Adapting the MS score for detection of macrophage activation syndrome in adult-onset Still's disease. Response to 'Application of MS score in macrophage activation syndrome patients associated with adult onset Still's disease' by Wang *et al*

We are grateful to Wang *et al*[1] for testing our diagnostic score for macrophage activation syndrome (MAS)[2] in their patients with adult onset Still disease (AOSD). Because it is increasingly recognised that systemic juvenile idiopathic arthritis (sJIA) and AOSD represent the same disease occurring at different ages[3 4] and considering that the two illnesses share a similar risk for MAS, it is important to investigate whether the current diagnostic tools are applicable to both conditions.

Wang and colleagues evaluated retrospectively the capacity of the MAS/sJIA (MS) score to detect MAS in AOSD by comparing 60 patients with MAS, whose diagnosis was made by HLH-2004 criteria and confirmed by the caring rheumatologists, with 390 patients without MAS. They found that the application of the MS score with the cut-off of ≥ −2.1 obtained in our study yielded a maximum sensitivity of 100%, but poor specificity (29.8%) and a low kappa value (0.32). These findings indicated that the MS score had strong capacity to detect MAS, but inadequate ability to discriminate patients with MAS from patients without MAS.

However, by conducting a receiver operating characteristic curve analysis of the MS score on their patient data, the authors found that a score cut-off of ≥ −1.08 increased considerably the specificity (95%), without compromising the sensitivity (94.1%). The kappa value rose to 0.78 and the area under the curve was as high as 0.98. Wang *et al* concluded that although the MS score is suitable to capture MAS in patients with AOSD, its cut-off value should be modified from ≥ −2.1 to ≥ −1.08 to achieve the best diagnostic performance.

Although these conclusions are certainly supported by the results of the analyses, it is, nevertheless, necessary to highlight the remarkable differences in the frequency of clinical features and in laboratory values between the AOSD patients with MAS in the series of Wang *et al* and the patients with sJIA-associated MAS enrolled in our study,[2 5] which are shown in table 1. The most striking disparity regards the frequency of central nervous system (CNS) disease and haemorrhagic manifestations, which were recorded in 35% and 20.4% of sJIA-MAS patients, respectively, but were observed in only one patient each in the AOSD-MAS sample. Of the other clinical features, splenomegaly was more common in AOSD-MAS patients, whereas arthritis was more prevalent in sJIA-MAS patients. Among laboratory parameters, platelet count and fibrinogen level were, on average, lower in AOSD-MAS patients, whereas ferritin was higher in sJIA-MAS patients. In interpreting ferritin value, it should be taken into account that in AOSD-MAS patients it was likely underestimated as the upper limit of detection in Wang *et al* centres was 1500 ng/mL.

It appears, therefore, clear that the discordance in the MS score cut-off between our study and that of Wang *et al* largely depends on the aforementioned diversities between their AOSD-MAS patients and our sJIA-MAS sample. Note that in the developmental process of the MS score, CNS dysfunction and haemorrhagic manifestations revealed the strongest discriminative properties and were, therefore, assigned the highest weights. Whether the discordant prevalence of these clinical symptoms is due to a different timing of patient assessment over the course of MAS or to diversities in the clinical phenotype of MAS between the two illnesses, cannot be established. Needless to say that the technical limitations in ferritin measurement introduced a bias in Wang *et al* analyses, given the major diagnostic role of this biomarker in MAS.

Table 1 Demographic, clinical, laboratory and histopathological features of AOSD and sJIA patients with MAS*

Feature	MAS in sJIA† (n=362)	MAS in AOSD‡ (n=60)
Females	208 (57.5)	18 (30.0)
Median (IQR) age at onset of MAS, years	8.1 (4.0–13.2)	29.0 (22.0–37.0)
Fever	341/355 (96.1)	60/60 (100.0)
Splenomegaly	201/347 (57.9)	50/60 (83.3)
Active arthritis	230/354 (65.0)	19/60 (31.6)
Central nervous system disease	122/349 (35.0)	1/60 (1.7)
Haemorrhagic manifestations	71/348 (20.4)	1/60 (1.7)
Median (IQR) laboratory parameters		
Platelet count, x10^9/L	144 (86–269)	90 (60–144)
Lactate dehydrogenase, units/L	1203 (666–2345)	1024 (599–2145)
Triglycerides, mg/dL	234 (151–318)	208 (161–335)
Fibrinogen, mg/dL	267 (152–437)	151 (104–219)
Ferritin, ng/mL	5353 (1500–13 040)	1500 (1500–1500)§
Bone marrow haemophagocytosis	149/249 (59.8)	39/60 (65.0)
Death	28/347 (8.1)	13/60 (21.7)

*Data are number positive/number with information available (%), unless otherwise indicated.
†Adapted from Davì *et al*, Arthritis Rheumatol 2014;66:2871–80.
‡Adapted from Wang *et al*, Ann Rheum Dis 2019, in press.
§The upper limit of ferritin detection was 1500 ng/mL.
AOSD, adult onset Still disease; MAS, macrophage activation syndrome; sJIA, systemic juvenile idiopathic arthritis.

Despite these caveats, Wang and coworkers are to be commended for drawing attention to the importance of harmonising the diagnostic tools across AOSD and sJIA. Additional studies in series of AOSD and sJIA patients are needed to compare the characteristics of MAS between the two illnesses and to identify the cut-off of the MS score that is most helpful to recognise timely this dreadful complication.

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REFERENCES

1 Wang R, Li T, Ye S, *et al*. Application of MS score in macrophage activation syndrome patients associated with adult onset Still's disease. *Ann Rheum Dis*. 2019:annrheumdis-2019-216286.
2 Minoia F, Bovis F, Davì S, *et al*. Development and initial validation of the MS score for diagnosis of macrophage activation syndrome in systemic juvenile idiopathic arthritis. *Ann Rheum Dis* 2019.
3 Inoue N, Shimizu M, Tsunoda S, *et al*. Cytokine profile in adult-onset still's disease: comparison with systemic juvenile idiopathic arthritis. *Clinical Immunology* 2016;169:8–13.
4 Nirmala N, Brachat A, Feist E, *et al*. Gene-Expression analysis of adult-onset still's disease and systemic juvenile idiopathic arthritis is consistent with a continuum of a single disease entity. *Pediatr Rheumatol Online J* 2015;13.
5 Davì S, Minoia F, Pistorio A, *et al*. Performance of current guidelines for diagnosis of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. *Arthritis Rheumatol* 2014;66:2871–80.