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Original Article

Usefulness of the severity classification for predicting drug-free remission in Japanese patients with adult-onset Still's disease

Akihito Maruyama[a], Ayako Kokuzawa[b], Yusuke Yamauchi[c], Yohei Kirino[d], Hideto Nagai[d], Yasushi Inoue[e], Toshiyuki Ota[f], Yutaka Chifu[g], Satomi Inokuchi[c], Hiroki Mitoma[c], Mitsuteru Akahoshi[a], Mariko Sakai[a], Akihide Ohta[h], Masahiro Iwamoto[b] and Yoshifumi Tada[a,*]

[a]Department of Rheumatology, Faculty of Medicine, Saga University, Saga, Japan
[b]Department of Rheumatology and Clinical Immunology, Jichi Medical University, Shimotsuke, Japan
[c]Department of Medicine and Biosystemic Science, Kyushu University Graduate School of Medical Sciences, Fukuoka, Japan
[d]Department of Stem Cell and Immune Regulation, Yokohama City University Graduate School of Medicine, Yokohama, Japan
[e]Division of Rheumatology, Japanese Red Cross Fukuoka Hospital, Fukuoka, Japan
[f]Center for Rheumatic Diseases, Iizuka Hospital, Iizuka, Japan
[g]Division of Internal Medicine, Saiseikai Karatsu Hospital, Karatsu, Japan
[h]Suigo-en Kohokai Group Medical Corporation, Fukuoka, Japan

*Correspondence: Yoshifumi Tada; taday@cc.saga-u.ac.jp; Department of Rheumatology, Faculty of Medicine, Saga University, 5-1-1 Nabeshima, Saga 849-8501, Japan.

ABSTRACT

Objectives: To investigate the usefulness of severity classification for predicting outcomes in patients with adult-onset Still's disease (AOSD).

Methods: This was a multi-centre retrospective cohort study. AOSD patients were classified into mild, moderate, and severe groups based on severity classification (Japanese Ministry of Health, Labour and Welfare) during the initial treatment, and clinical features were compared among these groups. The primary endpoints were the AOSD-related mortality and drug-free remission rate. For comparison, the same analysis was performed in parallel for patient groups stratified by the modified Pouchot systemic score.

Results: According to severity classification, 49 (35%), 37 (26%), and 56 patients (39%) were classified into mild, moderate, and severe groups, respectively. Patients in the severe group showed higher frequency of severe complications and the use of biological agents. Although AOSD-related survival was not significantly different ($p = .0776$), four of the five fatal cases were classified into the severe group. The severe group showed a reduced rate of drug-free remission ($p = .0125$). Patient groups classified by systemic score did not correlate with survival or drug-free remission.

Conclusions: Severity classification is useful for predicting outcomes in patients with AOSD.

KEYWORDS: Adult-onset Still's disease; prognosis; remission; severity classification

Introduction

Adult-onset Still's disease (AOSD), a systemic inflammatory disease with spiking fever, arthritis, and evanescent rash as its three main symptoms, develops in young to senior adults [1]. Typical laboratory findings for AOSD patients include leucocytosis with neutrophilia, elevated transaminase and C-reactive protein (CRP) levels, absence of autoantibodies, and hyperferritinemia [2–5]. In addition, AOSD patients sometimes develop systemic complications, including serositis, pneumonitis, disseminated intravascular coagulation (DIC), and macrophage activation syndrome (MAS), in which case, strong immunosuppressive therapy is required [6–9]. The aetiology and pathogenesis of the inflammatory response in AOSD are still unclear, but it is thought that the excessive production of cytokines, including interleukin (IL)-1, IL-6, IL-18, tumour necrosis factor-α (TNF-α), and interferon-γ, produced by macrophages and T cells, is considered to play an important role [9–11]. The treatment of AOSD remains controversial. Systemic corticosteroids are usually the first-line therapy, and in addition, methotrexate (MTX), calcineurin inhibitors (CIs), and biological agents, mainly IL-1 and IL-6 inhibitors are used in severe or refractory cases [11–13].

To construct an effective treatment strategy and predict patient outcomes, it is important to evaluate the severity and activity of AOSD. For the assessment of severity and activity of AOSD, the systemic score proposed by Pouchot *et al.* [14] and modified by Rau *et al.* [15] is well known. However, these methods are not commonly used in daily clinical practice, and their usefulness in predicting outcomes of AOSD

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patients is not well investigated. Regarding clinical factors that predict poor prognosis, association of MAS or AOSD complications, high ferritin, elderly onset, and systemic score have been shown in previous studies [16–22]. However, the significance of these markers varies among studies; therefore, our knowledge is still limited.

In Japan, the severity classification was developed by the Japanese Ministry of Health, Labour and Welfare in 2015 and is applied for certification of intractable diseases [23]. However, this classification has not yet been validated for its usefulness. In this retrospective multi-centre cohort study, we analysed the associations between the severity classification and clinical features, treatment, survival, and drug-free remission and examined whether this system is useful for predicting outcomes of patients with AOSD.

Patients and methods

Patients and the severity classification

We retrospectively reviewed the medical records of patients with AOSD who were hospitalised and diagnosed at four university hospitals and affiliated hospitals between January 2006 and September 2016. Diagnosis of AOSD was made according to Yamaguchi's classification criteria [24]. Patients were classified into mild, moderate, and severe groups according to the severity classification (Japanese Ministry of Health, Labour and Welfare) at the time of diagnosis and initial treatment. The score was calculated as the sum of the following: serositis (1), DIC (2), MAS (2), neutrophil ratio $\geq$85% (1), serum ferritin $\geq$3000 ng/ml (1), prominent lymphadenopathy (1), and refractoriness to corticosteroid therapy [$\geq$0.4 mg/kg of prednisolone (PSL)] (1). Patients with severity scores of 0–1, 2, and 3 or higher were classified into the mild, moderate, and severe groups, respectively. Clinical features, therapy, and prognosis were compared between the groups.

For comparison of this system, we applied the systemic score of modified Pouchot [15] (abbreviated as mPSS) at the time of diagnosis for another classification of AOSD patients, and similarly analysed its association with the clinical features and prognosis. The mPSS scores disease activity from 0 to 12, adding 1 point for each of the following manifestations: fever, evanescent rashes, sore throat, arthritis, myalgia, pleuritis, pericarditis, pneumonitis, lymphadenopathy, hepatomegaly or abnormal liver function tests, elevated leukocyte count >15,000/μl, and serum ferritin >3000 μg/l. Based on the distribution of mPSS, we classified patients with a score of 0–4, 5–6, and 7 or higher into low, moderate, and high activity groups, respectively.

This study was approved by the Saga University Hospital Ethics Committee (no. 2016-11-15) and registered with University Medical Information Network-Clinical Trial Registry (UMIN-CTR) (trial registration number: UMIN000024945). Informed consent was obtained by using an opt-out system. The study was performed in accordance with the ethical standards laid down in an appropriate version of the World Medical Association (WMA) Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subject.

Primary and secondary endpoints

The primary endpoints were associations of patient classification with AOSD-related survival and drug-free remission rate. Secondary endpoints were associations of patient classification with the use of advanced therapies including biologic agents, CIs, and plasmapheresis. The usefulness of predicting the outcomes of patients with AOSD was compared between severity classification and mPSS.

Data collection and management

We extracted clinical findings from patient records, including age, sex, time from onset to diagnosis, symptoms, organ involvement, complications, laboratory data, treatment, survival, and time to drug-free remission. Laboratory data were collected at the time of AOSD diagnosis. The normal range for ferritin level differed between men and women and among hospitals. However, because the upper limit of normal was similar in each hospital, we used the raw data for analysis. MAS was diagnosed based on the criteria for autoimmune-associated haemophagocytic syndrome described by Kumakura *et al.* [25], hemophagocytic lymphohistiocytosis (HLH)-2004 guidelines [26], or classification criteria for MAS in patients with AOSD that we proposed recently [27]. DIC was diagnosed based on the diagnostic criteria of the Japanese Society on Thrombosis and Hemostasis [28]. Drug-free remission was defined as remission of AOSD in the absence of any immunosuppressive drugs, including corticosteroids that lasted for at least 6 months. Time to drug-free remission was defined as the duration between the diagnosis and termination of immunosuppressive treatment against AOSD.

Statistical analysis

Results from continuous variables are presented as the median with 25th and 75th percentiles for non-normally distributed data or the mean $\pm$ standard deviation for normally distributed data. Categorical data were expressed as percentages. Statistical evaluation was performed using a contingency table test (chi-square test) to identify significant differences. The Kruskal–Wallis test with Dunn's multiple comparisons test or Student's *t*-test was used for quantitative variables. Survival curves were calculated using the Kaplan–Meier method, and the log-rank test for trend was used to identify differences. All statistical analyses were performed using Prism version 9 software (GraphPad, San Diego, CA, USA).

Results

Patient characteristics

The patient characteristics of the entire cohort are shown in Table 1. The mean age at diagnosis was 48.8 years, 72.5% of patients were female, and 8 patients died during the follow-up period. Pleuritis developed in 14.1%, MAS in 12.7%, DIC in 7.7%, and pericarditis in 6.3% of patients. Advanced treatments included methylprednisolone (mPSL) pulse therapy (28.1%), cyclosporine (47.9%), biological agents (13.4%), and plasma exchange (2.8%). The severity classification score ranged from 0 to 8, peaked at 2, and showed a non-normal distribution (Figure 1(a)), whereas the mPSS ranged from 2 to 11, peaked at 5 and 6, and showed a normal distribution (Figure 1(b)). These patients were classified into mild, moderate, and severe groups based on the severity classification (49, 37, and 56 patients, respectively), as well as low, moderate, and high activity groups based on mPSS (27, 66, and 49 patients, respectively). Although there was a loose correlation between severity classification and mPSS classification, significant mismatches existed (Supplementary Table S1). In

Table 1. Patient characteristics.

Clinical features		Laboratory data		Treatment regimens	
Mean age at diagnosis (years)[a]	48.8 ± 19.1	WBCs (/mm^3)[b]	12,505 (9100, 16,200)	PSL	142 (100)
Female	103 (72.5)	Neutrophils (/mm^3)[b]	10,564 (7496, 14,381)	Maximal dose (mg/day)[a]	46.3 ± 18.4
Follow-up (years)[b]	3.2 (1.6, 5.5)	Haemoglobin (g/dl)[b]	11.2 (10.2, 12.4)	mPSL pulse therapy	40 (28.1)
Onset to diagnosis (days)[b]	30 (17, 57)	Platelets (×10^3/mm^3)[b]	28.3 (20.4, 35.7)	MTX	29 (20.4)
Deaths	8 (5.6)	ESR (mm/h)[b,c]	73.0 (48.0, 103.0)	Cyclosporine	68 (47.9)
Clinical findings		CRP (mg/dl)[b]	10.9 (6.0, 16.6)	Tacrolimus	7 (4.9)
High fever (>39°C)	117 (82.4)	Total protein (g/dl)[b]	6.80 (6.50, 7.30)	Other immunosuppressants[h]	5 (3.5)
Skin rash	119 (83.8)	AST (U/l)[b]	50.5 (33.0, 91.5)	Biological agents	19 (13.4)
Arthralgia	111 (78.2)	ALT (U/l)[b]	47.0 (23.0, 84.5)	Anti-TNF drugs	7 (4.9)
Lymphadenopathy	80 (56.3)	γ-GTP (U/l)[b,d]	57.5 (26.8, 123.3)	Tocilizumab	15 (10.6)
Hepatosplenomegaly	50 (35.2)	LDH (U/l)[b]	449.0 (314.0, 639.3)	Plasma exchange	4 (2.8)
Sore throat	95 (66.9)	Creatinine (mg/dl)[b]	0.580 (0.495, 0.745)		
Myalgia	42 (29.6)	IgG (mg/dl)[b,e]	1295 (1135, 1660)	PSL only	55 (38.7)
Complications		Ferritin (ng/ml)[b]	3810 (1507, 14,037)	PSL + MTX	16 (11.3)
Pleuritis	20 (14.1)	RF positive[f]	11 (8.0)	PSL + CIs	58 (40.8)
Pericarditis	9 (6.3)	ANA positive[g]	21 (14.9)	PSL + MTX + CIs	13 (9.2)
Interstitial pneumonitis	1 (0.7)				
MAS	18 (12.7)				
DIC	11 (7.7)				

The number of patient and percentages (%) are shown.
[a]Mean and standard deviation,
[b]median and 25th and 75th percentiles in parenthesis,
[c]$n = 115$,
[d]$n = 139$,
[e]$n = 123$,
[f]$n = 138$,
[g]$n = 141$,
[h]azathioprine 2, intravenous cyclophosphamide 2, and mizoribine 1.
γ-GTP: gamma-glutamyl transpeptidase; RF: rheumatoid factor; ANA: anti-nuclear antibody; IgG: Immunoglobulin G.

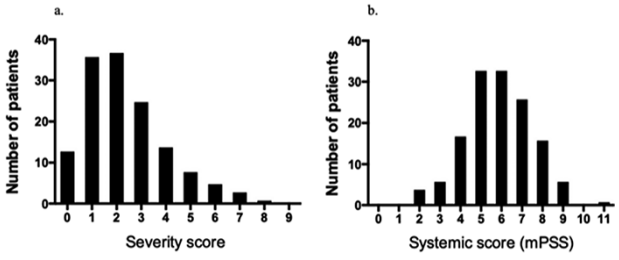

Figure 1. The distribution of clinical scores of patients with AOSD.
(a) Severity classification. (b) mPSS.

the mild group, 19 patients (39%) were graded as low, 23 (47%) as moderate, and 7 (14%) as high activity; in the moderate group, 4 patients (11%) were graded as low, 21 (57%) as moderate, and 12 (32%) as high activity; in the severe group, four (7%) patients were graded as low, 22 (39%) as moderate, and 30 (54%) as high activity.

Clinical features and complications

Clinical features and AOSD-associated complications are summarised in Table 2. On comparison among groups classified by severity classification, the frequencies of high fever ($p = .0346$), lymphadenopathy ($p = .0475$), pleuritis ($p = .0020$), pericarditis ($p = .0258$), MAS ($p < .0001$), and DIC ($p = .0001$) showed a significant increase with severity. On comparison, the groups stratified by mPSS, high fever ($p < .0001$), skin rash ($p < .0001$), arthralgia ($p = .0008$), lymphadenopathy ($p < .0001$), sore throat ($p < .0001$), myalgia ($p < .0001$), pleuritis ($p = .0077$), and pericarditis ($p = .0015$) showed a trend of increasing frequency with activity (Supplementary Table S2). Although the severity classification correlated with the mPSS, and vice versa, the two classifications showed a different spectrum of associations regarding symptoms and complications. The severity classification was mainly associated with AOSD-related complications, whereas the mPSS classification was associated with major symptoms of AOSD. Age at onset, sex, and time from onset to diagnosis did not differ among the groups classified using either method.

Laboratory data

On comparison among groups by severity classification, white blood cell counts (WBCs) ($p = .0012$), neutrophil counts ($p = .0001$), platelet ($p = .0005$), CRP ($p = .0017$), total protein ($p = .0009$), aspartate aminotransferase (AST) ($p = .0002$), lactose dehydrogenase (LDH) ($p < .0001$), and ferritin ($p < .0001$) levels were significantly higher in the severe group (Table 3). On comparison among groups classified by the mPSS, WBCs ($p = .0283$), neutrophils ($p = .0149$), total protein ($p = .0452$), AST ($p = .0008$), alanine aminotransferase (ALT) ($p = .0227$), LDH ($p < .0001$), and ferritin ($p = .0018$) were significantly different (Supplementary Table S3).

Treatments

The therapies and drugs used during the initial treatment were compared. On comparison among the groups classified by severity classification, the maximal PSL dose was higher in the severe group ($p = .0025$). Frequencies of

Table 2. Clinical features at onset.

	Severity classification			
	Mild ($n=49$)	Moderate ($n=37$)	Severe ($n=56$)	p value
Mean age at diagnosis (years)[a]	44.0 ± 17.2	51.5 ± 17.6	51.3 ± 21.1	.0915
Sex (female)	34 (69.4)	29 (78.4)	40 (71.4)	.8399
Follow-up (years)[b]	3.0 (1.0, 5.0)	2.8 (1.6, 5.5)	3.5 (2.6, 8,2)	.0616
Onset to diagnosis (days)[b]	34 (24, 70)	30 (21, 51)	21 (13, 62)	.1347
Deaths	1 (2.0)	1 (2.7)	6 (10.7)	.0509
Clinical findings				
High fever (>39°C)	36 (73.5)	31 (83.8)	50 (89.3)	.0346
Skin rash	38 (77.6)	32 (86.5)	49 (87.5)	.1731
Arthralgia	38 (77.6)	31 (83.8)	42 (75.0)	.7276
Lymphadenopathy	22 (44.9)	22 (59.5)	36 (64.3)	.0475
Hepatosplenomegaly	15 (30.6)	12 (32.4)	23 (41.1)	.2573
Sore throat	35 (71.4)	27 (73.0)	33 (58.9)	.1651
Myalgia	13 (26.5)	13 (35.1)	16 (28.6)	.8422
Complications				
Pleuritis	3 (6.1)	2 (5.4)	15 (26.8)	.0020
Pericarditis	1 (2.0)	1 (2.7)	7 (12.5)	.0258
Interstitial pneumonitis	1 (2.0)	0 (0.0)	0 (0.0)	.2200
MAS	0 (0.0)	2 (5.4)	16 (28.6)	<.0001
DIC	0 (0.0)	0 (0.0)	11 (19.6)	.0001
Systemic score[a]	4.86 ± 1.43	6.03 ± 1.50	6.61 ± 1.53	<.0001

The number of patient and percentages (%) are shown.
[a]Mean and standard deviation,
[b]median and 25th and 75th percentiles in parenthesis.

Table 3. Laboratory and immunologic findings.

		Severity classification			
	N	Mild ($n=49$)	Moderate ($n=37$)	Severe ($n=56$)	p value
WBCs (/mm^3)	142	10,980 (7315, 13,300)	12,790 (9650, 16,215)	14,705 (10,225, 19,043)	.0012
Neutrophils (/mm^3)	142	8512 (5274, 11,207)	10,584 (7849, 14,560)	13,070 (9208, 16,646)	.0001
Haemoglobin (g/dl)	142	11.30 (10.40, 12.60)	11.10 (10.00, 12.20)	11.25 (10.20, 12.50)	.2864
Platelets (×10^3/mm^3)	142	29.80 (23.25, 37.25)	30.70 (25.20, 40.20)	23.30 (15.45, 31.83)	.0005
ESR (mm/h)	115	71.0 (55.0, 105.0)	88.5 (63.8, 113.0)	68.5 (38.5, 97.5)	.1716
CRP (mg/dl)	142	9.54 (4.13, 14.60)	8.53 (3.85, 16.28)	14.42 (9.29, 20.24)	.0017
Total protein (g/dl)	142	7.10 (6.60, 7.60)	6.95 (6.63, 7.40)	6.65 (5.80, 7.08)	.0009
AST (U/l)	142	39.0 (27.5, 60.5)	50.0 (32.0, 81.0)	75.5 (43.3, 106.0)	.0002
ALT (U/l)	142	41.0 (19.0, 70.5)	50.0 (20.0, 79.5)	58.5 (31.3, 90.3)	.1929
γ-GTP (U/l)	139	45.0 (24.0, 123.0)	60.0 (26.5, 122.8)	71.0 (28.0, 127.0)	.6615
LDH (U/l)	142	342.0 (216.5, 492.5)	423.0 (335.5, 626.5)	557.0 (442.0, 987.8)	<.0001
Creatinine (mg/dl)	142	0.580 (0.500, 0.720)	0.600 (0.490, 0.760)	0.580 (0.470, 0.770)	.9849
IgG (mg/dl)	123	1291 (967, 1604)	1283 (1177, 1783)	1319 (1122, 1637)	.4563
Ferritin (ng/ml)	142	1531 (801, 2700)	4169 (1996, 9924)	13,472 (4710, 31,297)	<.0001
RF positive[a]	138	6 (12.8)	1 (2.7)	4 (7.1)	.3338
ANA positive[a]	141	7 (14.6)	3 (8.3)	11 (19.3)	.4648

The median and 25th and 75th percentiles in parenthesis are shown.
[a]Number of patients and (%).

mPSL pulse therapy ($p<.0001$), cyclosporine ($p<.0001$), immunosuppressants other than CIs and MTX ($p=.0465$), biological agents ($p=.0039$), anti-TNF drugs ($p=.0107$), tocilizumab ($p=.0465$), and plasma exchange ($p=.0247$) showed a significant increase with severity (Table 4). Biological agents were used in 4.1%, 10.8%, and 23.2% of patients in the mild, moderate, and severe groups, respectively (Table 4). On comparison among groups classified by mPSS, frequencies of mPSL pulse therapy ($p=.0418$) and cyclosporine ($p=.0139$) showed a correlation with increased activity, but there was no difference in the use of biological agents among the low, moderate, and high groups (Supplementary Table S4). The percentage of patients treated only with PSL correlated with severity classification (61.2%, 48.6%, and 12.5% in the mild, moderate, and severe groups, respectively, Table 4), but not with the mPSS group (44.4%, 45.5%, and 26.5%, in the low, moderate, and high groups, respectively, Supplementary Table S4).

All-cause and AOSD-related mortality and drug-free remission

Eight patients died during the observation period; however, three of them were not AOSD-related fatal cases (two patients from subarachnoid haemorrhage and one patient from breast cancer). The causes of death in other patients were pneumonia (two patients), sepsis, sepsis with pneumocystis pneumonia and aspergillosis, and cytomegalovirus infection. Among them, four patients were classified into the severe group and one patient in the moderate group according to the severity

Table 4. Treatment regimens.

	Severity classification			
	Mild ($n = 49$)	Moderate ($n = 37$)	Severe ($n = 56$)	p value
PSL	49 (100)	37 (100)	56 (100)	1.0000
Maximal dose (mg/day)[a]	39.5 ± 15.1	43.9 ± 14.7	53.9 ± 20.6	.0025
mPSL pulse therapy	2 (4.1)	6 (16.2)	32 (57.1)	<.0001
MTX	11 (22.4)	5 (13.5)	13 (23.2)	.8900
Cyclosporine	9 (18.4)	17 (45.9)	42 (75.0)	<.0001
Tacrolimus	2 (4.1)	2 (5.4)	3 (5.4)	.7674
Other immunosuppressants[b]	0 (0.0)	1 (2.7)	4 (7.1)	.0465
Biological agents	2 (4.1)	4 (10.8)	13 (23.2)	.0039
Anti-TNF drugs	0 (0.0)	1 (2.7)	6 (10.7)	.0107
Tocilizumab	2 (4.1)	4 (10.8)	9 (16.1)	.0465
Plasma exchange	0 (0.0)	0 (0.0)	4 (7.1)	.0247
PSL only	30 (61.2)	18 (48.6)	7 (12.5)	<.0001
PSL + MTX	9 (18.4)	1 (2.7)	6 (10.7)	.2415
PSL + CIs	8 (16.3)	14 (37.8)	36 (64.3)	<.0001
PSL + MTX + CIs	2 (4.1)	4 (10.8)	7 (12.5)	.1395

The number of patients and percentages in (%).
[a]Mean and standard deviation,
[b]azathioprine 1 in the moderate group; intravenous cyclophosphamide 2, azathioprine 1, and mizoribine 1 in the severe group.

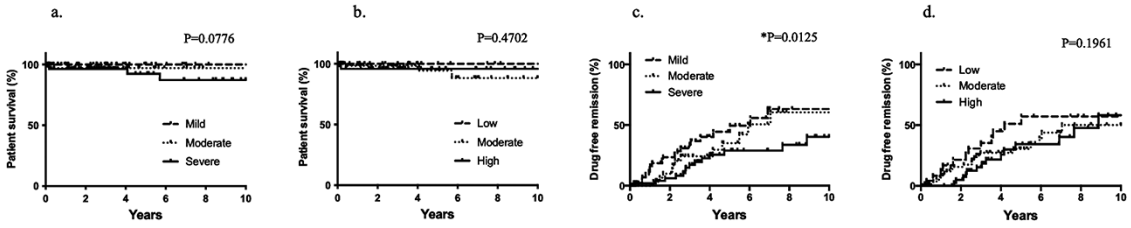

Figure 2. Survival and drug-free remission of patients with AOSD. (a) AOSD-related survival of groups classified by severity classification. (b) AOSD-related survival of groups classified by mPSS. (c) Time course of drug-free remission in groups classified by severity classification. Log-rank test for trend shows a significant difference among these groups ($p = .0125$). (d) Time course of drug-free remission in groups classified by mPSS.

classification. AOSD-related survival was not significantly different in these groups but that of the severe group tended to decrease, as per the log-rank test for trend [$p = .0776$, Figure 2(a)]. Fatal patients in the severe group showed pleuritis (three patients), MAS (two patients), and DIC (one patient), with high levels of ferritin and corticosteroid refractoriness. On analysis of groups classified by mPSS, two fatal patients were classified into the high group and three into the moderate group. The AOSD-related survival was not different among the three groups [$p = .4702$, Figure 2(b)]. These data suggested that severity classification corresponded more to fatality than mPSS.

Forty-six patients achieved drug-free remission during the follow-up period. As shown in Figure 2(c), there was a trend between severity classification and the drug-free remission rate ($p = .0125$). The 5-year drug-free remission rates in the mild, moderate, and severe groups were 49.5%, 35.1%, and 28.9%, respectively. However, the time course of drug-free remission was not significantly different among groups classified by mPSS [$p = .1961$, Figure 2(d)]. The 5-year drug-free remission rates in the low, moderate, and high groups were 51.1%, 30.5%, and 34.3%, respectively. Four patients (two patients in the severe group and two patients in the moderate group by severity classification; one patient in the high group, one patient in the moderate group, and two patients in the low group by mPSS) out of 46 showed a recurrence after cessation of treatment. These results indicate that severity classification is more useful for predicting drug-free remission than mPSS in this cohort.

Discussion

In this study, we investigated the usefulness of severity classification in predicting the prognosis of patients with AOSD. Our results revealed that the classification correlated with the achievement of drug-free remission and that AOSD-related survival tended to be reduced in the severe group; however, mPSS classification was not associated with prognosis or drug-free remission. Thus, the severity classification of AOSD was more useful than mPSS for predicting prognosis and drug-free remission in this cohort.

Although understanding of the pathogenesis and treatment of the disease has evolved, the disease course and the prognosis of AOSD are difficult to predict especially at the time of diagnosis and initial treatment. It is not clear whether the severity or activity of the disease in the initial course is associated with long-term outcomes. Therefore, it is noteworthy that the severity classification could be used as a guide for the treatment and predicting long-term outcomes. Several studies have investigated the prognosis of AOSD and showed that various clinical factors, including MAS, interstitial lung disease, AOSD complications, high CRP, high ferritin, systemic score, and elderly onset, were associated with poor survival or unfavourable disease course [16–22]. Regarding survival, MAS was the most significant factor in previous studies [16, 17]. In addition, patients who fulfilled the classification criteria of MAS, which were developed for patients with systemic juvenile inflammatory arthritis [29], showed a poorer prognosis [30]. It was shown that AOSD-related

complications, including MAS, kidney failure, and myocarditis, also have a strong association with mortality [16].

In the current analysis, 16 out of 18 patients who showed MAS were classified into the severe group because MAS was scored 2 and high serum ferritin that is usually observed with MAS was scored 1 in this system. This scoring system emphasises on the complications as it includes MAS, DIC, and serositis as components, and these scores summed up to 5 (out of a maximum of 9). As MAS and DIC, uncommon complications, were weighted to 2 points, and consequently the distribution of patients showed a non-normal pattern, this classification may be powerful in distinguishing severe patients with these complications. Due to the very low AOSD-related mortality rate in our population (5 patients, 3.5%), AOSD-related survival was not statistically different among mild, moderate, and severe groups. However, it is suggested that patients in the severe group may be at a risk of poor prognosis, because four fatal cases were classified into the severe group, whereas two patients were classified into the high group by mPSS.

On the other hand, mPSS includes 3 complications (pleuritis, pericarditis, and pneumonitis) and six symptoms (fever, evanescent rashes, sore throat, arthritis, myalgia, and lymphadenopathy) out of 12 constituent items. This indicates that AOSD-specific major symptoms weigh higher than complications in mPSS and that MAS is not included as a constituent. In the present study, although the frequency of major AOSD symptoms correlated with the classification by mPSS, MAS and DIC showed no difference among the high, moderate, and low groups. Serum ferritin levels were higher in the severe group (classified by severity classification) as well as the high activity group (classified by mPSS), but the difference was relatively smaller in the latter. Ruscitti *et al.* reported that the systemic score was associated with prognosis and that patients with a systemic score $\geq$7 (corresponding to the high group in this study) showed poorer prognosis [16]. However, the odds ratio was relatively lower than that of AOSD-related complications (1.49 and 33.52, respectively). The discordance between this report and the current study might have been due to different clinical features, especially AOSD-related complications and patient survival. As indicated before, the mortality rate was very low, and it was difficult to evaluate the contributing factors.

In addition to survival, we investigated the time course of drug-free remission as a marker of long-term outcomes. This may be an important and ultimate goal for the patients. The drug-free remission rate was lower in the severe group according to severity classification, whereas it was not different among groups stratified by mPSS. These data further support the usefulness of severity classification for predicting outcomes. Previous studies investigated the clinical factors associated with non-survival outcomes, including relapse and the monophasic disease pattern [18, 21, 31, 32]. Polyarthritis, lymphadenopathy, MAS, higher levels of LDH or erythrocyte sedimentation rate (ESR), intensity of the initial therapy, and initial corticosteroid dose were reported as related factors. However, no studies have analysed the outcomes by using a termination of therapy. This study showed that drug-free remission was an achievable goal for many patients with AOSD and that its possibility may be predicted by using severity classification in the initial phase. Furthermore, it was suggested that clinical factors related to good survival and drug-free remission were common.

Biological agents, especially anti-IL-1 and anti-IL-6 drugs are more frequently used to treat patients with refractory systemic or articular symptoms of AOSD; however, tocilizumab, anti-IL-6 receptor antibody, and anti-TNF agents have been used in Japan [9, 12, 13, 33–35]. It has been reported that biological agents were used due to inadequate response to corticosteroids and/or anti-rheumatic drugs, the sparing effect of corticosteroids, and MAS [36]. Plasma exchange was performed in patients with severe complications, including MAS and thrombotic thrombocytopenic purpura [37, 38]. The current study suggests that patients classified in the severe group may require advanced therapy in the course of treatment, because biological agents and plasma exchange were more frequently used in the severe group. In contrast, the percentage of patients treated only with corticosteroids was higher in the mild group. Thus, these findings suggest that severity classification could be a guide for choosing advanced therapies.

There are several potential limitations in the present study. Data were not extracted from a compulsory disease registry but from self-reported information that may be prone to bias. There were fewer fatal cases in this study compared to previous reports that may be a possible bias for analysing prognostic factors. In addition, the frequency of complications may differ between this study and previous studies, which could induce different results. For example, DIC was frequent, but pneumonitis was rare in our cohort. Finally, although drug-free remission was an important parameter in this analysis, the decision to reduce or terminate therapeutic drugs depended on the attending physician. It is well known that AOSD patients frequently relapse, even after the cessation of corticosteroid treatment and some patients were reported to have disease recurrence in this study. Therefore, a longer observation period may be necessary to analyse drug-free remission.

In conclusion, the severity classification of AOSD is more useful than mPSS for predicting prognosis and drug-free remission in Japanese patients with AOSD. A prospective large-scale study is necessary to confirm our results.

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Supplementary data

Supplementary data is available at *Modern Rheumatology* online.

Conflict of interest

Y.K. received a consultation fee from Amgen, M.I. received a royalty from Chugai, and Y.T. received a speaker's fee from Chugai.

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