Predictors of Disease Activity in Juvenile Idiopathic Arthritis at 12 and 24 Months After Diagnosis

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Abstract

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Objective: Identification of characteristics associated with risk of active disease in Juvenile Idiopathic Arthritis (JIA) could inform treatment strategies early in the disease state. This study evaluates JIA disease activity outcomes and patient characteristics associated with active disease at 12- and 24-months post diagnosis from a single large US center.

Methods: Disease activity status at 12- and 24-months after diagnosis was assessed retrospectively from 2004 – 2018 and categorized as “active” or “inactive” disease based on a modification of the Wallace criteria. The prevalence of disease activity was examined in relation to clinical and demographic characteristics identified at the time of JIA diagnosis and 3 months later. Patients without follow up at either 12 or 24 months were not included in the main analysis for this time point. The primary analysis cohort was separated into three time of diagnosis cohorts which align with availability of novel biologic DMARD medications, and prevalence of

active disease was examined for clinical and demographic characteristics of interest with particular attention to the most contemporary cohort (1/1/014 – 12/31/2018). A sensitivity analysis included patients on whom follow-up information was not available, with the presumption of these patients likely had inactive disease.

Results: A total of 1151 JIA subjects were included, with 38% having oligoarticular disease. At 12 months, a 40-50% higher prevalence of active disease was noted in children five years and older, when compared to those less than five years old. Additionally, those with active disease 3 months after diagnosis had a higher prevalence of active disease at 12 months than those who were inactive at 3 months (relative prevalence (RP) 1.48 (95% CI 1.22, 1.78)). Relative to children with monoarticular involvement, those with polyarticular RF-negative (RP 1.22 (95% CI 1.01, 1.38)), psoriatic arthritis (RP 1.34 (95% CI 1.06, 1.68)), or enthesitis related arthritis (ERA) (RP 1.23 (95% CI 0.99, 1.53) had a higher prevalence of active disease. At 24 months, a higher prevalence of active disease was seen in children 10 years or older compared to those under five years (RP 1.5 (95% CI 1.19, 1.88)), in children with polyarticular RF-, psoriatic arthritis, and ERA (though to a lesser extent than at 12 months), and in those with active disease at 3 months (RP 1.28 (95% CI 1.02, 1.59)). The prevalence of active disease was 25% smaller in the most recent time period than in the earliest period (RP=0.75 (95% CI 0.62, 0.92), but the predictors of disease activity at 12 and 24 months after diagnosis were broadly similar over time.

Conclusion: In this large center, real world cohort, JIA patient characteristics associated with active disease at 12 and 24 months included older age at diagnosis, polyarticular RF-, psoriatic arthritis, or ERA categories, and the presence of active disease at 3 months after diagnosis.

Overall, the modest associations demonstrated are broadly in agreement with those seen in earlier studies, but offer little guidance for patient management. Further work is needed to identify predictors of active disease during the 1-2 years following a diagnosis of JIA.

Juvenile idiopathic Arthritis (JIA) has an estimated prevalence of 30 per 100,000 in North American and European populations.[1] JIA currently is categorized into seven mutually exclusive non-homogeneous categories by International League of Associations for Rheumatology (ILAR) criteria [2,3], based on number of joints affected, serologic status and presence of other factors such as psoriasis and age at presentation. In contrast, the proposed Paediatric Rheumatology International Trials Organisation (PRINTO) classification [4] is based on proposed homogeneous biological subgroups, similar to adult inflammatory arthritis classification schemes.[5]

Prior studies have described prognostic factors for JIA disease outcomes. Children in the oligoarticular ILAR category have been identified as having a relatively favorable chance of achieving disease remission [6], while those in the polyarticular [7–11] and enthesitis related arthritis (ERA) categories have the highest chance of unfavorable outcomes [6,12–14]. Beyond category, previously identified prognostic factors for poor disease outcomes include: rheumatoid factor (RF) positivity [8,9,11,13,15]; elevated ESR and CRP at diagnosis and persistent elevation of either C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) [7,8,16–19]; longer duration of disease prior to treatment; and higher baseline Juvenile Arthritis Disease Activity Score (JADAS)[10,16,20]. In addition, early hip [8,15], wrist [14,18] or ankle [14,16,18,19] involvement has been suggested as predicting poor disease outcomes. Further, many of these studies have largely been conducted prior to the availability of biologic disease modifying anti-rheumatic drugs (bDMARDs) whose efficacy typically is greater than that of prior treatment interventions.

The goal of the present study was to re-examine predictors of response to therapy in patients with JIA in a large, single center US based cohort, with a focus on patients diagnosed during the bDMARD era.

Methods

Population

This was a retrospective cohort study from a single quaternary center, Seattle Children's Hospital (SCH), evaluating JIA patients diagnosed during 2004 – 2018. Patients were identified using ICD-10 codes for JIA (M0.80, M08.0, M0.81, M0.82, M0.83, M0.84, M0.88, M0.89, M45.9, L40.54, L40.59, 720.0, 696.0, 714.32, 714.31, 714.33, 714.30, 364, and H20), and de-identified data was extracted from the Electronic Medical Records (EMR). We included patients with a JIA diagnosis by ILAR criteria or by the treating pediatric rheumatologist at the SCH Rheumatology Department. All patients were required to have been diagnosed and treated exclusively at SCH for the duration of the study follow-up period of 24 months. We excluded patients with systemic JIA, defined as the presence of arthritis accompanied by fever, serositis and rash, concomitant inflammatory bowel disease, and patients who had undergone treatment with immunosuppressive therapy prior to JIA diagnosis or for a condition other than JIA, such as inflammatory bowel disease. This study was approved by the Seattle Children's Hospital IRB through a no participant contact protocol (study00002839).

Data was extracted from a central de-identified patient database housed at SCH, and individual medical charts were reviewed to identify demographic and clinical characteristics of participants as of the time of JIA diagnosis. Patient predictor variables included: age at diagnosis, date of diagnosis, sex, inflamed joint count at diagnosis, duration of symptoms prior to diagnosis, presence of uveitis , race, ethnicity, primary language spoken, insurance status, distance between patients home and treating rheumatologist, serologic status (including anti-nuclear antibody (ANA), RF, cyclic citrullinated peptide (CCP), and human leukocyte antigen B27 (HLA-B27)), and disease category by ILAR and PRINTO JIA classifications. ILAR categories [2,3] included

oligoarticular, polyarticular rheumatoid factor (RF) positive, polyarticular RF negative, psoriatic, and enthesitis related arthritis (ERA). Polyarticular patients without information regarding RF status were classified as being "polyarticular RF unknown". PRINTO categories [4] included seronegative, seropositive, and spondyloarthropathy. RF and CCP positive status indicate that at least one positive RF test had been recorded. We also documented disease activity at 3 months after diagnosis.

Subjects JIA disease activity status was determined at 12 months from the date of diagnosis, and again at 24 months. We utilized a modified version of the Wallace criteria [21] for the absence of active disease (mCID): no active inflamed joints; no fever, rash, serositis, splenomegaly or generalized lymphadenopathy attributable to JIA; no active uveitis; and physician global assessment of 0/10. ESR and CRP measurements were not used in defining active disease as they were not reliably tested across all subject visits. Patients were characterized as follows: 1) active disease, defined as failure to meet the criteria for mCID, 2) meeting criteria for mCID at time of assessment. Subjects in mCID could be either taking or not taking anti-rheumatic medications. Information from the visit closest to (and within three months of) 12 and 24 months from the diagnosis visit was used to document each subject's status.

Demographic and clinical characteristics were evaluated within the whole JIA cohort. Prevalence of both outcomes (and 95% confidence intervals (CI)) were calculated for each predictor variable. The relative prevalence of active disease (and the 95% CI) associated with each predictor variable was calculated at 12 and 24 months.

A secondary analysis divided patients by time period of diagnosis. Time periods were designated as (early 1/1/2004-12/31/2008), (mid 1/1/2009 – 12/31/2013), and (late 21/1/014 – 12/31/2018), selected to reflect changes in the availability of DMARD medications. The

approved bDMARD medications were limited to Enbrel in the early group, to which adalimumab and abatacept were added in 2008, followed by a substantial expansion of approved bDMARDs later on, including tocilizumab in 2013 and golimumab, along with the addition of targeted synthetic (ts)DMARD tofacitinib in 2020. Disease activity prevalence ratios and 95% confidence intervals were calculated at 12 and 24 months for each diagnosis period group. Subject characteristics associated with the presence of active disease in the initial analysis were re-examined separately for their association with disease activity at 12 months in subjects diagnosed during each of the three time periods.

Subjects with missing disease status at both the 12- and 24-month timepoint were excluded from the analysis; subjects with data at either timepoint were included in analysis at that timepoint. In a sensitivity analysis, subjects who had been excluded due to missing follow-up data were categorized as having inactive disease at their missing time point of 12 or 24 months, given a presumption that the absence of follow-up most likely meant that the subject did not have active disease at that time.

Results

A total of 1315 children diagnosed with JIA were included in the study cohort. Of these, 1151 were included in the primary analysis, 1115 subjects with their disease activity assessed at 12 months, and 1027 with an assessment at 24 months. 164 subjects were missing activity data at both 12 and 24 months and were excluded from the primary analysis. Demographic, clinical, and laboratory data are reported in Table 1 for all 1151 patients included.

Outcomes at 12 months (Table 2, Panel A)

We observed a 40-50% higher prevalence of active disease at 12 months in older subjects when compared to younger (≤5.0 years) subjects, with a relative prevalence (RP) of 1.41 (95% CI 1.14, 1.74) for 5.1–10.0-year-olds and 1.45 (95% CI 1.20, 1.76) for 10.1–16.0-year-olds. Subjects with an active joint count of >10 at diagnosis had a RP of 1.23 (95% CI 1.0, 1.52) for active disease, relative to those with a single inflamed joint. Subjects whose distance from home zip code to treating rheumatologist fell between 30-120 miles had a RP 1.16 (1.01, 1.36) compared to those whose zip code fell within 30 miles of treating rheumatologist. In patients who lived greater than 120 miles away, the association with active disease was weaker RP 1.07 (95%CI 0.85, 1.33). The presence of persistent active disease at the 3-month follow-up visit was associated with an increased prevalence of active disease at 12 months (RP of 1.48, 95% CI 1.22, 1.78).

Subjects diagnosed with ILAR polyarticular RF negative, psoriatic arthrtis, and ERA had an increased prevalence of active disease at 12 months - RPs of 1.22 (95% CI 1.01, 1.38), 1.34 (95% CI 1.06, 1.68), and 1.23 (95% CI 0.99-1.53), respectively, compared to subjects in the oligoarticular JIA category. There was no appreciable difference in the prevalence of active disease at 12 months among patients in the three PRINTO classification groups. Similarly, there was little difference in active disease prevalence based on serologic status, including ANA, RF, CCP, or HLAB27 positivity.

The prevalence of active disease 12 months after diagnosis was 25% smaller in the most recent time period (late) relative to that in the early period (RP=0.75 (0.62, 0.92)). (Table 2 – Panel A) During 2014-18, the size of the associations with disease activity in relation to age, type

of arthritis, and the presence of disease activity at three months were broadly similar to those seen in earlier years, but with a lesser level of statistical precision (Table 3).

Outcomes at 24 months (Table 2, Panel B)

Similar to 12-month outcomes, higher prevalence of active disease was noted in the oldest age group (10.1-16.0 years) when compared to the youngest (≤5.0 years) group (RP=1.5, (95% CI 1.19, 1.88)). Presence of ≥12 months of symptoms prior to JIA diagnosis was associated with active disease (RP of 1.33 (95% CI 1.05, 1.69), relative to subjects with <3 months of symptoms prior to diagnosis. The presence of persistent active disease at 3-month follow-up visit was associated with an increased prevalence of active disease at 24 months (RP of 1.28 (95% CI 1.02, 1.59). The increased risks associated with the presence of polyarticular RF negative and psoriatic arthritis, and with ERA, were smaller than at 12 months. There were no appreciable differences in prevalence of active disease among subjects categorized using the PRINTO classification criteria, or serologic status.

Sensitivity analysis

12.5% of subjects were missing activity data at both 12 and 24 months (164/1315). In the primary analysis, at 12 months 3% (36/1115) were missing activity data, and at 24 months 10.8% (124/1027). Disease activity missingness was spread relatively evenly across diagnosis time periods at 12 months, with 1.4% (4/28) during the early-time period (2004 – 2008), 3% (17/574) during the mid-time period (2009 – 2013), and 5% (15/296) for the late-time period (2014 – 2018). In the analysis which included all subjects regardless of missing follow up, subjects with oligoarticular disease were overrepresented in the proportion of the population in whom follow-up assessments at 12 or 24 months were not obtained. In this analysis we made the reasonable assumption that patients with lack of follow up likely had inactive disease at those time points.

The analysis based on the inclusion of all subjects led to an observed 14-46% higher prevalence of activity in subjects in the other four ILAR categories when compared to oligoarticular subjects, with prevalence ratios ranging from 1.14 (95% CI 0.76, 1.71) to 1.46 (95% CI 1.15, 1.85). (Table 4).

Discussion

This retrospective cohort study from a single large US quaternary care center re-examined predictors of response to therapy in patients with JIA diagnosed between 2004 and 2018, with a specific focus on patients diagnosed more recently in the era of increased access to bDMARD agents.

This analysis is limited most notably by the retrospective nature of the study and by missing data. 164 patients were lost to follow up in our study and could not be included in the final analysis. 152 patients (13.2%) could not be categorized as polyarticular RF positive or negative due to missing serology data. For the same reason,148 patients (13%) could not be sorted into PRINTO category.

We attempted to mitigate the problem of missing outcome data by conducting a sensitivity analysis which assumed no disease activity among patients who did not return for care; this did not give rise to any notable changes in our findings regarding characteristics and their predictive ability.

For our study, only one positive RF value was required for a patient to be considered RF positive. Additionally, we utilized a modification of the Wallace criteria for our definition of inactive disease (mCID), as ESR and CRP were not consistently available in the electronic medical record for all visits. However, we feel this reflects clinical practice as ESR and CRP are

not reliably obtained at every visit especially if the child is doing clinically well and this should not diminish findings from the study. Additionally, it would have been informative to evaluate patients based on medications received during the first 24 months after diagnosis, as treatment interventions have the potential to alter disease course and outcomes of interest. However, this granularity of detail was not available in our database at time of analysis, and would be an avenue for future study in a larger database.

Further, JIA patients', disease activity in real life reflects a continuum along which patients may move between inactive and active disease states frequently. Our study's point in time assessments at 3, 12 and 24 months after diagnosis does not account for this continuum of disease activity. Finally, over the time period of this study, treatment patterns for all categories of JIA have shifted, with new bDMARDs or tsDMARDs obtaining FDA approval and this could have impacted our outcomes. We attempted to mitigate this with our time period analysis, as noted above.

In our study, patients with the highest prevalence of active disease at 12 and 24 months were those in the polyarticular RF negative, psoriatic, and ERA categories. These findings were present in our primary analysis cohort in general and persisted in patients diagnosed during 2014-2018. These associations were somewhat smaller at 24 months of follow up, possibly reflecting that these patients received more aggressive treatment early in the disease course, in line with generally accepted treatment recommendations. [9,14,22] Previous literature largely supports the above groups as being at higher risk for poor disease control. [9,10,14] In a study examining patients from 1980 – 1985 (N=133) who were followed for disease activity for 14.9 years[8], polyarticular disease was associated with persistent JIA (OR 1.40 (95% CI 0.81, 2.43) compared to oligoarticular subjects. Additionally, the Nordic cohort[23] reported on patients from

1997 – 2000 (N=440), and observed that polyarticular RF negative patients had an OR of 2.2 (95% CI 1.3, 3.6) for non-achievement of remission off medications, while psoriatic patients had an OR of 0.7 (95% CI 0.1, 3.4) and ERA patients had an OR of 1.5 (95% CI 0.7, 3.1). In the REaCCH-Out cohort from 2005 – 2007 (N=882) [14], patients with polyarticular RF negative, psoriatic, and ERA all had decreased likelihood of obtaining inactive disease within 6 months of diagnosis compared to oligoarticular subjects, odds ratio (OR) 0.38 (95%CI 0.18, 0.80), 0.69 (95%CI 0.24, 2.05), and 0.46 (95%CI 0.18, 1.17), respectively. Additionally, in a study of Italian JIA patients receiving methotrexate during 2000 – 2013 (N=406),[7] failure to achieve inactive disease was relatively more common among those with polyarticular disease (OR 1.3 (95% CI 0.8, 2.1)), or ERA (OR 3.9 (95% CI 1.2, 11.8)) compared to oligoarticular patients.

We also evaluated preliminary proposed PRINTO classification groups, and did not find any PRINTO category to be associated with disease activity at 12 or 24 months after JIA diagnosis. PRINTO categories attempt to identify homogeneous JIA categories based on biologically plausible schema. However, our evaluation of the seropositive population may have been limited by missingness in our serologic status data. Further studies are needed to more thoroughly evaluate the prediction of longer-term disease status based of PRINTO classification categories.

We also noted an association between active disease and older age at diagnosis at both 12 and 24 months. A similar association has not consistently been seen in earlier studies, with Guzman *et al* [14] and Rypdal *et al* [23] reporting minimal to no association with age and disease activity outcomes in larger cohorts, and Flato *et al* reporting an modest association between persistent disease and age.[8] Because the prior research has been largely based on the experience of patients diagnosed in the pre- and early-bDMARD era, it is conceivable that an association

between older age at diagnosis and a poorer prognosis is only now becoming evident. Further, older age at diagnosis could be correlated with a longer time to presentation to a rheumatology provider and this association may be confounded. Given the modest nature of the associations we noted, further study is needed to better understand if age of disease onset is truly a predictor of disease status early in the course of JIA.

Similar to other studies in polyarticular [24,25] and oligoarticular [26]categories, our study, noted that patients with persistent active disease 3 months after diagnosis had an approximately 50% higher prevalence of active disease at 12 and 24 months. These all suggest that achievement of early disease control with inactive disease at both 3 months and certainly within 1 year of diagnosis are important for longstanding disease control and prevention of morbidity.

Conclusion

Using real world data on JIA patients treated at a large single US medical center, we observed the presence of active disease at 12 and 24 months to be modestly elevated in children with older age at diagnosis (5-16 years), and in those with polyarticular RF negative, psoriatic, or ERA categories. Additionally, the presence of persistent active disease at 3 months was associated with active disease being present at 12 and 24 months. These latter observations largely align with those from earlier studies, and lend support to the hypothesis that early achievement of disease control in JIA has positive longer-term consequences.

Nonetheless, because of the limited sensitivity and specificity of any of the identified characteristics in forecasting prognosis, their presence offers but little guidance for management of patients recently diagnosed with JIA. Further work is needed to identify and evaluate stronger predictors of the persistence of active disease as novel therapeutic agents become available.

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Ethics This manuscript has been seen and approved by all contributing authors; all work is original. Ethical approval was obtained through the Seattle Children's Hospital Institutional Review Board. This study complies with the Declaration of Helsinki.

Data availability Dr. Balay-Dustrude 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, data is available upon formal request.

Table 1: Table 1: Demographic and disease characteristics of JIA patients from 2004 – 2018 included in the primary analysis.

	Total N=1151 (%)		Total N=1151 (%)
Sex		**ILAR category**	
Female	786 (68.3)	Oligoarticular	444 (38.6)
Age at diagnosis (years)		Polyarticular RF-	239 (20.8)
0 – 5	329 (28.6)	Polyarticular RF+	44 (3.8)
5.1 – 10	297 (25.8)	Enthesitis Related Arthritis	158 (13.7)
10.1 - <16	525 (45.6)	Psoriatic	114 (9.9)
Active joint count		**PRINTO category**	
1	258 (22.4)	Seronegative	657 (65.5)
2 - 4	390 (33.9)	Seropositive	88 (8.8)
5 - 9	243 (21.1)	Spondyloarthritis	258 (25.7)
≥10	260 (22.6)	**Unclassified due to missing serology**	
Symptom onset prior to diagnosis (months)		ILAR - polyarticular RF unknown	152 (13.2)
<3.0	351 (30.5)	PRINTO - missing CCP & RF	148 (12.9)
3.1 – 6.0	300 (26.1)	**Uveitis**	200 (17.4)
6.1 – 12.0	209 (18.2)	**Disease activity at 3 months**	
≥12.0	291 (25.3)	Active	744 (69.0)
Distance to rheumatologist (miles)		Inactive	335 (31.0)
≤30	599 (52.0)	Missing	72 (6.3)
31 – 120	396 (34.4)	**Serologic status**	
>120	162 (14.1)	**ANA**	
Diagnosis time period		Negative	428 (48.6)
Early 1/1/2004 - 12/31/2008	281 (24.4)	Positive	453 (51.4)
Mid 1/1/2009 - 12/31/2013	574 (49.9)	Missing	270 (23.5)
Late 1/1/2013 - 12/31/2018	296 (25.7)	**RF**	
Race and ethnicity		Negative	671 (90.6)
American Indian, Alaska Native NH	25 (2.4)	Positive	70 (9.4)
Asian NH	57 (5.4)	Missing	410 (35.6)
Black NH	26 (2.4)	**CCP**	
Hispanic	155 (14.6)	Negative	561 (92.4)
Native Hawaiian, Pacific Islander NH	6 (0.6)	Positive	46 (7.6)
Other NH	45 (4.2)	Missing	544 (47.3)
White NH	748 (70.4)	**HLAB27**	
Missing	89 (7.7)	Negative	566 (83.4)
Primary language		Positive	113 (16.6)
English	1073 (93.2)	Missing	472 (41)
Language other than English	78 (6.8)		
Missing	116 (10.1)		
Insurance			
Medicaid	390 (34.3)		
Private	677 (59.6)		
Self-pay	25 (2.2)		
Tricare	44 (3.9)		
Missing	15 (1.3)		

Rheumatoid Factor (RF), Cyclic Citrullinated Peptide (CCP). Antinuclear Antibody (ANA). ILAR: International League Against Rheumatism. PRINTO: Paediatric Rheumatology International Trials Organisation. NH: non-Hispanic

Missing values represent proportion of entire cohort missing and are not included in prevalence calculations for each characteristic.

Table 2: Prevalence of JIA disease activity (active and inactive disease) and relative prevalence for JIA active disease within the primary cohort and each demographic and disease characteristic subgroup, at 12 months (Panel A) and 24 months (Panel B)

Panel A: 12 month JIA Outcomes	**Active disease**			**Inactive disease**			**RP active disease**	**95% CI**
	n	**Prevalence**	**95% CI**	**n**	**Prevalence**	**95% CI**		
N = 1115	449	40%	(37, 43)	666	60%	(57, 63)		
Sex								
Male	135	38%	(32, 43)	219	62%	(56, 67)	1.00	
Female	314	41%	(37, 45)	447	59%	(55, 62)	1.08	(0.92, 1.27)
Age at diagnosis (years)								
<5	99	31%	(25, 36)	223	69%	(64, 74)	1.00	
5.1 - 10	125	43%	(37, 50)	164	57%	(51, 63)	1.41	(1.14, 1.74)
10.1 - <16	225	45%	(40, 49)	279	55%	(51, 60)	1.45	(1.20, 1.76)
Joint count at diagnosis								
1	92	37%	(30, 44)	154	63%	(56, 69)	1.00	
2 - 4	145	39%	(33, 44)	231	61%	(57, 67)	1.03	(0.84, 1.27)
5 - 9	95	40%	(33, 47)	143	60%	(53, 66)	1.07	(0.85, 1.34)
≥10	117	46%	(39, 52)	138	54%	(48, 60)	1.23	(1.00, 1.52)
Symptoms prior to diagnosis (months)								
<3.0	130	38%	(33, 44)	208	62%	(56, 67)	1.00	
3.1 – 6.0	110	37%	(32, 44)	184	63%	(57, 68)	0.97	(0.79, 1.19)
6.1 – 12.0	86	42%	(35, 40)	118	58%	(51, 64)	1.10	(0.88, 1.35)
≥12.0	123	44%	(38, 50)	156	56%	(25, 38)	1.15	(0.94, 1.38)
Distance to rheumatologist (miles)								
≤30	219	38%	(33, 42)	362	62%	(58, 66)	1.00	
31 - 120	167	41%	(35, 48)	212	59%	(52, 66)	1.16	(1.01, 1.36)
≥120	66	42%	(34, 41)	93	58%	(51, 66)	1.10	(0.89, 1.36)
Uveitis								
No uveitis	375	41%	(37, 44)	544	59%	(56, 63)	1.00	
Uveitis	74	38%	(30, 45)	122	62%	(56, 69)	0.93	(0.76, 1.13)
Disease activity at 3 months								
Active	315	43%	(39, 47)	412	57%	(52, 60)	1.48	(1.22, 1.78)
Inactive	95	29%	(23, 35)	229	71%	(66, 76)	1.00	
Diagnosis time period								
1/1/2004 - 12/31/2008	130	47%	(41, 53)	147	53%	(47, 59)	1.00	
1/1/2009 - 12/31/2013	219	39%	(35, 44)	338	61%	(56, 65)	0.84	(0.71, 0.99)
1/1/2013 - 12/31/2018	100	36%	(30, 42)	181	64%	(59, 70)	0.75	(0.62, 0.92)
ILAR category								
Oligoarticular	155	37%	(31, 41)	269	63%	(58, 68)	1.00	
Polyarticular RF-	127	42%	(37, 48)	174	58%	(52, 64)	1.22	(1.01, 1.38)
Polyarticular RF+	21	38%	(27, 52)	35	63%	(52, 77)	1.08	(0.73, 1.59)
Enthesitis Related Arthritis	68	45%	(37, 54)	83	55%	(47, 63)	1.23	(0.99, 1.53)
Psoriatic	55	49%	(40,59)	57	51%	(42, 61)	1.34	(1.06, 1.68)
PRINTO category								
Seronegative	266	39%	(35, 43)	418	61%	(57, 65)	1.00	
Seropositive	45	38%	(30, 48)	72	62%	(53, 71)	1.03	(0.78, 1.34)
Spondyloarthritis	115	47%	(40, 53)	132	53%	(47, 60)	1.16	(0.98, 1.37)
Serologic status								
ANA								

Negative	183	45%	(39, 49)	226	55%	(50, 60)	1.00	
Positive	172	39%	(34, 44)	272	61%	(57, 66)	0.87	(0.73, 1.02)
RF								
Negative	333	41%	(40, 49)	470	59%	(55, 62)	1.00	
Positive	33	38%	(34, 44)	54	62%	(52, 73)	0.95	(0.71, 1.28)
CCP								
Negative	319	42%	(39, 46)	433	58%	(53, 61)	1.00	
Positive	23	35%	(25, 48)	42	65%	(54, 77)	0.83	(0.55, 1.23)
HLAB27								
Negative	217	40%	(35, 44)	330	60%	(56, 65)	1.00	
Positive	49	46%	(36, 56)	58	54%	(44, 64)	1.15	(0.91, 1.45)

Panel B: 24 month JIA Outcomes	**Active disease**			**Inactive disease**			**RP active disease**	**95% CI**
Characteristic	**n**	**Prevalence**	**95% CI**	**n**	**Prevalence**	**95% CI**		
N = 1027	328	32%	(29, 35)	699	68%	(65, 71)		
Sex								
Male	94	30%	(24, 35)	222	70%	(64, 71)	1.00	
Female	234	33%	(28, 37)	477	67%	(65, 76)	1.11	(0.91, 1.35)
Age at diagnosis (years)								
0 – 5	74	25%	(19, 31)	219	75%	(70, 80)	1.00	
5.1 – 10	79	29%	(22, 35)	194	71%	(66, 77)	1.15	(0.87, 1.50)
10.1 - <16	175	38%	33, 42)	286	62%	(58, 67)	1.50	(1.19, 1.88)
Joint Count at diagnosis								
1	73	33%	(26, 40)	149	67%	(61, 74)	1.00	
2 - 4	100	29%	(23, 34)	249	71%	(67, 76)	0.86	(0.67, 1.11)
5 - 9	69	32%	(26, 39)	145	68%	(62, 74)	0.96	(0.73, 1.25)
≥10	86	36%	(23,34)	156	64%	(59, 71)	1.07	(0.83, 1.48)
Symptoms prior to diagnosis (months)								
<3.0	90	28%	(22, 34)	229	72%	(67, 77)	1.00	
3.1 – 6.0	92	33%	(26, 39)	188	67%	(62, 73)	1.16	(0.91, 1.48)
6.1 – 12.0	53	29%	(22, 37)	128	71%	(65, 79)	1.04	(0.78, 1.38)
≥12.0	93	38%	((31, 44)	154	62%	(56, 66)	1.33	(1.05, 1.69)
Distance to rheumatologist (miles)								
≤30	179	33%	(28, 37)	365	67%	(63, 71)	1.00	
31 - 120	106	31%	(24, 39)	237	69%	(62, 75)	0.93	(0.77, 1.14)
>120	43	31%	(21, 38)	97	69%	(63, 77)	0.93	(0.71, 1.23)
Uveitis								
No uveitis	270	32%	(28, 36)	568	68%	(64, 71)	1.00	
Uveitis	58	31%	(23, 38)	131	69%	(62,76)`	0.95	(0.75, 1.21)
Disease status at 3 months								
Active	225	33%	(29, 37)	453	67%	(63, 70)	1.28	(1.02, 1.59)
Inactive	76	26%	(20, 320	216	74%	(69, 79)	1.00	
Diagnosis time period								
1/1/2004 - 12/31/2008	100	39%	(41, 54)	156	61%	(55, 67)	1.00	
1/1/2009 - 12/31/2013	146	29%	(34, 43)	364	71%	(67, 75)	0.73	(0.60, 0.90)
1/1/2013 - 12/31/2018	82	31%	(29, 42)	179	69%	(63, 75)	0.80	(0.64, 1.02)
ILAR category								
Oligoarticular	112	29%	(24, 34)	271	71%	(66, 75)	1.00	
Polyarticular RF-	90	32%	(26, 38)	193	68%	(63, 74)	1.12	(0.88, 1.43)

Polyarticular RF+	20	38%	(24, 51)	33	62%	(51, 77)	1.34	(0.89, 2.03)
Enthesitis Related Arthritis	48	35%	(27, 44)	90	65%	(58, 74)	1.20	(0.91, 1.58)
Psoriatic	39	38%	(28, 47)	65	63%	(53, 72)	1.29	(0.96, 1.72)
PRINTO category								
Seronegative	188	30%	(25, 34)	440	70%	(67, 74)	1.00	
Seropositive	43	39%	(30, 49)	66	61%	(52, 71)	1.28	(0.94, 1.72)
Spondyloarthritis	80	35%	(28, 42)	147	65%	(59, 71)	1.15	(0.93, 1.42)
Serologic status								
ANA								
Negative	125	33%	(27, 38)	253	67%	(62, 72)	1.00	
Positive	136	33%	(28, 38)	272	67%	(62, 72)	1.01	(0.82, 1.23)
RF								
Negative	238	32%	(28, 36)	504	68%	(64, 71)	1.00	
Positive	31	38%	(27,49)	50	62%	(52, 73)	1.25	(0.91, 1.71)
CCP								
Negative	217	31%	(27, 35)	473	69%	(65, 72)	1.00	
Positive	26	42%	(30, 56)	36	58%	(47, 71)	1.21	(0.82, 1.78)
HLAB27								
Negative	173	35%	(30, 39)	328	65%	(61, 70)	1.00	
Positive	39	37%	(27, 47)	66	63%	(54, 73)	1.08	(0.82, 1.42)

Rheumatoid Factor (RF), Cyclic Citrullinated Peptide (CCP). Antinuclear Antibody (ANA). ILAR: International League Against Rheumatism. PRINTO: Paediatric Rheumatology International Trials Organisation. Relative prevalence RP. CI: Confidence interval. JIA: juvenile idiopathic arthritis. Modified Wallace criteria [15] for Inactive disease (mCID) defined by no active inflamed joints, no fever, rash, serositis, splenomegaly or generalized lymphadenopathy attributable to JIA, no active uveitis, and physician global assessment of 0/10.

Table 3: Diagnosis time period analysis, prevalence, relative prevalence and 95% confidence intervals for JIA active disease at 12 months.

	1/1/2004-12/31/2008				1/1/2009 – 12/31/2013				1/1/2014 – 12/31/2018			
	n=130	**Prevalence**	**RP**	**95% CI**	**n=219**	**Prevalence**	**RP**	**95% CI**	**n=100**	**Prevalence**	**RP**	**95% CI**
Age (years)												
0 – 5	43	40%	1.00		39	27%	1.00		17	23%	1.00	
5.1 – 10	39	51%	1.28	(0.94, 1.77)	62	44%	1.61	(1.16, 2.23)	24	31%	1.39	(0.82, 2.36)
10.1 - <16	48	50%	1.29	(0.96, 1.76)	118	41%	1.56	(1.16, 2.1)	59	41%	1.83	(1.16, 2.9)
Joint count at diagnosis												
1	29	39%	1.00		32	35%	1.00		30	33%	1.00	
2 - 4	40	44%	1.13	(0.78, 1.62)	74	37%	1.03	(0.74, 1.43)	29	31%	0.93	(0.62, 1.41)
5 - 9	22	41%	1.04	(0.68, 1.60)	54	40%	1.11	(0.78, 1.56)	22	36%	1.03	(0.66, 1.59)
≥10	39	62%	1.58	(1.12, 2.22)	59	40%	1.12	(0.80, 1.57)	19	37%	1.06	(0.67, 1.67)
Symptom Onset												
<3.0	41	43%	1.00		55	37%	1.00		34	31%	1.00	
3.1 – 6.0	36	43%	1.00	(0.72, 1.41)	49	34%	0.87	(0.64, 1.18)	25	35%	1.12	(0.74, 1.69)
6.1 – 12.0	27	56%	1.31	(0.94, 1.84)	45	41%	1.09	(0.80, 1.47)	14	28%	0.89	(0.49, 1.42)
≥12.0	26	47%	1.10	(0.77, 1.58)	70	41%	1.11	(0.84, 1.45)	27	40%	1.31	(0.88, 1.93)
Distance to Rheumatologist (miles)												
<30 miles	63	43%	1.00		102	36%	1.00		54	32%	1.00	
31-120 miles	49	47%	1.07	(0.81, 1.41)	89	43%	1.18	(0.94, 1.47)	29	43%	1.25	(0.89, 1.78)
>120 miles	17	63%	1.44	(1.02, 2.02)	28	39%	1.09	(0.79, 1.52)	17	30%	0.86	(0.55, 1.36)
ILAR Category												
Oligoarticular	54	42%	1.00		72	35%	1.00		30	27%	1.00	
Polyarticular RF-	33	57%	1.41	(1.05, 1.91)	54	43%	1.18	(0.90, 1.56)	17	31%	1.08	(0.65, 1.76)
Polyarticular RF+	7	70%	1.69	(1.07, 2.65)	6	32%	0.85	(0.43, 1.69)	4	27%	0.96	(0.39, 2.32)
Enthesitis Related Arthritis	12	50%	1.20	(0.76, 1.88)	34	41%	1.19	(0.87, 1.63)	22	42%	1.48	(0.96, 2.28)
Psoriatic	11	48%	1.20	(0.75, 1.91)	29	55%	1.48	(1.09, 2.01)	15	39%	1.36	(0.83, 2.23
PRINTO Category												
Seronegative	83	46%			123	39%			45	28%		
Seropositive	12	57%	1.21	(0.81, 1.82)	14	33%	0.85	(0.54, 1.33)	9	36%	1.24	(0.70, 2.19)
Spondyloarthritis	22	48%	1.04	(0.74, 1.46)	59	47%	1.21	(0.97, 1.52)	34	40%	1.36	(0.95, 1.93)
Disease Activity at 3 months												
Active	93	51%	1.53	(1.09, 2.13)	164	42%	1.52	(1.14, 2.02)	58	34%	1.29	(0.87, 1.90)
Inactive	28	34%	1.00		41	27%	1.00		26	26%	1.00	

Footnote: Rheumatoid Factor (RF). ILAR: International League Against Rheumatism. PRINTO: Paediatric Rheumatology International Trials Organisation. Relative prevalence RP. CI: Confidence interval. JIA: juvenile idiopathic arthritis

Table 4: Sensitivity analysis: prevalence of subject demographic characteristics and relative prevalence for JIA active disease at 12- and 24-months. Subjects who had been excluded due to missing follow up were categorized as not having active disease at their missing time point of 12 or 24 months.

	Total N=1315 (%)	Relative prevalence of active disease 12 months (RP)	95% CI	Relative prevalence for active disease 24 months (RP)	95% CI
Sex					
Male	422 (32.1)	1.00		1.00	
Female	893 (67.9)	1.10	(0.93, 1.29)	1.05	(0.88, 1.25)
Age at diagnosis					
0 – 5	386 (29.4)	1.00		1.00	
5.1 – 10	337 (25.6)	1.45	(1.16, 1.80)	1.19	(0.90, 1.57)
10.1 - <16	592 (45.0)	1.51	(1.20, 1.80)	1.56	(1.23, 1.98)
Joint count at diagnosis					
1	300 (22.8)	1.00		1.00	
2 – 4	444 (33.8)	1.05	(0.84, 1.30)	0.88	(0.68, 1.14)
5 – 9	280 (21.3)	1.13	(0.89, 1.42)	1.01	(0.76, 1.33)
≥10	290 (22.1)	1.30	(1.04, 1.61)	1.14	(0.88, 1.48)
Missing	1 (0.1)				
Symptom onset prior to diagnosis (months)					
<3.0	395 (30.1)	1.00		1.00	
3.1 – 6.0	341 (26.0)	0.96	(0.78, 1.18)	1.15	(0.90, 1.48)
6.1 – 12.0	244 (18.6)	1.06	(0.84, 1.31)	0.98	(0.73, 1.32)
≥12.0	334 (25.4)	1.12	(0.92, 1.36)	1.29	(1.01, 1.65)
Missing	1 (0.1)				
Distance to rheumatologist (miles)					
≤30	660 (50.8)	1.00		1.00	
31-120 miles	443 (34.1)	1.15	(0.98, 1.35)	0.92	(0.75, 1.12)
≥120	203 (15.6)	0.97	(0.77,1.21)	0.79	(0.59, 1.06)
Missing	15 (1.1)				
Diagnosis time period					
1/1/2004 – 12/31/2008	312 (23.7)	1		1	
1/1/2009 - 12/31/2013	657 (50.0)	0.81	(0.68, 0.96)	0.78	(0.65, 0.93)
1/1/2013 - 12/31/2018	346 (26.3)	0.72	(0.58, 0.88)	70	(0.56, 0.88)
ILAR category					
Oligoarticular	532 (40.7)	1.00		1.00	
Polyarticular RF-	265 (20.3)	1.33	(1.08, 1.61)	1.23	(0.95, 1.59)
Polyarticular RF+	50 (3.8)	1.14	(0.76, 1.71)	1.43	(0.93, 2.20)
Enthesitis Related Arthritis	170 (13.0)	1.37	(1.09, 1.71)	1.34	(1.07,1.79)
Psoriatic	126 (9.6)	1.46	(1.15, 1.85)	1.41	(1.04, 1.92)
PRINTO category					
Seronegative	764 (66.6)	1.00		1.00	
Seropositive	107 (9.3)	0.98	(0.73, 1.31)	1.22	(0.88, 1.68)
Spondyloarthritis	277 (24.1)	1.27	(1.06, 1.50)	1.25	(1.00, 1.57)
Uveitis dx					
No Uveitis	1104 (84.0)	1.00		1.00	
Uveitis	211 (16.0)	1.02	(0.83, 1.24)	1.06	(0.83, 1.35)
Disease activity at 3 months					

Active	794 (67.9)	1.00		1.00	
Inactive	376 (32.1)	0.64	(0.52, 0.7)	0.73	(0.58, 0.92)
Missing	145 (11.0)				
Serologic status					
ANA					
Negative	487 (48.6)	1.00		1.00	
Positive	516 (51.4)	0.87	(0.73, 1.02)	1.01	(0.82, 1.24)
Missing	312 (23.7)				
RF					
Negative	757 (90.0)	1.00		1.00	
Positive	84 (10.0)	0.90	(0.65, 1.23)	1.17	(0.83, 1.64)
Missing	474 (36.0)				
CCP					
Negative	641 (91.6)	1.00		1.00	
Positive	59 (8.4)	0.73	(0.93, 1.51)	1.07	(0.7, 1.62)
Missing	615 (46.8)				
HLAB27					
Negative	641 (83.8)	1.00		1.00	
Positive	124 (16.2)	1.19	(0.93, 1.51)	1.19	(0.84, 1.48)
Missing	550 (41.8)				

Footnote: Rheumatoid Factor (RF), Cyclic Citrullinated Peptide (CCP). Antinuclear Antibody (ANA). ILAR: International League Against Rheumatism. PRINTO: Paediatric Rheumatology International Trials Organisation. Relative prevalence RP. CI: Confidence interval. JIA: juvenile idiopathic arthritis.

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