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Review Article

Predictors of disease activity score improvement in pediatric rheumatology patients with rheumatoid arthritis

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Abstract

Background: Composite disease activity indices such as the juvenile arthritis disease activity score (JADAS) and its clinical variant now anchor treat-to-target management of pediatric rheumatoid arthritis, yet the pace and completeness of score improvement after treatment initiation vary widely between children.

Objective: This review synthesizes the published evidence on baseline and early-treatment predictors of disease activity score improvement in pediatric patients with polyarticular and oligoarticular rheumatoid arthritis (juvenile idiopathic arthritis).

Methods: We synthesized inception-cohort studies, randomized biologic and treat-to-target trials, national registries, and long-term outcome cohorts addressing disease activity score trajectory, response definitions, and their baseline predictors.

Findings: Rheumatoid-factor-positive polyarticular subtype, high baseline joint count and poor functional status, and longer delay between symptom onset and effective therapy each predict slower, less complete score improvement, while early achievement of inactive disease and management under a structured treat-to-target protocol predict a more favorable and more sustained trajectory; composite models combining these domains consistently outperform any single baseline variable.

Conclusions: Disease subtype and seropositivity, baseline disease burden, time to effective treatment, and adherence to score-driven treat-to-target escalation together explain much of the variation in disease activity score improvement among children with rheumatoid arthritis, and prospective validation of these predictors under contemporary treat-to-target protocols remains a priority for the field.

Keywords: juvenile idiopathic arthritis; disease activity score; JADAS; treat-to-target; pediatric rheumatology

1. Introduction

Juvenile idiopathic arthritis, the umbrella term for the chronic inflammatory joint disease still widely called pediatric rheumatoid arthritis in clinical shorthand, is the most common chronic rheumatic disease of childhood and a leading cause of acquired disability when treatment is delayed or under-intensified [1,2]. Pediatric rheumatology adopted composite activity scoring later than adult rheumatology, and the juvenile arthritis disease activity score (JADAS), together with its clinical variant cJADAS that omits the acute-phase reactant, is now the dominant instrument for quantifying disease burden and tracking response to therapy in polyarticular and oligoarticular disease [3,4]. Treat-to-target strategies built around serial score measurement, escalating therapy whenever a target activity state is not reached within a defined window, have since been formally endorsed by international task forces, mirroring the paradigm that transformed adult rheumatoid arthritis outcomes [5,6].

The rate and magnitude of disease activity score improvement after treatment initiation varies enormously between children, and a substantial minority fail to reach even a modest response within six to twelve months regardless of agent used [7,8]. Identifying which baseline clinical, laboratory, and treatment-related characteristics predict a favorable trajectory matters both for individualizing treatment intensity at diagnosis and for setting realistic expectations, since uncontrolled disease can produce joint damage, growth disturbance, and long-term functional impairment [9,10]. This review synthesizes the literature on predictors of disease activity score improvement in pediatric polyarticular and oligoarticular rheumatoid arthritis, drawing on inception cohorts, randomized biologic and treat-to-target trials, and long-term registries.

2. Measuring disease activity and defining improvement in children

Composite disease activity indices were developed because single measures, such as active joint count alone, correlate poorly with physician and parent global assessments of how a child is doing. The JADAS combines a physician global assessment, a parent or patient global assessment of well-being, an active joint count capped at a defined maximum, and, in the full JADAS, the erythrocyte sedimentation rate, into a single continuous score validated against physician-rated flare and the preliminary American College of Rheumatology pediatric response criteria [3,11]. The clinical variant, cJADAS, omits the laboratory component and performs comparably to the full score across most settings, allowing scoring at the point of care without a same-day laboratory result, which has accelerated its adoption in treat-to-target protocols [12].

Table 1: Validated JADAS/cJADAS disease activity state cut-offs and categorical response definitions used to classify a child's trajectory as improved [4,13,14].

Activity state / definition	Instrument	Approximate cut-off	Clinical interpretation
Inactive disease	cJADAS10, oligoarticular	≤1.0	No active joints; treatment target
Inactive disease	cJADAS10, polyarticular	≤1.0	No active joints; treatment target
Minimal disease activity	JADAS / PhGA-based criteria	Low residual activity	Acceptable interim state, escalate if not sustained
High disease activity	cJADAS10, polyarticular	>8.5	Prompts treatment escalation under treat-to-target
Clinically meaningful improvement	JADAS change score	≥ minimal clinically important difference	Distinguishes true response from measurement noise

Defining meaningful score improvement, as opposed to random measurement fluctuation, required its own validation work. Consolaro and colleagues established cut-offs for minimal, moderate, and high disease activity states, and later derived a minimal clinically important difference for JADAS change, giving investigators a principled threshold for classifying a trajectory as a true response [4]. Clinically inactive disease and minimal

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disease activity, first operationalized for polyarticular disease by Magni-Manzoni and colleagues and later incorporated into American College of Rheumatology provisional criteria, provide categorical endpoints many cohorts use alongside continuous JADAS change [13,14]. Systematic review evidence suggests the proportion reaching clinically inactive disease within the first year ranges from under a quarter in rheumatoid-factor-positive polyarticular disease to well over half in oligoarticular disease [15].

3. Demographic and disease-subtype predictors

Age at onset and disease subtype are among the most consistently reported predictors of score trajectory. Children with rheumatoid-factor-positive polyarticular disease, which most closely mirrors adult seropositive rheumatoid arthritis serologically and in erosive potential, tend to show slower and less complete improvement than children with oligoarticular or rheumatoid-factor-negative polyarticular disease, even after adjusting for treatment intensity [16,17]. The Canadian ReACCh-Out inception cohort, following more than fifteen hundred children, found that rheumatoid-factor-positive polyarticular category, elevated baseline active joint count, and low baseline physical function independently predicted a more severe, slower-resolving course [9]. The same cohort's early outcome analyses showed younger age at onset predicted a more favorable trajectory in oligoarticular disease but a less favorable one in polyarticular disease, so age effects are not uniform across subtypes [7].

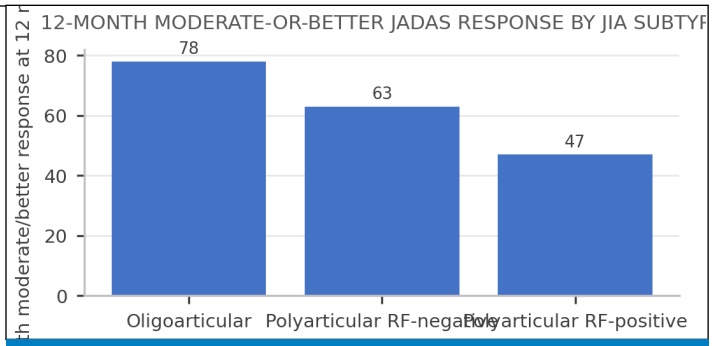


Figure 1: Proportion of children reaching a moderate or better JADAS response within 12 months of treatment initiation by juvenile idiopathic arthritis subtype, highest in oligoarticular disease and lowest in rheumatoid-factor-positive polyarticular disease, drawn from inception-cohort trajectory analyses [9,7].

Sex differences are reported less consistently; several cohorts find a modestly worse trajectory in girls with polyarticular disease, attributable partly to higher rheumatoid-factor and anti-cyclic citrullinated peptide antibody positivity, though the effect is small relative to subtype and baseline activity [18,19]. Longer disease duration before diagnosis, and correspondingly delayed disease-modifying therapy, is among the more actionable predictors: Albers and colleagues found a shorter interval to methotrexate initiation independently predicted a better response at six months, a finding echoed in later cohorts and cited to justify early, aggressive treatment [20,21]. Population-based Nordic follow-up data spanning nearly two decades similarly found longer diagnostic delay predicted a worse long-term trajectory [22].

4. Treatment-related and treat-to-target predictors

The single most consistent predictor of disease activity score improvement is the treatment strategy itself: both the specific agent used and, increasingly, whether it is deployed within a formal treat-to-target protocol. Methotrexate, the first-line conventional agent for polyarticular disease, produces improvement in a majority of children within three to six months, though a substantial minority fail an adequate trial and require biologic escalation [23,24]. The pivotal etanercept trial by Lovell and colleagues, and subsequent trials of abatacept and tocilizumab, established that biologic therapy

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improves disease activity in patients refractory to methotrexate, with response speed depending substantially on baseline activity and prior treatment exposure [25,26,27]. Davies and colleagues, modeling etanercept response from registry data, found lower baseline physician global assessment and shorter disease duration predicted a more favorable response, echoing the methotrexate literature [28].

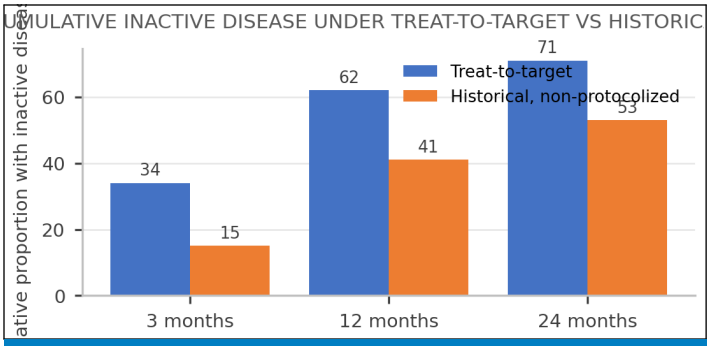


Figure 2: Cumulative proportion of newly diagnosed patients reaching clinically inactive disease at 3, 12, and 24 months under a protocolized treat-to-target strategy compared with historical non-protocolized care, showing an earlier and more complete response under score-driven escalation [21,12].

Formal treat-to-target trials provide the strongest prospective evidence that treatment strategy, not merely drug selection, independently predicts the trajectory. Hissink Muller and colleagues randomized newly diagnosed polyarticular patients to three structured initial-treatment arms tied to JADAS thresholds and found all three produced substantial, broadly comparable improvement at twenty-four months, with early achievement of inactive disease at three months predicting sustained low activity thereafter [21]. Swart and colleagues, evaluating cJADAS as the instrument driving treat-to-target decisions in routine practice, found scheduled score-driven escalation correlated with a faster time to inactive disease than historical, non-protocolized care [12]. Patients requiring sequential biologic switches after an inadequate first-agent response, described in the Dutch national biologic registry by Otten and colleagues, showed slower, less complete improvement overall, underscoring that response to the first agent carries independent prognostic weight [29,30].

5. Laboratory, inflammatory, and biomarker predictors

Baseline erythrocyte sedimentation rate and C-reactive protein, the acute-phase reactants in the full JADAS, are imperfect but reproducible predictors of subsequent trajectory: higher baseline inflammatory markers generally predict a larger absolute drop in score but not necessarily a higher probability of reaching an inactive-disease target [3,31]. Rheumatoid-factor and anti-cyclic citrullinated peptide antibody positivity, beyond their role in classification, independently predict more protracted, less complete improvement, consistent with adult rheumatoid arthritis literature linking seropositivity to a more erosive phenotype [17,16]. Antinuclear antibody positivity, more common in young girls with oligoarticular disease, associates primarily with uveitis risk rather than joint score trajectory, though it is often included as a covariate given its correlation with age and sex [1].

Functional status at baseline, captured by the childhood health assessment questionnaire, adds independent predictive information beyond joint counts and acute-phase reactants. The ReACCh-Out severity model found poor baseline physical function, together with rheumatoid-factor-positive polyarticular subtype and high active joint count, formed the strongest composite predictor of a severe, slowly improving course, outperforming any single laboratory value [9]. Quality-of-life and fatigue measures, though correlated with concurrent activity score, show more modest independent value for predicting future trajectory once baseline activity and subtype are accounted for [32].

6. Long-term trajectory and predictors of sustained response

Beyond initial response, long-term follow-up literature addresses which baseline factors predict sustained improvement rather than an early response followed by

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relapse. The population-based Nordic cohort, followed for eighteen years, found early achievement of inactive disease, younger age at onset, and persistent oligoarticular subtype predicted both a favorable early trajectory and a substantially higher probability of remission off medication by adulthood, while extended oligoarticular and rheumatoid-factor-positive polyarticular subtypes carried the least favorable long-term trajectories [22,33]. Minden and colleagues, in a German cohort followed into early adulthood, similarly found subtype at onset and time to first remission were the strongest predictors of functional outcome measured more than a decade later [31].

Table 2: Baseline and early-treatment predictors of disease activity score trajectory reported across major inception and long-term outcome cohorts [22,31,36,9].

Predictor	Direction of association	Representative cohort(s)
Rheumatoid-factor-positive polyarticular subtype	Slower, less complete improvement	ReACCh-Out; Nordic JIA cohort
Longer diagnostic/treatment delay	Slower improvement, worse long-term trajectory	Nordic JIA cohort; Dutch inception cohort
Early achievement of inactive disease (by ~3 months)	Predicts sustained low activity	UK prospective cohort; treat-to-target trial
High baseline active joint count and poor function	Predicts a more severe overall course	ReACCh-Out severity model
Younger age at oligoarticular onset	More favorable long-term trajectory	Nordic JIA cohort; German outcome cohort

Older natural-history cohorts, predating composite scores and biologic therapy, provide context for how much the treatment era has shifted these trajectories. Fantini and colleagues, following a large Italian cohort largely before biologic availability, found substantially lower remission rates than contemporary biologic-era cohorts [34]. Anink and colleagues, in a Dutch inception cohort spanning the early biologic era, found intermediate outcomes consistent with a gradual, treatment-driven improvement over the study decades [35]. Shoop-Worrall and colleagues, analyzing a large UK prospective cohort, found inactive disease common but frequently transient, and a shorter time to first achieving it among the strongest predictors of a subsequently sustained low-activity state [36].

7. Discussion

Across the literature reviewed here, four categories of baseline and early-treatment characteristic emerge repeatedly as predictors: disease subtype and seropositivity, baseline disease burden as captured by joint count, physician global assessment, and functional status, time from symptom onset to effective therapy, and the treatment strategy itself, particularly treat-to-target escalation [9,21,20]. No single factor dominates, and composite prediction models combining several domains consistently outperform any individual variable [28,23].

Cohort studies spanning multiple treatment eras conflate improvements from more effective drugs with improvements from earlier diagnosis and more consistent monitoring, and few are powered to fully disentangle subtype-specific predictors from era effects [37,10]. Reported predictors also vary by which activity index a cohort used and which improvement threshold was applied, so cross-study comparison of effect sizes warrants caution even where directional findings agree [38,39].

8. Conclusion

Disease activity score improvement in pediatric patients with polyarticular and oligoarticular rheumatoid arthritis is shaped most consistently by disease subtype and seropositivity, baseline disease burden, time to initiation of effective therapy, and adherence to a structured treat-to-target treatment strategy, with composite models combining these domains outperforming any single baseline variable in predicting an individual child's trajectory [9,21]. As treat-to-target protocols built around JADAS and cJADAS become standard practice, prospective validation of predictive models derived from earlier, less

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protocolized cohorts will be needed to confirm that the same baseline factors retain their predictive value under contemporary score-driven management, and future work should prioritize harmonizing which activity index and improvement threshold are used so that predictors identified across cohorts can be compared directly [12,4].

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