Neutrophil-to-Lymphocyte Ratio and System Score Could Predict the Occurrence of Macrophage Activation Syndrome in Patients with Adult-Onset Still's Disease

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ABSTRACT

Objective: To investigate the characteristics of Adult-onset Still's disease (AOSD) patients with macrophage activation syndrome (MAS) and explore the risk factors for the development of MAS.

Study Design: A case-control study.

Place and Duration of the Study: Department of Rheumatology and Immunology, the Second Hospital of Anhui Medical University, Anhui, China, from January 2008 to June 2024.

Methodology: AOSD patients with MAS (AOSD-MAS) and without MAS (AOSD-nonMAS) were compared. Clinical features and laboratory results from two groups were analysed using the independent samples t-test or Mann-Whitney U test. Fisher's exact test or Pearson's Chi-square test was used to compare the variables between the two groups. The multivariable logistic regression analysis was applied to identify AOSD with MAS-associated factors. The value of risk factors in predicting MAS occurrence was carried out by a receiver operating characteristic validation analysis.

Results: MAS patients showed higher prevalence of sore throat, splenomegaly and abnormal liver function, a lower prevalence of arthrodynia and higher levels of neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, alanine aminotransferase, aspartate aminotransferase, lactic dehydrogenase, serum ferritin, D-Dimer levels, and a higher AOSD system score, along with a lower lymphocyte count ($p < 0.05$). Multivariate logistic regression analysis identified NLR and AOSD system scores as predictors of MAS. An optimised threshold of 17.455 and 5.500 for NLR and AOSD system score yielded a sensitivity of 84.60% (38.50) and a specificity of 91.00%, (47.40).

Conclusion: Early detection of MAS in AOSD may be facilitated by monitoring these factors, particularly NLR and AOSD system scores.

Key Words: *Adult-onset still's disease, Macrophage activation syndrome, Risk factor.*

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INTRODUCTION

Adult-onset Still's disease (AOSD), a rare inflammatory disease with unknown aetiology, primarily presents with spiking fever, skin rash, arthrodynia or arthritis, elevated white blood cell (WBC) count, and hyperferritinaemia in patients.[1,2] Generally, AOSD patients have a fair prognosis with a mortality of approximately 1-3%.[2] However, some patients may develop major serious complications such as fulminant hepatitis, myocarditis, or macrophage activation syndrome (MAS). These complications dramatically increase the mortality of AOSD patients.[3] MAS is a reactive haemophagocytic lymphohistiocytosis, which is often secondary to some rheumatic diseases such as AOSD and systemic lupus erythematosus.

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Sufferers with MAS may develop typical symptoms such as remittent fever, hepatosplenomegaly, coagulopathy, cytopenias, hyperferritinaemia, and haemophagocytosis on bone marrow aspirates. It is reported that 10-15% of AOSD patients develop MAS.[4] MAS may dramatically raise the mortality risk of AOSD patients considering a significantly lower survival rate of AOSD patients with MAS than those without MAS.[5] AOSD and MAS share highly similar clinical and biological symptoms and indicators to some extent, posing a great challenge to distinguish between the two clinical phenotypes.

Particularly, there are few studies on identifying valuable variables that predict the subsequent development of MAS in AOSD. Accordingly, the present study was conducted to screen potential risk factors for the development of MAS in patients with AOSD by comparing the general data and clinical and laboratory characteristics of AOSD patients with and without MAS. It is expected that this study may provide clinicians with more information for early diagnosis and prompt treatment of MAS in AOSD.

METHODOLOGY

A total of 105 AOSD patients visited the Second Hospital of Anhui Medical University, Anhui, China, from January 2008 to

July 2024. Twenty-six patients accompanied with MAS. All included AOSD patients were diagnosed based on the diagnostic criteria proposed by Yamaguchi *et al*.[6] MAS diagnosis followed the haemophagocytic lymphohistiocytosis (HLH)-2004 guidelines.[7] This study excluded patients with missing data at the time of diagnosis and patients with tumours, infections or other rheumatic diseases. Patients were scored according to the AOSD system score proposed by Pouchot *et al*. including fever, pleuritis, pneumonia, skin rash, pericarditis, hepatomegaly or abnormal liver function tests, lymphadenopathy, splenomegaly, abdominal pain, increased WBC count >15,000/mm^3, sore throat, and myalgia (each clinical feature for one point).[8] Pleurisy or pleural effusion and parenchymal lesions were evaluated by chest radiography or chest CT, pericardial effusion or pericarditis by echocardiography, and hepatomegaly and lymph nodes by ultrasound. AOSD patients combined with MAS were defined as the AOSD-MAS group, and patients without MAS as the AOSD-nonMAS group.

The study was approved by the Ethics Committee of the hospital (Approval No. YX2023-169). The clinical characteristics and laboratory results of the enrolled patients were recorded and collected at the time of diagnosing AOSD and MAS by reviewing their past medical records. Clinical data included gender, age, disease duration, fever, sore throat, arthrodynia, skin rash, hepatomegaly, splenomegaly, and lymphadenopathy. Laboratory tests included WBC, neutrophil count (NEU), lymphocyte count, haemoglobin (Hb), platelet (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and γ-glutamyltransferase (γ-GT), lactic dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), and hypersensitive C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), serum ferritin (SF) levels, triglyceride (TG), fibrinogen (FIB), D-Dimer, and rheumatoid factor (RF).

The Kolmogorov-Smirnov test and the Shapiro-Wilk's test were used to determine if the data came from normal distribution. For quantitative data of clinical characteristics and laboratory data that conformed to a normal distribution between the two groups, an independent-sample t-test was used, presented by the mean ± standard deviation ($\bar{x}\pm s$). The non-parametric statistical tests were used to compare the study's continuous variables by Mann-Whitney U test. The Mann-Whitney U test was employed to examine the clinical and laboratory manifestation between the two groups and the results were represented by the median and interquartile range M (P25, P75). Fisher's exact test or Pearson's Chi-square test were applied for the clinical characteristics of the patients. Any variable having a significant unvariable result ($p < 0.05$) was selected as a possible candidate for multivariable logistic regression analysis. The multivariable logistic regression analysis was applied to evaluate the predicted factors of MAS development in AOSD. The value of risk factors in predicting MAS occurrence identified through multivariable logistic regression was carried out by a receiver operating characteristic (ROC) validation analysis and areas under the ROC curves (AUC). Counting data were shown with the number of cases and frequency percentage (n, %). A p-value less than 0.05 was considered to be statistically significant.

RESULTS

A total of 105 patients with AOSD were enrolled in this study, including 26 cases with MAS and 79 without MAS. The male-to-female ratio was 24:55 in the AOSD-nonMAS group and 8:18 in the AOSD-MAS group, respectively. All patients had fever (≥38.5°C). No significant differences were found in gender, age, course, fever, sore throat, skin rash, myalgia, lymphadenopathy, and hepatomegaly between the AOSD-MAS group and the AOSD-nonMAS group (all $p > 0.05$). There were higher possibilities of splenomegaly and abnormal liver function in the AOSD-MAS group than those in the AOSD-nonMAS group ($p < 0.05$). In addition, the AOSD-MAS group had a lower prevalence of arthrodynia compared to the AOSD-nonMAS group ($p < 0.05$). The details are shown in Table I.

The levels of NLR, PLR, ALT, AST, LDH, D-Dimer, and SF as well as the AOSD system score were obviously higher in the AOSD-MAS group than those in the AOSD-nonMAS group, and lymphocytes count was obviously lower than that in the latter group (all $p < 0.05$). There were no significant differences in the levels of WBC, NEU, Hb, PLT, ALP, γ-GT, ESR, CRP, TG, and FIB between the groups (all $p > 0.05$). The above results are shown in Table II.

Table I: Clinical characteristics of AOSD with MAS and AOSD without MAS.

Parameters	ASOD-nonMAS group (n = 79) n (%)	AOSD-MAS group (n = 26) n (%)	Z	p-value
Gender (female) (%)	55 (69.62%)	18 (69.23%)	-	>0.99
Age, M (P25, P75) years	36.00 (27.00, 54.00)	33.00 (24.50, 56.25)	-0.936	0.349
Course, M (P25, P75) days	15.00 (10.00, 30.00)	15.00 (10.00, 21.00)	-0.537	0.591
Fever (≥38.5℃)	79 (100.00%)	26 (100.00%)	-	-
Sore throat	60 (75.95%)	20 (76.92%)	-	>0.99
Arthrodynia	63 (79.75%)	15 (57.69%)	-	0.038
Skin rash	73 (92.41)	26 (100.00%)	-	0.332
Myalgia	48 (60.75%)	11 (42.31%)	-	0.115
Lymphadenopathy	57 (72.15%)	23 (88.46%)	-	0.114
Splenomegaly	21 (26.58%)	14 (53.85%)	-	0.016
Hepatomegaly	1 (1.27%)	1 (3.85%)	-	>0.99
Abnormal liver function	42 (53.16%)	21 (80.77%)	-	0.020

The Mann-Whitney U test, Fisher's exact probability, and Pearson's Chi-Square test were used to compare the AOSD-MAS group and the AOSD-nonMAS group. Statistical significance was expressed by p-value <0.05.

Table II: Laboratory examination of AOSD with MAS and AOSD without MAS.

Parameters	AOSD-nonMAS group (n = 79)	AOSD-MAS group (n = 26)	Z/T	p-value
WBC (×10^9/L)	13.87 ± 5.90	13.96 ± 7.13	-0.065	0.186
NEU (×10^9/L)	10.95 (7.58, 14.01)	10.40 (8.09, 17.12)	-0.308	0.758
Lymphocytes count (×10^9/L)	1.30 (1.00, 1.91)	0.87 (0.52, 1.20)	-3.664	<0.001
NLR	7.34 (4.97, 12.18)	11.50 (7.39, 25.85)	-2.774	0.006
Hb (g/L)	112.00 (101.00, 121.00)	109.50 (103.75, 124.25)	-0.401	0.688
PLT (×10^9/L)	299.22 ± 116.29	228.62 ± 89.61	2.828	0.312
PLR	208.76 (140.85, 302.59)	280.05 (176.30, 404.90)	-2.034	0.042
ALT (U/L)	35.00 (20.00, 70.00)	57.50 (28.5, 158.75)	-2.183	0.029
AST (U/L)	38.00 (26.00, 58.00)	63.00 (41.50, 124.75)	-3.030	0.002
ALP (U/L)	94.00 (80.00, 119.50)	100.50 (84.75, 192.25)	-1.545	0.122
γ-GT (U/L)	42.00 (23.00, 89.00)	57.50 (29.25, 140.25)	-1.363	0.173
LDH (U/L)	340.00 (259.25, 451.75)	43.50 (317.25, 650.25)	-2.919	0.004
CRP (mg/L)	89.42 (48.60, 152.20)	135.59 (56.53, 228.60)	-1.670	0.095
ESR (mm/h)	42.50 (22.75, 62.75)	41.00 (35.75, 60.75)	-0.288	0.774
SF (ng/ml)	2419.50 (754.25, 4931.50)	8261.50 (4111.00, 13390.25)	-4.231	<0.001
TG (mmol/L)	1.09 (0.88, 1.43)	1.24 (0.95, 1.52)	-1.272	0.203
FIB (g/L)	5.19 (4.07, 6.45)	5.86 (3.70, 6.81)	-0.650	0.515
D-Dimer (μg/ml)	3.41 (1.53, 5.09)	5.18 (2.86, 9.21)	-2.420	0.016
AOSD system score	6.00 (5.00, 7.00)	6.5 (6.00, 8.00)	-3.317	0.001

The Mann-Whitney U test and Independent samples t-tests were used to compare the AOSD-MAS group and the AOSD-nonMAS group.
WBC: White blood cell, NEU: Neutrophil count, NLR: Neutrophil-to-lymphocyte ratio, Hb: Haemoglobin, PLT: Platelet, PLR: Platelet-to-lymphocyte ratio, AST: Aspartate amino-transferase, ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, γ-GT: γ-glutamyltransferase, LDH: Lactic dehydrogenase, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, SF: Serum ferritin, TG: Triglyceride, FIB: Fibrinogen.

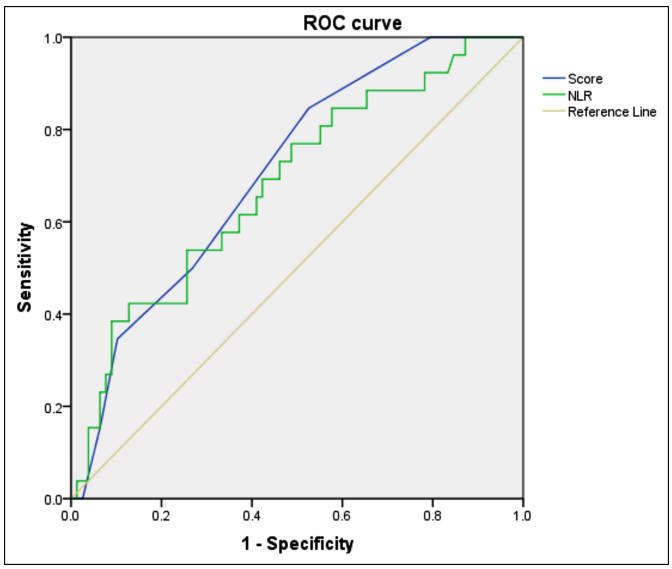

Figure 1: The ROC curve of NLR and AOSD system score.

Multivariate logistic regression analysis was used to evaluate the risk of MAS by comparing AOSD patients with and without MAS according to their laboratory results at baseline. The results showed that NLR (p = 0.017) and AOSD system score (p = 0.029) were independent risk factors for MAS in AOSD patients.

The optimal cut-off value for predicting MAS in AOSD patients was determined at the maximum value, which was estimated by sensitivity + 1-specificity in the ROC curve. Among these variables, NLR and AOSD system scores with cut-off values of 17.455 and 5.500, showed the greatest sensitivity (38.5% and 84.6%), specificity (91.0% and 47.4%), and AUC values (0.682 and 0.709) for diagnosing AOSD with MAS (Figure 1).

DISCUSSION

MAS is a multiple organ-involved severe disease clinically, with a significant negative impact on the survival of patients, especially in the absence of timely diagnosis. AOSD and MAS share similar clinical manifestations and laboratory examination results. Therefore, it is difficult to identify MAS in the clinical setting. Meanwhile, the occurrence of MAS may increase the mortality rate of AOSD patients. In addition, there is still a poor understanding of the predictive factors for MAS in AOSD. In view of the above, the current study mainly analysed and discussed the risk factors of MAS in AOSD patients by collecting clinical data and laboratory examination results of AOSD patients.

Among 105 AOSD patients included in the present study, 26 (24.76%) cases developed MAS, with higher incidence compared with the previous study.[4] Splenomegaly and abnormal liver function were common clinical features of MAS.[9] The presence of splenomegaly was associated with MAS occurrence. A previous study reported similar proportions of hepatomegaly and abnormal liver function in AOSD with MAS and without MAS.[10] In the present study, splenomegaly and abnormal liver function were more common in AOSD patients with MAS, while no difference was found in the prevalence of hepatomegaly between the two groups. In addition, AOSD patients without MAS were more prone to arthrodynia, yet with unclear reasons.

In a follow-up study of 119 patients with AOSD in Italy, Ruscitti *et al*. found that lymphadenopathy and abdominal pain were predictive factors of MAS.[11] Bae *et al*. reported that thrombocytopaenia, anaemia, and hepatomegaly could predict the occurrence of MAS according to a retrospective analysis of the features of 109 AOSD patients in Korea.[12] Wakabayashi *et al*. found that β2-microglobulin was related to the occurrence of MAS in 23 AOSD cases in Japan.[13] In this

study, AOSD patients had reduced lymphocyte count. Lymphopenia was believed to be related to apoptosis in inflammatory states.[14] Jin *et al*. retrospectively discovered that lymphopenia could predict the clinical phenotype and poor prognosis in anti-MDA5 antibody-positive dermatomyositis patients.[15] For the first time, the present study reported a lower lymphocyte count in AOSD patients with MAS than in those without MAS.

Both WBC and PLT are crucial indices in inflammatory diseases. Neutrophils are the main cells that function significantly in adaptive immunity and inflammatory response. PLT can release cytokines that regulate and amplify inflammation through various mechanisms.[16] NLR and PLR are the markers of inflammation. Multiple studies have shown that the two markers can be used to evaluate the inflammatory activities in various diseases such as systemic lupus erythematosus, dermatomyositis, and AOSD.[17-19] In this study, NLR and PLR levels were higher in AOSD patients with MAS, indicating more aggressive inflammatory activities in these patients. Further multivariate logistic regression analyses indicated that NLR might be an independent risk factor for MAS occurrence in AOSD. Furthermore, LDH plays a major role in converting lactic acid into pyruvate within cells, which may increase in the case of injured tissues or destroyed cells. Elevated LDH is considered an indicator for monitoring tissue ischaemia, suggesting a poor outcome in MAS patients. Higher LDH levels in the AOSD patients with MAS may reveal more severe tissue or cell damage, which may facilitate the diagnosis of MAS clinically. The AOSD patients with MAS also had higher D-Dimer, suggesting that patients may have more severe disease at the diagnosis.

High ferritin level is a characteristic marker for the diagnosis of AOSD, evaluation of disease activity and identification of MAS, especially when the increase in SF is over five-fold.[20,21] Similarly, this study showed that AOSD patients with MAS had higher SF levels. In addition, the AOSD system score was identified as the risk factor. The AOSD system score was proposed by Pouchot *et al*. AOSD patients with higher AOSD system scores would have more extensive viscera involvement and more severe physical condition.[8] Previous studies had shown that the AOSD system score greater than seven was a risk factor for MAS, which would suggest an elevated mortality rate.[22,23] In the present study, a higher AOSD system score was associated with MAS in AOSD patients, and a score over 5.5 was a risk factor for predicting the occurrence of MAS. There are still several limitations in the study. Firstly, the study was a single-centre, small-sample retrospective case-control study, rather than a randomised controlled trial. Secondly, this study failed to collect comprehensive laboratory examination results at the corresponding time points in some patients, which restricted the further comparison of MAS severity. Therefore, the results of the current study remain to be verified by a multi-centre and large-sample controlled trial.

CONCLUSION

NLR may be a risk factor of MAS in AOSD patients. Meanwhile, the AOSD system score is also a risk factor for predicting MAS occurrence. Findings in this study may guide clinicians to diagnose and treat AOSD patients timely and effectively. It may provide additional reference for diagnosing MAS in AOSD patients at an early stage, and decrease MAS-related AOSD mortality consequently.

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ETHICAL APPROVAL:
The study was approved by the Ethics Committee of the Second Affiliated Hospital and Anhui Medical University (No: YX2023- 169).

PATIENTS' CONSENT:
All patients provided written informed consent.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
LC, HZ, DL: Participated in the study design, experimental operation, data analysis and interpretation, and manuscript writing.
LQ: Conceived the study and supervised the whole process.
All authors approved the final version of the manuscript to be published.

REFERENCES

1. Petros E, Apostolos K, Peter H, Kavita R, Ramakrishna G S, Priscila N. Adult-onset Still's disease in focus: Clinical manifestations, diagnosis, treatment, and unmet needs in the era of targeted therapies. *Semin Arthritis Rheum* 2021; **51(4)**:858-74. doi: 10.1016/j.semarthrit.2021.06.004.
2. Bella YM, Said I, William B, Petros E. Racial/Ethnic variations in morbidity and mortality in adult onset still's disease: An analysis of national dataset. *Semin Arthritis Rheum* 2019; **49(3)**:469-73. doi: 10.1016/j.semarthrit.2019.04.004.
3. Manuel RC, Pilar BZ, Armando LG, Munther AK, Xavier B. Adult haemophagocytic syndrome. *Lancet* 2014; **383 (9927)**:1503-16. doi: 10.1016/S0140-6736(13)61048-X.
4. Fukaya S, Yasuda S, Hashimoto T, Oku K, Kataoka H, T Horita, *et al*. Clinical features of haemophagocytic syndrome in patients with systemic autoimmune diseases: Analysis of 30 cases. *Rheumatology (Oxford)* 2008; **47(11)**: 1686-91. doi: 10.1093/rheumatology/ken342.
5. Ahn SS, Yoo BW, Jung SM, Lee SW, Park YB, Song JJ. Application of the 2016 EULAR/ACR/PRINTO classification criteria for macrophage activation syndrome in patients with adult-onset still disease. *J Rheumatol* 2017; **44(7)**:996-1003. doi: 10.3899/jrheum.161286.

6. Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H, *et al.* Preliminary criteria for classification of adult Still's disease. *J Rheumatol* 1992. **19 (3)**:424-30.
7. Jan-Inge H, Annacarin H, Maurizio A, R Maarten E, Alexandra HF, Shinsaku I, *et al*. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lympho-histiocytosis. *Pediatr Blood Cancer* 2007; **48(2)**:124-31. doi: 10.1002/pbc.21039.
8. Pouchot J, Sampalis JS, Beaudet B, Carette S, Decary F, Salusinsky-Sternbach M, *et al*. Adult Still's disease: Manifestations, disease course, and outcome in 62 patients. *Medicine (Baltimore)* 1991; **70(2)**:118-36.
9. Alexei AG, Horne AC, Benedetti FD . Macrophage activation syndrome in the era of biologic therapy. *Nat Rev Rheumatol* 2016; **12(5)**:259-68. doi: 10.1038/nrrheum.2015.179.
10. Yang XP, Wang M, Li TF, Li W, Zhang L, Liu SY. Predictive factors and prognosis of macrophage activation syndrome associated with adult-onset still's disease. *Clin Exp Rheumatol* 2019; **121(6)**:83-8.
11. Ruscitti P, Iacono D, Ciccia F, Emmi G, Cipriani P, Grembiale RD, *et al*. Macrophage activation syndrome in patients affected by adult-onset still disease: Analysis of survival rates and predictive factors in the gruppo Italiano di ricerca in reumatologia clinica e sperimentale cohort. *J Rheumatol* 2018; **45(6)**:864-72. doi: 10.3899/jrheum.170955.
12. Bae CB, Jung JY, Kim HA, Suh CH. Reactive hemophagocytic syndrome in adult-onset Still disease: Clinical features, predictive factors, and prognosis in 21 patients. *Medicine (Baltimore)* 2015; **94(4)**:e451. doi: 10.1097/MD.0000000000000451.
13. Wakabayashi K, Inokuma S, Matsubara E, Onishi K, Asashima H, Nakachi S, *et al*. Serum β2-microglobulin level is a useful indicator of disease activity and hemophagocytic syndrome complication in systemic lupus erythematosus and adult-onset Still's disease. *Clin Rheumatol* 2013; **32(7)**:999-1005. doi: 10.1007/s100 67-013-2220-8.
14. de Jager CP, van Wijk PT, Mathoera RB, de Jongh-Leuvenink J, van der Poll T, Wever PC, *et al*. Lymphocytopenia and neutrophil-lymphocyte count ratio predict bacteremia better than conventional infection markers in an emergency care unit. *Crit Care* 2020; **14(5)**:R192. doi: 10.1186/cc9309.
15. Jin QW, Fu LJ, Yang HX, Chen XX , Lin S, Huang ZG, *et al*. Peripheral lymphocyte count defines the clinical phenotypes and prognosis in patients with anti-MDA5-positive dermatomyositis. *J Intern Med* 2023; **293(4)**:494-507. doi: 10.1111/joim.13607.
16. Maouia A, Rebetz J, Kapur R, Semple JW. The immune nature of platelets revisited. *Transfus. Med Rev* 2020; **34(4)**: 209-20. doi: 10.1016/j.tmrv.2020.09.005.
17. Cho JC, Liang S, Lim SHH, Lateef A, Tay SH, Mak A. Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio reflect disease activity and flares in patients with systemic lupus erythematosus-A prospective study. *Joint Bone Spine* 2020; **89(4)**:105342. doi: 10.1016/j.jbspin.2022.105342.
18. Li MQ, Yan SY, Dong RR, Xiang WZ, Ma ZZ, Yang QR. Elevated platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio in patients with polymyositis/ dermatomyositis: A retrospective study. *Clin Rheumatol* 2023; **42(6)**:1615-24. doi: 10.1007/s10067-023-06542-7.
19. Karima DA, Nadia AH, Fifi O, Chafia DM, Farida M, Mohamed M, *et al.* Validation of the neutrophil-to-lymphocyte ratio as a new simple biomarker of adult onset Still's disease: A STROBE-Compliant prospective observational study. *Medicine (Baltimore)* 2022; **101(32)**:e29970. doi: 10.1097/MD.0000000000029970.
20. Coffernils M, Soupart A, Pradier O, Feremans W, Neve P, Decaux G. Hyperferritinemia in adult onset Still's disease and the hemophagocytic syndrome. *J Rheumatol* 1992; **19(9)**:1425-7.
21. Piero R, Francesco U, Onorina B, Francesco M, Bozzalla CE, Susanna N, *et al.* Cytokine profile, ferritin and multivisceral involvement characterise macrophage activation syndrome during adult-onset Still's disease. *Rheumatology (Oxford)* 2022; **62(1)**:321-9. doi: 10.1093/rheumatology/keac247.
22. Piero R , Paola C, Francesco M , Daniela I , Francesco C , Vasiliki L, *et al*. Adult-onset Still's disease: Evaluation of prognostic tools and validation of the systemic score by analysis of 100 cases from three centers. *BMC Med* 2016; **14(1)**:194. doi: 10.1186/s12916-016-0738-8.
23. Piero R , Carmela R , Luciana B, Paola C , Vasiliki L, Onorina B, *et al.* Macrophage activation syndrome in Still's disease: Analysis of clinical characteristics and survival in paediatric and adult patients. *Clin Rheumatol* 2017; **36(12)**:2839-45. doi: 10.1007/s10067-017-3830-3.