



Five-Year Outcomes of Systemic-Onset Juvenile Idiopathic Arthritis in India: Insights into Disease Course and Predictive Factors

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Abstract

Objective: Systemic-onset juvenile idiopathic arthritis (sJIA) follows a variable and unpredictable course, with long-term outcomes remaining inconsistent worldwide despite therapeutic advancements. This study aimed to evaluate the disease course and clinical outcomes of the sJIA cohort after 5-year follow-up.

Methods: The study retrospectively analyzed 100 sJIA patients with at least 5 years of follow-up. Ten patients were excluded due to insufficient data. Data on demographics, clinical features, treatments, outcomes, and complications were collected.

Results: The mean age at disease onset was 6.75 ± 3.64 years, with a median follow-up of 7 years. Common clinical manifestations included fever (100%), arthritis (96%), rash (55%), and hepatosplenomegaly (32%). Polyarticular arthritis was observed in 70.83% of cases. Treatment modalities included Non-steroidal anti-inflammatory drugs (100%), steroids (89%), methotrexate (86%), thalidomide (31%), lenalidomide (21%), and tocilizumab (13%). While 11% of patients responded to NSAIDs alone, 46% achieved remission with glucocorticoids and methotrexate. A total of 46% of the patients exhibited a monocyclic disease course, and 27% of the patients had polycyclic and persistent courses. On multivariate analysis, diagnostic delay (odds ratio (OR) = 1.02, 95% CI: 1.01-1.03) and symmetric arthritis (OR = 2.36, 95% CI: 1.65-3.32) were identified as key predictors of persistent disease. Common complications included infections (20%), joint damage (14%), and macrophage activation syndrome (11%). At 5 years, 62% achieved drug-free remission, 16% remained in remission on medication, and 21% had active disease. Mortality was noted in 1 patient due to a suspected cerebrovascular accident or meningitis.

Conclusion: Delayed diagnosis and symmetric arthritis at onset increased the risk of persistent disease, highlighting the need for early and aggressive treatment for better outcomes.

Keywords: Juvenile systemic arthritis, lenalidomide, macrophage activation syndrome, thalidomide, tocilizumab

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Introduction

Systemic-onset juvenile idiopathic arthritis (sJIA) is a subtype of JIA. It is seen in children under the age of 16 years, characterized by the occurrence of fever for at least 2 weeks, occurring daily (quotidian) for at least 3 consecutive days, arthritis in 1 or more joints, with at least one of the following: evanescent erythematous rash, generalized lymphadenopathy, hepatomegaly, splenomegaly, or serositis.¹ According to Western literature, it accounts for about 10%-20% of the JIA population, whereas in certain parts of Asia, it constitutes approximately 30%-40% of all JIA cases.²⁻⁴

Systemic-onset juvenile idiopathic arthritis follows 3 distinct courses: monocyclic (single episode of the disease associated with clinical remission within 2 years of onset), polycyclic (multiple episodes of the disease with clinical remission in between), or persistent disease course (characterized by persistent disease activity without achieving clinical remission).^{5,6} The patients with monocyclic disease course tend to have a shorter duration of disease (can last from a few months up to a couple of years) with better outcomes.⁷ However, in the pre-biologic era, patients with persistent disease required continuous treatment with glucocorticoids and other disease-modifying anti-rheumatic drugs (DMARDs) for disease control. Despite the availability of biologic therapies, approximately 20% of patients continued to experience refractory disease,

characterized by active arthritis, systemic symptoms, or both.⁷

While the landscape of sJIA treatment has evolved to prioritize biologic response modifiers as the primary, first-line approach according to new guidelines,^{8,9} clinicians continue to face challenges in managing sJIA, particularly in resource-limited settings such as India. Due to the high cost of biologics and limited health insurance coverage, out-of-pocket expenditure becomes a substantial burden for many patients. This often necessitates a reliance on conventional DMARDs and corticosteroids. Consequently, clinicians are often compelled to maintain patients on high-dose steroids for extended durations, which, while effective in controlling acute inflammation, is associated with a greater risk of significant adverse effects. This often leads clinicians to sequentially add multiple conventional DMARDs to achieve and maintain remission, representing an adapted treatment strategy in these environments.

The course of the disease can be complicated by infections, macrophage activation syndrome (MAS) (subclinical and overt), growth retardation, osteoporosis, and interstitial lung disease.⁶

Timely diagnosis and the initiation of early and prompt treatment are essential to prevent long-term joint damage and deformities. This retrospective study was undertaken to analyze the disease course and outcomes at 5-year follow-up of the patient cohort.

Methods

A retrospective chart review was conducted on patients diagnosed with sJIA according to the International League of Associations for Rheumatology classification criteria. The study included patients diagnosed between January 1, 2010, and December 31, 2017, all of whom had completed a minimum of 5 years of follow-up by the study end date of December 31, 2022.

Main Points

- A delayed systemic-onset juvenile idiopathic arthritis diagnosis (>6 months) may increase the likelihood of a persistent disease course in the long term.
- Symmetric arthritis at onset is associated with a higher risk of developing a persistent disease course.
- Remission can still be achieved at 5 years in a community with resource constraints, with limited use of biologics.

Patients were diagnosed with sJIA based on the presence of fever for at least 2 weeks, occurring daily (quotidian) for at least 3 consecutive days, arthritis in 1 or more joints, with at least one of the following: evanescent erythematous rash, generalized lymphadenopathy, hepatomegaly, splenomegaly, or serositis.¹

For the purpose of this study, patients were retrospectively categorized into 3 risk groups based on their clinical and laboratory profiles at disease onset. A low-risk presentation was defined by mild, intermittent fever and oligoarticular arthritis, without significant systemic or laboratory abnormalities. These patients were initially managed with NSAIDs. A moderate-risk presentation, characterized by persistent high fevers, polyarticular arthritis, and elevated inflammatory markers, prompted the use of systemic corticosteroids and conventional DMARDs. Patients with a high-risk presentation, including severe systemic illness or features suggestive of MAS, were treated with aggressive therapies, including multiple DMARDs or biologics. This stratification was used as an analytical framework to evaluate the treatment escalation strategies employed at the center. The risk categories were derived from institutional clinical experience and align with the management principles commonly applied in resource-constrained settings, where access to biologic therapies is limited and treatment decisions are often individualized based on the clinical response. Accordingly, this retrospective classification reflects the systematic clinical judgement exercised by the treating physicians during the study period.

Remission, or clinically inactive disease, as defined by Wallace criteria, included the following: absence of active arthritis, fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; absence of active uveitis; normal ESR or CRP level; and a physician's global assessment of disease activity indicating clinical disease quiescence.¹⁰ Inactive disease was further classified into clinical remission on medication (a minimum of 6 continuous months of inactive disease while receiving medication) and clinical remission off medication (12 months of inactive disease while not receiving any anti-arthritis or anti-uveitis medications).¹⁰ Subclinical disease activity, such as isolated elevated ESR or CRP without other signs of active disease, was considered inactive if all other Wallace criteria, including physician global assessment for clinical inactive disease, were met.

Macrophage activation syndrome was defined by the PRINTO (Paediatric Rheumatology

International Trials Organization) criteria (fever, ferritin >684 ng/dL and any 2 of the following: platelet count <181 × 10⁹/L, aspartate aminotransferase > 48 U/L, triglycerides >156 mg/dL, fibrinogen <360 mg/dL).¹¹

Joint damage was defined by the treating pediatric rheumatologist during routine follow-up, based on clinical evidence (contractures, deformities like Boutonnière or Swan neck, micrognathia) or radiological findings. The lack of a standardized scoring system is acknowledged as a study limitation.

Symmetric arthritis was defined as simultaneous involvement of the same joint areas on both sides of the body. However, bilateral involvement of proximal interphalangeal joints, metacarpophalangeal joints, or metatarsophalangeal joints was accepted without absolute symmetry.¹²

Diagnostic delay was defined as the duration in months from the onset of first symptoms attributable to sJIA to the date of confirmed diagnosis.

Retrospective data were collected in a standardized protocol and analyzed. Data on patient demographics, clinical presentation, treatment strategies, adverse effects, complications, and disease course were systematically collected and monitored throughout the follow-up period. Patients on thalidomide and lenalidomide underwent a focused neurological examination at each follow-up visit to screen for signs of peripheral neuropathy. Nerve conduction studies were not used as a routine screening tool but were performed in symptomatic patients to confirm the diagnosis and assess the severity of nerve involvement.

Ethical clearance was obtained from the Institutional Ethics Committee on April 4, 2024 Manipal Hospitals, Bangalore. Given the retrospective nature of the study, the requirement for individual patient informed consent was waived by the ethics committee.

Statistical analysis was done using SPSS 20.0 and Datatab online statistical packages. Descriptive statistics were used to summarize the demographic, clinical, and laboratory characteristics of the cohort. Continuous variables, such as age and diagnostic delay, are presented as mean ± standard deviation (SD) or median with interquartile range where appropriate. Categorical variables are presented as frequencies and percentages.

To compare clinical features and outcomes across the 3 disease courses (monocyclic, polycyclic, and persistent), differences in continuous variables were assessed using the independent sample *t*-test and analysis of variance. Differences in nominal variables were assessed using the chi-square test and Fisher's exact test.

For the predictive model, a univariate analysis was conducted to identify factors associated with a persistent disease course. Variables with a statistically significant association ($P < .05$) in this analysis were then included in a multivariate binary logistic regression model. The variables included in the model were diagnostic delay, cervical spine involvement, symmetric joint involvement, growth retardation, and joint damage. Odds ratios (OR) with 95% CI were calculated for the predictors in the multivariate model. A *P*-value of less than .05 was considered statistically significant. Multicollinearity among the independent variables was assessed using Variance Inflation Factors (VIFs). Variables demonstrating significant collinearity ($VIF > 5$) or strong clinical/statistical correlation (e.g., active joint count and symmetry) were evaluated, and the most clinically representative variable was retained to ensure the stability and parsimony of the multivariate model.

Due to the retrospective nature of the study, a complete case analysis was performed, and instances of missing data for specific variables are noted in the results. To evaluate the potential for bias introduced by missing outcome data, a sensitivity analysis was performed assuming a "worst case scenario" where all missing response data were categorized as nonresponders.

Results

A total of 317 JIA patients diagnosed between 2010 and 2017 were identified, of which 110

were diagnosed with sJIA (34.7%). After excluding 10 patients who were lost to follow-up, 100 sJIA patients with at least 5 years of follow-up were enrolled in the study. The study cohort comprised 52 males and 48 females, with a male-to-female ratio of 1.08 : 1. The mean age at disease onset was 6.75 ± 3.64 years, while the mean age at diagnosis was 7.48 ± 3.75 years. The mean diagnostic delay was 9 ± 11 months, and the median follow-up duration was 7 years (6-8.5 years). It was found that 46/100 of the patients followed a monocyclic course, while 27/100 each had polycyclic and persistent disease courses.

The key clinical features of the patients with sJIA are shown in Figure 1. Polyarticular arthritis was present in 68/96 (70.83%) of sJIA patients, while 29/96 (30.2%) had symmetric arthritis at onset. Arthritis developed within 6 months of diagnosis in 4% of patients who initially presented with febrile illness without arthritis.

Table 1 compares the clinical features and laboratory characteristics at the time of diagnosis, along with disease course and outcomes of patients with monocyclic, polycyclic, and persistent disease courses.

Univariate analysis revealed that diagnostic delay ($P=.01$), cervical spine involvement ($P=.03$), symmetric joint involvement ($P=.006$), growth retardation ($P=.009$), and joint damage ($P=.01$) were significantly associated with a persistent disease course. However, multivariate regression analysis identified only diagnostic delay and symmetric joint involvement as the primary predictors of a persistent disease course. Each additional month of diagnostic delay was associated with a 1.02-fold increased odds of a persistent disease course (OR= 1.02, 95% CI: 1.01-1.03, $P=.002$). Furthermore, patients with symmetric joint involvement at onset had 2.36 times higher odds of a persistent disease course compared to those with

asymmetric involvement (OR=2.36, 95% CI: 1.65-3.32, $P=.0001$).

To ensure the stability of the model, checks for multicollinearity were performed. A moderate positive correlation was identified between active joint count and symmetric joint involvement ($r_{pb}=0.39$). This statistically confirms that patients with higher joint counts are significantly more likely to present with a symmetric pattern; however, the correlation is not "perfect" (1.0), meaning some patients with higher joint counts still present asymmetrically, and vice versa. This indicates that symmetric involvement effectively explains the variance otherwise provided by the active joint count, thereby justifying the exclusion of the latter from the final multivariate model to prevent model instability due to multicollinearity.

Patients were stratified into treatment groups based on disease severity at presentation. A low-risk group, comprising 11/100 patients (10/46 in the monocyclic group and 1/27 in the polycyclic group), was successfully managed with NSAID monotherapy. The remaining 89/100 patients, who were classified as having moderate-to-high risk disease, were treated with intravenous methylprednisolone (10-30 mg/kg) followed by oral glucocorticoids as a part of the treatment protocol. Out of 4 patients who had only systemic manifestations at presentation without arthritis, 3 achieved clinical remission with NSAIDs and steroids. Methotrexate was the initial DMARD used in 86/100 patients who did not respond to NSAIDs. A total of 46/100 achieved remission with glucocorticoids and methotrexate. Patients with sJIA who exhibited either a partial response or difficulty tapering steroids within the first 3-6 months of therapy were offered the option of either a biologic response modifier or a second-line DMARD. Figure 2 illustrates a flowchart depicting the treatment strategy followed by the treating physicians during the study period.

Thalidomide was used in 31/100 (31%) patients, with 7/31 (22.6%) discontinuing it within 2-3 months due to adverse effects. Among the remaining 24 patients, steroids were successfully tapered in 12/24 (50%), while 8/24 (33.33%) experienced disease flares on steroid tapering and follow-up data were unavailable for 4/24 (16.67%) patients. Systemic improvement was observed in 15/24 (62.5%) patients, whereas articular improvement was seen only in 10/24 (41.67%) patients. The dose of thalidomide used in the patients was 2-3 mg/kg/day with a mean treatment duration of $14.7 \pm$

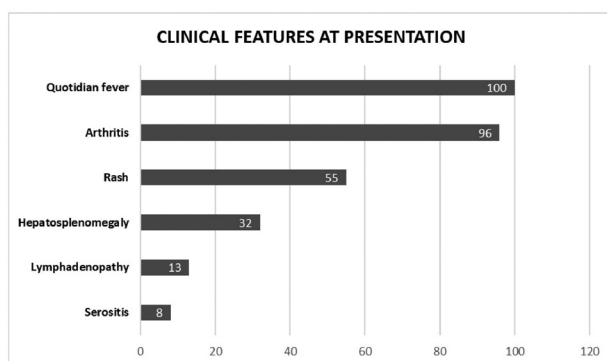


Figure 1. Horizontal bar diagram showing the main clinical features of patients with systemic onset juvenile idiopathic arthritis.

Table 1. Comparison of Salient Clinical Features and Laboratory Characteristics at the Time of Diagnosis, Along with Disease Course and Outcomes of Patients

Groups	Monocyclic (1) (n=46)	Polycyclic (2) (n=27)	Persistent (3) (n=27)	P
Age at onset (months), (mean ± SD)	87.5 ± 41	72.7 ± 48.3	80 ± 42.5	.3 (group 1-2) .3 (group 1-3)
Diagnostic delay (months), (mean ± SD)	6.5 ± 6.9	8.1 ± 6.2	13.9 ± 17.7	.02 (group 1-2) .01 (group 1-3)
Active joint count at onset, (mean ± SD)	12.5 ± 15.1	15.8 ± 17.5	18.5 ± 18.4	.3 (group 1-2) .3 (group 1-3)
Cervical spine involvement, n (%)	9 (20.45)	10 (38.5)	13 (50)	.1 (group 1-2) .03 (group 1-3)
Polyarticular arthritis, n (%)	29 (65.9)	19 (73)	20 (76.9)	.7 (group 1-2) .5 (group 1-3)
Symmetric arthritis, n (%)	5 (11.36)	10 (38.5)	14 (53.8)	.008 (group 1-2) .006 (group 1-3)
Hb (g/dL), (mean ± SD)	10.3 ± 2	10.3 ± 1.7	9.6 ± 1.7	.2 (group 1-2) .2 (group 1-3)
TLC (cells/mm ³) (mean ± SD)	17152 ± 8480	15440 ± 7262	15430 ± 6154	.4 (group 1-2) .4 (group 1-3)
Platelet count (cells/mm ³) (Mean ± SD)	441391.3 ± 194163.8	444259.3 ± 187369.6	460074.1 ± 197714	.8 (group 1-2) .8 (group 1-3)
ESR (mm/hr) (mean ± SD)	67.5 ± 29	61.4 ± 30.5	70 ± 39	.5 (group 1-2) .5 (group 1-3)
MAS, n (%)				
1 episode	2 (4.35)	4 (14.8)	3 (11.1)	.5 (group 1-2)
2 episodes	—	1 (3.7)	—	.1 (group 1-3)
3 episodes	—	—	1 (3.7)	
Drug-free remission, n (%)	46 (100)	15 (55.6)	1 (3.7)	
Remission on drugs, n (%)	—	8 (29.6)	8 (29.6)	.001 (group 1-2)
Active disease, n (%)	—	4 (14.8)	17 (63)	<.001 (group 1-3)
Death, n (%)	—	—	1 (3.7)	
Joint damage, n (%)	2 (4.3)	4 (14.8)	8 (29.6)	.006 (group 1-3) .003 (group 1-2)

The bold values signify statistically significant parameters.

8.23 months. Adverse effects observed with thalidomide use included somnolence in 4/31 (12.9%) patients, itching in 1/31 (3.2%), and oral ulcers in 1/31 (3.2%). Sensory neuropathy was suspected in 5/31 (16.2%) patients. However, these adverse effects were severe enough in only 7/31 (22.6%) patients, necessitating drug withdrawal.

Lenalidomide (dose 5 mg alternate days if <20 kg body weight and 5 mg once-daily if >20 kg body weight) was used in 21/100 (21%) of patients, with 1/21 (4.76%) discontinuing the drug at 3 months due to intolerance (somnolence). Among the remaining 20 patients, steroid tapering was successful in 8/20 (40%), while 7/20 (35%) patients experienced a flare on tapering of the steroids and follow-up data were unavailable for 5/20 (25%)

patients. Improvement in systemic symptoms was observed in 10/20 (50%) patients, whereas improvement in arthritis was seen in 7/20 (35%) patients. Lenalidomide was generally well-tolerated, with hyperpigmentation being the most common side effect seen in 6/21 (28.57%) patients. No instances of peripheral neuropathy related to lenalidomide were observed during the study period.

Tocilizumab was used in 13/100 (13%) patients at a standard dose of 8 mg/kg in children weighing >30 kg and 12 mg/kg in children weighing <30 kg. The drug was initiated at 2-week intervals in all the patients, which was gradually tapered to once every 3-4 weeks after 3-6 months, depending on the clinical response. The mean duration of treatment with Tocilizumab was 39 ± 27.8 months.

Steroids were successfully tapered in 12/13 (92.3%) patients, while 1/13 (7.7%) patients experienced a disease flare. Systemic remission was achieved in 12/13 (92.3%) patients, whereas 1/13 (7.7%) showed no systemic improvement. Articular response varied, with complete response seen in 6/13 (46%) patients, partial response in 3/13 (23.1%) patients, and no response in 4/13 (30.7%) patients. No adverse effects were observed with Tocilizumab.

Among the other drugs used, 2 patients experienced methotrexate intolerance, presenting with abdominal pain and vomiting, while 1 patient developed skin rashes due to naproxen. Steroid-related side effects included osteoporosis in 4 patients and steroid-induced cataract in 1 patient.

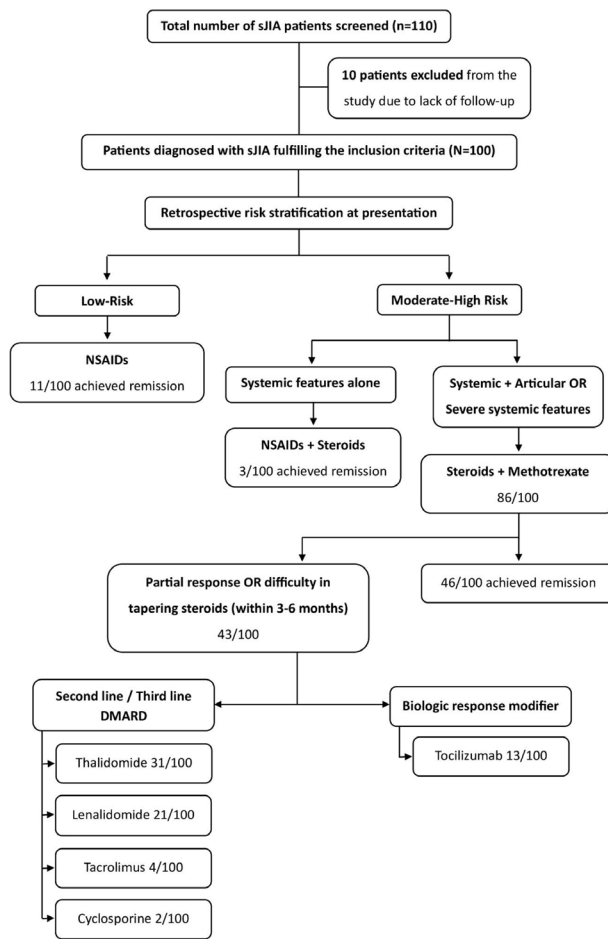


Figure 2. Observed treatment escalation patterns in the systemic onset juvenile idiopathic arthritis cohort.

Apart from drug-induced side effects, disease-related complications were also notable, with infections being the most common (20%), followed by joint damage (14%), MAS (14 episodes in 11% of patients), growth retardation (9%), and osteoporosis (4%).

Infections were observed in 20/100 patients, including varicella and pneumonia in 5 patients each, and pulmonary tuberculosis in 2 patients. The remaining 8 patients experienced minor infections like recurrent upper respiratory infections and acute gastroenteritis.

Joint damage was observed in 14/100 of sJIA patients, presenting as contractures and micrognathia (4.3% in the monocyclic group, 14.8% in the polycyclic group, and 29.6% in the persistent group). As expected, the persistent disease group exhibited a significantly higher incidence of joint damage, with a *P*-value of .01.

Macrophage activation syndrome was more frequently observed in patients with a polycyclic or persistent disease course compared to those with a monocyclic course, though this difference was not statistically significant.

Three patients had MAS at the time of diagnosis, and 11 patients had MAS at any point in time during the 5-year duration. Recurrent MAS occurred in 2 patients—1 with a polycyclic course who experienced 2 episodes and another with a persistent course who had 3 episodes. However, due to resource constraints at the time, genetic analysis to exclude congenital HLH could not be performed in these

patients. Data on serum ferritin levels were available for only 7 patients, with missing data attributed to the retrospective nature of data collection. Notably, there was no mortality due to MAS.

Decreased bone mineral density was suspected in 4 patients—2 presented with low backache, 1 had a vertebral compression fracture, and 1 had a pathological femur neck fracture. DEXA (Dual-Energy X-ray Absorptiometry) scan couldn't be done due to cost constraints or unavailability, and the children were treated with bisphosphonates.

The serial follow-up, disease course, and outcomes of 5 years are shown in Table 2.

At the 5-year follow-up of the cohort, 62/100 patients achieved drug-free remission, while 16/100 remained in remission with ongoing treatment. However, 21/100 patients continued to have active disease despite ongoing therapy. Mortality was reported in 1 patient, suspected to have suffered a cerebrovascular accident or meningitis.

All the patients in the cohort remained true to the diagnosis of sJIA throughout the disease course. However, genetic analysis to rule out other autoinflammatory syndromes could not be done due to the limited availability of services.

Discussion

Though sJIA is one of the most common clinical conditions seen in pediatric rheumatology clinics across the globe, there is a dearth of information about the course and medium- and long-term outcomes, especially from the Indian subcontinent. This study is an effort in that direction.

Table 2. Follow-up Data (N = 100) and Outcome at 5-year Follow-up

	Clinical Status During 5-year Follow-up (%)				
	1 year	2 years	3 years	4 years	5 years
In remission (%)	56	63	70	75	78
Active disease (%)					
Systemic features + arthritis	25	8	4	6	2
Predominantly arthritis	19	29	26	19	19
Outcomes at 5-year follow-up					
Disease course	Drug-free remission	Remission on drugs	Active disease		
Monocyclic (n = 46) (%)	100	—	—		
Polycyclic (n = 27) (%)	55.6		29.6		14.8
Persistent (n = 27) (%)	3.7		29.6		63

Systemic onset JIA accounted for 34.7% of the JIA cohort, which is consistent with findings from other studies in the Indian subcontinent, in contrast to the lower prevalence of 10%-20% reported in Western literature.^{3,4} This difference might be attributed to the differences in genetic predisposition and referral bias.

The demographic features were comparable with the other studies of sJIA patients.¹³⁻¹⁶ However, significant diagnostic delay was found in the study (median 6 months), similar to another Indian study (median 9.6 months),¹⁵ whereas it was far less in Western cohorts (median 1 month and 4 months, respectively).^{7,13,16}

Monophasic illness formed the major subset of the sJIA cohort, in contrast to the study by Sag et al where polycyclic disease course has been reported as the dominant subset.¹⁴ This might reflect the genetic differences between the various populations and would require validation by future genetic studies.

Analysis of the 3 disease courses revealed a statistically significant difference in diagnostic delay, particularly between the monocyclic and persistent disease courses, with delayed referral being the primary contributing factor. This finding suggests that a longer diagnostic delay increases the likelihood of the disease progressing to a persistent state. The authors feel that, when the “window of opportunity” passes by as hypothesized by Nigrovic et al, the disease goes into a persistent disease course as has been validated by the study.¹⁷ Similarly, Wulfrat NM et al mentioned the correlation between the delay in diagnosis and the ongoing presence of active disease.¹⁸

A total of 4% of the patients did not have arthritis at onset, and this is much less than other studies, which have reported the absence of arthritis in about 10%-20% of sJIA patients at disease onset.^{13,14} In the cohort, arthritis was polyarticular in 70.83% of cases, in contrast to the study by Sag E et al, wherein 81% of patients were oligoarticular at the onset.¹⁴

In the study, remission was achieved in 11% of cases with NSAIDs alone, while 46% of patients attained remission with glucocorticoids and methotrexate. Tocilizumab was used in only 13% of cases, similar to the other study from India, where the tocilizumab usage was about 9%. This is significantly less when compared to 40%-80% usage as in the Western cohorts.¹³⁻¹⁶

Baris et al reported a biologic usage rate of 66% in their cohort, with 37% achieving

remission off medications, 25% remaining in remission while on treatment, and 14% continuing to have active disease at a median follow-up of 69 months.¹³ In a study conducted in a similar setting, where biologic usage was 9%, 23% of sJIA patients had persistent disease at a median follow-up of 66 months.¹⁵ Sag E et al reported biologic use in 80% of patients, with 40% achieving remission off medications, 49% in remission on treatment, and 11% continuing to have active disease at a median follow-up of 84 months.¹⁴ More recently, Barut K et al studied 168 sJIA patients, reporting biologic use in 42.8%. Their findings showed higher remission rates, with 48.8% achieving drug-free remission, 49.9% in remission on treatment, and only 1.3% having persistent disease.¹⁶

The global trend in sJIA management increasingly emphasizes the early use of biologic therapies, particularly IL-1 and IL-6 inhibitors, as first-line agents to control systemic inflammation rapidly and prevent long-term complications. This approach, based on the concept of “window of opportunity,” aims to achieve remission before irreversible joint damage occurs. The study, conducted in a resource-constrained setting, highlights a different treatment paradigm, relying more heavily on conventional DMARDs and sequential polytherapy due to limited access to biologics. A total of 31% of the patients were treated with the sequential addition of other DMARDs (Thalidomide/Lenalidomide/Cyclosporine/Tacrolimus). Despite this, the remission rates were relatively favorable, suggesting that in settings where early biologic access is challenging, tailored conventional DMARD strategies can still yield positive outcomes, particularly in patients who follow a monocyclic disease course. This provides valuable real-world data from a low-resource environment, contributing to the debate on optimal treatment strategies in diverse healthcare settings.

In the study, the higher remission rates—despite delayed diagnosis and less frequent use of biologics—may be explained by a larger proportion of children following a monocyclic disease course. This is a key finding that differentiates the cohort from some Western studies. The prevalence of monocyclic disease in the cohort might suggest a genetic or environmental predisposition that leads to a milder disease course in a significant subset of Indian sJIA patients. Furthermore, the authors are tempted to think that the individualized treatment with DMARD polytherapy could have played a role in achieving better outcomes. This personalized approach, adapting treatment based on

individual patient response and tolerance to available medications, may have compensated for the limited access to advanced biologic therapies. This underscores the potential efficacy of a diversified DMARD approach in resource-constrained settings.

When complications due to the disease or as a result of immunosuppression were examined, infections were the most prevalent at 20%, which was lower than the study by Dewoolkar et al (30%), but much higher than 11% in the Western cohort by Baris et al. When the rate of MAS episodes was compared, it was found to be similar to those reported in Indian and Turkish studies but significantly lower than in European studies (30%-36%).¹³⁻¹⁶ Whether this reflects a true difference or if occult MAS was underrecognized in the study remains uncertain. Additionally, in the study, 8% of children demonstrated stunted growth, leading to the initiation of growth hormone therapy in 2 of them. This aligned with the study by Barut et al, which reported growth failure in 11.3% of patients in their cohort.¹⁶ About 15% of the participants experienced adverse reactions to medications. These rates of complications closely mirrored those documented in the other Indian study.¹⁵

This paper provides valuable insights into sJIA outcomes from an Indian perspective, differentiating it from previously published Indian cohorts by its extended 5-year follow-up, detailed analysis of various DMARDs, including thalidomide and lenalidomide, and a comprehensive assessment of factors influencing disease course. While other Indian studies have provided important baseline data on sJIA prevalence and characteristics, this study offers a deeper understanding of long-term trajectories and the effectiveness of a diverse treatment approach in a setting with limited biologic access. Specifically, the high rate of monocyclic disease and the favorable remission rates despite limited biologic use present a unique perspective compared to Western literature and contribute to a more nuanced global understanding of sJIA.

Limitations

The retrospective nature of the study, while allowing for a comprehensive review of a large cohort over an extended period, inherently poses certain limitations. There were instances of missing data, particularly regarding complete ferritin levels for all suspected MAS episodes and objective assessments like DEXA scans for osteoporosis. This could potentially lead to an underestimation of the true incidence of

these complications. Furthermore, “joint damage” was recorded as a binary variable based on clinical and radiological documentation rather than standardized scoring systems such as Juvenile Arthritis Damage Index (JADI-A or JADI-E) or the Childhood Health Assessment Questionnaire. This approach is a significant limitation, as a binary definition may obscure the spectrum of severity ranging from mild functional limitation to severe joint destruction. The treatment options employed in the study, particularly the higher reliance on non-biologic DMARDs and lower biologic usage, are a reflection of the resource constraints and local treatment guidelines prevalent during the study period, which may differ significantly from contemporary international standards advocating for early biologic initiation. This study’s findings, therefore, should be interpreted within the context of these resource limitations and the specific treatment landscape in India. Future prospective studies with standardized data collection protocols and access to a broader range of diagnostic tools are warranted to validate these findings and provide more precise insights into long-term outcomes and complications.

Conclusions

Delayed diagnosis and symmetric arthritis increased the risk of persistent disease, highlighting the need for early and aggressive treatment during the “window of opportunity” for improving long-term outcomes in sJIA. Although the sizable cohort, standardized follow-up, and uniform data collection strengthen the study, its retrospective nature limited certain clinical and laboratory data, highlighting the need for prospective validation. Notably, despite delayed diagnoses and less frequent use of biologics compared to Western cohorts, the study demonstrated relatively favorable remission rates, a finding that can be attributed, in part, to a higher proportion of patients exhibiting a monocyclic disease course and potentially the individualized approach to DMARD polytherapy. This suggests that effective management strategies can be adapted to resource-constrained environments, offering valuable insights for global sJIA care.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Artificial Intelligence Usage Statement: This study used artificial intelligence tool (Google Gemini AI) to improve language and edit grammar during the preparation of the manuscript.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Manipal Hospitals, Bangalore (Approval no: EC/RENEW/INST/2024/17014, Date: April 4, 2024).

Informed Consent: Verbal informed consent was obtained from the patients/patient who agreed to take part in the study.

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