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ORIGINAL ARTICLE

Disease activity score for still's disease

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Abstract

Objective To develop the Still's Disease Activity Score (SDAS).

Methods We used data from the prospective adult-onset Still's disease cohort study and evaluated the disease activity. An expert group selected the most frequent, reproducible, and objective variables significantly modified in statistical analysis when comparing patients in the active group and in the remission group. These criteria were weighted to design the Still's Disease Activity Score (SDAS). The Delphi method was used to appreciate the level of disease activity. Total SDAS was calculated for each patient and compared to final consensus experts.

Results At the diagnosis, all patients had an active disease ($n = 80$), while 48 patients were in remission at 6 months. The SDAS criteria were weighted as follows: fever ≥ 38.5 °C (1 point), rash (1 point), joint involvement (arthralgia: 1 point, swollen joints count "SJC": 1–3 SJC: 2 points, ≥ 4 SJC: 3 points), physician global assessment VAS ≥ 5/10 or a raise in physician VAS ≥ 2/10 (3 points), patient VAS ≥ 5 or a raise in patient VAS ≥ 2/10 (1 point), and CRP (> 10 mg/l: 1 point, ≥ 100 mg/l: 2 points). At 6 months, the consensus was achieved for 76 (95%) patients with 40 in remission (0–1 point), 8 in low disease activity (2–3 points), 16 in moderate disease activity (4–7 points), and 12 in severe disease activity (≥ 8 points).

Conclusion The Still's Disease Activity Score is a valid and sensitive assessment of the disease activity and the therapeutic response in Still's disease, despite its heterogeneous manifestations and patterns with systemic and articular forms.

Key Points

- *The Still's Disease Activity Score (SDAS) is a good simple tool to assess the activity of the disease in a stable state for a week.*
- *The SDAS is developed specifically for Still's disease without the need for an application or a calculator to calculate SDAS in routine clinical practice.*
- *SDAS is a composite score classifying the disease activity in remission, low disease activity, moderate disease activity, and severe disease activity despite its heterogeneous patterns (systemic and articular forms).*
- *The SDAS is a valid, reliable, and sensitive score and can be useful to guide the therapeutic strategy in clinical practice and in research.*

Keywords CRP · Fever · Physician VAS · Still's Disease Activity Score (SDAS)

Introduction

Still's disease (SD) is a rare autoinflammatory disease with rheumatic and systemic manifestations and gathered currently the adult (adult-onset Still's disease (AOSD)) and pediatric onset (systemic juvenile idiopathic arthritis (SJIA)) of the disease in a single disease and name [1, 2].

Several sets of classification criteria have been proposed for AOSD. The most used are Yamaguchi and Fautrel classifications [3, 4]. Currently, a concise diagnostic algorithm is proposed to improve the diagnostic approach [5].

Still's disease is characterized by different heterogeneous disease courses defined as monocyclic pattern with a single systemic episode (30%), polycyclic pattern with multiple systemic relapses alternating with remission (30%), and chronic form with persistent arthralgia or arthritis and systemic symptoms (40%). Nearly, one third of the

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patients with a chronic form have an erosive arthritis [6–9]. Life-threatening complications with organ damage and macrophage activation syndrome increased the morbidity and the mortality [10, 11].

High rate of relapses characterized the disease course in Still's disease, particularly in the chronic form [11]. Stringent remission criteria need a crucial assessment of the disease activity to improve functional and radiographic outcomes and systemic manifestations. Thus, SD needs the development of an accurate tool specific to evaluate the disease activity.

Different rheumatoid arthritis Disease Activity Scores were used to evaluate the response to several biologic agents in AOSD [12]. Nevertheless, these scores were not developed specifically to SD and could not be adapted for the assessment of disease activity in this heterogeneous disease with systemic manifestations and organ damage. Moreover, residual activity can lead to poor outcomes.

The design of a specific disease activity index for Still's disease is important for the tight control of the disease activity and the therapeutic adjustments particularly the use of biological therapy and corticosteroids sparing.

The objective of this study is to design a Disease Activity Score for Still's disease useful in clinical practice, clinical trials, and biologic agent development.

Methods

We used data from the prospective adult-onset Still's disease cohort study [5, 20] and evaluated the disease activity at the diagnosis, 3 months, 6 months, and 12 months.

Study design

We conducted a multicenter prospective longitudinal nationwide study in tertiary rheumatology and internal medicine departments. Seventeen tertiary centers (5 rheumatology, 11 internal medicine, 1 infectious disease) participated to the study between December 2016 and December 2019 for recruitment. The follow-up was carried out by 16 departments from December 2016 to December 2020 (5 rheumatology and 11 internal medicine). The study protocol was approved by the Ethics Committee of the University of Algiers 1 Benyoucef Benkhedda.

Patients and data collection

Patients with established AOSD diagnosis according to the referring physician were successively included. Patients fulfilled the Yamaguchi classification 1992 or Fautrel classification 2002 with the exclusion of any cause that can explain the clinical picture. All clinical features, biological data, and therapeutic modification related to the disease activity were collected in a consensual and standardized clinical form at baseline and during follow-up (3 months, 6 months, and 12 months).

The referring physician is a senior rheumatologist or internal medicine specialist experienced in disease activity assessment in rheumatic diseases. A patient with a flare is evaluated by the local medical team before the increase of the corticosteroid dosage or the therapeutic modification.

Patients were classified as in active disease by the presence of two or more criteria of Yamaguchi classification and fever or high CRP (> 10 mg/l) [13].

The inactive disease was defined as having no active arthritis, no systemic features, and a physician global assessment indicating no activity [2].

The principal investigator (K.D.A) gathered subsequently all data in a unique database to conduct the statistical analysis. We excluded patients who were less than 18 years old, those who did not consent, or those who had missing data and insufficient follow-up. A written informed consent was obtained from each patient for the participation in the study.

Disease activity assessment protocol

The principal investigator selected 20 candidate items (see the "Definitions and variables" section) for disease activity assessment based on a systematic literature review. These items were integrated in the standardized clinical form.

Step 1: Patients were classified as having an active or inactive disease by the referring physician and the principal investigator (active and inactive diseases were already predefined). The clinical state should be stable for a week. All clinical and biological features should be related to the disease activity.

Step 2: During three meetings, an expert group (two Ph.D. in rheumatology "C.D.M and F.M" and three Ph.D. in internal medicine "AB, F.O, and N.B" with 10 years experience in taking care of patients with Still's disease) selected the most frequent [present in more than 50% of patients: fever (80, 100%), rash (70, 87%), arthralgia (75, 93.8%), arthritis (54, 67.5%)] and reproducible (variables described as present or absent: fever, rash, and arthritis) variables significantly modified in statistical analysis when comparing active group and inactive group at 3 months and 12 months.

Moreover, objective (CRP mg/l) and consistently shown to be clinically important and sensitive to change (physician global assessment and patient global assessment) variables significantly modified in statistical analysis when comparing

the active group and inactive group at 3 months and 12 months were selected by the expert group.

All these criteria are clinically important, sensitive to change, and reliable and were already validated as component measures within the core set of validated Disease Activity Scores in Still's disease particularly Pouchot's score and systemic Juvenile Idiopathic Arthritis Disease Activity Score (sJADAS). Therefore, individual validation of each variable was not required [14–16].

The selected criteria were weighted to design the Still's Disease Activity Score (SDAS) based on a systematic literature review and the experts' adjudication to simplify the calculation and the use of this score in routine clinical practice. The physician global assessment, polyarthritis (≥ 4 SJC), and high CRP are clinically important in the disease activity assessment and had the highest weight [2, 13–16].

Step 3: The Delphi method was used to appreciate the level of disease activity of each patient at 6 months. Ten experts in systemic and rheumatic diseases (all Ph.D. in rheumatology and internal medicine and have already taken care of patients with Still's disease for at least 5 years: NL, FM, CDM, AB, NB, FO, BT, FH, CH, BB) were asked to evaluate the patient's disease activity (inactive disease, low activity, moderate activity, severe activity).

The consensus was made if more than 80% of the experts agreed on the level of disease activity according to the Likert scale (1: strongly disagreed, 2: disagreed, 3: neutral/uncertain, 4: agreed, 5: strongly agreed).

Three rounds were conducted in structured meetings; the consensus was achieved in October 2020 with a level of agreement of 90%.

Step 4: Total SDAS was calculated for each patient and compared to final consensus experts to determine cut points for inactive, low activity, moderate activity, and severe activity.

Step 5: Statistical analysis has been carried out to evaluate the performance of SDAS by comparing the mean physician global assessment, the mean CRP, and the mean corticosteroid dose between the different groups of patients classified according to the level of disease activity including subgroups with systemic form and articular form at 6 months and 12 months.

Definitions and variables

Active disease or flare was defined by the presence of two or more criteria of Yamaguchi classification and fever or high CRP (> 10 mg/l) [13].

Clinically inactive disease is defined as no active arthritis, no systemic features, and physician global assessment indicating no activity [2].

Corticosteroid dependence: The presence of one or more criteria of Yamaguchi classification and fever or high CRP when tapering corticosteroids less than 10 mg/day after initial remission [13].

Assessment of the disease activity included fever, rash, swollen joints count, tender joints count, physician global assessment on visual analogue scale (VAS) (0–10), patient global assessment on VAS (0–10), pain assessment on VAS (0–10), myalgia, pharyngitis, pleuritis, pneumonitis, lymphadenopathy, pericarditis, abdominal pain, C-reactive protein (normal value < 6 mg/l), erythrocyte sedimentation rate, neutrophils count, neutrophil-to-lymphocyte ratio (normal range, 0.78 to 3.53), liver enzymes, serum ferritin (normal range, 50–200 µg/l), Disease Activity Score 28 joints (DAS-28 CRP), and therapeutic modification (corticosteroids dose) [16–20].

Disease course: Three different clinical patterns were considered: the monocyclic or self-limited course defined as a single period (less than 12 months) followed by persistent remission, the polycyclic or intermittent course is considered if recurrent relapses occurred between complete remissions, and the chronic course if the symptoms persist more than a year. The chronic course was subdivided on systemic and articular forms [17, 18].

Statistical analysis

The calculation of the study size was based on the inclusion of all cases during the 4-year study period, as adult-onset Still's disease is a rare disease.

In the descriptive study, qualitative variables were described with counts (percentage) and quantitative variables with mean ± standard deviation.

To identify the clinical and biological items significantly correlated to the disease activity, patients with active disease at the diagnosis and patients in remission at 3 months and 12 months were compared.

Among the items significantly associated to the disease activity in statistical analysis, six items were selected by the expert committee and were weighted to design the SDAS.

To evaluate the performance of SDAS, the mean physician global assessment, the mean CRP, and the mean corticosteroid dose in the different groups of patients classified according to SDAS (remission, low disease activity, moderate disease activity, and severe disease activity) including subgroups with systemic forms and articular forms were compared at 6 months.

The searches for associations between the different variables were performed using Pearson's chi-square test for qualitative variables; when the conditions for applying the test are not met, Yates' correction is applied and Fisher's exact test for small samples.

A comparison of means was made with Student's *t* test for the quantitative variables. Moreover, the comparison of several means was performed by analysis of variance (ANOVA test).

Comparative analysis of clinical and biological variables between AOSD patients in active and remission state was performed in a univariate way.

A $p < 0.05$ was considered statistically significant. The data analysis was performed with SPSS software (version 23).

Results

Population characteristics

The patient's demographics and clinical profiles have been previously reported [5, 20]. Eighty patients with AOSD were included. The main clinical characteristics were a mean age of 33.76 ± 13 years with 61.2% ($n = 49$) female. The most frequent clinical features were fever ($n = 80$, 100%), arthralgia ($n = 75$, 93.7%), skin rash ($n = 70$, 87.5%), deterioration of general condition ($n = 67$, 83.7%), and pharyngitis ($n = 66$, 82.5%).

The association fever, arthralgia, and rash were present at the diagnosis in 65 (81%) patients, while only 16 patients (20%) had lymphadenopathies and splenomegaly.

The laboratory findings were notable for high CRP ($n = 80$, 100%), leukocytes > 10,000 ($n = 67$, 83.7%), anemia ($n = 71$, 88%), high ferritin ($n = 70$, 87.5%), and polynucleosis (neutrophils ≥ 80% in 51, 63.7%). Furthermore, 36% ($n = 29$) of patients had a high level of ferritin greater than tenfold the upper normal value.

The neutrophils-to-lymphocytes ratio was ≥ 4 in 75 (93.7%) patients with a mean NLR of 10 ± 10.24. Thirty-seven (78.7%) among 47 patients with available glycosylated ferritin had low glycosylated ferritin ≤ 20%, while 42 (89.3%) patients had a glycosylated ferritin ≤ 25%.

All patients received corticosteroids, whereas seven of them received non-steroidal anti-inflammatory drugs as the first line of treatment particularly diclofenac. Forty-eight patients (60%) required a second line of treatment with sDMARD specially methotrexate (46, 57.5%).

Treatment with biologic agents was prescribed 20 times in 16 patients (20%). Anakinra was the most prescribed ($n = 7$) and effective biologic therapy ($n = 5$).

The chronic pattern concerned 56 patients (70%) among them, 19 (34%) had articular form, and 37 (64%) had systemic form, while the polycyclic pattern concerned 15 patients (18.7%) and the self-limited pattern concerned 9 patients (11.3%). Erosive arthritis was noted in 19 (23.7%) patients or one third of the chronic pattern (19/56: 33.4%).

Life-threatening complications with organ damage occurred in 11 patients who presented 14 complications. These complications were 6 reactive hemophagocytic lymphohistiocytosis, 2 disseminated intravascular coagulation, 4 myocarditis, 1 acute respiratory distress syndrome, and 1 fulminant hepatitis.

Disease activity assessment

At the diagnosis, all patients had an active disease ($n = 80$, 100%), while 52 patients were in remission at 3 months, 48 patients were in remission at 6 months, and 49 patients were in remission at 12 months. Only 5 patients were lost to follow-up at 12 months.

Several clinical and biological variables were significantly correlated to the disease activity in statistical analysis at 3 months (Table 1) and 12 months (Table 2) particularly fever ≥ 38.5 °C ($p < 10^{-6}$), rash ($p < 10^{-6}$), pharyngitis ($p < 10^{-6}$), TJC ($p < 10^{-6}$), SJC ($p < 10^{-6}$), pleuritis ($p = 0.02$), pericarditis ($p = 0.001$), abdominal pain ($p = 0.02$), physician VAS ($p < 10^{-6}$), patient VAS ($p < 10^{-6}$), pain VAS ($p < 10^{-6}$), CRP ($p < 10^{-6}$), ESR ($p < 10^{-6}$), liver enzymes ($p = 0.004$), polynucleosis ($p < 10^{-6}$), and serum ferritin ($p < 10^{-6}$).

Moreover, DAS-28 ($p < 10^{-6}$) and corticosteroid dose ($p < 10^{-6}$) were significantly correlated to the disease activity.

Design of the Still's Disease Activity Score (SDAS)

Among the variables significantly associated to the disease activity in statistical analysis, the most frequent, reproducible clinically important, sensitive to change, reliable, and objective items were selected to specify the SDAS.

The six selected items were weighted as follow: fever ≥ 38.5 °C (1 point), rash (1 point), joint involvement (arthralgia: 1 point, swollen joints count "SJC": 1–3 SJC: 2 points, ≥ 4 SJC: 3 points), physician global assessment on visual analogue scale (VAS) ≥ 5/10 or a raise in physician VAS ≥ 2/10 (3 points), patient global assessment on VAS ≥ 5 or a raise in patient VAS ≥ 2/10 (1 point), and CRP (> 10 mg/l: 1 point, ≥ 100 mg/l: 2 points) (Table 3).

At 6 months, the disease activity assessment was carried out for each patient by the experts. The consensus was achieved for 76 (95%) patients with 40 inactive (remission), 8 low disease activity, 16 moderate disease activity, and 12 severe disease activity. Initially, the disease activity assessment performed by the referring physician and the principal investigator classified 48 patients as in remission and 28 patients in active disease or flare (Fig. 1).

Table 1 Comparative analysis of the main clinical and biological variables of Still's disease patients with active disease at the diagnosis and patients in remission at 3 months

	Patients with active disease at the diagnosis ($n=80$) Age: 33.76 ± 13 Females: 49 (61.2%)	Patients with inactive disease at 3 months ($n=52$)	p value
Deterioration of general conditions	67/80 (83.8)	0/52 (00)	$p<10^{-6}$
Fever	80/80 (100)	0/52 (00)	$p<10^{-6}$
Rash	70/80 (87.5)	3/52 (5.8)	$p<10^{-6}$
Pharyngitis	66/80 (82.5)	1/52 (1.9)	$p<10^{-6}$
TJC mean	11.6 ± 8.7	1.25 ± 1.57	$p<10^{-6}$
SJC mean	4.9 ± 4.2	0.019 ± 0.13	$p<10^{-6}$
Pain VAS	7.72 ± 2.29	1.73 ± 1.63	$p<10^{-6}$
Patient VAS	7.95 ± 1.9	1.23 ± 1.47	$p<10^{-6}$
Physician VAS	5.86 ± 1.47	0.57 ± 0.84	$p<10^{-6}$
Pericarditis	14/80 (17.5)	1/52 (1.9)	$p=0.005$
Pleuritis	10/80 (12)	1/52 (1.9)	$p=0.06$
Abdominal pain	18/80 (22)	1/52 (1.9)	$p=0.05$
ESR (mm)	106 ± 22	25.57 ± 14.87	$p<10^{-6}$
CRP (mg/l)	130 ± 26	11.13 ± 7.12	$p<10^{-6}$
Polynucleosis mean %	80 ± 7.6	68.28 ± 9.73	$p<10^{-6}$
Mean Béta2microglobuline	2.04 ± 0.99	0.29 ± 0.6	$p<10^{-6}$
Liver enzymes (UI/l) mean	59.63 ± 88.27	28.98 ± 19.11	$p=0.4$
GGT (UI/l)	70.7 ± 67	39.8 ± 25.13	$p=0.001$
Leukocytes count ≥ 10,000/mm^3	67/80 (83.7)	24/52 (46.2)	$p=5.10^{-5}$
NLR ≥ 4	75/80 (93.7)	6/52 (11.6)	$p<10^{-6}$
Polynucleosis ≥ 75%	68/80 (85)	20/52 (38.5)	$p<10^{-6}$
Ferritin > N	70/80 (87.5)	21/52 (40.4)	$p<10^{-6}$
Ferritin ≥ 5N	59/80 (73.7)	00 (00)	$p<10^{-6}$
Béta2-microglobuline > N	6/22 (27.2)	0/11 (00)	$p=0.1$
DAS-28 CRP	5.63 ± 0.93	2.31 ± 0.79	$p<10^{-6}$
Prednisone (mg/day) mean	52.18 ± 22.20	20.67 ± 9.9	$p<10^{-6}$

CRP C-reactive protein, *DAS28* Disease Activity Scores 28 joint count, *ESR* erythrocyte sedimentation rate, *GGT* gamma glutamate transferase, *NLR* neutrophil-to-lymphocyte ratio, *SJC* swollen joints count, *TJC* tender joints count

The SDAS was calculated for each patient and compared to final consensus experts to determine the cut points for remission, low disease activity, moderate disease activity, and severe disease activity.

The cut points for SDAS were 0–1 point in the inactive group, 2–3 points in the low disease activity group, 4–7 points in the moderate activity group, and ≥ 8 points in the severe disease activity group.

Evaluation of the performance of SDAS at 6 months

To evaluate the performance of SDAS in the assessment of the disease activity, the mean physician global assessment, the mean CRP, and the mean corticosteroid dose were calculated and compared between the different groups of patients classified according to the level of disease activity.

Characteristics of the inactive disease group (SDAS: 0–1 point)

Forty patients (52.6%) were classified in the inactive disease group. There was no fever, rash, or arthritis in this group. However, mild arthralgia was present in 10 (25%) patients. The physician global assessment on the visual analogue scale (VAS) was 00 for all patients, and the patient global assessment on VAS was ≤ 1 in all patients. The mean CRP was 4.02 ± 2.9 mg/l. The corticosteroid dose was ≤ 10 mg/day.

Table 2 Comparative analysis of the main clinical and biological variables of patients with active disease at the diagnosis and patients in remission at 12 months

	Patients with active disease at the diagnosis ($n=80$) Age: 33.76 ± 13 Females: 49 (61.2%)	Patients with inactive disease at 12 months ($n=49$)	p value
Deterioration of general conditions	67/80 (83.8)	6/49 (12.2)	$p<10^{-6}$
Fever	80/80 (100)	0/49 (00)	$p<10^{-6}$
Rash	70/80 (87.5)	1/49 (02)	$p<10^{-6}$
Pharyngitis	66/80 (82.5)	1/49 (02)	$p<10^{-6}$
SJC	54/80 (67.5)	0/49 (00)	$p<10^{-6}$
TJC mean	11.6 ± 8.7	0.63 ± 0.90	$p<10^{-6}$
SJC mean	4.9 ± 4.2	00	–
Pain VAS	7.72 ± 2.29	1.06 ± 1.40	$p<10^{-6}$
Patient VAS	7.95 ± 1.9	0.57 ± 1.19	$p<10^{-6}$
Physician VAS	5.86 ± 1.47	0.18 ± 0.56	$p<10^{-6}$
Pericarditis	14/80 (17.5)	00 (00)	$p=0.001$
Pleuritis	10/80 (12.5)	00 (00)	$p=0.02$
Abdominal pain	18/80 (22.5)	00 (00)	$p=0.02$
ESR (mm)	106 ± 22	16.4 ± 7.57	$p<10^{-6}$
CRP (mg/l)	130 ± 26	5.18 ± 5.61	$p<10^{-6}$
Liver enzymes (UI/l) mean	59.63 ± 88.27	22.95 ± 7.97	$p=0.004$
GGT (UI/l)	70.7 ± 67	34.59 ± 11.66	$p=0.0002$
Polynucleosis mean %	80 ± 7.6	65.71 ± 6.71	$p<10^{-6}$
Leukocytes count ≥ 10,000/mm^3	67/80 (83.7)	3/49 (06.1)	$p<10^{-6}$
Polynucleosis ≥ 75%	68/80 (85)	8/49 (16.3)	$p<10^{-6}$
Ferritin > N	70/80 (87.5)	2/49 (4.9)	$p<10^{-6}$
Ferritin ≥ 5N	59/80 (73.9)	00 (00)	$p<10^{-6}$
DAS-28 CRP	5.63 ± 0.93	1.92 ± 0.66	$p<10^{-6}$
Prednisone (mg/day) mean	52.18 ± 22.20	4.59 ± 4.18	$p<10^{-6}$

CRP C-reactive protein, *DAS28* Disease Activity Scores 28 joint count, *ESR* erythrocyte sedimentation rate, *GGT* gamma glutamate transferase, *SJC* swollen joints count, *TJC* tender joints count, *VAS* visual analogue scale

Characteristics of the low disease activity group (SDAS: 2–3 points)

Eight patients (10.5%) had a low disease activity. There was no fever, rash, or arthritis. However, arthralgia was present in all patients. The physician's global assessment on VAS was ≤ 2 in all patients, and the patient's global assessment on VAS was 2–3 in six patients and 5–6 in two patients. The mean CRP was 17.4 ± 6.6 mg/l. The corticosteroid dose was ≤ 15 mg/day.

Characteristics of the moderate disease activity group (active group) (SDAS: 4–7 points)

Sixteen patients (21%) had a moderate disease activity. The clinical profile was notable for fever ($n=8$, 50%), rash ($n=11$, 68.7%), arthralgia ($n=16$, 100%), and arthritis ($n=6$, 37.5%). The mean physician global assessment on VAS was 2.8 ± 1.27, and the mean patient global assessment on the visual analogue

Table 3 Still's Disease Activity Score (SDAS)

Criteria[a]	Points
Fever ≥ 38.5 °C	1 point
Rash	1 point
Joints involvement	
Arthralgia	1 point
1–3 SJC	2 points
≥ 4 SJC	3 points
Physician VAS ≥ 5 or a raise in physician VAS ≥ 2/10	3 points
Patient VAS ≥ 5 or a raise in patient VAS ≥ 2/10	1 point
CRP > 10 mg/l	1 point
≥ 100 mg/l	2 points
SDAS	**Total points**
Inactive disease or remission	0–1point
Low disease activity	2–3 points
Moderate disease activity	4–7 points
Severe disease activity	≥ 8 points

SJC swollen joints count, *VAS* visual analogue scale

[a]The items are related to the disease activity and not to other conditions (infections)

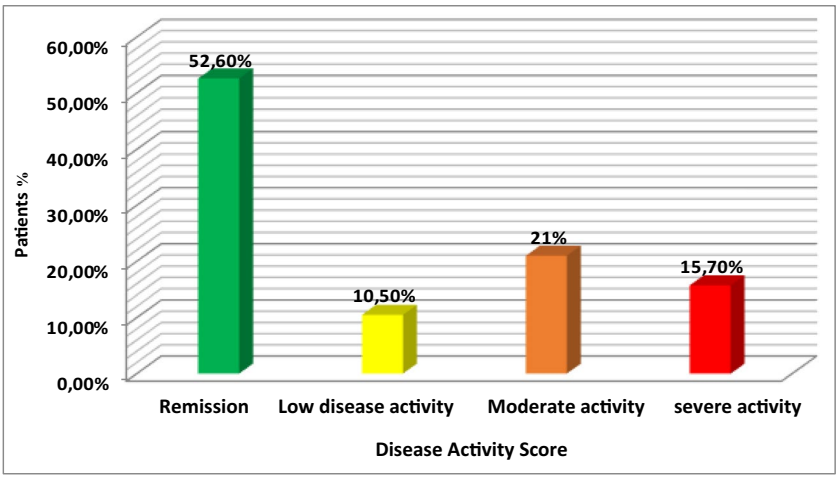

Fig. 1 Disease activity assessment in patients with Still's disease according to experts' consensus and the Still's Disease Activity Score (SDAS) at 6 months. Remission (0–1 point), low disease activity (2–3 points), moderate disease activity (4–7 points), and severe disease activity (≥8 points)

scale was 4.1 ± 1.5. The mean CRP was 51.56 ± 47.1 mg/l and the mean corticosteroids dose 27.5 ± 15.8 mg/day.

Characteristics of the high disease activity group (SDAS ≥ 8 points)

Twelve (15.7%) had a high disease activity. The clinical profile was notable for fever ($n = 10$, 83%), rash ($n = 8$, 66.6%), arthralgia ($n = 12$, 100%), and arthritis ($n = 9$, 75%). The mean physician global assessment on VAS was 6 ± 0.95, and the patient global assessment on VAS was > 5 for all patients. The mean CRP was 87.16 ± 73.35 mg/l and the mean corticosteroids dose 44.16 ± 22.74 mg/day.

Comparative analysis between the different groups

The mean physician global assessment on VAS was significantly higher in the severe disease activity group compared with the moderate disease activity group (2.8 ± 1.27, 6 ± 0.95, $p < 10^{-6}$). Moreover, the mean corticosteroid dose was significantly higher in the severe disease activity group compared with the moderate disease activity group (27.5 ± 15.8, 44.16 ± 22.74, $p = 0.02$). The mean CRP was higher in the low disease activity group compared with the inactive group (17.4 ± 6.6, 4.02 ± 2.9, $p = 0.05$).

Evaluation of the performance of SDAS in patients with systemic and articular pattern

Characteristics of the patients with a systemic pattern of Still's disease

Twenty-one patients with a systemic pattern were in remission at 6 months and were reclassified according to SDAS as inactive disease ($n = 18$) and low disease activity ($n = 3$).

Comparative analysis showed a significant difference in CRP between the inactive disease group and the low disease activity group, respectively (4.83 ± 3.38, 17.33 ± 2.51, $p = 3.10^{-5}$).

Characteristics of the patients with an articular pattern of Still's disease

Eight patients with articular pattern relapsed at 6 months and were reclassified according to SDAS as in low disease activity ($n = 2$, arthralgia), moderate activity ($n = 3$, SJC: 1–2), and severe activity ($n = 3$, SJC ≥ 4).

Validation of the SDAS at 12 months

Twenty-six patients relapsed at 12 months and were reclassified according to the SDAS as in moderate disease activity ($n = 13$) and severe disease activity ($n = 13$), while 30 were in low disease activity and 19 were in inactive disease. Five patients were lost to follow-up.

The mean physician global assessment on VAS was significantly higher in the severe disease activity group compared with the moderate disease activity group and inactive disease group, respectively (5.69 ± 1.1, 3.15 ± 0.89, 0.10 ± 0.45, $p < 10^{-6}$). Moreover, the mean patient global assessment on VAS was significantly higher in the severe disease activity group compared with the moderate disease activity group and inactive disease group, respectively (7.69 ± 1.79, 4.38 ± 0.96, 0.31 ± 1.0, $p = 0.02$).

Comparative analysis showed a significant difference in CRP between the inactive disease group and the moderate disease activity group, respectively (3.42 ± 4.46, 39.84 ± 22.31, $p = 0.03$), and between the moderate activity group and the severe activity group (39.84 ± 22.31, 86.6 ± 46.23, $p = 0.004$).

Moreover, the mean corticosteroid dose was significantly higher in the moderate disease activity group compared with

Table 4 Disease activity assessment according to Still's Disease Activity Score in patients at 12 months

	Inactive disease ($n=19$)	Moderate disease activity ($n=13$)	Severe activity ($n=13$)	p value
SDAS	0–1 point	4–7 points	≥08 points	
Physician VAS (0–10) mean	0.10 ± 0.45	3.15 ± 0.89 $\mathbf{p < 10^{-5}}$	5.69 ± 1.1	$p < 10^{-6}$
Patient VAS (0–10) mean	0.31 ± 1.0	4.38 ± 0.96	7.69 ± 1.79 $\mathbf{p < 10^{-4}}$	$p = 0.02$
CRP (mg/l) (mean)	3.42 ± 4.46 $\mathbf{p = 0.03}$	39.84 ± 22.31	86.6 ± 46.23 $\mathbf{p = 0.004}$	$p = 0.08$
Corticosteroids dose mg/day (mean) 1 month before	3.68 ± 3.66 $\mathbf{p = 0.001}$	11.5 ± 6.8	13.6 ± 5	$p = 0.06$
Corticosteroids dose mg/day (mean) Current dose at 12 months	00	29.2 ± 18.3	35.7 ± 21	-

CRP C-reactive protein, *SDAS* Still's Disease Activity Score, *VAS* visual analogue scale

the inactive disease group (11.5 ± 6.8, 3.68 ± 3.66, $p = 0.001$) (Table 4).

The Still's Disease Activity Score is a composite measure to assess the disease activity in Still's disease despite its heterogeneous manifestations and patterns. It can be used in clinical practice and research to evaluate more accurately the disease activity particularly in the development of biological therapy. An external validation in another population is desirable.

Limitations of this study

The clinical judgement in the assessment of the disease activity depends on the qualification and the experience of the physicians and may be limited by a subjective evaluation.

An external validation of the SDAS including the children population is desirable.

Discussion

The Disease Activity Score is a good simple tool to assess the level of disease activity in Still's disease, despite its heterogeneous patterns with systemic and chronic articular forms. This is the first prospective study focused on the disease activity assessment in adult-onset Still's disease with disease activity classification in inactive disease, low disease activity, moderate disease activity, and high disease activity.

The SDAS is a composite score that can be calculated in routine clinical practice without needing a specific application or calculator. It is composed of six items and calculated by arithmetic sum. These items should be related to the disease activity and not due to differential conditions, particularly the occurrence of an acute viral or bacterial infection in patients under corticosteroids or immunosuppressive therapy.

In rheumatic diseases, stringent remission criteria are crucial to improve outcomes and to validate new-targeted therapy in clinical trials [21, 22]. Severe disease activity at the time of diagnosis or in relapses may suggest the early use of biological agents particularly anakinra or tocilizumab [1, 21].

Adult-onset Still's disease and systemic juvenile arthritis are considered currently the same disease and should be called "Still's disease"; several studies showed high similarities in the clinical profile, the biological features, and the genetic pattern. Both innate immunity and adaptive immunity are implicated in the pathophysiology of Still's disease with strong evidence of major histocompatibility complex (MHC) II genetic susceptibility [1, 2]. Therefore, the SDAS can be extrapolated to evaluate disease activity in SJIA.

Still's disease is a complex rheumatic disease that has specific clinical, biological, and disease course manifestations. About 40% of patients had a chronic course, and one third of them had a structural damage. Moreover, life-threatening complications and hypersensitivity features can occur with poor prognosis [19]. Therefore, a specific management and accurate assessment of the disease activity should be performed to control the disease activity and to avoid articular and organ damage. Novel activity biomarkers such as IL-18, S100A12, and other composite measures are proposed to evaluate the disease activity in Still's disease [19, 23].

Still's disease activity assessment has been proposed by some studies particularly the systemic score proposed by Pouchot and recently validated by Ruscitti et al. A systemic score higher than 7 points is correlated to life-threatening complications and death [14].

This systemic score was already modified by Rau et al. who replaced splenomegaly and abdominal pain by ferritin ≥ 3000 µg/l and arthritis. The mean score is significantly higher in patients with active disease compared with patients with chronic (inactive) disease (5.60 ± 1.93, 1.16 ± 0.98, $p < 0.001$) [15]. However, this score may not specify accurately the level of the disease activity in patients without systemic features particularly swollen joints count, the physician global assessment, and the CRP were not integrated in this score.

Moreover, several studies reporting the efficacy and safety of biologic agents assessed the disease activity in Still's disease using different rheumatoid arthritis scores particularly the Disease Activity Score (DAS-28) by Puechal and Vittale [24, 25] and the American College of Rheumatology (ACR) response criteria by Lequerré and Nordstom [26, 27]. These scores were not designed for Still's disease and do not include fever, rash, or other systemic manifestations of the disease, which can underestimate the residual disease activity.

The recent clinical trial for the development of Tadeking alpha defined an active disease as the presence of two or more criteria of Yamaguchi and fever or high CRP which can be useful to detect a flare [13]. Nevertheless, an accurate assessment is needed to appreciate the level of the disease activity, to define remission criteria, and to modify the therapeutic approach.

A common disease activity index for autoinflammatory diseases (AIDAI) was proposed and validated for several hereditary recurrent fever syndromes [28]. However, the assessment of the disease activity is based on a questionnaire fulfilled by the patient without a physician appreciation and the duration required is 30 days.

Clinically inactive disease (CID) was developed to specify efficacy outcome measure in pediatric patients and was used in the EULAR guidelines for the management of Still's disease. CID is defined as no active arthritis, no fever, no uveitis, normal ESR (20 mm/h), and physician global assessment indicating no activity. Nevertheless, it was not validated in adult Still's disease [29].

Recently, a Disease Activity Score for adult-onset Still's disease was proposed by Kalyoncu et al. The score is composed of five items: fever (2 points), arthralgia (2 points), ≥ 2 arthritis (1 point), ferritin ≥ 350 ng/ml (1 point), and neutrophils ≥ 65% (1 point). A score ≥ 4 points indicated an active disease. Despite the fact that the component's criteria were selected through a logistic regression model, the disease activity in patients without systemic features could be difficult to evaluate. Moreover, the remission cutoff value was not defined. An external validation in other countries would be interesting [30].

Despite the therapeutic window and early use of biologic agent opportunity proposed by experts in Still's disease, several countries worldwide do not have access to biologic therapy. The high cost and side effects of these medications should be considered [1, 2, 21].

Early use strategy of methotrexate like in rheumatoid arthritis can be proposed in Still's disease to improve the response rate and the tight control of the disease activity. The high rate of flares under corticosteroids and life-threatening complications need an early prescription of synthetic or biologic disease-modifying anti-rheumatic drugs [31–34].

The strategy treat to target and the tight control of the disease activity need stringent remission criteria. The SDAS is a simple tool, valid, and reproducible to evaluate accurately the disease activity in clinical practice and can also be a useful score in clinical trials evaluating biologic agents. An external validation in another population is desirable.

The advances in the comprehension of the pathophysiology of Still's disease suggest several therapeutic pathways and need better tools to appreciate specifically the disease activity in Still's disease with its heterogeneous manifestations and patterns [1].

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Declarations

Disclosures None.

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