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ORIGINAL ARTICLE

Proposal for a simple algorithm to differentiate adult-onset Still's disease with other fever of unknown origin causes: a longitudinal prospective study

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Abstract

Objective To identify several clinical and/or laboratory parameters which can differentiate adult-onset Still's disease (AOSD) from other causes of fever of unknown origin (FUO) and create a clinician-friendly algorithm for this purpose.

Methods FUO patients hospitalized between March 2015 and September 2017 were recruited prospectively. AOSD patients diagnosed between 2001 and 2017 in our department were analyzed. Clinical and laboratory parameters were recorded for all patients. A multivariate analysis was performed to identify possible parameters related to the discrimination of AOSD from FUO.

Results We recruited 69 AOSD patients (51 females, 74%) and 87 patients (43 females, 49.4%) evaluated for FUO. Median ages were 45 (30–57) and 45 (30–62), respectively. Arthralgia, rash, sore throat, neutrophilia, serum ferritin level higher than 5 times of the upper limit, and elevated lactate dehydrogenase levels were associated with the likelihood of diagnosing AOSD; on the other hand, the number of daily fever peaks equal or greater than 3 was associated with the unlikelihood of diagnosing AOSD. After the clinical feasibility assessment of possible parameters derived from the multivariate analysis, in the setting of fever, two clinical (arthralgia, sore throat) and two laboratory (ferritin level, neutrophilia) parameters were selected to develop an algorithm for discrimination of AOSD and FUO.

Conclusion Presence of arthralgia, hyperferritinemia, sore throat, and neutrophilia suggests AOSD in patients presenting as FUO. This study proposes a clinician-friendly algorithm for the first time in current literature to discriminate AOSD from other causes of FUO.

Keywords Adult-onset Still's disease · Fever of unknown origin · Inflammation

Introduction

Adult-onset Still's disease (AOSD) is a rare, chronic, multisystem, and auto-inflammatory disorder. Although firstly described in 1971, etiopathogenesis of the disease needs to be elucidated [1]. Epidemiological data about its prevalence is limited and changing from 1 to 67 per 1.000.000 between different geographic areas and estimated crude incidence rate of 2.2 and 3.4 per 1.000.000 among males and females, respectively, in Japan [2–4]. Clinically, it resembles a pediatric counterpart. High-spiking fever, maculopapular rash, arthralgia or arthritis, pharyngitis, hepatosplenomegaly, and lymphadenopathy are typical findings of patients with AOSD. Leukocytosis with neutrophilia, elevated levels of acute phase reactants like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), transaminitis, markedly elevated ferritin levels, and the absence of rheumatoid factor (RF) and antinuclear antibody (ANA) are typical laboratory picture of a patient with AOSD [5, 6]. Rare clinical situations like macrophage activating syndrome (MAS), disseminated intravascular coagulation (DIC), adult respiratory distress syndrome (ARDS), thrombotic thrombocytopenic purpura (TTP), liver failure, and myocarditis may be seen during disease course [7, 8]. Several diagnostic criteria were proposed for AOSD.

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Diagnosis of AOSD is a clinical challenge; as the precondition underlined in Yamaguchi criteria, other possible diagnoses which may present with fever must be excluded [9, 10].

Fever of unknown origin (FUO) is one of the most complicated and time-consuming clinical situations that comprises a large list of differential diagnosis. The classical approach to FUO can divide this list into three main subgroups: rheumatologic, malignant, and infectious causes. According to a study by Pizzo et al., the evaluation for FUO can lengthen the duration of hospitalization for 19 days [11]. Approximately 60% of AOSD patients were presented as FUO and about 15–20% of patients evaluated for FUO had the diagnosis of AOSD, according to different large-scale studies [6, 12, 13]. As the complexity of FUO evaluation, prolonged hospitalization and the importance of the early diagnosis of rare manifestations like MAS-related to AOSD were all considered; can any clinical and/or laboratory parameter differentiate AOSD from other causes FUO? The aim of this prospective study was to determine a simple diagnostic algorithm to differentiate patients with AOSD from other FUO causes.

Patients and methods

Study design and patient selection

This is a prospective, one-centered, observational study conducted between March 2015 and September 2017. Patients diagnosed with AOSD between 2001 and 2017 in our department were recruited. Patients admitted to the Hacettepe University Hospitals, inpatients sections of the Department of Internal Medicine for FUO at the study period (from March 2015 to September 2017) were recruited.

Patients who had a body temperature higher than 38.3 °C for at least 3 weeks without an established cause of fever after 1 week of hospitalization were diagnosed as FUO [14]. Data of patients with FUO were collected prospectively for 30 months. All patients were evaluated and diagnosed by experts of related field using a routine protocol which included infection assessments with blood and urine cultures, ultrasonography, echocardiography, computerized tomography and/or magnetic resonance imaging, PET-CT, and tissue biopsy, if needed. All patients fulfilling the FUO criteria described above were considered for recruitment; however, if a certain diagnosis could not be established after all diagnostic procedures, patients were excluded from analysis. Patients without informed consent and who were not admitted were also excluded. If patients had the diagnosis of AOSD after evaluation, they were recruited to AOSD group.

Diagnosis of AOSD was considered by expert rheumatologists after exclusion of other possible causes, not according to any published diagnostic criteria; but on the other hand, all patients were also assessed for whether they met the Yamaguchi criteria or not. Patients without informed consent were excluded. Data of AOSD patients were recorded retrospectively from patients' files and/or hospital automatization system.

Hacettepe University Ethical Committee approved the study prior to data collection (Approval number: GO 17/84-05). We obtained patients' written consents prior to data collection.

Assessment of the patients

Several clinical parameters, including age, gender, peak body temperature, time of fever, number of fever peak, presence of rash, arthritis, arthralgia, myalgia, pharyngitis, lymphadenopathy, hepatomegaly, splenomegaly, pleuritis, pericarditis, aseptic meningitis, myocarditis, multi-organ failure, DIC, ARDS, liver failure, and macrophage activation syndrome (MAS), were recorded. Similarly, laboratory parameters, including hemoglobin, neutrophil (> 6.4 × 1000/mm), leukocyte (> 10.2 × 1000/mm), thrombocyte (> 388 × 1000/mm), ferritin (> 336 ng/ml), aspartate aminotransferase (AST > 35 IU), alanine aminotransferase (ALT > 35 IU), gamma-glutamyl transferase (GGT > 35 IU), lactate dehydrogenase (LDH > 247 IU), bilirubin (> 1.2 mg/dl), albumin (< 3 g/dl), ESR (> 20 mm/h), CRP (> 0.8 mg/dl), triglyceride (> 150 mg/dl), high-density lipoprotein (HDL < 35 mg/dl), fibrinogen (> 320 mg/dl), vitamin B_{12} (> 590 ng/dl), RF and anti-citrullinated cyclic protein (> 20 IU), complement 3 (C3 > 152 mg/dl), and complement 4 (C4 > 36 mg/dl) levels, of all patients were recorded. Upper or lower limits were given in brackets above, and these limits were the same for both genders. For patients with AOSD, these parameters were recorded at the time of diagnosis and before glucocorticoid treatment. For parameters studied several times, we recorded the lowest or the highest value before glucocorticoid treatment.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences software (version 23.0; IBM Corporation, Armonk, NY, USA). The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov-Smirnov, skewness and curtosis) to determine whether or not they are normally distributed. The data of descriptive analysis were expressed as either mean ± standard deviation (SD) or the median, interquartile range. Categorical variables were compared with the chi-square test or Fisher's exact test where appropriate. The Student *t* test and Mann-Whitney *U* test were used to compare the normally and non-normally distributed continuous data between two

groups, respectively. For the multivariate analysis, the possible factors identified with univariate analyses were further entered into the logistic regression analysis to determine independent predictors of patient outcome. After the clinical feasibility assessment of possible parameters derived from multivariate analysis and depending on the odds ratios of each parameter, we developed an algorithm. Positive predictive values (PPV) for isolated or combined presence of symptoms, physical examination findings, and positive laboratory tests were calculated. The Hosmer-Lemeshow goodness of fit statistics was used to assess model fit. A 5% type-I error level was used to infer statistical significance.

Results

Demographic, clinical, and laboratory features of all cases

Total 156 patients ($n = 69$ (44.2%), for AOSD; $n = 87$ (55.8%), for FUO) were included. Sixty-five of 69 (94.2%) AOSD patients met the Yamaguchi criteria. Fifteen AOSD patients were diagnosed during the study period while being evaluated for FUO. While 51 (74%) patients were female in the AOSD group, 43 (49.4%) patients were female in the FUO group. Median ages of patients were similar in two groups (45 (30–57) years for AOSD and 45 (30–62) for FUO, $p = 0.49$). Table 1 shows the clinical features of both groups.

Total leukocyte count (× 1000/mm) was significantly higher in AOSD group when it was compared with patients with FUO (13.5 (10.1–19.6) vs. 6 (3.8–9.4), respectively, $p < 0.001$). Leukocytosis was present in 64.5% of AOSD patients, and 18.4% of patients were with FUO ($p < 0.001$). Total neutrophil count (× 1000/mm) was significantly higher in AOSD group when compared with patients with FUO (12 (7.2–17.9) vs. 3.8 (2.1–6.9), $p < 0.001$). Neutrophilia was present in 82.3% of AOSD patients, and 29.9% of patients were with FUO ($p < 0.001$). Median ferritin levels of AOSD and FUO groups were 1705 ng/ml (657–6417) and 424 ng/ml (141–1188), respectively, and significantly higher in AOSD group ($p < 0.001$). Also, hyperferritinemia was more prevalent in AOSD group (98.4% vs. 51.7%, $p < 0.001$). To increase the specificity of the final model, another analysis for ferritin levels was done by admitting the cut-off value for hyperferritinemia as 5 times of upper normal limit (UNL) which was consistent with current literature [15]. "Hyperferritinemia > 5 × UNL" was also more prevalent in AOSD group (53.4% vs. 18.4%, $p < 0.001$). Details of the laboratory features of the groups are given in Table 2.

The FUO group was also divided into three subgroups: rheumatologic ($n = 31$, 35.6%), infectious ($n = 28$, 32.2%), and malignant ($n = 28$, 32.2%) causes. The distribution of diagnosis, clinical, and laboratory features of each subgroup is given in Appendix tables 1, 2, and 3, respectively.

Univariate and multivariate analyses

After the identification of possible factors for predicting AOSD by univariate analysis, logistic regression analysis was done to determine independent predictors of AOSD. Details of univariate and multivariate analyses are given in Table 3. As we did not know the pre-treatment ferritin levels of 6 AOSD patients, they were excluded from the analysis for algorithm generation. After the clinical feasibility assessment of possible parameters derived from multivariate analysis and depending upon the odds ratio of each parameter, in the setting of fever, two clinical (arthralgia, sore throat) and two laboratory (ferritin level, neutrophilia) parameters were selected to develop an algorithm for discrimination of AOSD and FUO (Fig. 1**).** We assessed the goodness of fit statistics by the Hosmer-Lemeshow goodness of fit ($p = 0.08$). As adding "the presence of rash" made no statistical contribution, we did not include this parameter to the final algorithm. In addition, we did not include LDH levels because of the lack of statistical significance as shown in Table 3.

The overall sensitivity and specificity of our algorithm were 59/63 (93.7%) and 83/87 (95.4%), respectively, for AOSD.

Discussion

In this study, we compared the basic clinical and laboratory features of patients with AOSD and patients with other causes of FUO to find parameter(s) that can enable to detect patients who have the high likelihood of being diagnosed with AOSD. Evaluation of patients with FUO is exhausting, time-consuming, and expensive [16]. Besides this, several epidemiological studies revealed that the AOSD was one of the most common rheumatologic causes of FUO [12, 13]. So, making differentiation of these two clinical entities with a simple algorithm is invaluable. In our study, multivariate analyses, identified four clinical (arthralgia, rash, sore throat favor AOSD, the number of daily fever peaks equal or greater than 3 favors FUO) and three laboratory (neutrophilia, serum ferritin level ≥ × 5, and elevated lactate dehydrogenase levels favor AOSD) parameters that can differentiate these two clinical scenarios. Further analysis revealed that the presence or absence of arthralgia in a patient with FUO was the most powerful clinical finding in this manner. The absence of arthralgia excluded the diagnosis of AOSD substantially. In the presence of arthralgia, it was reasonable to measure ferritin level firstly. While normal ferritin levels highly excluded AOSD, levels ≥ × 5 of upper normal limit (UNL) highly suggested AOSD. However, the major diagnostic challenge was seen

Table 1 Demographic and clinical features of patients with AOSD and FUO

Parameter	AOSD $n = 69$ n (%)	FUO $n = 87$ n (%)	p value
Peak body temperature (C°) *	39.0 (39–40)	39.3 (38.8–39.8)	0.65
Time of fever			*< 0.001*
1. Morning	1 (1.5)	5 (5.7)	NS
2. Noon	0	5 (5.7)	NS
3. Evening	14 (20.3)	26 (29.9)	NS
4. Night	38 (55.1)	12 (13.9)	*< 0.001*
5. Throughout the day	5 (7.2)	28 (32.2)	*< 0.001*
6. No pattern	11 (15.9)	11(12.6)	NS
Number of fever peaks			0.27
1. 1	28 (40.5)	36 (41.3)	NS
2. 2	21 (30.4)	26 (30.0)	NS
3. 3	4 (5.8)	16 (13.8)	*0.002*
4. No pattern	16 (23.3)	13 (14.9)	NS
Arthralgia	66 (95.7)	33 (37.9)	< 0.001
1. Ankle	49 (74.2)	18 (54.5)	NS
2. Wrist	49 (74.2)	18 (54.5)	*0.048*
3. Knee	43 (65.2)	18 (54.5)	NS
4. Metacarpophalangeal	43 (65.2)	17 (51.5)	NS
5. Proximal interphalangeal	41 (62.1)	19 (57.6)	NS
6. Metatarsophalangeal	24 (36.4)	3 (3.4)	*0.004*
7. Hip	10 (15.2)	7 (21.2)	NS
Pharyngitis	54 (78.0)	10 (11.5)	*< 0.001*
Rash	49 (71.0)	17 (19.5)	*< 0.001*
Arthritis	37 (53.6)	13 (14.9)	*< 0.001*
Myalgia	33 (47.8)	39 (44.8)	0.70
Hepatomegaly	28 (40.6)	36 (41.4)	0.92
Splenomegaly	23 (33.3)	24 (27.6)	0.43
Lymphadenopathy	19 (27.5)	49 (56.3)	*< 0.001*
Pericarditis	7 (10.1)	7 (8.0)	0.78
Macrophage activation syndrome	7 (10.1)	2 (2.3)	*0.037*
Pleuritis	5 (7.2)	12(13.8)	0.30
Multi-organ failure	4 (5.8)	3 (3.4)	0.70
Aseptic meningitis	2 (2.9)	3 (3.4)	0.84
Liver failure	3 (4.3)	2 (2.3)	0.65
Disseminated intravascular coagulation	2 (2.9)	2 (2.3)	0.81
Adult respiratory distress syndrome	1 (1.4)	2 (2.3)	0.70
Myocarditis	1 (1.4)	0	0.44

p values written in italic form were statistically significant

*Peak body temperature expressed as median (IQR), other parameters given as percentage of patients within the group positive for mentioned parameter

in patients who had ferritin levels higher than the upper limit but lower than the 5 times of upper limit. In this situation, the presence of a sore throat and/or neutrophilia was helpful for discrimination.

The duration from the beginning of symptoms to diagnosis of AOSD was reported approximately 4 months although it can prolong to 3 years [17]. This delay in diagnosis prolongs hospitalization and increases the cost; besides, it can trigger the emergence of rare complications of AOSD (e.g., MAS, DIC, and ARDS) [18]. Also, the chronic articular pattern is more common among patients with AOSD who had a diagnostic delay [18]. So, clinicians must have a high level of suspicion. Studying early diagnostic approaches seems logical. In 2005, Crispin et al. published a study that tried to differentiate patients with AOSD and patients presented with FUO [19]. In this study, only 26 patients with AOSD recruited

Table 2 Laboratory features of patients with AOSD and FUO

	AOSD†	FUO††	*p* value
Hemoglobin (mg/dl)*	10.8 ± 1.9	9.7 ± 2.0	*0.002*
Anemia (%)	87.1	93.1	0.26
Leukocyte(× 1000/mm)**	13.5 (10.1–19.6)	6 (3.8–9.4)	*< 0.001*
Leukocytosis (%)	64.5	18.4	*< 0.001*
Neutrophil (× 1000/mm)**	12 (7.2–17.9)	3.8 (2.1–6.9)	*< 0.001*
Neutrophilia (%)	82.3	29.9	*< 0.001*
Ferritin (ng/ml)**	1705 (657–6417)	424 (141–1188)	*< 0.001*
Hyperferritinemia			
> UNL (%)	98.4	51.7	*< 0.001*
> 5 × UNL (%)	53.4	18.4	*< 0.001*
Thrombocyte (× 1000/mm)*	382 ± 183	239 ± 154	*< 0.001*
Thrombocytosis (%)	50	13.8	*< 0.001*
AST > UNL (%)	61.3	59.8	0.85
ALT > UNL (%)	61.3	48.3	0.13
LDH > UNL (%)	92.5	63.2	< 0.001
Bilirubin (mg/dl)**	0.51 (0.38–0.88)	0.6 (0.47–1.02)	0.082
Albumin (g/dl)*	3.15 ± 0.61	2.95 ± 0.52	*0.039*
Hypoalbuminemia (%)	39.7	55.2	*0.009*
ESR > 100 mm/h (%)	15.9	24.1	0.30
CRP > UNL (%)	100	97.7	0.51
Triglyceride (mg/dl)**	171 (110–226)	176 (116–229)	0,25
HDL (mg/dl)**	32 (20–46)	26.25 (18–35)	*< 0.001*
Hypo-HDL (%)	54	74.4	*0.03*
Fibrinogen (mg/dl)*	505 ± 252	464 ± 188	0.77
Vitamin B_{12} (ng/dl)**	398 (256–573)	290 (195–542)	0.39
RF > UNL (%)	3.6	23	0.002
Anti-CCP > UNL (%)	0	5.7	*0.009*
C3 (mg/dl)*	151 ± 37	124 ± 44	*0.001*
C4 (mg/dl)*	26 ± 9.7	26 ± 12.4	0.99

p values written in italic form were statistically significant

AST, aspartate aminotransferase; *ALT*, alanine aminotransferase; *Anti-CCP*, anti-cyclic citrullinated peptide; *C4*, complement 4; *C3*, complement 3; *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *HDL*, high-density lipoprotein; *LDH*, lactate dehydrogenase; *RF*, rheumatoid factor; *UNL*, upper normal limit

*Given as mean ± standard deviation; **Given as median (range)

† *n* is variable and:

= 62 for hemoglobin, leukocyte, neutrophil, thrombocyte, AST, ALT

= 63 for ferritin

= 58 for bilirubin and albumin

= 63 for ESR and CRP

= 46 for triglyceride and HDL

= 53 for LDH

= 42 for fibrinogen, vitamin B_{12}, C4, C3

= 55 for RF and anti-CCP

†† *n* is 87

and evaluated retrospectively. However, they found several clinical parameters (pharyngitis, arthritis, rash) to differentiate AOSD and FUO that were similar to our study [19]. Interestingly, neutrophilia was the most powerful laboratory parameter in that study [19]. Unfortunately, they could not include ferritin, an invaluable laboratory parameter, in the analysis due to methodological constraint [19].

In our study, we found ferritin levels ≥ 5 times of UNL as the most distinctive laboratory parameter. In a study by Fautrel et al., they tried to define the diagnostic value of ferritin and

Table 3 Results of univariate and multivariate analyses

Variables	Univariate analysis			Multivariate analysis		
	Odds Ratio	Confidence Interval (CI)	*p* value	Odds Ratio	Confidence Interval (CI)	*p* value
Favors Still's						
Fever at night	7.66	3.53–16.5	*< 0.001*			
Rash	10.08	4.80–21.2	*< 0.001*	31.3	3.6–271.9	*0.002*
Arthritis	6.58	3.09–14.01	*< 0.001*			
Arthralgia	36	10.46–123.83	*< 0.001*	158.1	4.3–5755.8	*0.006*
Sore throat	27.72	11.58–66.33	*< 0.001*	20.8	2.8–154.7	*0.003*
History of hemophagocytosis	4.79	0.96–23.89	0.079			
Neutrophilia	10.87	4.90–24.13	*< 0.001*	18.4	2.6–132.3	*0.004*
Thrombocytosis	6.25	2.84–13.72	*< 0.001*			
Ferritin ≥ 5 × UNL	4.88	2.34–10.16	*< 0.001*	132.8	7.1–2502.9	*0.001*
LDH	7.12	2.35–21.59	*< 0.001*	6.2	0.76–50.9	0.087
C3	3.20	1.47–7.00	*0.003*			
Female gender	2.90	1.46–5.73	*0.002*			
Favors FUO						
Fever peak number ≥ 3	3.66	1.16–11.52	*0.019*	69	2.2–2114.4	*0.015*
Pleuritis	2.04	0.68–6.12	*0.19*			

p values written in italic form were statistically significant

FUO, fever of unknown origin; *LDH*, lactate dehydrogenase; *C3*, complement 3; *UNL*, upper normal limit (for ferritin, 336 ng/ml)

glycosylated ferritin in AOSD patients and found the sensitivity and specificity of ferritin levels ≥ 5 times of UNL 40.8% and 80%, respectively [10]. When the levels of glycosylated ferritin were lower than 20% in combination with ferritin levels ≥ 5 times of UNL, sensitivity and specificity were raised to 43.2% and 92.9%, respectively [10]. But in that study, approximately one-fifth of the patients with AOSD were inactive [10]. So, this may explain this condition, because sensitivity of ferritin levels ≥ 5 times of UNL was reported as 69% and 74% in another series [20, 21]. In routine daily

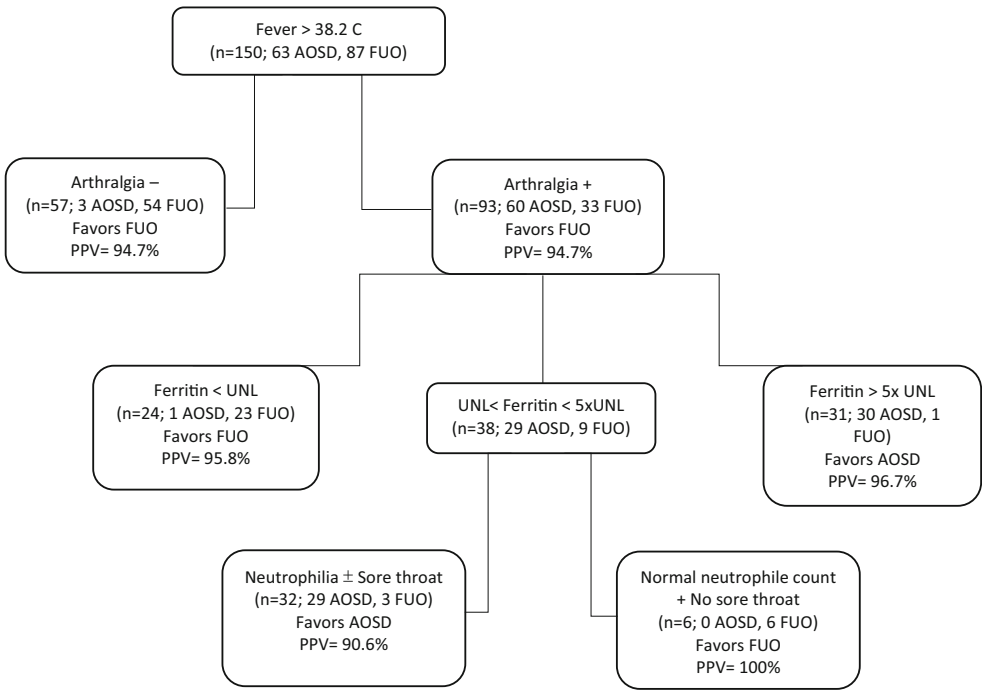

Fig. 1 Algorit0068m for discrimination of adult-onset Still's disease and other causes of fever of unknown origin. AOSD, adult-onset Still's disease; FUO, fever of unknown origin; UNL, upper normal limit (for ferritin, 336 ng/ml); PPV, positive predictive value

clinical practice, many centers cannot measure glycosylated ferritin levels. It was also not available in our center, so we cannot include this parameter to our analysis. In fact, ferritin levels are elevated in several diseases including immune disorders (e.g., rheumatoid arthritis and antiphospholipid syndrome), liver diseases (e.g., hepatitis C and hemochromatosis), storage disorders (e.g., Gaucher's disease), malignancies (e.g., leukemia and lymphoma) [22]. But when the combination of "FUO + arthralgia + ferritin levels ≥ 5 times of UNL" is present, this highly suggests the diagnosis of AOSD. When FUO and arthralgia are present, but ferritin level is between normal and 5 times of UNL, the presence of a sore throat and/or neutrophilia favors the diagnosis of AOSD. The criteria published by Yamaguchi et al. contain "leukocytosis with > 80% neutrophilia" as a major criterion [9]. However, solely "neutrophilia" was found more valuable in our multivariate analysis, as Crispin et al. reported before [19].

One of the major limitations of our study is the presence of the relatively small number of patients in each FUO subgroup. Because of this reason, we could not have analyzed and compared each subgroup and patients with AOSD. Another limitation of our study is that we could not study any potential biological marker that can differentiate AOSD from other causes of FUO (e.g., interleukin (IL)-18 and protein S100A12 (calgranulin c)) because of methodological and financial reasons [23]. Also, another limitation of our study is the need for further external validation. Due to the retrospective recording of much of the AOSD patients, recall bias may be possible; however, in order to minimize the risk of recall bias, we contacted all patients and verified all clinical pictures which they had during diagnosis.

In summary, in this study, we compared the clinical and laboratory features of AOSD patients and patients evaluated for FUO and we developed a clinician-friendly, easy-to-use algorithm to discriminate these two clinical entities. Although there is a strong correlation between the presence of AOSD and the levels of IL-18, utility and contribution of adding these parameters to our algorithm need to be elucidated with further studies.

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Compliance with ethical standards

Hacettepe University Ethical Committee approved the study prior to data collection (Approval number: GO 17/84-05). We obtained patients' written consents prior to data collection.

Disclosures None.

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