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Validation of the neutrophil-to-lymphocyte ratio as a new simple biomarker of adult onset Still's disease

A STROBE-Compliant prospective observational study

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Abstract

This study was performed to investigate the role of neutrophil-to-lymphocyte ratio (NLR) in the diagnosis of adult onset Still disease (AOSD) and its performance to improve the sensitivity of the classifications criteria (Yamaguchi and Fautrel Classifications).

We conducted a multicenter prospective nationwide case-control study in Internal medicine, Rheumatology and Infectious disease departments, to include successively patients with suspected AOSD (2 or more major criteria of Yamaguchi or Fautrel classifications). All clinical and biological features were collected in a consensual and standardized clinical assessment at baseline and during follow-up. A receiving operating characteristic (ROC) curve was used to reassess the cutoff value of NLR. After determination of the cutoff value for NLR by ROC curve, 2 composite sets (Yamaguchi classification + NLR as a major criterion and Fautrel classification + NLR as a major criterion) were performed and evaluated.

One hundred sixty patients were included, 80 patients with AOSD and 60 controls with different diagnoses. Twenty patients with incomplete data were excluded. The cutoff value for NLR equals 4 (area under the curve, AUC: 0.82). The NLR was ≥ 4 in 93.7% (75/80) of AOSD patients with a sensitivity of 93.8% and specificity of 61.7%. The association of NLR as a major criterion with the classification of Yamaguchi or Fautrel improved their sensitivity, respectively for Fautrel (76.3% to 92.5%, $P = .004$) and Yamaguchi (78.8% to 90%, $P = .05$).

This study validates the NLR as a good simple biomarker of AOSD with a cutoff value of 4 and high sensitivity (93.8%). The addition of NLR (NLR ≥ 4) as a major criterion to the classifications (Yamaguchi and Fautrel) improved significantly their sensitivity and accuracy.

Abbreviations: ANA = antinuclear antibodies, Anti-CCP = anticyclic citrullinated peptide, AOSD = adult onset Still disease, AUC = area under the curve, CI = confidence interval, CRP = C-reactive protein, DNI = delta neutrophil index, ER = erythrocyte sedimentation rate, GF = glycosylated ferritin, HIV = human immunodeficiency virus, NLR = neutrophil-to-lymphocyte ratio, NPV = negative predictive value, OR = odds ratio, PPV = positive predictive value, RHL = reactive hemophagocytic lympho-histiocytosis, RF = rheumatoid factor, ROC = receiver operating characteristic.

Keywords: Adult Onset Still Disease, classification criteria, diagnosis, glycosylated ferritin, neutrophil-to-lymphocyte ratio, typical rash

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Adult onset Still disease (AOSD) is a rare multigenic autoinflammatory disease. It is just another facet of childhood onset Still disease or systemic juvenile idiopathic arthritis, described a century ago by George Frederic Still. Usually, it affects young adults with a female predominance.[1–3]

The most common manifestations are high spiking fever, maculopapular rash, polyarthralgia, sore throat, lymphadenopathy, and serositis. The main laboratory findings are high ferritin with low glycosylated ferritin (GF) (≤20%), high C-reactive protein, leukocytosis with neutrophilia, and elevated liver enzymes. Nevertheless, the clinical expressions of AOSD can be heterogeneous especially in early stage of the disease, which can be a diagnostic challenge for physicians.[4–6] Moreover, delayed diagnosis can lead to life-threatening complications such reactive hemophagocytic lympho-histiocytosis (RHL) and myocarditis.[7,8]

Currently, the diagnosis of AOSD is based on classifications criteria, in the lack of specific clinical manifestation or biological biomarker. Several sets of classifications criteria have been proposed for AOSD. The most used are Yamaguchi and Fautrel classifications.[9,10] Thus, several studies searched specific biomarkers for AOSD. A preliminary study suggested that delta neutrophil index (DNI, the ratio of immature granulocytes) may discriminate AOSD from sepsis.[11] Moreover, beta-2 microglobulin was higher in AOSD patients and may be a diagnostic tool in AOSD.[12] These results should be confirmed.

The neutrophil-to-lymphocyte ratio (NLR) is an inflammatory biomarker that reflects systemic inflammation. The NLR is the absolute number of neutrophils divided by the absolute number of lymphocytes, measured in routine blood count.[13] It has been evaluated in several diseases and higher NLR was associated to poor prognosis in major cardiac events, ischemic stroke and cancer.[14] The neutrophil percentage ≥ 80% is a major criterion in Fautrel and Yamaguchi classifications.[9,10,15] The NLR could be a new simple biomarker of AOSD more sensitive than neutrophil count and should be useful in AOSD diagnosis as suggested by Seo et al.[13]

Herein, we aimed to validate the NLR as a diagnostic biomarker in AOSD. This is the first study to evaluate the effect of NLR on the sensitivity and the accuracy of the classifications criteria. Moreover, the role of other biomarkers in AOSD have been investigated (GF, DNI, and Beta-2 microglobulin).

2. Patients and methods

2.1. Study design

We conducted a multicenter prospective nationwide case-control study in internal medicine, rheumatology and infectious diseases departments. Seventeen tertiary centers (11 internal medicine, 5 rheumatology, 1 infectious diseases) participated in the study between December 2016 and December 2019, to include patients with suspected AOSD based on the presence of 2 or more major criteria of Yamaguchi classification and or Fautrel classification. The study protocol was approved by the Institutional Review Board of the University of Algiers 1.

2.2. Patients

Patients with suspected AOSD were successively included in the different centers. At inclusion, all clinical and biological features were collected in a consensual and standardized clinical assessment at baseline and during follow-up by the referring physician. The principal investigator (K.A.D) gathered subsequently all data in a unique database to conduct the statistical analysis.

We excluded patients who had <18 years old or those who did not consent. A written informed consent was obtained from each patient for the participation in the study.

The classification procedure was as follow: patients were classified as AOSD by the referring physician (step 1). AOSD patients classified by the principal investigator, should met also Yamaguchi and or Fautrel criteria (step 2). Patients were classified as controls if different diagnoses (autoimmune diseases, auto inflammatory diseases, infectious diseases, neoplastic diseases, and hypersensitivity conditions) were defined.

A multidisciplinary expert group (senior internist and rheumatologist authors of this article) certified the final diagnosis for cases and controls if the criteria were not satisfied (step 3). Patients with incomplete data or insufficient follow-up were excluded.

Fautrel and Yamaguchi classifications were applied for AOSD patients and controls to test their discriminative performance. Each patient was followed up for at least 12 months.

Both groups were matched for sex, ethnic origin (all white north African) and clinical complications. The mean age in both groups was in the third decade.

2.3. Variables

Clinical variables were defined as present or absent: spiking fever (≥39°C, 38.3–38.9°C, hectic fever), joint symptoms (arthralgia, arthritis, number of affected joints), myalgia, skin rash (typical rash: transient macular or maculopapular non-pruritic rash, atypical cutaneous eruption: urticarial rash, persistent eruption, purpura, dermographism), lymphadenopathy, splenomegaly, hepatomegaly, abdominal pain, pharyngitis, pleuritis, pericarditis, myocarditis, neurological involvement, ophthalmological involvement, renal involvement, and digestive involvement.[2,8–10,15]

Biological variables were defined as normal or abnormal according to their predefined threshold: leukocytosis (≥10,000/mm), neutrophilia (≥80%, ≥ 75%, mean neutrophil count), lymphopenia (lymphocytes < 1500), NLR (normal range: 0.78 to 3.53),[16] mean hemoglobin, and platelets.

We have also reassessed the cutoff value of NLR in AOSD through the receiver operating characteristic curve (ROC). After determination of the cutoff value for NLR by ROC curve, 2 composite sets (Yamaguchi classification + NLR as a major criterion and Fautrel classification + NLR as a major criterion) were applied to each patient.

The Delta neutrophil index (DNI) is the immature granulocytes fraction provided by a blood cell analyzer (ADVIA 2120). DNI was determined by subtracting the fraction of mature polymorphic neutrophils from the sum of myeloperoxidase-reactive cells: DNI = [the neutrophil sub fraction + the eosinophil sub fraction] – [the polymorphic neutrophils sub fraction]. This result was confirmed by blood smear. A DNI > 2% was considered abnormal and may be a predictor factor of severe sepsis. DNI may discriminate AOSD from sepsis.[11]

We have also tested liver enzymes (alanine aminotransferase, aspartate aminotransferase, lactates deshydrogenase, gamma

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glutamyl transferase), Beta-2 microglobuline (0.9–2.6 mg/L), C-reactive protein (<6 mg/L), mean erythrocyte sedimentation rate, negative ANA (<1/80), negative rheumatoid factor (FR), negative anticyclic citrullinated peptide (anti-CCP), negative antiphospholipids, Increased serum ferritin (upper normal value and upper than 5-fold the normal value) and low GF (≤20% and ≤25%). The GF was not measurable or interpretable when the ferritin rate was low or in normal range.[10]

2.4. Statistical analysis

The calculation of the study size was based on the inclusion of all cases and controls during the 3-years study period, as AOSD is a rare disease.

Descriptive statistics included percentages, means, and standard deviations. Comparative analysis of clinical and biological variables between AOSD patients and controls was performed in univariate way then in multivariate with multiple logistic regression. The searches for associations between the different variables were performed using Pearson chi-square test for qualitative variables, when the conditions for applying the test were not met Yates' correction was applied. The Fisher exact test was used for small samples.

Comparison of means was made with Student t test for the quantitative variables. Moreover, the comparison of several means was performed by analysis of variance (ANOVA test).

The results were expressed in odds ratio with their 95% confidence interval. They were statistically significant if P was <.05.

The cutoff value of NLR was determined by the receiver operating characteristic curve (ROC). The sensitivity, specificity, positive predictive value, negative predictive value and accuracy were calculated for Yamaguchi classification, Fautrel classification, Yamaguchi + NLR, Fautrel + NLR. Data analysis was performed with SPSS software (version 23).

3. Results

3.1. Population characteristics

We included 160 patients, of which 80 patients with a definite AOSD patients (63 classified according to Yamaguchi criteria, 61 classified according to Fautrel criteria and 17 classified according to expert adjudication) and 60 control patients. 20 patients with incomplete data or insufficient follow-up were excluded. Patients with AOSD were followed up from 12 months (75 patients) to 36 months (35 patients).

The control group included: autoimmune and auto inflammatory diseases (55%), infectious diseases (23.3%), neoplastic diseases (10%) and hypersensitivity conditions (11.7%). In this group, the autoimmune and autoinflammatory diseases were: systemic lupus erythematosus (n = 10), systemic vasculitis (n = 8) including granulomatosis with polyangeitis (n = 4), eosinophilic granulomatosis with polyangeitis (n = 3) and giant cells arteritis (n = 1), rheumatoid arthritis (n = 4), Behçet disease (n = 4) Polymyositis (n = 2), familial Mediterranean fever (n = 2), and Sweet syndrome (n = 2), while infectious diseases were: sepsis (n = 10), tuberculosis (n = 2), HIV (n = 1), leptospirosis (n = 1) and neoplastic diseases were: Hodgkin lymphoma (n = 2), non-Hodgkin lymphoma (n = 2), prostate cancer (n = 1), bladder cancer (n = 1), and finally the hypersensitivity conditions were chronic urticaria (n = 6) and salazopyrin toxicity (n = 1).

3.2. Clinical and laboratory findings in AOSD patients

The mean age of AOSD patients was 33.76 ± 13 years and 61.2% were female. The most frequent clinical features were: fever (100%), arthralgia (93.7%), rash (87.5%), deterioration of general condition (83.7%), and sore throat (82.5%).

The association fever, arthralgia, and rash were present at the diagnosis in 65 (81%) patients. The GF with a cutoff value ≤ 25% was more frequent than the cutoff value ≤ 20% respectively (89.3%, 78.7%).

3.3. Univariate analysis

AOSD patients were younger than controls (P = .01). Several manifestations were significantly more frequent in AOSD patients: high spiking fever ≥ 39C° ($P < 10^{-6}$, OR = 24), typical rash ($P = 3 \times 10^{-5}$, OR = 14) and particularly the transient and macular aspect of the rash (OR = 24, OR = 41) (Table 1).

The DNI and serum Beta-2 microglobulin were not discriminative for AOSD (P = .8, P = .4). The GF was unmeasurable in 41 controls who had a normal or low serum ferritin. A low GF was more frequent in AOSD patients than controls, particularly when it was <25% (GF ≤ 20%: OR: 25.6, GF ≤ 25% OR: 58.8) (Table 2).

3.4. The NLR: cutoff value, sensitivity, and specificity

NLR was significantly associated to AOSD compared to controls respectively (mean NLR: 10 ± 10.24, 4.48 ± 4.55, $P = 10^{-4}$). The optimal cutoff value that best distinguished AOSD from controls was determined at the maximum value which was estimated by sensitivity + 1- specificity in the ROC curve. Among the NLR thresholds (values), the cutoff value of 4, showed the greatest sensitivity (93.8%, [95% CI: 85.4–97.7]), specificity (61.7%, [95% CI: 48.2–73.6]), and AUC value 0.82 [95% CI: 0.74–0.90] as a diagnostic biomarker for AOSD (Fig. 1).

NLR ≥ 4 was more frequent in AOSD patients compared to controls (93.7%, 38.3%, $P < 10^{-6}$, OR: 24.1 [95% CI: 7.8–79.7]). Furthermore, NLR was high in 24 AOSD patients despite a neutrophil percentage <80%.

The clinical complication that can affect NLR value was RHL. Nevertheless, the 2 groups were matched for this complication and the percentage of RHL was low (6 patients, 7.5%) in the AOSD group, which can not affect the AUC or ROC curve. Moreover, NLR remained high in patients with RHL because of the low rate of lymphocytes.

3.5. Multivariate analysis

Six variables were independently associated to AOSD: typical rash (P = .007), fever ≥ 39°C (P = .003), pharyngitis (P = .002), arthritis (P = .003), NLR (NLR ≥ 4) (P = .002), and GF ≤ 20 % (P = .019) (Table 3).

3.6. Discriminative performance of Yamaguchi set, Fautrel set, and composite sets (Yamaguchi + NLR, Fautrel + NLR)

Some major criteria were modified which affected the sensitivity of the classifications. Atypical rash was present in 32, neutrophil percentage was <80% in 29 and GF was higher than 20% in 10. Hence, 17 AOSD diagnoses were missed by Yamaguchi set and 19 AOSD diagnoses were missed by Fautrel set. Nevertheless, NLR was high (NLR ≥ 4) in 24 AOSD patients despite a neutrophil percentage <80%. Thus, the addition of NLR as a major criterion to these classifications reclassified as AOSD 9 missed AOSD patients by Yamaguchi criteria and 13 missed AOSD patients by Fautrel criteria while none of controls were reclassified as AOSD.

The association of NLR as a major criterion to Fautrel classification and Yamaguchi classification improved significantly their sensitivity respectively for Fautrel (76.3% to 92.5%, P = .004) and Yamaguchi (78.8% to 90%, P = .05). However, the specificity of Fautrel and Yamaguchi classifications was high respectively 96.7% and 100%.

Table 1

Univariate analysis of the main characteristics for AOSD patients and controls.

Variables	AOSD patients, n = 80 %	Controls, n = 60 %	*P*	Odds ratio [CI 95%]
Age	33.76 ± 13	39.5 ± 14		0.01
Sex-ratio M/F	0.63	0.46		–
Deterioration of general condition	67/80 (83.7)	32/60 (53.3)	9×10^{-5}	4.5 [1.9–10.6]
Fever	80/80 (100)	46/60 (76.7)	5×10^{-6}	–
T, 39°C–40°C	76/80 (95)	28/46 (60.8)	$<10^{-6}$	12.2 [3.5–47.1]
Hectic fever	58/80 (72.5)	5/46 (10.8)	$<10^{-6}$	21.6 [6.9–71,9]
Rash	70/80 (87.5)	26/60 (43.3)	$<10^{-6}$	9.5 [3.7–23.2]
Typical rash	38/70 (54.3)	2/26 (7.7)	$<3 \times 10^{-5}$	14.2 [2.9–94.7]
Atypical rash	32/70 (45.7)	24/26 (92.3)	3×10^{-5}	0.1 [0.01–0.34]
Macular rash	59/70 (84.3)	3/26 (11.5)	$<10^{-6}$	41.12 [9.3–210.3]
Transient rash	64/70 (91.4)	8/26 (30.7)	$<10^{-6}$	24 [6.5–95.5]
Sore throat	66/80 (82.5)	10/60 (16.6)	$<10^{-6}$	23.6 [8.9–64.3]
Arthralgia	75/80 (93.8)	53/60 (88.3)	.2	1.9 [0.5–7.7]
Myalgia	55/80 (68.8)	27/60 (45)	.004	2.7 [1.3–5.7]
Arthritis	54/80 (67.5)	15/60 (25)	10^{-5}	6.2 [2.8–14.2]
N° pain joints	11.6 ± 8.7	5.62 ± 4.5	10^{-5}	–
N° swollen joints	4.9 ± 4.2	3.3 ± 2.5	.1	–
Liver dysfunction	57/80 (71.2)	27/60 (45)	.001	3 [1.4–6.5]
Lymphadenopathy	16/80 (20)	6/60 (10)	.1	2.5 [0.8–6.9]
Splenomegaly	11/80 (13.8)	2/60 (3.3)	.03	4.6 [0.9–31.5]
Pleuritis	10/80 (12.5)	3/60 (05)	.1	2.7 [0.6–13.1]
Pericarditis	14/80 (17.5)	5/60 (8.3)	.1	2.3 [0.7–7.9]

AOSD = adult onset Still disease, CI = confidence interval.

Table 2

Univariate analysis of the main laboratory findings for AOSD patients and controls.

Variables	AOSD patients, n = 80 %	Controls, n = 60 %	*P*	Odds ratio [CI 95%]
Leukocytosis	67/80 (83.7)	20/60 (33.3)	$<10^{-6}$	10.3 [4.3–25]
Neutrophils ≥ 75%	68/80 (85)	16/60 (26.6)	$<10^{-6}$	15.6 [6.3–39.8]
Neutrophils ≥ 80%	51/80 (63.7)	10/60 (16.6)	$<10^{-6}$	8.8 [3.6–21.8]
Mean neutrophils %	80 ± 7.6	67.56 ± 11.61	$<10^{-6}$	–
Lymphopenia %	15 (18.7)	16 (26.7)	.3	
Mean NLR	10 ± 10.24	4.48 ± 4.55	10^{-4}	–
DNI > 2%	3/80 (3.75)	1/60 (1.7)	.8	–
Mean hemoglobin, g/dL	9.6 ± 1.7	10.96 ± 2	4×10^{-4}	–
Mean ESR rate, mm	106 ± 22	74.1 ± 42.9	$<10^{-6}$	–
Mean CRP, mg/L	136.8 ± 87.57	86.68 ± 87.47	.001	–
Beta-2 microglobulin (> N)	6/22 (27.2)	2/16 (12.5)	.4	2.6 [0.4–22.6]
Mean beta-2 microglobulin	2.04 ± 0.99	1.56 ± 0.72	.1	–
Serum ferritin > N	70/80 (87.5)	19/60 (31.7)	$<10^{-6}$	15.11 [5.9–39.4]
Serum ferritin ≥ 5 N	59/80 (73.7)	4/60 (7.8)	$<10^{-6}$	39.3 [11.7–146] 25.9 [2.6–630.9]
Glycosylated ferritin ≤ 25%	42/47 (89.2)	1/08 (12.5)	$<10^{-6}$	58.8 [5.1–1585]
Negative ANA	72/80 (90)	46/60 (76.7)	.03	2.7 [0.97–8.1]
Negative anti-CCP	80/80 (100)	54/60 (90)	.01	–
Negative FR	80/80 (100)	54/60 (90)	.01	–

ANA = antinuclear antibodies, Anti-CCP = anticyclic citrullinated peptide, AOSD = adult onset Still disease, CI = confidence interval, CRP = C-reactive protein, DNI = delta neutrophil index, ERS = erythrocyte sedimentation rate, NLR = neutrophil-to-lymphocyte ratio, RF = rheumatoid factor.

These composite sets improved also the accuracy of the classifications, respectively, for Fautrel classification (85% to 94.3%) and Yamaguchi classification (87.8% to 94.3%). Two patients in Fautrel classification were falsely classified as AOSD (1 HIV, 1 meningitis), while the application of the exclusion criteria in Yamaguchi classification implicated that none of controls was classified as AOSD (Table 4).

4. Discussion

This prospective study validates the NLR (NLR ≥ 4) as a good diagnostic biomarker of AOSD with high sensitivity (93.8%). This is the first study to investigate the effect of NLR on the sensitivity and the specificity of the classifications criteria. The addition of NLR to the classifications (Yamaguchi and Fautrel classifications) as a major criterion improved significantly their sensitivity with maintaining high specificity.

The NLR has been recently reported as a new biomarker of AOSD more sensitive than neutrophils count, with a cut-off value of 3.08 to differentiate AOSD from controls.[13] Nevertheless, this cutoff value was near from the normal range, recently estimated from 0.78 to 3.53 with a mean of 1.65 ± 1.96.[16] Hence, the cutoff value of NLR was reassessed in this study.

Crispin et al published an interesting study reporting the mean neutrophils and lymphocytes counts in AOSD patients.[17] Thus, mean NLR in this study equals 10.9, which is frankly high.

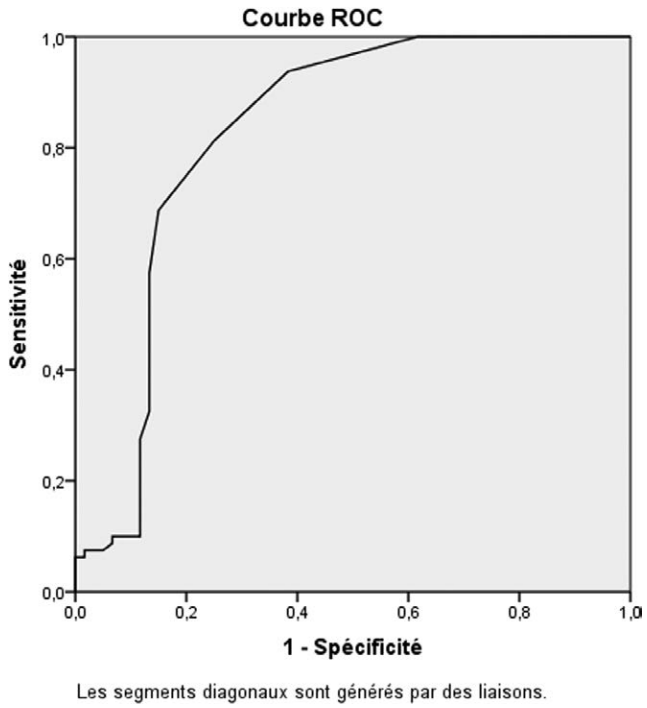

Figure 1. Receiving operating characteristic curve for the neutrophil-to-lymphocyte ratio in adult onset Still disease patients and controls. Area under the curve for the neutrophil-to-lymphocyte ratio was 0.82 [95% CI: 0.74–0.90] with a cutoff value of 4 (normal range: 0.78 to 3.53). CI = confidence interval.

Table 3

Multivariate analysis with multiple logistic regression.

Criteria	Adjusted odds ratio	Confidence interval 95%	*P*
Typical rash	24.01	2.35–245.30	.007
Fever ≥ 39c°	17.34	2.6–113.37	.003
NLR ≥ 4	11.10	2.35–52.3	.002
Pharyngitis	10.23	2.36–44.34	.002
Arthritis	9.01	2.07–39.142	.003
Glycosylated ferritin ≤ 20%	1.59	1.08–2.35	.019

NLR = neutrophil-to-lymphocyte ratio.

NLR is a simple inexpensive biomarker, routinely measured in blood count. It reflects systemic inflammation with intervention of the innate immune system (neutrophil count) and adaptive immunity (lymphocyte count). NLR was evaluated in several diseases and was associated with poor prognosis in infectious diseases, cardiac events and cancer.[14]

In this cohort, NLR was high (NLR ≥ 4) in 24 AOSD patients despite a neutrophil percentage <80 %. The addition of NLR as a major criterion to Yamaguchi and Fautrel criteria reclassified as AOSD 9 missed AOSD patients by Yamaguchi criteria and 13 missed AOSD patients by Fautrel criteria while none of controls were reclassified as AOSD. Furthermore, the 2 classifications (Fautrel and Yamaguchi) had a high specificity, which was helpful to rule out confusable diseases.

Some studies reported also modifications in major criteria such as neutrophil percentage <80% in 30% to 40% of cases and GF higher than 20% in 30% to 40% of cases.[6,10,18] Moreover, atypical rash was often reported in recent studies.[19–21]

Lebrun et al reported that GF (≤20%) showed a good specificity and improved the sensitivity of Yamaguchi criteria thanks to a composite set (98.2%).[6] Several studies including our showed that ferritin ≥ 5-fold upper the limit of the normal and GF ≤ 20% had a good diagnostic value.[6,10] In our study, GF with a cutoff value of ≤ 25% (89.2%) was more frequent than the cutoff value of ≤ 20% (78.7%) and may be considered for AOSD diagnosis.

The low level of GF is due to the deficiency in glycosylation process of the ferritin that cannot follow a high ferritin production.[22] However, GF was not available in most centers and can be low in other diseases such as RHL.[23–25] In addition, GF rate raised in remission period.[26] We confirmed these findings in our study.

Delta neutrophil index and Beta-2 microglobulin were not specific for AOSD and did not discriminate AOSD patients from controls in our cohort.

The most specific clinical manifestation of AOSD is erythematous or pink macular, transient and recurrent rash concomitant with the fever. Moreover, fever and arthralgia are the most frequent manifestations. In several studies including our, the association "rash, fever and arthralgia" was present in <80% of patients.[2,9,15] The severity of AOSD can be attributed to its life-threatening complications with organ damage, particularly, RHL, coagulation disorder, myocarditis, heart failure, tomponade, pulmonary arterial hypertension, acute respiratory distress syndrome, pancreatitis, and fulminant Hepatitis.[7,8] In our cohort, the complications occurred in 11 patients, particularly 6 RHL.

Despite a better knowledge of the clinical picture of AOSD, the diagnostic delay remains long, especially in atypical presentations. The classifications criteria are used to classify patients in clinical research into homogeneous groups.[27–31] Their use is also based on the experience of the physician who should rule out confusable diseases.[6,9,17,32,33]

Thus, the diagnosis can be difficult in early stage of the disease and needs exclusion of infections, malignancies and other immune-mediated inflammatory diseases. In the present study, NLR improved the diagnostic approach and the accuracy of Fautrel and Yamaguchi classifications respectively (94.3%, 100%).

Yamaguchi classification was the most sensitive (96.2%) and the most used in clinical research, but the exclusion procedure was costly, needed time and missed AOSD diagnoses through the requirement of negative antinuclear antibodies and other serologies.[6,17,27]

Therefore, in typical picture of the disease, particularly: typical rash, high spiking fever, arthralgia and pharyngitis lasting

Table 4

Evaluation of AOSD classifications criteria.

Classification criteria	AOSD, n = 80	Controls, n = 60	Sensitivity %	Specificity %	PPV %	NPP %	Accuracy %
Yamaguchi	63	0	78.8 [67.9–86.8]	100 [92.5–100]	100 [92.8–100]	77.9 [66.7–86.3]	87.8
Yamaguchi and NLR ≥ 4	72	0	90 [80.7–95.3]	100 [92.5–100]	100 [93.7–100]	88.2 [77.6–94.4]	94.3
Fautrel	61	2	76.3 [65.2–84.8]	96.7 [87.5–99.4]	96.8 [88–99.4]	75.3 [64–84.1]	85
Fautrel and NLR ≥ 4	74	2	92.5 [83.8–96.9]	96.7 [87.5–99.4]	97.3 [90–99.5]	90.6 [80.1–96.1]	94.3

AOSD = adult onset Still disease, NLR = neutrophil-to-lymphocyte ratio, NPV = negative predictive value, PPV = positive predictive value.

2 weeks or longer with a high ferritin, low GF, high CRP, high neutrophil count and high NLR, the diagnosis of AOSD should be considered to allow early healthcare.[1,10,13,15,29]

The main limit of our study was the number of controls, we wished to include 1 AOSD case for 1 control. However, 20 patients were excluded for insufficient data and follow-up. Moreover, NLR can be high in other diseases, particularly infectious diseases and needs to be interpreted carefully.

This prospective study validates the NLR as a good diagnostic biomarker of AOSD with a cutoff value of 4 and high sensitivity (93.8%). An update of the classification criteria for AOSD may be proposed including the NLR and the GF to improve the diagnostic approach and the clinical research in this rare systemic disease.

5. Key messages

NLR (≥ 4) is a good simple biomarker of AOSD with a high sensitivity and may replace the neutrophil percentage (≥80%) in the classifications criteria (Yamaguchi and Fautrel classifications).[9,10,13]

Although, NLR is not very specific, its addition as a major criterion to Yamaguchi and Fautrel classifications improved significantly their sensitivity and their accuracy with maintaining high specificity for these composite sets[9,10,13]

This study confirms the performance of Yamaguchi and Fautrel classifications and the GF (≤20%) in the diagnosis of AOSD.[6,9,10]

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Author contributions

Karima Daghor Abbaci : wrote the paper, collected the data, concieved and designed the study
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Fifi Otmani : revised critically the article
Chafia Dahou Makhloufi : revised critically the article
Farida Mechid: contributed to the data collection
Mohamed Makrelouf : revised critically the article
Amel Otmane : performed the laboratory analysis
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