

Risk Factors of Persistently Active Disease among Filipino Children with Systemic Juvenile Idiopathic Arthritis: a 10-Year Study in a Tertiary Hospital



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ABSTRACT

Background: Systemic juvenile idiopathic arthritis (SJIA) is one of the most common subtypes of arthritis among children in southeast Asia with higher progression of disease activity. Unsuccessful control of the disease may lead to long-term disability resulting in functional limitations that would affect productivity of the individual.

Objective: The study determined the risk factors for persistently active disease among Filipino children aged 2 weeks to 18 years diagnosed with SJIA seen in the Section of Pediatric Rheumatology of the University of Santo Tomas Hospital (USTH) from June 2009 to June 2019.

Methodology: A retrospective cohort study was done involving chart review of both clinical division and private division patients. The following parameters were determined: sex, age at diagnosis, time elapsed from symptom onset to diagnosis, joint involvement, inflammatory markers and extra-articular manifestation. Statistical analysis included frequencies, percentages and logistic regression for the risk factors of interest.

Results: One hundred twenty-seven patients with SJIA who were appropriately treated for at least three years were included. Among which, 88 (69%) developed persistently active disease. Among them, 36 (41%) were diagnosed at 1-5 years old. Many were diagnosed ($n=54$, 61%) after five weeks. The most commonly affected joints were the wrists, knees and ankles. The most common contracture noted involved the cervical joint. Only 33 (26%) patients received biologic agents. Risk factors identified for the development of persistent disease activity were low hemoglobin levels at the time of diagnosis and after one month of treatment, elevated platelet count after a month, substantial joint count after three months and increased ESR after 6 months.

Conclusion: The change or improvement of the joint count and in hemoglobin, platelet count and ESR levels after appropriate treatment may determine the risk for persistently active disease in Filipino children with SJIA.

INTRODUCTION

Systemic juvenile idiopathic arthritis (SJIA) is one of the subtypes of arthritis seen in children characterized by systemic manifestations such as fever, rash and elevated inflammatory markers.[1] This type of systemic arthritis is distinctly found in children. Studies have documented variation in the prevalence of different subtypes of juvenile idiopathic

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arthritis (JIA) in different parts of the globe. Such a difference may be attributed to varied ethnicity and genetic factors.[2] Systemic arthritis and enthesitis-related arthritis are observed to be the most common subtype in southeast Asia.[3]

It is essential to recognize that any form of JIA has a chronic course which needs to be controlled immediately to prevent progression to joint contractures and functional limitations. In a 30-year follow-up among JIA patients, 41% had active disease or were on medication. Remarkably, 28% of patients reported many symptoms despite treatment after 30 years.[4] Control of the disease manifestations of SJIA is characteristically challenging as both articular and systemic features should be addressed. Conventional medications such as nonsteroidal anti-inflammatory drugs, prednisone and methotrexate are affordable and easily accessible in the country. However, biologic therapeutic agents are not readily available in the Philippines. SJIA has a significantly higher progression of disease activity.[5] Unsuccessful control of the disease would eventually lead to long-term disability affecting the productivity of the individual.

It was documented by a study of Consolaro et al. (2019) that patients who are living in countries with lower gross domestic product (GDP) such as the Philippines had greater disease activity and joint damage than those living in countries with a high GDP. This may be attributed to various factors such as delay in the referral to a pediatric rheumatologist and the inaccessibility to biological therapy.[3]

In the Philippines, there is no study as of yet that determines the risk factors for persistently active disease among children with SJIA. Such a study would document the disease burden of SJIA patients highlighting the need for improved medical attention among these patients.

OBJECTIVES OF THE STUDY

This study aimed at determining the risk factors of persistently active disease among patients 2 weeks to 18 years old with SJIA seen in the Section of Pediatric Rheumatology of the University of Santo Tomas Hospital (USTH) from June 2009 to June 2019.

METHODOLOGY

This was a single center retrospective cohort study. Patients aged 2 weeks to 18 years old seen in the

Section of Pediatric Rheumatology of the USTH (Clinical Division and the Private Division) were included as long as they had followed up for at least three years and took medications according to medical instruction during the three-year follow-up. Those with SJIA overlap and those with concomitant malignancies were excluded.

Approval from the University of Santo Tomas Hospital - Research Ethics Committee (USTH-REC) was obtained prior to data collection. Permission from the USTH Medical Director, Data Privacy Officer, Head of the Ambulatory Care Services and the attending pediatric rheumatologist were obtained as well.

Patient records from June 2009 to June 2019 were collected. The total number of subjects included was less compared to the sample size computed mainly because of the inclusion criterion that the patient should have been diagnosed and treated for at least three years. This serves as one limitation of the study.

Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) version 23. Frequencies and percentages were determined. Chi-square test was done to compare categorical variables, while T-test was done to compare numerical variables. Logistic regression was used to determine the risk factors of interest in this study.

RESULTS

A total of 127 patients with SJIA were included in the study; among which, 88 (69%) developed persistent disease activity (Table 1). Majority of the patients were diagnosed within 0-4 weeks (n=53, 42%); however, it was evident that a significant number of patients were diagnosed late, that is, at ≥ 5 weeks. A considerable number of patients likewise had disease duration of ≥ 3 years.

For articular features, 31 (24%) patients presented with no active joint involvement at the time of presentation (Table 2). This would suggest that systemic features were predominant at the time of presentation and that synovitis presented later in the disease course. Notably, more patients with persistent disease activity (n=21) had no active synovitis at the time of presentation compared to those without persistent disease activity (n=10). The most commonly affected joints at the time of presentation were the wrist (n=54, 42%), knee

Table 1. Baseline characteristics of patients

		PERSISTENT DISEASE ACTIVITY (n=88)	NON-PERSISTENT DISEASE ACTIVITY (n=39)	TOTAL (n=127)
Sex	Male	44 (50%)	24 (62%)	68 (54%)
	Female	44 (50%)	15 (38%)	59 (46%)
Age at Diagnosis	1–5 years	36 (41%)	13 (33%)	49 (38.6%)
	6–10 years	31 (35%)	17 (44%)	48 (37.8%)
	11–18 years	21 (24%)	9 (23%)	30 (23.6%)
Time Elapsed From Symptom Onset to Diagnosis	0–4 weeks	34 (38%)	19 (49%)	53 (42%)
	5–36 weeks	36 (41%)	16 (41%)	52 (41%)
	37–48 weeks	6 (7%)	4 (10%)	10 (8%)
	> 49 weeks	12 (14%)	0 (0%)	12 (9%)
Disease Duration	3–5 years	52 (59%)	34 (87%)	86 (68%)
	6–10 years	32 (36%)	5 (13%)	37 (29%)
	11–15 years	4 (5%)	0 (0%)	4 (3%)

Table 2. Joints involved at the time of presentation among SJIA patients

Joints Involved at the time of presentation	Persistent Disease Activity (n=88)	Non-Persistent Disease Activity (n=39)	Total (n=127)
None	21 (24%)	10 (26%)	31 (24%)
Cervical	3 (3%)	2 (5%)	5 (4%)
Elbow	11 (13%)	4 (10%)	15 (12%)
Wrist	40 (46%)	14 (36%)	54 (42%)
Hip	4 (5%)	4 (10%)	8 (6%)
Knee	50 (57%)	18 (46%)	68 (53%)
Ankle	32 (37%)	12 (31%)	44 (35%)
Small joints of the hands and feet	13 (15%)	6 (15%)	19 (15%)

(n=68, 53%) and ankle (n=44, 35%), similar to what was reported in previous studies.[1,6] Interestingly, five (4%) patients already had cervical joint involvement, as well as eight (6%) patients who had hip involvement at the time of presentation. The joint count for both study groups significantly decreased from the time of diagnosis until after six months of treatment (Table 3). A remarkable difference between the two groups is that patients with persistent disease activity consistently had more joint involvement. Moreover, patients with persistent disease activity developed more joint contractures as compared to those without persistent disease activity. The most common joint contracture noted among patients involved the cervical joint manifesting with limitation of cervical extension (n=19, 15%).

As for the extra-articular features, all patients presented with fever which is a requirement for the diagnosis of SJIA, specifically, quotidian fever. Majority of the patients (n=90, 71%) likewise presented with an evanescent rash. Only one patient presented with uveitis.

With regard to the standard medications for SJIA, all of the study patients received prednisone; while a majority of them received methotrexate (n=112, 88%) as well. Thirty-three patients (26%) received biologic agents, ie., 30 (24%) with tocilizumab, 2 (1.6%) with anakinra and 1 (0.8%) with etanercept.

Table 4 shows the different probability coefficients for different variables. Hemoglobin at diagnosis and at one month of treatment had statistically significant negative probability coefficients. That

Table 3. Interval joint count among SJIA patients

JOINT COUNT	PERSISTENT DISEASE ACTIVITY (n=88)	NON-PERSISTENT DISEASE ACTIVITY (n=33)	TOTAL	P-VALUE*
At diagnosis	Mean = 3.1	Mean = 2.6	Mean = 2.8	0.418
1-2 Joints	45 (51%)	25 (64%)	70 (55%)	
3-5 Joints	27 (31%)	10 (26%)	37 (29%)	
> 6 Joints	16 (18%)	4 (10%)	20 (16%)	
After 1 month	Mean = 2.1	Mean = 1.3	Mean = 1.7	0.215
0 Joint	33 (38%)	24 (61%)	57 (45%)	
1-2 Joints	24 (27%)	8 (21%)	32 (25%)	
3-5 Joints	24 (27%)	3 (8%)	27 (21%)	
> 6 Joints	7 (8%)	4 (10%)	11 (9%)	
After 3 months	Mean = 1.7	Mean = 0.8	Mean = 1.2	0.330
0 Joint	47 (53%)	27 (69%)	74 (58%)	
1-2 Joints	15 (17%)	8 (20%)	23 (18%)	
3-5 Joints	20 (23%)	3 (8%)	23 (18%)	
> 6 Joints	6 (7%)	1 (3%)	7 (6%)	
After 6 months	Mean = 1.7	Mean = 0.6	Mean = 1.1	0.023
0 Joint	44 (50%)	33 (85%)	77 (61%)	
1-2 Joints	23 (26%)	2 (5%)	25 (20%)	
3-5 Joints	11 (13%)	3 (8%)	14 (11%)	
> 6 Joints	10 (11%)	1 (2%)	11 (8%)	

*Significant if p-value is less than or equal to the 0.05 level of significance. Computed using chi-square test

Table 4. Logistic Regression on the Risk Factors for Developing a Persistent Disease

Variables	Coefficients	p-value*
Constant	1.947	0.038
Joint Count after 3 months	0.878	0.037
HGB at Diagnosis	-0.043	0.025
HGB after a month	-0.034	0.004
PLT after a month	0.007	0.043
ESR after 6 months	0.115	0.007

* Significant if p-value is less than or equal to the 0.05 level of significance

HGB - hemoglobin

PLT - platelet count

ESR - Erythrocyte Sedimentation Rate

is, low hemoglobin at diagnosis, as well as, no improvement or minimal increase of hemoglobin one month after treatment is predictive of persistent disease activity. On the other hand, statistically significant positive probability coefficients were noted indicating that increased platelet count after a month, increased joint count after three months and elevated erythrocyte sedimentation rate (ESR) despite

treatment for six months increase the likelihood of developing persistent disease activity.

Age at diagnosis, time elapsed from symptom onset to diagnosis, joint count at diagnosis and at time intervals, as well as, involvement of specific joints were not identified to be risk factors for persistently active disease. Moreover, extra-articular features such as rash, generalized lymphadenopathy,

hepatosplenomegaly, serositis and uveitis were not recognized as statistically significant risk factors.

DISCUSSION

The present study documented that 69% of patients with SJIA developed persistent disease activity. Patients with persistent disease activity despite adequate treatment were the focus of this study mainly because of its increased likelihood of developing functional limitations that contribute to the potentially decreased productivity of an individual. Risk factors noted to be associated with persistent disease activity in this study were low hemoglobin at diagnosis and after one month of treatment, increased platelet count after a month, increased joint count after three months and elevated ESR despite treatment for six months.

Children diagnosed at age 1-5 years comprised the majority of the study group (n=49, 38.6%), which likewise coincides with the established epidemiology that the peak age of onset of SJIA is between 1-5 years of age.[1] It has been reported by previous studies that early onset SJIA, that is, before 18 months of age, is associated with worse outcomes presenting with severe arthritis leading to significant disability.[1,3,7]

With regard to the time elapsed from symptom onset to diagnosis, it was evident that a significant number of patients were diagnosed late. Most of the patients with persistent disease activity (n=36, 41%) were diagnosed after 5-36 weeks. It is noteworthy to mention that many patients do not fulfill the International League of Associations for Rheumatology (ILAR) classification criteria for SJIA early in the disease course because they do not meet the strict definition of the quotidian fever or because arthritis presented later in the course.[1] This poses as a challenge for the pediatric rheumatologist in the diagnosis of these patients. Early recognition of the disease and timely referral to a pediatric rheumatologist is paramount in instituting early appropriate treatment for these patients. Timely interventions and medications given to these patients would greatly improve their health status.

Polyarticular joint involvement is characteristic of SJIA. In the present study, the most commonly affected joints at the time of presentation and during the disease course were the wrist, knee and ankle similar to what was reported by previous studies.

[1,8] Interestingly, a few patients already had cervical joint, as well as, hip joint involvement at the time of presentation. Arthritis of the hip and/or the cervical spine are one of the recognized features of poor prognosis among SJIA patients.[1,8] It was evident that patients with persistent disease activity developed more joint contractures as compared to those without persistent disease activity. Joint contracture may occur as a result of joint damage leading to ankylosis or a limitation of the range of motion due to prolonged immobility. Those patients who developed joint contractures acquired functional limitations that may persist until adulthood leading to a decrease in their productivity.

Among the medications given, only 33 patients (26%) received biologic agents. The low number of patients who received biologic agents does not mean that only a few patients need it. In fact, many of the patients warrant treatment with biologic agents but are unable to receive it due to financial constraints. In the present study, it was observed that tocilizumab was given for those with persistent disease activity despite conventional treatment with prednisone and methotrexate. However, in developed countries, there is a move to treat all SJIA patients with biologic therapy at the time of diagnosis to take advantage of a so-called "window of opportunity" to attain immediate disease control among patients at risk for chronic, destructive and therapy-resistant arthritis.[9] Unfortunately, in the Philippines, this is not feasible since biologic agents are costly and not readily available nationwide.

It is imperative that we follow the disease course of these patients to determine the risk factors for developing persistently active disease. Singh-Grewal et al. (2006) proposed that features at three and six months, and not at diagnosis, are predictive of the disease course and time to remission. Their study noted that factors predictive of a polycyclic or persistent disease course include the following: fever and active arthritis at three months and an ESR >26 mm/hr and corticosteroid use at six months. [10] Similarly, a study by Bartoli et al. (2008) documented that a reduction in the American College of Rheumatology (ACR) Pedi 70 score after six months of treatment with methotrexate corresponded to the decrease in active joint counts and having inactive disease after five years.[11] Spiegel et al. (2000) concluded that the need for corticosteroids

at six months after diagnosis was a predictor of poor functional outcome.[12]

CONCLUSION AND RECOMMENDATIONS

The identified risk factors for the development of persistent disease activity are as follows: low hemoglobin levels at the time of diagnosis and after one month of treatment, elevated platelet count after a month, substantial joint count after three months and increased ESR after six months. This highlighted the importance of evaluating patients for each follow-up period and correlating findings of the present visit to their previous ones.

Notably, out of 127, only 33 patients (26%) received biologic agents, which are important in aborting the possibility of developing chronic, destructive arthritis if given early in the course. Government action is needed to improve affordability and accessibility of these biologic agents.

This study was greatly limited by its retrospective nature which was largely dependent on what was reported on the patient's medical records. Moreover, no attempt to use standardized measure of disease activity was done. A prospective study that uses standardized measure of disease activity, as well as, identifies and monitors all possible risk factors, is recommended.

Finally, the small number of patients included in the study may not be representative of the actual population of patients with SJIA. A population-based study, instead of the one that is hospital-based is likewise recommended.

DISCLOSURE

The researchers claim no conflicts of interest.

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