The Mid-Range of the Adjusted Level of Ferritin Can Predict the Chronic Course in Patients with Adult Onset Still's Disease

SANG-WON LEE, YONG-BEOM PARK, JUNG-SOO SONG, and SOO-KON LEE

ABSTRACT. ***Objective.*** To find a measure that can predict the disease course in patients with adult onset Still's disease (AOSD).

Methods. We retrospectively investigated the medical records of 71 hospitalized patients with AOSD. Patients were divided according to chronic and nonchronic disease course. The initial laboratory results were defined as those at the time of admission, the extremely deviated laboratory results as the highest or the lowest results, and the adjusted laboratory results as area under the curve divided by the days of hospitalization. All measures were compared and the odds ratio (OR) for the chronic disease pattern was assessed.

Results. The mean age was 39.7 ± 13.5 years and women accounted for 63 of the total 71 (88.7%). Thirty patients (42.3%) had self-limited disease, 9 (12.7%) intermittent disease, and 23 (32.4%) the chronic disease pattern (32.4%). Nine patients (12.7%) died. The initial levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and ferritin, the highest levels of lactate dehydrogenase (LDH) and ferritin, and the adjusted level of ferritin in patients with chronic disease were significantly higher than those with nonchronic disease. Among them, only the middle range of the adjusted ferritin level (784.1~4120.0 ng/ml) was found to have a significant predictive value for the chronic disease pattern (OR 81.7, p = 0.007).

Conclusion. A novel measure, the adjusted level of ferritin during the first hospitalization, might be useful to predict progression to chronic disease in patients with AOSD. (First Release Dec 1 2008; J Rheumatol 2009;36:156–62; doi:10.3899/jrheum.080537)

Key Indexing Terms:
ADULT ONSET STILL'S DISEASE FERRITIN DISEASE PROGRESSION

Adult onset Still's disease (AOSD) is a rare systemic inflammatory disease of unknown cause that is characterized by spiking high fever, typical rash, and arthralgia[1]. Since AOSD has diverse clinical presentations and mimics various other inflammatory diseases, the diagnosis might be established by exclusive criteria, and there was no consensus on its incidence and prevalence[1,2]. In addition, the clinical manifestations and outcomes of AOSD vary according to patient's geographic and ethnic background[3-5]. AOSD has 3 disease courses — self-limited, intermittent, and chronic disease patterns — and each affects about one-third of patients with AOSD[2,6-8]. Previous studies reported that patients with the chronic disease pattern generally exhibited more disability and worse prognosis than those with other patterns, and rash as well as polyarthritis at disease onset were predictors of the progression to the chronic disease pattern[6,7]. Also, it has been suggested that a level of ferritin that was increased by 5 times the normal upper limit of reference range was associated with progression to the chronic AOSD[9]. However, these predictive values for progression to chronic pattern had different significance in each study, suggesting the limitations of the small number of subjects due to the low incidence of AOSD, and geographical and ethnic differences.

We investigated the clinical manifestations, laboratory findings, treatment modality, and outcomes, compared those results according to disease course, and assessed a useful predictive measure for progression to the chronic disease pattern in patients with AOSD.

MATERIALS AND METHODS

Subjects. We retrospectively investigated the medical records of 71 patients (63 women, 8 men) who were admitted to Yonsei University Severance

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Hospital and Chung-Ang University Hospital, and diagnosed with AOSD from January 2000 through May 2007. All subjects fulfilled Yamaguchi's criteria for AOSD, composed of fever, arthralgia, typical rash, and leukocytosis as major criteria, and sore throat, lymphadenopathy and/or splenomegaly, deterioration in liver function, and negative rheumatoid factor and antinuclear antibody as minor criteria; more than 5 criteria including at least 2 major criteria are necessary for the diagnosis[1]. To exclude infectious disease or malignancy, in all subjects, cultures and serologic markers for bacteria, viruses, fungi, and mycobacterium, tuberculin skin test and Quantiferon tuberculosis gold tests, and computed tomography (CT) scans ranging from neck to abdomen were performed. Lag time was defined as the period between onset of symptom and diagnosis of AOSD, and followup time was defined as the period between diagnosis of AOSD and final visit to the outpatients' clinic. Patients with AOSD who were observed for less than 12 months were excluded. The approval of institutional review boards was obtained for our study.

Clinical manifestations. On admission, clinical manifestations including fever, typical rash, arthralgia or arthritis, myalgia, lymphadenopathy, sore throat, splenomegaly, hepatomegaly or abnormal liver function tests, abdominal pain, leukocytosis, pleuritis, pericarditis, pnemonitis, weight loss, and kidney involvement were also assessed. Pleuritis and lung parenchymal involvement were evaluated through chest radiograph or chest CT scan, and pericarditis and pulmonary hypertension were evaluated by echocardiography. Kidney involvement was defined as hematuria > 5 red blood cells per high-power field or proteinuria > 500 mg per 24 h on urinalysis more than 2 times. Out of 71 patients, 11 underwent skin biopsy, and 19 underwent lymph node biopsy. Bone marrow biopsy was performed in 28 patients and liver biopsy was performed in 8 patients. Medications administered for AOSD were defined as those from hospitalization to final visit. When a patient received intravenous (IV) glucocorticoid pulse therapy followed by oral high-dose glucocorticoid, only glucocorticoid pulse therapy was counted. High-dose glucocorticoid was defined as > 0.5 mg/kg.

Laboratory measures. White blood cell count, hemoglobin, platelet count, erythrocyte sedimentation rate (ESR), and levels of C-reactive protein (CRP), creatinine, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH) and ferritin were measured. The initial level of a measure was defined as the first laboratory result of blood tests measured on admission and the extremely deviated level of a measure as the highest or lowest laboratory result during hospitalization. We introduced a novel measure, the adjusted level of a measure, and defined it as the result of area under the curve (AUC) of accumulated results divided by the days of hospitalization. When a patient underwent blood tests 5 times during hospitalization, a result was carried forward to the last result, as shown in Figure 1. For instance, the result of a measure taken on Day 1 was applied to Days 2 and 3, when blood tests were not performed, and another result was measured on Day 4, leading to a tiered graph. When AUC obtained from the graph was divided by the total days of hospitalization, the mean value was defined as the adjusted level of a measure. All laboratory measures were improved within normal limits of each measure before patients were discharged; although the normal range of serum ferritin is different between men and women, since there were no differences in sex distribution between patients with chronic and nonchronic disease, we used an absolute ferritin level for the analysis, irrespective of sex. We distributed each measure into the 3 ranges, the high, middle, and low range, where one-third of patients were evenly included in each range.

Disease courses. Remission was defined as the absence of articular and systemic laboratory evidence of disease activity for at least 2 consecutive months. Self-limited pattern was characterized by a single episode of less than 1 year but more than 2 months' duration, followed by at least 1 year remission. Intermittent pattern was defined as recurrent flare less than 1 year and complete remission between flares. Chronic disease pattern was defined as at least 1 episode of active disease lasting longer than 1 year[2,8]. Expired patients were defined as those who were diagnosed with AOSD and died during first hospitalization, so they were not classified into any disease pattern. All subjects were divided into 2 groups according to disease course: the chronic and the nonchronic disease pattern (self-limited and intermittent patterns).

Statistical analysis. All statistical analyses were conducted using the SPSS package for Windows version 11.5 (SPSS Inc., Chicago, IL, USA). The levels of continuous variables were expressed as mean ± standard deviation. A chi-squared test was applied to determine the frequencies of sex distribution, clinical manifestations, and treatment modality among the groups. Significant differences in age, lag time, followup time, and laboratory results among the groups were examined by Mann-Whitney test. We used Spearman correlation to evaluate the correlations among the laboratory measures. The odds ratio (OR) of the measures with significant differences between the 2 patterns and correlations among one another, was assessed via the multivariate logistic regression test. The cutoff value for the prediction of progression to the chronic disease pattern was presumed using the receiver-operation characteristic curve. For all statistical evaluations of the results, $p < 0.05$ was considered to be statistically significant.

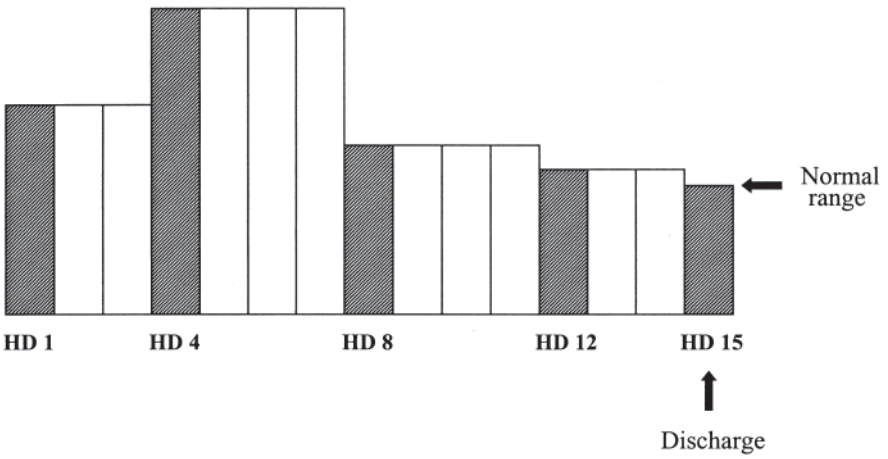

Figure 1. Definition of the adjusted level of laboratory measures. When a patient underwent blood tests 5 times during hospitalization, the result was carried forward to the last result. For instance, the result of a measurement on Day 1 was applied to Days 2 and 3, when blood tests were not performed, leading to a tiered graph. When area under the curve obtained from the graph (for 15 days) was divided by the total days of hospitalization, the mean value was defined as the adjusted level of a measure. HD: hospital day.

RESULTS

Patients' characteristics, clinical manifestations, disease courses, and biopsy findings. Table 1 provides the baseline characteristics of AOSD patients. The mean age of patients was 39.7 ± 13.5 (range 19–76) years, the mean lag time was 3.5 ± 7.5 (range 0–48) months, and the mean followup time was 38.1 ± 28.0 (range 12–94) months. The most common clinical manifestation was fever (100%), followed by typical rash (85.0%) and arthralgia (83.3%). Thirty out of the total 71 patients showed the self-limited disease pattern (42.3%), 9 the intermittent pattern (12.7%), and 23 the chronic pattern (32.4%). Nine patients died during the first hospitalization (12.7%). Disseminated intravascular coagulation (DIC) with cardiopulmonary shock was the most common cause of death (6 patients) and each of the remaining 3 patients had fulminant hepatitis, pulmonary hypertension, and intraperitoneal hemorrhage, respectively.

Superficial perivenular infiltration of inflammatory cells was the most common skin biopsy finding (10 out of 11 patients) and erythema nodosum was found in 1 patient. On lymph node biopsy, 13 out of 19 patients showed reactive hyperplasia, 5 dermatopathic lymphadenopathy, and 1 no abnormal finding. Nearly normal bone marrow biopsy findings were observed in 19 out of 28 patients, followed by myelofibrosis in 6, hemophagocytosis in 2, and panhypoplasia in 1 patient. Liver biopsy performed in 8 patients proved nonspecific hepatitis in 5 patients, and hemophagocytosis and histiocytosis in 2 patients, respectively.

Table 1. Characteristics, clinical manifestations disease course, and biopsy results in patients with adult onset Still's Disease (n = 71).

Characteristic	
Age, yrs	39.7 ± 13.5 (19–76)
Sex, F/M	63/8
Lag time, mo	3.5 ± 7.5 (0–48)
Followup time, mo	38.1 ± 28.0 (12–94)
Clinical manifestations, n (%)	
Fever	71 (100)
Arthralgia	60 (84.5)
Typical rash	59 (84.3)
Myalgia	50 (70.4)
Lymphadenopathy	48 (67.6)
Sore throat	41 (56.9)
Splenomegaly	26 (36.6)
Weight loss	23 (32.4)
Hepatomegaly	21 (29.6)
Abdominal pain	17 (23.9)
Kidney involvement	12 (16.9)
Pericarditis	10 (14.1)
Pleuritis	9 (15.0)
Lung involvement	5 (6.9)
Pulmonary hypertension	1 (1.4)
Disease course, n (%)	
Self-limited	30 (42.3)
Intermittent	9 (12.7)
Chronic	23 (32.4)
Death	9 (12.7)
Cause of death, n	
DIC with cardiopulmonary shock	6
Fulminant hepatitis	1
Pulmonary hypertension	1
Intraperitoneal hemorrhage	1

DIC: disseminated intravascular coagulation. Continuous variables are expressed as mean ± standard deviation.

Comparison of characteristics, clinical manifestations, initial treatment medications, and laboratory findings between nonsurvivors and survivors. There were no differences in age and sex, but nonsurvivors had a shorter lag period than survivors. Splenomegaly, hepatomegaly, and pleuritis were found more frequently in nonsurvivors than survivors. Nonsurvivors had taken relatively intensive treatment regimens, compared with survivors. There were no differences in initial and adjusted measures between the 2 groups. However, nonsurvivors had lower results in lowest hemoglobin, platelet count, and albumin than survivors.

Comparison of characteristics, clinical manifestations, and initial treatment medications between patients with chronic and nonchronic disease. We have defined the self-limited pattern as well as the intermittent pattern as the nonchronic disease pattern. In this comparison, we examined the 62 surviving patients with AOSD (9 patients died). There were no differences in age, sex, and lag time between the 2 patterns. Patients with the chronic disease pattern of AOSD had longer followup time, and they had pericarditis and pleuritis more frequently than those with nonchronic disease (significant findings, Table 2). However, there were no significant differences in the administered medications.

Comparison of initial, extremely deviated, and adjusted levels of laboratory results between patients with chronic and nonchronic disease. Table 3 shows initial, extremely deviated, and adjusted levels of laboratory results between patients with chronic and nonchronic disease. In patients with the chronic disease pattern, the mean initial level of ESR decreased, while mean levels of AST, ALT, and ferritin were increased significantly, compared with those with the nonchronic disease pattern. Patients with chronic disease showed significantly decreased platelet counts and albumin levels, and increased levels of creatinine, LDH, and ferritin compared with the nonchronic patients. In addition, patients with chronic disease had significantly lower mean adjusted level of ESR and platelet count, but higher mean adjusted level of ferritin compared with the nonchronic patients.

Correlations of laboratory measures between patients with chronic and nonchronic disease. We evaluated the correlations of laboratory measures that showed significant differences between the 2 disease patterns. The mean initial and adjusted levels of ESR, mean lowest and adjusted platelet counts, mean lowest levels of albumin, and mean highest levels of creatinine did not exhibit any significant correlations with other significant measures. By contrast, the mean adjusted level of ferritin, the initial levels of AST, ALT, and ferritin, and the highest levels of LDH and ferritin were significantly well correlated with one another.

Table 2. Comparison of characteristics, clinical manifestations, and initial treatments between patients with chronic and nonchronic disease.

Measure	Nonchronic, n = 39	Chronic, n = 23	p
Age, yrs	39.5 ± 13.8	41.3 ± 12.1	NS
Sex, M/F	4/35	3/20	NS
Days of first hospitalization, n	26.1 ± 8.4	29.2 ± 10.3	NS
Lag time, mo	4.9 ± 9.7	1.6 ± 1.7	NS
Followup time, mo	31.9 ± 23.7	48.3 ± 32.4	0.043
Clinical manifestations*, n (%)			
Fever	39 (100.0)	23 (100.0)	NS
Arthralgia	33 (84.6)	19 (82.6)	NS
Arthritis	31 (79.5)	18 (78.3)	NS
Typical rash	31 (79.5)	19 (82.6)	NS
Myalgia	27 (69.2)	15 (65.2)	NS
Lymphadenopathy	27 (69.2)	14 (60.9)	NS
Sore throat	23 (59.0)	11 (47.8)	NS
Splenomegaly	11 (28.2)	9 (39.1)	NS
Weight loss	12 (30.8)	6 (26.1)	NS
Hepatomegaly	9 (23.1)	6 (26.1)	NS
Abdominal pain	10 (25.7)	3 (13.0)	NS
Kidney involvement	6 (15.4)	3 (13.0)	NS
Pericarditis	2 (5.1)	6 (26.1)	0.017
Pleuritis	2 (5.1)	5 (21.7)	0.046
Lung involvement	5 (12.8)	0 (0)	NS
Treatment regimen†, n (%)			
Steroid pulse therapy	13 (33.3)	9 (39.1)	NS
High-dose steroid	15 (38.5)	8 (34.8)	NS
Low and moderate-dose steroid	11 (28.2)	4 (17.4)	NS
Methotrexate	7 (18.0)	6 (26.1)	NS
Cyclosporin A	11 (28.2)	3 (13.0)	NS
Cyclophosphamide	7 (18.0)	3 (13.0)	NS
Anti-TNF-α blockade	3 (7.7)	0 (0)	NS
Hydroxychloroquine	4 (10.3)	5 (21.7)	NS
NSAID	39 (100)	23 (100)	NS

* Clinical manifestations documented during the first hospitalization. † Medications administered during the first hospitalization. TNF: tumor necrosis factor; NSAID: nonsteroidal antiinflammatory drugs; NS: not significant. Continuous variables are expressed as mean ± standard deviation. For all statistical evaluations. $p < 0.05$ was considered statistically significant.

The measure that can predict the disease course in AOSD. Although the mean adjusted level of ferritin, the initial levels of AST, ALT, and ferritin, and the highest levels of LDH and ferritin showed significant differences between the 2 disease patterns and good correlations among those measures, only the mean adjusted level of ferritin was revealed as a significantly useful measure to predict the disease course in patients with AOSD. The middle range of the adjusted level of ferritin (784~4120 ng/ml) was found to be a significant predictor of progression to the chronic disease pattern (OR 81.715, 95% CI 3.241~2060.227, p = 0.007]. But its high range did not show any significance (Table 4).

Since initial ferritin level, highest ferritin level, and adjusted level of ferritin were obtained from the same patient, they could affect one another. When we analyzed measures except the initial and highest ferritin levels (initial AST, initial ALT, highest LDH, and adjusted ferritin level), we found that the adjusted level of ferritin also had a significant predictive value for progression to chronic disease in AOSD [OR 97.025, p = 0.002, 95% CI for Exp(B) = 5.328~1766.826].

DISCUSSION

We analyzed the clinical manifestations and laboratory results in order to investigate a measure for prediction of the progression to chronic disease in patients with AOSD, and found that a novel measure, the mid-range of the adjusted level of ferritin during the first hospitalization, might be useful to predict progression to chronic disease in patients with AOSD (Table 4). Similar to previous reports, systemic involvement including pericarditis and pleuritis was more frequently observed in our patients with the chronic disease pattern of AOSD, and several laboratory measures including the initial level of ferritin showed significant differences between the 2 patterns[6,7,9]. However, we did not find any significant association of the clinical and laboratory measures with progression to chronic disease, except the adjusted level of ferritin. Moreover, prognostic factors of the sys-

Table 3. Comparison of the initial, extremely deviated, and adjusted levels of laboratory results between patients with chronic and nonchronic disease.

Measure	Nonchronic, n = 39	Chronic, n = 23	p
Initial levels*			
ESR, mm/h	64.7 ± 35.6	43.3 ± 27.3	0.028
CRP, mg/dl	9.5 ± 5.9	7.2 ± 4.6	NS
WBC/mm^3	13,723.1 ± 7150.7	15,130.4 ± 10,731.6	NS
Hemoglobin, g/dl	11.0 ± 1.8	10.4 ± 1.6	NS
Platelet/mm^3	309,846.2 ± 133,288.5	239,695.7 ± 136,281.9	NS
Albumin, mg/dl	3.4 ± 0.5	3.3 ± 0.8	NS
Creatinine, mg/dl	0.8 ± 0.3	0.8 ± 0.2	NS
AST, IU/l	52.6 ± 25.9	309.5 ± 129.8	0.001
ALT, IU/l	38.6 ± 31.2	195.7 ± 53.0	0.001
LDH, IU/l	977.4 ± 73.6	1411.8 ± 257.1	NS
Ferritin, ng/ml	5,315.6 ± 1,119.3	18,845.9 ± 6,361.8	0.003
Extremely deviated levels†			
Highest ESR, mm/h	83.1 ± 34.0	67.2 ± 31.7	NS
Highest CRP, mg/dl	13.4 ± 8.3	9.7 ± 5.4	NS
Highest WBC/mm^3	24,929.0 ± 3,259.1	31,042.6 ± 7,309.1	NS
Lowest Hemoglobin, g/dl	9.0 ± 1.5	8.5 ± 1.3	NS
Lowest Platelet/mm^3	298,307.7 ± 479,394.6	136,173.9 ± 118,251.5	0.012
Lowest Albumin, mg/dl	2.8 ± 0.6	2.6 ± 0.7	0.045
Highest Creatinine, mg/dl	0.9 ± 0.3	1.2 ± 0.8	0.013
Highest AST, IU/l	350.8 ± 254.6	361.5 ± 376.2	NS
Highest ALT, IU/l	382.3 ± 279.2	361.5 ± 376.2	NS
Highest LDH, IU/l	1,314.9 ± 736.3	2,948.4 ± 3,254.4	0.020
Highest Ferritin, ng/ml	11,729.5 ± 15,164.9	29,428.5 ± 33,412.4	0.002
Adjusted levels††			
Adjusted ESR, mm/h	75.5 ± 31.1	54.3 ± 25.1	0.008
Adjusted CRP, mg/dl	6.6 ± 3.9	5.4 ± 3.4	NS
Adjusted WBC/mm^3	18,525.6 ± 10,342.4	19,622.0 ± 11,276.0	NS
Adjusted Hemoglobin, g/dl	10.1 ± 1.5	9.6 ± 1.4	NS
Adjusted Platelet/mm^3	308,692.3 ± 140,993.5	229,447.8 ± 123,638.6	0.035
Adjusted Albumin, mg/dl	3.3 ± 0.5	3.1 + 0.7	NS
Adjusted Creatinine, mg/dl	0.8 ± 0.3	0.8 ± 0.2	NS
Adjusted AST, IU/l	174.0 ± 97.2	234.6 + 174.0	NS
Adjusted ALT, IU/l	190.8 ± 135.8	179.1 ± 100.6	NS
Adjusted LDH, IU/l	534.8 ± 325.1	542.8 ± 360.8	NS
Adjusted Ferritin, ng/ml	1,205.1 ± 1,486.6	9,715.4 ± 5,689.5	0.001

* First laboratory result of blood tests measured on admission. † Highest or lowest laboratory results during hospitalization. †† Area under the curve of results divided by total days of hospitalization. ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: white blood cell; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; NS: not significant. Continuous variables are expressed as mean ± standard deviation. For all statistical evaluations $p < 0.05$ was considered statistically significant.

temic type of juvenile idiopathic arthritis including high ESR level at onset of disease, fever, and polyarthritis, as reported previously[10,11], showed no significant association with the chronic disease course as in our study. These discrepancies, which we failed to elucidate, might be due to a limitation of chart review.

Although hyperferritinemia is known to be associated with inflammatory diseases, infectious diseases, or malignancies, the elevated level of ferritin remains among the unique characteristic of AOSD[12]. It was reported that levels of the proinflammatory cytokines such as interferon-γ, interleukin 1 (IL-1), IL-6, IL-8, IL-18, and tumor necrosis factor-α (TNF-α) were significantly increased in both sera and pathological tissues of patients with active or untreated AOSD[13-16], and that the synthesis of ferritin is regulated by those proinflammatory cytokines at various levels during development, cellular differentiation, proliferation, and inflammation[12]. These reports may imply that the level of ferritin might be a good biomarker to monitor the disease activity of AOSD. However, a serial inflammatory cascade from the proinflammatory cytokine to the synthesis of ferritin does not occur in a moment, but occurs sequentially. Therefore, it is more feasible to measure a series of the fluctuant concentrations of ferritin within a certain period of time than to measure the transient level of ferritin cross-sectionally, such as the initial level of ferritin or the highest

Table 4. Odds ratios for the progression to chronic disease in patients with AOSD.

Ranges of each Measure	p	OR	95% CI
Adjusted level of ferritin			
Low (< 784.0)			
Middle (784.0–4120.0)	0.007	81.715	3.241–2,060.227
High (> 4120.0)	0.266	0.083	0.001–6.643
Initial level of AST			
Low (< 51.0)			
Middle (51.0–75.0)	0.187	0.026	0.000–5.912
High (> 75.0)	0.833	1.597	0.021–123.580
Initial level of ALT			
Low (< 24.0)			
Middle (24.0–55.0)	0.749	0.472	0.005–46.742
High (> 55.0)	0.353	13.244	0.057–3,088.790
Initial level of ferritin			
Low (< 2169.8)			
Middle (2169.8–6856.1)	0.629	2.821	0.042–188.954
High (> 6856.1)	0.512	0.364	0.018–7.482
Highest level of LDH			
Low (< 938.0)			
Middle (938.0–1880.0)	0.897	0.820	0.040–16.650
High (> 1880.0)	0.374	7.302	0.091–584.777
Highest level of ferritin			
Low (< 4839.7)			
Middle (4839.7–15,900.0)	0.862	0.680	0.009–51.962
High (> 15,900.0)	0.370	0.203	0.006–6.625

* Each measure was distributed into the 3 ranges, high, middle, and low range, where one-third of patients were evenly included in each range. AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase.

level of ferritin, in order to evaluate disease activity, remedial values, and the possibility of progression to the chronic disease course of AOSD precisely. We serially measured laboratory indicators during the first hospitalization, and adjusted them to the total days of hospitalization, to determine consecutive states in patients with AOSD.

Since the pathophysiology or pathogenesis of AOSD remains unclear, despite indirect evidence, it was difficult to elucidate the relationship between the adjusted level of ferritin and the chronic disease course of AOSD in our study. Considering the regulatory effects of proinflammatory cytokines on the level of ferritin, an increased adjusted level of ferritin might mean continuously or extremely elevated levels of proinflammatory cytokines, which are also known to be capable of induction of inflammation such as synovitis. Thus, it could be postulated that increased adjusted level of ferritin might reflect the lasting increased levels of those cytokines, resulting in increasing the susceptibility to arthritis as well as the relapse rate of AOSD, through altered immune-system effects[2].

Hyperferritinemia is also associated with hemophagocytic syndrome other than AOSD[12]. In order to remove the confounding effect, we excluded those patients who were proven to have hemophagocytic syndrome on bone marrow and liver biopsies (2 patients died) and assessed the statistical significance again. The statistics still showed that the adjusted level of ferritin was a significant useful measure for prediction of progression to chronic disease in patients with AOSD (OR 81.512, p = 0.008).

In addition, the high range of the adjusted level of ferritin did not show any significance, in contrast to its mid-range. Coffernils, *et al* reported that the inflammatory state caused by AOSD could not explain ferritin levels higher than 3500 ng/ml, and extremely high levels of ferritin might be induced by hyperactivity of histiocytes and hemophagocytosis, not related to the disease entity of AOSD[17]. In our study, we had the limitation that we had not performed bone marrow or liver biopsies in all patients. Therefore, supposing that we had performed biopsy of bone marrow or liver in all patients, we could have proven the reason that the high range of the adjusted level of ferritin did not show any significant predictive value for chronicity of AOSD.

In contrast to hemophagocytosis, myelofibrosis, which is associated with decreased iron deposits, might also affect the level of ferritin, so we excluded subjects who showed myelofibrosis on bone marrow biopsy. Five out of 6 patients who showed myelofibrosis on bone marrow biopsy died. Only 1 out of 6 patients survived and showed the chronic pattern of AOSD. When we analyzed the data excluding this patient (total 61 patients), we found similar results, that the adjusted level of ferritin was useful to predict the chronic disease course of AOSD (OR 80.110, p = 0.008).

Interestingly, in our adjusted laboratory results, the measures of low ESR, low platelet counts, and high ferritin levels

were frequently seen in patients with the chronic disease pattern as compared with the nonchronic disease pattern. However, these features might also be seen in AOSD patients with complications of macrophage activation syndrome or DIC. Although we could not exclude DIC in survivors with AOSD, according to the laboratory results, there were no survivors with AOSD who met the criteria for diagnosis of DIC. But we assumed that there must have been negligible DIC components related to AOSD and they might affect the ESR level, platelet counts, and ferritin level. Since all patients had not undergone bone marrow biopsies, we could not prove this relation.

The ability to predict the chronic disease course of AOSD may contribute significantly to the prevention of chronic disease through better early management. We supposed that there is a theoretical triangle among the proinflammatory cytokines, disease activity, and level of ferritin, based on recent evidence. (1) Recently, new biologic agents such as anti-TNF-α blockades and anti-IL-1 antagonists have proven to be highly effective in most patients with AOSD[2,16-20]; (2) the concentration of ferritin is regulated by the proinflammatory cytokines[12]; and (3) the level of ferritin might reflect the disease activity of AOSD[9]. Moreover, several cytokines that were correlated with disease activity were found to increase in patients with the chronic disease pattern of AOSD, suggesting that the increased level of ferritin associated with the high disease activity and high concentration of proinflammatory cytokines could drive AOSD to the chronic disease pattern[21]. Thus, when we disrupt the cycle of proinflammatory cytokines using effective biological agents earlier in patients with AOSD who have increased adjusted levels of ferritin and do not respond to classic immunosuppressive therapy, we might prevent the chronic disease course. In our study, similarly, the only nonchronic disease pattern was observed in 3 patients who were treated with TNF-α blockade, but this had no statistical significance ($p = 0.173$) due to the small number of subjects.

We assessed the cutoff value of the adjusted level of ferritin for prediction of the chronic disease course. With this result, when the cutoff value of the adjusted level of ferritin for prediction of chronic AOSD was set as 784 ng/ml, the sensitivity was 95.7% and the specificity was 48.7%; when the cutoff value was set as 4120 ng/ml, the sensitivity decreased to 82.6%, but the specificity increased to 94.9% (OR 0.910, 95% CI 0.822~0.998, $p < 0.01$). Whereas when the cutoff value was set as 2,530 ng/mL, the sensitivity still remained as 95.7% and the specificity increased to 92.3%, suggesting that the adjusted level of ferritin of 2530 ng/ml might be a critical cutoff value for progression to the chronic disease pattern of AOSD. Since our study had several limitations of the small number of subjects, the retrospective design, and results obtained from only 2 medical centers, another complementary study will be needed.

A novel measure, the adjusted level of ferritin during the first hospitalization, might be useful to predict progression to chronic disease in patients with AOSD.

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