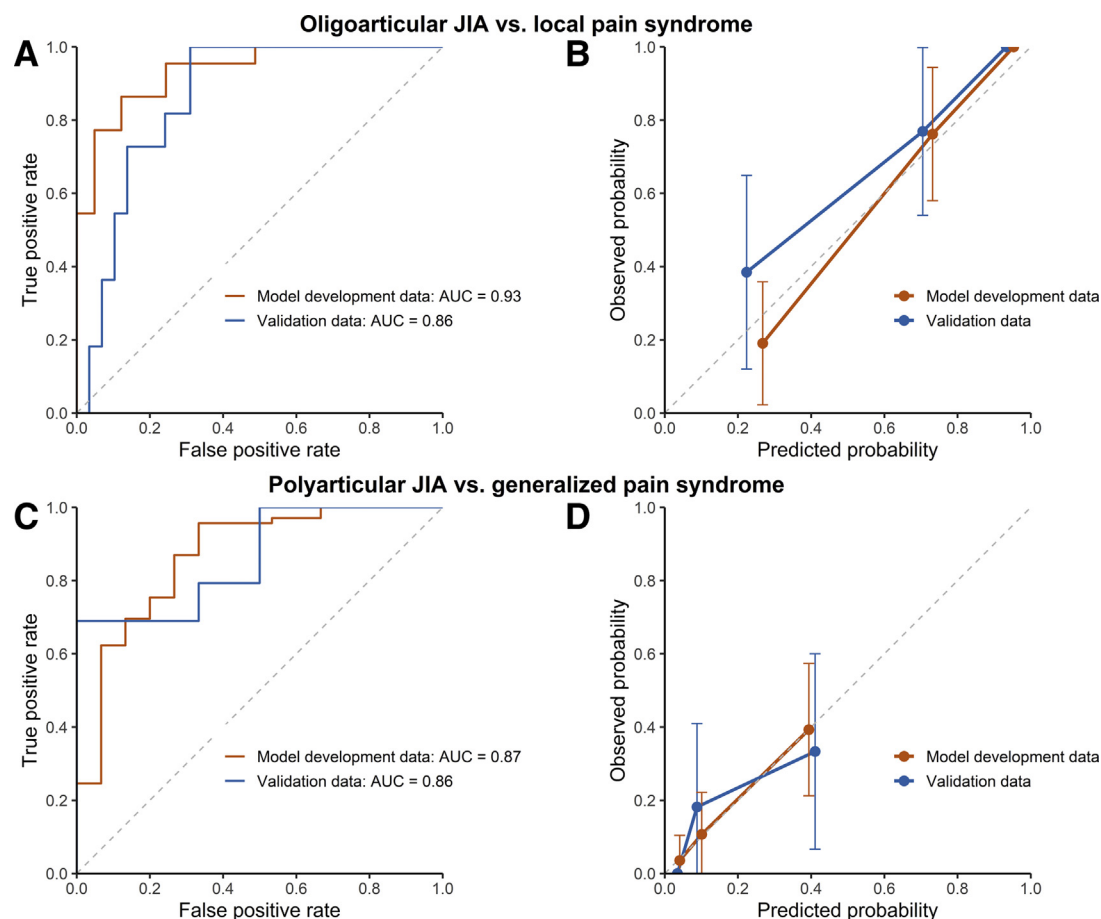


Figure 3. Performance of prediction models from secondary analyses for oligoarthritis versus local pain syndrome and polyarthritis versus generalized pain syndrome. **A** and **C**, Receiver operating characteristic curves of false-positive and true-positive rates for different thresholds of predicted probabilities. **B** and **D**, Calibration plots of mean predicted probabilities versus frequencies of the outcome within tertiles of the data. Vertical bars indicate 95% CIs.

Table II. Extended characteristics of patients in the model development data (N = 196)

Characteristics	JIA (N = 97)	CMPS (N = 99)	P value
Demographics			
Age at first visit, y, median (IQR), y	11.5 (5.4-14.7)	14.8 (12.2-16.1)	<.01*
Females, n (%)	67 (69.1)	82 (82.8)	<.03*
JAMAR items			
Functional ability during previous 4 wk, n (%)			
Difficulty running on flat ground (JAFS 1)	60 (63.2) (N = 95)	53 (53.5)	.18
Difficulty walking up 5 steps (JAFS 2)	49 (51.6) (N = 95)	44 (44.4)	.32
Difficulty jumping forward (JAFS 3)	56 (60.9) (N = 92)	52 (53.6) (N = 97)	.31
Difficulty squatting (JAFS 4)	62 (66.0) (N = 94)	63 (64.3) (N = 98)	.81
Difficulty bending down (JAFS 5)	41 (43.2) (N = 95)	45 (45.9) (N = 98)	.70
Difficulty carrying out activities with fingers (JAFS 6)	27 (28.1) (N = 96)	47 (48.0) (N = 98)	<.01*
Difficulty opening and closing fists (JAFS 7)	19 (19.8) (N = 96)	25 (25.5) (N = 98)	.34
Difficulty squeezing with hands (JAFS 8)	25 (26.3) (N = 95)	38 (38.4)	.07*
Difficulty opening a door (JAFS 9)	15 (17.0) (N = 88)	13 (13.1)	.46
Difficulty opening a tap or jar (JAFS 10)	22 (24.4) (N = 90)	27 (27.3)	.66
Difficulty stretching out arms (JAFS 11)	12 (12.8) (N = 94)	14 (14.1)	.78
Difficulty putting hands behind neck (JAFS 12)	7 (7.6) (N = 92)	18 (18.2)	.04*
Difficulty looking over shoulder (JAFS 13)	10 (10.5) (N = 95)	23 (23.2)	.02*
Difficulty looking up (JAFS 14)	7 (7.4) (N = 94)	19 (19.4) (N = 98)	.02*
Difficulty biting (JAFS 15)	1 (1.1) (N = 95)	3 (3.1) (N = 98)	.35
VAS pain, median (IQR)	5.0 (2.5-7.0)	6.0 (3.5-7.5)	.09*
Number of painful/swollen joints, median (IQR)	2 (1-4)	4 (2-7)	<.01*
Pain/swelling in finger(s), n (%)			
No	71 (73.2)	59 (59.6)	Reference
Asymmetric	10 (10.3)	10 (10.1)	.70
Symmetric	16 (16.5)	30 (30.3)	.02*
Pain/swelling in wrist(s), n (%)			
No	74 (76.3)	71 (71.7)	Reference
Asymmetric	13 (13.4)	9 (9.1)	.48
Symmetric	10 (10.3)	19 (19.2)	.11
Pain/swelling in elbow(s), n (%)			
No	86 (88.7)	87 (87.9)	Reference
Asymmetric	7 (7.2)	5 (5.1)	.57
Symmetric	4 (4.18)	7 (7.1)	.40
Pain/swelling in shoulder(s), n (%)			
No	85 (87.6)	80 (80.8)	Reference
Asymmetric	8 (8.2)	4 (4.0)	.32
Symmetric	4 (4.1)	15 (15.2)	.02*
Pain/swelling in hip(s), n (%)			
No	89 (91.8)	71 (71.7)	Reference
Asymmetric	4 (4.1)	10 (10.1)	.06*
Symmetric	4 (4.1)	18 (18.2)	<.01*
Pain/swelling in knee(s), n (%)			
No	36 (37.1)	41 (41.4)	Reference
Asymmetric	36 (37.1)	14 (14.1)	<.01
Symmetric	25 (25.8)	44 (44.4)	.20
Pain/swelling in ankle(s), n (%)			
No	72 (74.2)	61 (61.6)	Reference
Asymmetric	11 (11.3)	7 (7.1)	.58
Symmetric	14 (14.4)	31 (31.3)	<.01*
Pain/swelling in toe(s), n (%)			
No	79 (81.4)	83 (83.8)	Reference
Asymmetric	9 (9.3)	11 (11.1)	.75
Symmetric	9 (9.3)	5 (5.1)	.27
Pain/swelling in neck, n (%)	15 (15.5)	41 (41.4)	<.01*
Pain/swelling in lower back, n (%)	12 (12.4)	27 (27.3)	.01*
Morning stiffness, n (%)	69 (71.9) (N = 96)	65 (65.7)	.35
Fever, n (%)	7 (7.2)	5 (5.1)	.53
Skin rash, n (%)	20 (20.8) (N = 96)	7 (7.1)	<.01*
VAS disease activity, median (IQR)	4.5 (2.5-6.5)	3.0 (1.5-6.0)	.08*
State of illness, n (%)			
Remission	6 (6.3)	2 (2.1)	Reference
Persistent activity	75 (78.9)	74 (78.7)	.19
Relapse	14 (14.7) (N = 95)	18 (19.1) (N = 94)	.13
Attending school, n (%)	76 (78.4)	94 (94.9)	<.01*
Quality of life during previous 4 wk, n (%)			
Difficulty with self-care (JQL 1)	45 (50.0) (N = 90)	30 (32.3) (N = 93)	.02*
Difficulty taking a 15-minute walk or walking up stairs (JQL 2)	72 (76.6) (N = 94)	81 (84.4) (N = 96)	.18
Difficulty carrying out activities requiring a lot of energy (JQL 3)	76 (78.4) (N = 93)	87 (88.8) (N = 98)	.17
Difficulty doing at-school activities or playing with friends (JQL 4)	63 (73.3) (N = 86)	74 (76.3) (N = 97)	.64

(continued)

Table II. Continued

Characteristics	JIA (N = 97)	CMPS (N = 99)	P value
Had pain (JQL 5)	90 (94.7) (N = 95)	99 (100.0)	.99
Felt sad/depressed (JQL 6)	48 (51.1) (N = 94)	65 (66.3) (N = 98)	.03*
Felt nervous/anxious (JQL 7)	42 (44.2) (N = 95)	46 (48.4) (N = 95)	.56
Trouble getting along with other children (JQL 8)	16 (17.0) (N = 94)	19 (19.8) (N = 96)	.62
Difficulty concentrating (JQL 9)	50 (55.6) (N = 90)	66 (67.3) (N = 98)	.10*
Felt dissatisfied with appearance or abilities (JQL 10)	29 (35.4) (N = 82)	44 (45.4) (N = 97)	.18
VAS well-being, median (IQR)	3.5 (1.0-6.0)	3.8 (1.0-6.4)	.56
Satisfied with illness, n (%)	12 (12.6) (N = 95)	11 (11.2) (N = 98)	.76

*Variables with $P < .10$ were included in multivariable logistic LASSO regression.

Table IV. Characteristics of patients in the validation data (N = 91)

Characteristic	JIA (N = 48)	CMPS (N = 43)
Demographics		
Age at first visit, y, median (IQR)	11.4 (5.1-14.7)	15.3 (12.2-16.3)
Females, n (%)	25 (52.1)	36 (83.7)
JAMAR items		
Functional ability during previous 4 wk, n (%)		
Difficulty running on flat ground (JAFS 1)	26 (55.3) (N = 47)	27 (62.8)
Difficulty walking up 5 steps (JAFS 2)	20 (43.5) (N = 46)	23 (53.5)
Difficulty jumping forward (JAFS 3)	25 (53.2) (N = 47)	21 (50.0) (N = 42)
Difficulty squatting (JAFS 4)	29 (60.4)	29 (67.4)
Difficulty bending down (JAFS 5)	22 (46.8) (N = 47)	23 (53.5)
Difficulty performing activities with fingers (JAFS 6)	12 (25.0)	16 (37.2)
Difficulty opening and closing fists (JAFS 7)	10 (21.3) (N = 47)	10 (23.3)
Difficulty squeezing with hands (JAFS 8)	13 (27.1)	15 (34.9)
Difficulty opening a door (JAFS 9)	9 (19.6) (N = 46)	2 (4.7)
Difficulty opening a tap or jar (JAFS 10)	10 (22.7) (N = 44)	12 (27.9)
Difficulty stretching out arms (JAFS 11)	7 (14.9) (N = 47)	5 (11.6)
Difficulty putting hands behind neck (JAFS 12)	5 (10.4)	2 (4.7)
Difficulty looking over shoulder (JAFS 13)	3 (6.5) (N = 46)	12 (27.9)
Difficulty looking up (JAFS 14)	2 (4.2)	8 (18.6)
Difficulty biting (JAFS 15)	3 (6.2)	2 (4.7)
VAS pain, median (IQR)	4.0 (1.0-7.0)	6.0 (4.3-8.0)
Number of painful/swollen joints, median (IQR)	1.5 (1.0-4.0)	4.0 (1.5-7.5)
Pain/swelling in finger(s), n (%)		
No	36 (75.0)	27 (62.8)
Asymmetric	4 (8.3)	3 (7.0)
Symmetric	8 (16.7)	13 (30.2)
Pain/swelling in wrist(s), n (%)		
No	33 (68.8)	27 (62.8)
Asymmetric	11 (22.9)	3 (7.0)
Symmetric	4 (8.3)	13 (30.2)
Pain/swelling in elbow(s), n (%)		
No	42 (87.5)	37 (86.0)
Asymmetric	2 (4.2)	2 (4.7)
Symmetric	4 (8.3)	4 (9.3)
Pain/swelling in shoulder(s), n (%)		
No	41 (85.4)	29 (67.4)
Asymmetric	4 (8.3)	3 (7.0)
Symmetric	3 (6.2)	11 (25.6)
Pain/swelling in hip(s), n (%)		
No	46 (95.8)	34 (79.1)
Asymmetric	1 (2.1)	2 (4.7)
Symmetric	1 (2.1)	7 (16.3)
Pain/swelling in knee(s), n (%)		
No	13 (27.1)	23 (53.5)
Asymmetric	24 (50.0)	4 (9.3)
Symmetric	11 (22.9)	16 (37.2)
Pain/swelling in ankle(s), n (%)		
No	37 (77.1)	29 (67.4)
Asymmetric	9 (18.8)	4 (9.3)
Symmetric	2 (4.2)	10 (23.3)
Pain/swelling in toe(s), n (%)		
No	45 (93.8)	38 (88.4)
Asymmetric	1 (2.1)	2 (4.7)
Symmetric	2 (4.2)	3 (7.0)
Pain/swelling in neck, n (%)	5 (10.4)	22 (51.2)
Pain/swelling in lower back, n (%)	3 (6.2)	13 (30.2)
Morning stiffness, n (%)	33 (68.8)	30 (71.4) (N = 42)
Fever, n (%)	8 (16.7)	1 (2.3)
Skin rash, n (%)	10 (20.8)	4 (9.3)
VAS disease activity, median (IQR)	4.5 (1.0-6.5)	5.0 (2.3-7.5)
State of illness, n (%)		
Remission	4 (8.3)	0 (0.0)
Persistent activity	36 (75.0)	34 (81.0)
Relapse	8 (16.7)	8 (19.0) (N = 42)
Attending school, n (%)	36 (75.0)	42 (97.7)
Quality of life during previous 4 wk, n (%)		
Difficulty with self-care (JQL 1)	20 (44.4) (N = 45)	15 (35.7) (N = 42)
Difficulty taking a 15-min walk or walking up stairs (JQL 2)	32 (68.1) (N = 47)	37 (86.0)
Difficulty carrying out activities that require a lot of energy (JQL 3)	36 (80.0) (N = 45)	38 (88.4)
Difficulty doing at-school activities or playing with friends (JQL 4)	24 (55.8) (N = 43)	35 (83.3) (N = 42)

(continued)

Table IV. Continued

Characteristic	JIA (N = 48)	CMPS (N = 43)
Had pain (JQL 5)	45 (93.8)	43 (100.0)
Felt sad/depressed (JQL 6)	22 (47.8) (N = 46)	29 (69.0) (N = 42)
Felt nervous/anxious (JQL 7)	22 (46.8) (N = 47)	25 (62.5) (N = 40)
Trouble getting along with other children (JQL 8)	7 (14.9) (N = 47)	12 (27.9)
Difficulty concentrating (JQL 9)	28 (58.3)	31 (72.1)
Felt dissatisfied with appearance or abilities (JQL 10)	13 (31.0) (N = 42)	18 (42.9) (N = 42)
VAS well-being, median (IQR)	3.5 (1.4-6.0)	5.0 (2.8-7.0)
Satisfied with illness, n (%)	6 (12.5)	7 (17.1) (N = 41)

Table V. Distribution of subtypes of patients with JIA and CMPS

Disorders	Model development data (N = 196)	Validation data (N = 91)
JIA, n (%)		
Total	97 (100.0)	48 (100.0)
Enthesitis-related arthritis	14 (14.4)	2 (4.2)
Oligoarthritis	53 (54.6)	33 (66.7)
Psoriatic arthritis	9 (9.3)	0 (0.0)
RF ⁻ polyarthritis	8 (8.2)	5 (10.4)
RF ⁺ polyarthritis	7 (7.2)	2 (4.2)
Systemic arthritis	3 (3.1)	6 (12.5)
Undifferentiated arthritis	3 (3.1)	1 (2.1)
CMPS, n (%)		
Total	97 (100.0) [*]	42 (100.0) [†]
Local pain [‡]	27 (27.8)	13 (31.0)
Generalized pain [§]	70 (72.2)	29 (69.0)

RF, rheumatoid factor.

^{*}For 2 patients, no subtype could be determined.[†]For 1 patient, no subtype could be determined.[‡]At maximum 1 painful joint group.[§]Two or more painful joint groups.