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ORIGINAL RESEARCH

# Still's disease continuum from childhood to elderly: data from the international AIDA Network Still's disease registry

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## ABSTRACT

**Objective** Still's disease is more frequently observed in the paediatric context, but a delayed onset is not exceptional both in the adulthood and in the elderly. However, whether paediatric-onset, adult-onset and elderly-onset Still's disease represent expressions of the same disease continuum or different clinical entities is still a matter of controversy. The aim of this study is to search for any differences in demographic, clinical features and response to treatment between pediatric-onset, adult-onset and elderly-onset Still's disease.

**Methods** Subjects included in this study were drawn from the International AutoInflammatory Disease Alliance Network registry for patients with Still's disease.

**Results** A total of 411 patients suffering from Still's disease were enrolled; the disease occurred in the childhood in 65 (15.8%) patients, in the adult 314 (76.4%) patients and in the elderly in 32 (7.8%) patients. No statistically significant differences at post-hoc analysis were observed in demographic features of the disease between pediatric-onset, adult-onset and elderly-onset Still's disease. The salmon-coloured skin rash (p=0.004), arthritis (p=0.009) and abdominal pain (p=0.007) resulted significantly more frequent among paediatric patients than in adult cases, while pleuritis (p=0.015) and arthralgia (p<0.0001) were significantly more frequent among elderly-onset patients compared with paediatric-onset subjects. Regarding laboratory data, thrombocytosis was significantly more frequent among paediatric patients onset compared with adult-onset subjects (p<0.0001), while thrombocytopenia was more frequent among elderly-onset patients although statistical significance was only bordered. No substantial differences were observed in the response to treatments.

**Conclusions** Despite some minor difference between groups, overall, demographic, clinical, laboratory and treatments aspects of Still's disease were similarly



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### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ An overlap between adult-onset and pediatric-onset Still's disease has been increasingly suggested.

### WHAT THIS STUDY ADDS

⇒ This study identifies only minor differences in demographic, clinical and laboratory features of patients with Still's disease disregarding the age at disease onset.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study provides more evidence about the overlapping clinical and laboratory Still's disease manifestations across the age at the disease onset.

observed in patients at all ages. This supports that pediatric-onset, adult-onset and elderly-onset Still's disease is the same clinical condition arising in different ages.

## INTRODUCTION

Still's disease is a rare systemic polygenic autoinflammatory condition of unknown aetiology involving several environmental, genetic and immunological factors.[1] It has been more frequently described in the paediatric context, but a delayed onset is not exceptional both in the adulthood and in the elderly.[2–4]

Preliminary laboratory studies show that Still's disease has similar pathogenesis disregarding the age at disease onset.[5–8] Similarly, most of clinical and laboratory features, along with the response to anti-interleukin (IL)-1 agents, are similarly observed in paediatric and adult-onset disease.[9–11] Therefore, it has been suggested that pediatric-onset and adult-onset diseases are the same clinical entity occurring at different periods of life; however, this topic is still a matter of controversy.

An additional topic to investigate is whether subjects with a very late disease onset represent a clinical condition belonging to the same disease continuum or a further disease phenotype with own disease features. In this work, we aimed to investigate any significant difference in demographic, clinical and laboratory features of paediatric-onset, adult-onset and elderly-onset Still's disease, along with differences in the response to the most frequently employed treatments in such patients.

## MATERIALS AND METHODS

Patients included in this study were drawn from the International AutoInflammatory Disease Alliance (AIDA) Network registry for patients with Still's disease[12] at March 2023.

All patients were diagnosed with Still's disease, classified according to the internationally accepted criteria: Yamaguchi and/or Fautrel for adult patients[13 14] and the International League of Associations for Rheumatology (ILAR) and/or the Paediatric Rheumatology INternational Trials Organisation (PRINTO) criteria for patients aged<16 years.[15 16]

The objective of this study is to search for any differences between patients with pediatric-onset, adult-onset and elderly-onset Still's disease. With this aim, patients recruited in the International AIDA Network registry for patients with Still's disease were distinguished into three groups according to the different age at disease onset. Specifically, patients complaining of the onset of symptoms by 16 years of age were included in the pediatric-onset group; the adult-onset group included patients with Still's disease onset between 16 and 60 years of age, as previously described.[17 18] Patients with onset of symptoms from the age of 60 years were included in the elderly group. Figure 1 represents the flow diagram with patients' segregation into the three different study groups. The figure also illustrates the fulfilment of the more widely used classification criteria in childhood and adulthood.

Clinical and laboratory data resulted statistically significant among the three study groups were further analysed by comparing pediatric-onset patients, young adults (16–39 years), adults (40–59 years) and elderly-onset of Still's disease. This further patients distinction was aimed at assessing any possible similarities and differences between the paediatric and young adult group as well as the adult group with elderly-onset patients. The endpoint of the study consisted in the identification of any statistically significant difference between the three groups regarding demographic, clinical and laboratory variables observed from the disease onset to the last follow-up assessment. Moreover, statistically significant differences were searched among groups regarding the response to the more frequently employed treatment approaches in all the three study groups.

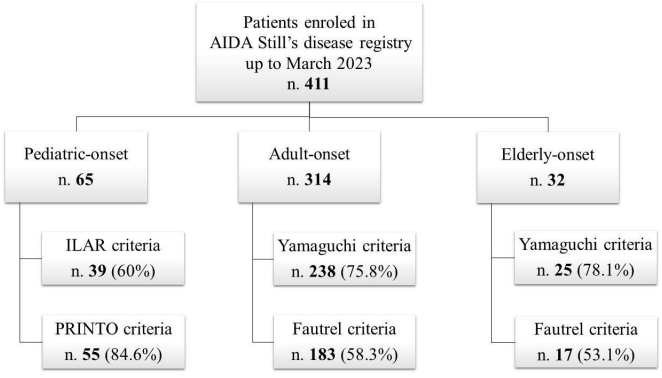



**Figure 1** Flow diagram showcasing the distribution of the enrolled AIDA patients into the three study groups (pediatric-onset, adult-onset and elderly-onset patients) and the fulfilment of classification criteria used before and after the age of 16 (ILAR criteria,[15] PRINTO criteria,[16] Yamaguchi criteria,[13] Fautrel criteria[14]). AIDA, AutoInflammatory Disease Alliance, ILAR, International League of Associations for Rheumatology; PRINTO, Pediatric Rheumatology International Trials Organization.



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Disease duration was defined as the time elapsing between the onset of symptoms and the diagnosis of Still's disease. Disease course was distinguished into monocyclic, polycyclic and chronic articular according to Cush *et al*, with the monocyclic and the polycyclic courses being characterised by a prevalent systemic inflammatory involvement and the latter consisting of a more prevalent musculoskeletal affection with a less prominent systemic inflammation. The monocyclic course typically resolves within 12 months from the start of symptoms, while the polycyclic course lasts longer, with intercritical quiescence.[19] Continuous fever referred to a fever course with temperature remaining above normal throughout the day, with a constant fashion; remittent fever was defined for patients with temperature remaining above normal throughout the day, but with fluctuations; transient fever was referred to temperature elevated for several hours with intervals characterised by temperature dropping back to normal; undulant fever refers to a fever course resembling Brucellosis (with no evidence of infection). Liver involvement was defined as occurrence of hepatomegaly and/or signs of hepatic failure and/or hepatitis and or increase in hepatic liver enzymes. Arthritis was meant as the presence of articular inflammation in one site (monarthritis), from two to four joints (oligoarthritis) or more than four joints (polyarthritis). Cardiac involvement included endocarditis, myocarditis, arrhythmias and cardiac tamponade. Vascular involvement included stroke, critical limb-threatening ischaemia, rupture of abdominal aortic aneurysm, rupture of an intracranial aneurysm, bowel infarction, pulmonary embolism and deep vein thrombosis. Regarding treatment outcomes, *complete response* was defined as the resolution of all disease-related clinical manifestations, with decrease to normal values of all laboratory inflammatory parameters. *Partial response* was defined as persistence of clinical manifestations with remarkable decrease in their severity, as reported by patients, with inflammatory laboratory parameters normalised or only slightly increased. *Failure* was meant as persistence of fever-associated clinical manifestations and/or no decrease of laboratory inflammatory markers. A *relapse* was defined as reappearance of Still's disease related clinical manifestations during the course of treatment. Macrophage activation syndrome (MAS) was classified according to 2016 criteria developed for systemic juvenile idiopathic arthritis and/or the HLH-2004 criteria and/or the HScore.[20–22] Pleuritis was diagnosed through a combination of clinical and radiological elements; thoracentesis was performed only when required for clinical reasons.

Laboratory findings, included blood count, C reactive protein (CRP), erythrocyte sedimentation rate, serum levels of ferritin, thrombocytosis, hypergammaglobulinaemia and lactate dehydrogenase, were investigated at the time of disease onset. The reference ranges depended on the laboratory of the recruiting centres.

All patients or parents (or legal guardian) signed the informed consent to participate to the AIDA project.

Regarding statistical computations, descriptive statistics included mean, standard deviation (SD), range, median and interquartile range (IQR), as required. Data distribution was evaluated by the Shapiro-Wilk test. Global computations were performed using the analysis of variance test or the Kruskal-Wallis test for quantitative data, as required by data distribution; the $\chi^2$ test was used for qualitative data. Post-hoc analysis was performed with the t-test or the Mann-Whitney test for quantitative data and with $\chi^2$ test or with the Fisher exact test according to the frequency counts and the expected frequencies. Bonferroni correction was applied for multiple comparisons and Yates correction was applied to $\chi^2$ test, when required. Significance level was set at 95% ($p<0.05$); p values were two tailed in all cases. Statistical analysis was plotted through the RStudio software, V.4.3.0.

## RESULTS

We enrolled 411 patients diagnosed with Still's disease. The disease onset occurred in the childhood in 65 (15.8%) patients, in the adult 314 (76.4%) patients and in the elderly in 32 (7.8%) patients. The ethnicity was as follows: Caucasian in 300 (73%) cases; Arab in 40 (9.7%) cases; Hispanic in 19 (4.6%) cases; Black in 7 (1.7%) cases; Asian in 2 (0.5%) cases; Jewish and Native American in 1 case; in 41 cases ethnicity was not provided. Yamaguchi's criteria[13] were met in 236 (75.2%) adult patients and in 24 (74%) subjects with elderly disease onset (p=1.0); adult and elderly patients fulfilled Fautrel's criteria[14] in, respectively, 183 (58.3%) and 16 (50%) cases (p=0.46). For patients aged<16 years, PRINTO criteria[16] were fulfilled in 55 (84.6%) subjects and ILAR criteria[15] were met in 39 (60%) paediatric cases.

Table 1 summarises demographic features of patients enrolled. Undulant fever was reported more frequently among patients with adult (p=0.0003) and elderly onset (p=0.0009). Conversely, a global statistically significant difference was observed among groups in the disease duration at diagnosis and in the frequency of the chronic articular disease course, but with no statistically significant difference at post-hoc analysis.

Table 2 describes the frequency of Still's disease clinical features in the three study groups. The salmon-coloured skin rash (p=0.004) and abdominal pain (p=0.007) resulted significantly more frequent among patients with Still's disease with pediatric onset than those with adult onset, while no significant differences were observed with elderly-onset patients. Pleuritis (p=0.015) and arthralgia (p<0.0001) were significantly more frequent among elderly-onset patients compared with pediatric-onset subjects. Arthritis was significantly more frequent in pediatric-onset patients than among adult-onset patients (p=0.009); nevertheless, no differences were observed in the number of joints involved, as the frequency of monarthritis, oligoarthritis and polyarthritis did not differ among groups in a significant fashion. A global



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statistically significant difference was observed in the MAS frequency, but with no significance at post-hoc analysis.

Table 3 provides laboratory data distinguished according to the age at Still's disease onset. Thrombocytosis was significantly more frequent among pediatric-onset patients compared with adult-onset subjects (p<0.0001), while thrombocytopenia was more frequent among elderly-onset patients although statistical significance was only bordered. The frequency of increased lactate dehydrogenase showed a global statistical significance with no post-hoc statistically significant differences among groups.

Table 4 includes clinical and laboratory features resulted to differ in a statistically significant fashion between pediatric-onset, adult-onset and elderly-onset patients. These variables were further analysed after a distinction of adult patients into young adults (16–39 years) and adults (40–59 years). Salmon-coloured skin rash was less frequently encountered among young adults, reaching statistical significance towards paediatric patients; pleuritis was less frequent in the paediatric group, with a statistically significant difference when compared with adults; thrombocytosis was more frequent in the paediatric group, reaching statistical significance towards both young adults and adults.

Methotrexate (MTX), leflunomide, cyclosporine A, sulfasalazine and azathioprine were the conventional disease-modifying antirheumatic drugs (cDMARDs) used in this cohort of patients. Figure 2 represents their frequencies in the three groups of patients. MTX resulted significantly less frequent in paediatric patients compared with adults (p=0.002) and elderly (p=0.0001) patients.

Regarding response to treatment, the response to MTX used as monotherapy did not differ significantly among groups. The frequency of failure was characterised by

**Table 1** Demographic and clinical features of patients enrolled, according to the age at disease onset

| | Pediatric onset (n=65) | Adult onset (n=314) | Elderly onset (n=32) | P value |
|---|---|---|---|---|
| Sex (n males/females) | 32/33 | 122/192 | 14/18 | 0.28 |
| Age at disease onset, years (mean±SD) | 8.8±4.6 | 33.75±11.38 | 68.15±5.3 | – |
| Age at diagnosis, years (mean±SD) | 10.6±7.1 | 33.40±11.70 | 68.92±5.34 | – |
| Disease duration at diagnosis, years median (IQR) | 0.1 (0.0–0.625) | 0.2 (0.1–1.325) | 0.15 (0.1–0.52) | 0.049 |
| Disease duration at enrollment, years median (IQR) | 4.25 (0.9–10.85) | 4.9 (2.19–9.65) | 4 (1.3–7.63) | 0.38 |
| Disease course | | | | |
| Monocyclic, n (%) | 19 (29.2) | 105 (33.4) | 9 (28.1) | 0.70 |
| Polycyclic, n (%) | 16 (24.6) | 85 (27.1) | 5 (15.6) | 0.36 |
| Chronic articular, n (%) | 19 (29.2) | 57 (18.2) | 11 (34.4) | 0.02 |
| Unknown, n (%) | 11 (16.9) | 67 (21.3) | 7 (21.9) | 0.22 |
| Number of attacks/year, median (IQR) | 2 (1.25–3) | 2 (1-3) | 1 (1–1.2) | 0.24 |
| Duration of attacks, days (range) | 15 (10–20) | 20 (10–30) | 15 (3–35) | 0.15 |
| Highest body temperature reached during attacks (°C) (mean±SD) | 39.6±0.8 | 39.5±0.8 | 39.14±0.62 | 0.06 |
| Trigger inducing the disease, n (%) | 15 (23.1) | 45 (14.3) | 5 (15.6) | 0.21 |
| Fever course | | | | |
| Continuous, n (%) | 12 (18.5) | 55 (17.5) | 4 (12.5) | 0.75 |
| Remittent, n (%) | 28 (43.1) | 106 (33.8) | 9 (28.1) | 0.25 |
| Transient, n (%) | 13 (20) | 30 (9.6) | 4 (12.5) | 0.054 |
| Undulant, n (%) | 0 (0) | 42 (13.4) | 6 (18.8) | 0.004* † |
| Not reported, n (%) | 12 (18.5) | 81 (25.8) | 9 (28.1) | 0.42 |

Global p values were obtained with Kruskal-Wallis test for quantitative data and with $\chi^2$ test for qualitative data. Post-hoc analysis was performed with the $\chi^2$ test or with the Fisher exact test according to the expected frequencies.
*Refers to a statistically significant differences after Bonferroni correction (p<0.017) between the pediatric-onset group and the adult-onset group.
†Refers to a statistically significant differences after Bonferroni correction (p<0.017) between the pediatric-onset group and the elderly-onset group.
n, number.



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**Table 2** Frequency of clinical features related to Still's disease among patients with pediatric, adult and elderly onset

| | Pediatric onset (n=65) | Adult onset (n=314) | Elderly onset (n=32) | P value |
|---|---|---|---|---|
| Sore throat, n (%) | 31 (47.7) | 170 (54.1) | 16 (50) | 0.60 |
| Salmon coloured skin rash, n (%) | 50 (76.9) | 179 (57) | 18 (56.3) | 0.01* |
| Atypical skin rash, n (%) | 13 (20) | 79 (25.2) | 3 (9.4) | 0.11 |
| Splenomegaly, n (%) | 21 (32.3) | 103 (32.8) | 9 (28.1) | 0.86 |
| Liver involvement, n (%) | 18 (27.7) | 105 (33.4) | 13 (40.6) | 0.43 |
| Lymphadenopathy, n (%) | 36 (55.3) | 144 (45.6) | 17 (32.1) | 0.31 |
| Thoracic pain, n (%) | 2 (3.1) | 33 (10.5) | 3 (9.4) | 0.17 |
| Pneumonia, n (%) | 3 (4.6) | 17 (5.4) | 2 (6.3) | 0.94 |
| Pleuritis, n (%) | 2 (3.1) | 46 (14.6) | 6 (18.8) | 0.02† |
| Pericarditis, n (%) | 8 (12.3) | 36 (11.5) | 6 (18.8) | 0.49 |
| Abdominal pain, n (%) | 16 (24.6) | 35 (11.1) | 3 (9.4) | 0.01* |
| Peritonitis, n (%) | 1 (1.5) | 2 (0.6) | 0 (0.0) | 0.65 |
| Myalgia, n (%) | 30 (46.2) | 151 (48.1) | 16 (50) | 0.93 |
| Arthralgia, n (%) | 58 (89.2) | 254 (80.9) | 21 (65.6) | 0.02† |
| Arthritis, n (%) | 44 (67.7) | 154 (49) | 18 (56.3) | 0.02* |
| Monarthritis, n (%) | 5 (11.3) | 6 (5.9) | 1 (5.6) | 0.16 |
| Oligoarthritis, n (%) | 17 (38.6) | 61 (39.6) | 9 (50) | 0.67 |
| Polyarthritis, n (%) | 17 (38.6) | 75 (48.6) | 6 (33.3) | 0.28 |
| MAS,‡ n (%) | 11 (16.9) | 25 (7.9) | 1 (3.1) | 0.03 |
| ARDS, n (%) | 0 (0) | 5 (1.6) | 1 (3.1) | 0.44 |
| Fulminant hepatitis, n (%) | 0 (0) | 2 (0.6) | 0 (0) | 0.73 |
| Cardiac complications, n (%) | 3 (4.6) | 5 (1.6) | 0 (0) | 0.19 |
| Vascular complications, n (%) | 0 (0) | 4 (1.3) | 0 (0) | 0.54 |
| New disease manifestations developed over time, n (%) | 6 (9.2) | 37 (11.8) | 2 (6.3) | 0.56 |

P values were obtained with the $\chi^2$ test; post-hoc analysis was performed with the $\chi^2$ test or with the Fisher exact test according to the expected frequencies.
*Refers to a statistically significant differences after Bonferroni correction (p<0.017) between the pediatric-onset group and the adult-onset group.
†Refers to a statistically significant differences at post-hoc analysis after Bonferroni correction (p<0.017) between the pediatric-onset group and the elderly-onset group.
‡MAS was diagnosed in all cases with the criteria proposed by Ravelli *et al*.[20] Three patients fulfilled the HLH-2004 criteria.[22]
ARDS, acute respiratory distress syndrome; MAS, macrophage activation syndrome; n, number.

a global significance towards a higher frequency in the paediatric group; however, no statistical significance was obtained at post-hoc analysis between paediatric-onset and adult-onset cases (p=0.07) and between paediatric and elderly cases (p=0.13).

Table 5 describes the response to biotechnological agents employed as monotherapy in the three groups of patients; no differences were observed in the response according to the different age at onset, except for the frequency of patients experiencing relapses during tocilizumab treatment, which was significantly more frequent among patients with pediatric-onset compared with adult-onset subjects (p=0.008).

Table 6 reports treatment outcome to biotechnological agents combined with MTX in the three groups of patients. No statistically significant differences were observed in the treatment response among paediatric, adult and elderly cases.

Tumour necrosis factor (TNF) inhibitors administered as monotherapy in this cohort were etanercept (ETN) (n=3), infliximab (IFX) (n=2) in the paediatric group; IFX (n=9), ETN (n=6), adalimumab (ADA) (n=2), golimumab (GOL) (n=1), certolizumab pegol (n=1) among adults; ETN (n=1) in elderly cases. The TNF inhibitors combined with MTX were ETN (n=1) in paediatric cases, IFX (n=3),ETN (n=1), ADA (n=1), GOL (n=1) in adult cases; no TNF inhibitor combined with MTX were used in elderly cases. Figure 3 describes the long-term drug survival for biotechnological agents used in the three age groups.

At start of biotechnological treatments, oral corticosteroids were used in 23/65 (35.4%) pediatric-onset cases, in 125/314 (39.8%) adult patients, and in 10/32 (31.3%)



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**Table 3** Laboratory data reported in the first inflammatory episode among patients with pediatric onset, adult onset and elderly onset

| | Pediatric onset (n=65) | Adult onset (n=314) | Elderly onset (n=32) | P values |
|---|---|---|---|---|
| ESR as mm/hour, median (IQR) | 88.5 (55.75–106.25) | 78.5 (54–102) | 100 (64.50–116.50) | 0.31 |
| CRP as mg/dL, median (IQR) | 13.05 (8.075–18.525) | 13.00 (6.8–23.6) | 13.30 (6–33) | 0.85 |
| Anaemia, n (%) | 31 (47.7) | 144 (45.9) | 20 (62.5) | 0.2 |
| Leukocytosis, n (%) | 38 (58.5) | 182 (58) | 19 (59.4) | 0.99 |
| Ferritin serum levels as ng/mL, median (IQR) | 1597.7 (518.8–2753.2) | 1852 (699.60–6908) | 2482 (1038–9348) | 0.20 |
| Thrombocytopenia, n (%) | 4 (6.2) | 22 (7) | 6 (18.8) | 0.05 |
| Thrombocytosis, n (%) | 25 (38.5) | 43 (7.3) | 4 (12.5) | <0.0001* |
| Abnormal liver tests, n (%) | 19 (29.2) | 120 (38.2) | 10 (31.3) | 0.32 |
| Hypergammaglobulinaemia, n (%) | 7 (10.8) | 38 (12.1) | 5 (15.6) | 0.79 |
| Increased LDH, n (%) | 26 (40) | 80 (25.5) | 11 (34.4) | 0.04 |
| LDH serum level as mg/mL, median (IQR) | 469 (373.5–607.8) | 508 (395.8–776.5) | 536 (513.5–612) | 0.53 |

Global p values were obtained with Kruskal-Wallis test for quantitative data and with $\chi^2$ test for qualitative data. Post-hoc analysis was performed with the $\chi^2$ test or with the Fisher exact test according to the expected frequencies.
*Refers to a statistically significant differences at post-hoc analysis after Bonferroni correction (p<0.017) between the pediatric-onset group and the adult-onset group.
CRP, C reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; n, number.

elderly-onset subjects (p=0.55). At the last follow-up visit, systemic corticosteroids were still employed in 4/23 (17.4%) pediatric-onset patients, 29/125 (23.2%) adult subjects and 1/10 (10%) patient in elderly-onset group (p=0.67).

## DISCUSSION

Still's disease is a pathological condition capable of arising at any age.[2–4] Nevertheless, Still's disease is more widely studied in paediatric and early adulthood settings, while it is more rarely found in older age. Although rarer to meet, Still's disease in the elderly is not an exceptional diagnosis and needs to be more deeply investigated in order to assess any differences and peculiarities with respect to paediatric and early adult-onset patients. On the other side, an increasing number of laboratory and clinical evidence supports that paediatric-onset and adult-onset Still's disease represent the same condition arising in different ages.[5–8] Despite this, further evidence supporting overlap between paediatric form of disease and adult-onset disease is still needed.

Looking at past literature, patients with elderly onset showed a higher prevalence in females,[2] a lower frequency

**Table 4** Clinical and laboratory features found to significantly discriminate pediatric, adult and elderly patients were reanalysed distinguishing adult patients into two further groups, that are young adults (aged 16–39) and adults (aged 40–59)

| | Pediatric onset (n=65) | Adult onset | | Elderly onset (n=32) | P value |
|---|---|---|---|---|---|
| | | AYA (n=206) | Adult (n=108) | | |
| Salmon coloured skin rash, n (%) | 50 (76.9) | 109 (50.7) | 70 (64.8) | 18 (56.3) | 0.004* |
| Pleuritis, n (%) | 2 (3.1) | 26 (12.4) | 20 (18.5) | 6 (18.8) | 0.01† |
| Abdominal pain, n (%) | 16 (24.6) | 23 (11) | 12 (11.1) | 3 (9.4) | 0.04 |
| Arthralgia, n (%) | 58 (89.2) | 169 (80.9) | 85 (78.7) | 21 (65.6) | 0.04 |
| Arthritis, n (%) | 44 (67.7) | 101 (48.3) | 53 (49.1) | 18 (56.3) | 0.05 |
| MAS, n (%) | 11 (16.9) | 18 (8.6) | 7 (6.5) | 1 (3.1) | 0.08 |
| Thrombocytosis, n (%) | 25 (38.5) | 26 (12.4) | 17 (15.7) | 4 (12.5) | <0.0001* ‡ |
| Increased LDH, n (%) | 26 (40) | 58 (27.6) | 22 (20.4) | 11 (34.4) | 0.04 |

Global p values were obtained with the $\chi^2$ test; post-hoc analysis was performed with the $\chi^2$ test or the Fisher exact test according to the sample sizes and the expected frequencies; Bonferroni correction was used for pairwise computations (p<0.008).
*Refers to a statistically significant difference after between the pediatric-onset group and the young adults.
†Refers to a statistically significant difference between the pediatric-onset group and the elderly-onset group.
‡Refers to a statistically significant difference between the pediatric-onset group and the adult-onset group.
LDH, lactate dehydrogenase; MAS, macrophage activation syndrome; n, number.



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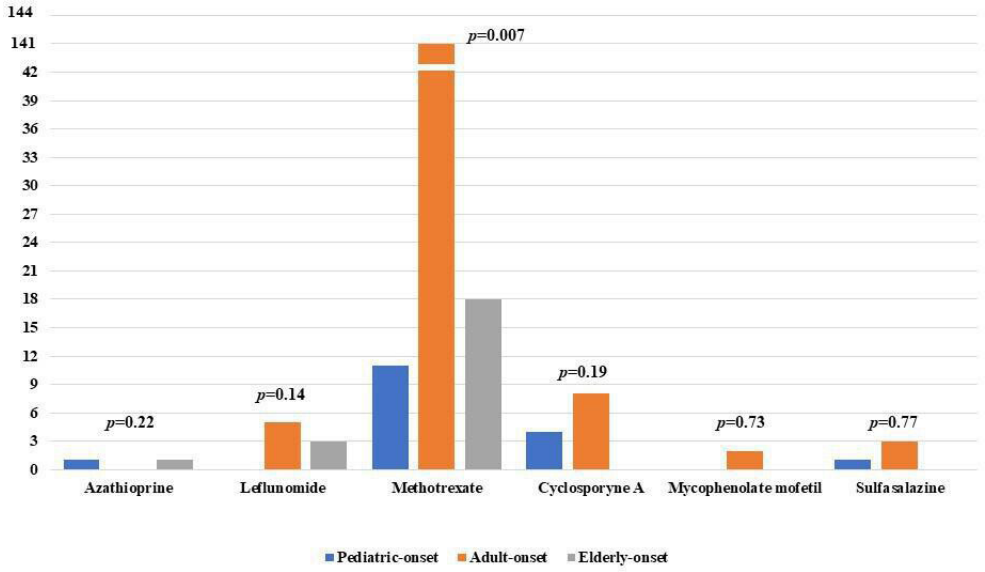



**Figure 2** Frequency of use of the different conventional disease-modifying antirheumatic drugs (cDMARDs) in the different groups (pediatric-onset, adult-onset and elderly-onset patients).

of the typical Still's disease symptoms, including salmon-coloured skin rash, sore throat, lymphadenopathy, splenomegaly and a higher frequency of pleuritis.[4 17 23] Pericarditis was also identified more frequently among elderly-onset patients, with age predicting the development of serositis and parenchymal lung disease.[18] Data about complications including MAS and disseminated intravascular coagulation are inconsistent, with some authors describing a higher frequency[2 4 17] and other an equal frequency[24 25] in adult patients when compared with cases with earlier onset. Similarly, serum ferritin levels were reported higher in the elderly group,[25] but in some cases with no statistical significance.[18 24] Leucocytosis was reported more frequently among elderly-onset cases in one study.[18]

Our results disclosed a higher frequency of pleuritis, pericarditis, lung parenchymal involvement and a slight reduced frequency of salmon-coloured skin rash, splenomegaly, lymphadenopathy and the polycyclic disease course in the elderly group. However, except for pleuritis, none of these clinical features met statistical significance. In particular, pleuritis was significantly more frequent in the elderly group compared with the pediatric-onset group, while no statistical difference was observed between the elderly group and adult-onset group. The higher frequency of pleuritis in later age is also confirmed when adult patients were subdivided into young adults and adults; actually, pleuritis was significantly more frequent among patients aged 40–59 years than in paediatric patients. The frequency of pleuritis was similar in the elderly group and among patients aged between 40 and 59 (roughly 18%), but significance towards the paediatric group was obtained only among the latter due to the smaller sample size of elderly-onset patients. In addition, arthralgia but not arthritis resulted significantly more frequently in the elderly group than in the paediatric group.

A higher risk of relapses[4 25] and a less frequent drug-free remission[17] have been previously reported in the elderly group; in the present study, no statistically significant difference was observed between the elderly-onset group ant the other two groups in terms of response to therapy, number of patients undergoing relapses during treatment with MTX, biotechnological agents used alone or in combination with MTX. These findings seem to contradict previous experience,[4 17 25] but this could be related to the relatively low number of patients treated with each therapeutic approach and to the specific outcomes investigated.

As a whole, we identified much less differences between patients with elderly Still's disease onset and the other patients' groups. Consequently, based on our findings, we do not confirm the presence of a specific subset of patients characterised by an elderly disease onset with distinctive clinical features; however, we confirm that typical Still's disease clinical characteristics may be less frequent in such cases, but not to the extent of defining an atypical clinical picture. This could be related to the more conservative statistical approach used in this study, ensuring specific results at the expense of sensitivity.

Looking at differences between the pediatric-onset group and adult-onset Still's disease patients, a few differences have been highlighted. In particular, undulant fever course was never reported in the paediatric group, while the salmon-coloured skin rash, arthritis and abdominal pain were significantly more frequent among patients with the pediatric-disease onset. Surprisingly, while paediatric patients were more exposed to salmon-coloured skin rash, this manifestation resulted



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**Table 5** Treatment outcome to biotechnological agents employed in pediatric-onset, adult-onset and elderly-onset patients in terms of frequency of complete and partial response, treatment failure, number of patients experiencing relapses during treatment and frequency of treatment discontinuation due to lack or loss of efficacy and long-term disease remission

| | | Pediatric onset (n=65) | Adult onset (n=314) | Elderly onset (n=32) | P values |
|---|---|---|---|---|---|
| Anakinra, n | | 16 | 55 | 9 | |
| Response | Complete, n (%) | 11 (68.8) | 35 (63.6) | 7 (77.8) | 0.69 |
| | Partial, n (%) | 3 (18.8) | 19 (34.5) | 2 (22.2) | 0.41 |
| | Failure, n (%) | 2 (12.5) | 1 (1.8) | 0 (0) | 0.12 |
| Relapses, n (%) | | 3 (18.8) | 15 (27.3) | 3 (33.3) | 0.69 |
| Discontinuation | Lack/loss of efficacy, n (%) | 3 (18.8) | 11 (20) | 1 (11.1) | 0.82 |
| | Long-term remission, n (%) | 3 (18.8) | 6 (10.9) | 1 (11.1) | 0.70 |
| | AEs, n (%) | 1 (6.3) | 3 (5.5) | 2 (22.2) | 0.20 |
| Canakinumab, n | | 10 | 40 | 2 | |
| Response | Complete, n (%) | 7 (70) | 22 (55) | 1 (50) | 0.67 |
| | Partial, n (%) | 3 (30) | 14 (35) | 1 (50) | 0.86 |
| | Failure, n (%) | 0 (0) | 4 (10) | 0 (0) | 0.52 |
| Relapses, n (%) | | 4 (40) | 16 (40) | 1 (50) | 0.96 |
| Discontinuation | Lack/loss of efficacy, n (%) | 2 (20) | 5 (12.5) | 0 (0) | 0.70 |
| | Long-term remission, n (%) | 3 (30) | 3 (7.5) | 0 (0) | 0.12 |
| | AEs, n (%) | 0 (0) | 0 (0) | 0 (0) | NA |
| Tocilizumab, n | | 5 | 33 | 3 | |
| Response | Complete, n (%) | 4 (80) | 25 (75.8) | 3 (100) | 0.62 |
| | Partial, n (%) | 0 (0) | 8 (20) | 0 (0) | 0.24 |
| | Failure, n (%) | 1 (10) | 0 (0) | 0 (0) | 0.12 |
| Relapses, n (%) | | 4 (80) | 6 (18.2) | 1 (33.3) | 0.01* |
| Discontinuation | Lack/loss of efficacy, n (%) | 2 (40) | 5 (15.2) | 0 (0) | 0.28 |
| | Long-term remission, n (%) | 2 (40) | 4 (12.1) | 0 (0) | 0.20 |
| | AEs, n (%) | 0 (0) | 1 (3.0) | 0 (0) | 0.88 |
| Anti-TNF, n | | 5 | 19 | 1 | |
| Response | Complete, n (%) | 4 (80) | 9 (47.4) | 1 (100) | 0.28 |
| | Partial, n (%) | 0 (0) | 10 (52.6) | 0 (0) | 0.07 |
| | Failure, n (%) | 1 (20) | 0 (0) | 0 (0) | 0.12 |
| Relapses, n (%) | | 0 (0) | 6 (31.6) | 0 (0) | 0.29 |
| Discontinuation | Lack/loss of efficacy, n (%) | 1 (20) | 10 (52.6) | 0 (0) | 0.28 |
| | Long-term remission, n (%) | 1 (20) | 2 (10.5) | 0 (0) | 0.79 |
| | AEs, n (%) | 0 (0) | 1 (5.3) | 0 (0) | 0.71 |

Global p values were obtained with the $\chi^2$ test. Post-hoc analysis was performed with the Fisher exact test.
*Refers to a statistically significant differences at *post-hoc* analysis after Bonferroni correction ($p<0.017$) between the pediatric-onset group and the adult-onset group.
AEs, adverse events; n, number; TNF, tumour necrosis factor.

less frequent in young adults aged 16–39 rather than in adults aged 40–59 and elderly subjects.

The higher frequency of arthritis in the paediatric group could be related to the wide use of ILAR criteria to classify Still's disease in the paediatric context, which requires the presence of arthritis as a mandatory item.[15] MAS was more frequent in the paediatric disease group, but with no statistically significant difference. From a laboratory perspective, thrombocytosis was significantly more frequent among paediatric patients. Again, the lack of statistical significance towards the elderly group is caused by the limited sample size of patients aged>60. Ruscitti *et al* have recently published a similar article aimed at assessing differences between pediatric-onset and adult-onset disease. Their results showed several significant differences capable of highlighting remarkable



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**Table 6** Treatment outcome to biotechnological agents employed in combination with methotrexate in pediatric-onset, adult-onset and elderly-onset cases

| | | Pediatric onset (n=65) | Adult onset (n=314) | Elderly onset (n=32) | P values |
|---|---|---|---|---|---|
| Anakinra, n | | 1 | 11 | 2 | |
| Response | Complete, n (%) | 1 (100) | 7 (63.6) | 1 (50) | 0.69 |
| | Partial, n (%) | 0 (0) | 3 (27.3) | 0 (0) | 0.59 |
| | Failure, n (%) | 0 (0) | 1 (9.1) | 1 (50) | 0.86 |
| Interruption of concomitant MTX, n (%) | | 0 (0) | 6 (54.5) | 0 (0) | 0.24 |
| Discontinuation | Lack/loss of efficacy, n (%) | 0 (0) | 4 (36.4) | 1 (50) | 0.69 |
| | Long-term remission, n (%) | 0 (0) | 1 (9.1) | 0 (0) | 0.86 |
| | AEs, n (%) | 0 (0) | 2 (18.2) | 1 (50) | 0.52 |
| Canakinumab, n | | 3 | 7 | 1 | |
| Response | Complete, n (%) | 3 (100) | 6 (85.7) | 0 (0) | 0.07 |
| | Partial, n (%) | 0 (0) | 0 (0) | 1 (100) | 0.004 |
| | Failure, n (%) | 0 (0) | 1 (14.3) | 0 (0) | 0.73 |
| Interruption of concomitant MTX, n (%) | | 0 (0) | 2 (28.6) | 0 (0) | 0.50 |
| Discontinuation | Lack/loss of efficacy, n (%) | 1 (33.3) | 2 (28.6) | 0 (0) | 0.80 |
| | Long-term remission, n (%) | 2 (66.6) | 2 (28.6) | 0 (0) | 0.38 |
| | AEs, n (%) | 0 (0) | 0 (0) | 0 (0) | NA |
| Tocilizumab, n | | 2 | 6 | 3 | |
| Response | Complete, n (%) | 2 (100) | 4 (66.6) | 3 (100) | 0.36 |
| | Partial, n (%) | 0 (0) | 1 (16.7) | 0 (0) | 0.63 |
| | Failure, n (%) | 0 (0) | 1 (16.7) | 0 (0) | 0.63 |
| Interruption of concomitant MTX, n (%) | | 0 (0) | 4 (66.6) | 2 (66.6) | 0.23 |
| Discontinuation | Lack/loss of efficacy, n (%) | 0 (0) | 3 (50) | 0 (0) | 0.18 |
| | Long-term remission, n (%) | 2 (100) | 2 (33.3) | 2 (66.6) | 0.23 |
| | AEs, n (%) | 0 (0) | 2 (33.3) | 0 (0) | 0.36 |
| Anti-TNF, n | | 1 | 6 | 0 | |
| Response | Complete, n (%) | 0 (0) | 2 (33.3) | 0 (0) | 1.00 |
| | Partial, n (%) | 0 (0) | 0 (0) | 0 (0) | NA |
| | Failure, n (%) | 1 (100) | 4 (66.7) | 0 (0) | 1.00 |
| Interruption of concomitant MTX, n (%) | | 0 (0) | 2 (33.3) | 0 (0) | 1.00 |
| Discontinuation | Lack/loss of efficacy, n (%) | 1 (100) | 4 (66.7) | 0 (0) | 1.00 |
| | Long-term remission, n (%) | 0 (0) | 2 (33.3) | 0 (0) | 1.00 |
| | AEs, n (%) | 0 (0) | 0 (0) | 0 (0) | NA |

Global p values were obtained with the $\chi^2$ test.
AEs, adverse events; MTX, methotrexate; n, number; TNF, tumour necrosis factor.

disparities in the prevalence of many clinical manifestations, especially those typically related to Still's disease diagnosis.[26] Comparing our data with those reported by Ruscitti *et al*, this discrepancy is widely related to the remarkably higher frequency of sore throat, lymphadenopathy, splenomegaly, pericarditis, myalgia, and leukocytosis in our cohort of paediatric patients.[26] Actually, our clinical findings are similar to that reported by Neau *et al*, who identified a similar clinical presentation between paediatric and adult groups, except for sore throat and myalgia, which were more frequent in adults in their study.[27] Neau *et al*[27] identified a statistically significant difference between paediatric and adult-onset groups in the CRP and serum ferritin levels. In this regard, ferritin levels have been distinguished between adult and elderly cases in our non-paediatric patients, probably affecting the difference between paediatric and adult groups.

The wide age of onset may contribute to the disease heterogeneity; thus, based on its clinical relevance, this feature has been used in deriving diverse patient clusters in Still's disease by data mining techniques.[25 28] Furthermore, although many findings support the hypothesis



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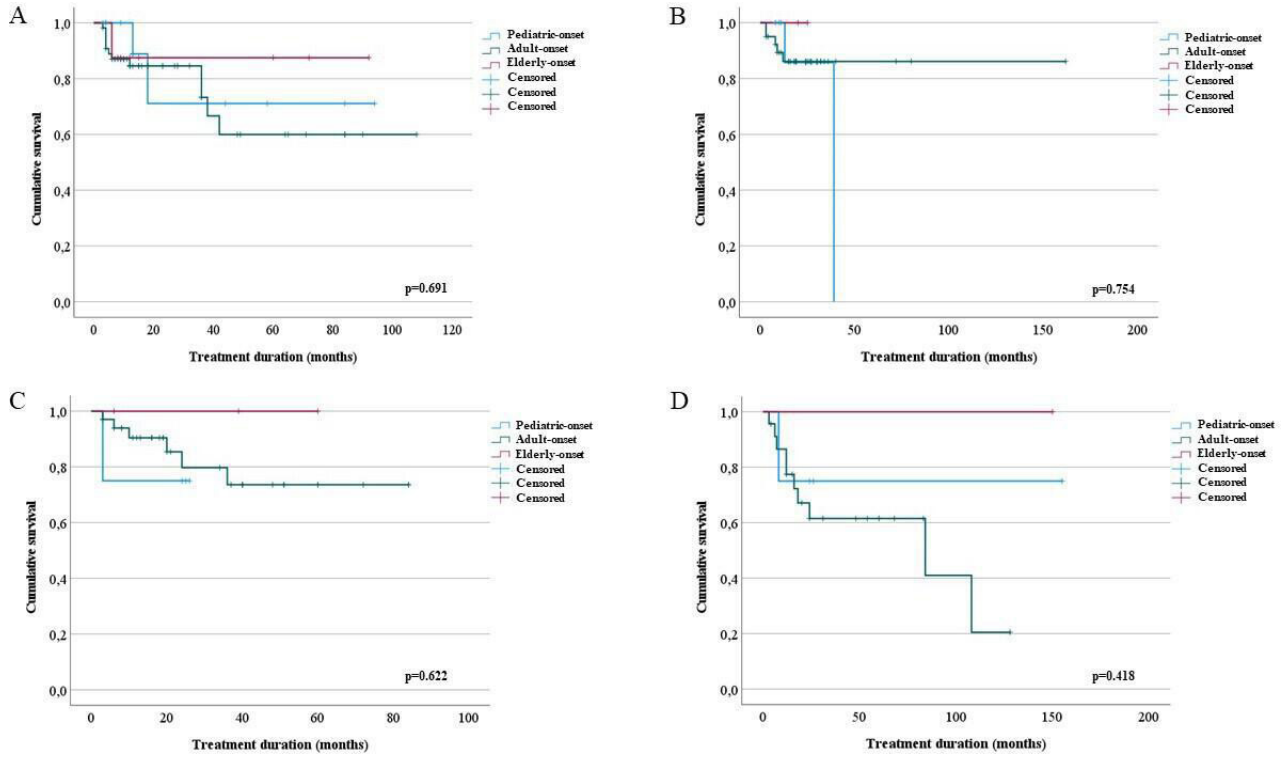



**Figure 3** Kaplan-Meier curves with p values obtained with the Log-rank test. The drug survival was assessed in the three age groups (pediatric, adult and elderly onset) for anakinra (A), canakinumab (B), tocilizumab (C), and tumour necrosis factor (TNF) inhibitors.

of pediatric and adult onset of Still's disease being a continuum of the same continuum condition, additional issues in adults may impact their prognosis, such as smoking habit, comorbidities and ageing-related frailty.[18 29–31]

Excluding the number of patients experiencing disease relapses during tocilizumab therapy, no differences were observed in the treatment outcome to biotechnological agents used either as monotherapy or combined with MTX and/or glucocorticoids. Similarly, no differences were observed in the drug retention rate of the different IL targeting agents used in this study. Altogether, these findings support a similar response to currently employed treatment approaches and, consequently, a unique clinical continuum including both pediatric-onset and adult-onset Still's disease.

The main limitation of the study is in the relatively low number of elderly-onset cases, which is quite comparable to that previously reported in other studies. Also, the number of cases with a poor treatment outcome in the three groups was low due to the high effectiveness of therapies. This has made statistics less powerful in assessing therapeutic differences between groups. Noteworthy, no deaths have been reported in the registry so far. This could conceal a selection bias, as investigators may have omitted the recruitment of deceased patients. Moreover, response to treatments was relegated to biotechnological agents and to combination treatment between cDMARDs and biologics. This decision was taken in order to avoid a bias related to a different use of cDMARDs as monotherapy between paediatricians and physicians dealing with Still's disease. Indeed, any difference would have reflected a different perspective between physicians rather than a pathophysiological difference among groups. Despite these limitations, this is the first study aimed at assessing Still's disease subdividing patients into three groups according with the age at disease onset, in order to identify any differences in this continuum of patients.

In conclusion, the present study highlights only minor differences among groups in both demographic, clinical, laboratory and treatments aspects of Still's disease. This supports that paediatric-onset, adult-onset and elderly-onset Still's disease could be the same clinical condition arising in different ages; however, genetic and molecular assessments should be performed on the same age groups to confirm findings observed from a clinical and laboratory perspective.

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**Data availability statement** Data are available upon reasonable request. All data relevant to the study are included in the article.

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