ORIGINAL RESEARCH article

# Systemic onset juvenile idiopathic arthritis a single-center experience at Tripoli Children's Hospital, Libya

**Soad S. Hashad** [1, 2 *] and **Safaa A. Alghannam** [1]

[1] Tripoli Children's Teaching Hospital, Ministry of Health, Tripoli, Libya
[2] Department of Pediatrics, Faculty of Medicine, University of Tripoli, Tripoli, Libya
[*] Author to whom correspondence should be addressed

**Article number:** 18, **Received:** 09-09-2025, **Accepted:** 25-12-2025, **Published online:** 02-01-2026



**HOW TO CITE THIS**

Hashad SS, Alghannam SA. Systemic onset juvenile idiopathic arthritis a single-center experience at Tripoli Children's Hospital, Libya. Mediterr J Med Med Sci. 2026; 2(1): 1-8. [Article number: 18]. https://doi.org/10.5281/zenodo.18135161

***Keywords:*** Arthritis, juvenile rheumatoid, Libya, MAS, rheumatology

**Abstract:** Systemic onset Juvenile Idiopathic Arthritis (sJIA) is a severe subtype of juvenile idiopathic arthritis, characterized by significant morbidity and mortality due to its multisystem involvement and risk of life-threatening complications such as macrophage activation syndrome. This study aimed to characterize the demographic and clinical profile of sJIA patients managed at the Tripoli Children's Hospital. Medical records of pediatric patients diagnosed with sJIA according to ILAR criteria, those who received follow-up care during 2021 were reviewed. Of 35 records, 32 patients met the inclusion criteria. Findings indicated that female patient's prevalence by 71.9%. The mean age at diagnosis was 6.28 years, with male patients diagnosed significantly younger than female. Referral times varied with 25.0% referred within two months, 46.9% between 2-6 months, and 28.1% experiencing delays exceeding six months. No association was found between gender or age at diagnosis and referral time. Clinical presentation often included a triad of fever, arthritis, and rash. Skin rash was observed in 65.6% of the patients, lymphadenopathy in 25.0%, of the hepatosplenomegaly in 9.0% of patients, and serositis in 6.3% of patient. Large joints were most frequently involved, with the knee and wrist being the most common. Oligoarticular pattern was present in 75.0% of the patients, while 25.0% had polyarticular pattern. Joint deformities were observed in 40.0%, with the knee being the most affected. Other complications included short stature, cataract, osteoporosis, and delayed puberty. Macrophage activation syndrome developed in certain patients, mostly in female patients. Delayed referral (exceeding six months) was associated with more extensive joint involvement and a broader spectrum of complications, with 33.3% showing no disease damage, compared to of those referred within two months. This study highlights the demographic and clinical characteristics of sJIA in Libya, emphasizing the significant burden of complications and the impact of delayed referral on disease outcomes.

## Introduction

Juvenile Idiopathic Arthritis (JIA) is the most common rheumatologic disease in the pediatric age group, which is reported to occur as frequently as juvenile diabetes mellitus DM. JIA is characterized by persistent arthritis of unknown etiology with onset before 16 years of age and lasting for at least six weeks [1]. Its global prevalence ranges from 3.8 to 400 per 100,000 children, with an incidence of 1.6 to 23 new cases per 100,000 children annually [2]. It is classified according to the ILAR classification system into seven categories: systemic arthritis, oligoarthritis, rheumatoid factor-positive polyarthritis, rheumatoid factor-negative polyarthritis, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis [1]. Each subtype

presents with distinct clinical features, genetic predispositions, pathophysiology, and prognosis. Systemic Juvenile Idiopathic Arthritis (sJIA) is a severe and significant subtype of JIA associated with the highest morbidity and mortality among the JIA subtypes due to its multisystem involvement and risk of life-threatening complications such as macrophage activation syndrome (MAS), which is classified as a secondary form of hemophagocytic lymphohistiocytosis (HLH) [3]. According to the ILAR, sJIA is diagnosed when arthritis in one or more joints is accompanied or preceded by a daily high-grade fever of at least two weeks' duration [3]. The fever pattern is distinctive, typically rising in the evening or early in the morning with rapid return to baseline, during which the child may appear well. In some cases, the rash demonstrates an isomorphic response known as the Koebner phenomenon [4, 5]. Once the arthritis presents are frequently polyarticular and destructive, with involvement of the wrists, knees, hips, temporomandibular joints, and cervical spine [5].

Hip involvement is associated with poor prognosis and may lead to early joint destruction requiring surgical intervention [6]. Unlike other JIA subtypes that are primarily autoimmune, sJIA is increasingly recognized as an autoinflammatory disorder. It is mediated largely by the innate immune system, with interleukin IL-1, IL-6, and IL-18 playing central roles in disease pathogenesis [4, 5]. These proinflammatory cytokines contribute to the systemic features, persistent inflammation, and severe articular damage seen in affected patients [6]. sJIA accounts for 10.0% to 20.0% of all JIA cases in North America and Europe [6]. The majority of Saudi Arabian studies reported sJIA as the most predominant subtype in their population [7]. Its incidence is estimated to be between 0.3 and 0.8 cases per 100,000 children annually. It typically affects males and females equally, with a peak presentation between 1 and 5 years of age [1, 4]. Treatment has evolved from NSAIDs, corticosteroids, and conventional disease-modifying antirheumatic drugs to cytokine-targeted biologics. IL-1 inhibitors and IL-6 inhibitors have shown remarkable efficacy in controlling systemic symptoms and preventing long-term joint damage. In regional contexts, resource limitations may delay access to biologics, increasing reliance on steroids and methotrexate. This discrepancy was noted in Libyan, Saudi, and Emirati [8, 7, 9] cohorts, where long-term corticosteroid use contributed to growth impairment and other complications. Complications associated with sJIA can be severe and life-threatening [5]. MAS is the most lethal complication with a high mortality rate estimated between 8.0%-20.0% [5]. MAS can occur at any point during the disease course or as an initial presentation. 10.0% of sJIA patients develop overt MAS, although subclinical MAS is likely more frequent and underdiagnosed [10]. Other complications include chronic arthritis, joint damage and deformity, growth retardation, osteoporosis, and amyloidosis [5]. Psychosocial and functional impairments frequently affect the quality of life in these patients, who are susceptible to infections due to immunosuppressive therapies [11]. Disease-associated mortality rates have been reported between 0.5% (USA) and 1.0% (Europe) [12]. Early and aggressive treatment is crucial for improving outcomes and preventing long-term complications. Long-term follow-up studies have shown that early biologic therapy is associated with better functional outcomes and reduced joint damage [13]. However, delayed diagnosis and insufficient access to care in low-resource settings remain major barriers to optimal outcomes [8]. This study aims to show the demographic, clinical features, delayed referral, and complications among patients diagnosed and followed at the Tripoli Children's Hospital as a retrospective study over a 21-year period.

## Materials and methods

*Study design and setting:* This is a retrospective case series that was carried out at Tripoli Children's Hospital, a major tertiary center in Tripoli and the most important referral rheumatology center in Libya. It contains a well-structured pediatric sub-specialty unit, including pediatric rheumatology.

*Patient population:* The study involved reviewing medical records of pediatric patients diagnosed with sJIA according to the ILAR criteria who underwent follow-up care, including hospital admissions or visits at the outpatient clinics at the Hospital over a 21-year period. A total of 32 patients were identified. Other JIA subtypes were excluded.

*Ethical considerations:* Ethical approval was obtained from the relevant institutional authority (TCH, 002/2024). As this was a retrospective study using medical records, all data were anonymized, and confidentiality was maintained throughout the study.

*Data collection:* Data were obtained retrospectively from patients' medical records diagnosed with sJIA and followed up in the pediatric rheumatology clinic from January 2001 to December 2021. The diagnosis of sJIA was based on the use of ILAR criteria. Different variables were obtained, including demographic data, presenting symptoms, and complications for each patient. A preformed case sheet was used to obtain the relevant data from the medical records.

*Data analysis:* The collected data were entered and analyzed using SPSS version 20. Descriptive statistics were used to summarize patient data. A Mann-Whitney *U* test was used to explore the difference between the groups. Associations between variables were explored where appropriate. P<0.05 was considered significant.

## Results

Thirty-five cases were reviewed at the Rheumatology unit of Tripoli Children's Hospital from 2001 to 2021. 32 patients met the sJIA ILAR criteria and were included in the analysis. Of these, 71.9% of the patients were female and 28.1% patients were male, resulting in a male-to-female ratio of 1: 2.5. The age at diagnosis ranged from 1 to 13 years, with a mean age of 6.28 years (±3.5 years) (**Figure 1**). The mean age at diagnosis was 4.3 years for males and 7.0 years for females. A Mann-Whitney *U* test showed that this difference was significant, with males diagnosed at a younger age than females (U=55.5, Z=-2.021, p=0.043).

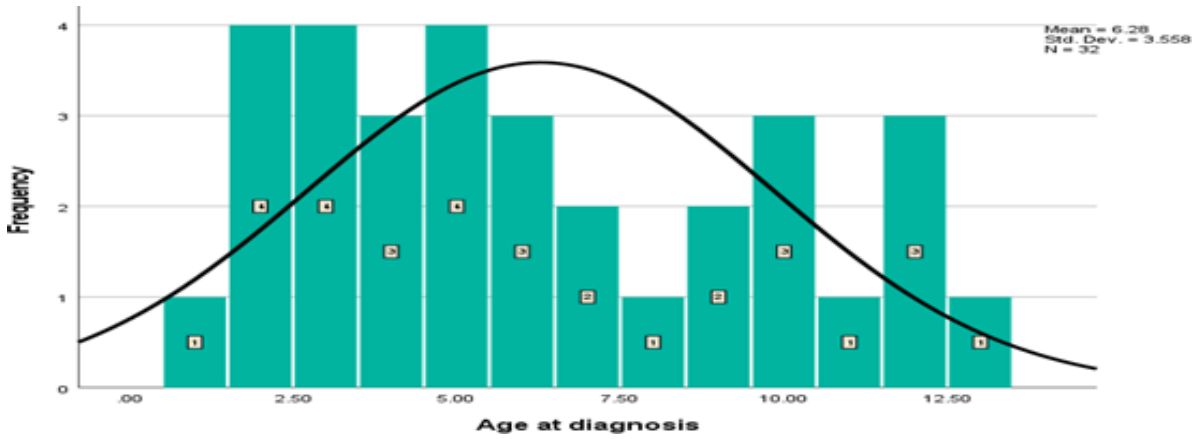


**Figure 1:** Age distribution of sJIA Libyan patients

Referral time from symptom onset to specialist evaluation varied widely: One-quarter of patients were referred within two months, nearly half between 2 and 6 months, and the remaining experienced referral delays exceeding six months (28.1%) (**Table 1**). There was no significant association between gender and referral time ($\chi^2$ (2)=4.81, p=0.09), indicating that referral delays were similar for males and females. No significant association was found between age at diagnosis and referral time (p=0.368).

**Table 1:** Referral time of sJIA Libyan patients

| | Frequency | Percent |
|---|---|---|
| less than 2m | 8 | 25.0 |
| between 2 and 6 months | 15 | 46.9 |
| more than 6 months | 9 | 28.1 |
| Total | 32 | 100.0 |

The distribution of diagnoses among the 32 patients with sJIA varied over the study period, with the majority diagnosed between 2009 and 2011. Specifically, 21.9% were diagnosed in 2009, 18.8% in 2010, and 15.6% in 2011, representing a peak during those three years (56.3% of all cases). Diagnosis rates were lower and more sporadic before and after this period, with isolated cases in 2004, 2006, 2012, 2016-2018, and 2020 (**Figure 2**).

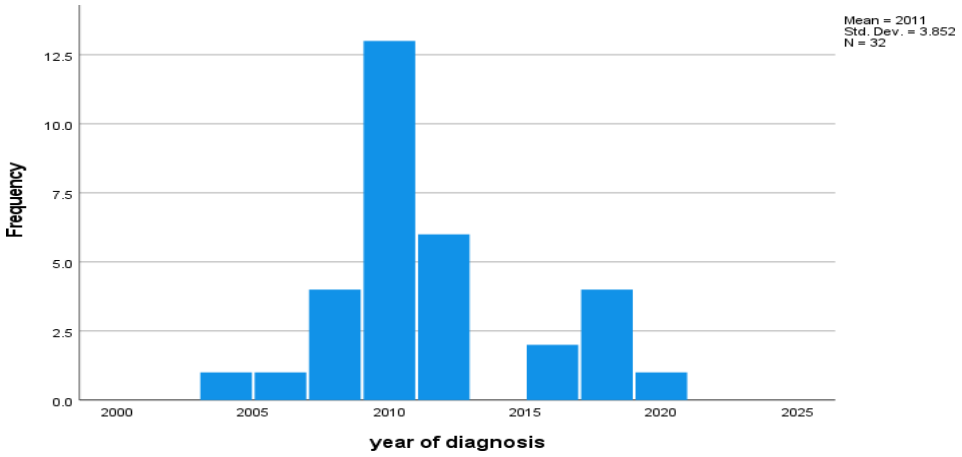


**Figure 2:** Distribution of year of diagnosis of sJIA Libyan patients

Referral time of patients diagnosed with sJIA was compared across two decades (2001-2010 and 2011-2021). Between 2001 and 2010, the majority of cases (42.1%) were referred within 2-6 months of symptom onset, while 26.3% of the patients were referred within two months, and 31.6% patients experienced a delay exceeding six months. In the subsequent decade (2011-2021), the distribution remained similar, with most patients (53.8%) referred between 2 and 6 months. The proportion of early referrals (<2 months) decreased to 23.1% patients, and delayed referrals (>6 months) also fell to 23.1% patients (**Figure 3**). Overall, while the 2-6-month referral window remained the most common across both periods, there was a modest reduction in both very early and excessively delayed referrals in the later decade. This trend suggests a gradual movement toward a narrower and more consistent referral timeframe, though opportunities remain for improving early recognition and prompt referral of sJIA cases.

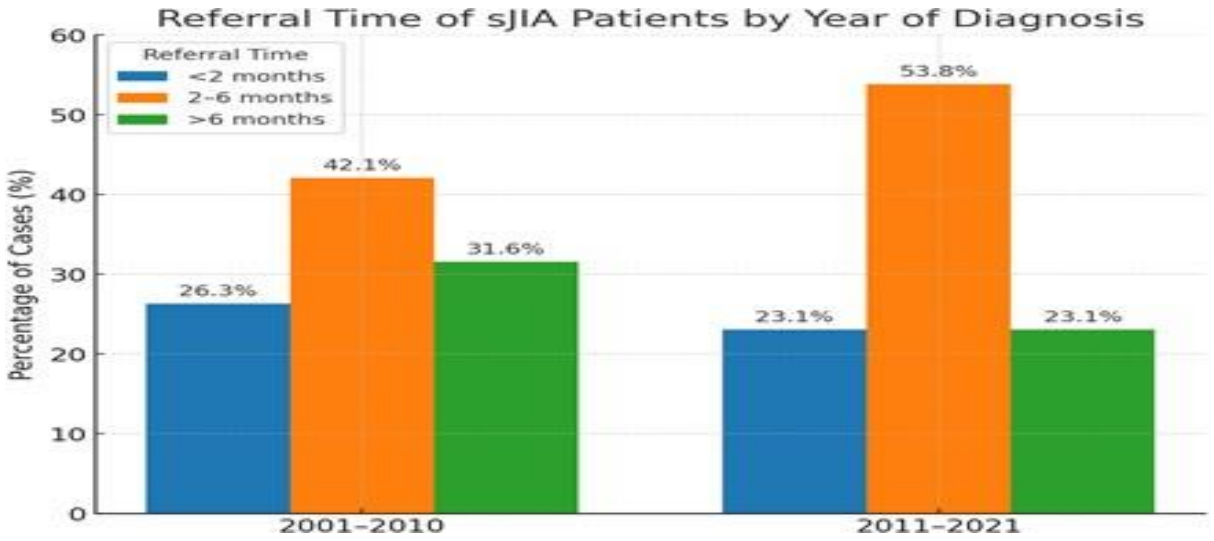


**Figure 3:** Referral time of sJIA patients by year of diagnosis

In **Figure 4**, 43.8% of cases presented with a triad of fever, arthritis, and rash. Skin rash was reported in 65.6% patients, while 34.4% patients did not exhibit any cutaneous manifestations. Lymphadenopathy was observed in 25.0% of the cases, hepatosplenomegaly in 9.0%, and serositis was identified in 6.3% patients. Hepatomegaly and serositis were seen mainly in older children (ages: 11-13 years).

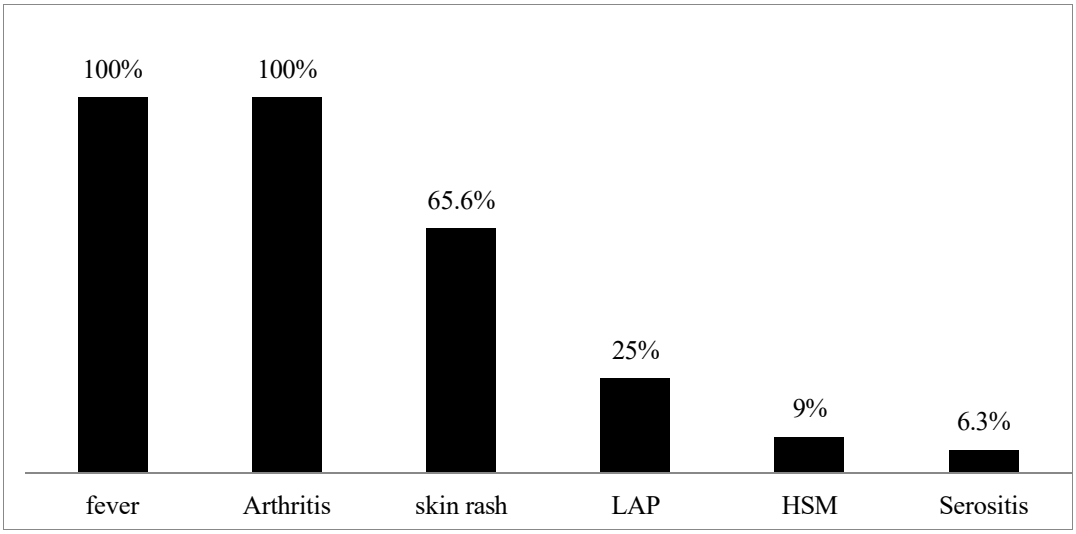


**Figure 4:** Frequency of ILAR criteria at the time of diagnosis

Among the 32 patients with sJIA, large joints were more frequently involved. The knee was the most commonly affected joint (56.0%), followed by the wrist (50.0%), hip (28.0%), and elbow (25.0%). Temporomandibular joint involvement was observed in 9.0% patients, while axial joints such as the spine and sacroiliac joints were involved in 9.0% patients, representing the least affected joints (**Figure 5**).

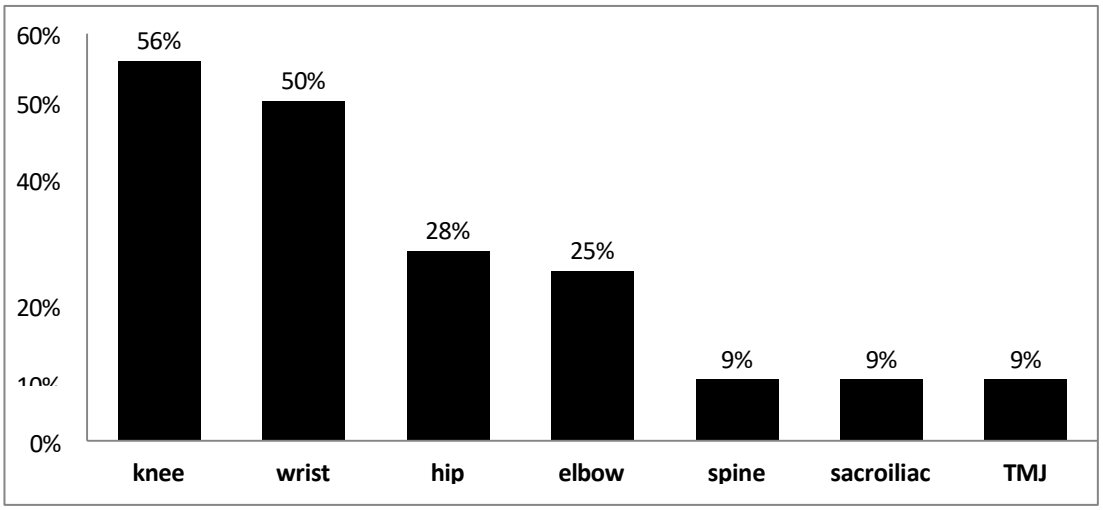


**Figure 5:** Percentage of affected joints in sJIA patients

Regarding joint involvement patterns, 75.0% of the patients had Oligoarticular disease (≤4 joints involved), while 25.0% of the patients had polyarticular disease (>4 joints involved). The mean number of involved joints was 4.13 (SD=1.83) with a range of 1 to 8 joints (**Table 2**).

**Table 2:** Pattern of joint involvement of sJIA Libyan patients at the time of diagnosis

| Pattern of joint involvement | Frequency | Percent |
|---|---|---|
| **(≤ 4 joints)** | 24 | 75.0% |
| **(> 4 joints)** | 08 | 25.0% |
| **Total** | 32 | 100% |

Joint deformities were present in 40.0% of patients, with the knee accounting for 25.0% of all deformed joints. Other complications identified included short stature (12.5%), cataract (6.3%), osteoporosis (confirmed by DEXA scan) 6.3% and delayed puberty (3.1%) (**Table 3**). Additionally, MAS was developed in 12.5% of patients, affecting predominantly females.

**Table 3:** Complications of sJIA in the affected children

| Complication | Frequency | Percent |
|---|---|---|
| **Joint Deformity** | 12 | 40.0% |
| **MAS** | 04 | 12.5% |
| **Osteoporosis** | 02 | 06.3% |
| **Cataract** | 02 | 06.3% |
| **Short Stature** | 04 | 12.5% |
| **Delayed Puberty** | 01 | 03.1% |

In **Table 4**, joint deformity was more frequently observed complication among those with a higher number of involved joints. While patients with limited joint involvement had no detectable damage, damage was present across various levels of joint involvement, with deformities and combinations of deformities with other systemic complications observed more frequently in patients with broader joint involvement patterns.

**Table 4:** Disease damage, complications distribution based on the number of involved joints in sampled patients

| Number of affected joints | Any disease damage (n=16) | No damage (n=16) | Total |
|---|---|---|---|
| **≤ 4 joints** | 11 | 15 | **26** |
| **> 4 joints** | 05 | 01 | **6** |
| **Total** | **16** | **16** | **32** |

Referral time appeared to be associated with the extent of joint involvement and damage. Patients referred within 2 months (n=8) mostly had limited joint involvement and fewer complications, with 62.5% showing no disease damage. In contrast, those referred after more than 6 months (n=9) had more extensive joint involvement and a broader spectrum of damage, with 33.3% showing no complications. Patients referred between 2-6 months (n=15) had an intermediate pattern of joint involvement and damage. These findings suggest that delayed referral may contribute to more severe and varied disease outcomes.

## Discussion

The current study presents one of the few systematic evaluations of sJIA in the region, offering valuable insights into its demographic and clinical characteristics. Several studies highlight regional variations in the prevalence of sJIA among children in Arab countries. In the UAE, sJIA accounts for 7.1% of JIA cases. In Morocco, a study identified nine patients with sJIA, suggesting a relatively low prevalence [9]. In contrast, the majority of studies from Saudi Arabia have reported sJIA as the most predominant JIA subtype in their population [7, 14]. While several studies have reported an equal gender distribution in sJIA, this study revealed a female predominance (72.0%), aligning with findings from another study conducted in Saudi Arabia [7]. Conversely, a study in Turkey reported a male predominance (56.0%) [11]. This discrepancy may be attributed to variation in sample size, geographic location, genetic predisposition, and demographic factors across different populations. This observed female predominance deviates from several international studies, which commonly report an equal or nearly equal gender distribution in sJIA, suggesting potential regional variation or referral bias within the study population. The age at diagnosis varies across studies, but most patients are diagnosed before the age of 10 years. In the Afro-Caribbean population, the mean age at diagnosis was 7.5 years (range: 1.2-14.9 years) [15], while single-center studies in Saudi Arabia and Turkey have reported a mean age of six years [7, 11], which is consistent with this study's mean of 6.28 years. Another study reported a lower mean age of 4.5 years [16]. These variations highlight the diverse age of onset in different populations. Additionally, some patients may experience delays in diagnosis due to initial nonspecific symptoms. These findings are consistent with the known typical age of onset for sJIA, which primarily affects young children.

Regarding referral time, one study conducted in the French Overseas Departments of America found that the median time from symptom onset to diagnosis was two months (range: 0.1-12.0 months) [14], while in this

study, the referral delay ranged from 2 to 6 months. Notably, 28.0% of the cases experienced a delay of more than six months before referral to a specialized clinic, underscoring a critical gap in early detection. Such delays may stem from the nonspecific nature of initial symptoms, including fever and joint pain, which can be mistaken for common viral infections or other benign conditions. Timely recognition of sJIA is crucial, as early intervention can help prevent long-term complications and improve patient outcomes. The hallmark symptoms of sJIA, including fever and arthritis, were present in all patients at diagnosis, aligning with the ILAR diagnostic criteria. In this study, arthritis was observed in all patients at the time of diagnosis, with 65.6% presenting with a skin rash [17, 18]. In a single-center study in Saudi Arabia, 73.0% of the patients presented with the characteristic triad of fever, arthritis, and rash. The remaining 27.0% exhibited fever and arthritis [7]. Other studies have reported arthritis in 78.7% and 73.0% of patients [7, 11].

Notably, not all sJIA patients present with arthritis initially. In a Turkish study, 20.0% of patients exhibited prominent systemic symptoms without arthritis at onset [11]. Some patients may initially present with recurrent episodes of fever and rash, with arthritis developing later [19]. Therefore, the absence of arthritis at the initial presentation should not rule out sJIA. This study found that large joints were the most frequently affected, with the knee being the most commonly involved joint, followed by the wrist. These findings are consistent with a previous retrospective study collected from three medical centers in Pennsylvania [20]. However, in another study done in Toronto, Canada, the hip was the most commonly affected joint [6]. Regarding disease pattern, 75.0% of the patients presented with an oligoarticular pattern, contrasting with a Turkish study where 18.7% of patients developed a polyarticular pattern [11]. This distinction is significant, as oligoarticular onset disease is generally associated with a better prognosis in other forms of juvenile idiopathic arthritis. However, in sJIA, even limited joint involvement can lead to severe disability if not adequately managed. In a French Afro-Caribbean cohort, more than half of the patients experienced MAS during childhood, with 32.0% presenting with MAS at onset [15]. In a Turkish study, 36.0% of patients had at least one MAS episode, and 24.0% presented with MAS at diagnosis, with males mostly presenting with MAS [11]. In contrast, this study found a significantly lower prevalence of MAS. Though eight patients had MAS at diagnosis, and five developed MAS during disease flares [15].

*Conclusion:* The data of this study provides valuable insights into the demographic, clinical presentation, and referral delay in sJIA patients. The findings highlight shared and distinctive features compared to regional and international data, such as a female predominance, delayed referral in a significant proportion of cases, and a relatively low incidence of macrophage activation syndrome. The study underscores the importance of early recognition and intervention to mitigate long-term complications and reduce treatment burden.

## References

1. Goldmuntz EA, White PH. Juvenile idiopathic arthritis: A review for the pediatrician. Pediatrics in Review. 2015; 27(4): e24-e32. doi: 10.1542/pir.27-4-e24
2. Thierry S, Fautrel B, Lemelle I, Guillemin F. Prevalence and incidence of juvenile idiopathic arthritis: A systematic review. Joint Bone Spine. 2014; 81(2): 112-117. doi: 10.1016/j.jbspin.2013.09.003
3. Wu EY, Rabinovich CE. Juvenile idiopathic arthritis. In: Nelson textbook of Pediatrics. 2021; 196: 1471-1482. Elsevier Science Publisher, New York, USA. ISBN-10: 0323883052.
4. Thomas J. Systemic-onset juvenile idiopathic arthritis Sawhney S, Aggarwal A. In: Pediatric rheumatology: A clinical viewpoint. Springer, Singapore. 2017; 219-227. ISBN: 978-981-10-1749-0.
5. Ross E, Ronald M, Lucy R. Juvenile idiopathic arthritis. In: Textbook of Pediatric Rheumatology. Elsevier Science Publisher, New York, USA. 2016; 188-214. ISBN: 978-0-323-24145-8.
6. Batthish M, Feldman BM, Babyn P, Tyrrell PN, Schneider R. Predictors of hip disease in the systemic arthritis subtype of juvenile idiopathic arthritis. The Journal of Rheumatology. 2011; 38(5): 954-958. doi: 10.3899/jrheum.101146
7. Basahl E, AlSwealh M, Bahawi Y, Aloufi F, Nashawi M. Characteristic phenotypes of systemic juvenile idiopathic arthritis patients in a single Tertiary Hospital in Saudi Arabia and the effectiveness of the treatment:

a retrospective record review. Annals of Rheumatology and Autoimmunity. 2024; 4(2): 41-45. doi: 10.4103/ara.ara_13_24
8. Hashad S, Etayari HM, Almsellati IA, Etfil MN, Altwati A, Awhida Z. E27 Performance of systemic juvenile idiopathic arthritis classification criteria: One-centre experience-Libya. British Journal of Rheumatology. 2023; 63(3): kead323.027. doi: 10.1093/rheumatology/kead323.027
9. Khawaja K, Masalawala M, Naeem A, Sharif E, Afrooz I, Aljaberi N. Ab1445 the United Arab Emirates juvenile idiopathic arthritis registry: Preliminary results of patient demographics, subtype distribution, clinical features, treatment and outcome. Annals of the Rheumatic Diseases. 2023; 82(S1): 1950-1952. doi: 10.1136/annrheumdis-2023-eular.3528
10. Zhang K, Biroschak J, Glass DN, Thompson SD, Finkel T, Passo MH, et al. Macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis is associated with MUNC13-4 polymorphisms. Arthritis and Rheumatology. 2008; 58(9): 2892-2896. doi: 10.1002/art.23734
11. Frosch M, Stojanovic J. Macrophage activation syndrome in systemic juvenile idiopathic arthritis. Clinical and Experimental Rheumatology. 2018; 36(2): 215-223. doi: Nil.
12. Tu Z-Q, Zhang W-Q. Macrophage activation syndrome (MAS) systemic juvenile idiopathic arthritis (SJIA), pathogenesis, diagnosis treatment. European Medical Journal. 2017; 2(1): 100-105. doi: 10.33590/emjallergyimmunol/10312775
13. Hashad SS, Etayari HM, Altwati AA. Anakinra treatment for systemic onset juvenile idiopathic arthritis in Libyan Children. Mediterranean Journal of Pharmacy and Pharmaceutical Sciences. 2025; 5(4): 38-46. doi: 10.5281/zenodo.17553885
14. Hashad SS, Alghareeri S. Juvenile psoriatic arthritis patients at Tripoli Children's Hospital. Mediterranean Journal of Medical Research. 2025; 2(4): 230-238. doi. 10.5281/zenodo.17610647
15. Sağ E, Uzunoğlu B, Bal F, Sönmez HE, Demir S, Bilginer Y, Ozen S. Systemic onset juvenile idiopathic arthritis: A single center experience. The Turkish Journal of Pediatrics. 2019; 61(6): 852-858. doi: 10.24953/turkjped.2019.06.005
16. Bruck N, Schnabel A, Hedrich CM. Current understanding of the pathophysiology of systemic juvenile idiopathic arthritis (sJIA) and target-directed therapeutic approaches. Clinical Immunology. 2015; 159(1): 72-83. doi: 10.1016/j.clim.2015.04.018
17. Alkwai HM, Mirza A, Abdwani R, Asiri A, Bakry R, Alenazi A, et al. Consensus clinical approach for a newly diagnosed systemic juvenile idiopathic arthritis among members of the pediatric rheumatology Arab group. International Journal of Pediatrics and Adolescent Medicine. 2021; 8(3): 129-133. doi: 10.1016/j.ijpam.2021.05.003
18. Behrens EM, Beukelman T, Gallo L, Spangler J, Rosenkranz M, Arkachaisri T, et al. Evaluation of the presentation of systemic onset juvenile rheumatoid arthritis: Data from the Pennsylvania Systemic Onset Juvenile Arthritis Registry (PASOJAR). The Journal of Rheumatology. 2008; 35(2): 343-348. PMID: 18085728.
19. Felix A, Delion F, Suzon B, Pallara-Sirven S, Elenga N, Quartier P, et al. Systemic juvenile idiopathic arthritis in French Afro-Caribbean children, a retrospective cohort study. Pediatric Rheumatology Online Journal. 2022; 20(1): 98. doi: 10.1186/s12969-022-00766-8
20. Foley CM, McKenna D, Gallagher K, McLellan K, Alkhdher H, Lacassagne S, et al. Systemic juvenile idiopathic arthritis: The Great Ormond Street Hospital experience (2005-2021). Frontiers in Pediatrics. 2023; 11: 1218312. doi: 10.3389/fped.2023.1218312

**Author contribution:** Both authors contributed equally.
**Conflict of interest:** The authors declare the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
**Ethical issues:** The authors completely observed ethical issues, including plagiarism, informed consent, data fabrication or falsification, and double publication or submission.
**Data availability statement:** The raw data that support the findings of this article are available from the corresponding author upon reasonable request.
**Author declarations:** The authors confirm that they have followed all relevant ethical guidelines and obtained any necessary IRB and/or ethics committee approvals.
**Generative AI disclosure:** No generative AI was used in the preparation of this manuscript.