Adult-onset Still's disease with elderly onset: results from a multicentre study

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Abstract

Objective

In this study, we aimed to describe the clinical characteristics, life-threatening complications occurrence, and mortality of adult-onset Still's disease (AOSD) patients with elderly onset.

Methods

A multicentre retrospective study of prospectively followed-up AOSD patients included in Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale (GIRRCS) cohort was performed.

Results

Out of 221 assessed patients, 37 (16.7%) had an onset of the disease aged over 60 years. When compared with younger patients, these were characterised by a higher prevalence of pericarditis (p=0.008), comorbidities (p<0.0001), and mortality (p=0.023). Age predicted the presence of serositis in both univariate (HR: 1.02, 95%CI: 1.01–1.03, p=0.007) and multivariate analyses (HR: 1.02, 95%CI: 1.01–1.04, p=0.007). Age was also a significant predictor of parenchymal lung disease in both univariate (HR: 1.03, 95%CI: 1.01–1.05, p=0.017) and multivariate analyses (HR: 1.03, 95%CI: 1.00–1.05, p=0.048). Furthermore, age resulted to be a negative predictor of polycyclic pattern only in univariate analysis (HR: 0.99, 95%CI: 0.97–1.00, p=0.048). Finally, age significantly predicted the mortality in both univariate (HR: 1.03, 95%CI: 1.00–1.06, p=0.034) and multivariate analyses (HR: 1.05, 95%CI: 1.01–1.08, p=0.012).

Conclusion

Clinical features of AOSD patients in the elderly were described in our cohort. Although the main clinical characteristics were similar comparing older and younger patients, patients aged over 60 years at disease onset were characterised by an increased prevalence of serositis, comorbidities, mostly cardiometabolic, and a higher mortality rate. Age predicted the presence of parenchymal lung disease and mortality, and it could be considered a negative prognostic factor in AOSD.

Key words

adult-onset Still's disease, aging, serositis, parenchymal lung disease, comorbidities

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Introduction

Aging is a physiological, multidimensional, and irreversible process, occurring in humans over time. This is a complex and individualised process, comprising changing in biological, psychological, and social factors (1). Presently, increasing life expectancy leads to an increase of elderly population, more susceptible to the development of a chronic disease (1). Interestingly, multiple lines of evidence have recently suggested that some diseases, generally affecting young adults, may be nowadays described in the elderly, although possibly associated with different clinical signs or complications (2). In this context, a possible occurrence of adult-onset Still's disease (AOSD) in elderly has been suggested (3-5). This is an inflammatory disorder of unknown origin usually observed in young adults and it is equally distributed between women and men (6). AOSD may be categorised as a multigenic autoinflammatory disorder at the crossroads of autoinflammatory and autoimmune diseases since both innate and adaptive arms of the immune system are involved (7). Patients with AOSD are typically characterised by spiking fever, arthritis, evanescent skin rash associated with internal organ involvement (6, 7). The available epidemiologic results suggest AOSD as a rare disease with an incidence between 0.16 and 0.4/100000 people and a prevalence between 1 and 34 cases/1 million people (6-8). A characteristic hyperferritineamia is also observed in these patients (7). Furthermore, life-threatening complications may occur, mostly represented by macrophage activation syndrome (MAS), a secondary form of haemophagocytic lymphohistiocytosis, and parenchymal lung disease (8). As far as treatment is concerned, AOSD requires an immunosuppressive therapeutic strategy targeting inflammatory signs and symptoms of the disease (7-9). Concerning clinical disease courses, monocyclic, polycyclic, and chronic patterns are usually described, according to clinical phases of flare and remission during the follow-up of the patients (9). Because of the relatively low number of cases described so far, the clinical features of AOSD patients in elderly are not entirely characterised yet (3, 4). In addition, the management of elderly patients may be complicated by an increased prevalence of comorbidities (10). These are infrequently taken into account in AOSD patients, considering its rarity and clinical course, which may be characterised by a single episode of the disease.

On these bases, in this study, we aimed to describe the clinical characteristics, life-threatening complications occurrence, and mortality of AOSD patients with an elderly onset. The manifestations of these patients were also compared with those with a younger onset to evaluate possible age-related clinical differences. Furthermore, the predictive role of age was evaluated on clinical features and disease outcomes. Finally, in these patients, an assessment of associated comorbidity was also performed.

Methods

Study design and settings

A retrospective longitudinal study, from January 2001 to April 2021, was provided to analyse clinical features, life-threatening complications occurrence, and mortality in AOSD patients with onset in elderly. AOSD patients, who were included in the Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale (GIRRCS) cohort, were evaluated. All Rheumatologic Centres involved in GIRRCS study of AOSD patients were characterised by high expertise on management of this disease and in inception cohort studies. All included patients fulfilled Yamaguchi's criteria for AOSD (11) and potential mimickers were excluded before the diagnosis, as better detailed below (12). A comparison between AOSD patients older than 60 years with others was performed to parallel with available literature in this field (4) and to provide a descriptive comparison of the possible different findings. Afterwards, a more accurate assessment of these patients was performed according to different age groups to furtherly assess possible clinical differences in more detail. Considering the spread distribution of the age as continuous variable and the number of patients included in GIRRCS cohort, we decided to further strat-

ify our findings according to narrower age intervals to highlight other possible differences. Furthermore, possible correlations among age and clinical manifestations, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ferritin, and systemic score were evaluated. Finally, the potential predictive role of age on MAS, mortality, lung involvement, disease pattern, and serositis, was investigated, by using clinical features associated with a poor prognosis, including gender, systemic score, and comorbidity (12).

The local Ethics Committee (Comitato Etico Azienda Sanitaria Locale 1 Avezzano/Sulmona/L'Aquila, L'Aquila, Italy; protocol number 0139815/16) approved the study, which was performed according to the Good Clinical Practice guidelines and the Declaration of Helsinki. After approval of our ethic committee, we collected written informed consents for patients presently and actively followed-up in each centre. However, given the retrospective nature of the study, for those patients who were no longer followed-up (lost to follow-up or died during the time-period of assessment), after having made every reasonable effort to contact them, we used the fully anonymised clinical data according to the Italian Law on privacy only for research purposes without any other intended aim (Garante per la protezione dei dati personali, Autorizzazione n. 9/2016 - Autorizzazione generale al trattamento dei dati personali effettuato per scopi di ricerca scientifica - 15 dicembre 2016 (5805552)).

In reporting the results, we followed the STROBE checklist.

Definition of cases

To be included in the analysis, all patients with AOSD fulfilled the diagnostic criteria proposed by Yamaguchi *et al*. (11). MAS diagnosis was defined according to the diagnostic criteria proposed by Fardet et al and/or Batu et al for the assessment of MAS development in the context of a rheumatic diseases (13-15). Parenchymal lung disease was codified as reported in previous studies on AOSD and its juvenile counterpart, in which characteristic subsets of disease-related pulmonary involvement were described (16, 17). A baseline assessment of potential mimickers was performed, including infections, cancers, and other autoimmune or autoinflammatory diseases. Infections were ruled out by blood cultures, serology and PCR analyses, chest radiographs, and abdominal echography. Differential diagnoses with malignancies were assessed by chest radiographs and abdominal echography, and blood samples. Despite these examinations, in the case of further suspicion of malignancy, computed tomography (CT) and/or positron emission tomography/CT were employed. For patients with possible haematologic cancers, we also performed BM examination and lymph node biopsy. Autoimmune diseases were evaluated and excluded by blood tests, antinuclear antibodies, anticitrullinated peptide antibodies, rheumatoid factor, and antineutrophil cytoplasmic antibodies. Finally, we evaluated possible differential diagnoses with autoinflammatory diseases by the execution of gene analyses and clinical evaluation. Additional details are available elsewhere (12).

Clinical variables and data sources

Data were collected reviewing the clinical charts of each involved patient. Clinical features, systemic score, life-threatening complications, laboratory markers, comorbidities, and therapies, and patterns of the disease, were registered.

The presence of the following clinical features at the time of diagnosis were recorded: fever, evanescent skin rash, arthralgia, arthritis, myalgia, lymphadenopathy, sore throat, splenomegaly, hepatomegaly, abdominal pain. Taking these features together, systemic score was assessed for each patient, assigning 1 point to each of 12 manifestations: fever, typical rash, pleuritis, pneumonia, pericarditis, hepatomegaly or abnormal liver function tests, splenomegaly, lymphadenopathy, leucocytosis >15000/mm^3, sore throat, myalgia, and abdominal pain (maximum score: 12 points) (14). In addition, at the time of diagnosis and during follow-up, each patient was assessed for the occurrence of AOSD-related life-threatening complications defined according to aforementioned criteria. Leucocytosis >15000/mm^3, ESR, CRP, and serum ferritin levels were also registered.

In our cohort, we defined the presence of comorbidities at the time of AOSD assessment as coexisting medical conditions distinct from the principal diagnosis for which the patient was enrolled in this study (18, 19). Comorbidities were also codified as being cardiometabolic and non-cardiometabolic comorbidities as reported in available literature (19). Cardiometabolic comorbidities included hypertension, type 2 diabetes, dyslipidaemia, cardiovascular diseases, whereas other comorbidities were codified as non-cardiometabolic ones. Hypertension was defined when patient blood pressure was reported to be consistently measured >130 mmHg for systolic and >80 mmHg for diastolic, or the need of anti-hypertensive drugs (20). Patients were defined as having T2D if fasting plasma glucose ≥126 mg/dL in two different evaluations, or in the presence of classic symptoms of hyperglycaemia or hyperglycaemic crisis with a random plasma glucose 200 mg/dL (11.1 mmol/L), or if antidiabetic therapies were administered (21). Obesity was defined if body mass index over 30, as codified by WHO. Cardiovascular disease was defined as the presence of subclinical or clinical atherosclerosis. Subclinical atherosclerosis was defined as the presence of carotid and/or peripheral arteries atherosclerotic lesions detected by ultrasound imaging. Clinical atherosclerosis was defined as the presence of one of the following: myocardial infarction, congestive heart failure, cerebrovascular disease including transitory ischaemic attack and/or stroke and clinically relevant peripheral artery disease.

At the end of follow-up, patients were categorised into three different disease courses, monocyclic, polycyclic, and chronic patterns, and mortality whichever the course, as previously performed (6, 9). Thus, these patients were stratified in four different subsets (*i.e*. monocyclic, polycyclic, and chronic patterns, and mortality).

A monocyclic course was defined as a single episode for >2 months but <1 year, followed by sustained remission through the entire follow-up period. A polycyclic course was characterised by recurrent systemic flares with remission between flares. A chronic course was defined as ≥1 episode of persistent symptoms lasting >1 year. Finally, patients who died during follow-up were categorised in the death group. AOSD-related death was defined as death associated with AOSD or its complications. The therapeutic strategies were also registered as previously performed (22, 23). Therapies used at the time of diagnosis and during the follow-up were categorised as follows: low/medium dose of glucocorticoids (GCs): ≤0.5 mg/kg/day of prednisone; high dose of GCs: >0.5 mg/kg/day of prednisone; synthetic disease-modifying anti-rheumatic drugs (sDMARDs); and biologic DMARDs (bDMARDs).

We minimised the effects of possible biases and missing data by a careful definition of each variable and a relatively simple study design. Since AOSD is a rare disease, we designed the present evaluation without a specific sample size estimation.

Statistical methods

Firstly, statistics provided a descriptive analysis of patient characteristics, and collected results were presented as mean and standard deviation (SD) or median and interquartile range (IQR), according to their distribution. Older and younger patients were grouped, and clinical characteristics were compared by either parametric or non-parametric t-tests for continuous variables, and Chi-squared test for categorical ones, as appropriate. The possible correlations between age and clinical manifestations, ESR, CRP, ferritin, and systemic score, were estimated by using either a point-biserial coefficient or Pearson correlation analyses. Furthermore, Cox regression analyses were performed to evaluate the possible predictive role of age on clinical features and disease outcomes. Univariate and multivariate analyses were built accordingly. In multivariate regression models, in addition to age, clinical characteristics associated with poor prognosis, on AOSD patients, were considered, namely gender, systemic score, and comorbidity (9, 24). The purposeful selection process of covariates started by a univariate analysis of each variable; any variable having a significant univariate test and or a clinical relevance was considered a possible candidate for the multivariate analysis. At the end of this multistep process of deleting and refitting, the multivariate model was built, and HR estimations of significant associations with MAS were provided. Because of the relatively simply study design, we had a very low percentage of missing data; patients were removed from the study if they had missing values which were considered to be relevant for the analysis.

Two-sided p-values <0.05 were considered as being statistically significant. The Statistics Package for Social Sciences (SPSS v. 17.0, SPSS Inc.) was used for all analyses.

Table I. Clinical characteristics of patients with AOSD with elderly onset.

Clinical characteristics	37 AOSD patients ≥60 years	184 AOSD patients <60 years	p-values
Age, years, mean ± SD	69.1 ± 5.4	36.1 ± 11.6	/
Male gender, n (%)	22 (59.5)	92 (50.0)	0.368
Clinical characteristics			
Fever, n (%)	37 (100)	182 (98.9)	0.999
Arthralgia, n (%)	30 (81.1)	158 (85.9)	0.691
Rash, n (%)	25 (67.6)	136 (73.9)	0.424
Arthritis, n (%)	27 (73.0)	118 (64.1)	0.347
Myalgia, n (%)	23 (62.2)	117 (63.6)	0.854
Liver involvement, n (%)	22 (59.5)	107 (58.2)	0.999
Sore throat, n (%)	22 (59.5)	106 (57.6)	0.858
Lymph node involvement, n (%)	20 (54.1)	90 (48.9)	0.593
Spleen involvement, n (%)	18 (48.7)	84 (45.7)	0.857
Pericarditis, n (%)	15 (40.5)	34 (18.5)	**0.008**
Pleuritis, n (%)	12 (32.4)	33 (17.9)	0.071
Abdominal pain, n (%)	5 (13.5)	20 (10.9)	0.580
Systemic score, mean ± SD	6.0 ± 2.1	5.7 ± 1.9	0.475
Laboratory findings			
CRP, mg/L, median (IQR)	76.0 (97.6)	52.0 (102.7)	0.149
ESR, mm/h, median (IQR)	75.2 ± 35.1	64.4 ± 32.2	0.098
Ferritin, ng/mL, median (IQR)	1500.0 (4336.5)	1001.5 (2323.8)	0.055
Leucocytosis > 15000/mm^3, n (%)	21 (56.8)	122 (66.3)	0.346
Complications			
MAS, n (%)	7 (18.9)	19 (10.3)	0.161
Parenchymal lung disease, n (%)	6 (16.2)	17 (9.2)	0.236
Therapies			
Low dose of GCs, n (%)	17 (46.0)	85 (46.2)	0.999
High dose of GCs, n (%)	19 (51.4)	86 (46.7)	0.719
sDMARDs, n (%)	21 (56.8)	122 (66.3)	0.346
bDMARDs, n (%)	10 (27.0)	77 (41.9)	0.098
Disease pattern			
Monocyclic, n (%)	14 (37.8)	54 (29.4)	0.332
Polycyclic, n (%)	9 (24.3)	82 (44.6)	**0.028**
Chronic, n (%)	8 (21.6)	39 (21.2)	0.999
Mortality, n (%)	6 (16.2)	9 (4.9)	**0.023**
Follow-up year, median (IQR)	3.8 (5.5)	3.0 (3.5)	0.252

AOSD: adult-onset Still's disease; n: number of patients, SD: standard deviation; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IQR: interquartile range; MAS: macrophage activation syndrome; GCs: glucocorticoids; sDMARDs: synthetic disease-modifying anti-rheumatic drugs; bDMARDs: biologic disease-modifying anti rheumatic drugs.

Results

Clinical characteristics of AOSD with elderly onset

The present study evaluated 221 AOSD patients, mostly men (51.6%) and with

Table II. Clinical characteristics of assessed patients with AOSD stratified according to the age of onset.

	Age ≥65 years 29 patients	55-64 years 15 patients	45-54 years 39 patients	35-44 years 61 patients	25-34 years 41 patients	18-25 years 36 patients
Male gender, n (%)	17 (58.6)	6 (40.0)	25 (64.1)	31 (50.8)	17 (41.5)	18 (50.0)
Clinical characteristics						
Fever, n (%)	29 (100.0)	15 (100.0)	39 (100.0)	61 (100.0)	41 (100.0)	34 (94.4)
Skin rash, n (%)	18 (62.1)	12 (80.0)	30 (76.9)	42 (68.9)	29 (70.0)	30 (83.3)
Sore throat, n (%)	18 (62.1)	8 (53.3)	17 (43.6)	33 (54.1)	27 (65.9)	25 (69.4)
Myalgia, n (%)	18 (62.1)	9 (60.0)	23 (59.0)	42 (68.9)	30 (73.2)	18 (50.0)
Joint features						
Arthralgia, n (%)	24 (82.8)	13 (86.7)	31 (79.5)	56 (91.8)	39 (95.1)	25 (69.4)
Arthritis, n (%)	20 (69.0)	12 (80.0)	30 (76.9)	35 (57.4)	25 (61.0)	23 (63.9)
Multi-visceral involvement						
Liver involvement, n (%)	18 (62.1)	9 (60.0)	19 (48.7)	37 (60.7)	26 (63.4)	20 (55.5)
Lymph-adenomegaly, n (%)	16 (55.2)	8 (53.3)	18 (46.2)	24 (39.3)	22 (53.7)	22 (61.1)
Splenomegaly, n (%)	14 (48.3)	6 (40.0)	20 (51.3)	26 (42.6)	19 (46.3)	17 (47.2)
Pericarditis, n (%)	10 (34.5)	7 (46.7)	8 (20.5)	15 (24.6)	5 (12.2)	4 (11.1)
Pleuritis, n (%)	8 (27.6)	8 (53.3)	9 (23.1)	14 (23.0)	4 (9.8)	2 (5.6)
Abdominal pain, n (%)	4 (13.8)	1 (6.7)	6 (15.4)	8 (13.1)	6 (14.6)	0 (0.0)
Systemic score, mean ± SD	5.9 ± 2.2	6.2 ± 2.5	5.5 ± 2.2	5.8 ± 1.9	5.9 ± 1.6	5.6 ± 1.7
Laboratory						
Leucocytosis >15000/mm^3, n (%)	17 (58.6)	9 (60.0)	21 (53.9)	39 (63.9)	30 (73.2)	27 (75.0)
CRP, mg/L, median (IQR)	94.0 (115.6)	50.5 (86.2)	40.0 (106.9)	75.0 (100.7)	25.0 (97.0)	72.0 (160.7)
ESR, mm/h, mean ± SD	76.0 ± 34.4	81.9 ± 36.9	60.1 ± 29.3	63.9 ± 32.7	63.0 ± 31.5	66.4 ± 34.5
Ferritin, ng/mL, median (IQR)	1500.0 (4414)	3347.5 (7422)	1002.0 (2662.2)	895.0 (1885.5)	1125.6 (1204.3)	1200 (3328)
Life-threatening complications						
MAS, n (%)	4 (13.8)	5 (33.3)	2 (5.1)	4 (6.6)	4 (9.8)	7 (19.4)
Parenchymal lung disease, n (%)	6 (20.7)	1 (6.7)	6 (15.4)	6 (9.8)	3 (7.3)	1 (2.8)
Disease patterns, comorbidities, mortality						
Monocyclic, n (%)	11 (37.9)	4 (26.7)	11 (28.2)	23 (37.7)	10 (24.4)	9 (25.0)
Polycyclic, n (%)	8 (27.6)	5 (33.3)	15 (38.5)	23 (37.7)	18 (43.9)	22 (61.1)
Chronic, n (%)	6 (20.7)	4 (26.7)	11 (28.2)	11 (18.0)	11 (26.8)	4 (11.1)
Comorbidities, n (%)	27 (93.1)	10 (66.7)	23 (59.0)	25 (41.0)	14 (34.2)	10 (27.8)
Non cardiometabolic comorbidities, n (%)	17 (58.6)	6 (40.0)	18 (46.2)	18 (29.5)	15 (36.6)	10 (27.8)
Cardiometabolic comorbidities, n (%)	15 (51.7)	7 (46.7)	7 (17.9)	8 (13.1)	2 (4.9)	0 (0.0)
Death, n (%)	4 (13.8)	2 (13.3)	2 (5.1)	4 (6.6)	2 (4.9)	1 (2.8)

AOSD: adult-onset Still's disease; n: number of patients; SD: standard deviation; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IQR: interquartile range; MAS: macrophage activation syndrome.

a mean age of 41.6±16.4 years (Table I). Patients were followed-up for a median of 3.0 (IQR 3.8) years. Almost all assessed patients experienced fever (99.1%). The other main clinical characteristics were arthralgia (85.1%), skin rash (72.9%), arthritis (65.6%), and myalgia (63.4%). In this cohort, a significant increase of inflammatory markers at the time of diagnosis was observed: ferritin 1120.0 ng/ml (IQR 2861.5), ESR 66.2 ± 32.9 mm/h, and CRP 53.9 mg/L (IQR 104.5). Furthermore, analysing therapies, 93.7% patients were treated with GCs, both low and high dosages, 64.7% with s-DMARDs and 39.4% with bDMARDs.

Out of these patients, 37 (16.7%) had an onset of the disease aged over than 60 years. All these patients (100%) showed fever. When compared with younger patients, these were characterised by a higher prevalence of pericarditis (age ≥60: 40.5% *vs*. age <60: 18.5%, p=0.008) and, although not significant, of pleuritis (age >60: 32.4% *vs*. age <60: 17.9%, p=0.071). No other significant differences were observed comparing other clinical characteristics between these groups of patients. Analysing disease courses, a lower rate of polycyclic pattern was registered in AOSD patients older than 60 years (age ≥60: 24.3% *vs*. age <60: 44.6%, p=0.028). Furthermore, a higher mortality rate was observed in these older patients (age ≥60: 16.2% *vs*. age <60: 4.9%, p=0.023).

In addition, we furtherly stratified the clinical characteristics of our cohort by using narrower age subgroups to better assess the impact of age on these features (Table II). The subset of patients aged over 65 years, at the diagnosis of AOSD, were mostly characterised by fever (100.0%), arthralgia (82.8%), and arthritis (69.0%). Concerning life-threatening complications, MAS was observed in 13.8% of these patients, and parenchymal lung disease in 20.7%. The latter resulted more increased in

this subset than others. Comorbidities were also recorded in 93.1% of these patients, a higher prevalence than other subgroups. Furthermore, increased CRP levels characterised this subset of patients (94.0 mg/L (IQR 115.6)). Finally, a higher mortality rate (13.8%) was observed in patients aged over 65 years at the onset of the disease. All causes of death were related to AOSD and the development of its severe complications, MAS, and/or lung involvement, which led to an uncontrollable multi-organ failure syndrome.

Analysing other subgroups of patients (namely patients aged 55–64 years, 45–54 years, 35–44 years, from 25–34 years, from 18–24 years), similar clinical characteristics were recorded at the time of diagnosis (Table II). Fever, arthralgia, arthritis, and skin rash were the most common clinical manifestations, at the time of diagnosis, across all age subgroups. A similar rate of life-threatening manifestations was also observed in all assessed subgroups of patients. A low frequency of comorbidities was reported in subgroups of younger patients than others.

Comorbidities

Patients with disease onset older than 60 years were distinguished by an increased rate of comorbidity (age ≥60: 86.5% *vs*. age <60: 40.2%, $p<0.0001$), both cardiometabolic (age ≥60: 51.4% *vs*. age <60: 10.9%, $p<0.001$) and non-cardiometabolic ones (age ≥ 60: 54.1% *vs*. age <60: 34.8%, $p=0.040$). Specifically, in older patients we observed that 51.4% were affected by hypertension, 18.9% type 2 diabetes, 10.8% chronic obstructive pulmonary disease, 10.8% dyslipidaemia, 10.8% thyroid disease, 5.4% gastrointestinal diseases, 5.4% kidney failure, 2.7% depressive syndrome, and 2.7% obesity. In younger patients, we found that 7.6% were affected by high blood pressure, 5.4% thyroid disease, 4.4% dyslipidaemia, 2.7% gastrointestinal diseases, 1.6% type 2 diabetes, 1.6% depressive syndrome, and 1.1% obesity.

Correlations of age with AOSD clinical characteristics

Correlations among age and clinical

Table III. Correlations between age and clinical parameters in assessed patients with AOSD.

	Age		
	Coefficient/*p*-value		Coefficient/*p*-value
Male gender	0.085/0.211	Systemic score	0.010/0.877
Arthralgia	0.028/0.681	Leucocytosis	0.142/**0.034**
Arthritis	0.095/0.158	ESR	0.094/0.178
Myalgia	0.029/0.666	CRP	0.009/0.900
Sore throat	0.086/0.202	Ferritin	0.066/0.344
Skin rash	0.088/0.194	Monocyclic	0.070/0.303
Pleuritis	0.227/**0.001**	Polycyclic	0.209/**0.002**
Pericarditis	0.213/**0.001**	Chronic	0.076/0.262
Liver involvement	0.015/0.827	Mortality	0.158/**0.019**
Splenomegaly	0.002/0.972	Comorbidity	0.443/**0.000**
Abdominal pain	0.089/0.189	MAS	0.023/0.732
Lymph nodes involvement	0.018/0.789	Lung disease	0.168/**0.012**

AOSD: adult-onset Still's disease; CRP: C reactive protein; ESR: erythrocyte sedimentation rate; MAS: macrophage activation syndrome.

Table IV. Cox regression analyses assessing the predictive role of age on AOSD clinical features.

Clinical variables	HR	95% CI	*p*-value
	Mortality – univariate analysis		
Age	1.03	1.00-1.06	**0.034**
	Mortality – multivariate analysis		
Age	1.05	1.01-1.08	**0.012**
Gender	3.21	0.99-10.39	0.051
Systemic score	1.21	0.97-1.50	0.096
Comorbidity	0.32	0.09-1.15	0.079
	MAS – univariate analysis		
Age	1.01	0.98-1.03	0.666
	MAS – multivariate analysis		
Age	1.01	0.98-1.03	0.592
Gender	0.75	0.32-1.72	0.491
Systemic score	1.53	1.25-1.86	**<0.0001**
Comorbidity	0.67	0.28-1.61	0.368
	Parenchymal lung disease – univariate analysis		
Age	1.03	1.01-1.05	**0.017**
	Parenchymal lung disease – multivariate analysis		
Age	1.03	1.00-1.05	**0.048**
Gender	0.36	0.13-0.99	**0.047**
Systemic score	1.90	1.46-2.40	**<0.0001**
Comorbidity	1.08	0.42-2.76	0.871
	Polycyclic pattern - univariate analysis		
Age	0.99	0.97-1.00	**0.048**
	Polycyclic pattern- multivariate analysis		
Age	0.99	0.98-1.00	0.165
Gender	1.18	0.77-1.80	0.445
Systemic score	1.03	0.93-1.16	0.547
Comorbidity	0.82	0.51-1.32	0.406
	Serositis - univariate analysis		
Age	1.02	1.01-1.03	**0.007**
	Serositis - multivariate analysis		
Age	1.02	1.01-1.04	**0.007**
Gender	1.07	0.63-1.84	0.789
Systemic score	1.45	1.28-1.64	**<0.0001**
Comorbidity	0.67	0.38-1.19	0.169

AOSD: adult-onset Still's disease; HR: hazard ratio; CI: confidence interval; MAS: macrophage activation syndrome.

manifestations were exploratively exploited (Table III). Our analysis showed that pleuritis and pericarditis positively correlated with age (coefficient=0.227, p=0.001; coefficient=0.213, p=0.001, respectively). In addition, the occurrence of parenchymal lung disease was significantly related with age (coefficient=0.168, p=0.012). A negative correlation was also found between age and leucocytosis >15000/mm^3 (coefficient=-0.142, p=0.034). No further correlations were retrieved with other laboratory abnormalities. Furthermore, the presence of comorbidities positively correlated with age (coefficient=0.443, p<0.0001). Moreover, age was negatively related to the polycyclic pattern (coefficient=-0.209, p=0.002). Finally, although with a weak strength, a correlation between mortality and age was retrieved (coefficient=0.158, p=0.019).

Predictive role of age on AOSD clinical characteristics and outcomes

In our cohort of AOSD patients, regression models, both univariate and multivariate, were built to evaluate the predictive role of older age on the likelihood of the presence of serositis, life-threatening complications, polycyclic pattern, and mortality. These features were chosen based on the results of significant correlations and clinical relevance of such manifestations in managing AOSD patients. In multivariate analyses, in addition to age, gender, systemic score, and comorbidity were added as markers of disease severity (9, 24). Regression models are reported in Table IV.

The predictive role of age was assessed on the presence of serositis; considering the relatively low prevalence, pericarditis and pleuritis were assessed together. In both univariate (HR: 1.02, 95%CI: 1.01–1.03, p=0.007) and multivariate analyses (HR: 1.02, 95%CI: 1.01–1.04, p=0.007), age was significantly associated with the presence of serositis. Age was also a significant predictor of parenchymal lung disease in both univariate (HR: 1.03, 95%CI: 1.01–1.05, p=0.017) and multivariate analyses (HR: 1.03, 95%CI: 1.00–1.05, p=0.048). No significant results were observed assessing the predictive role of age on occurrence of MAS. Furthermore, age resulted to be a negative predictor of polycyclic pattern only in univariate analysis (HR: 0.99, 95%CI: 0.97–1.00, p=0.048). Finally, age significantly predicted the mortality of our AOSD patients in both univariate (HR: 1.03, 95%CI: 1.00–1.06, p=0.034) and multivariate analyses (HR: 1.05, 95%CI: 1.01–1.08, p=0.012).

Discussion

In this study, clinical features of AOSD with elderly onset were reported in a a retrospective longitudinal study in a large cohort of patients. Patients aged over 60 years at disease onset were characterised by an increased prevalence of serositis, comorbidities, mostly cardiometabolic, and a higher mortality rate. Furthermore, age resulted to be a significant predictor of the presence of parenchymal lung disease and mortality. These findings would be the first systematic description of AOSD with elderly onset in a European Country.

Although AOSD is considered a disease of young adults, different works suggested a possible onset in the elderly (3-5). In our cohort, around 15% of patients had a disease onset when aged over 60 years. These were characterised by a higher prevalence of serositis, both pericarditis and pleurisy, mirroring what was already reported in available literature about AOSD with late onset (3,4). In addition, a lower rate of polycyclic pattern was reported in our AOSD patients with elderly onset. Although younger age of onset may be associated with a chronic disease course (25), few studies assessed AOSD with elderly onset so far. Therefore, further research is needed to fully evaluate this issue.

Compared to the available literature, mainly derived from Asiatic populations (3-5), some differences were reported in our cohort of AOSD patients with elderly onset than other works. A predominance of female gender was not observed, whereas a more balanced gender distribution characterised our patients across all age subgroups. Differently, we did not record neither the occurrence of atypical skin rash nor a lower prevalence of sore throat in our cohort when compared with available literature about that (3-5). Taking together these observations, this apparent discrepancy could be related to a different interaction between environmental factors and genetic background in explaining diverse clinical manifestations in Asian and European patients with AOSD. Some genetic polymorphisms have been recently proposed on Asiatic patients with AOSD, which have not been replicated in European populations so far (26, 27).

In our cohort, we also assessed the occurrence of life-threatening complications; a similar rate of MAS and parenchymal lung disease was observed comparing AOSD patients with elderly onset than others. However, age was significantly correlated with the presence of parenchymal lung disease. The latter should be carefully evaluated in older patients with AOSD since it is associated with a poor prognosis (28-30). The predictive role of age about parenchymal lung disease, which we observed in AOSD, may appear to be conflicting with findings on the juvenile counterpart of the disease (31). However, a longer exposition to environmental or occupational factors could possibly explain this finding (32). Finally, we did not observe the occurrence of disseminated intravascular coagulation in our patients differently from what was previously reported (3-5).

The mortality rate of AOSD patients with elderly onset was higher in our cohort, as it could be envisaged. In this context, the multi-organ involvement is the leading cause of mortality but also the presence of comorbidities may contribute to a poor prognosis in AOSD (24, 33). An increased rate of comorbidity was observed in our older patients, both cardiometabolic and non-cardiometabolic, which is associated with a higher risk of complications and death (34). In addition, the presence of cardiometabolic comorbidities may be associated with a poor prognosis in cytokine storm syndrome, a typical feature of a more severe AOSD (35, 36). Furthermore, comorbidities are usually associated with polypharmacy, consequently increasing the risk of iatrogenic effects, and complicating the treatment of these patients (37). Thus, the

possible drug interactions may make more difficult the therapeutic management of AOSD patients with elderly onset, which should be characterised by multiple immunosuppressive drugs (38). The management of these patients could be furtherly complicated by increased frailty associated with older age, a syndrome characterised by a decrease of strength, endurance, reduced physiological function, and increased the individual's vulnerability (39).

As observed in any retrospective study, different limitations may limit the validity of our results suggesting a cautious generalisation of these findings. The correlation coefficients suggested a weak association between age and clinical features, advocating a prudent interpretation of these data. In addition, considering the multicentre retrospective design a selection bias could occur. Taking together these limitations and considering the rarity of the disease, the results of our work should be fully confirmed in further studies.

In conclusion, clinical features of AOSD patients with elderly onset were described in our multicentre cohort. Patients aged over 60 years at disease onset were distinguished by an increased prevalence of serositis, and comorbidities, mostly cardiometabolic. Furthermore, a higher mortality rate was observed in these patients. Age resulted also to be a significant predictor of the presence of parenchymal lung disease and mortality. Thus, an older age of onset may be associated with a poor prognosis in AOSD, and the management of these patients may be considered challenging.

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