
Association between fever pattern and clinical manifestations of adult-onset Still's disease: unbiased analysis using hierarchical clustering

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ABSTRACT

Objective. To perform unbiased analysis of fever patterns and to investigate their association with clinical manifestations and outcome of patients with adult-onset Still's disease (AOSD).

Methods. AOSD patients who were treated as in-patients from 2004 through 2015 were grouped according to 24-hour body temperature (BT) by hierarchical clustering using a Euclidean distance metric with complete linkage. The clinical and laboratory characteristics of the groups were then examined.

Results. Hierarchical clustering partitioned 70 AOSD patients into three distinct groups. Group 1 (n=14) had the highest mean BT ($38.1 \pm 0.4^\circ\text{C}$) and the widest variation in BT ($2.7 \pm 0.9^\circ\text{C}$). Group 2 (n=35) had a lower mean BT ($37.4 \pm 0.3^\circ\text{C}$) and a smaller variation ($2.1 \pm 0.7^\circ\text{C}$). Group 3 (n=21) had the lowest mean BT ($36.7 \pm 0.3^\circ\text{C}$) and the smallest variation ($1.5 \pm 0.6^\circ\text{C}$). Clinical features and extent of organ involvement did not differ significantly between groups. However, Group 1 had lower platelet counts and higher lactate dehydrogenase, ferritin levels, and prothrombin time than the other groups. In addition, Group 1 exhibited higher risk of having a macrophage activation syndrome (MAS) and tended to require more intense treatment with corticosteroids and immunosuppressant to achieve clinical remission as compared to other groups.

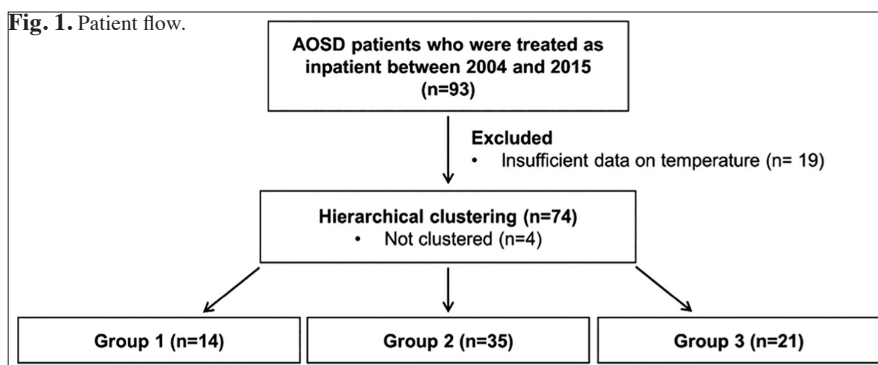
Conclusion. Hierarchical clustering identified three distinct fever patterns in patients with AOSD. Higher BT was associated with wider variations in diurnal temperature, higher risk of developing MAS, more intense treatment, and longer time to clinical remission, suggesting that fever pattern is a prognostic factor for AOSD.

Introduction

Adult onset Still's disease (AOSD) is a systemic inflammatory febrile disease characterised by high fever, arthralgia and arthritis, a salmon pink rash, lymphadenopathy, and serositis in a setting of elevated serum inflammatory markers, and extremely high serum ferritin levels (1, 2). AOSD can be self-limited with a single episode (monocyclic course), recurrent with multiple flares separated by remission (polycyclic course) or persistent with polyarthritis rather than systemic inflammation (chronic course) (3). In some AOSD patients, macrophage activation syndrome (MAS) or other life-threatening complications such as thrombotic thrombocytopenic purpura and acute respiratory distress syndrome, may occur (4-6).

Classically, the fever associated with AOSD is intermittent with a quotidian or double-quotidian pattern, in which body temperature (BT) falls to the normal between fever spikes (7). However, a significant subset of AOSD patients exhibit persistently high fever, with little temperature fluctuation (8). Since fever is a dynamic result of pyogenic and antipyretic mechanisms, the distinct fever pattern might reflect the underlying immune dysregulation and also be associated with unique clinical features and prognosis of AOSD (9). This possibility is supported by the observation that AOSD patients who develop MAS exhibit sustained fever pattern rather than characteristic remitting-spiking temperature curves (10, 11). Ruscitti *et al.* showed that systemic score, which included the presence of fever as one of 12 AOSD manifestations, was associated with increased mortality of AOSD patients (12), but the fever pattern has not been studied yet as a prognostic factor of AOSD.

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Fig. 1. Patient flow.

To minimise subjective bias, we first analysed the fever patterns of 70 patients with AOSD using an unsupervised clustering method and then assessed whether fever pattern was associated with distinct clinical characteristics and outcome of AOSD patients.

Materials and methods

Patients and data collection

Patients with AOSD, who were treated as inpatients at Seoul National University Hospital from 2004 through 2015, were enrolled. AOSD was diagnosed according to the Yamaguchi criteria (13). Information about demographics, clinical and laboratory features, presence of comorbidities at the time of diagnosis, treatment regimens, and long-term disease course were ascertained by reviewing electronic medical records.

Systemic score was obtained on a scale ranging from 0 to 12, with 1 point awarded for each of the follow-

ing symptoms: fever, typical rash, sore throat, lymphadenopathy, leukocyte $\geq 15,000/\text{mm}^2$, myalgia, abdominal pain, hepatomegaly, splenomegaly, pneumonia, pleuritis, and pericarditis (8). Risk of having a MAS was estimated in HScore using the online calculator (saintantoine.aphp.fr/score) (14). In regard to the long-term clinical course, patients were classified into four groups; monocyclic, polycyclic, chronic course and AOSD-related death (3). The study was approved by the Institutional Review Board of the Seoul National University Hospital. The need for informed consent was waived as the study involved minimum risk due to its retrospective nature and no identifiable information was used.

Analysis of fever pattern

BT was retrieved from electronic vital-sign sheets. BT on Day 1 was omitted from the analysis since many of the data points were missing. BT was

noted at six time points (*i.e.*, 0, 5, 9, 13, 15, and 21 h) during a 24 hour period on Days 2, 3 and 4 of hospitalisation. Missing BT values at specific time points were replaced with a mean temperature value (calculated from 2 h before to 2 h after the time point) or imputed via cubic spline interpolation (15). Fever was defined as an axillary temperature $>37.2^\circ\text{C}$ or as an oral temperature $>37.8^\circ\text{C}$.

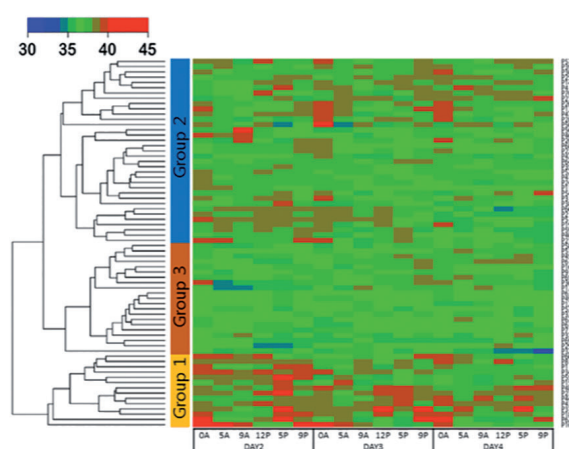
Hierarchical clustering

Samples were clustered using a Euclidean distance metric with complete linkage. The optimal number of clusters was determined by the KL index as previously described (16). A heatmap and dendrogram for fever curves were generated using R software.

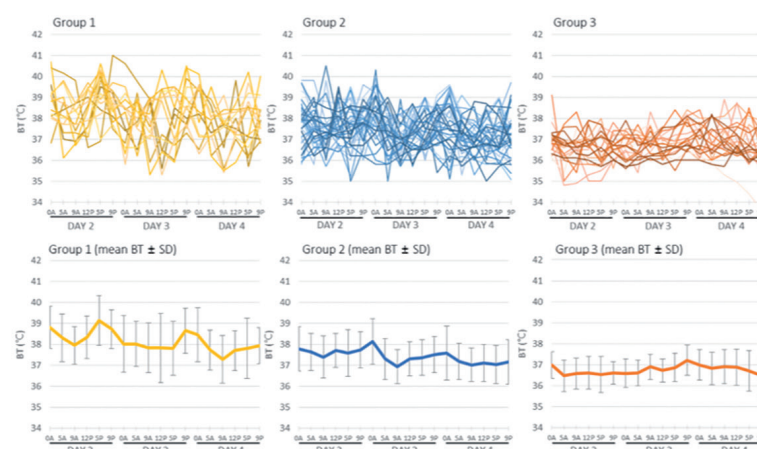
Statistical analysis

Continuous variables (normally distributed) were expressed as the mean \pm standard deviation (SD) and groups were compared using Student's t-test or analysis of variance, followed by post-hoc analyses with Bonferroni correction. Variables not following a normal distribution were expressed as the median \pm interquartile range (IQR) and groups were compared using the Mann-Whitney U test or Kruskal-Wallis test with Dunn's multiple test, as appropriate. The Chi-square or Fisher's exact test was used to compare categorical variables between groups. Logistic

A. Heatmap



B. Individual temperature curves

**Fig. 2.** Hierarchical cluster analysis of fever pattern.

(A) Seventy patients with AOSD were assigned to three distinct groups. The clustering is presented as a heat map and dendrogram. The bar code (top left) represents a colour temperature scale. (B) Individual temperature curves (upper panels) and mean body temperature (lower panels) according to three fever patterns.

regression analysis was performed to compare prognosis of AOSD patients according to fever pattern. All analyses were performed using IBM SPSS (statistics version 22, Chicago, IL, USA). A p value <0.05 was considered statistically significant.

Results

Baseline characteristics of patients

We identified 93 patients with AOSD who were treated as inpatients from 2004 through 2015. Of these, 19 with incomplete medical records were excluded. Hierarchical clustering partitioned 70 of the remaining 74 patients into three distinct groups. The four patients who could not be clustered were excluded from further analyses (Fig. 1). The mean age of the patients was 44.5 ± 17.3 years. The median follow-up duration was 17 [6–51] months.

Fever pattern

Group 1 ($n=14$) had the highest mean BT ($38.1 \pm 0.4^\circ\text{C}$) and the widest variation in BT ($2.7 \pm 0.9^\circ\text{C}$). Group 2 ($n=35$) had a lower mean BT ($37.4 \pm 0.3^\circ\text{C}$) and a narrower variation in BT ($2.1 \pm 0.7^\circ\text{C}$). Group 3 ($n=21$) had the lowest mean BT ($36.7 \pm 0.3^\circ\text{C}$) and the narrowest variation in BT ($1.5 \pm 0.6^\circ\text{C}$) (Fig. 2, panel A and Table I).

In Groups 1 and 2, fever spiked in late afternoon or early evening. The lowest BT was observed in the early morning (Fig. 2, panel B). The majority of patients (78.6%) became afebrile at least once a day. Interestingly, only 6 (42.9%) of 14 patients in Group 1 regained a normal temperature at least once during the day, whereas 82.9% of patients in Group 2 and 95.2% in Group 3 did so (Table I).

Clinical and laboratory features according to fever pattern

There were no differences between the groups in terms of age, sex, and comorbidities (Table I). The prevalence of typical AOSD features (e.g., arthritis, skin rash, sore throat, lymphadenopathy, and hepatosplenomegaly) did not differ between groups (Table II). Furthermore, clinical features such as aseptic meningitis and serositis did not differ. Only the prevalence of lung

Table I. Baseline characteristics of patients with AOSD according to fever pattern.

	Group 1 ($n=14$)	Group 2 ($n=35$)	Group 3 ($n=21$)	p value
Fever	14 (100)	35 (100)	21 (100)	1.000
Mean peak BT, $^\circ\text{C}$	40.0 ± 0.5	39.2 ± 0.6	38.0 ± 0.6	<0.001
Mean BT, $^\circ\text{C}$	38.1 ± 0.4	37.4 ± 0.3	36.7 ± 0.3	<0.001
Daily BT variation, $^\circ\text{C}$	2.7 ± 0.9	2.1 ± 0.7	1.5 ± 0.6	<0.001
Normal BT during day	6 (42.9)	29 (82.9)	20 (95.2)	<0.001
Female gender, n (%)	10 (71.4)	22 (62.9)	17 (81.0)	0.404
Age, years	38.4 ± 14.7	47.5 ± 16.8	43.6 ± 19.1	0.240
Diabetes mellitus, n (%)	0 (0)	5 (14.3)	0 (0)	0.114
Hypertension, n (%)	0 (0)	6 (17.1)	2 (9.5)	0.290
Cancer, n (%)	0 (0)	0 (0)	1 (4.8)	0.500
Follow-up, month	18 [4 - 68]	20 [6 - 50]	14 [5 - 51]	0.668
Clinical course, n (%)				0.429
Monocyclic course	5 (35.7)	21 (60.0)	8 (38.1)	
Polycyclic course	7 (50.0)	10 (28.6)	10 (47.6)	
Chronic course	2 (14.3)	4 (11.4)	3 (14.3)	
Death*	0 (0)	1 (2.9)	1 (4.8)	
AOSD-related death	0 (0)	0 (0)	0 (0)	

Results are in mean \pm SD, median [IQR], or n (%).

AOSD, adult-onset Still's disease; BT, body temperature.

*Cause of death: Infective endocarditis (Group 2), dilated cardiomyopathy (Group 3)

involvement (e.g., pneumonitis) differed between the groups ($p=0.014$), with a higher prevalence in Group 1 (28.6%) than in Group 2 (2.9%) or 3 (19%). There were no differences in leukocyte counts, haemoglobin levels, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) levels. However, Group 1 had lower platelet counts and higher lactate dehydrogenase (LDH), ferritin levels, and prothrombin time-International Normalised Ratio (PT-INR) than the other two groups (Table II).

Group 1 had increased risk of having a reactive haemophagocytic syndrome (RHS) or MAS than Group 2 (HScore: 122.4 ± 29.0 vs. 84.7 ± 42.7 , $p=0.039$) and Group 3 (HScore: vs. 83.5 ± 53.8 , $p=0.019$). The systemic score, which measures the extent of organ involvement in AOSD, tended to be higher in Group 1 (6.4 ± 2.1) than Group 2 (5.2 ± 1.6) or Group 3 (5.7 ± 1.7) ($p=0.101$). The proportion of the patients who had systemic score ≥ 7 was higher in Group 1 than Group 2 (50.0% vs. 20.0%, $p=0.036$) and tended to be higher than Group 3 (vs. 28.6%, $p=0.198$).

Treatment and outcome according to fever pattern

The majority of patients (95.7%) received corticosteroids. In addition,

53% of patients required conventional or biologic DMARDs. Patients in Group 1 tended to require a higher cumulative corticosteroid dose. In addition, more patients in Group 1 received cyclophosphamide and required three or more DMARDs. Moreover, among the biologic DMARDs, tocilizumab was more often administered in Group 1 than the other groups (Table III).

Overall, the outcome of AOSD patients was good. Of the 70 patients examined, two (2.9%) died during the follow-up period; one patient in Group 2 died of infective endocarditis and one patient in Group 3 died of heart failure. There was no AOSD-related death in all three groups. Two of the 70 AOSD patients (2.9%) had MAS, and no difference was observed in the rate of MAS between the groups (Table II). The long-term clinical course categorised by monocyclic, polycyclic and chronic course did not differ between the groups (Table I).

Logistic regression analysis on prognosis according to fever pattern

We compared the prognosis of AOSD between three groups according to the fever patterns by using logistic regression analysis. Considering the low event number of MAS or AOSD-related death, we performed regression analysis using systemic score and

Table II. Clinical and laboratory features of the AOSD patients according to fever pattern.

	Group 1 (n=14)	Group 2 (n=35)	Group 3 (n=21)	p value
Arthritis	5 (35.7)	17 (48.6)	12 (57.1)	0.464
Rash	12 (85.7)	27 (77.1)	18 (85.7)	0.716
Sore throat	9 (64.3)	20 (57.1)	10 (47.6)	0.626
Lymphadenopathy	9 (64.3)	17 (48.6)	9 (42.9)	0.493
Splenomegaly	9 (64.3)	15 (42.9)	9 (42.9)	0.393
Hepatomegaly	5 (35.7)	11 (31.4)	5 (23.8)	0.788
Myalgia	8 (57.1)	23 (65.7)	15 (71.4)	0.712
Pericardial effusion	2 (14.3)	2 (5.7)	1 (4.8)	0.583
Pleural effusion	4 (28.6)	7 (20)	4 (19)	0.799
Pneumonitis	4 (28.6)	1 (2.9)	4 (19)	0.014
Leukocyte, $\times 10^3/\mu\text{L}$	18.3 \pm 14.8	13.9 \pm 7.5	19.5 \pm 12.2	0.139
ANC, $\times 10^3/\mu\text{L}$	15.8 \pm 14.4	11.7 \pm 6.9	16.3 \pm 10.6	0.178
Hemoglobin, g/dL	11 \pm 1.7	11.2 \pm 1.6	10.2 \pm 1.4	0.077
Platelets, $\times 10^3/\mu\text{L}$	198.9 \pm 68	321.8 \pm 138.8	298 \pm 186	0.031
ESR, mm/hr	81 [58 - 96]	88 [70 - 97]	95 [65 - 118]	0.398
CRP, mg/dL	18 [8 - 26]	13 [7 - 18]	14 [9 - 25]	0.350
AST, IU/L	155 [79 - 277]	58 [38 - 142]	79 [43 - 237]	0.059
ALT, IU/L	116 [63 - 207]	77 [26 - 142]	83 [32 - 166]	0.424
LDH, IU/L	752 [264 - 1331]	338 [203 - 1436]	507 [218 - 1875]	0.002
Ferritin, ug/mL	9160 [5186 - 40545]	2187 [746 - 5669]	4401 [1360 - 6873]	0.013
PT INR	1.21 [1.15 - 1.31]	1.10 [1.08 - 1.21]	1.07 [1.03 - 1.20]	0.038
aPTT, sec	36.9 \pm 7.2	37.5 \pm 9	34.8 \pm 8.9	0.558
Fibrinogen, mg/dL	487 \pm 248	549 \pm 198	454 \pm 201	0.292
Anti-nuclear antibody	1/14 (7.1)	7/33 (21.2)	7/21 (33.3)	0.185
ANA titer >1:80	0 (0)	0 (0)	3/21 (14.3)	0.026
Rheumatoid factor	1/14 (7.1)	3/33 (9.1)	1/20 (5)	1.000
Systemic score*	6.4 \pm 2.1	5.2 \pm 1.6	5.7 \pm 1.7	0.101
Systemic score ≥ 7	7 (50)	7 (20)	6 (28.6)	0.110
HScore [†]	122.4 \pm 29.0	84.7 \pm 42.7	83.5 \pm 53.8	0.019
MAS	1 (7.1)	0 (0)	1 (4.8)	0.328

Results are in mean \pm SD, median [IQR], or n (%).

ANA: anti-nuclear antibody; ANC: absolute neutrophil count; ALT: alanine transaminase; AOSD: adult-onset Still's disease; AST: aspartate transaminase; BT: body temperature; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase; MAS: macrophage activation syndrome; PT INR: prothrombin time international normalised ratio; aPTT: activated partial thromboplastin time.

*Systemic score ranged from 0 to 12, with 1 point awarded for each of the following symptoms: fever, typical rash, sore throat, lymphadenopathy, leukocytosis $\geq 15,000/\text{mm}^3$, myalgia, abdominal pain, hepatomegaly, splenomegaly, pneumonia, pleuritis, and pericarditis.

[†]HScore estimates the risk of developing macrophage activation syndrome (<http://saintantoine.aphp.fr/score/>).

long-term clinical course as outcome variables. We used the validated systemic score cut-off value of 7 to predict AOSD-related death as previously reported (12). Therefore, outcome variables were dichotomised as systemic score ≥ 7 versus < 7 and one disease course versus the others. As Group 2 had the largest number of patients, it was set as the reference group. The patients in Group 1 had 4-fold increased risk of having systemic score ≥ 7 than Group 2. Regarding the long-term clinical course, Group 1 patients tended to have more polycyclic and chronic course than Group 2, but this difference was not statistically significant (Supplementary Table I).

Discussion

To the best of our knowledge, this study is the first to use hierarchical clustering to investigate fever patterns in patients with AOSD. This approach identified three distinct fever patterns. Patients with higher BT experienced greater daily fluctuations in temperature, whereas those with lower mean temperature tended to show smaller variations in diurnal temperature, suggesting an association between the degree of fever and temperature fluctuation. Patients with higher BT had higher HScore and higher systemic score, tended to require more intense treatment, and took longer time to achieve clinical remission. Therefore, the fever

pattern itself might be an independent prognostic factor of AOSD.

Physiologically, BT is regulated around a set point by a thermoregulatory unit in the hypothalamus and follows a diurnal pattern (9, 17, 18). Endogenous antipyretics such as adrenocorticotrophic hormone and cortisol rise in the early morning and fall in the evening (19). Accordingly, the lowest and highest BT are observed in early morning and late evening, respectively (17). During inflammatory responses initiated by infection or autoimmune disease, inflammatory cytokines increase the temperature set point, leading to a febrile response (20, 21). Since the endogenous antipyretic mechanism is still effective, the fever curves associated with most infectious diseases or systemic inflammatory diseases follow a diurnal pattern, although BT rarely falls back to the normal range (22). By contrast, the BT of the majority of AOSD patients remained within the normal range in the morning despite high fever spikes in evening. The classic remitting high spiking fever was observed in 78.6% of patients. Thus, this quotidian fever pattern remains a key clinical feature of AOSD (23, 24).

To our surprise, fever patterns were not associated with the particular clinical features of AOSD (*i.e.*, arthritis, skin rash, lymph node enlargement, leukocytosis, or CRP elevation). However, higher fever spikes tended to be associated with higher ferritin, higher LDH levels, prolonged PT-INR and lower platelet counts, all of which resemble the laboratory characteristics of MAS (25, 26). In addition, only 42.9% of patients in Group 1 showed remitting temperature as compared to 82.9% in Group 2 and 95.2% in Group 3. In line with this, patients with higher fever spikes (Group 1) also had higher HScore, which estimates the risk of having MAS in patients with rheumatic diseases (14).

Interestingly, LDH level was the highest in Group 1. Although LDH level was not included in the final HScore model, LDH levels were higher in patients with hemophagocytic syndrome than those without it (14). Therefore, higher fever is associated with the

Table III. Treatment of the patients with AOSD according to fever pattern.

	Group 1 (n=14)	Group 2 (n=35)	Group 3 (n=21)	p-value
Cumulative CS, mg	5388 [1045-39358]	3335 [0-22603]	4223 [0-21838]	0.229
HCQ, n (%)	1 (7.1)	4 (11.4)	8 (38.1)	0.031
CYC, n (%)	1 (7.1)	1 (2.9)	1 (4.8)	0.793
Biologic DMARDs, n (%)	2 (14.3)	2 (5.7)	4 (19.0)	0.254
Tocilizumab	2 (14.3)	2 (5.7)	2 (9.5)	0.615
Abatacept	0 (0.0)	0 (0.0)	1 (4.8)	0.306
TNF inhibitor	0 (0.0)	0 (0.0)	1 (4.8)	0.306
Anakinra	0 (0.0)	0 (0.0)	0 (0.0)	-
No. of DMARD* ≥ 2 , n (%)	5 (36.0)	4 (11.0)	8 (38.0)	0.036
No. of DMARD* ≥ 3 , n (%)	4 (29.0)	1 (3.0)	4 (19.0)	0.014
Time to 1st remission [†] , days	108 [43-202]	68 [45-89]	79 [36-157]	0.446

Results are in mean \pm SD, median [IQR] or n (%).

AOSD: adult-onset Still's disease; CS: corticosteroids; HCQ: hydroxychloroquine; CYC: cyclophosphamide; DMARDs: disease-modifying anti-rheumatic drugs; TNF: tumor necrosis factor.

*Included methotrexate, sulfasalazine, leflunomide, azathioprine, cyclosporine and biologic DMARDs, and excluded HCQ and CYC.

[†]Remission is defined as the absence of clinical and laboratory evidence of inflammation.

higher LDH levels, higher HScore and so prognosis as well. By contrast, there was no significant difference in both leukocyte count and absolute neutrophil count (ANC) among the three groups, although Group 2 tended to have lower leukocyte count and ANC than the other two groups.

The positive rate of anti-nuclear antibody (ANA) in all patients included in this study was 22.1% (15/68), which was higher than 9.0 to 10.0 % in previous studies (27, 28). However, ANA titer of all patients in Group 1 and 2 were $\leq 1:80$ and three of 7 patients in Group 3 had high titer of ANA of 1:160. A higher frequency of ANA positivity (25.8%) was also reported in Japanese cohort of AOSD patients (29). However, there were no other signs or symptoms suggestive of connective tissue diseases in patients with positive ANA. The patients with higher fever tended to require a higher cumulative steroid dose and longer treatment duration to achieve remission. Although half of the patients in Group 1 had systemic score ≥ 7 (i.e. Group 1 was associated with 4-fold increased risk of having systemic score ≥ 7), which associated with higher risk of AOSD associated mortality, long-term clinical course did not differ between groups. In addition, AOSD patients in this study had overall good prognosis. Only two patients died of unrelated medical issues (infectious endocarditis and heart failure).

This might be explained by the fact that patients in Group 1 received more intensified treatment including tocilizumab. Of note, none of the patients received Interleukin (IL)-1 inhibitors due to a local regulatory limitation. Instead, tocilizumab was used in patients with profound systemic inflammatory response who did not respond adequately to corticosteroids alone or in combination with other DMARDs (30, 31). Taken together, the analysis of fever pattern might help to identify AOSD patients who are at risk of AOSD-related mortality and might need more intense treatment.

Cyclophosphamide could be an alternative to biologic DMARDs in refractory AOSD patients with MAS (32). In this study, three patients, in whom cytopenia progressed and ferritin level increased despite corticosteroid in combination with MTX and/or azathioprine therapy, were treated with oral cyclophosphamide (1.5~2 mg/kg/day). However, two of three patients did not improve and they were treated eventually with tocilizumab, suggesting that tocilizumab might be more effective than cyclophosphamide.

A strength of the current study is the introduction of hierarchical clustering in fever pattern analysis. This approach provides an unparalleled advantage for objective pattern analysis because it does not involve subjective interpretation of BT. However, this retrospective

study has several limitations. First, the number of enrolled patients was rather small for a more robust statistical analysis as it was a single centre study. Second, the effects of the antipyretic medications such as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) on BT were not investigated. Third, since only hospitalised AOSD patients were included, the present findings might not be generalisable to all AOSD patients. Fourth, glycosylated ferritin, which was more predictive of AOSD, was not measured. Last, but not least, further studies are needed to investigate the immunologic mechanism underlying quotidian fever patterns in AOSD.

In conclusion, hierarchical clustering analysis identified three distinct fever patterns in patients with AOSD. Higher temperature at the time of diagnosis was associated with higher risk of MAS or AOSD-related mortality, more intense treatment and a longer time to clinical remission. Thus, the fever pattern might be a prognostic factor for AOSD. A larger prospective study is needed to confirm these findings.

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