BPR MCS
Bulletin of Pioneering Researches of Medical and Clinical Science

Bulletin of Pioneering Researches of Medical and Clinical Science

Available online: https://bprmcs.com
2026 | Volume 6 | Issue 1 | Page: 94-103

Spectrum and Determinants of Non-Classical Complications in Adult-Onset Still's Disease: A Multicenter Spanish Cohort Study

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Abstract

This research aimed to explore the frequency of atypical or non-classical complications in adult-onset Still's disease (AOSD), excluding macrophage activation syndrome (MAS), and to identify the factors associated with their occurrence. A multicenter cross-sectional analysis was carried out on AOSD patients listed in the Spanish registry focused on Still's disease.
In total, 107 individuals (67% female) participated in the study, and 64 of them (59.8%) presented with non-classical complications. These complications consisted of macrophage activation syndrome in 9.5%, unusual skin lesions in 38.8%, heart-related problems in 22.7% (including pericarditis, myocarditis, pulmonary arterial hypertension, and noninfectious endocarditis), pleuritis in 28.9%, short-term lung shadows in 4%, notable headaches in 14.1%, lower belly discomfort accompanied by peritonitis signs in 8.4%, and secondary amyloidosis in 0.9%. Multivariate logistic regression revealed that lymphadenopathy (OR 2.85, 95% CI 1.03–7.91, P = 0.044) and the systemic score (SSC) index (OR 1.86, 95% CI 1.29–2.69, P = 0.001) were independent predictors of the emergence of non-classical manifestations. On the other hand, the presence of classic exanthema correlated with a decreased likelihood of such complications (OR 0.32, 95% CI 0.11–0.95, P = 0.041). Apart from the standard symptoms and MAS, a large share of AOSD patients experience rare complications, several of which carry a risk of becoming life-threatening. Clinicians should account for these issues when assessing and monitoring patients. Prompt detection and appropriate treatment play a key role in substantially lowering illness burden and death rates.

Keywords: Adult-onset Still disease, Clinical manifestations, Prognostic, AOSD

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Received: 21 November 2025
Revised: 28 February 2026
Accepted: 03 March 2026

How to Cite This Article: Mansour A, Saeed O. Spectrum and Determinants of Non-Classical Complications in Adult-Onset Still's Disease: A Multicenter Spanish Cohort Study. Bull Pioneer Res Med Clin Sci. 2026;6(1):94-103. https://doi.org/10.51847/jkaWvjR7p4

Introduction

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory condition that typically features spiking fevers, a fleeting skin rash, joint inflammation, elevated white blood cell counts, and markedly elevated ferritin levels [1-5]. Frequent accompanying signs encompass painful swallowing, muscle aches, liver dysfunction (increased liver enzymes possibly with liver enlargement), swollen lymph nodes, and spleen enlargement [1-5].
Recent findings underscore the notable variability in AOSD, including how it presents, its intensity, and its long-term behavior. Although the underlying causes are not fully understood, some individuals go on to develop serious, potentially fatal issues. These may involve macrophage activation syndrome (MAS), irregular skin

changes, and problems affecting the blood, heart, lungs, kidneys, or nervous system [1-6].

The current investigation set out to evaluate the occurrence rate and variety of non-classical complications among AOSD cases, independent of MAS, and to determine which factors are associated with their development.

Materials and Methods

This multicenter project examined cases from a nationwide Spanish project on Still's disease that covered both systemic juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD). The present evaluation focused solely on AOSD patients and included both long-standing and newly presenting cases managed within rheumatology or internal medicine services at major Spanish hospitals. Inclusion required a definite AOSD diagnosis by accepted criteria and a minimum follow-up of 1 year at the study centers. To achieve sufficient diversity, at least 10 centers across different parts of Spain had to participate, and patient enrollment spanned a 10-month window.

Medical chart review was undertaken retrospectively using a structured data-gathering plan. Details on the design and overall profile of the JIA-Still SERPE registry are presented in an earlier publication [7]. Cases were excluded if more than 50% of the essential information from their records could not be obtained. Data gathered for this work covered: (A) basic demographic and disease-related information such as age, gender, initial presentation pattern, and illness trajectory; (B) the classification systems employed (Cush [8], Yamaguchi [9], and Fautrel [10]); (C) symptoms recorded at the beginning and over the course of the illness; (D) assessments of life quality via the EuroQoL instrument and physical function via the Health Assessment Questionnaire (HAQ); (E) blood test outcomes (ESR, C-reactive protein, hemoglobin, total leukocytes, neutrophils, platelets, ferritin levels, and complete liver panels) together with results from imaging studies (X-rays, musculoskeletal ultrasound, heart ultrasound, and computed tomography [CT]); and (F) any lasting damage or complications stemming from the condition itself or from therapies used.

A thorough data entry sheet, along with a detailed codebook, was prepared to promote uniform collection and interpretation, with clear definitions for each variable and built-in checks for accuracy.

All participants, or their legal representatives for those under age, gave written consent allowing the use of their personal health information. Entries were made into a protected web-based system created specifically for the project. All information was managed with strict confidentiality in line with European data protection standards. The entire protocol followed the ethical guidelines of the Declaration of Helsinki and the International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use.

Statistical analysis. Continuous data are summarized as mean ± standard deviation (SD) or as median with interquartile range (IQR, 25th–75th percentile), depending on their distribution. Categorical data are displayed as counts and percentages. Prevalence figures for atypical features, along with their 95% confidence intervals (CIs), were determined based on a Poisson distribution. Group comparisons for numerical variables used either the Student's t-test or the Mann–Whitney U test, depending on whether the data followed a normal distribution. For categorical variables, the chi-squared test or Fisher's exact test was applied as suitable.

Bivariate and multivariate logistic regression analyses were then conducted. The outcome variable was defined as the occurrence of any atypical or non-classical complication. Explanatory variables encompassed demographic details, key clinical traits identified in the initial comparisons, pattern of disease evolution, laboratory measurements, and scores from the systemic score system. Any variable judged clinically meaningful or showing a p-value below 0.25 during bivariate testing was advanced to the multivariate stage. Statistical significance was established at $P < 0.05$.

Results and Discussion

This analysis involved 107 cases collected from 14 hospitals across several regions of Spain. **Table 1** outlines the key demographic, clinical, and laboratory details of the group. Women made up the majority of the sample (67%), and the median age at diagnosis was 40.6 years (IQR 30.2–53.8). The median delay from initial symptoms until diagnosis was 0.13 years (IQR 0.06–0.44). A positive family history for comparable illnesses was present in 30.2% of participants. The Yamaguchi criteria were met by the highest number of patients (85%), followed by the Cush criteria (58.9%) and the Fautrel criteria (54.2%).

Table 1. Core characteristics observed in the 107 patients suffering from AOSD.

Patient characteristics and clinical features (n = 107)	
Variable	**Value**
Total number of patients	107
Demographic data	

Sex (female/male)	71 (67%) / 36 (33%)
Age at disease onset, median (IQR)	40.7 (28.4–56.3)
Age at diagnosis, median (IQR)	40.6 (30.2–53.8)
Interval from onset to diagnosis (years), median (IQR)	0.13 (0.06–0.44)
Diagnostic criteria fulfillment	
Yamaguchi criteria	91 (85%)
Fautrel criteria	58 (54.2%)
Cush criteria	63 (58.9%)
Baseline Clinical Features	
Fever	98 (100%)
Typical rash (exanthema)	81 (82.6%)
Constitutional symptoms	44 (44.4%)
Morning stiffness	60 (64.5%)
Arthralgia	101 (99%)
Arthritis	71 (68.9%)
Chronic/persistent arthritis	34 (43%)
Sore throat (odynophagia)	80 (78.4%)
Splenomegaly	27 (28.4%)
Liver involvement	28 (29.5%)
Hepatosplenomegaly	37 (38.9%)
Lymphadenopathy	43 (43.4%)
Serositis	30 (32.3%)
Laboratory findings	
ESR ≥ 30 mm/h (n = 302)	90 (92.8%)
Ferritin ≥ 1500 ng/dL	52 (56.5%)
Ferritin level, mean ± SD (ng/dL)	6053 ± 9779
Hemoglobin < 12 g/dL	39 (37.1%)
Leukocyte count ≥ 15,000/mm³	45 (43.7%)
Platelet count ≥ 400,000/mm³	26 (29.5%)
ALT ≥ 40 U/L	52 (57.8%)
AST ≥ 40 U/L	50 (58.1%)
GGT ≥ 40 U/L	61 (73.5%)
Treatment Requirements	
Glucocorticoid therapy required	63 (63.6%)
Use of biologic agents	57 (58.8%)
Disease Course	
Monocyclic (single episode)	29 (27.4%)
Polycyclic (recurrent episodes)	29 (27.4%)
Chronic persistent course	48 (45.3%)
Disease Course	
Monocyclic (single episode)	29 (27.4%)
Polycyclic (recurrent episodes)	29 (27.4%)
Chronic persistent course	48 (45.3%)

Figures are presented as n (%), except where different measures apply. Percentages shown for individual items reflect calculations based solely on patients with recorded data for that item.

Fever appeared universally (100%), joint pain in 99%, actual arthritis in 68.9%, and the classic rash in 82.6%. Additional regularly seen signs were a painful throat in 78.4%, general constitutional symptoms in 44.4%, liver abnormalities in 29.5%, swollen lymph nodes in 43.4%, and an enlarged spleen in 28.4%.

An increased erythrocyte sedimentation rate (ESR ≥ 30 mm/h) occurred in 92.8% of individuals. Average ferritin reached 6053 ng/dL (SD: ± 9779), and levels of 1500 ng/dL or more were recorded in 56.5% of the cohort. White blood cell counts surpassing 15,000/mm³ were noted in 43.7% of patients. Liver enzyme elevations (ALT, AST, or GGT > 40 U/L) affected more than half the group. Glucocorticoid therapy was prescribed for 63.6% of patients, and biologic treatments became necessary in 58.8%. Disease evolution followed a single-flare pattern in 27.4%, a recurrent-flare pattern in 27.4%, and a chronic ongoing pattern in 45.3%.

Non-classical clinical manifestations

Within the full set of 107 patients, 64 (59.8%; 95% CI: 46.06 to 76.38) showed at least one of the following unusual features **(Table 2)**:

Table 2. Rates of atypical or non-classical complications recorded in this group of 107 adult-onset Still's disease patients.

Complication	Cases, n (%)	95% confidence interval
Macrophage activation syndrome (missing data = 2)	10 (9.5%)	4.57–17.51
Atypical cutaneous manifestations (missing data = 9)	38 (38.8%)	27.44–53.22
Cardiac involvement overall (missing data = 10)	22 (22.7%)	14.21–34.34
├─ Pericardial involvement	18 (18.5%)	11.0–29.33
├─ Myocardial inflammation (myocarditis)	4 (4.1%)	1.12–10.56
├─ Suspected pulmonary arterial hypertension	6 (6.2%)	2.27–13.46
└─ Inflammatory valvular disease	1 (1%)	0.03–5.74
Primary pulmonary involvement (missing data = 10)	—	—
├─ Pleural disease	28 (28.9%)	19.18–41.72
└─ Transient pulmonary infiltrates	4 (4%)	1.09–10.24
Headache (missing data = 8)	13 (14.1%)	7.52–24.16
Peritonitis (missing data = 0)	9 (8.4%)	3.85–15.97
Secondary amyloidosis (missing data = 3)	1 (0.9%)	0.02–5.36

Data appear as absolute numbers and percentages. Associated 95% confidence intervals (CIs) were obtained under the assumption of a Poisson distribution.

MAS, as defined by the Ravelli criteria or supported by histopathological evidence, occurred in 10 of 105 patients (9.5%; 95% CI: 4.57 to 17.51). The study identified no examples of other major blood disorders, including thrombotic thrombocytopenic purpura or widespread intravascular clotting.

Atypical skin abnormalities, reviewed by a dermatologist, were found in 38 of 98 patients (38.8%, 95% CI: 27.44 to 53.22). Predominant patterns involved ongoing itchy raised spots and flat lesions arranged in streaks reminiscent of flagellate erythema, together with rash forms resembling hives.

Involvement of the heart was detected in 22 out of 97 patients (22.7%, 95% CI: 14.21 to 34.34). This category included 18 instances of pericardial inflammation (18.5%, 95% CI: 11.0 to 29.33) verified through standard heart ultrasound and/or chest CT scans; 4 instances of heart muscle inflammation (4.1%, 95% CI: 1.12 to 10.56) diagnosed based on matching complaints, increased troponin values, unspecific ECG shifts, and ultrasound confirmation; 6 instances of probable pulmonary arterial hypertension (PAH) (6.2%, 95% CI: 2.27 to 13.46) spotted via standard heart ultrasound; and 1 instance of inflammatory damage to the heart valves (1%, 95% CI: 0.03 to 5.74) established with both standard and advanced swallowing-type heart ultrasounds.

Involvement affecting the pleura and lungs: pleural inflammation, verified via chest radiography and/or chest CT, affected 28 out of 97 patients (28.9%, 95% CI: 19.18 to 41.72). Brief episodes of lung shadowing, once infection and fluid backup in the lungs had been excluded, appeared in 4 out of 100 patients (4%, 95% CI: 1.09 to 10.24) on plain chest films and/or detailed chest CT imaging.

Pronounced headaches were reported by 13 of 92 patients (14.1%, 95% CI 7.52 to 24.16). In selected situations, aseptic inflammation of the brain coverings was objectively verified by spinal fluid sampling combined with brain CT or MRI.

Inflammation of the abdominal lining (peritonitis), confirmed by scans demonstrating free fluid inside the abdomen (ultrasound or abdominal CT), was recorded in 9 of the 107 patients (8.4%, 95% CI: 3.85 to 15.97). When all varieties of serosal inflammation (pleural, pericardial, or peritoneal) were combined, the overall rate in the studied population reached 30.9% (30/97, 95% CI: 22.60 to 40.70).

Secondary amyloid buildup, confirmed by tissue sampling, was present in 1 of 104 patients (0.9%; 95% CI: 0.02 to 5.36).

Long-term consequences, defined as either visible structural changes on imaging (X-ray or joint ultrasound) or a measurable decline in daily function, were observed in 14% of the entire group (15/107; 95% CI 8.68 to 21.84). Details regarding the occurrence of further lasting problems associated with the condition or the therapies applied are provided in **Table 3**.

Table 3. Rates of permanent sequelae or ongoing damage resulting from the illness itself or from therapeutic interventions.

Outcome	Number of cases, n (%)	95% confidence interval
Chronic organ damage	15 (14.1%)	0.07–0.20
Functional limitation	4 (4%)	0.009–0.07
Secondary amyloidosis	1 (1%)	0.0–0.02
Growth impairment (stunting)*	1 (1%)	0.0–0.02
Avascular necrosis	1 (1%)	0.0–0.02
Cataract formation	5 (4.8%)	0.009–0.09
Osteoporotic fractures	5 (4.8%)	0.009–0.09
Depressive disorder	7 (6.7%)	0.01–0.11

The age at which symptoms began in this patient was 18.2 years. Results are displayed as absolute numbers and percentages. The 95% confidence intervals (CIs) were calculated assuming a Poisson distribution.

Predictors of development of non-classical clinical manifestations

The comparative analysis **(Table 4)** revealed that individuals who experienced complications showed a markedly higher rate of lymphadenopathy (52.4% versus 27.8%; P = 0.018) and, as anticipated, elevated scores on the systemic score system index (6.6 versus 5.3; P = 0.0002). These patients also tended to follow a chronic disease pattern, displayed higher ferritin concentrations, more frequent liver enzyme elevations, greater liver enlargement, and a greater requirement for intensive corticosteroid doses and biologic agents. However, these observations did not reach statistical significance.

Table 4. Outcomes of the comparison between patients with and without non-classical clinical manifestations.

Variable	No complications (n = 43)	With complications (n = 64)	P-value
Fever	34 (100%)	64 (100%)	—
Typical skin rash	22 (64.7%)	32 (50.0%)	0.164
Splenomegaly	8 (25.8%)	19 (29.7%)	0.694
Hepatomegaly	7 (22.6%)	21 (32.8%)	0.305
Sore throat (odynophagia)	27 (71.0%)	53 (82.8%)	0.163
Lymph node enlargement	10 (27.8%)	33 (52.4%)	0.018
Arthritis	27 (69.2%)	44 (68.7%)	0.959
Shoulder involvement	—	2 (22.2%)	1.000
Disease course pattern			0.112
├─ Monocyclic	11 (26.2%)	18 (28.1%)	
├─ Polycyclic	16 (38.1%)	13 (20.3%)	
└─ Chronic persistent	15 (35.7%)	33 (51.6%)	
Requirement for high-dose glucocorticoids	30 (55.6%)	43 (68.2%)	0.206
Use of biologic therapy	30 (55.6%)	37 (60.7%)	0.622
Age at disease onset (mean ± SD)	39.4 ± 16.6	44.2 ± 17.8	0.256
ESR (mm/h), mean ± SD	80.4 ± 26.4	73.9 ± 30.8	0.281
CRP (mg/dL), mean ± SD	25.4 ± 36.9	34.1 ± 61.3	0.776
Ferritin (ng/dL), mean ± SD	4879 ± 6797	6741 ± 11,164	0.955
Hemoglobin (g/dL), mean ± SD	11.1 ± 1.6	11.5 ± 1.7	0.212
Leukocyte count (/mm³), mean ± SD	14,118 ± 6,177	14,286 ± 5,905	0.836
ALT, mean ± SD	69.1 ± 89.6	84.9 ± 122.7	0.942
AST, mean ± SD	77 ± 65.7	83.3 ± 121.9	0.440
GGT, mean ± SD	103.7 ± 87.2	163 ± 195.7	0.428
Systemic score (SSC index), mean ± SD	5.3 ± 1.5	6.6 ± 1.7	0.0002

Results are expressed as mean ± standard deviation (SD) or as numbers and percentages. Percentages for each characteristic were computed using only those patients with available data for the variable. SSC = systemic score system.

In the multivariate logistic regression model **(Table 5)**, lymphadenopathy (OR 2.85, 95% CI: 1.03–7.91, P = 0.044) and the systemic score system (SSC) index (OR 1.86, 95% CI: 1.29–2.69, P = 0.001) emerged as independent factors linked to the appearance of non-classical clinical manifestations. By contrast, the presence of typical exanthema was connected to a lower likelihood of developing these complications (OR 0.32, 95% CI: 0.11–0.95, P = 0.041).

Table 5. Variables predicting the development of non-classical clinical manifestations.

Variable	Bivariate analysis OR [95% CI] (P-value)	Multivariate analysis OR [95% CI] (P-value)
Age at disease onset	1.02 [0.99–1.04] (0.190)	—
Female sex	0.71 [0.31–1.65] (0.431)	—
Typical skin rash (exanthema)	0.54 [0.23–1.28] (0.166)	0.32 [0.11–0.95] (0.041)
Sore throat (odynophagia)	1.96 [0.75–5.10] (0.167)	—
Lymph node enlargement	2.86 [1.18–6.90] (0.019)	2.85 [1.03–7.91] (0.044)
Disease course pattern		
├─ Monocyclic	1 (reference)	—
├─ Polycyclic	0.50 [0.17–1.42] (0.190)	—
└─ Chronic persistent	1.34 [0.51–3.54] (0.549)	—
Ferritin levels (ng/dL)	1.00 [0.99–1.00] (0.383)	—
Hemoglobin (g/dL)	1.13 [0.89–1.43] (0.306)	1.32 [0.96–1.79] (0.087)
Systemic score (SSC index)	1.61 [1.22–2.12] (0.001)	1.86 [1.29–2.69] (0.001)
Requirement for high-dose glucocorticoids	1.72 [0.74–4.00] (0.208)	—
Use of biologic therapy	1.23 [0.53–2.84] (0.622)	—

Beyond the standard symptoms and macrophage activation syndrome, over half of all patients diagnosed with AOSD experience uncommon clinical features that deserve careful attention, especially when assessing and monitoring the condition. Prompt identification and swift management remain critical to lowering illness burden and death rates.

In addition to the well-known fleeting rash, unusual skin changes have been described in as many as 14% of AOSD cases in earlier reports [11], rising to 38.8% in the present group. The predominant and characteristic findings consist of persistent itchy papules and plaques that commonly vary in hue from red to brown or purple [11, 12]. These lesions may develop scaling or crusting and tend to appear mainly on the back, upper trunk, belly, and the outer sides of the arms and legs. A streak-like arrangement is often noted, probably linked to the Koebner phenomenon, producing a whip-like or flagellate erythema pattern. Under the microscope, such lesions display a typical appearance featuring isolated or grouped dying or dead keratinocytes in the superficial skin layers, along with inflammatory cells gathered around blood vessels in the upper and mid portions of the dermis [11]. Less often, other presentations such as hives or hive-like rashes can be seen [11, 12]. These skin findings can emerge at any point during the illness but are most frequent among those with ongoing and intense disease activity. Identifying this particular form is important for timely recognition of AOSD, as it often signals sustained disease activity and the potential need for more aggressive therapeutic approaches [11, 12].

Heart-related complications rank among the most frequent internal organ problems in AOSD. They can sometimes be the very first sign of the disease and constitute one of the leading reasons for early death linked to this condition [1-6, 13]. In the current series, the rate reached 22.7%, which aligns closely with the 29% figure reported by Bodard and colleagues [13]. Pericarditis, with or without fluid accumulation, is the most common cardiac issue. Earlier investigations have reported its occurrence in 10%-37% of patients [1-6, 14] (and 11.5% among AOSD cases in the international AIDA Network Still's disease registry) [15]. No precise rate for cardiac tamponade has been reported in the literature to date. After pericarditis, inflammation of the heart muscle is the next most common cardiac problem, with reported frequencies of around 7% in published data [16, 17], compared with 4.1% in our patients. Pericarditis and myocarditis frequently coexist (myopericarditis), appearing together in 54% of reported cases [16, 17]. Myocarditis usually develops early, arising within the initial twelve months in 80% of affected individuals, and is already evident at the moment of AOSD diagnosis in 54% of them [17]. Those who develop myocarditis in the setting of AOSD are typically younger

and more often male (75%) [16, 17]. Typical complaints include fever, chest discomfort, shortness of breath, and rapid heartbeat. For this reason, AOSD deserves consideration whenever acute febrile myocarditis is encountered.

Other less common complications include PAH and noninfectious endocarditis. The frequency of PAH, previously estimated at 4.8% among AOSD patients followed for more than 33 years [18], closely matches the 6.2% rate recorded in our group. Involvement of the heart valves has rarely been reported [19]. The exact mechanisms underlying these complications remain unclear, yet treatment with corticosteroids generally proves beneficial. When tissue samples were examined, histology typically revealed a fibrinoid or fibrinous material.

In the present series, pleuritis occurred in 28.9% of cases and lung tissue involvement in 4%. Pleuritis is the leading pulmonary feature of AOSD, with reported clinical rates ranging from 10% to 28% across earlier studies [1-6, 14] (14.6% in the international AIDA disease registry) [15]. It tends to accompany intense disease activity and is viewed as a marker of poorer outlook in AOSD. Detection of serositis at the time of diagnosis—whether pericarditis in some patients [20] or pleuritis in others [21]—has been associated with a higher likelihood of later need for biologic treatments. Several researchers recommend introducing biologics sooner in these situations [21]. Interstitial lung disease has been noted in 5.3% of AOSD patients [22, 23] and appears in two separate patterns. (1) The first pattern consists of acute respiratory distress syndrome (ARDS), seen in 40% of such cases and limited to individuals with a systemic disease profile; it arises as an early event, either at disease onset or within the initial year. This presentation usually includes shortness of breath, cough, and widespread lung shadows, occasionally with diffuse bleeding into the air spaces [22, 23]. (2) The second pattern is interstitial lung disease (ILD) without ARDS, observed in 60% of affected patients and showing imaging features of organizing pneumonia, nonspecific interstitial pneumonia (NSIP), or interstitial changes that cannot be further classified. In this group, lung problems were the first sign of AOSD in half the cases, while cough and shortness of breath were the dominant complaints (72% and 44%, respectively) [22, 23]. Physical examination of the lungs rarely reveals abnormal sounds. Nearly all of these patients belonged to the systemic subtype of AOSD.

Headache is a fairly frequent complaint, either at symptom onset or during disease flares. Previous publications have described it in 7% to 12% of patients [23-25], while our cohort showed a rate of 14.1%. Both the central and peripheral nervous systems may become involved. Aseptic meningitis is the most common neurological complication, accounting for 64.3% of all nervous system complications [24-26]. Although uncommon, additional neurological issues include inflammation of the brain and meninges, epileptic seizures, occluded or bleeding brain vessels, Miller-Fisher syndrome, demyelinating brain disease, cranial nerve paralysis, symmetric sensory changes in the limbs, and hearing impairment due to nerve damage [24-26]. While nervous system problems are usually regarded as a later development, they have sometimes appeared as the opening feature of AOSD, especially when aseptic meningitis is present.

Lower abdominal discomfort occurs with some regularity in AOSD and has been reported in up to 13% of cases [27] (11.1% in the AIDA Network registry) [15]. Possible explanations include enlargement of the liver and spleen, inflammation of abdominal lymph nodes, or inflammation of the peritoneal lining, although the precise cause is rarely confirmed. In our patients, imaging studies detected peritonitis in 8.4% of the group.

AA amyloidosis (AAA) represents an uncommon complication of AOSD that generally emerges after many years of follow-up, stemming from ongoing or repeated inflammation caused by inadequate disease management. Most descriptions come from individual case reports involving long-standing, treatment-resistant joint-dominant AOSD accompanied by extended disease duration and often linked to joint damage [28]. Its true frequency in AOSD remains undetermined. In the current cohort, secondary amyloidosis was verified in 1% of patients, underscoring how rarely it appears in this condition.

One of the main difficulties when managing AOSD lies in spotting reliable indicators already present at diagnosis that can flag patients more likely to develop atypical or non-classical complications, some of which carry a risk of becoming life-threatening. Pinpointing such predictors is particularly important today, given the availability of potent yet relatively safe biologic medications (including canakinumab, anakinra, tocilizumab, and anti-TNF agents). Establishing the most suitable treatment plans may help reduce the total exposure to glucocorticoids over time. In our series, patients who developed complications showed a clearly higher incidence of lymphadenopathy and elevated values on the systemic score index.

Limited information is available in this area. In the present investigation, lymphadenopathy and the systemic score index emerged as factors associated with the appearance of non-classical clinical manifestations. One reasonable explanation is that lymphadenopathy signals intensified systemic inflammation and immune system overactivation caused by abundant cytokine release (e.g., IL-1β, IL-6, IL-18) [1-6, 29]. Such widespread inflammatory processes could increase the likelihood of non-classical complications by further exacerbating immune imbalance

and involving multiple organs. Moreover, lymphadenopathy may point to more aggressive disease forms that commonly feature atypical presentations. Elevated systemic score values recorded at diagnosis have proven to be the most reliably confirmed predictive element. In a recent large-scale analysis of 597 AOSD patients drawn from the Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale (GIRRCS) AOSD-Study Group and the Autoinflammatory Disease Alliance Network Still Disease Registry, a systemic score of 7 or higher was found to strongly forecast a life-threatening disease trajectory (OR = 3.36) [30]. When the individual elements of the systemic score were examined separately, both liver involvement and lung disease stood out as meaningful indicators of a potentially fatal course. Wahbi *et al*. [31] recently proposed catastrophic adult-onset Still's disease (CAOSD) as a separate category characterized by critical organ dysfunction necessitating intensive care unit admission. The main life-threatening issues they described included cardiac problems (myocarditis and tamponade), severe breathing difficulties (including ARDS), and clotting disorders such as disseminated intravascular coagulation. These critical events mostly occurred during the initial flare of the illness, characterized by a sudden onset and an intense systemic inflammatory response. When compared with 41 AOSD patients who did not develop organ failure, multivariate analysis identified three independent risk factors for life-threatening complications: lack of joint pain, younger age at onset, and a shorter time gap between the start of fever and hospital admission [31]. In a separate French study, 33% of patients developed organ-related complications [32]. Fever exceeding 39.5 °C was associated with a monocyclic disease pattern, while arthritis and low platelet counts correlated with chronic and complicated forms of AOSD, respectively [32]. However, this link may be influenced by confounding factors, since the most frequent serious complication in that series was MAS, a condition almost always accompanied by thrombocytopenia. Younger individuals faced the greatest chance of not responding to initial standard therapies.

When reviewing the findings of this study, several potential limitations deserve attention: (1) the observational and retrospective nature of the design, which carries the possibility of information bias arising from incomplete or inaccurate record-keeping and the risk of under-detecting certain complications; (2) restricted generalizability of the sample; (3) enrollment of patients who did not all meet the same diagnostic standard; (4) possible selection biases stemming from inconsistent evaluation methods across centers; and (5) missing or partial information regarding the biologic treatments used and long-term patient monitoring, given that the study was confined to a single cross-sectional assessment and could not deliver robust data on these elements. Despite these constraints, the present work represents the first dedicated examination of the frequency of these atypical manifestations in AOSD within a comparatively sizable group of patients affected by this uncommon illness, mirroring everyday clinical reality. It constitutes the largest series analyzed to date in this setting and provides important, high-quality data on the occurrence of these complications.

Conclusion

In conclusion, apart from the usual clinical features and MAS, a substantial number of patients with AOSD encounter uncommon complications, several of which carry the potential to become life-threatening. These issues merit close attention, especially when assessing and following patients over time. Prompt identification and appropriate intervention are vital for decreasing illness burden and death rates. Additional research will be required to determine whether the non-classical complications documented in AOSD also occur in individuals with sJIA, particularly given the growing recognition that the two conditions form part of a continuous disease spectrum [33].

Acknowledgments: The authors thank the CERCA Program of the Generalitat de Cataluña and the Bellvitge Biomedical Research Institute (IDIBELL) for their valuable institutional support.

Conflict of interest: None

Financial support: This study was funded by a grant from the Spanish Society for Paediatric Rheumatology (SERPE). SERPE received unrestricted grants from Sobi and Novartis to support the design, logistics, analysis team, and infrastructure of its registry. However, this study was conducted independently and is not part of any corporate-sponsored research efforts.

Ethics statement: The Ethics Committee of Hospital Sant Joan de Déu reviewed and approved this study under code EPA-05-17 on 27 April 2017. This study complies with the precepts of good practice and confidentiality and was approved by the ethics committees of all participating hospitals. The data were confidentially processed in accordance with European norms. This study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use.

Patients, or their legal guardians for minors, signed an informed consent form to collect their data.

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