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Siqi TAN[1]
Ziyan CHEN[2]
Yueqi QIU[1]
Suhan ZHANG[1]
Yanshan ZHU[1]
Xiaochao ZHANG[1]
Siying LI[1]
Cheng CAO[3]
Yuwen SU[1]
Yu LIU[1,]

[1] Department of Dermatology, The Second Xiangya Hospital, Central South University, Changsha, People's Republic of China
[2] Department of Neurosurgery, Xiangya Hospital, Central South University, Changsha, People's Republic of China
[3] Department of Outpatient, Hunan Provincial Center for Disease Control and Prevention, Changsha, People's Republic of China

Reprints: Yuwen Su
<suyuwen1963@csu.edu.cn>
<dr.yuliu@csu.edu.cn>

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Prognostic factors for adult-onset Still disease: a retrospective analysis of 90 patients in China

Background: Adult-onset Still disease (AOSD) is a systemic auto-inflammatory disorder that can be divided into monocyclic, polycyclic and chronic arthritis subtypes based on the clinical course. Since the prognoses of the three patterns of AOSD are substantially different, it is important to identify clinical indices that can be used to differentiate them. *Objectives:* To investigate the clinical features of the three patterns of AOSD in order to determine possible prognostic factors. *Materials & Methods:* Clinical records of inpatients admitted with a probable diagnosis of AOSD to the Second Xiangya Hospital of Central South University between 2009 and 2019 were retrospectively studied. Ninety patients were divided into a monocyclic group, a polycyclic group and a chronic arthritis group. *Results:* The average age at onset was 39.01 ± 13.04 years, and female to male ratio was 3.3. Elevated white blood cell (WBC) count, even beyond 15×10^9/L, and increased serum level of interleukin-6 (IL-6) >5.3 pg/mL (upper limit of normal value) were associated with the recurrence of AOSD, while the presence of rash and increased level of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) were more commonly seen in the monocyclic group. *Conclusion:* Our results indicate that gender, presence of rash, WBC count, serum level of IL-6, and ALT and/or AST are promising prognostic factors for AOSD. However, larger cohorts are needed to validate these factors due to the limitations of the retrospective study design and relatively small sample size.

Key words: adult-onset Still disease, alanine aminotransferase, interleukin-6, leukocytosis, monocyclic pattern, polycyclic pattern

Adult-onset Still disease (AOSD) is classified as a polygenic auto-inflammatory disorder at the "crossroads" of autoinflammatory and autoimmune diseases [1]. The incidence of AOSD was estimated to be 0.16 - 6.77 per 100,000 inhabitants per year [2-5]. The prevalence in females was reported to be slightly higher than that in males, with a more obvious female predominance in Asia [5-9]. However, the prevalence of AOSD in China remains unclear. The age distribution of patients with AOSD is bimodal, with one peak between 15 and 25 years old and another between 35 and 45 years old [10]. The critical clinical features of AOSD include a high spiking fever, arthralgia, skin rashes, and marked leukocytosis with neutrophilia [11]; other laboratory test abnormalities, such as an increased erythrocyte sedimentation rate (ESR) and increased serum levels of ferritin and C-reactive protein (CRP), are also observed in most cases [12]. However, the diagnosis of AOSD is usually delayed due to the lack of specific biomarkers. Different diagnostic criteria have been proposed for AOSD, among which Yamaguchi's criteria are the most widely used and the most sensitive [13]. Fautrel's diagnostic criteria are the most specific, but the need to measure the level of glycosylated ferritin limits its application [14].

Based on the clinical course, AOSD can be divided into a monocyclic pattern and a non-monocyclic pattern, which includes a polycyclic pattern and a chronic continuous pattern [12]. The prognosis of the monocyclic pattern is much better than that of the non-monocyclic pattern, as the monocyclic course is self-limited, while the polycyclic and chronic patterns are more prolonged and are associated with greater costs [15]. However, it is difficult to determine the difference among the three subtypes in the early stage of the disease.

Although the pathogenesis of AOSD remains unclear, it is believed that increased expression of proinflammatory cytokines contributes to the development of AOSD [16]. At present, empiric therapy is still the main therapeutic modality for AOSD. Glucocorticoids are the first-line therapy for the disease. However, the administration of large doses and the long-term use of corticosteroids may increase the frequency of adverse effects. For patients with glucocorticoid dependence, conventional disease-modifying anti-rheumatic drugs (cDMARDs) should be considered. Recently, due to the improved understanding of the pathogenesis of the disease and the emergence of a large number of biological agents [11], targeted therapies have been applied for the treatment of AOSD, including interleukin-1 (IL-1) blockade, IL-6 antagonists, and anti-tumour necrosis factor-α (TNF-α) antibodies [17]. In addition, a novel drug targeting IL-18 is currently undergoing clinical trials and is considered a promising treatment [18].

In this study, we described the demographic features of 90 AOSD patients in our centre and analysed and compared the

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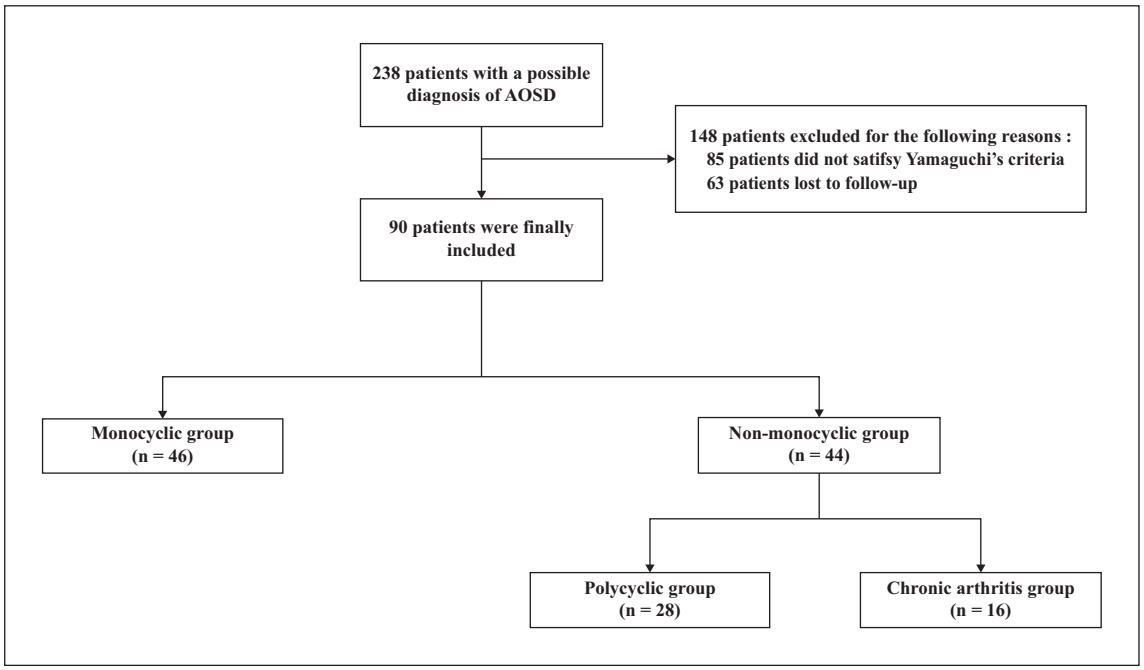

Figure 1. Workflow of patient selection and classification.

clinical and laboratory characteristics, including the levels of proinflammatory cytokines and skin biopsies of patients with the three subtypes of AOSD. Additionally, the monocyclic pattern and non-monocyclic pattern of AOSD in the early stage were compared based on these indices.

Methods

Study design, setting and participants

We performed a retrospective study of AOSD patients diagnosed in the Second Xiangya Hospital from 2009 to 2019. We collected demographic, clinical, laboratory and therapeutic data for patients with a possible diagnosis of AOSD from the electronic hospital information system (HIS) of our hospital. Then, we excluded those who did not satisfy Yamaguchi's criteria and those who were lost to follow-up. Out of 238 patients, 90 patients were finally included. This study was conducted in accordance with Good Clinical Practice, the Declaration of Helsinki, and the recommendations of the local ethics committee rules of our centres.

Inclusion criteria

Yamaguchi's criteria were used to diagnose AOSD. The four major criteria are fever $\geq$39 °C persisting for one week, arthralgia for more than two weeks, rash and leucocytosis ($\geq 10 \times 10^9$/L) with $\geq$80% granulocytes. The five minor criteria are sore throat, recent development of significant lymphadenopathy, hepatomegaly and/or splenomegaly, liver dysfunction, and negative for rheumatoid factor (RF) and antinuclear antibody (ANA). The diagnosis of AOSD requires $\geq$five criteria, including two or more major criteria, to be met. Infections, malignancies and other rheumatic diseases were excluded.

Patient classification

Based on the three classic clinical patterns of AOSD [19], we conducted telephone follow-up calls and classified the 90 patients into a monocyclic group ($n = 46$), polycyclic group ($n = 28$) and chronic arthritis group ($n = 16$) (*figure 1*).

Statistical analysis

Normally distributed variables are described as mean $\pm$ standard deviation (SD) and non-normally distributed variables are described as median $\pm$ interquartile range. When items were missing, we used the valid percentages (the percent occurrence out of the number of valid samples) to describe the probability of an event. Continuous variables are summarized as the means and standard error of the means (or medians and quartiles). Categorical variables are reported as proportions and percentages. Comparisons between groups were performed with one-way ANOVA, Brown-Forsythe test, or Kruskal-Wallis test; P values less than 0.05 were considered statistically significant. The statistical calculations were performed using the Statistical Package for Social Sciences 25.0 (SPSS, Chicago, IL, United States) and GraphPad Prism software version 8.0 for Windows (GraphPad Software, San Diego, California, USA).

Results

Demographic features

The average age at onset of the patients in our study was 39.01 $\pm$ 13.04 years old, ranging from 11 to 74 years old. Of the 90 patients, 21 (23.3%) were male and 69 (76.7%) were female; the female to male ratio (F/M) was

3.3:1. Most patients were admitted to the Department of Rheumatology (35; 38.9%), Department of Dermatology (29; 32.2%), and Department of Infection (15; 16.7%), while the rest of the patients (11; 12.2%) were admitted to the Emergency Department, Respiratory Department and Gerontology Department.

Clinical features

All patients had fevers, and 85 (94.4%) had high fevers (temperature $\geq$39 °C). Most patients (74.4%) recalled no obvious causes of the fever, while five patients (5.6%) claimed to have caught a cold before the onset of the fever. As presented in *table 1*, we compared the clinical and laboratory characteristics of patients evaluated at admission. Eighteen patients (20.0%) had moderate-to-severe anaemia. WBC counts in the range of 10-15 $\times$ 10^9/L were observed in 29 patients (32.2%), and 42 patients (46.7%) had WBC counts >15 $\times$ 10^9/L. The platelet count (mean $\pm$ SD: 293.20 $\pm$ 96.36 $\times$ 10^9/L) was elevated in 30 patients (33.3%).

Fifty-six patients (63.6%) had elevated alanine transaminase (ALT) and/or aspartate transaminase (AST) levels. Hypoalbuminemia was observed in 84 patients (93.3%).

Eighty-five patients (96.6%) had elevated CRP or hs-CRP (hypersensitive C-reactive protein) levels (mean $\pm$ SD: 115.29 $\pm$ 70.23 mg/L). The erythrocyte sedimentation rate (ESR) was elevated in 83 patients (92.2%). Most of the patients had significantly elevated serum ferritin levels; 33 patients (37.9%) had serum ferritin levels of 1,000-10,000 ng/mL, and 45 patients (51.7%) had serum ferritin levels greater than 10,000 ng/mL.

Table 1. Demographic characteristics and clinical data of the patients.

Variables	Total (n = 90)	Monocyclic group (n = 46)	Polycyclic group (n = 28)	Chronic arthritis group (n = 16)
Demographics				
Average age at onset (y),				
Mean $\pm$ SD	39.01 $\pm$ 13.04	41.63 $\pm$ 12.61	34.75 $\pm$ 14.63	38.94 $\pm$ 9.59
Gender (%male)	21 (23.3)	8 (17.4)	13 (46.4)	0 (0.0)
Clinical features				
Arthralgia, *n* (%)	66 (73.3)	36 (78.3)	17 (60.7)	13 (81.2)
Rash, *n* (%)	67 (74.4)	41 (89.1)	14 (50.0)	12 (75.0)
Urticarial papules	15 (22.72)	12 (30.00)	1 (7.14)	2 (16.67)
Typical skin manifestation*	49 (74.24)	27 (67.50)	12 (85.71)	10 (83.33)
Other skin manifestations	2 (3.03)	1 (2.50)	1 (7.14)	0 (0.00)
Lymphadenopathy, *n* (%)	62 (68.9)	32 (69.6)	22 (78.6)	8 (50.0)
Sore throat, *n* (%)	56 (62.2)	29 (63.0)	17 (60.7)	10 (62.5)
Myalgia, *n* (%)	49 (54.4)	24 (52.2)	17 (60.7)	8 (50.0)
Laboratory work-up				
WBC count ($\times$$10^9$/L),	15.41 $\pm$ 5.72	13.73 $\pm$ 6.02	18.56 $\pm$ 7.73	14.74 $\pm$ 4.87
Mean $\pm$ SD	42 (46.7)	15 (32.6)	18 (64.3)	9 (56.2)
WBC>15 $\times$ 10^9/L, *n* (%)	85.15 $\pm$ 7.67	83.75 $\pm$ 7.32	87.14 $\pm$ 7.79	85.73 $\pm$ 8.11
PMN (%), Mean $\pm$ SD	73 (81.1)	34 (73.9)	25 (89.3)	14 (87.5)
PMN>80%, *n* (%)	107.39 $\pm$ 18.89	107.35 $\pm$ 17.58	110.32 $\pm$ 21.18	102.38 $\pm$ 18.4
Hb (g/L), Mean $\pm$ SD	18 (20.0)	9 (19.6)	5 (17.9)	4 (25.0)
Hb<90 g/L, *n* (%)	14.22 $\pm$ 2.22	14.00 $\pm$ 1.93	14.67 $\pm$ 2.60	14.09 $\pm$ 2.30
RDW (%), Mean $\pm$ SD	293.20 $\pm$ 96.36	285.54 $\pm$ 102.70	312.46 $\pm$ 94.60	281.50 $\pm$ 79.39
PLT ($\times$$10^9$/L), Mean $\pm$ SD	30 (33.3)	15 (32.6)	11 (39.3)	4 (25.0)
PLT>UL, *n* (%)	56 (63.6)	35 (76.1)	14 (51.9)	7 (46.7)
ALT/AST>UL, n (%)	30.25 $\pm$ 4.47	30.74 $\pm$ 4.60	29.25 $\pm$ 4.35	30.59 $\pm$ 4.30
Albumin (g/L), Mean $\pm$ SD	115.29 $\pm$ 70.23	106.38 $\pm$ 65.45	117.43 $\pm$ 58.99	136.01 $\pm$ 96.76
CRP (mg/L), Mean $\pm$ SD	78.84 $\pm$ 30.82	74.29 $\pm$ 32.57	82.36 $\pm$ 21.34	85.75 $\pm$ 38.69
ESR (mm/h), Mean $\pm$ SD	0.22 $\pm$ 0.49	0.16 $\pm$ 0.37	0.44 $\pm$ 1.15	0.20 $\pm$ 0.30
PCT (ng/mL), Median $\pm$ quartile	486.60 $\pm$ 412.15	532.10 $\pm$ 403.90	441.15 $\pm$ 462.80	430.95 $\pm$ 199.20
LDH (μ/L), Median $\pm$ quartile	11755.58 $\pm$ 31407.09	7050.88 $\pm$ 26214.07	17427.6 $\pm$ 35618.56	5298.47 $\pm$ 30159.54
Ferritin (ng/mL),	9 (15.8)	6 (18.8)	3 (18.8)	0 (0.0)
Median $\pm$ quartile	35 (50.7)	21 (58.3)	7 (33.3)	7 (58.3)
Positive ASO, *n* (%)	28 (40.6)	21 (58.3)	4 (19.0)	3 (25.0)
Positive virus antibodies, *n* (%)	14 (28.6)	6 (22.2)	5(33.3)	3 (42.9)
Positive anti-HSV-1 IgG, *n* (%)	7 (14.6)	1 (3.7)	3 (21.4)	3 (42.9)
Positive Mycoplasma spp. Ab, *n* (%)				
Positive Chlamydia spp. Ab, *n* (%)				
Positive Legionella spp. Ab, n (%)	3 (6.2)	0 (0.0)	2 (14.3)	1 (14.3)

% refers to valid percentages.WBC: white blood cell; PMN: polymorphonuclear neutrophils Hb: haemoglobin, RDW: Red blood cell volume distribution width; UL: Upper limit; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; PCT: procalcitonin; LDH: lactate dehydrogenase; ANA: antinuclear antibody; RF: rheumatoid factor; anti-HSV-1 IgG Ab: immunoglobulin G against herpes simplex virus 1.

Table 2. Cytokine profile and other examinations.

Variables	Total ($n = 90$)	Monocyclic group ($n = 46$)	Polycyclic group ($n = 28$)	Chronic arthritis group ($n = 16$)
IL-6 (pg/mL),				
Median ± quartile	30.70 ± 64.15	24.04 ± 42.74	71.48 ± 142.99	34.88 ± 52.72
IL-6>UL, *n* (%)	40 (85.1)	16 (69.6)	15 (100.0)	9 (100.0)
Other examinations				
Splenomegaly, *n* (%)	29 (32.2)	13 (28.3)	11 (39.3)	5 (31.3)
Hepatomegaly, *n* (%)	9 (10.0)	3 (6.5)	5 (17.9)	1 (6.2)
Haemophagocytosis, *n* (%)	5 (7.8)	1 (3.0)	2 (9.5)	2 (20.0)

% refers to valid percentages; IL-6: interleukin-6.

Table 3. Treatment regimen and medication options.

Variables	Total ($n = 90$)	Monocyclic group ($n = 46$)	Polycyclic group ($n = 28$)	Chronic arthritis roup ($n = 16$)
Steroid pulse therapy, *n* (%)	2 (2.2)	1 (2.2)	0 (0.0)	1 (6.3)
High-dose glucocorticoids, *n* (%)	59 (65.6)	27 (58.7)	19 (67.9)	13 (81.3)
Medium-dose glucocorticoids, *n* (%)	19 (21.1)	10 (21.7)	7 (25.0)	2 (12.5)
Low-dose glucocorticoids, *n* (%)	2 (2.2)	0 (0)	2 (7.1)	0 (0.0)
DMARDs	43 (48.3)	19 (42.2)	14 (50.0)	10 (62.5)
MTX, *n* (%)	24 (27.0)	7 (15.6)	11 (39.3)	6 (37.5)
IVIG, *n* (%)	17 (19.1)	8 (17.8)	6 (21.4)	3 (18.8)
Antibiotics of special use, *n* (%)	42 (47.2)	19 (42.2)	15 (53.6)	8 (50.0)
Time of intervention; day, median ± quartile	10.00 ± 24.00	10.00 ± 21.00	9.50 ± 24.25	10.00 ± 23.25
Period with NSAIDs; day, median ± quartile	15.00 ± 20.50	19.00 ± 20.50	14.00 ± 28.00	19.00 ± 20.00
Period with steroids; day, median ± quartile	24.50 ± 23.00	24.00 ± 21.50	30.00 ± 31.50	19.00 ± 34.00
Period with max steroids; day, median ± quartile	30.50 ± 24.25	29.50 ± 20.75	34.00 ± 39.00	131.00 ± 25.50

% refers to valid percentages. High-dose glucocorticoids: prednisone>1 mg/(kg/d); medium-dose glucocorticoids: prednisone ≥0.5 mg/(kg/d),<1 mg/(kg/d); low-dose glucocorticoids: prednisone ≤0.5 mg/(kg/d).DMARDs: disease-modifying antirheumatic drugs, antibiotics of special use: antibiotics of restricted use, such as imipenem, meropenem, teicoplanin and vancomycin (according to Guiding principles for Clinical Application of antibiotics of the Ministry of Health (in Chinese)). Max steroids: the maximum dose of steroids applied during hospitalization.

Cytokine profile

The serum levels of IL-2, IL-4, IL-6, IL-10, IL-17A, TNF-α and interferon-γ (IFN-γ) were detected in some of the patients using enzyme-linked immunosorbent assays (ELISAs). As shown in *table 2*, IL-6 was tested in 47 patients and was elevated in most of the patients (85.1%; median ± quartile: 30.70 ± 64.15 pg/mL). The level of IL-10 was elevated in nine patients (69.2%; median ± quartile: 6.73 ± 4.74 pg/mL). A minority of the patients (<30%) had elevated levels of IL-2, IL-4, IL-17A, TNF-α and IFN-γ.

Skin histopathology results and other examinations

In total, 23 patients underwent skin biopsies. We found that 21 patients (91.3%) had lymphocyte infiltration in the superficial dermis, 13 patients (56.5%) had neutrophil infiltration and nine patients (39.1%) had eosinophil infiltration. Necrotic keratinocytes were observed in 15 patients (65.2%) and hyperkeratosis was observed in nine patients (39.1%). Basal cell liquefaction was observed in eight patients (34.8%), and parakeratosis was found in five patients (21.7%). Collagen hyaline degeneration, dermal oedema, epidermal atrophy and dyskeratosis were also reported in individual patients.

All patients underwent abdominal computed tomography (CT) or ultrasound examinations. Sixty-one patients underwent a bone marrow smear, and as presented in *table 2*, haemophagocytosis was observed in five patients (7.8%).

Associated diseases

One patient had a history of alopecia areata and two patients suffered from Graves disease and Hashimoto's thyroiditis, respectively, whose thyroid functions were in the normal range during hospitalization. Two patients had suffered from malignant diseases and received radical resection: breast cancer was diagnosed in one patient and duodenal carcinoma was diagnosed in the other; no sign of recurrence was observed in these two patients.

Treatment regimen and medication options

As shown in *table 3*, most patients (87.8%) received systematic glucocorticoids. Methotrexate (MTX) was the most commonly used immunosuppressant (27.0%). Intravenous immunoglobulin (IVIG) was used in 17 patients (19.1%) who failed to achieve clinical remission after corticosteroid treatment. Eighty (88.9%) patients received antibiotic therapy before a definite diagnosis. Due to the difficulty in excluding infectious disease, doctors tried to treat with specific antibiotics before administering systematic corticosteroids. In total, 81 patients (90.0%) achieved clinical remission after treatment. The average length of stay (ahLOS) (referring to the period of hospitalisation when

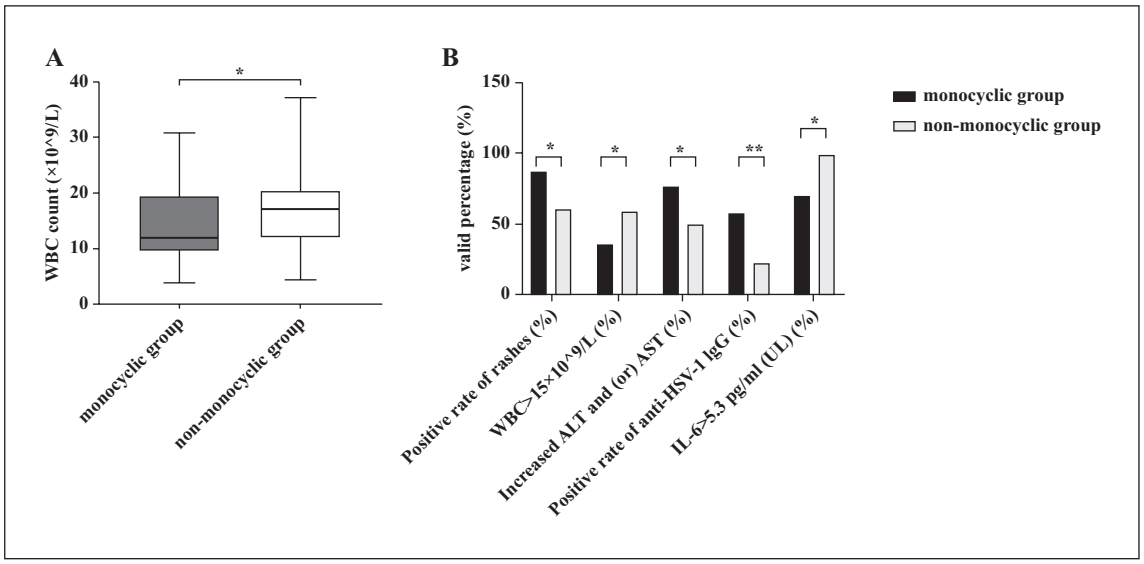

Figure 2. Prognostic factors related to monocyclic and non-monocyclic subtypes of AOSD. WBC > 15×10^9/L and IL-6 > UL were more commonly seen in non-monocyclic patients (**A**), while abnormal AST/ALT level, rash and positive anti-HSV-1 IgG were more frequent in the monocyclic group (**B**).

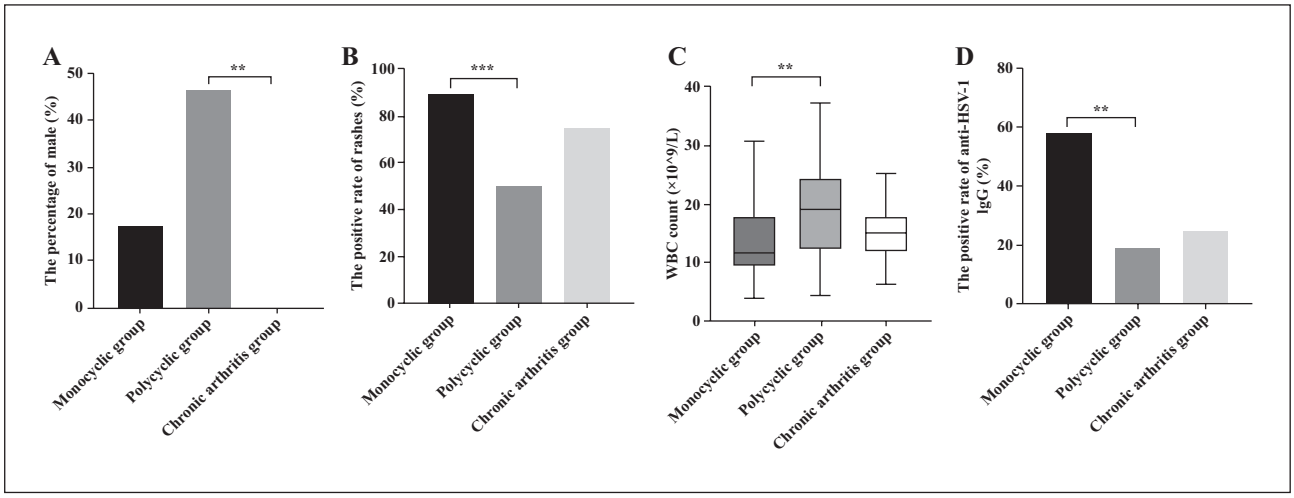

Figure 3. Prognostic factors related to monocyclic, polycyclic and chronic arthritis subtypes of AOSD. Compared with the chronic arthritis group, the proportion of males was significantly lower in the polycyclic group (**A**). Rash (**B**) and positive anti-HSV-1 IgG (**D**) were more commonly seen in the monocyclic group, and leukocytosis (**C**) was significantly higher in the polycyclic group.

patients were first diagnosed with AOSD in our centre) in the hospital was 18.00 ± 13.00 days. The percentage of patients who received treatment in the early stage (within two weeks) showed no significant difference among the three groups.

Prognostic factors related to the clinical course of AOSD

Elevated WBC counts ($p = 0.034$) (*figure 2A*), particularly greater than 15×10^9/L ($p = 0.036$), and increased serum levels of IL-6 ($p = 0.012$) were more commonly seen in non-monocyclic patients (*figure 2B*). However, increased levels of AST or ALT ($p = 0.020$), the presence of rash ($p = 0.011$) and positive anti-HSV-1 IgG ($p = 0.007$) were more frequently seen in the monocyclic group (*figure 2B*). Furthermore, leukocytosis ($p = 0.0067$) and male preponderance ($p = 0.0067$) were significantly greater in the polycyclic group (*figure 3*).

Discussion

AOSD is a rare systemic auto-inflammatory disease that lacks prognostic factors and evidence-based therapy [20]. In this study, we collected and followed AOSD patients in our centre, and analysed and determined promising predictors of clinical course.

In terms of clinical manifestation, all our patients experienced fever and 94.4% of them suffered high fever (T≥39 °C), which is in line with published data [21-24]. It has been reported that fever often precedes the onset of other manifestations [25]. Arthritis occurs in 64-100% of AOSD patients and usually affects the wrists, knees and ankles [11, 14, 26]. In our series, 66 patients (73.3%) experienced arthritis, but 54.5% of them (36 patients) turned out to be monocyclic over follow-up which suggests that most arthralgia is transient. Typical and atypical skin manifestations of AOSD are observed by dermatologists [27, 28]. The typical skin manifestation of AOSD is salmon-pink macular or maculopapular erythema, mostly on the trunk and proximal limbs [29]. In addition, atypical skin manifestations such as persistent plaques and linear pigmentation, fixed plaques and urticarial lesions have also been frequently described [30]. In our study, 67 patients (74.4%) had skin manifestations. The presence of rash was significantly more commonly seen in patients with a monocyclic course (*figures 2, 3*).

We found that inflammatory markers such as WBC count, CRP, ESR, and PCT were usually elevated at different levels in AOSD patients, which is similar to previous studies [31]. The levels of inflammatory markers are non-specific for diagnosis but usually correlate with the activity and severity of AOSD [11, 32, 33]. Therefore, these markers are called "proxy" and "mechanistic" markers as they might be involved in the pathogenic process [32]. The WBC count was significantly higher in the polycyclic group, which indicates that the WBC count could be used as a promising tool to predict prognosis. Although most (91.6%) of the AOSD patients in our series showed elevated levels of LDH, there was no significant difference among the studied groups, and the role of LDH in disease pathogenesis remains unclear.

Infections with some microorganisms, especially DNA viruses such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), rubella virus and human herpes virus 6 (HHV-6), are associated with AOSD [24, 34]. Elevated titres of antibodies against Chlamydia trachomatis or Mycoplasma pneumoniae have also been reported in some cases [35-29]. In our study, the positive rate of antibodies against viruses was 50.7%, which indicated that infections might contribute to the pathogenesis of AOSD. In particular, the positive rate of anti-HSV-1 IgG in AOSD patients was 40.6%, which was lower than that of the general population in China (52.0%-94.2%) [35].

Skin biopsy may be helpful in the diagnosis of AOSD. Infiltration of neutrophils between collagen bundles is a constant histopathological manifestation of AOSD [30]. Persistent pruritus eruption (PPE), presenting with a histological finding of dyskeratotic keratinocytes, is a specific skin manifestation in AOSD [36]. In addition, atypical persistent rash (APSE) is a new manifestation of AOSD, which presents a unique pathological feature of necrotic keratinocytes shown in the upper third of the epidermis [37].

Studies have proposed that proinflammatory cytokines, such as IL-1β, IL-6, IL-10, IL-18 and TNF-α, play important roles in the pathogenesis of AOSD [33, 38]. In addition, IL-18 and IL-33 may also represent potential targets for the treatment of AOSD [39, 40]. In our study, we found that the level of IL-10 also increased slightly in most of the patients (69.2%). However, the difference in IL-10 expression was not statistically significant among groups.

Systematic corticosteroids are still the first-line therapy for the treatment of AOSD, and immunosuppressant agents are the second-line therapy [41]. In this study, the average hospital length of stay (ahLOS) was 18.00 ± 13.00 days (median ± quartile). Most (91.1%) patients received systematic corticosteroid therapy and 95.1% of them received a median to high dose (prednisone≥0.5 mg/(kg/d)). Due to the increased levels of proinflammatory cytokines, biological agents have recently been used to treat AOSD. Biological agents targeting TNF-α, IL-1 and IL-6 have been shown to be efficacious for the treatment of AOSD [42].

Generally, the clinical course of AOSD falls into one of three patterns: monocyclic, polycyclic and chronic arthritis [19, 26, 43]. Over the average follow-up period of 3.73 years (range: 1.00-10.67 years), 46 patients experienced a monocyclic course, 28 patients presented with a polycyclic course, and 16 patients had a chronic arthritis course. The timing of intervention showed no significant influence on subsequent development into different patterns, indicating that the timing of intervention does not alter the course of the disease. Male patients made up a relatively larger percentage in the polycyclic group while no male patient was classified in the chronic arthritis group in our study. As mentioned above, rash and positive anti-HSV-1 IgG were more commonly seen in the monocyclic group, and the WBC count was significantly higher in the polycyclic group (*figure 3*).

Since the prognoses for the monocyclic pattern were much better than those for the polycyclic and chronic patterns, we further divided our patients into a monocyclic and non-monocyclic group (including polycyclic and chronic AOSD). Investigation of the clinical indices between the two subtypes revealed that WBC count ($>15 \times 10^9$/L) and increased levels of IL-6 (>5.3 pg/mL; upper limit of normal value) were more commonly seen in non-monocyclic patients, while increased levels of AST and (or) ALT, rash and positive anti-HSV-1 IgG were more frequent in the monocyclic group. WBC $>15 \times 10^9$/L was found to be a significant risk factor for a protracted course, which is in agreement with previous observations [26].

However, this study has some limitations. First, this was a retrospective study based on electronic medical records and telephone follow-up. Patients who were lost to follow-up or did not fulfil the Yamaguchi criteria due to incomplete documentation of medical records were excluded, which might have resulted in bias. Second, this was a single-centre study, and the sample size was limited. Third, because most patients were not admitted to dermatology departments, the descriptions of skin manifestations were imprecise and non-specific. Thus, we failed to determine the potential relationships between rash types and prognosis. Therefore, further investigations are needed to verify these conclusions.

In summary, the results of our study indicate that leukocytosis ($>15 \times 10^9$/L) and increased IL-6 levels could be considered predictive factors for recurrence, while rash, upregulated AST and/or ALT levels and positive anti-HSV-1 IgG may be signs of a positive prognosis. These factors identified as being related to the prognosis of AOSD could be used to predict the clinical subtypes of AOSD, which

could help inform on the management of AOSD patients in the future. ■

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