



## Original article

# Clinical characteristics of obese patients with adult-onset Still's disease. Data from a large multicentre cohort



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## ARTICLE INFO

## Article history:

Accepted 12 April 2023

Available online 18 April 2023

## Keywords:

Obesity

Body mass index

Adult-onset Still's disease

## ABSTRACT

**Objectives:** To evaluate the impact of obesity in patients with adult-onset Still's disease (AOSD) and to assess their clinical characteristics and disease outcomes.

**Methods:** The clinical features of AOSD patients with a body mass index (BMI)  $\geq 30$  were assessed among those included in the multicentre *Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale* (GIRRCS) cohort.

**Results:** Out of 139 AOSD patients, who had BMI registered in our database, 26 (18.7%) had a BMI  $\geq 30$ . A lower rate of sore throat ( $P < 0.05$ ), pericarditis ( $P < 0.05$ ), and pleuritis ( $P < 0.05$ ) was shown in obese patients. Additionally, obese patients showed higher values of C-reactive protein (CRP) ( $P < 0.05$ ) and ferritin ( $P < 0.05$ ) than others. Furthermore, obese patients were characterised by biologic disease-modifying antirheumatic drug (bDMARD) failure in subsequent follow-up ( $P < 0.05$ ). They also presented higher rate of comorbidity than non-obese patients ( $P < 0.05$ ). Finally, obesity predicted the presence of a chronic disease course in both univariate (HR: 1.72, 95%CI: 1.03–2.51,  $P < 0.05$ ) and multivariate analyses (HR: 1.85, 95%CI: 1.45–2.89,  $P < 0.05$ ). Obesity was also a significant predictor of bDMARD failure in AOSD patients in both univariate (HR: 3.03, 95%CI: 1.42–6.45,  $P < 0.01$ ) and multivariate analyses (HR: 3.59, 95%CI: 1.55–8.27,  $P < 0.01$ ).

**Conclusion:** Obese patients at the time of diagnosis of the disease were characterised by a lower prevalence of sore throat, serositis, as well as by higher values of CRP and ferritin. Obesity was also a predictive factor for a chronic disease course and bDMARD failure, thus highlighting a subset of patients with AOSD to be carefully managed.

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## 1. Introduction

Over the last few decades, obesity has become an increasing public health problem worldwide; this is characterised by an abnormal or excessive fat accumulation [1]. The most common method

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to evaluate this issue is the assessment of body mass index (BMI), a value over 30 is commonly used as threshold to identify the presence of obesity [1]. A prompt recognition of this condition is of importance since it increases the morbidity and mortality of the patients [2]. In the context of rheumatic diseases, multiple lines of evidence reported the presence of obesity as a common clinical feature [3,4]. In addition, it is associated with a higher inflammatory activity, disability, and a less response to administered therapies [5,6]. The chronic inflammatory process due to the obesity may contribute to the inflammatory burden of the rheumatic diseases worsening the patient clinical picture [7]. In fact, the presence of obesity has been considered as a negative prognostic factor in these patients [8,9]. Despite multiple lines of evidence in rheumatic diseases [4–9], the clinical impact of obesity in adult-onset Still's disease (AOSD) has not been entirely clarified so far. AOSD is a rare inflammatory disease usually characterised by fever, arthritis, and evanescent skin rash associated with a typical hyperferritinemia [10,11]. These patients may also experience a multiorgan involvement requiring the administration of immunosuppressive therapies [12,13]. Analysing disease courses, three clinical patterns of AOSD are usually identified:

- monocyclic, characterised by a single episode;
- polycyclic, characterised by multiple flares, alternating with remission;
- chronic, related to a persistent active disease with associated polyarthritis.

Furthermore, this disease may be burdened by life-threatening complications, mainly macrophage activation syndrome (MAS), a secondary form of hemophagocytic lymphohistiocytosis (HLH), and pulmonary disease [14–16]. Interestingly, the prognosis of AOSD and its complications may be affected by the presence of comorbidities, suggesting the relevance of their assessment in the management of these patients [17,18]. However, the impact of obesity in patients with AOSD has not been fully investigated yet. On these bases, in our study, we aimed at evaluating the clinical impact of obesity in AOSD patients. We assessed the clinical features of obese patients in respect to others. Finally, the impact of obesity was evaluated on disease outcomes over time.

## 2. Methods

### 2.1. Study design and patients

From January 2001 to April 2021, clinical features of patients with AOSD characterised by a BMI  $\geq 30$  were assessed among those evaluated in *Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale* (GIRRCs) cohort, a multicentre study. This is a retrospective study of patients with AOSD who were prospectively followed-up in involved centres. All included patients fulfilled Yamaguchi's criteria for AOSD, and potential mimickers were excluded before the diagnosis, as elsewhere better detailed [14–18]. To fully assess the impact of obesity on inflammatory markers in patients with AOSD, we also evaluated consecutive obese patients (BMI  $\geq 30$ ) referred to our outpatient clinics for musculoskeletal complaints and in whom the diagnosis of immune-mediated inflammatory disease (IMID), cancer, or other infective diseases were excluded after appropriate clinical, imaging, and laboratory investigations. These obese patients without IMID were 2:1 age-, gender-, and BMI-matched with obese AOSD patients. This population included patients with fibromyalgia, osteoarthritis, and other non-inflammatory painful musculoskeletal conditions. In reporting the results, we followed the STROBE checklist.

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 Ethic Committee, we collected written informed consents for patients presently and actively followed-up in each centre. However, since the retrospective nature of the study, for those patients who were not anymore 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 anonymized 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*).

### 2.2. Clinical variables to be assessed

Data were collected reviewing the clinical charts of each patient attending the involved centres. The presence of obesity was evaluated at the time of diagnosis of the disease; only patients with available data about BMI were assessed. The presence of obesity was evaluated by using BMI in categorising patients as obese (BMI  $\geq 30$  kg/m<sup>2</sup>) or non-obese (BMI  $< 30$  kg/m<sup>2</sup>). These parameters were collected at the time of diagnosis of the disease by the physicians in charge of the patient. A comparison between obese and non-obese patients was performed accordingly. Clinical features, systemic score, life-threatening complications, laboratory markers, comorbidities, and therapies, and patterns of the disease, were registered, as already done [14–18]. Furthermore, the following clinical features at the time of diagnosis were recorded: fever, typical rash, arthralgia or arthritis, myalgia, lymphadenopathy, sore throat, splenomegaly, hepatomegaly or abnormal liver function tests, lymph node involvement, abdominal pain, sore throat, pleuritis, pericarditis. In addition, at the time of diagnosis and during the subsequent follow-up, each patient was assessed for the presence of AOSD-related complications, identified as per available literature [11,18–20]. C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and ferritin were recorded at the time of diagnosis of the disease. This population included patients with fibromyalgia, osteoarthritis, and other non-inflammatory painful musculoskeletal conditions. In this cohort, the presence of comorbidities was also collected at the time of AOSD diagnosis and defined as coexisting medical conditions distinct from the principal diagnosis [21]. At the end of follow-up, patients were categorised into three different disease courses, monocyclic, polycyclic, chronic patterns, and mortality whichever the course, as previously performed [22]. The therapeutic strategies, including low and high dosages of glucocorticoids (GCs), conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), and biologic DMARDs (bDMARDs) were also listed, as previously performed [23,24]. At the time of diagnosis, GCs were defined as high dosage if administered at 0.8–1 mg/kg/day of prednisone-equivalent whereas as low/intermediate dosage if given at 0.2–0.3 mg/kg/day [23]. The failure of bDMARDs was also recorded as codified as patients changing the drug due to inefficacy. The latter was defined according to clinical judgment of the physician in charge on the patients, lacking specific therapeutic guidelines and validated disease activity scores in AOSD.

### 2.3. Statistical analysis

Statistics firstly provided a descriptive assessment of registered clinical features of assessed patients. Collected continuous variables were presented as mean and standard deviation (SD) or median and interquartile range (IQR) according to their distribu-

**Table 1**  
Descriptive characteristics of obese patients with AOSD and BMI  $\geq 30$  as compared to patients with AOSD and BMI  $< 30$ .

Clinical characteristics	113 patients with BMI $< 30$	26 patients with BMI $\geq 30$
Age, years, mean $\pm$ SD	40.2 $\pm$ 17.3	39.3 $\pm$ 13.6
Male gender, <i>n</i> (%)	46 (40.7)	12 (46.2)
Clinical features		
Fever, <i>n</i> (%)	112 (99.1)	25 (96.2)
Arthralgia, <i>n</i> (%)	95 (84.1)	20 (76.9)
Skin rash, <i>n</i> (%)	78 (69.0)	22 (84.6)
Arthritis, <i>n</i> (%)	64 (56.6)	16 (61.5)
Myalgia, <i>n</i> (%)	70 (61.9)	17 (65.4)
Liver involvement, <i>n</i> (%)	64 (56.6)	16 (61.5)
Sore throat, <i>n</i> (%) <sup>a</sup>	72 (63.7)	10 (38.5)
Lymph node involvement, <i>n</i> (%)	62 (54.9)	11 (42.3)
Spleen involvement, <i>n</i> (%)	51 (45.1)	9 (34.6)
Pericarditis, <i>n</i> (%) <sup>a</sup>	33 (29.2)	2 (7.7)
Pleuritis, <i>n</i> (%) <sup>a</sup>	29 (25.7)	2 (7.7)
Abdominal pain, <i>n</i> (%)	10 (8.8)	2 (7.7)
Systemic score, mean $\pm$ SD	5.9 $\pm$ 1.9	5.4 $\pm$ 1.8
Laboratory markers		
CRP, mg/L, median (IQR) <sup>a</sup>	52.0 (84.3)	109.2 (117.0)
ESR, mm/h, median (IQR)	64.0 (58.5)	88.5 (62.5)
Ferritin, ng/mL, median (IQR) <sup>a</sup>	1020.0 (2087)	1267.0 (1172)
Life-threatening complications		
MAS, <i>n</i> (%)	10 (8.8)	1 (3.8)
Parenchymal lung disease, <i>n</i> (%)	12 (10.6)	0 (0.0)
Therapies		
Low/intermediate dosage of GCs, <i>n</i> (%)	8 (7.1)	2 (7.7)
High dosage of GCs, <i>n</i> (%)	26 (23.0)	3 (11.5)
csDMARDs, <i>n</i> (%)	44 (38.9)	13 (50.0)
bDMARDs, <i>n</i> (%)	30 (26.5)	14 (53.8)
IL-1 inhibitors, <i>n</i> (%)	26 (86.7)	8 (57.1)
IL-6 inhibitor, <i>n</i> (%)	4 (13.3)	6 (42.8)
bDMARD failure, <i>n</i> (%) <sup>a</sup>	16 (53.3)	12 (85.7)
IL-1 inhibitor failure, <i>n</i> (%)	13 (81.2)	8 (66.7)
IL-6 inhibitor failure, <i>n</i> (%)	3 (18.8)	4 (33.3)
Disease pattern and comorbidity		
Monocyclic, <i>n</i> (%)	39 (34.5)	9 (34.6)
Chronic, <i>n</i> (%)	51 (45.1)	13 (50.0)
Polycyclic, <i>n</i> (%)	18 (15.9)	3 (11.5)
Mortality, <i>n</i> (%)	5 (4.4)	1 (3.8)
Comorbidity, <i>n</i> (%) <sup>a</sup>	58 (51.3)	19 (73.1)

AOSD: adult-onset Still's disease; BMI: body mass index; *n*: number of patients, SD: standard deviation; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; IQR: interquartile range; MAS: macrophage activation syndrome; GCs: glucocorticoids; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; bDMARDs: biologic disease-modifying anti-rheumatic drugs.  $P < 0.05$  was considered statistically significant.

<sup>a</sup>  $P < 0.05$ .

tion. The distribution of BMI was assessed by Shapiro-Wilk test. Clinical characteristics were compared, according to the presence of obesity, by either parametric or non-parametric *t*-tests for continuous variables, and Chi-squared test for categorical ones, as appropriate. Laboratory markers were also compared stratifying the results according to narrower classes of BMI (i.e., normal weight: BMI  $< 25$ , overweight:  $25 \leq$  BMI  $< 30$ , obesity: BMI  $\geq 30$ ). Furthermore, the values of CRP were compared between obese patients with AOSD and obese patients without IMID. In addition, possible correlations among values of BMI, ferritin, and CRP were estimated by Spearman's rank correlation coefficient. Moreover, regression analyses were exploited to characterise obese patients about their outcomes over time. Cox regression analyses were performed to evaluate the role of obesity on predicting different disease courses and bDMARD failure in our cohort. Multivariate analyses were adjusted for age, gender, and systemic score, which was used as marker of disease severity [16–18]. These same regression analyses were also performed using the value of patient BMI as continuous variable. In addition, the model about bDMARD failure was also built adjusting for concomitant use of low/intermediate dosage of GCs and csDMARDs. Due to the relatively simple study design, few retrieved missing data were managed by exclusion of these from analyses. Two-sided *P* values  $< 0.05$  were considered as being statistically significant. The Statistics Package for Social Sciences (SPSS for Windows, version 22.0, SPSS Inc., Chicago, IL, USA) was used for all analyses.

### 3. Results

#### 3.1. Descriptive statistics

In this study, 139 AOSD patients, who had BMI registered in our database, were evaluated, as summarised in Table 1. Considering the whole cohort, BMI resulted  $24.7 \pm 4.3$  (minimum: 17.1, maximum: 41.0); this variable turned out to be normally distributed ( $W = 0.95$ ,  $P < 0.001$ ). Out of 139 AOSD patients, 26 (18.7%) had a BMI  $\geq 30$  and were defined as affected by obesity (BMI:  $32.3 \pm 3.3$ ). Among these, 46.2% were men and with a mean age of  $39.3 \pm 13.6$  years. Concerning main clinical features, almost all obese patients with AOSD (96.2%) were characterised by fever. Other main clinical features described were skin rash (84.6%), arthralgia (76.9%), myalgia (65.4%), and arthritis (61.5%). A comparison between obese and non-obese patients was performed. Obese patients with AOSD did not significantly differ in main clinical features than others. However, a lower rate of sore throat was shown in obese patients (BMI  $\geq 30$ : 38.5% vs BMI  $< 30$ : 63.7%,  $P < 0.05$ ) than others. Pericarditis (BMI  $\geq 30$ : 7.7% vs BMI  $< 30$ : 29.2%,  $P < 0.05$ ), and pleuritis (BMI  $\geq 30$ : 7.7% vs BMI  $< 30$ : 25.7%,  $P < 0.05$ ) were less frequently recorded in these patients with AOSD. No additional clinical differences were retrieved comparing obese patients in respect to others about MAS, administration of GCs, and development of monocyclic disease course. Although not significant (BMI  $\geq 30$ : 53.8% vs BMI  $< 30$ : 25.5%, non-significant), obese patients were

more frequently treated with bDMARDs. Specifically, 8 patients were treated with IL-1 inhibitors whereas 6 with IL-6 inhibitor. No difference in the time of administration of bDMARDs was observed between obese and non-obese patients (BMI  $\geq 30$ : 3 [12] months vs BMI  $< 30$ : 6 [12] months, non-significant).

Furthermore, obese patients were characterised by a higher prevalence of bDMARD failure in the subsequent follow-up (BMI  $\geq 30$ : 85.7% vs BMI  $< 30$ : 53.3%,  $P < 0.05$ ). In this context, no difference was retrieved assessing bDMARD failure based on the route of administration since assessed patients were mostly treated with subcutaneous IL-1 inhibitors. Moreover, a higher rate of comorbidities was registered in patients with obesity (BMI  $\geq 30$ : 73.1% vs BMI  $< 30$ : 51.3%,  $P < 0.01$ ), mainly high blood pressure and type 2 diabetes. Descriptively, disease patterns were also evaluated according to BMI subcategories in obese patients with AOSD. In 2 patients with BMI  $\geq 40$ , a chronic pattern and a death were recorded, whereas in 4 patients with BMI  $\geq 35$  but  $< 40$ , 3 chronic disease courses and a monocyclic pattern were registered. In other 20 patients with BMI  $\geq 30$  but  $< 35$ , 9 chronic and 3 polycyclic disease courses were observed, whereas 8 patients had a monocyclic pattern.

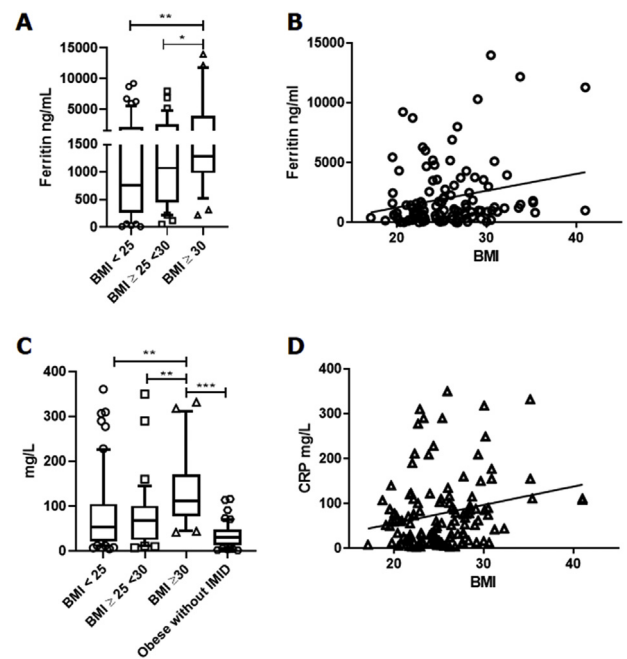
### 3.2. Obese patients with adult-onset Still's disease (AOSD) were characterised by higher levels of CRP and ferritin

Obese patients with AOSD showed higher values of ferritin (BMI  $\geq 30$ : 1267.0 ng/mL [IQR 1172.0], vs BMI  $< 30$ : 1020.0 ng/mL [IQR 2087.0],  $P < 0.05$ ) and CRP (BMI  $\geq 30$ : 109.2 mg/L [IQR 117.0] vs BMI  $< 30$ : 52.0 mg/L [IQR 84.3],  $P < 0.05$ ) than others. Considering these findings, we further stratified these laboratory parameters, which resulted to be significantly different between groups, according to narrower classes of BMI (i.e., normal weight: BMI  $< 25$ , overweight:  $25 \leq$  BMI  $< 30$ , obesity: BMI  $\geq 30$ ). As reported in Fig. 1, obese patients with AOSD had higher values of ferritin than normal weight ( $P < 0.01$ ) and/or overweight patients ( $P < 0.05$ ). Similarly, we retrieved obese patients with AOSD had higher values of CRP than normal weight ( $P < 0.01$ ) and/or overweight patients ( $P < 0.01$ ). Obese patients with AOSD had also higher values of CRP than 2:1 age-, gender-, and BMI-matched obese patients without IMID (Age:  $39.8 \pm 13.2$  years, 24 male gender out 52 patients, BMI:  $32.4 \pm 3.1$ , CRP 33.8 mg/L [IQR 34.4],  $P < 0.001$ ). Finally, we assessed possible correlations between values of BMI and these inflammatory markers. The Spearman's rank correlation coefficient turned out to be  $R = 0.539$ , pointing out a monotonic effect between CRP and BMI ( $P < 0.05$ ). Similarly, ferritin correlated with BMI ( $P < 0.05$ ), the Spearman's rank correlation coefficient resulted  $R = 0.473$ .

### 3.3. Obesity may predict the development of a chronic disease course and bDMARD failure in patients with AOSD

Regression models, both univariate and multivariate, were built to evaluate the predictive role of obesity on outcome over time in patients with AOSD. Obesity predicted the development of a chronic disease course in both univariate (HR: 1.72, 95%CI: 1.03–2.51,  $P < 0.05$ ) and multivariate analyses (HR: 1.85, 95%CI: 1.45–2.89,  $P < 0.05$ ). Similarly, patient BMI showed to be a predictive factor for the development of a chronic disease course in both univariate (HR: 1.12, 95%CI: 1.01–1.24,  $P < 0.05$ ) and multivariate analyses (HR: 1.14, 95%CI: 1.01–1.32,  $P < 0.05$ ).

Multivariate analyses were adjusted for possible confounding variables including age, gender, and systemic score. These results are summarised in Table 2. We also assessed if the presence of obesity could predict the achievement of monocyclic pattern or the development of polycyclic disease course, but non-significant results were obtained (data not shown). In addition, according to our analysis, obesity resulted to be a significant predictor of the



**Fig. 1.** Comparison of the distribution of inflammatory marker levels according to narrower classes of BMI (i.e., normal weight: BMI  $< 25$ , overweight:  $25 \leq$  BMI  $< 30$ , obesity: BMI  $\geq 30$ ) and their correlation. A) ferritin in patients with BMI  $< 25$ : 762.0 ng/mL (IQR 654.0); ferritin in patients with  $25 \leq$  BMI  $< 30$ : 1020.0 (IQR 897.0); ferritin in patients with BMI  $\geq 30$ : 1267.0 ng/mL (IQR 1172.0); \*,  $P < 0.05 > 0.01$ ; \*\*,  $P \leq 0.01 > 0.001$ ; B) ferritin significantly correlated with BMI ( $R = 0.473$ ,  $P = 0.014$ ); C) C-reactive protein (CRP) in patients with BMI  $< 25$ : 49.2 mg/L (IQR 56.4); CRP in patients with  $25 \leq$  BMI  $< 30$ : 55.2 mg/L (IQR 77.5); CRP in patients with BMI  $\geq 30$ : 109.2 mg/L (IQR 117.0); CRP in obese patients without inflammatory immune-mediated disease (IMID): 33.8 mg/L (IQR 34.4); \*\*,  $P \leq 0.01 > 0.001$ ; \*\*\*,  $P \leq 0.001$ ; D) CRP significantly correlated with BMI ( $R = 0.539$ ,  $P = 0.012$ ).

**Table 2**

Regression analyses exploiting the possible predictive role of obesity and BMI on the development of a chronic disease course in patients with AOSD.

Clinical Variables	HR	95% CI
Development of a chronic disease course		
Univariate analysis		
Obesity <sup>a</sup>	1.72	1.03–2.51
Multivariate analysis		
Obesity <sup>a</sup>	1.85	1.45–2.89
Age	1.02	0.99–1.04
Male gender	0.90	0.74–1.07
Systemic score	1.82	0.89–3.73
Univariate analysis		
BMI <sup>a</sup>	1.12	1.01–1.24
Multivariate analysis		
BMI <sup>a</sup>	1.14	1.01–1.32
Age	0.98	0.96–1.01
Male gender	0.65	0.32–1.34
Systemic score	1.12	0.92–1.35

Abbreviations: AOSD: adult-onset Still's disease; BMI: body mass index; HR: hazard ratio; 95%CI: 95% confidence interval.  $P < 0.05$  was considered statistically significant.

<sup>a</sup>  $P < 0.05$ .

failure of at least one bDMARD in patients with AOSD in both univariate (HR: 3.03, 95%CI: 1.42–6.45,  $P < 0.01$ ) and multivariate analyses (HR: 3.59, 95%CI: 1.55–8.27,  $P < 0.01$ ). This model was adjusted for age, male gender, and systemic score. Furthermore, obesity showed to be a predictive factor for bDMARD failure (HR: 6.80, 95%CI: 4.05–28.99,  $P < 0.01$ ), adjusting the model for systemic score, low/intermediate dosage of GCs, and csDMARDs. The latter resulted to be negatively associated with bDMARD failure in this analysis (HR: 0.02, 95%CI: 0.00–0.14,  $P < 0.01$ ). Patient BMI resulted

**Table 3**  
Regression analyses exploiting the possible predictive role of obesity and BMI on the bDMARD failure in patients with AOSD.

Clinical variables	HR	95% CI
bDMARD failure		
Univariate analysis		
Obesity <sup>a</sup>	3.03	1.42–6.45
Multivariate analysis		
Obesity <sup>a</sup>	3.59	1.55–8.27
Age	0.99	0.97–1.02
Male gender	0.45	0.20–1.02
Systemic score	0.88	0.71–1.09
Multivariate analysis		
Obesity <sup>a</sup>	6.80	4.05–28.99
Systemic score	0.96	0.75–1.23
Low/intermediate dosage of GCs	0.99	0.99–1.00
csDMARDs <sup>a</sup>	0.02	0.00–0.14
Univariate analysis		
BMI <sup>a</sup>	1.21	1.10–1.24
Multivariate analysis		
BMI <sup>a</sup>	1.23	1.10–1.38
Age	0.999	0.97–1.02
Male gender	0.47	0.20–1.08
Systemic score	0.88	0.70–1.10
Multivariate analysis		
BMI <sup>a</sup>	1.41	1.21–1.64
Systemic score	0.95	0.73–1.24
Low/intermediate dosage of GCs	0.99	0.99–1.00
csDMARDs <sup>a</sup>	0.25	0.01–0.31

AOSD: adult-onset Still's disease; BMI: body mass index; HR: hazard ratio; 95%CI: 95% confidence interval bDMARDs: biologic disease-modifying anti-rheumatic drugs; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs.  $P < 0.05$  was considered statistically significant.

<sup>a</sup>  $P < 0.01$ .

a predictive factor of bDMARD failure in both univariate (HR: 1.21, 95%CI: 1.10–1.24,  $P < 0.01$ ) and multivariate analyses (HR: 1.23, 95%CI: 1.10–1.38,  $P < 0.01$ ). This multivariate analysis was adjusted for possible confounding variables including age, gender, and systemic score. Furthermore, patient BMI was a predictive factor for bDMARD failure (HR: 1.41, 95%CI: 1.21–1.64,  $P < 0.01$ ) adjusting the model for systemic score, low/intermediate dosage of GCs, and csDMARDs. Also in this model, the administration of csDMARDs resulted to be negatively associated with bDMARD failure (HR: 0.25, 95%CI: 0.01–0.31,  $P < 0.01$ ). These findings are reported in [Table 3](#).

#### 4. Discussion

In this study, clinical features of obese patients with AOSD were described in a large multicentre cohort. These patients did not differ from the others in the main clinical features, considering the rate of fever, skin rash, and joint involvement. However, they were characterised by a lower rate of sore throat, serositis, as well as by higher values of CRP and ferritin. In our cohort, the values of BMI directly correlated with those of CRP and ferritin. Furthermore, the presence of obesity, at the time of diagnosis of the disease, predicted the development of a chronic disease course and bDMARD failure in these patients.

Almost 20% of our patients were obese at the time of diagnosis of the disease, highlighting a clinical feature to consider in managing AOSD. The main clinical features were similar comparing patients with a BMI  $\geq 30$  at disease onset than others, considering the frequency of fever, skin rash, and joint involvement. However, some clinical differences were retrieved. In fact, obese patients with AOSD were characterised by a lower rate of sore throat and serositis. Although more difficulty evaluated in obese patients, these findings may be more prevalent in other clinical subsets of AOSD [25,26]. Therefore, the assessment of obesity may provide an additional

feature to consider in the stratification of AOSD and its clinical heterogeneity.

In addition, obese patients with AOSD were characterised by increased values of both CRP and ferritin than others with normal weight and overweight. To date, obese patients with AOSD had also higher values of CRP than age-, gender-, and BMI-matched obese patients without IMID. Moreover, BMI directly correlated with both CRP and ferritin. This is of relevance considering the prognostic role of these laboratory parameters in the context of AOSD which were associated with the occurrence of life-threatening complications and mortality [27,28]. Furthermore, a growing body of evidence has described how the adipocytes and macrophages infiltrating the adipose tissue may produce pro-inflammatory molecules and may trigger the production of acute-phase reactants [29–31]. Therefore, the concomitant presence of obesity in AOSD may contribute to the induction of a pathogenic loop between inflammation in adipose tissue and altered immune response, enhancing the inflammatory burden of the disease as a possible multiplicative factor [32,33].

In our cohort, obese patients with AOSD were also characterised by an increased rate of comorbidities, mainly high blood pressure and type 2 diabetes. Given that the insulin resistance may have a substantial impact on the activity of the immune system, this feature may contribute to the development of an aberrant inflammatory process [34]. Nevertheless, the concomitant presence of comorbidities and obesity may negatively affect the clinical picture of AOSD [16–18]. In fact, these patients may be considered as at higher risk of complications, less able to tolerate specific procedures, and less responsive to the administered therapy. Furthermore, the concomitant presence of comorbidities may be associated with polypharmacy making more difficult the therapeutic management because of possible drug interactions. In addition, the cardiovascular burden of obesity is suggested in patients with rheumatic diseases, highlighting the importance of assessing this feature [35].

Moreover, obesity was a predictive factor for the development of chronic disease course and it could be associated with bDMARD failure in our patients with AOSD. To date, a potential “dose effect” of BMI was also proposed by our results in furtherly reinforcing the hypothesis that obesity may negatively impact the clinical scenario of these patients. This finding may parallel with what observed in rheumatoid arthritis in which obesity is associated with a poor prognosis [32]. In fact, obesity is related with a higher disease activity, an enhanced disability, and a less probability to achieve the clinical remission [3–7,32]. All these features may contribute to the development of a chronic disease course in AOSD, which identifies those patients needing a continuous treatment because of a persistent active disease, usually associated with polyarthritis and disability [10,11,36]. Considering that the obesity is associated with a more intense inflammatory process, it could be possible to speculate that these patients with AOSD may need of a more aggressive early therapeutic strategy to possibly reduce the development of a chronic disease course. Looking at the precision medicine in AOSD [25], specific designed prospective studies are needed to tailor the treatment on patient clinical picture. In addition, a negative impact of obesity on the pharmacokinetics of administered drugs could be associated with bDMARD failure [37]. In fact, a high BMI may be associated with a more rapid clearance, a higher volume of distribution, and a consequent low concentration of bDMARDs [38]. This phenomenon may depend on a non-linear and saturable process of bDMARD internalization mediated by its target in adipose tissue, which is known as “antigenic sink” [39]. Therefore, a thorough evaluation of obesity as a possible effect modifier of bDMARDs is warranted in AOSD as proposed in other inflammatory diseases [40]. Finally, our analysis suggested the role of the administration csDMARDs, which was negatively associated with bDMARD failure in our cohort. Multiple lines of evidence reported the clinical

usefulness of the combination therapy between csDMARDs and bDMARDs in managing patients with AOSD [12,13,24,25].

As observed in any retrospective study, different limitations may limit the validity of our results suggesting a cautious generalization of these findings. In addition, considering the multicentre design, a selection bias could occur. Our cohort showed a higher rate of obesity in patients with AOSD (around 20%) than general Italian population (around 11%); this finding could be related to a possible disease misdiagnosis and previous empirical long term-therapy with GCs. Although a higher rate of bDMARD failure was shown in our study, it must be pointed out that this cohort is not specifically designed to evaluate the efficacy of any drug. Therefore, the results about bDMARDs should be cautiously interpreted. Furthermore, due to the retrospective design, more accurate ways of measuring obesity were not available, such as bioelectrical impedance analysis, waist circumference, and/or waist-to hip ratio. In addition, considering the positive correlations between values of ferritin, CRP, and BMI, the rationale of further studies could be provided to evaluate specific pro-inflammatory cytokines in contributing to the production of ferritin and CRP in this context. Thus, 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, the clinical features of obese patients with AOSD patients were evaluated in our cohort. Obese patients at the time of diagnosis of the disease were characterised by a lower rate of sore throat, serositis, as well as by higher values of CRP and ferritin. Furthermore, the values of BMI directly correlated with those of CRP and ferritin suggesting a possible relationship between obesity and inflammatory burden of the disease. The presence of obesity was also a predictive factor for the development of a chronic disease course and it could be associated with bDMARD failure. Although further studies are needed, our results may suggest the evaluation of obesity in identifying a subset of patients with AOSD to be carefully managed. Finally, additional studies are also needed to fully evaluate if the modifications of BMI could influence the disease course of patients with AOSD.

### Ethics approval and consent to participate

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.

### Consent for publication

Not applicable, all the patients' data are de-identified.

### Availability of data and material

All data relevant to the study are included in the article.

### Disclosure of interest

The authors declare that they have no competing interest.

### Funding

No funding for this study.

### Authors' contributions

All authors made substantial contributions to the conception or design of the work, the acquisition and interpretation of data.

All authors contributed to the critical review and revision of the manuscript and approved the final version. All the authors agreed to be accountable for all aspects of the work.

### Acknowledgements

None.

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