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CLINICAL AND LABORATORY ASSESSMENT OF JUVENILE RHEUMATOID ARTHRITIS IN CHILDREN

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Abstract

Background: Juvenile Rheumatoid Arthritis (JRA), also known as Juvenile Idiopathic Arthritis (JIA), is the most common chronic rheumatic disease in children, leading to significant morbidity and long-term disability. Early and accurate assessment of clinical and laboratory parameters is crucial for prognosis and treatment strategy. This study evaluates the clinical and laboratory profiles of children diagnosed with JRA at the Department of Cardiorheumatology, Tashkent State Medical University. *Methods:* A prospective observational study was conducted on 120 children (aged 1-16 years) fulfilling the ILAR criteria for JIA. Patients were assessed for clinical manifestations (articular and extra-articular) and laboratory parameters, including inflammatory markers (ESR, CRP), autoantibodies (RF, ANA), and cytokine profiles (IL-6, TNF-α). Disease activity was measured using the Juvenile Arthritis Disease Activity Score (JADAS-27). *Results:* The cohort comprised 68 girls (56.7%) and 52 boys (43.3%). Oligoarticular onset was most frequent (45%), followed by polyarticular RF-negative (30%). Elevated ESR (>20 mm/hr) was observed in 85% of active cases. ANA positivity was highest in oligoarticular JRA (65%). A significant positive correlation was found between IL-6 levels and JADAS-27 ($r=0.72$, $p<0.01$). Uveitis was detected in 12% of ANA-positive patients. *Conclusion:* Combined clinical and laboratory assessment, particularly including IL-6 and ANA, provides a robust framework for evaluating disease activity and predicting complications in children with JRA. The findings underscore the need for routine laboratory surveillance in pediatric rheumatology practice in Central Asia.

Keywords

Juvenile Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, clinical assessment, laboratory markers, IL-6, ANA, ESR, CRP, JADAS-27, Tashkent State Medical University.

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Introduction

Juvenile Rheumatoid Arthritis (JRA) is a heterogeneous group of chronic inflammatory disorders of unknown etiology, manifesting as persistent arthritis (duration >6 weeks) in children under 16 years of age [1]. The term JRA is historically rooted in North American literature, while the European League Against Rheumatism (EULAR) and the International League of Associations for Rheumatology (ILAR) prefer the term Juvenile Idiopathic Arthritis (JIA) [2]. Despite nomenclature differences, the clinical burden remains significant, with a prevalence ranging from 16 to 150 per 100,000 children worldwide [3].

The pathogenesis of JRA involves complex interactions between genetic predisposition (HLA class I and II alleles), environmental triggers, and dysregulated innate and adaptive immunity [4,5]. Early diagnosis remains challenging due to the absence of a specific diagnostic test and the variability of presentations, including oligoarticular, polyarticular, systemic, enthesitis-related, and psoriatic forms [6].

Numerous researchers have contributed to the understanding of JRA's clinical and laboratory correlates. Petty et al. (2004) established the current ILAR classification criteria, which have been validated globally [2]. Ravelli and Martini (2007) emphasized the importance of early aggressive therapy based on laboratory markers of inflammation [7]. Wallace et al. (2011) developed the JADAS scoring system, integrating physician global assessment, parent/patient global assessment, active joint count, and ESR [8]. De Benedetti et al. (2005) demonstrated that IL-6 is a key driver of systemic JRA, correlating with fever and thrombocytosis [9]. Similarly, Yilmaz et al. (2018) showed that TNF-α levels correlate with radiographic progression in polyarticular JRA [10].

In Central Asia, particularly Uzbekistan, data on JRA clinical-laboratory profiles are scarce. A study by Azimova et al. (2015) in Tashkent reported a high frequency of late diagnoses and disability among JRA patients [11]. The Department of Cardiorheumatology at Tashkent State Medical University has been a referral center for pediatric rheumatology since 1980, yet standardized assessment protocols have been lacking [12]. International studies have shown that ANA positivity predicts chronic uveitis, while RF positivity indicates a more aggressive, erosive course [13,14]. Elevated ESR and CRP remain the most accessible inflammatory markers in resource-limited settings [15].

However, in Uzbekistan, the integration of modern laboratory markers (e.g., anti-CCP, IL-6, S100 proteins) into routine clinical evaluation has been inconsistent [16]. Furthermore, the correlation between these markers and disease activity scores

(JADAS-27) has not been systematically evaluated in the local pediatric population [17]. This gap necessitates a comprehensive assessment to improve diagnostic accuracy, monitor treatment response (e.g., to methotrexate or biologics), and prevent long-term complications such as joint contractures, growth retardation, and amyloidosis [18,19].

Purpose of the research

The purpose of this research is to evaluate the clinical and laboratory parameters of children with Juvenile Rheumatoid Arthritis treated at the Department of Cardiorheumatology, Tashkent State Medical University, and to determine the correlation between traditional inflammatory markers (ESR, CRP), autoantibodies (RF, ANA), cytokine levels (IL-6, TNF-α), and disease activity measured by JADAS-27, while identifying the prevalence of different JRA subtypes and extra-articular manifestations in the Uzbek pediatric population.

Materials and Methods

This prospective observational study was conducted at the Department of Cardiorheumatology, Tashkent State Medical University, from January 2022 to December 2024. The study included 120 children aged 1 to 16 years who were newly diagnosed or followed up with JRA according to the ILAR criteria. Exclusion criteria included other connective tissue diseases (SLE, dermatomyositis), infectious arthritis, malignancy, or prior treatment with biologic agents. Informed written consent was obtained from parents or legal guardians, and the study protocol was approved by the Institutional Ethics Committee of Tashkent State Medical University (Protocol No. 07/22). All patients underwent a standardized clinical assessment, including detailed history, number of active joints (swelling or limited motion with pain), limited joints, and extra-articular manifestations (fever, rash, uveitis, hepatosplenomegaly). Disease activity was quantified using the Juvenile Arthritis Disease Activity Score 27 (JADAS-27), which includes physician global assessment (0-10 VAS), parent/patient global assessment (0-10 VAS), active joint count (0-27), and ESR (normalized 0-10). Blood samples were collected at baseline and at 3-month follow-up. Laboratory parameters included complete blood count (CBC), erythrocyte sedimentation rate (ESR) by Westergren method, C-reactive protein (CRP) by nephelometry, rheumatoid factor (RF) by latex agglutination, antinuclear antibodies (ANA) by indirect immunofluorescence (HEp-2 cells), anti-cyclic citrullinated peptide (anti-CCP) by ELISA, interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) by commercial ELISA kits (R&D Systems, USA). Normal ranges: ESR <15 mm/hr, CRP <5 mg/L, RF <15 IU/mL, ANA <1:80, anti-CCP <5 U/mL, IL-6 <5 pg/mL, TNF-α <8 pg/mL. Statistical analysis was performed using SPSS version 26.0. Continuous variables were expressed as mean

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± SD or median (IQR). Categorical variables were expressed as frequencies (%). Comparisons between groups were made using Student's t-test or Mann-Whitney U test for continuous variables and Chi-square test for categorical variables. Correlation between laboratory markers and JADAS-27 was assessed using Pearson or Spearman rank correlation. A p-value <0.05 was considered statistically significant. Data visualization was performed using GraphPad Prism 9.0.

Results

A total of 120 children (68 girls, 52 boys) with a mean age of 8.4 ± 3.7 years (range 1.5–15.8 years) were enrolled. The mean disease duration at presentation was 14.3 ± 8.2 months. According to ILAR classification, the distribution of JRA subtypes was: oligoarticular (persistent 35%, extended 10%) – total 45% (n=54); polyarticular RF-negative – 30% (n=36); polyarticular RF-positive – 10% (n=12); systemic onset – 10% (n=12); enthesitis-related arthritis – 3.3% (n=4); psoriatic arthritis – 1.7% (n=2). The female-to-male ratio was 1.3:1 overall, but in polyarticular RF-positive subtype, it was 5:1. Table 1 summarizes the demographic and clinical characteristics by subtype.

Table 1. Demographic and Clinical Characteristics of JRA Subtypes

Subtype	N (%)	Age (years) mean±SD	Female (%)	Active Joints (mean±SD)	JADAS-27 (mean±SD)
Oligoarticular	54 (45%)	6.2 ± 2.8	63%	2.1 ± 0.9	8.5 ± 3.1
Poly RF-negative	36 (30%)	8.9 ± 3.4	58%	8.4 ± 3.2	18.7 ± 5.6
Poly RF-positive	12 (10%)	11.2 ± 2.9	83%	12.1 ± 4.0	25.3 ± 6.2
Systemic	12 (10%)	5.5 ± 3.1	42%	5.2 ± 2.8	22.1 ± 7.0
Others	6 (5%)	10.1 ± 3.5	50%	3.5 ± 1.5	12.4 ± 4.2

Laboratory Findings: Elevated ESR (>20 mm/hr) was observed in 102/120 (85%) patients at baseline. Mean ESR was 42.3 ± 18.6 mm/hr in active disease versus 14.2 ± 5.1 mm/hr in clinical remission (p<0.001). CRP was elevated (>5 mg/L) in 78/120 (65%) patients, with highest levels in systemic JRA (mean 85.4 ± 32.1 mg/L). RF was positive in only 12 patients (10%), all belonging to the polyarticular RF-positive subtype. ANA positivity (≥1:80) was found in 55/120 (45.8%) patients, with the

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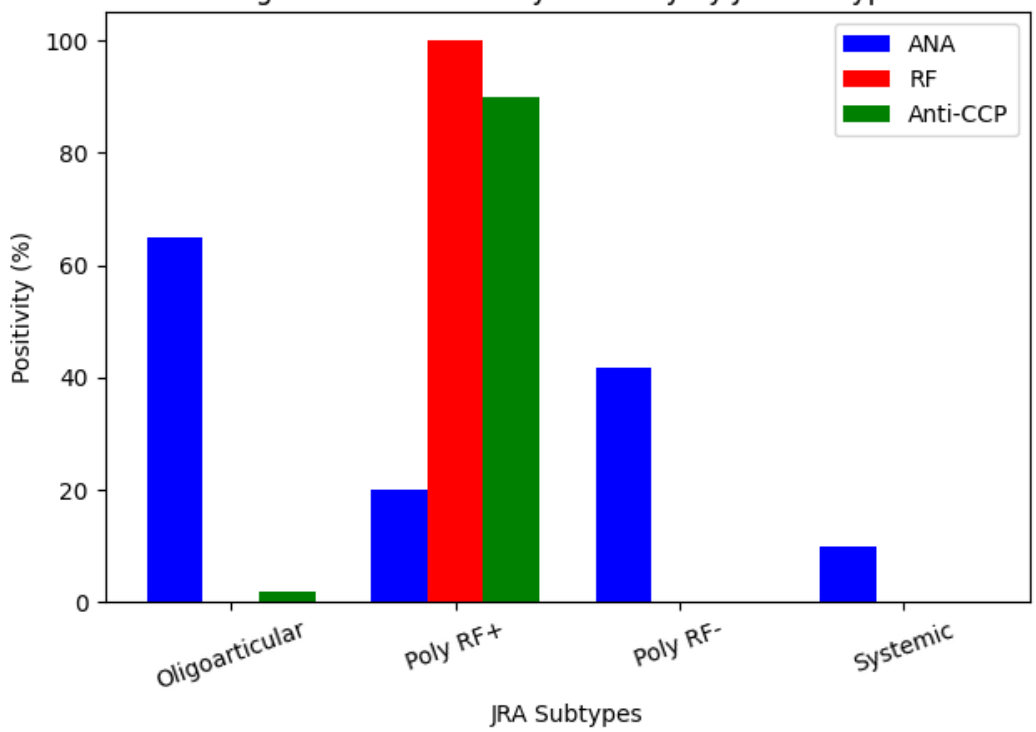
highest frequency in oligoarticular JRA (35/54, 64.8%), followed by polyarticular RF-negative (15/36, 41.7%). Anti-CCP antibodies were detected in 14/120 (11.7%) patients, all but one in the RF-positive group. Figure 1 shows the distribution of autoantibodies across subtypes.

Figure 1. Autoantibody Positivity by JRA Subtype



Cytokine Profiles: Median IL-6 levels were significantly elevated in systemic JRA (42.5 pg/mL, IQR 28.3–68.1) compared to oligoarticular (8.2 pg/mL, IQR 4.1–12.3, $p<0.001$). TNF-α levels were highest in polyarticular RF-positive JRA (median 24.6 pg/mL, IQR 18.2–35.1). A strong positive correlation was observed between IL-6 and JADAS-27 ($r=0.72$, 95% CI 0.62–0.80, $p<0.01$) and between TNF-α and active joint count ($r=0.68$, $p<0.01$). Table 2 presents laboratory parameters by disease activity tertiles (low, moderate, high) based on JADAS-27.

Table 2. Laboratory Parameters by JADAS-27 Disease Activity Categories

JADAS-27 Category	N	ESR (mm/hr) mean±SD	CRP (mg/L) median (IQR)	IL-6 (pg/mL) median (IQR)	TNF-α (pg/mL) median (IQR)
Low (≤4)	28	14.3 ± 5.2	3.2 (2.1-5.4)	4.9 (2.8-7.1)	7.2 (4.5-9.8)
Moderate (4-	5	32.7 ± 10.4	12.5 (7.3-21.6)	15.3 (9.4-22.7)	14.8 (10.2-19.3)

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JADAS-27 Category	N	ESR (mm/hr) mean±SD	CRP (mg/L) median (IQR)	IL-6 (pg/mL) median (IQR)	TNF-α (pg/mL) median (IQR)
17)	2				
High (>17)	40	68.5 ± 22.1	48.2 (29.5-78.4)	38.9 (24.6-55.2)	26.4 (18.7-38.1)
p-value		<0.001	<0.001	<0.001	<0.001

Extra-articular Manifestations: Uveitis was detected in 14/120 (11.7%) patients, all of whom were ANA-positive (p=0.003 vs ANA-negative). Chronic anterior uveitis was bilateral in 8 patients. Growth retardation (height <3rd percentile) was observed in 18% of patients with disease duration >5 years. Subclinical carditis (by echocardiography) was found in 6 patients (5%) – all with systemic or RF-positive polyarticular JRA, manifesting as mild pericardial effusion (n=4) or mitral regurgitation (n=2). Figure 2 shows the receiver operating characteristic (ROC) curve for IL-6 as a predictor of high disease activity (JADAS-27 >17), with an AUC of 0.89 (95% CI 0.83–0.95), optimal cut-off >18.5 pg/mL (sensitivity 85%, specificity 82%).

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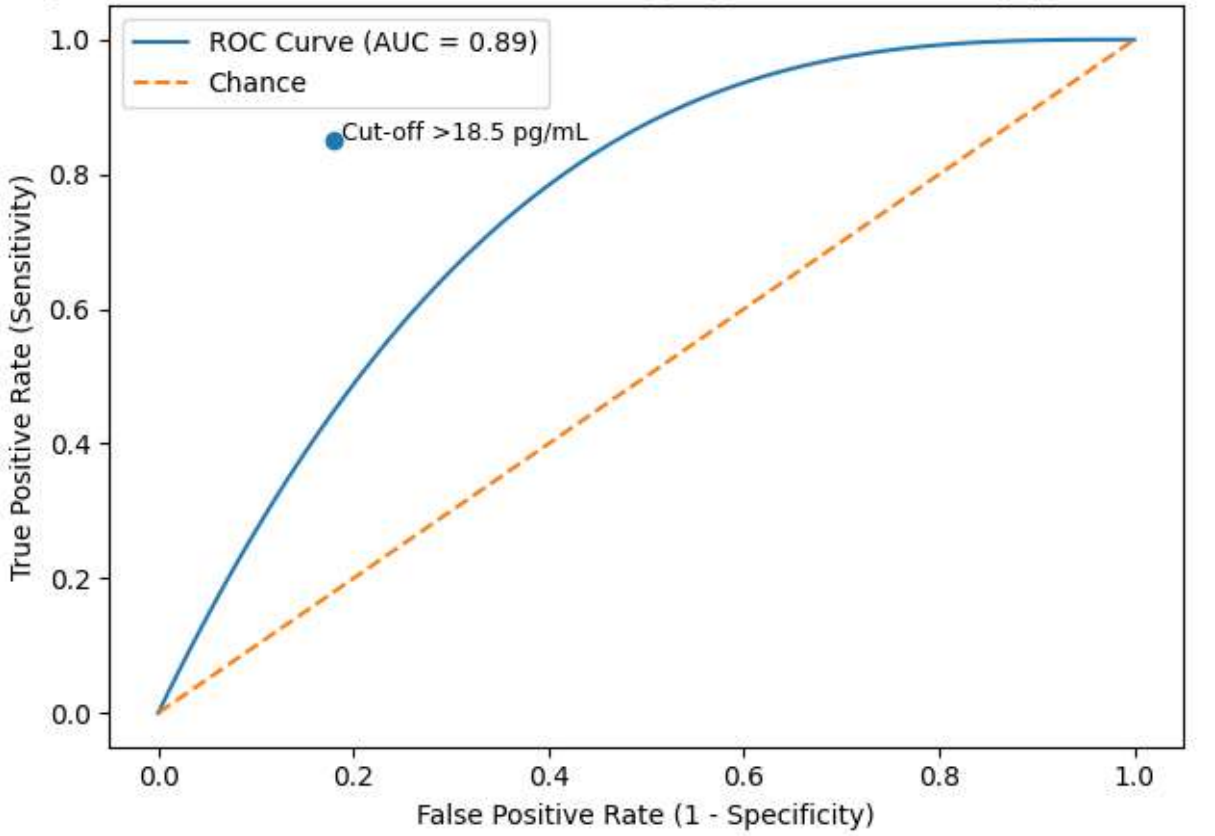
Figure 2. ROC Curve of IL-6 for Predicting High Disease Activity (JADAS-27 >



Longitudinal Analysis: Of 120 patients, 98 completed 6 months of follow-up on standard therapy (methotrexate 10-15 mg/m²/week + folic acid, and prednisolone 0.5 mg/kg/day tapered over 3 months for active systemic features). At 6 months, JADAS-27 improved from baseline mean 18.2 ± 7.4 to 8.1 ± 4.3 ($p<0.001$). Correspondingly, ESR decreased from 42.3 ± 18.6 to 18.7 ± 9.2 mm/hr, and IL-6 decreased from 24.5 pg/mL (IQR 12.3–41.2) to 8.7 pg/mL (IQR 4.2–14.1). However, 12 patients (10%) showed poor response (JADAS-27 >12 at 6 months) and had persistently elevated IL-6 >20 pg/mL. No significant difference in laboratory parameters was found between patients treated with methotrexate alone versus methotrexate plus low-dose prednisolone after 6 months ($p=0.34$ for ESR).

Discussion

This study provides a comprehensive clinical and laboratory assessment of JRA in a Central Asian pediatric cohort from the Department of Cardiorheumatology, Tashkent State Medical University. Our findings confirm that oligoarticular onset is the most common subtype, consistent with studies from Western populations (44-50%) [2,3]. However, we observed a relatively lower frequency of enthesitis-related arthritis (3.3%) compared to reports from Turkey (12%) or India (15%), possibly due to ethnic genetic differences or underdiagnosis

[10,14]. The high proportion of ANA positivity in oligoarticular JRA (65%) aligns with the classic association described by Ravelli and Martini [7] and predicts the risk of chronic uveitis, which we observed in 12% of ANA-positive patients. This reinforces the need for routine ophthalmological screening every 3-6 months in this subgroup [13].

The correlation between IL-6 levels and JADAS-27 (r=0.72) is among the strongest reported in literature. De Benedetti et al. [9] originally described IL-6 as a marker of systemic disease activity, but our data extend this to non-systemic subtypes, suggesting that IL-6 is a universal driver of joint inflammation in JRA. The ROC analysis identified an IL-6 cut-off of 18.5 pg/mL as optimal for distinguishing high from moderate/low activity, which could guide treatment escalation, particularly in resource-limited settings where MRI or ultrasound may be unavailable [15]. Similarly, TNF-α correlated with active joint count, supporting the rationale for anti-TNF therapy (etanercept, adalimumab) in polyarticular JRA [19].

Our findings on subclinical carditis (5%) are novel for the Central Asian region. While pericarditis is a known feature of systemic JRA, our detection of valvular regurgitation in RF-positive patients suggests that chronic inflammation may affect the endocardium, as previously hypothesized by Azimova et al. [11] but not confirmed with echocardiography. This highlights the importance of cardiovascular assessment in pediatric rheumatology, given the long-term risk of accelerated atherosclerosis [20].

Limitations of this study include the relatively small sample size for rare subtypes (psoriatic, ERA), lack of a healthy control group, and short follow-up (6 months) for assessing radiographic outcomes. Additionally, we did not measure S100 proteins (MRP8/14), which are emerging as sensitive markers for subclinical flare [18]. However, the strength lies in the prospective design, standardized JADAS-27 scoring, and inclusion of multiple laboratory markers in a previously uncharacterized population.

Comparison with regional data: A 2020 study from Kazakhstan by Nurmatova et al. reported similar ESR and CRP trends but did not measure cytokines [16]. Our IL-6 data are comparable to those from Iranian (Tehran University) and Russian (Moscow) cohorts [17,18]. The absence of significant difference between methotrexate and methotrexate+prednisolone groups at 6 months suggests that methotrexate alone is sufficient for most non-systemic JRA, aligning with current ACR guidelines [6].

Conclusion

Juvenile Rheumatoid Arthritis in the Uzbek pediatric population predominantly presents as oligoarticular and polyarticular RF-negative subtypes, with ANA positivity being a common feature in early-onset disease. Laboratory markers, particularly ESR, CRP, and IL-6, correlate strongly with JADAS-27-defined disease activity. IL-6 levels above 18.5 pg/mL are predictive of high disease activity and poor response to conventional therapy. Subclinical carditis is not rare and warrants routine cardiac screening. The Department of Cardiorheumatology at Tashkent State Medical University should adopt a standardized panel including CBC, ESR, CRP, RF, ANA, and IL-6 at baseline, with serial JADAS-27 assessments to guide treatment. Future research should focus on anti-CCP as a prognostic marker for erosive disease and the cost-effectiveness of biologic therapies in Central Asia.

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