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Original article

Characteristics and risk factors of relapses in patients with adult-onset Still's disease: a long-term cohort study

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Abstract

Objectives. To describe the detailed characteristics and explore the potential risk factors of relapses in patients with adult-onset Still's disease (AOSD).

Methods. We enrolled patients with AOSD admitted to the Department of Rheumatology and Immunology, Ruijin Hospital from August 2016 to September 2019. Kaplan–Meier curves and the log rank test were used to estimate the cumulative relapse probability and persistent remission rate before the first occurrence of relapse. The multivariate Cox proportional hazard method was utilized to identify risk factors associated with relapses of AOSD.

Results. A total of 122 patients with AOSD were enrolled with a median follow-up of 12.6 months. Among them, 26 (21.3%) patients had at least one relapse. The cumulative relapse rates of AOSD patients were 14.42%, 21.79%, 24.81% and 28.57% at 6, 12, 18 and 36 months, respectively. According to the multivariate analysis, intensive treatment (odds ratio: 6.848; 95% CI: 2.441, 19.211) and macrophage activation syndrome (odds ratio: 4.020, 95% CI: 1.564, 10.322) were associated with increased risk of relapse.

Conclusion. Our study indicated that relapses occurred in at least one-fifth of patients with AOSD, and patients with high disease severity at initial attack may have an increased risk of relapse, which needs more intensive therapy and close follow-up.

Key words: adult-onset Still's disease, relapse, risk factors, intensive treatment, macrophage activation syndrome

CLINICAL SCIENCE

Rheumatology key messages

- The relapse of adult-onset Still's disease (AOSD) is 21.3%.
- Intensive treatment and macrophage activation syndrome were risk factors of relapse in AOSD.
- Rheumatologists should monitor tightly AOSD patients with greater disease severity.

Introduction

Adult-onset Still's disease (AOSD) is an autoinflammatory disease, mainly characterized by spiking fever, arthralgia or arthritis, evanescent rash, sore throat and leucocytosis [1–4]. Based on the major manifestations and episodes of systemic symptoms at disease onset and during follow-up, AOSD can be divided into three distinct patterns: a monocyclic course, a multicyclic course and a chronic articular course [1, 5, 6]. Relapses

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are frequently observed in patients with the multicyclic and chronic articular course. However, the characteristics and risk factors of relapses in AOSD have not been fully addressed. Timely assessment of the probability of disease relapse would be helpful to make appropriate treatment decisions. Therefore, we aimed to assess the relapse rate in patients with AOSD and identify the potential risk factors.

Methods

Enrolment

Patients diagnosed with AOSD fulfilling Yamaguchi's criteria were consecutively enrolled between August 2016 and September 2019 in the Department of Rheumatology and Immunology, Ruijin Hospital, and followed up prospectively [7]. All patients were aged between 16 and 75 years old. Informed consent was obtained from all patients. This survey was approved by the Institutional Research Ethics Committee of Ruijin Hospital (ID: 2016–62) and conformed to the principles of the Declaration of Helsinki.

Data collection

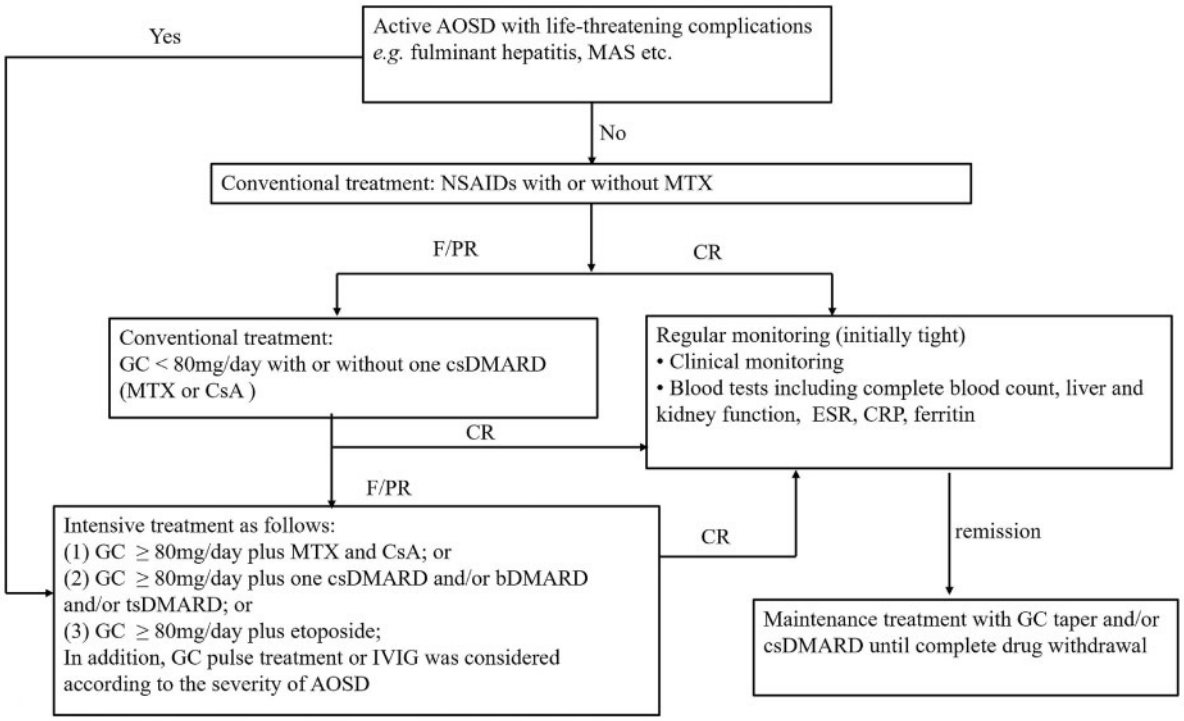
The collected data included demographic characteristics, clinical manifestations, and laboratory data such as complete blood count, liver function tests, ESR, CRP, serum ferritin, cytokine profiles, and cell subsets. A modified Pouchot score was used to assess the disease activity of AOSD [8]. Data on each subject were recorded until the occurrence of the first relapse or the last clinical visit.

Treatment

The treatment strategy for AOSD in our center is summarized in Fig. 1 and included two stages: an initial treatment period and a maintenance treatment period, when the dosage of glucocorticoid equivalent to prednisone was maintained at $\leq$10 mg/day.

NSAIDs were the first-line treatment to relieve the symptoms, followed by methotrexate unless contraindication. If the treatment target was not achieved with NSAIDs, glucocorticoid alone and glucocorticoid plus one conventional synthetic DMARD (csDMARDs) such as methotrexate or ciclosporin A were considered. The treatments mentioned above were considered conventional treatments. If there were life-threatening complications, such as fulminant hepatitis, macrophage activation syndrome, or the failure or partial response of conventional treatment mentioned above, glucocorticoid plus two csDMARDs, glucocorticoid plus one csDMARD and/or biologic DMARD (bDMARD; e.g. TNF inhibitor, etanercept; IL-6 inhibitor, tocilizumab) and/or a targeted synthetic DMARD (tsDMARD; e.g. janus kinase inhibitor,

Fig. 1 Work-up of management of patients with active AOSD



AOSD: adult-onset Still's disease; bDMARD: biologic DMARD; CR: complete response; CsA: cyclosporine A; csDMARD: conventional synthetic DMARD; F: failure; GC: glucocorticoid; MAS: macrophage activation syndrome; MTX: methotrexate; PR: partial response; tsDMARD: targeted synthetic DMARD.

tofacitinib), or glucocorticoid plus etoposide was applied to intensify the treatment. The initial glucocorticoid treatment was administered for 2–4 weeks and was gradually decreased until maintenance treatment period according to the evaluation of clinical manifestation and laboratory parameters. When glucocorticoid was absolutely discontinued, DMARDs were tapered to complete drug withdrawal in sustained remission patients. IVIGs were used in AOSD patients with severe complications.

Definitions

Patients who had fever and/or inflammatory arthralgia/arthritis and/or any suggestive cutaneous lesions and/or sore throat attributed to AOSD were thought to be clinically active; otherwise, they were considered inactive [9]. We defined a relapse as a recurrence of two or more of the above-mentioned manifestations with at least one elevated inflammatory indicator including ESR, CRP or ferritin, and further required either an increase in the glucocorticoid dose and/or immunosuppressive agents or a restart of glucocorticoids and/or biologic agents, which was also confirmed by an experienced rheumatological team after exclusion of infection, allergy, disease, etc. Secondary haemophagocytic lymphohistiocytosis (HLH) induced by autoinflammatory/autoimmune disorders is called macrophage activation syndrome (MAS). MAS secondary to AOSD in our study was diagnosed according to the 2004 HLH criteria [10]. The effectiveness of treatment was defined previously [11, 12]: complete response was considered when all initial clinical manifestations and abnormal laboratory tests had been resolved; partial response was considered when all but one initial clinical manifestation or abnormal laboratory test had been resolved; failure was considered when two or more clinical manifestations or abnormal laboratory tests persisted. Remission was defined as the disappearance of systemic symptoms and normalization of laboratory evidence of disease activity. The time to relapse was the duration of remission after discharge. The primary outcome was the first relapse during follow-up period.

Statistical analysis

Continuous data are presented as median (interquartile range, IQR) and were compared by Mann–Whitney *U*-test or Kruskal–Wallis test. Categorical data were described as frequencies (percentages) and were analysed by χ^2 test or Fisher's exact test. Kaplan–Meier curves and the log-rank test were used to estimate the cumulative relapse probability and persistent remission rate of the first occurrence of relapse. The receiver operating characteristic (ROC) curve was used to determine the related cut-off values. Cox proportional hazard models with the likelihood ratio forward selection method were performed to identify baseline risk factors of relapses in AOSD. All statistical analyses were performed using SPSS Statistics (version 23.0; IBM Corp., Armonk, NY, USA). A two-tailed P-value <0.05 was considered statistically significant.

Results

Cohort characteristics

A total of 122 hospitalized patients with active AOSD were consecutively enrolled during the study period. The characteristics of the enrolled patients are presented in Table 1. The median age of the patients was 35.0 (27.0–51.3) years old with a female predominance (83.6%). The disease duration of enrolled AOSD patients was 2.4 (1.0–9.8) months and the median follow-up period was 12.6 (4.6–22.4) months. The common clinical manifestations were fever (92.6%), typical rash (86.9%), arthralgia (84.4%), sore throat (63.9%) and abnormal liver function (54.1%); 59.8% AOSD patients had ferritin >5 times the upper limit of normal and 44.3% had leukocytes $>15 \times 10^9$/l. The median modified Pouchot score was 6 (4–7). The relapsed patients had higher incidence of MAS (38.5% *vs* 9.4%, $P < 0.0001$), higher levels of white blood cell ($P = 0.015$) and alanine aminotransferase ($P = 0.024$), higher proportion of $CD3^+CD8^+$ ($P = 0.014$) and lower proportion of $CD16^+CD56^+$ ($P = 0.040$). AOSD patients with relapse had increased proportion of intensive treatment ($P < 0.0001$), including higher initial dose of glucocorticoids ($P = 0.008$) and wider application of IVIG ($P = 0.001$).

Probability and characteristics of relapse

The persistent remission rates were 86.58%, 78.21% and 71.43% (Fig. 2A) and cumulative relapse rates were 14.42%, 21.79% and 28.57% at 6, 12 and 36 months, respectively (Fig. 2B). Twenty-six (21.3%) patients suffered at least one relapse after discharge. To be specific, 21 (80.8%) AOSD patients relapsed once; two (7.7%) patients relapsed twice; and three (11.5%) patients relapsed three times during the follow-up period (Fig. 2C). The median time to relapse was 4.8 (1.5–8.7) months. Before the relapse, 19 (73.1%) out of 26 relapsed patients were treated with glucocorticoid (≤10 mg/day) and DMARD, two (7.7%) patients with glucocorticoid only (>10 mg/day), two (7.7%) patients with DMARD only, two (7.7%) patients with complete drug discontinuation, and one (3.8%) patient with glucocorticoid (>10 mg/day) combined with DMARD (Fig. 2D). All relapsed patients were given an increase of glucocorticoid and/or DMARD. After adjusting the medication, the symptoms were relieved.

Comparison of different initial treatments and the relationship with relapse

During the initial treatment stage, 12 out of 92 patients who received conventional treatment ended up relapsing, and 14 out of 30 patients who received the intensive treatment ended up relapsing. The cumulative relapse rates in the conventional treatment and intensive

Table 1 Comparison of baseline characters between relapsed and non-relapsed AOSD patients

Feature	All active patients ($n = 122$)	Relapsed patients ($n = 26$)	Non-relapsed patients ($n = 96$)	*P*-value
Demographics				
Age, median (IQR), years	35.0 (27.0–51.3)	34.5 (27.8–43.8)	36.0 (27.0–52.0)	0.659
Female, *n* (%)	102 (83.6)	21 (80.8)	81 (84.4)	0.660
Duration, median (IQR), months	2.4 (1.0–9.8)	2.5 (1.5–11.3)	2.1 (1.0–8.4)	0.529
Clinical features				
Fever, *n* (%)	113 (92.6)	25 (92.6)	88 (91.7)	0.437
Typical rash, *n* (%)	106 (86.9)	22 (84.6)	84 (87.5)	0.699
Arthralgia, *n* (%)	103 (84.4)	21 (80.8)	82 (85.4)	0.562
Arthritis, *n* (%)	44 (36.1)	9 (34.6)	35 (36.5)	0.862
Pleuritis, *n* (%)	26 (21.3)	8 (30.8)	18 (18.8)	0.184
Pneumonia, *n* (%)	27 (22.1)	6 (23.1)	21 (21.9)	0.896
Pericarditis, *n* (%)	19 (15.6)	3 (11.5)	16 (16.7)	0.522
Myalgia, *n* (%)	34 (27.9)	11 (42.3)	23 (24.0)	0.064
Lymphadenopathy, *n* (%)	89 (73.0)	16 (61.5)	73 (76.0)	0.140
Splenomegaly, *n* (%)	51 (41.8)	13 (50.0)	38 (39.6)	0.339
Hepatomegaly, *n* (%)	9 (7.4)	2 (7.7)	7 (7.3)	0.945
Abnormal liver function, *n* (%)	66 (54.1)	16 (61.5)	50 (52.1)	0.391
Sore throat, *n* (%)	78 (63.9)	18 (69.2)	60 (62.5)	0.526
Abdominal pain, *n* (%)	5 (4.1)	1 (3.8)	4 (4.2)	0.941
White blood cells $>15 \times 10^9$/l, *n* (%)	54 (44.3)	14 (53.8)	40 (41.7)	0.267
Modified Pouchot score, median (IQR)	6.00 (4.00–7.00)	6.00 (4.00–7.25)	6.00 (4.00–7.00)	0.229
AOSD associated complications				
Disseminated intravascular coagulopathy, *n* (%)	0 (0)	0 (0)	0 (0)	—
Fulminant hepatitis, *n* (%)	0 (0)	0 (0)	0 (0)	—
PAH, *n* (%)	5 (4.1)	2 (7.7)	3 (3.1)	0.297
MAS, *n* (%)	19 (15.6)	10 (38.5)	9 (9.4)	**<0.0001**
Laboratory data				
White blood cells, median (IQR), $\times 10^9$/l	10.2 (6.7–14.1)	12.6 (8.4–23.1)	9.3 (6.2–12.8)	**0.015**
Neutrophils, median (IQR), %	79.0 (69.8–85.1)	81.1 (73.0–87.0)	78.1 (68.0–85.0)	0.127
ALT, median (IQR), IU/l	28.0 (14.8–56.3)	44.5 (23.8–82.3)	25.0 (13.3–50.8)	**0.024**
AST, median (IQR), IU/l	39.5 (22.0–70.3)	37.5 (26.8–72.5)	41.0 (21.0–69.8)	0.610
ALP, median (IQR), IU/l	90.0 (72.8–145.5)	121.5 (81.0–191.3)	88.5 (70.5–120.8)	0.058
GGT, median (IQR), IU/l	45.5 (26.5–103.0)	62.5 (27.8–141.5)	43.5 (25.5–86.3)	0.230
LDH, median (IQR), IU/l	390.0 (277.0–581.0)	462.0 (281.3–656.3)	378.0 (266.0–566.5)	0.365
ESR, median (IQR), mm/h	56.0 (30.0–83.1)	56.0 (22.7–96.0)	56.0 (32.5–82.8)	0.724
CRP, median (IQR), mg/l	53.3 (17.7–113.3)	72.3 (16.1–135.8)	51.3 (18.6–105.5)	0.478
Liver function tests >5 ULN, *n* (%)	11 (9.0)	4 (15.4)	7 (7.3)	0.201
Ferritin >5 ULN, *n* (%)	73 (59.8)	17 (65.4)	56 (58.3)	0.515
Cytokine profiles				
IL-1β, median (IQR), pg/ml	5.68 (5.00–9.94)	5.68 (5.00–10.70)	5.69 (5.00–9.65)	0.689
IL-2 receptor, median (IQR), U/ml	1233.5 (832.8–1799.0)	1544.5 (829.5–2287.8)	1160.0 (832.8–1772.0)	0.243
IL-6, median (IQR), pg/ml	21.3 (8.49–38.70)	17.6 (5.8–46.6)	21.6 (8.65–36.23)	0.915
IL-8, median (IQR), pg/ml	105.0 (41.6–268.0)	95.8 (30.1–246.0)	110.5 (41.8–268.8)	0.821
IL-10, median (IQR), pg/ml	9.52 (5.44–17.4)	14.2 (8.14–19.3)	8.54 (5.27–17.25)	0.123
TNF-α, median (IQR), pg/ml)	15.5 (10.2–21.7)	20.65 (9.90–34.48)	15.30 (10.20–20.20)	0.095
Immune cell subsets				
$CD3^+CD4^+$, median (IQR), %	40.5 (31.5–49.1)	37.2 (30.8–46.4)	41.5 (32.8–50.3)	0.294
$CD3^+CD8^+$, median (IQR), %	32.3 (25.1–45.0)	41.2 (32.0–52.7)	31.5 (24.3–40.2)	**0.014**
$CD19^+$, median (IQR), %	8.4 (5.0–12.2)	7.8 (2.8–11.9)	8.5 (5.6–13.4)	0.313
$CD16^+CD56^+$, median (IQR), %	8.9 (6.2–14.0)	7.5 (5.6–8.7)	10.7 (6.3–14.1)	**0.040**
Intensity of treatment in initial induction				
Conventional treatment, *n* (%)	92 (75.4)	12 (46.2)	80 (83.3)	**<0.0001**
Intensive treatment, *n* (%)	30 (24.6)	14 (53.8)	16 (16.7)	
Initial dose of prednisolone, median (IQR), mg/kg day	1.82 (1.13–3.02)	2.61 (1.79–3.45)	1.70 (1.00–2.48)	**0.008**
Application of etoposide, *n* (%)	10 (8.2)	4 (15.4)	6 (6.3)	0.132
Application of biologic agents, *n* (%)	2 (1.6)	1 (3.8)	1 (3.8)	0.380

(continued)

TABLE 1 Continued

Feature	All active patients ($n = 122$)	Relapsed patients ($n = 26$)	Non-relapsed patients ($n = 96$)	*P*-value
Tofacitinib, *n* (%)	4 (3.3)	2 (7.7)	2 (2.1)	0.154
Application of IVIG, *n* (%)	18 (14.8)	9 (34.6)	9 (9.4)	**0.001**

χ^2 or Fisher's exact test for proportions and the Mann–Whitney *U*-test for continuous variables were used to compare factors between patients with and without relapse. $P < 0.05$ is shown in bold type. ALP: alkaline phosphatase; ALT: alanine aminotransferase; AOSD: adult onset still's disease; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase; IQR: interquartile range; LDH: lactate dehydrogenase; MAS: macrophage activation syndrome; PAH: pulmonary artery hypertension; ULN: upper limit of normal.

treatment groups were 19.3% and 62.4%, respectively. There was a significant difference in the relapse rate between these two groups ($P < 0.0001$, Fig. 3A). We found no significant differences in age, gender, disease duration or laboratory parameters between the two groups (Table 2). However, an increased incidence of MAS was observed in the intensive treatment group, accompanied with elevated levels of alkaline phosphatase (ALP) and gamma-glutamyl transpeptidase, and reduced $CD16^+CD56^+$ (Table 2). Moreover, we found the initial dosage of glucocorticoid was higher in the intensive treatment group than in the conventional treatment group ($P < 0.0001$); besides, a wider application of etoposide, bDMARD and IVIG was observed in the conventional treatment group (Table 2).

Potential risk factors of relapse in AOSD

To evaluate the potential risk factors of relapse in AOSD, we further performed Cox regression analysis (Table 3). The univariate analysis results indicated that the relapses were associated with myalgia, modified Pouchot score $\geq$6.5, white blood cell $\geq 13.2 \times 10^9$/l, ALP $\geq$135.5 U/l, $CD3^+CD8^+$ $\geq$30.2%, initial dosage of equivalent to prednisolone $\geq$2.18 mg/kg day, intensive treatment, application of etoposide and application of IVIG. Given the association between the covariates, multiple Cox regression models including significant candidates in univariate analysis and the stepwise selection (likelihood ratio) method were applied. The results demonstrated the intensive treatment (OR: 6.848; 95% CI: 2.441, 19.211) was an independent risk factor of relapse in AOSD compared with the conventional treatment. Of importance, MAS, a life-threatening condition of AOSD, was also identified as an independent predictor of relapse in AOSD patients (OR: 4.020; 95% CI: 1.564, 10.322), which indicated that AOSD patients with a higher level of disease severity had an increased risk of relapse. In addition, the cumulative relapse rates in MAS patients were 36.24%, 52.18% and 71.31% at 3, 6 and 12 months, respectively. The Kaplan–Meier curve showed that the cumulative relapse rates of the MAS group were higher than those without ($P < 0.0001$) (Fig. 3B).

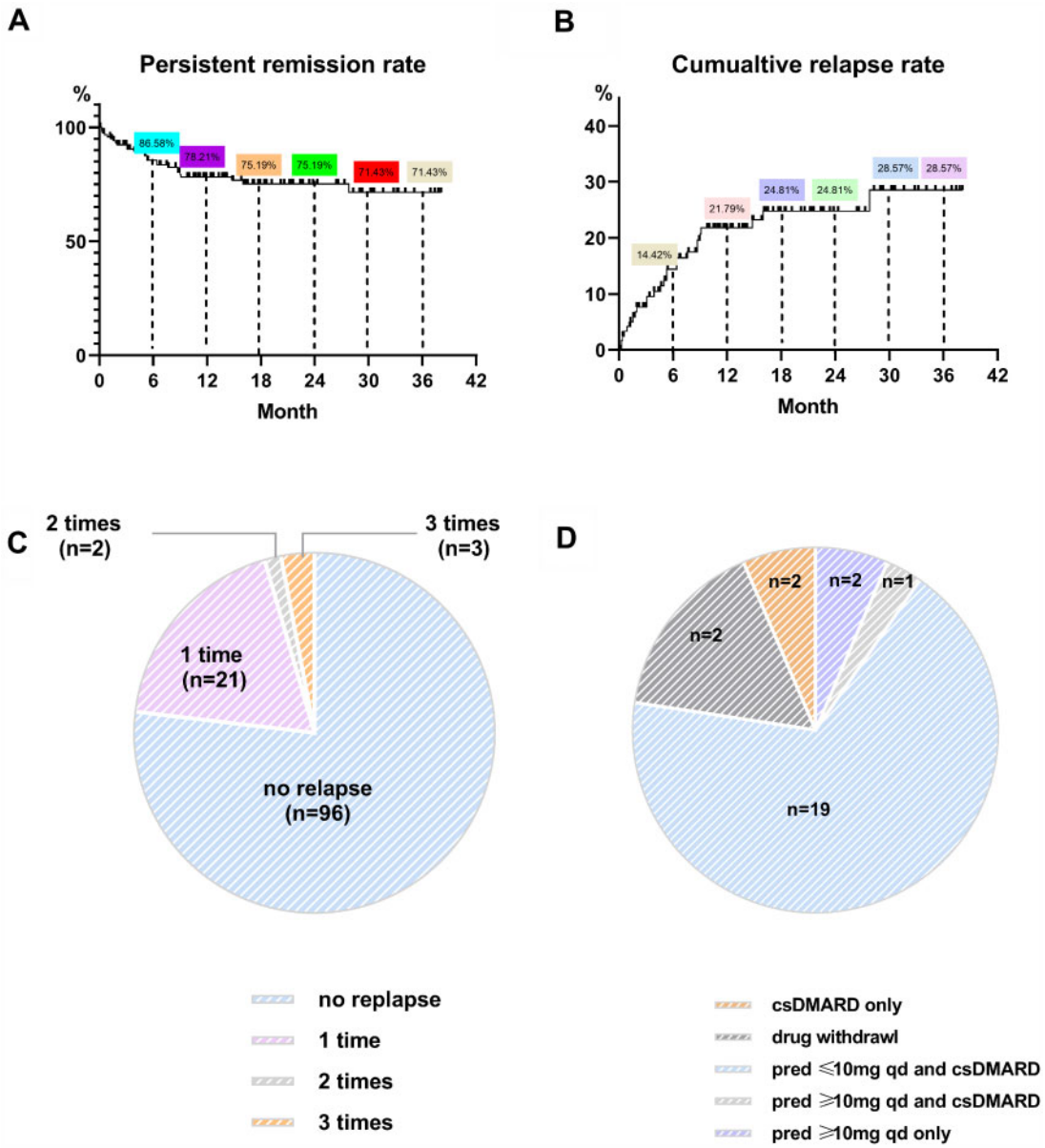
Discussion

AOSD is relatively benign, but relapses are frequent in real-world practice. To date, few studies have provided a relapse rate and reliable predictors of relapse in AOSD. Consequently, identification of predictors is of great significance for preventing recurrence. In this retrospective study, we investigated the probability and characteristics of relapse in 122 patients with AOSD and further explored the risk factors of relapse.

During follow-up, 21.3% of the patients relapsed, and the cumulative relapse rates were 14.42%, 21.79%, 24.81% and 28.57% at 6, 12, 18 and 36 months, respectively, indicating that relapse rate increased with the extension of follow-up time. Previous studies demonstrated the probability of relapse ranged from 29.5% to 46.9% [13–17], most of which were not calculated by survival analyses. Among these researches, a Turkish investigation that included 255 AOSD patients who were followed up for >1 year reported that the relapse rate was 36.1% [14]. Meanwhile, 46 out of 104 AOSD patients relapsed after an average follow-up of 41.6 months from Kong's group; the relapse rate was higher than for our group, which may be due to the longer follow-up time [17]. Interestingly, most of the relapses mentioned in this report occurred during the glucocorticoid tapering period, while 73.1% of relapses in our study occurred when the patients were treated with glucocorticoid $\leq$10 mg/day.

MAS, a severe complication of AOSD, shares similarities in clinical manifestations and pathophysiological processes with AOSD. Both AOSD and MAS are characterized by excessive activation of macrophages and subsequent cytokine storm. Previous investigation showed that AOSD complicated with MAS had worse prognosis, including higher relapse and increased mortality [18]. The data in our study showed the prevalence of AOSD complicated with MAS was 15.6%, which was similar to previous reports [19]. Moreover, we demonstrated that the incidence of MAS was an independent risk factor of relapse in AOSD patients [18]. It was reported that rare protein altering variants in the known MAS-associated genes and new candidate genes are present in systemic juvenile idiopathic arthritis

FIG. 2 Remission, relapse rate and the characteristics of relapse in our study

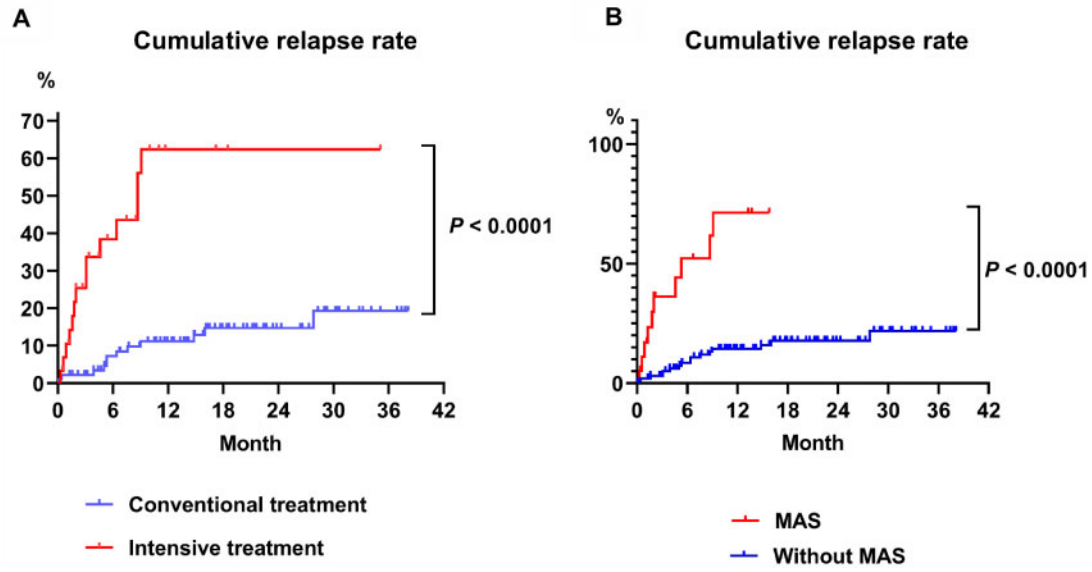


(**A**) The persistent remission rate in AOSD patients. (**B**) The cumulative relapse rate in AOSD patients. (**C**) The frequency of relapse. (**D**) The treatment before relapse. AOSD: adult-onset Still's disease; csDMARD: conventional synthetic DMARD.

complicated with MAS [20, 21]. Although the genetic variants in AOSD complicated with MAS are unknown, it is reasonable to speculate that there is a genetic predisposition to MAS in AOSD due to the homology between AOSD and systemic juvenile idiopathic arthritis [22, 23]. Besides the factors of shared genetic background, the activation of innate immunity is critical to the pathogenesis of AOSD. Despite lacking relevant research, we speculate that epigenetics of chromatin and innate memory mechanisms may contribute to a more susceptible response to stimulus, such as virus infection, leading to relapse in AOSD patients with MAS [24].

Similar to other autoimmune diseases such as rheumatoid arthritis and juvenile idiopathic arthritis, the requirement of intensive treatment was also associated with relapses in AOSD [25–27]. The prevalence of MAS was higher in the intensive treatment group than in the conventional treatment group, indicating higher disease severity in the group with intensive treatment. In keeping with this situation, we tend to initiate intensive treatment to cause the hyperinflammation to subside in these complicated patients. This is probably a reasonable explanation for the requirement of intensive treatment in severe relapsed groups. On the other hand, an

FIG. 3 Comparison of relapse rate according to the initial treatment, AOSD with MAS and without MAS



(**A**) The relapse rate in intensive treatment was higher than in conventional treatment group. (**B**) The relapse rate in patients with MAS was higher than in patients without MAS. AOSD: adult-onset Still's disease; MAS: macrophage activation syndrome.

insufficient starting dosage of glucocorticoid was the predictive factor of relapses according to the results from Kim *et al.* and Kong *et al.* [16, 17]. It is probably that the dose of glucocorticoid at initial stage was not sufficient to control the disease activity of AOSD, leading to the subsequent relapse as a result. Taken together, our results showed the more severe the disease activity, the higher the probability of relapse. However, there is no applicable assessment method of disease severity at present. To our knowledge, it was reported that a modified Pouchot score $\geq$7.0 was identified as a strong prognostic risk factor for AOSD-related death [28], which may partially reflect the disease severity. In our study, the association of modified Pouchot score $\geq$6.5 with increased risk of relapse lost significance in multivariable analysis, suggesting that modified Pouchot score may be a marker of disease severity, but not an independent determinant of relapse. Therefore, an updated and reliable disease severity measurements of AOSD is urgently needed. Presently, European League Against Rheumatism is supporting a project (CLI113) to develop and validate a disease activity score in AOSD, from which future studies on disease severity may be beneficial [29, 30]. Collectively, both intensive treatment and MAS indicated a greater disease severity in AOSD, suggesting patients with higher initial disease severity have a higher probability of relapses. Consequently, when considering de-escalation and discontinuation treatment, rheumatologists should be more cautious and monitor tightly patients with AOSD discussed here.

In addition to our research, different predictors were revealed in AOSD-related relapse. Lactate dehydrogenase was found to be a useful biomarker in AOSD undergoing treatment with tocilizumab [31]. A retrospective report from 104 Chinese patients with AOSD demonstrated that white blood cell $>30 \times 10^9$/l, serum ferritin $>$1500 ng/ml and ESR higher than 100 mm/h were correlated with relapse in AOSD by univariate analysis [17]. Besides, recently published data confirmed that AOSD-associated interstitial lung disease might be a higher risk factor of relapse [32]. Unexpectedly, not all the risk factors mentioned above were identified in our study, which may result from diverse study designs or research purposes. By contrast, we confirmed patients with MAS and intensive treatment, both of which indicated more serious disease severity of AOSD, were independent risk factors of relapse in AOSD.

With regards to cytokine profiles, there were no significant differences at baseline between conventional and intensive treatment groups, or relapsed and non-relapsed patient groups. Although the proportion of $CD3^+CD8^+$ cell subset of peripheral blood was higher in relapsed patients, it was not significantly associated with relapses according to multivariable analysis, indicating the $CD3^+CD8^+$ cell was a marker but not an independent risk factor of relapses.

Nonetheless, there were some limitations of this study. Firstly, this was a retrospective study that may inevitably have selection bias. Moreover, the enrolment date of some individuals was close to the termination,

Table 2 Comparing the differences of baseline characters between different initial treatments

Characteristic	Conventional treatment ($n = 92$)	Intensive treatment ($n = 30$)	*P*-value
Demographics			
Age, median (IQR), years	36.5 (25.3–53.0)	33.5 (29.0–42.8)	0.427
Female, *n* (%)	77 (83.7)	25 (83.3)	0.963
Duration, median (IQR), months	2.3 (1.0–7.2)	2.9 (1.3–25.3)	0.177
Clinical features			
Fever, *n* (%)	85 (92.4)	28 (93.3)	0.864
Typical rash, *n* (%)	82 (89.1)	24 (80.0)	0.198
Arthralgia, *n* (%)	78 (84.8)	25 (83.3)	0.849
Arthritis, *n* (%)	33 (35.9)	11 (36.1)	0.937
Pleuritis, *n* (%)	17 (18.5)	9 (30.0)	0.181
Pneumonia, *n* (%)	19 (20.7)	8 (26.7)	0.491
Pericarditis, *n* (%)	15 (16.3)	4 (13.3)	0.697
Myalgia, *n* (%)	23 (25.0)	11 (36.7)	0.216
Lymphadenopathy, *n* (%)	67 (72.8)	22 (73.3)	0.957
Splenomegaly, *n* (%)	35 (38.0)	16 (53.3)	0.140
Hepatomegaly, *n* (%)	6 (6.5)	3 (10.0)	0.527
Abnormal liver function, *n* (%)	49 (53.3)	17 (56.7)	0.745
Sore throat, *n* (%)	55 (59.8)	23 (76.7)	0.094
Abdominal pain, *n* (%)	4 (4.3)	1 (3.3)	1.000
White blood cells $>15 \times 10^9$/l, *n* (%)	41 (44.6)	13 (43.3)	0.906
Modified Pouchot score, median (IQR)	5.5 (4.00–7.00)	6.00 (4.00–7.3)	0.346
Liver function tests >5 ULN, *n* (%)	5 (16.7)	6 (6.5)	0.092
AOSD associated complications			
Disseminated intravascular coagulopathy, *n* (%)	0 (0)	0 (0)	—
Fulminant hepatitis, *n* (%)	0 (0)	0 (0)	—
PAH, *n* (%)	3 (3.3)	2 (6.7)	0.414
MAS, *n* (%)	6 (6.5)	13 (43.3)	**<0.0001**
Laboratory data			
White blood cells ($\times 10^9$/l)	6.3 (10.0–13.7)	11.6 (7.7–14.8)	0.162
Neutrophils, median (IQR), %	79.0 (68.2–84.8)	79.1 (72.9–89.3)	0.321
ALT, median (IQR), IU/l	25.5 (13.3–49.5)	42.5 (20.8–75.5)	0.076
AST, median (IQR), IU/l	40.5 (22.0–68.5)	36.0 (23.8–98.5)	0.397
ALP, median (IQR), IU/l	83.5 (70.0–119.0)	132.0 (84.8–197.3)	**0.001**
GGT, median (IQR), IU/l	41.0 (25.0–84.0)	66.0 (35.5–174.3)	**0.034**
LDH, median (IQR), IU/l	378.0 (268.0–546.0)	453.0 (280.5–678.5)	0.159
ESR, median (IQR), mm/h	52.5 (31.3–80.0)	67.5 (27.0–97.5)	0.662
CRP, median (IQR), mg/l	59.7 (17.9–106.8)	41.9 (16.0–139.0)	0.769
Liver function tests >5 ULN, *n* (%)	5 (16.7)	6 (6.5)	0.092
Ferritin >5 ULN	54 (58.7)	19 (63.3)	0.653
Cytokine profiles			
IL-1β, median (IQR), pg/ml	5.18 (5.00–9.35)	6.67 (5.00–13.10)	0.300
IL-2 receptor, median (IQR), U/ml	1203.0 (823.0–1736.8)	1344.0 (845.0–2403.0)	0.372
IL-6, median (IQR), pg/ml	18.90 (7.59–36.90)	24.4 (9.09–57.75)	0.352
IL-8, median (IQR), pg/ml	101.5 (41.4–251.8)	121.0 (44.5–298.5)	0.776
IL-10, median (IQR), pg/ml	8.54 (5.40–15.5)	14.5 (5.33–20.95)	0.170
TNF-α, median (IQR), pg/ml	15.30 (9.48–20.3)	15.30 (10.20–20.20)	0.159
Immune cell subsets			
$CD3^+CD4^+$, median (IQR), %	40.5 (31.4–48.7)	40.9 (32.7–50.7)	0.620
$CD3^+CD8^+$, median (IQR), %	31.5 (24.3–41.4)	33.1 (30.2–47.7)	0.190
$CD19^+$, median (IQR), %	8.5 (4.8–12.5)	7.9 (4.7–12.3)	0.753
$CD16^+CD56^+$, median (IQR), %	11.3 (6.3–15.7)	8.0 (5.6–9.3)	**0.019**
Initial dose of prednisolone, median (IQR), mg/kg day	1.68 (1.00–2.13)	3.10 (1.94–3.95)	**<0.0001**
Application of etoposide, *n* (%)	0 (0.0)	10 (8.2)	**<0.0001**
Application of biologic agents, *n* (%)	0 (0.0)	2 (6.7)	0.059
Tofacitinib, *n* (%)	0 (0.0)	4 (13.3)	**0.003**
Application of IVIG, *n* (%)	8 (8.7)	10 (33.3)	**0.001**

χ^2 or Fisher's exact tests for proportions and the Kruskal–Wallis test for continuous variables were used to compare factors between patients with different initial treatment. $P < 0.05$ is shown in bold type. ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase; IQR: interquartile range; LDH: lactate dehydrogenase; PAH: pulmonary artery hypertension; MAS: macrophage activation syndrome; ULN: upper limit of normal.

Table 3 Predictive factors for AOSD relapse

Parameter	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Myalgia	2.482 (1.137, 5.416)	**0.022**		
Modified Pouchot score ≥6.5	2.321 (1.055, 5.107)	**0.036**		
MAS	7.512 (3.275, 17.233)	**<0.0001**	4.020 (1.564, 10.322)	**0.004**
White blood cell ≥13.2 × 10^9/l)	2.959 (1.367, 6.402)	**0.006**		
ALP ≥135.5 IU/l	3.215 (1.482, 6.974)	**0.003**		
$CD3^+CD8^+$ ≥30.2%	4.120 (1.207, 14.065)	**0.024**		
Initial dose of prednisolone ≥2.18 mg/kg day	4.419 (1.979, 9.863)	**<0.0001**		
Intensive treatment	6.728 (3.038, 14.899)	**<0.0001**	6.848 (2.441, 19.211)	**<0.0001**
Application of etoposide	9.585 (2.818, 32.600)	**<0.0001**		
Application of IVIG	4.589 (2.030, 10.376)	**<0.0001**		

ROC analyses were used to determine values at the maximum Youden index as cut-off points for continuous variables. Variables identified in the univariate Cox regression analysis ($P < 0.05$) were entered into a conditional forward multivariable Cox regression model to predict risk factors of relapse. $P < 0.05$ is shown in bold type. ALP: alkaline phosphatase; AOSD: adult onset still's disease; MAS: macrophage activation syndrome; OR: odds ratio.

and as a result, the follow-up duration in these individuals might be too short to identify their relapse.

Conclusions

Overall, relapse of AOSD is frequent in real practice, and AOSD patients with a severe disease have an increased risk of relapse.

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Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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