Early Predictors of Longterm Outcome in Patients with Juvenile Rheumatoid Arthritis: Subset-Specific Correlations

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ABSTRACT. ***Objective.*** To determine early predictors of longterm outcome in juvenile rheumatoid arthritis (JRA) in a multicenter cohort.

Methods. Patients were selected if they were ≥ 8 years of age; the onset of arthritis occurred ≥ 5 years before study; and a diagnosis of JRA was made at a participating center. Outcome variables were scores on self-administered Childhood Health Assessment Questionnaires (CHAQ) and active disease duration. Possible explanatory variables assessed included characteristics present at onset, HLA alleles, in particular the rheumatoid arthritis associated shared epitope (RASE), and radiographic indicators of joint damage within 2 years of onset. Data for 393 patients were available. Multivariate analyses were performed for the total group and for each onset subtype.

Results. Male sex correlated with worse disability in systemic onset JRA but less disability in RF negative, and a shorter active disease duration in RF positive polyarticular onset JRA. Positive antinuclear antibody correlated with a longer active disease duration in patients with pauciarticular onset JRA. Younger age at onset predicted longer active disease duration in pauciarticular and RF negative polyarticular, and a shorter active disease duration in systemic onset JRA. Residence on a reserve, rather than native North American race, correlated with worse disability. The RASE correlated with less disability in systemic JRA; but no correlation with outcome was evident for patients with rheumatoid factor positive polyarticular JRA.

Conclusion. Variables predictive of longterm outcome in JRA are specific for each onset subtype. The most important early predictors were age at onset and sex of the patient. Place of residence may have a greater effect on disability than race. RASE may associate with a more favorable outcome in systemic onset disease. (J Rheumatol 2003;30:585–93)

Key Indexing Terms:
JUVENILE RHEUMATOID ARTHRITIS LONGTERM OUTCOME

The ability to predict disease outcome for children with chronic arthritis is an essential aid in the selection of therapeutic options. However, little is known about what factors are predictive of outcome. As the most useful predictors are those that are identifiable early in disease, we investigated correlations of longterm articular outcome with characteristics present at, or soon after, disease onset in a multicenter cohort of patients with juvenile rheumatoid arthritis (JRA). Variables evaluated included onset subtype, demographic and serologic characteristics, HLA alleles, and radiographic signs of damage within the first 2 years after onset. We also determined whether certain variables might modify the effects of onset subtype, or whether predictive variables might, on the other hand, differ among subtypes. In addition to disability, active disease duration was included as a longterm outcome. Prolonged active disease itself is an undesirable outcome and may also be considered an intervening variable as other measures such as disability or joint damage may increase as the duration of active arthritis increases[1-4]. For these reasons it is necessary to consider both disability and active disease duration to obtain a more complete understanding of possible predictors of longterm articular outcome.

While the association of various HLA alleles with different JRA subsets is well established in Caucasian populations, their potential use in predicting disease outcome has

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not been so well tested[5-7]. Although less well studied, available data suggest similar associations of HLA alleles with JRA in other races[8-11]. Earlier studies also suggest a correlation between DR4 and disease severity in children with JRA[12]. We therefore tested the hypothesis that HLA alleles correlate with disease outcome regardless of ethnic group or JRA onset subtype. In particular, in the case of the rheumatoid arthritis associated shared epitope (RASE)-bearing alleles we hypothesized a correlation with a worse prognosis, whereas for the alleles associated with pauciarticular JRA, DRB1*1104 and DRB1*0801, we expected an association with a better prognosis.

MATERIALS AND METHODS

Patients. Patients participating in a study of longterm outcomes of JRA have been described[13]. Briefly, inclusion criteria were an interval of ≥ 5 years since onset; age ≥ 8 years at the time of study; a minimum grade 3 reading level; and a diagnosis of JRA made at one of the participating centers, the Arthritis Centre in Vancouver, the Royal University Hospital in Saskatoon, or the Children's Hospital in Winnipeg. Exceptions to these criteria were one patient with onset at age 16.2 years and one with followup of 4.6 years. Diagnoses and onset subtype classifications were made by 1977 American College of Rheumatology criteria[14] with further subclassification of the polyarticular group into rheumatoid factor (RF) positive and negative subsets. Of 652 eligible patients, 393 participated in the study, and the remainder either refused participation or could not be located. Nonparticipants have been described[13]. The characteristics and disease outcomes of the patients studied are summarized in Table 1.

Procedures. The Childhood Health Assessment Questionnaire (CHAQ) was utilized as a measure of functional disability[15]. All patients completed a CHAQ at the time of study and 78% were also examined[13]. CHAQ scores were calculated as the mean score of the 8 categories of activities[13].

Inactive disease was defined as the absence of active arthritis on examination, whether a patient was receiving medications or not; remission was defined as a period of 2 years without active arthritis while no longer taking medication[13]. Active arthritis was defined as joint swelling or limitation of movement with heat, pain, or tenderness[13]. Active disease duration was calculated from time of onset of symptoms to time of study if arthritis was still active, or to time active arthritis was last documented if inactive or in remission[13]. For patients with intermittent disease the sums of periods of active arthritis were calculated as described[13].

Antinuclear antibody (ANA) tests were performed on mouse liver substrates during the 1970s and by HEp-2 cell lines thereafter. A positive ANA was defined as a positive test at a minimum of 1 in 20 dilution on mouse substrates and 1:40 on HEp-2 substrates on at least one occasion. Rheumatoid factors were confirmed by routine laboratory methods; a titer of ≥ 1 in 20 or > 20 international units was considered to be positive. DRB1 typing and subtyping were performed as described[10].

Analyses. For each outcome, namely disability and active disease duration, univariate analyses were performed first. Multivariate analyses were then done to determine independent predictors, assessing each variable while taking into account the effects of others. When all JRA subtypes were entered together, the analyses allowed comparisons to a reference group (pauciarticular) and the larger numbers allowed greater power to detect variables with significant correlation. The stratified analyses allowed a confirmation of significant effects within each onset subtype.

Age at onset, disease duration before the first visit to a study center, sex, onset subtype, race, place of residence, ANA positivity, HLA type, and joint space narrowing and erosions within 2 years after onset were entered as possible explanatory variables.

Because the main racial groups were Caucasian and native North American, race was dichotomized as native North American or non-native. Only patients whose parents were both North American native were included as native. Female sex and pauciarticular onset served as reference for sex and onset subtype, respectively. Residence was dichotomized as rural or nonrural (urban, suburban, and reserve) and as reserve or nonreserve (urban, suburban, and rural). Rural communities were nonsuburban locales with populations < 100,000.

All RASE-containing alleles, namely, HLA-DRB1*1001, 0101, 0401, 0404, 0405, 0408, and 1402, were considered together as a single variable[16]. DRB1*0801 and DRB1*1104 were each entered as separate vari-

Table 1. Patients' characteristics.

	Systemic	Pauciarticular	RF Negative Polyarticular	RF Positive Polyarticular
N	49	224	80	40
Age at onset, yrs [a]	6.2 (0.3–16.2)	3.3 (0.4–15.6)	5.4 (0.6–15.8)	10.2 (0.7–16.3)
Age at study, yrs [a]	17.7 (9.9–34.8)	16.9 (7.6–33.4)	18.7 (8–32.1)	24.7 (9.2–32.5)
Time from onset to study, yrs [a]	11.6 (5.0–23.6)	12.5 (4.6–24.8)	12.6 (5.1–23.8)	13.9 (6.5–23.5)
Time from onset to first visit, mo[a]	1.0 (0–14)	3 (0–139)	5 (0–125)	10.5 (0–84)
Male:female[b]	25:24	37:187	18:62	9:31
Caucasian:Native North American[c]:other[b]	42:2:5	207:4:13	57:14:9	21:18:1
Residence				
Urban or suburban:rural:reserve[b]	25:24:0	152:70:2	42:29:7	11:17:12
Positive ANA[d] (%)	5/45 (11)	135/215 (63)	45/79 (57)	32/40 (80)
RASE[d] (%)	16/39 (41)	40/150 (27)	24/67 (36)	26/35 (74)
DRB1*1104[d] (%)	2/39 (5)	21/150 (14)	2/67 (3)	1/35 (3)
DRB1*0801[d] (%)	1/39 (3)	38/150 (25)	10/67 (15)	3/35 (3)
Radiographic joint space narrowing within 2 yrs[d] (%)	6/20 (30)	3/56 (5)	5/38 (13)	7/22 (32)
Erosion within 2 yrs[d] (%)	7/20 (35)	5/56 (9)	6/38 (16)	12/22 (55)
CHAQ score[a]	0.25 (0–2.75)	0 (0–2.13)	0.19 (0–2.75)	0.62 (0–3.0)
Percentage of patients with CHAQ scores ≥ 0.75	34.7	11.2	26.3	47.5
Active disease duration, yrs[a]	5.2 (0.2–20.50)	4.7 (0.2–21.9)	7.0 (0.5–20.9)	10.8 (3.5–22.5)

[a] Median (range); [b] number of patients; [c] includes only those whose parents are both native North American; [d] number positive/number of tests done. RASE: RA shared epitope.

ables. Because the hypothesis was that HLA correlations with disease outcome occur in all ethnic groups, there was no stratification by race.

Statistical methods. Univariate analyses were performed by determination of Spearman's correlation coefficients, or by Mann-Whitney U or Kruskal-Wallis tests in the case of categorical variables. For active disease duration, Cox proportional hazards modeling was performed for each variable separately, with time to inactive disease status as the termination event in the survival analysis. Patients with active disease were censored to the time of study. In these analyses, a hazard ratio < 1.0 correlates with a longer active disease duration as the odds of remission at any given time are reduced; conversely, a hazard ratio > 1.0 correlates with a shorter active disease duration.

For multivariate analyses, multiple stepwise linear regression was used to identify predictors of CHAQ scores. To take differences in active disease duration into account, the analyses were adjusted for this parameter. To determine the odds of developing significant disability, conditional forward logistic regression analyses were used and the outcome chosen was a CHAQ score ≥ 0.75, as suggested by others[17]. Cox proportional hazard modeling was used to determine predictors of active disease duration. Possible interactions between onset subtype and other variables were assessed by entering their products.

As not all patients had complete data, separate analyses were performed for demographic data, demographic and HLA data, and demographic and radiographic data. However, the number of possible explanatory variables was reduced for stratified analyses of HLA alleles and radiographic changes so that the number of subjects in each analysis was at least 10 times the number of variables to ensure sufficient power. In general, the variables not entered were demographic items that showed no correlations in univariate analyses.

Analyses were performed by SPSS 10.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Univariate analyses. In the univariate analyses notable findings were a correlation of native North American race and residence on a reserve with both higher CHAQ scores and longer active disease duration when all patients were considered together (Tables 2A, 2B). Older age at onset correlated with shorter active disease duration for patients with pauciarticular or RF negative polyarticular onset (Table 2B).

All patients. The relative differences among onset subtypes and the complex interrelationships of the variables assessed were evident in multivariate analyses of the entire patient group (Table 3A). First, since active disease duration was highly correlated with disability (Table 3A, Analyses I and II), early predictors that affect the former, indirectly affect the latter. Positive ANA and age at onset were variables that affected disease duration but had no direct effects on disability; whereas male sex and residence on a reserve had effects only on disability without affecting disease duration (Table 3A). However, onset subtype affected active disease duration, but also had additional effects on disability (Table 3A).

Second, the interactions shown revealed that the effects of onset subtype were modified by other variables (Table 3A). In these analyses, the comparison group was all patients with pauciarticular onset JRA. For example, an older age at onset with systemic onset JRA predicted a longer active disease duration compared with pauciarticular onset JRA (Table 3A, Analysis III), and for each year of active disease, systemic onset JRA predicted greater disability (Table 3, Analysis I). Male sex with systemic onset correlated with worse disability (Table 3A, Analysis II). However, male sex combined with polyarticular RF negative or RF positive onset JRA predicted less disability (Table 3A, Analyses I and II).

HLA alleles were available for 291 patients. There were no predictive effects of RASE on active disease duration (analysis not shown). RASE by itself did not affect disability, but it modified the effect of systemic onset, predicting less disability than pauciarticular onset JRA when

Table 2A. Variables with significant correlations with CHAQ scores in univariate analyses.

Patient Group	Test Variable	p
All patients	Onset subtype	< 0.0001
	Age at onset[1]	0.001
	Time from onset to first clinic visit[2]	0.008
	Native North American race	< 0.0001
	Residence on a reserve	0.002
	Joint space narrowing within 2 yrs after onset	0.041
	Erosions within 2 yrs after onset	0.009
Systemic onset	RASE	0.016
Pauciarticular onset	Residence on a reserve	0.034
	Positive ANA	0.034
RF negative, polyarticular onset	Male	0.038

Analyses were by Mann-Whitney U or Kruskal-Wallis tests for categoric variables and by Spearman correlation coefficients for continuous variables. The following variables were assessed for both CHAQ score and active disease duration for each group: age at onset, time from onset to first visit, sex, native North American race, residence on a reserve, rural residence, ANA, RASE, HLA-DRB1*0801, HLA-DRB1*1104, erosions and joint space narrowing within 2 years after onset. CHAQ scores differed among JRA onset subtypes. Other variables with significant effects were positively correlated with CHAQ scores. [1]Correlation coefficient = 0.164; [2] correlation coefficient = 0.134. RASE: RA shared epitope.

Table 2B. Variables with significant correlations with active disease duration in univariate analyses.

Patient Group	Test Variable	Hazard Ratio (95% CI)	p
All patients	Onset subtype[a]		
	Pauciarticular	1.0	
	Systemic	0.84 (0.57, 1.26)	0.40
	RF – polyarticular	0.14 (0.07, 0.30)	< 0.0001
	RF + polyarticular	0.52 (0.36, 0.74)	< 0.0001
	Native North American race	0.30 (0.16, 0.57)	< 0.0001
	Residence on a reserve	0.30 (0.12, 0.72)	0.007
	Time from onset to first clinic visit	0.98 (0.96, 0.99)	< 0.0001
	Positive ANA	0.56 (0.43, 0.74)	< 0.0001
	Erosians within 2 yrs after onset	0.49 (0.24, 0.98)	0.045
Systemic onset	Erosions within 2 yrs after onset	0.17 (0.03, 0.87)	0.034
Pauciarticular onset	Age at onset	1.07 (1.02, 1.11)	0.005
	Positive ANA	0.46 (0.33, 0.65)	< 0.0001
RF negative, polyarticular onset	Age at onset	1.15 (1.07, 1.24)	< 0.0001
	Time from onset to first visit	0.96 (0.96, 1.0)	0.037
RF positive, polyarticular onset	Male	5.74 (1.27, 26.02)	0.023
	DRB1*1104	12.85 (1.13, 146.7)	0.04

Cox proportional hazards test was performed separately for each variable. A hazard ratio < 1.0 indicates correlation with longer active disease duration; hazard ratio > 1.0 correlates with shorter active disease duration. [a]Onset subtypes were assessed in a single analysis, using pauciarticular onset as the reference.

the 2 were both present (Table 3B). In contrast, RASE with polyarticular RF positive onset JRA had no significant effects (Table 3B).

Similar analyses revealed no predictive effects of HLA-DRB1*1104 and 0801 on CHAQ scores, the odds of a CHAQ score ≥ 0.75, or active disease duration (analyses not shown).

Early radiographs were available for 136 patients. In separate analyses, joint space narrowing or erosions within 2 years after onset were not predictive of CHAQ scores, a CHAQ score ≥ 0.75, or active disease duration (analyses not shown).

Multivariate analyses stratified by onset subtype. Although there were some differences, results of stratified analyses tended to confirm the interactions between onset subtype on the one hand and age at onset, sex, and RASE on the other that were expressed above.

Systemic onset. As above, male sex predicted worse disability, while RASE was highly protective (Table 4). Radiologic measures were not analyzed in multivariate tests due to the small number of patients with early radiographs.

Pauciarticular onset. Even though there were few patients with pauciarticular onset who resided on reserves or who had early joint space narrowing, these 2 variables were predictive of worse disability; but confidence intervals were wide (Table 5A). A positive ANA correlated with a longer, and an older age at onset with a shorter active disease duration (Table 5B).

RF negative polyarticular JRA. Male sex and rural residence predicted a better functional outcome for patients with RF negative polyarticular JRA); while as in pauciarticular onset JRA, an older age at onset correlated with a shorter active disease duration (Table 6).

RF positive polyarticular JRA. The only predictive variable for patients with polyarticular RF positive JRA was male sex, which correlated with a shorter active disease duration (Table 7). No predictive variables for disability among patients with RF positive polyarticular JRA were found in separate multivariate tests (analyses not shown). In particular, RASE did not predict worse disability.

DISCUSSION

Our study concentrated on patient characteristics present at disease onset or early in disease, as the intent was to identify those variables that may predict future outcome. Complex interrelationships were found among the variables studied. The main findings were: (1) Active disease duration was highly correlated with disability, and some variables primarily affected active disease duration, thereby indirectly affecting disability. Others had direct effects on disability that were not mediated through active disease duration, or had both types of effects. (2) Differences among onset subtypes were modified by other variables. (3) Predictive factors differed among onset subtypes. And (4) age at onset and sex were the most important early predictive variables. For example, sex and age at onset combined with onset subtype predicted significant differences in outcomes. Male sex predicted worse functional outcomes in systemic JRA, but was correlated with favorable outcomes in RF negative polyarticular and RF positive polyarticular JRA. Positive ANA was a predictive variable for longer active disease duration only for pauciarticular onset, while RASE was predictive of less disability only for patients with systemic onset.

Table 3A. Predictors of disability and active disease duration for all patients.

	Analysis I		Analysis II		Analysis III	
N	386		388		356	
Outcome variable	CHAQ score		CHAQ score ≥ 0.75		Active disease duration	
R^2	0.317		Cox and Snell 0.199			
Variables Entered	B (95% CI)	p	OR (95% CI)	p	Hazard Ratio (95% CI)	p
Age at onset	0.0095 (–0.008, 0.027)	NS	1.03 (0.91, 1.17)	NS	1.06 (1.02, 1.11)	0.008
Male	–0.079 (–0.24, 0.078)	NS	0.35 (0.095, 1.29)	NS	E	
Native North American	E		E		E	
Rural residence	E		E		E	
Residence on a reserve	0.31 (0.073, 0.54)	0.01	E		E	
Time to first visit	E		E		E	
Positive ANA	E		E		0.56 (0.42, 0.76)	< 0.0001
Active disease duration	0.029 (0.016, 0.042)	< 0.0001	1.17 (1.10, 1.24)	< 0.0001	—*	
Pauciarticular onset			1.0		1.0	
Systemic onset	0.16 (–0.21, 0.53)	NS	2.60 (0.38, 18.0)	NS	1.43 (0.68, 3.02)	NS
RF – polyarticular	0.041 (–0.33, 0.41)	NS	4.1 (1.24, 13.3)	0.021	0.33 (0.17, 0.65)	0.001
RF + polyarticular	0.51 (–0.21, 1.24)	NS	0.95 (0.053, 16.8)	NS	0.041 (0.002, 0.96)	0.047
Interacting variables						
Male and systemic onset	0.26 (–0.07, 0.60)	NS	8.17 (1.16, 57.3)	0.035	E	
Male and RF – polyarticular onset	–0.32 (–0.62, –0.016)	0.039	0.75 (0.094, 6.01)	NS	E	
Male and RF + polyarticular onset	–0.45 (–0.76, –0.14)	0.005	0.18 (0.037, 0.83)	0.028	E	
ANA and RF – polyarticular onset	E		E		E	
ANA and RF + polyarticular onset	E		E		E	
Age at onset and systemic onset	–0.017 (–0.055, 0.021)	NS	1.01 (0.82, 1.23)	NS	0.87 (0.79, 0.96)	0.005
Age at onset and RF – polyarticular onset	–0.0025 (–0.035, 0.03)	NS	0.94 (0.78, 1.12)	NS	1.04 (0.95, 1.13)	NS
Age at onset and RF + polyarticular onset	0.023 (–0.029, 0.075)	NS	1.22 (0.92, 1.62)	NS	1.09 (0.82, 1.44)	NS
Active disease duration and systemic onset	0.039 (0.007, 0.07)	0.017	E		—	
Active disease duration and RF – polyarticular onset	0.024 (–0.005, 0.052)	NS	E		—	
Active disease duration and RF + polyarticular onset	–0.02 (–0.053, 0.014)	NS	E		—	
Constant	–0.0047 (–0.15, 0.14)	NS	0.037	< 0.0001		

Regression coefficients (B) are given for variables entered in the final model. In analysis II, OR > 1.0 correlate with a greater risk of significant disability; in analysis III, a hazard ratio > 1.0 correlates with shorter active disease duration. Residence on a reserve correlated with higher CHAQ scores. Older age at onset correlated with shorter active disease duration; positive ANA and polyarticular RF negative and polyarticular RF positive onset JRA correlated with longer active disease duration. See text for explanation of other results. N: number of patients in the analysis. R^2: proportion of the variation explained by the regression. E: variables eliminated from the model. NS: not significant. *Variable not entered in the analysis. See Tables 2A and 2B for other abbreviations.

A correlation of a positive ANA with worse outcomes for patients with pauciarticular JRA has not been previously reported. Previous analyses have shown either no correlation or a decreased risk of disability in patients who were ANA positive[1,18]. However, in these studies all subtypes were considered together.

Contrary to our hypothesis, the results showed no correlation of HLA alleles with longterm outcome for most subsets of JRA. The apparent lack of correlation between RASE and outcome for patients with RF positive polyarticular onset in particular, may be due to an inadequate number of patients. The lack of association of HLA alleles with functional outcome has been reported in another cohort of patients with JRA, however[18]. Specific alleles tested included DR5 (which includes DRB1*1104) and DR1[18].

An exception was the correlation of RASE with less disability in systemic onset patients. While the correlation of DR4 with disease severity in systemic JRA has been contro-

Table 3B. Predictors of disability for all patients: predictive effect of HLA.

	Analysis I		Analysis II	
N	288		288	
Outcome variable	CHAQ score		CHAQ score ≥ 0.75	
R^2	0.322		Cox and Snell 0.240	
Variables Entered	B (95% CI)	p	OR (95% CI)	p
Male	–0.09 (–0.27, 0.094)	NS	0.45 (0.12, 1.75)	NS
Pauciarticular onset			1.0	
Systemic onset	0.340 (–0.24, 0.70)	0.067	5.81 (1.11, 30.4)	0.037
Polyarticular RF –	0.20 (–0.11, 0.51)	NS	4.50 (1.60, 12.7)	0.004
Polyarticular RF +	0.47 (–0.11, 1.05)	NS	2.12 (0.30, 14.8)	NS
RASE	0.12 (–0.056, 0.30)	NS	2.38 (0.74, 7.6)	NS
Active disease duration	0.03 (0.015, 0.046)	< 0.0001	1.17 (1.09, 1.26)	< 0.0001
Interacting variables				
Male and systemic onset	0.54 (0.17, 0.91)	0.005	18.0 (1.79, 180.1)	0.014
Male and RF – polyarticular onset	–0.16 (–0.49, 0.18)	NS	0.69 (0.082, 5.84)	NS
Male and RF + polyarticular onset	–0.29 (–0.62, 0.038)	0.083	0.22 (0.042, 1.18)	0.077
RASE and systemic onset	–0.58 (–0.95, –0.21)	0.002	0.037 (0.004, 0.36)	0.005
RASE and RF – polyarticular onset	–0.22 (–0.52, 0.088)	NS	0.38 (0.068, 2.07)	NS
RASE and RF + polyarticular onset	0.203 (–0.21, 0.61)	NS	3.60 (0.36, 36.2)	NS
Active disease duration and systemic onset	0.010 (–0.025, 0.045)	NS	E	
Active disease duration and RF – polyarticular onset	0.014 (–0.017, 0.044)	NS	E	
Active disease duration and RF + polyarticular onset	–0.009 (–0.045, 0.028)	NS	E	
Constant	–0.010 (–0.15, 0.13)	NS	0.026	< 0.001

Results of the final models are shown. Time to first visit, ANA, onset subtype with ANA, and onset subtype with age at onset were not entered as they were eliminated in the previous analyses (Table 3A). Variables eliminated were age at onset, native North American, rural residence, and residence on a reserve. See Tables 2A and 3A for abbreviations and explanations.

Table 4. Predictors of disability in patients with systemic onset JRA.

	Analysis I		Analysis II	
N	37		37	
Outcome variable	CHAQ score		CHAQ score ≥ 0.75	
R^2	0.225		Cox and Snell 0.417	
Variables Entered	B (95% CI)	p	OR (95% CI)	p
Active disease duration	0.046 (0.001, 0.092)	0.046	1.28 (1.02, 1.61)	0.035
Male	E		7.12 (1.05, 48.1)	0.044
RASE	–0.51 (–0.98, –0.042)	0.033	0.063 (0.008, 0.52)	0.010
Constant	0.56 (0.12, 0.99)	0.013	0.12	0.043

Male sex increased the odds of a CHAQ ≥ 0.75. In contrast, RASE predicted lower CHAQ scores and decreased the odds of a CHAQ score ≥ 0.75. Native North American race, ANA, time to first visit, HLA DRB1*0801 or 1104 were not entered in order to reduce the number of variables and allow sufficient power for the analysis. None of these variables showed significant correlations for patients with systemic onset in univariate analyses. Residence on a reserve was not entered as there were no patients with systemic onset living on reserves. When age at onset, male sex, rural residence, and active disease duration were entered, the number of patients was 47, and rural residence was also found to have significant correlations with CHAQ > 0.75 (OR 0.066, 95% CI 0.009, 0.504, p = 0.009) (analysis not shown). No explanatory variables for active disease duration were found (analyses not shown). See Tables 2A and 3A for abbreviations, symbols, and explanations.

versial, a higher frequency of DR4 in those with less severe systemic or articular involvement has been reported in another study[12,19,20]. The reasons for this protective effect are unclear.

Although the identification of early prognostic indicators in patients with JRA has been the subject of a number of reports, few variables present at onset have been found to correlate with longterm outcome[1,2,17,18]. In agreement with

Table 5A. Predictors of disability in patients with pauciarticular onset JRA.

	Analysis I		Analysis II		Analysis III	
N	221		56		221	
Outcome variable	CHAQ score		CHAQ score		CHAQ score ≥ 0.75	
R^2	0.174		0.208		Cox and Snell 0.087	
Variables Entered	B (95% CI)	p	B (95% CI)	p	OR (95% CI)	p
Age at onset	E		—		E	
Male	E		—		E	
Native North American	E		—		E	
Rural residence	E		—		E	
Residence on a reserve	0.51 (0.041, 0.97)	0.033	E		13.0 (0.75, 225)	0.079
Time to first visit	E		—		E	
Positive ANA	E		—		E	
Active disease duration	0.029 (0.020, 0.037)	< 0.0001	0.035 (0.008, 0.063)	0.013	1.18 (1.09, 1.28)	< 0.0001
Joint space narrowing within 2 yrs	—		0.610 (0.107, 1.11)	0.018	—	
Erosions within 2 yrs	—		E		—	
Constant	0.032 (–0.037, 0.10)	NS	–0.003 (–0.20, 0.194)	NS	0.032	< 0.001

Residence on a reserve was associated with worse CHAQ scores and a trend to increased odds of CHAQ ≥ 0.75. Joint space narrowing within 2 years after onset was also correlated with higher CHAQ scores. In separate mulivariate analyses, RASE, DRB1*0801, or DRB1*1104 were not significant predictors for CHAQ score or CHAQ score ≥ 0.75; and joint space narrowing or erosions were not predictive variables for CHAQ score > 0.75 (analyses not shown). See Tables 2A and 3A for other abbreviations and symbols.

Table 5B. Predictors of active disease duration in patients with pauciarticular onset JRA.

N	201	
Variables Entered	Hazard Ratio (95% CI)	p
Age at onset	1.06 (1.01, 1.11)	0.018
Male	E	
Native North American	E	
Rural residence	E	
Residence on a reserve	E	
Time to first visit	E	
Positive ANA	0.49 (0.35, 0.69)	< 0.0001

Positive ANA correlated with a longer, and older age at onset with a shorter, active disease duration. In separate multivariate analyses, RASE, DRB1*0801, DRB1*1104, or radiologic joint space narrowing or erosions were not predictive (analysis not shown). See Tables 2B and 3A for abbreviations, symbols, and explanations.

our results, one study reported less disability in male patients[1]. A young age at onset has also been shown to predict both more severe articular disease and a worse functional outcome for patients with systemic JRA in several reports[17,21,22], including hospital based studies[23,24]; but no effect was noted in other multivariate analyses including population based studies[1,2,18]. Our results suggest that age at onset may affect functional outcome indirectly through its effects on active disease duration.

Only 55% of native North American patients resided on reserves, therefore residence on a reserve could be assessed separately from race, and proved to be predictive of worse outcomes. The results suggest that native North American race itself may not be predictive of outcome, but other variables including onset subtype and place of residence may be more important. In turn, place of residence may correlate with access to health care, living conditions, and level of education. The chores described in the CHAQ may also be more difficult to perform in a reserve setting, resulting in higher scores. These possibilities require further study.

Other studies suggest that a polyarticular disease course may be important in determining disease outcome[1,2]. In our original analysis of this cohort, conversion to polyarticular arthritis occurred in 20% of patients with pauciarticular onset; however, this occurred at a median interval of 4 years from onset[13]. As such, we did not include this development in the analyses of early predictors.

The optimal instrument to use for longterm studies that involve patients of various age groups may be debated. Although most of the activities listed in the Health Assessment Questionnaire are included in the CHAQ, it should be acknowledged that the validation studies for the CHAQ did not include adults among the test subjects[15]. We chose the CHAQ as it includes activities relevant to a wide age range, including adults[15], and we preferred to use a single consistent instrument rather than use the HAQ for patients who had become adults.

The retrospective design limits analytic possibilities of this study. For example, other characteristics present at onset could not be included due to lack of adequate data collection. These included the number and distribution of affected joints and early laboratory variables such as sedimentation rate or C-reactive protein.

Table 6. Predictors of disability and active disease duration in patients with polyarticular RF negative onset JRA.

	Analysis I		Analysis II		Analysis III	
N	80		78		74	
Outcome variables	CHAQ score		CHAQ score ≥ 0.75		Active disease duration	
R^2	0.219		Cox and Snell 0.244			
Variables Entered	OR (95% CI)	p	OR (95% CI)	p	Hazard Ratio (95% CI)	p
Age at onset	E		E		1.15 (1.06, 1.24)	0.001
Male	–0.30 (–0.58, –0.013)	0.041	0.082 (0.009, 0.74)	0.026	E	
Native North American	E		E		E	
Rural residence	E		0.132 (0.028, 0.620)	0.010	E	
Residence on a reserve	E		E		E	
Time to first visit	E		E		E	
Active disease duration	0.052 (0.027, 0.077)	< 0.001	1.21 (1.05, 1.38)	0.006	—	
Constant	0.12 (–0.12, 0.35)	NS	0.161	0.007		

Male sex predicted lower CHAQ scores and decreased the odds of a CHAQ score ≥ 0.75. Older age at onset correlated with a shorter active duration. RASE, DRB1*0801 or DRB1*1104, or early joint space narrowing or erosions were not predictive variables in separate multivariate analyses (analyses not shown). See Tables 2A, 2B, 3A for abbreviations, symbols, and explanations.

Table 7. Predictors of active disease duration in patients with RF positive polyarticular onset JRA.

N	39	
Variables Entered	Hazard Ratio (95% CI)	p
Age at onset	E	
Male	5.74 (1.27, 26.02)	0.023
Native North American	E	
Residence on a reserve	E	

Male sex correlated with a shorter active disease duration. Rural residence, time from onset to first visit, and ANA were not entered in order to reduce the number of variables. These variables showed no correlations with outcome for patients with RF positive polyarticular onset in univariate tests. Joint space narrowing or erosions were not assessed in multivariate tests due to inadequate numbers of patients with early radiographs. See Tables 2B and 3A for abbreviations.

Potential sources of selection bias included the patients who did not participate in the study, and those who did not have HLA typing or lacked early radiographs. Although only 60% of eligible patients participated in the longterm followup study, our previous analysis of this cohort showed that nonparticipants had a slightly longer time interval since onset and were slightly older at the time of these studies[13]. In contrast, there were no differences in onset subtype distribution, age at onset, race, sex, or residence[13]. Since radiographs were performed on clinical indications, patients included in these analyses may be biased toward those with more severe disease. In addition, an estimated 15 patients whose onset may have been ≥ 5 years ago may have been excluded from this study because they were < 8 years of age. Some patient groups also lacked sufficient numbers, so the number of variables that could be entered in multivariate analyses was limited.

All these limitations restrict the conclusions that can be made from our analyses. Within these limitations, we show that some early predictors indirectly affect disability through effects on active disease duration; that early predictive variables are onset subtype-specific; and that age at onset and sex of the patient are the most important predictors of longterm outcome. Place of residence, rather than native North American origin, may have a greater predictive effect on longterm disability, but the exact variables underlying this observation require further examination.

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