SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS AND ARTHRALGIA - CAN IT BE DIAGNOSED EARLY WITHIN THE WINDOW PERIOD? – AN OBSERVATION OF SERUM BIOMARKERS AND ANALYSIS WITH OTHER DIFFERENTIAL CONDITIONS IN CHILDREN

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Abstract-Background: Systemic juvenile idiopathic arthritis (sJIA)is a cause of persisting arthralgia which is often missed. Diagnosing sJIA can be challenging, especially when overt arthritis is absent at presentation, highlighting the need for a diagnostic biomarker. Few recent studies have assessed potential biomarkers for sJIA, however, there is no consensus in detecting early. We conducted a study evaluating serum IL-1, IL-6, IL-18, S100A8, and S100A9 as potential diagnostic markers to distinguish sJIA from other conditions presenting as joint pain in children. **Methods**: A prospective study was conducted in our institute from May-2019 to October-2020 in children under 16 years, who had persisting arthralgia. Serum concentrations of IL-1, IL-6, IL-18, S100A9, and S100A8 were determined using ELISA kits. Receiver operating curve (ROC) analysis was used to determine the cut-off values for IL-1, IL-6, IL-18, S100A8, and S100A9 for differentiating sJIA from other causes of joint pain and fever. **Results**- Out of 47 children who presented with joint pain and fever 19 of them were eventually diagnosed with sJIA. In the other 28 children, arthralgia and fever was attributed to conditions other than sJIA (non-sJIA). The non-sJIA group comprised children with acute lymphoblastic leukemia, hemophagocytic histiocytosis, systemic lupus erythematosus, Kawasaki disease, Kikuchi disease, and inflammatory bowel disease. Serum levels of IL-18, S100A8, and S100A9 were significantly higher in patients with sJIA compared to the non-sJIA group ($p<0.05$). The area under the curve (AUC) was significant for IL-18(77.9%), S100A8 (74.9%), and S100A9 (71.2%). A serum IL-18 cut-off level of > 2030.45 pg/ml was useful for differentiating between sJIA and other diseases with a sen-

sitivity of 66.67% and specificity of 75.86% for the diagnosis of sJIA. **Conclusion-** Serum IL-18, S100A8, and S100A9 can be useful in differentiating sJIA early from other causes of persisting arthralgia in children provided with appropriate identification of symptomatology and suspicion.

Key words: - joint pain, JIA, inflammatory arthritis, systemic juvenile idiopathic arthritis, Arthralgia.

1. Introduction

Pyrexia of unknown origin (PUO) in children often poses a diagnostic challenge in clinical practice. Although infections account for the majority of children presenting with FUO, malignancies, and rheumatological diseases need to be identified or excluded early to commence appropriate treatment. Systemic juvenile idiopathic arthritis (s-JIA), a prototype of systemic rheumatic diseases in children accounts for a significant proportion of children presenting with FUO. Although this condition is typically characterized by quotidian fever, evanescent rash, and arthritis, patients often initially present with FUO with non-specific signs and symptoms. In some cases, arthritis may follow the onset of systemic features by weeks, months, or even years[1]. Diagnosing s-JIA in these cases is challenging and highlights the need for a diagnostic biomarker that could facilitate an earlier diagnosis of this condition and early institution of therapy, preferably within the so-called "window of opportunity", the time point early enough in the disease that intensive targeted therapy could be used to achieve early disease remission[2]. Systemic juvenile idiopathic arthritis is now considered an autoinflammatory disease. A dysregulated innate immune response with the overproduction of innate immune factors such as interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-18 (IL-18), and phagocyte-specific S100 proteins (S100A8, S100A9, S100A12) has been implicated in the pathogenesis of this disease[3]. Although few studies evaluating potential biomarkers in s-JIA have been published over the last few years, no such study has been conducted in the Indian population[4-9]. Hence, we conducted this study to evaluate serum IL-18, S100A8, and S100A9 (primary objective) and serum IL-1 and IL-6 (secondary objective) as potential diagnostic markers to distinguish systemic juvenile idiopathic arthritis (sJIA) from other conditions presenting as fever of unknown origin in children.

2. PATIENTS AND METHODS

This prospective cross-sectional study was conducted at Velammal Medical College, Madurai a tertiary care center in Tamil Nadu, during the period from May 2019 to October 2020. Patients who presented with joint pain associated with fever in <16years of age in the Outpatient department of Orthopaedics, pediatrics and rheumatology departments and are admitted for the evaluation of fever of unknown origin (defined as fever > 38.0°C (100.4°F) lasting for at least 12 days without a clear source) and whose parents consented for participation in this study were included[10]. Children who had received glucocorticoids and/or immunosuppressive drugs before presentation to our hospital

were excluded from the study. Based on the results of specificity of different parameters- IL-18 (97.6 %), S100A8 (97.6%), and S100A9 (82.9 %) for predicting sJIA observed in an earlier publication by Xia et al and with 95% confidence and 20% allowable error, the minimum sample sizes came to 11 based on both IL-18 and S100A8, and 34 based on S100A9)[4]. Since the highest one was 34, the calculated minimum sample size for this study was taken as 34.

The primary objective was to evaluate serum IL-18, S100A8, and S100A9 as potential diagnostic markers to distinguish systemic juvenile idiopathic arthritis (sJIA) from other conditions presenting as PUO in children. Secondary objective was to assess serum IL-1 and IL-6 as potential biomarkers for sJIA. Baseline characteristics of the patients, including demographic and clinical features (number of days of fever, presence of rash, arthralgia, arthritis, lymphadenopathy, splenomegaly, etc.) were noted. At the time of sampling of blood for routine investigations as per the PUO protocol (including complete blood count, erythrocyte sedimentation rate, C-reactive protein, and serum ferritin), were done and an additional 3ml. of venous blood was collected in a plain (red top) vacutainer. The sample was centrifuged for 5 minutes at 40 degrees C, and the supernatant serum was collected and preserved in a –80°C freezer. At the time of processing, the serum samples were retrieved and thawed at room temperature and the serum IL-1, IL-6, IL-18, S100A9, and S100A8 protein levels were detected by an enzyme-linked immunosorbent assay (ELISA) following the manufacturer's instructions. Human IL-1ß GENLISA TM ELISA, Human IL-6 GENLISATM ELISA, and Human IL-18 GENLISATM ELISA kits manufactured by Krishgen BioSystems, Mumbai, India, and Human S100 calcium binding protein A8 ELISA and Human S100 calcium binding protein A9 ELISA kits manufactured by KinesisDx, Los Angeles, USA were used for measuring the respective biomarker.

sJIA was diagnosed according to the newer classification criteria proposed by the Pediatric Rheumatology International Trials Organization (PRINTO)[11].Systemic lupus erythematosus (SLE) was diagnosed according to the Systemic Lupus Erythematosus International Corroborating Clinics (SLICC) criteria and Kawasaki Disease(KD) according to the American Heart Association guidelines[12,13].Hemophagocytic histiocytosis (HLH) was diagnosed by the 2004 revised diagnostic criteria for HLH[14] Acute lymphoblastic leukemia (ALL) was diagnosed based on compatible clinical and laboratory features with confirmation by bone marrow biopsy. Systemic infections were defined by the presence of compatible clinical features along with either body fluid evaluation and culture, tissue culture, or any imaging study suggestive of infection. Kikuchi-Fujimoto disease (KFD) was diagnosed based on compatible clinical and laboratory features with lymph node biopsy suggestive of necrotizing lymphadenitis. The diagnosis of inflammatory bowel disease (IBD) was made on a combination of clinical, radiologic, endoscopic, and histologic grounds.

Statistical analysis was performed using IBM SPSS version 26.0 software. Categorical variables were expressed using frequency and percentage. Numerical variables were represented using mean and standard deviation. To compare the statistical significance of the mean between the two groups independent t-test was used. For non-normal variables, median comparisons between two groups were performed using Mann Whitney U test. To test the statistical significance of the difference in the serum levels of

IL-1, IL-6, IL-18, S100A8, and S100A9 during active disease (at presentation) and inactive disease (following treatment), the Wilcoxon signed-rank test was used. Receiver operating curve (ROC) analysis was used to determine the cut-off values for IL-1, IL-6, IL-18, S100A8, and S100A9 for differentiating sJIA from other causes of fever. A p-value less than 0.05 was considered to be statistically significant.

3. Results

A total of 47 children (comprising 20 males and 27 females) who presented with joint pain and fever of unknown origin (FUO) were studied. Of these, nineteen children were eventually diagnosed with systemic juvenile idiopathic arthritis (sJIA). In the remaining 28 children, the joint pain and fever was attributed to causes other than sJIA (non-sJIA). The non-sJIA group comprised 6 children diagnosed with ALL, 5 children with HLH, 4 children each with SLE and systemic infections (one child each with pulmonary tuberculosis, abdominal tuberculosis, urinary tract infection, and Chromobacterium violaceum sepsis with multiple liver abscesses), 2 children each with KD, KFD, and IBD. This group also included one child each diagnosed with sweet syndrome with polyarthritis, drug rash with eosinophilia and systemic symptoms (DRESS), and post-infection multisystem inflammatory disease.

The sJIA group consisted of 10 males and 9 females with the mean age at presentation being 6.70 ± 4.40 years. The non-sJIA group comprised 10 males and 18 females and the mean age at presentation was 8.39 ± 5.22 years. As expected, arthritis and rash were more frequent in children with s-JIA compared to those in the non-sJIA group ($p< 0.05$). Absolute neutrophil (ANC) and platelet counts were significantly higher in the sJIA group compared to the non-sJIA group ($p< 0.05$). The baseline demographic, clinical, and laboratory characteristics of all the patients are shown in Table 1. The serum concentrations of IL-18, S100 A8, and S100A9 were significantly higher in the sJIA group compared to the non-sJIA group ($p< 0.05$) (Table 2). The serum concentrations of IL-1, IL-6, IL-18, S100A8, and S100A9 in patients with sJIA were compared with those in the subgroups within the broad category of "non-sJIA" comprising of 4 or more patients, viz., ALL, HLH, SLE and systemic infections.

Table-1: Baseline demographic, clinical and laboratory findings of patients in study

(n=47)	sJIA (n=19)	Non- sJIA (n=28)	p value
Demographic data			
Age (years), Mean (SD)	6.70 (4.40)	8.39 (5.22)	0.251
Male, n (%)	10 (52.6)	10 (35.7)	0.395
Clinical findings			
Days with fever, Median (IQR)	21 (15-42)	21 (10-44)	0.378
Rash, n (%)	15 (78.9)	10 (35.7)	0.009
Arthritis, n (%)	11 (57.8)	3 (10.7)	0.002
Arthralgia, n (%)	14 (73.6)	12 (42.8)	0.074

Lymphadenopathy, n (%)	12 (63.1)	12 (42.8)	0.285
Splenomegaly, n (%)	3 (15.7)	5 (26.3)	1.000
laboratory findings			
Hemoglobin (g/L), Mean (S.D)	95.9 (22.3)	96.9 (19.9)	0.878
ANC (x 10^9/L), Median (IQR)	13.52 (8.832-21.694)	4.60 (1.49-9.85)	< 0.001
Platelet count (x 10^9/L), Median (IQR)	502.0 (393.0- 591.0)	329.0 (159.25-440.25)	0.004
ESR (mm/hr), Median (IQR)	83.0 (53.0-97.0)	74.5 (38.0-93.75)	0.197
CRP (mg/L), Median (IQR)	105.07 (50.22-208.65)	46.16 (23.25-149.64)	0.083
Ferritin(mcg/L), Median (IQR)	1,005.0 (228.7-14,160)	277.15 (224.5-924.57)	0.065

*sJIA- systemic juvenile idiopathic arthritis, SD- standard deviation, IQR- interquartile range, ANC- absolute neutrophil count, ESR- erythrocyte sedimentation rate, CRP- C-reactive protein.

Table-2: Comparison of candidate markers in patients with sJIA and other causes of FUO in children (non- sJIA)

Candidate marker	sJIA (n=19)	Non- sJIA (n=28)	p value
	Median (IQR)	Median (IQR)	
IL-1 (pg/ml)	42.81 (3.77-94.57)	85.06 (12.34-248.45)	0.104
1L-6 (pg/ml)	25 (4.65-120.41)	9.73 (2.98-27.21)	0.106
1L-18 (pg/ml)	2,042.8 (1,998.3-2,063)	1,942.15 (1,227.62-2026)	0.001
S100A8 (ng/ml)	478.2 (291.5-576.4)	233.15 (145.6-446.95)	0.005
S100A9 (ng/ml)	465.1 (417.1-681)	239.05 (96.25-491.9)	0.018

*IL-interleukin-1, S100A8 - S100 calcium-binding protein A8, S100A9-S100 calcium-binding protein A9.

Serum IL-18 levels were significantly elevated in children with sJIA compared to those with ALL and SLE ($p < 0.05$). However, serum IL-18 did not exhibit any significant difference between sJIA and the subgroups of HLH and systemic infections. Serum S100A8 and S100A9 were significantly higher in sJIA compared to ALL but did not differ significantly when compared with the subgroups of SLE, HLH, and systemic infections. Serum IL-1 levels were significantly higher in patients with HLH compared to those with sJIA. Serum IL-6 concentrations did not exhibit any difference between the disease groups as depicted in table 3.

Table-3: Comparison of candidate markers in children with sJIA and non-sJIA subgroups (ALL, HLH, SLE and systemic infections)

Comparison between sJIA and ALL				
Candidate marker	**Statistical measure**	**sJIA (n=19)**	**ALL (n=6)**	**p value**
IL-1 (pg/ml)	Median (IQR)	42.81 (3.77-94.57)	23.63 (4.25-249.41)	0.877

IL-6(pg/ml)	Median (IQR)	25.0 (4.65-120.41)	10.64 (9.86-108.79)	0.975
1L-18 (pg/ml)	Median (IQR)	2,042.8 (1,998.3-2,063.0)	1,125.75 (789.67-2,001.85)	**0.002**
S100A8 (ng/ml)	Median (IQR)	478.2 (291.5-576.4)	200.4 (153.48-260.6)	**0.001**
S100A9 (ng/ml)	Median (IQR)	465.1 (417.1-681.0)	142.45 (94.2-347.02)	**0.017**
Comparison between sJIA and HLH				
Candidate marker	**Statistic**	**sJIA (n=19)**	**HLH (n=5)**	**p value**
IL-1 (pg/ml)	Median (IQR)	42.81 (3.77-94.57)	201.49 (75.27-289.3)	**0.036**
IL-6(pg/ml)	Median (IQR)	25.0 (4.65-120.41)	6.42 (1.75- 129.09)	0.297
1L-18 (pg/ml)	Median (IQR)	2,042.8 (1,998.3-2063.0)	2,043.5 (1,542.5-2,054.85)	0.534
S100A8(ng/ml)	Mean (SD)	448.1 (162.13)	302.92 (207.9)	0.203
S100A9(ng/ml)	Mean (SD)	514.32 (169.4)	384.76 (290.78)	0.204
Comparison between sJIA and SLE				
Candidate marker	**Statistic**	**sJIA (n=19)**	**SLE (n=4)**	**p value**
IL-1 (pg/ml)	Median (IQR)	42.81 (3.77-94.57)	4.98 (3.28-63.83)	0.366
IL-6(pg/ml)	Median (IQR)	25.0 (4.65-120.41)	5.2 (2.12-11.15)	0.097
1L-18 (pg/ml)	Median (IQR)	2,042.8 (1,998.3-2063.0)	1,580.1 (1,146.6-1,931.4)	**0.021**
S100A8 (ng/ml)	Mean (SD)	448.1 (162.13)	274.13 (178.87)	0.145
S100A9 (ng/ml)	Mean (SD)	514.32 (169.4)	303.7 (217.3)	0.146
Comparison between sJIA and systemic infections				
Candidate marker	**Statistic**	**sJIA (n=19)**	**Systemic infections (n=4)**	**p value**
IL-1 (pg/ml)	Median (IQR)	42.81 (3.77-94.57)	196.47 (56.02-259.9)	0.081
IL-6 (pg/ml)	Median (IQR)	25.0 (4.65-120.41)	27.28 (27.18-32.64)	0.845
1L-18 (pg/ml)	Median (IQR)	2,042.8 (1,998.3-2063.0)	1,671.5 (1,194.32-2,044.12)	0.162
S100A8 (ng/ml)	Mean (SD)	448.1 (162.13)	323.52 (237.13)	0.378
S100A9 (ng/ml)	Mean (SD)	514.32 (169.4)	330.97 (301.99)	0.100

On receiver operating curve (ROC) analysis, the area under the curve (AUC) for IL-1 and IL-6 were 34.7% and 64.1%, respectively. The AUC for IL-18, S100A8 and S100A9 were 77.9%, 74.9% and 71.2%, respectively. Thus, the AUC was significant for IL-18, S100A8, and S100A9; highest for IL-18, followed by S100A8 and S100A9. The selected cut-offs for IL-18, S100A8, and S100A9 are 2030.45 pg/ml, 416.6 ng/ml, and 555.10 ng/ml, respectively. With an AUC of 77.9.% and a cut-off value of 2030.45 pg/ml, IL-18 had a sensitivity of 66.67% and a specificity of 75.86% for the diagnosis of sJIA as shown in **Figure 1**. The positive predictive value was 65.21% and the negative predictive value was 77.03%. With an AUC of 74.9 % and a cut-off value of 416.6

ng/ml, S100A8 had a sensitivity of 63.16 % and a specificity of 75.00 % for the diagnosis of sJIA. The positive predictive value was 63.16 % and the negative predictive value was 75.00 %. With AUC 71.2 % and cut-off value 555.1 ng/ml, serum S100A9 had a sensitivity of 47.37 % and specificity of 82.14 % for the diagnosis of sJIA. The positive predictive value was 64.29 % and the negative predictive value was 69.70 % **(Table 4).**

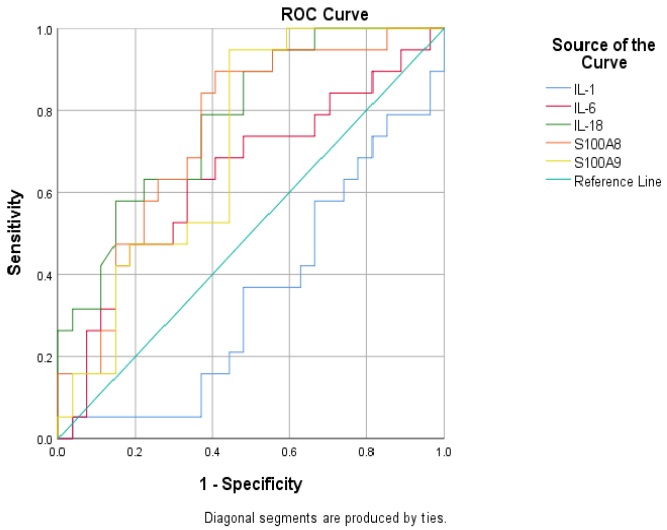

Figure-1: Receiver operating curves (ROC) for IL-1, IL-6, IL-18, S100A8 and S100A9 (IL- interleukin, S100A8- S100 calcium-binding protein A8, S100A9- S100 calcium-binding protein A9)

Table-4: Statistical measures for the diagnosis of candidate markers in sJIA

Candidate marker	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
IL-18 (pg/ml)	2030.45	66.67	75.86	65.21	77.03	72.14
S100A8 (ng/ml)	416.6	63.16	75.00	63.16	75.00	70.21
S100A9 (ng/ml)	555.1	47.37	82.14	64.29	69.70	68.09

4. Discussion

In this study, serum concentrations of IL-18, S100A8, and S100A9 were useful in distinguishing s-JIA from non-SJIA as a group and s-JIA from malignancy. Besides, serum IL-18 levels could discriminate s-JIA from SLE. None of the candidate markers helped differentiate s-JIA from infections. HLH is known to involve uncontrolled macrophage and T cell activation coupled with exuberant cytokine release, particularly IL-1β, IL-6, IL-18, and interferon-gamma (IFNγ)[15]. In our study, the serum IL-1 levels were significantly higher in patients with HLH compared to those with s-JIA. Similar to the findings of this study, Shenoi et al in their pilot study involving 20 subjects (10 with active s-JIA and 10 with febrile non-SJIA) found that serum concentrations of S100A8 and S100A9 were significantly higher in patients in the active s-JIA group compared to the non-SJIA group[9]. In that study, non-SJIA group comprised 6 patients with Kawasaki disease (KD), 3 patients with infections (viral lymphadenitis, pyelonephritis, and pneumonia), and one indeterminate.

Xia et al compared the serum concentrations of IL-6, IL-18, S100A8, and S100A9 in children with s-JIA and other diseases mimicking s-JIA, viz., acute lymphoblastic leukemia (ALL), KD, severe infections and other subtypes of juvenile idiopathic arthritis[4]. However, they did not include patients with other conditions such as SLE and HLH which have been included in our study. Serum IL-6 levels exhibited no significant difference between the disease groups. The serum S100A8 concentrations in the sJIA group were significantly higher compared to those of the ALL, other JIA subtypes, and healthy control groups but showed no significant difference compared to the severe infections and KD groups. The serum S100A9 concentrations in the sJIA group were significantly higher than those in the ALL and healthy control groups and showed no significant difference from the severe infections, KD, and other subtypes of JIA groups. The serum IL-18 level of the sJIA group was significantly higher than that of the other febrile disease groups (ALL, KD, severe infections). The observations in the aforementioned study were similar to our study in that there were no significant differences in the serum IL-6 levels between the disease groups and the serum S100A8 and S100A9 concentrations were significantly higher in patients with s-JIA compared to ALL, but not severe infections. In contrast to the findings of Xia et al, there was no statistically significant difference in the serum IL-18 levels between patients with s-JIA and severe infections in our study. The severe infections group included 4 patients in our study compared to 18 in that study. Similar to our study, Xia et al found that serum IL-18 had a larger area under the curve (AUC) compared to the other markers (IL-6, S100A8, and S100A9), indicating a relatively higher sensitivity and study. However, Xia et al reported a significantly higher sensitivity and specificity of serum IL-18 in predicting s-JIA (100% and 97.6%, respectively) compared to our study (66.67% and 75.86%, respectively).

Mizuta et al reported that the serum IL-18 cut-off value for differentiating s-JIA from other diseases (KD, SLE, juvenile dermatomyositis, leukemia, other subtypes of JIA, and periodic fever syndromes) was 4,800 pg/ml[5]. In their study, the ROC AUC value for serum IL-18 was 0.9958, and sensitivity and specificity were 97.1% and 99.1%, respectively. The AUC value, sensitivity, and specificity of serum IL-18 in that study

were much higher compared to the corresponding parameters in our study. These differences could be partly explained by differences in the kits used. Frosch et al found that the serum MRP-8/MRP14 (S100A8/S100A9) levels were significantly elevated in patients with active s-JIA compared to those with systemic infections, leukemia, and other inflammatory conditions such as neonatal onset multi-system inflammatory disease (NOMID), SLE, juvenile dermatomyositis and systemic vasculitides[7]. In our study, serum S100A8 and S100A9 were significantly higher in patients with s-JIA compared to the non-SJIA group and subgroup of ALL, however, they did not exhibit a significant difference between s-JIA and the subgroups of HLH, SLE, and severe infections.

The limitations of our study include a relatively smaller sample size for sub-group analysis and a lack of a group of healthy controls. A total of 47 children could be enrolled during the study period. There were only 4 children in the subgroup of systemic infections, an important differential of s-JIA. The ongoing COVID-19 pandemic resulting in fewer outpatient visits and a significant number of patients opting for teleconsultation appeared to have impacted the recruitment of patients during the stipulated study period. We did not recruit a group of age-matched healthy controls as this was considered not feasible due to ethical issues. Despite the above-mentioned limitations, the findings of this study add to the increasing body of evidence supporting the role of serum IL-18 and calprotectin (S100A8/S100A9) as potential diagnostic biomarkers for s-JIA. In the future with individualized medicine gaining further ground, these biomarkers would likely be widely used for early diagnosis of s-JIA and arriving at therapeutic decisions, such as tapering and stopping of immunosuppressive therapy.

5. Conclusion

Serum concentrations of IL-18, S100A8, and S100A9 can be useful in differentiating systemic juvenile idiopathic arthritis (sJIA) from other common causes of persisting joint pain and fever in children, suggesting their utility as diagnostic biomarkers for sJIA. In subgroup analysis, serum IL-18, S100A8, and S100A9 helped differentiate sJIA from ALL. Serum IL-18 concentrations differentiated sJIA from SLE.A serum IL-18 cut-off level of > 2030.45 pg/ml was useful for differentiating between sJIA and other diseases with a sensitivity of 66.67% and specificity of 75.86% for the diagnosis of sJIA.

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