The performance of the diagnostic scoring system or criteria for macrophage activation syndrome in systemic juvenile idiopathic arthritis for adult-onset Still's disease. A multicentre case-control study in China

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ABSTRACT

Objective. *To evaluate the performance of the diagnostic scoring system/criteria for macrophage activation syndrome (MAS) used in systemic juvenile idiopathic arthritis (sJIA) for adult-onset Still's disease (AOSD).*

Methods. *This retrospective case-control study included AOSD patients with and without MAS from six hospitals in China. The cut-off values that best discriminated MAS from active AOSD were determined by receiver operating characteristic (ROC) curve analysis. The performance of the present diagnostic scoring system/criteria for sJIA-MAS was evaluated in AOSD-associated MAS. The optimal critical value of the ROC curve replaces the relevant indicators of the existing scoring system and different models were tested for sensitivity/specificity.*

Results. *A total of 56 AOSD-associated MAS patients (AOSD-MAS) and 112 AOSD patients without MAS matched with age and sex treated at six centres between 2007 and 2017 were enrolled. The 2016 MAS in sJIA classification criteria had an overall sensitivity of 100.0% and specificity of 80.4% for classifying AOSD-MAS. Excluding hypertriglyceridaemia and substituting some other criteria with newly obtained cut-off values could increase specificity. An MS score ≥-2.1 yielded a sensitivity of 95.2% and a specificity of 76.6% in classifying AOSD-MAS. ROC curve analysis revealed that a score of -1.74 could best discriminate AOSD-MAS from AOSD without MAS. An MS score ≥ -1.74 yielded a sensitivity of 93.5% and a specificity of 92.6% in diagnosing AOSD-MAS (AUC=0.96, 95%CI: 0.93-0.99, p<0.0001).*

Conclusion. *The diagnostic tool for MAS in sJIA with modification appears to apply to AOSD-MAS.*

Introduction

Adult-onset Still's disease (AOSD) is an uncommon multisystemic autoinflammatory disease of unknown aetiology (1). It is characterised by multi-visceral involvement and heterogeneous clinical features, shifting from spiking fever, arthritis, evanescent rash, and hepatosplenomegaly to life-threatening complications. The diagnosis of AOSD requires the exclusion of infectious, autoimmune, neoplastic, and other autoinflammatory diseases. The macrophage activation syndrome (MAS) is a potentially life-threatening condition in patients with rheumatic diseases. It most commonly occurs in systemic juvenile idiopathic arthritis (sJIA), systemic lupus erythematosus (SLE), and AOSD (2). The incidence of MAS ranges from 12.3–15.0%, with mortality rates of 10–41% (3-5), requiring early recognition and prompt intervention. Still, MAS associated with AOSD (AOSD-MAS) shares many clinical characteristics (*e.g.* fever, hepatosplenomegaly, and lymphadenopathy) and biological characteristics (*e.g.* hyperferritinaemia) with the active phases of AOSD, representing a major challenge in making an early diagnosis.

Making a diagnosis of MAS is challenging since there are no unique clinical, biological, or pathologic features. MAS is traditionally identified based on the HLH-2004 criteria, except in sJIA (6). Still, increasing awareness of the poor detection power of HLH-2004 criteria in hyperinflammatory condi-

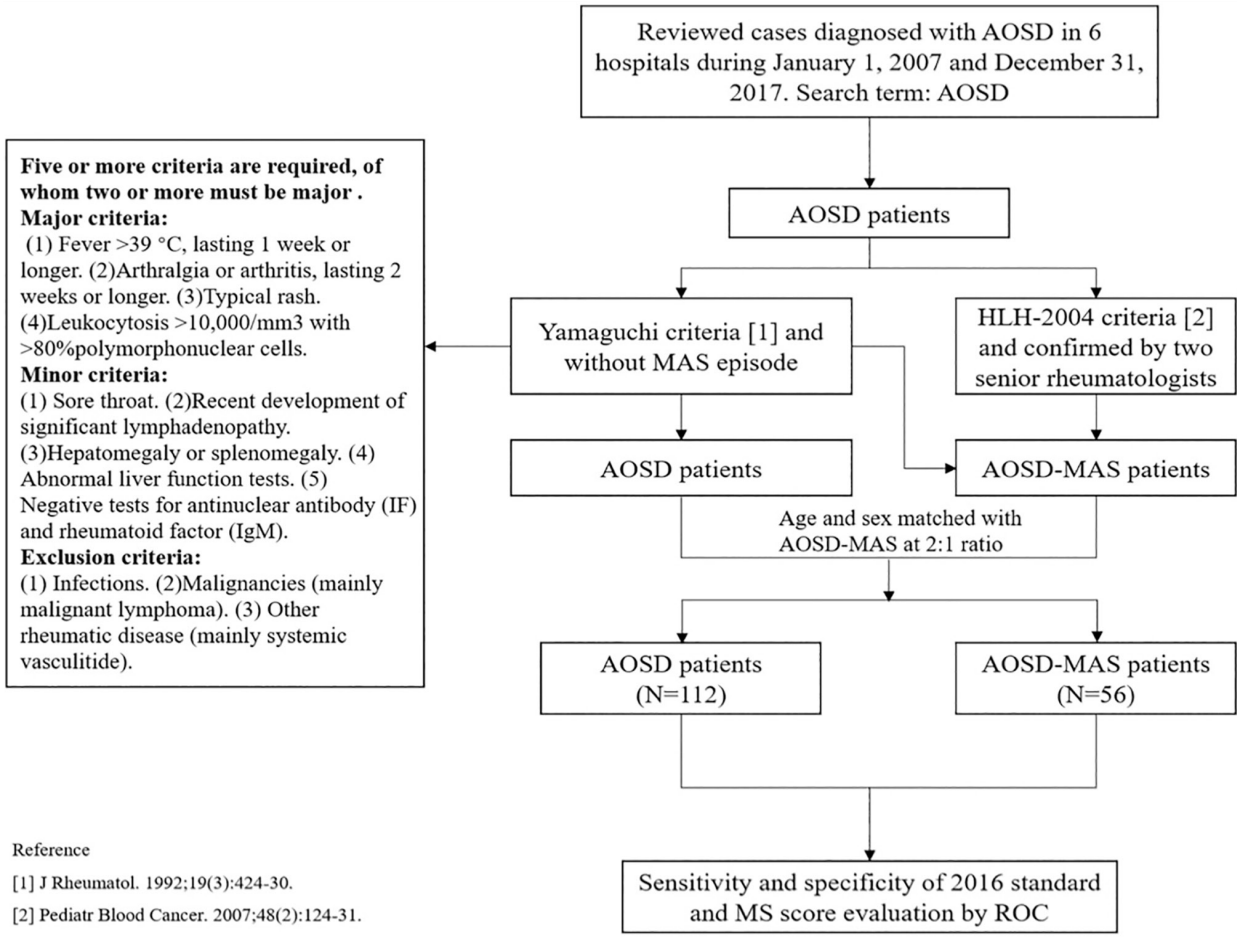

Fig. 1. Flow chart of patient registration.

tions led to the development of several criteria for MAS in specific conditions (sJIA and SLE) and reactive HLH (Hscore). In 2014, the haemophagocytic syndrome diagnostic (HS) score system was designed to identify the reactive haemophagocytic syndrome (RHS). It includes nine variables, some of which are characteristic features of the underlying disease itself. Still, most of the patients used for score validation was with tumour or infection, and only <5% were with rheumatic diseases. Therefore, the HS score system still requires validation (7). In 2016, the European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR)/Paediatric Rheumatology International Trials Organisation Collaborative Initiative (PRINTO) developed criteria that represented a major step towards more concrete diagnosis and earlier recognition of MAS in sJIA patients, with a sensitivity of 73% and specificity of 99% (8). In 2019, Minoia *et al*. reported an MS score for classifying MAS complicated with sJIA (9).

Considering the potential similarities between JIA and AOSD, we intended to evaluate the capacity of the 2016 criteria and the MS score for diagnosing MAS in AOSD.

Materials and methods

Study design and patients

AOSD-MAS patients treated at six university-affiliated tertiary hospitals across China, including five rheumatology centres and one haematology centre, between January 1, 2007, and December 31, 2017, were included in this retrospective study. AOSD patients without MAS matched with age and sex at the same period from the six centres were included as the control group (AOSD without MAS). All AOSD patients fulfilled the Yamaguchi criteria (10). In addition, MAS was diagnosed based on the HLH-2004 criteria (6) and further confirmed by two senior rheumatologists in all AOSD-MAS cases. The registration process of the patient is shown in Figure 1. The study was approved by the ethics committee of Peking University People's Hospital as the lead centre. Written informed consent was waived due to the retrospective nature of this study.

Data collection

A systematic search of the medical records was performed. We retrospectively reviewed the demographic features, clinical characteristics, laboratory findings, and pathologic features of the identified patients. The laboratory data were obtained on the day of MAS diagnosis (AOSD-MAS group) or the day of AOSD diagnosis (AOSD without MAS group).

Assessment of 2016 criteria and MS score

The 2016 sJIA-MAS standard for the

Table I. Comparison of demographic, clinical characteristics, and laboratory values of AOSD-MAS and AOSD without MAS patients.

Demographic features	AOSD-MAS (n=56)	AOSD without MAS (n=112)	*p*-value
Gender			0.357
Male (%)	12 (21.4)	32 (28.6)	
Female (%)	44 (78.6)	80 (71.4)	
MAS age, years, median (range)	35 (18,76)	-	-
AOSD age, years, median (range)	34 (18,76)	33 (18,78)	0.344
MAS interval, months, median (range)	5 (0, 96)	-	-
Clinical and laboratory features			
Fever (n, %)	56/56 (100.0)	112/112 (100.0)	-
Splenomegaly (n, %)	41/56 (73.2)	48/112 (42.9)	<0.001
Hepatomegaly (n, %)	8/56 (14.3)	13/112 (11.6)	0.621
Arthritis (n, %)	14/56 (25.0)	92/112 (82.1)	<0.001
Neurological involvement (n, %)	3/56 (5.4)	0	0.013
DIC (n, %)	7/56 (12.5)	0	<0.001
Hepatic failure (n, %)	7/56 (12.5)	0	<0.001
Fibrinogen <1.5 g/L (n, %)	27/56 (48.2)	0	<0.001
TG ≥3 mmol/L (n, %)	27/56 (48.2)	10/112 (8.9)	<0.001
Cytopenia at least two lineages (n, %)	40/56 (71.4)	0	<0.001
Neutrophils <1.0×10^9/L (n, %))	23/56 (41.1)	0	<0.001
Hb <90 g/L (n, %)	20/56 (35.7)	22/112 (19.6)	0.023
PLT <100×10^9/L (n, %)	31/56 (55.4)	0	<0.001
WBC (×10^9/L)	3.7 (1.9, 10.4)	14.5 (11.5, 19.6)	<0.001
Hb (g/L)	87 (76.8, 105.5)	103 (92, 112)	<0.001
PLT (×10^9/L)	82.5 (36,165.5)	342 (256, 426)	<0.001
ALT (U/L)	235 (54.8, 490.3)	49.5 (20.2, 121.5)	<0.001
AST (U/L)	199.5 (45.3, 838)	41 (20,86.7)	<0.001
Tbil (mmol/L)	15.5 (8.6, 39.1)	10.2 (7.6, 13.8)	<0.001
TG (mmol/L)	2.8 (2.1, 3.8)	1.3 (1.0, 2.2)	<0.001
LDH (U/L)	662 (437.5, 1808.8)	335 (219.8, 534.8)	<0.001
Fibrinogen (g/L)	162 (111.8, 286.5)	429.5 (346.3, 508.5)	<0.001
D-Dimer (μg/L)	2957.5 (1052.3,7584.5)	770 (338, 2241)	<0.001
ESR (mm/H)	23 (13.5, 41)	69 (33, 92)	<0.001
CRP (mg/L)	78.1 (41.8, 129.2)	36.4 (12.3, 79.3)	0.019
Ferritin (μg/L)	10,000 (2120.8, 41637.8)	2041 (945.8, 8499)	<0.001
Bone marrow hemophagocytosis (n, %)	38/56 (67.9)	3/112 (2.7)	<0.001
ICU admission (n, %)	10/56 (17.9)	4/112 (3.6)	0.003
Mortality (n, %)	5/56 (9.0)	3/112 (2.7)	0.119

Unless otherwise specified, values are the median (interquartile range). AOSD: adult-onset Still's disease; MAS: macrophage activation syndrome; WBC: white blood cell; Hb: hemoglobin; PLT: platelet; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; Tbil: total bilirubin; TG: triglycerides; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DIC, disseminated intravascular coagulation.

diagnosis MAS requires item #1 and at least two items among #2-5 (8): 1) ferritin >684 ng/mL, 2) platelet count ≤181×10^9/L, 3) aspartate aminotransferase (AST) >48 U/L, 4) triglycerides >156 mg/dL, and 5) fibrinogen ≤360 mg/dL). Then, the new cut-off values of the various indicators for the diagnosis of AOSD-MAS were calculated through ROC curves based on the data of AOSD-MAS patients (n=56) and AOSD without MAS (n=112). The evaluation of the MS score refers to the literature (9), according to the formula: (MS score = CNS involvement × 2.44 + haemorrhagic manifestations × 1.54 + arthritis ×(-1.30)+PLT count × (-0.003) + LDH × 0.001 + fibrinogen × (-0.004) + ferritin× 0.0001).

Definition

Neurological involvement was defined as the presence of mood changes, irritability, headache, lethargy, confusion, seizures, or coma. All patients routinely underwent bone marrow aspiration for identifying the presence or absence of primary blood system diseases.

Statistical analysis

Continuous variables were presented as medians with interquartile ranges, and categorical variables were presented as frequencies and percentages. The Kruskal-Wallis test or Mann-Whitney U-test was used to analyse the continuous variables, and the chi-square or Fisher exact test was used to analyse the categorical data. The receiver operating characteristic (ROC) curve analysis was used to identify the cut-off points of laboratory data. Statistical significance was declared at $p<0.05$. Statistical analyses were performed using SPSS statistics software 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Clinical and laboratory characteristics of AOSD-MAS and AOSD without MAS

A total of 56 AOSD-MAS patients, including 12 (21.4%) male and 44 (78.6%) females, were included. The median age was 35 years (range 18-76). The median duration from AOSD diagnosis to MAS was 5 months (range 0-96; <6 months in 35 cases). Table I shows the clinical and laboratory features of AOSD-MAS and AOSD without MAS. AOSD without MAS showed significantly lower frequencies of splenomegaly ($p<0.001$), neurological involvement ($p=0.013$), disseminated intravascular coagulation ($p<0.001$), and hepatic failure ($p<0.001$). The frequencies of abnormal laboratory findings were also lower in AOSD without MAS, in particular leukopenia, anaemia, thrombocytopenia, hypofibrinogenaemia, hypertriglyceridaemia (triglycerides (TG) ≥3 mmol/L), and haemophagocytosis in bone marrow ($p<0.001$). Besides those differences, the absolute changes in most laboratory indexes were also significantly different ($p<0.001$, except CRP, (Table I). For example, hyperferritinaemia was frequent both in AOSD-MAS (100%) and AOSD without MAS (96.4%), while serum ferritin levels in AOSD-MAS were remarkably higher ($p<0.001$). Serum levels of alanine aminotransferase (ALT), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and D-dimer, which are not included in the HLH-2004 criteria, were also different between AOSD-MAS and AOSD without MAS. The proportion of AOSD-MAS patients admitted to the ICU was higher than that of AOSD patients without MAS ($p=0.003$).

Table II. Predictive powers of individual parameters for the diagnosis of AOSD-MAS.

	ROC-AUC	Cut-off value	Sensitivity (%)	Specificity (%)	95%*CI*	*p*-value
PLT ($\times10^9$/L)	0.925	≤180	78.0	96.9	0.874-0.976	<0.001
Fibrinogen (g/L)	0.859	≤3.2	86.0	80.4	0.784-0.933	<0.001
WBC ($\times10^9$/L)	0.827	≤5.5	62.1	97.9	0.738-0.911	<0.001
LDH (U/L)	0.770	≥465	74.0	79.1	0.689-0.850	<0.001
D-dimer (μg/L)	0.764	≥2692	57.5	83.3	0.675-0.853	<0.001
AST (U/L)	0.763	≥118	62.0	85.4	0.674-0.852	<0.001
ESR (mm/h)	0.760	≤44.5	78.8	67.7	0.667-0.852	<0.001
ALT (U/L)	0.750	≥179.5	56.0	85.4	0.666-0.834	<0.001
Ferritin (μg/L)	0.723	≥9330.0	54.0	80.7	0.635-0.810	<0.001
Hb (g/L)	0.711	≤91.5	64.0	80.4	0.615-0.806	<0.001
CRP (mg/L)	0.316	≥68.2	68.4	48.1	0.224-0.407	<0.001
TG (mmol/L)	0.161	≥1.50	94.0	58.1	0.095-0.227	<0.001

AOSD with MAS: 56 cases; AOSD without MAS: 112 cases; ROC: Receiver Operating Characteristic; AUC: area under the curve; CI: confidence interval; MAS: macrophage activation syndrome; AOSD: adult-onset Still's disease; WBC: white blood cell; Hb: haemoglobin; PLT: platelet; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; TG: triglycerides; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Table III. Sensitivities and specificities of the 2016 EULAR/ACR/PRITO classification criteria for sJIA in the diagnosis of AOSD-MAS.

	Sensitivity (%)	Specificity (%)
Fulfilling criteria	100.0	80.4
Ferritin >684 μg/L	96.4	22.3
PLT ≤181×10^9/L	78.5	96.4
AST >48 U/L	71.4	42.9
TG >1.76 mmol/L	82.1	67.0
Fibrinogen ≤3.6 g/L	87.5	73.2

AOSD: adult-onset Still's disease; MAS: macrophage activation syndrome; PLT: platelet; AST: aspartate aminotransferase; TG: triglyceride.

Table IV. Sensitivities and specificities of the new models' ability to discriminate between AOSD-MAS and AOSD without MAS.

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7	Model 8
Ferritin >684 μg/L	+	+	+	+	+	+	+	-
Ferritin >9330 μg/L	-	-	-	-	-	-	-	+
PLT ≤180×10^9/L	+	+	+	+	+	-	+	+
AST >112 U/L	+	-	-	+	+	+	+	+
TG >1.76 mmol/L	+	+	+	-	+	+	-	+
Fibrinogen ≤3.2 g/L	+	+	+	+	+	+	+	+
WBC ≤5.5×10^9/L	+	+	-	+	-	+	-	-
ALT ≥179.5 U/L	-	+	+	-	-	-	-	-
Sensitivity (%)	92.0	92.0	90.0	88.0	86.0	86.0	80.0	50.0
Specificity (%)	87.6	87.7	87.7	94.8	87.6	88.7	94.8	93.1

+: inclusion in the model; -: exclusion from the model.

Laboratory predictors of MAS development in AOSD

A ROC curve analysis was performed to explore the utility of laboratory data to differentiate between AOSD-MAS and AOSD without MAS (Table II). The largest area under the curve (AUC) for platelets was 0.925, followed by fibrinogen (0.859), WBCs (0.827), LDH (0.770), D-dimer (0.764), and AST (0.763). TG levels seemed to be not useful for distinguishing AOSD-MAS from AOSD (AUC=0.161). White blood cell (WBC) count (5.5×10^9/L, within the normal reference range) showed the best specificity (97.9%) but low sensitivity (62.1%). Elevation of ALT (≥179.5 U/L), LDH (≥465 U/L), AST (≥118 U/L), and D-dimer (≥2692 μg/L), which are not included in the HLH-2004 criteria, might also be used as predictors of MAS development in AOSD. It is worth noticing that new cut-off values of ferritin (9330 μg/L) and fibrinogen (3.2 g/L) were remarkably higher than that defined by the HLH-2004 criteria (500 μg/L for ferritin and 1.5 g/L for fibrinogen).

Validation and modification of the 2016 EULAR/ACR/PRINTO criteria in AOSD-MAS

Since AOSD shares similarities with sJIA, it was hypothesised that the 2016 EULAR/ACR/PRINTO criteria for MAS associated with sJIA might be applicable for detecting AOSD-MAS patients. In the present study, the sensitivity of the 2016 criteria for identifying AOSD-MAS patients was 100.0%, and the specificity was 80.4% (Table III). Of the individual constituent criteria, ferritin levels (>684 ng/mL) showed the highest sensitivity (96.4%) but the lowest specificity (22.3%). Platelet counts (≤181×10^9/L) showed the highest specificity (96.4%). The specificity of AST was also low, with 64 (57.1%) AOSD without MAS patients fulfilling the AST (>48 U/L) criteria.

We revised the 2016 EULAR/ACR/PRINTO criteria by sequentially substituting the individual constituent criteria with the newly identified cut-off values, resulting in eight models, and determined the utility of the new models for classifying AOSD-MAS. As shown in Table IV, when substituting the ferritin cut-off value with the new one (>9330 μg/L), the sensitivity remarkably decreased to 50.0% (Model 8). If TG was excluded, and the newly identified cut-off values were used for the remaining three criteria (PLTs, AST, and fibrinogen), the specificity increased to 94.8% (Model 7). If we added WBC to Model 7, the specificity remained the same while the sensitivity increased to 88.0% (Model 4), which was the best among all models.

Validation and modification of the MS score in AOSD-MAS

We evaluated the capacity of the MS score in detecting AOSD-MAS pa-

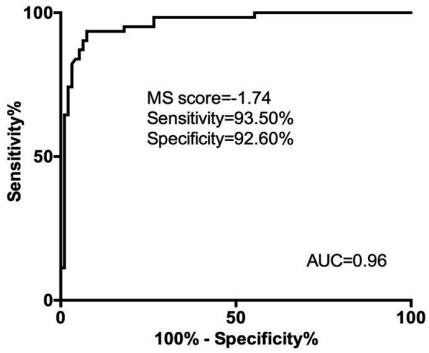

Fig. 2. The area under the receiver operating characteristic curve for the MS score in the diagnosis of AOSD-MAS.

tients. The MS score with a cut-off of ≥ -2.1 yielded a sensitivity of 95.2% and a specificity of 76.6%. The ROC curve analysis identified that a score of -1.74 could best discriminate AOSD-MAS from AOSD (Fig. 2). An MS score ≥ -1.74 yielded a sensitivity of 93.5% and a specificity of 92.6% in diagnosing AOSD-MAS (AUC=0.96, 95%CI: 0.93–0.99, p<0.0001).

Discussion

As one of the largest retrospective studies to date on AOSD-MAS (4, 5, 11-19), this study could provide valuable information for physicians to recognise AOSD-MAS patients. The results suggested that instead of absolute values, relative changes from baseline might be more useful for an early diagnosis of AOSD-MAS. In this study, the cut-off values of WBC, platelets, fibrinogen, and ferritin were examined, and they were higher than the minimum threshold level required by the HLH 2004 criteria. Due to the inflammatory nature of AOSD, WBC count, platelet count, and fibrinogen levels were often elevated in the active disease phase, so that decrease of those laboratory indexes, even to the normal reference range, could suggest the onset of MAS. Therefore, the cut-off values defined in the HLH-2004 criteria (developed for patients with primary HLH) might lead to an underdiagnosis of AOSD-MAS, especially in the early stage. The platelet cut-off value (<180×10^9/L, 78.0% sensitivity, 96.9% specificity, AUC=0.925) for AOSD-MAS in the present study was higher compared to a previous study with a smaller sample size (<121×10^9/L, 96.6% sensitivity, 95.2% specificity, AUC=0.98) (16). The ferritin cut-off (9330 μg/L) was also markedly higher than the 500μg/L criterion in HLH 2004, or that identified (662.5 μg/L) by a previous study in MAS associated with SLE (20). Yang *et al*. recently reported that ferritin >2000 μg/L (OR: 4.715, 95% CI: 1.12–19.86, p=0.035) was predictive of AOSD-MAS occurrence (19), while in our cohort, the median value of ferritin in AOSD without MAS was >2000 μg/L (2041 μg/L, IQR: 945.8–8499 μg/L), consistent with other studies (3000–11,000 μg/L in AOSD patients) (12, 16).

Despite many similarities between sJIA and AOSD, the diagnostic tool for MAS in sJIA should not be directly applied in AOSD-MAS without modification. Tada *et al*. tested the 2016 classification criteria for MAS in sJIA and concluded that it had high sensitivity but low specificity in identifying AOSD-MAS (21). The sample size in Tada's study (16 MAS patients) was smaller than in the present study (56 cases). Both studies determined new cut-off values for laboratory indexes, but the newly obtained cut-off values were different. New cut-off values of platelets and fibrinogen in the present study were mostly close to the 2016 EULAR/ACR/PRINTO criteria, while AST and ferritin levels were much higher. Non-criteria laboratory features, including ALT, WBC, and LDH, also added value to recognising AOSD-MAS, as shown by the present study. When the new cut-off value was used for ferritin, the sensitivity sharply dropped to 50.0%. Thus, several sets of criteria were explored based on the modification of the 2016 EULAR/ACR/PRINTO criteria without substituting the ferritin cut-off. These candidate criteria showed decreased sensitivities and increased specificities, and Model 4 (ferritin >684 μg/L, PLT ≤180×10^9/L, AST >112 U/L, fibrinogen ≤3.2 g/L, and WBC ≤5.5×10^9/L; TG was excluded from the criteria) showed excellent ability in differentiating AOSD patients with MAS from those without MAS (88.0% sensitivity and 94.8% specificity), thus indicating that TG is not an ideal candidate criterion for classifying MAS from active AOSD.

Recently, a diagnostic scoring system-MAS/sJIA (MS) score was developed to detect MAS in sJIA patients. This scoring system includes seven variables: central nervous system involvement, haemorrhage, arthritis, platelet count, lactate dehydrogenase, fibrinogen, and ferritin. A cut-off value ≥–2.1 revealed the best discriminatory performance with a sensitivity of 85.0% and a specificity of 95.0% (9). Wang *et al*. tested and modified the diagnostic score in AOSD-MAS patients and concluded that an MS score ≥–1.08 could best discriminate AOSD-MAS from AOSD with a sensitivity of 94.1% and a maximum specificity of 95.0% (22). Although the AOSD-MAS sample size in our cohort was similar to Wang's study, we obtained a different cut-off value of the MS score (≥ -1.74) to distinguish AOSD-MAS from AOSD (AUC=0.96, 93.5% sensitivity, 92.6% specificity), which might be partly due to differences in the study populations. For example, neurological involvement was lower in the present study and Wang *et al*. (22) than in Minoia *et al*. (9). Still, whether the different prevalence of clinical symptoms among sJIA-MAS and AOSD-MAS is due to different timing of patient assessment, a different definition of MAS, or differential clinical phenotypes of MAS between the two illnesses cannot be defined based on the available data, and comparative studies are required. In the present cohort, the LDH levels (662 (437.5, 1808.8) U/L) were lower in AOSD-MAS patients compared to that in Wang's study (1024 (599, 2145) U/L). In addition, the up-limit detection of ferritin (1500 ng/mL) in Wang's study was lower than in the present study (100,000 ng/mL), which could lead to different MS scores.

The present study has several limitations. Since the data were retrospectively collected, the findings might be biased. Data on fever pattern, fever days and the duration of the fever's highest body temperature were unavailable for most patients. Markers that are not routinely assessed (*e.g*. aldolase (23)) could not be analysed. Finally, there are no clear diagnostic criteria

for the diagnosis of MAS secondary to AOSD currently. Based on the HLH-2004 standard, there might be missed diagnosis of "immature" MAS cases with early-onset. In the present study, the MAS was diagnosed based on the HLH-2004 standard and further confirmed by two senior rheumatologists. Still, it can reduce the heterogeneity of cases and avoid underdiagnosis to a certain extent. In addition, some studies diagnose AOSD-MAS based on the HLH-2004 standard combined with the diagnosis of senior doctors (4, 5, 22). Further study with a prospective design might produce more valuable data.

In conclusion, although the clinical presentations of both AOSD-MAS and active AOSD are similar, the relative changes of laboratory data might help the physicians make an early diagnosis of AOSD-MAS. Present diagnostic tool for MAS in sJIA should not be directly applied in AOSD-MAS without modification. A new cut-off value of MS (≥ -1.74) can better distinguish AOSD-MAS from AOSD. Exclusion of TG, the addition of WBC, and substitution of the original cut-off values for platelets, AST, and fibrinogen of the 2016 MAS in sJIA classification could help build a more efficient system for recognising AOSD-MAS. Additional studies are needed to capture better similarities/differences of MAS in sJIA/AOSD and optimise the criteria.

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