The clinical assessment of lung involvement in patients with Still’s disease, results from the multicentre international AIDA Network Still's Disease Registry

The clinical assessment of lung involvement in patients with Still's disease, results from the multicentre international AIDA Network Still's Disease Registry

Piero Ruscitti[1], Antonio Vitale[2,3], Ilenia Di Cola[1], Valeria Caggiano[2,3], Pierpaolo Palumbo[4], Ernesto Di Cesare[1], Andrea Hinojosa-Azaola[5], Jiram Torres-Ruiz[5], Guillermo Arturo Guaracha-Basañez[5], Eduardo Martín-Nares[5], Giuseppe Lopalco[6], Maria Morrone[6], Florenzo Iannone[6], Henrique A Mayrink Giardini[7], Rafael Alves Cordeiro[7], Isabele Parente de Brito Antonelli[7], Onorina Berardicurti[8,9], Luca Navarini[8,9], Francesco Ciccia[10], Maria Chiara Visconti[10], Daniela Iacono[10], Haner Direskeneli[11], Sukran Erten[12], Haihong Yao[13], Maissa Thabet[14], Samar Tharwat[15,16], Gaafar Ragab[17,18], Verónica Gómez-Caverzaschi[19], Petros P Sfikakis[20], Lampros Fotis[21], Francesco La Torre[22], Armin Maier[23], Anastasios Karamanakos[24], Ibrahim A Almaghlouth[25,26], Micol Frassi[27], Abdurrahman Tufan[28], Marcello Govoni[29], Jurgen Sota[2,3], Gabriele Simonini[30], Giacomo Emmi[31,32], Francesca Li Gobbi[33], Paola Parronchi[34], Stefania Costi[35], Piercarlo Sarzi-Puttini[36], Daniela Opris-Belinski[37], Paolo Sfriso[38], Maria Tarsia[2,3], Maria Cristina Maggio[39], Sara Monti[40,41], Özgül Soysal Gündüz[42], Donato Rigante[43], Elena Bartoloni[44], Elena Verrecchia[45,46], Annamaria Iagnocco[47], Ombretta Viapiana[48], Elena Bargagli[49,3], Ezgi D Batu[50], Gian Domenico Sebastiani[51], Emanuela Del Giudice[52], Giovanni Conti[53], Luciana Breda[54], Antonio Gidaro[55], Maria Francesca Gicchino[56], Carla Gaggiano[2,3], Antonio Luca Brucato[57], Paola Triggianese[58], Joanna Makowska[59], Francesco Carubbi[60], Nicola Farina[61,62], Giuliana Guggino[63], Amato De Paulis[64], Maria Antonietta Mazzei[65,3], Nunzia Di Meglio[65,3], Alberto Lo Gullo[66], Alessandro Conforti[67], Benson Ogunjimi[68,69,70,71], Laura Calabrese[72,73,3], Pietro Rubegni[72,73,3], Annarita Giardina[74], Ewa Wiesik-Szewczyk[75], Alberto Balistreri[76,3], Claudia Fabiani[77,3], Bruno Frediani[2,3], Lorenzo Dagna[61,62], Roberto Giacomelli[8,9], Luca Cantarini[2,3]

1 - Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, L'Aquila, Italy; 2 - Department of Medical Sciences, Surgery and Neurosciences, Research Center of Systemic Autoinflammatory Diseases and Behçet's Disease Clinic, University of Siena, Siena, Italy; 3 - Azienda Ospedaliero-Universitaria Senese [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center] Siena, Italy; 4 - Department of Diagnostic Imaging, Area of Cardiovascular and Interventional Imaging, Abruzzo Health Unit 1, L'Aquila, Italy; 5 - Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; 6 - Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J) Policlinic Hospital, University of Bari, Bari, Italy; 7 - Rheumatology Division, Faculdade de Medicina, Hospital das Clínicas, Universidade de São Paulo, São Paulo, Brazil; 8 - Clinical and research section of Rheumatology and Clinical Immunology, Fondazione Policlinico Campus Bio-Medico, Via Álvaro del Portillo 200, 00128, Rome, Italy; 9 - Rheumatology,

Immunology and Clinical Medicine Unit, Department of Medicine, University of Rome "Campus Biomedico" School of Medicine, Rome, Italy; 10 - Department of Precision Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy; 11 - Department of Internal Medicine, Division of Rheumatology, Marmara University, Faculty of Medicine, Istanbul, Turkey; 12 - Department of Rheumatology, Faculty of Medicine Ankara City Hospital, Ankara Yıldırım Beyazıt University, Ankara, Turkey; 13 - Department of Rheumatology and Immunology, Peking University People's Hospital, and Beijing Key Laboratory for Rheumatism Mechanism and Immune Diagnosis (BZ0135), Beijing, China; 14 - Internal medicine department, Farhat Hached University Hospital, University of Sousse, Faculty of medicine of Sousse, Sousse, Tunisia; 15 - Rheumatology and Immunology Unit, Internal Medicine Department, Mansoura University, Mansoura, Egypt; 16 - Department of Internal Medicine, Faculty of Medicine, Horus University, New Damietta, Egypt; 17 - Internal Medicine Department, Rheumatology and Clinical Immunology Unit, Faculty of Medicine, Cairo University, Giza, Egypt; 18 - Faculty of Medicine, Newgiza University, 6th of October City, Egypt; 19 - Department of Autoimmune Diseases, Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Hospital Clínic of Barcelona [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center], University of Barcelona, Barcelona, Spain; 20 - Joint Academic Rheumatology Program, Medical School, National and Kapodistrian University of Athens, Athens, Greece; 21 - Department of Pediatrics, Attikon General Hospital, National and Kapodistrian University of Athens, Greece; 22 - Department of Pediatrics, Pediatric Rheumatology Center, Giovanni XXIII Pediatric Hospital, University of Bari, Bari, Italy; 23 - Rheumatology Unit, Department of Medicine, Central Hospital of Bolzano, Bolzano, Italy; 24 - Department of Rheumatology, "Evangelismos" General Hospital, Athens, Greece; 25 - Rheumatology Unit, Department of Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia; 26 - College of Medicine Research Center, College of Medicine, King Saud University, Riyadh, Saudi Arabia; 27 - Rheumatology and Clinical Immunology, Spedali Civili and Department of Clinical and Experimental Sciences, University of Brescia, [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center], Brescia, Italy; 28 - Gazi University Hospital, Department of Internal Medicine, Division of Rheumatology, Ankara, Turkey; 29 - Rheumatology Unit, Department of Medical Sciences, Azienda Ospedaliero-Universitaria S. Anna-Ferrara, University of Ferrara, Ferrara, Italy; 30 - NEUROFARBA Department, Rheumatology Unit, Meyer Children's Hospital IRCCS, University of Florence, Florence, Italy; 31 - Department of Medical, Surgical and Health Sciences, University of Trieste, Italy, and Clinical Medicine and Rheumatology Unit, Cattinara University Hospital, Trieste, Italy; 32 - Centre for Inflammatory Diseases, Monash University Department of Medicine, Monash Medical Centre, Melbourne, Australia; 33 - Rheumatology Unit, Hospital S. Giovanni di Dio, Azienda USL-Toscana Centro, Florence, Italy; 34 - Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy; 35 - Department of Clinical Sciences and Community Health, Research Center for Adult and Pediatric Rheumatic Diseases, University of Milan, Milan, Italy; 36 - Rheumatology Unit, IRCCS Ospedale Galeazzi - S. Ambrogio, Università degli Studi di Milano, Italy; 37 - Rheumatology and Internal Medicine Department, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; 38 - Rheumatology Unit, Department of Medicine, University of Padua, [European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) Center], Padua, Italy; 39 - University Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties (PROMISE) "G. D'Alessandro", University of Palermo, Palermo, Italy; 40 - Division of Rheumatology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; 41 - Department of Internal Medicine and Therapeutics, Università di Pavia, Italy; 42 - Division of Rheumatology, Department of Internal

Medicine, School of Medicine, Manisa Celal Bayar University, Manisa, Turkey; 43- Department of Life Sciences and Public Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy, Periodic Fever Research Center, Università Cattolica Sacro Cuore, Rome, Italy; 44 - Rheumatology Unit, Department of Medicine and Surgery, University of Perugia, Perugia, Italy; 45 - Rare Diseases and Periodic Fevers Research Centre, Università Cattolica del Sacro Cuore, Rome, Italy;
46 - Department of Aging, Neurological, Orthopedic and Head and Neck Sciences, Fondazione Policlinico Universitario Agostino Gemelli Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Rome, Italy; 47 - Academic Rheumatology Centre, Dipartimento Scienze Cliniche e Biologiche, Università degli Studi di Torino, Torino, Italy; 48 - Rheumatology Unit, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, Italy; 49 - UOC Respiratory Diseases and Lung Transplant, Department Medical Sciences, Surgery and Neurosciences, University of Siena, Siena, Italy; 50 - Department of Pediatric Rheumatology, Faculty of Medicine, Hacettepe University, Ankara, Turkey; 51 - UOC di Reumatologia, Azienda Ospedaliera San Camillo Forlanini, Roma, Italy; 52 - Pediatric and Neonatology Unit, Department of Maternal Infantile and Urological Sciences, Sapienza University of Rome, Latina, Italy; 53 - Pediatric Nephrology and Rheumatology Unit, Azienda Ospedaliera Universitaria (AOU), "G. Martino" Messina, Italy; 54 - Department of Paediatrics, University of Chieti-Pescara, Chieti, Italy; 55 - Department of Biomedical and Clinical Sciences Luigi Sacco, Luigi Sacco Hospital, University of Milan, Milan, Italy; 56 - Department of Woman, Child and of General and Specialized Surgery, University of Campania "Luigi Vanvitelli", Naples, Italy; 57 - Pediatric Unit, Fatebenefratelli Hospital, Milan, Italy; 58 - Rheumatology, Allergology and Clinical Immunology, Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy; Molecular Medicine and Applied Biotechnology, University of Rome Tor Vergata, Rome, Italy; 59 - Department of Rheumatology, Medical University of Lodz, Zeromskiego 113, 90-549 Lodz, Poland; 60 - Department of Life, Health & Environmental Sciences and Internal Medicine and Nephrology Unit, Department of Medicine, University of L'Aquila and ASL Avezzano-Sulmona-L'Aquila, San Salvatore Hospital, L'Aquila, Italy; 61 - Faculty of Medicine, Università Vita-Salute San Raffaele, Milan, Italy; 62 - Unit of Immunology, Rheumatology, Allergy and Rare Diseases, IRCCS Ospedale San Raffaele, Milan, Italy; 63 - Rheumatology Section, Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties, University Hospital P. Giaccone, Palermo, Italy; 64 - Department of Translational Medical Sciences, Section of Clinical Immunology, University of Naples Federico II, Naples, Italy; Center for Basic and Clinical Immunology Research (CISI), WAO Center of Excellence, University of Naples Federico II, Naples, Italy; 65 - Unit of Diagnostic Imaging, Department of Medical, Surgical and Neuro Sciences and of Radiological Sciences, University of Siena, Azienda Ospedaliero-Universitaria Senese, 53100, Siena, Italy; 66 - UOSD Reumatologia, ARNAS Garibaldi, Catania, Italy; 67 - U.O. Medicina Generale, Ospedale San Paolo di Civitavecchia, ASL Roma 4, Civitavecchia, Rome, Italy; 68 - Antwerp Unit for Data Analysis and Computation in Immunology and Sequencing, University of Antwerp, Antwerp, Belgium; 69 - Antwerp Center for Translational Immunology and Virology, Vaccine and Infectious Disease Institute, University of Antwerp, Antwerp, Belgium; 70 - Department of Paediatrics, Antwerp University Hospital, Antwerp, Belgium; 71 - Center for Health Economics Research and Modeling Infectious Diseases, Vaccine and Infectious Disease Institute, University of Antwerp, Antwerp, Belgium; 72 - Dermatology Unit, Department of Medical, Surgical and Neurological Sciences, University of Siena, Siena, Italy; 73 - Institute of Dermatology, Catholic University of the Sacred Heart, Rome, Italy; 74 - Department of Clinical Medicine, Internal Medicine Unit with Rheumatology, Dermatology, Diabetology and Tertiary Diabetic Foot Healthcare, National Relevance and High Specialization Hospital Trust ARNAS Civico, Di

Cristina, Benfratelli, Palermo, Italy; 75 - Department of Internal Medicine, Pneumonology, Allergology and Clinical Immunology, Central Clinical Hospital of the Ministry of National Defense, Military Institute of Medicine, National Research Institute, Warsaw, Poland; 76 - Bioengineering and Biomedical Data Science Lab, Department of Medical Biotechnologies, University of Siena, Siena, Italy; 77 - Ophthalmology Unit, Department of Medicine, Surgery and Neurosciences, University of Siena, Italy.

From the International AIDA (AutoInflammatory Diseases Alliance) Network and from the Autoinflammatory Diseases Working Group of the Italian Society of Rheumatology (SIR)

-Name and address of authors responsible for correspondence:

Luca Cantarini, MD, PhD; Research Center of Systemic Autoinflammatory Diseases, Behçet's Disease Clinic and Rheumatology-Ophthalmology Collaborative Uveitis Center, Department of Medical Sciences, Surgery and Neurosciences, University of Siena, Siena, Italy. Policlinico "Le Scotte", Viale Bracci 1, 53100 Siena, Italy; e-mail: cantariniluca@hotmail.com

Piero Ruscitti, MD, PhD; Department of Biotechnological and Applied Clinical Sciences, University of L'Aquila, Delta 6 Building, Via dell'Ospedale, PO box 67100, L'Aquila; email: piero.ruscitti@univaq.it

-A short running head title:

Lung involvement in Still's disease

Key messages

- The characteristics of patients with Still's disease and lung involvement were described in the AIDA network.

- Patients with parenchymal lung disease frequently showed sore throat, pericarditis, and high systemic score.

- IL-1 or IL-6 inhibitors did not result to be associated with the parenchymal lung involvement.

Abstract

Objectives: To assess the lung involvement in patients with Still's disease, an inflammatory disease assessing both children and adults. To exploit possible associated factors for parenchymal lung involvement in these patients.

Methods: A multicenter observational study was arranged assessing consecutive patients with Still's disease characterized by the lung involvement among those included in the AIDA (AutoInflammatory Disease Alliance) Network Still's Disease Registry. Still's disease-lung involvement was defined by the presence of pleuritis, parenchymal features, acute respiratory distress syndrome (ARDS), and/or pulmonary arterial hypertension.

Results: In total, 90 patients with Still's disease and lung involvement were assessed (mean age 36.3 ± 17.8 years, 35.6% male sex). Among them, 13.3% of patients were paediatrics. These patients with lung involvement mainly showed pleuritis in 72.2% of cases, parenchymal features in 34.4%, ARDS in 9.5%, and pulmonary arterial hypertension in 2.3%. After that we focused on patients characterised by parenchymal lung involvement, which is an emergent issue of clinical concern. These patients with parenchymal lung disease were significantly characterized by sore throat, pericarditis, and higher values of systemic score than others. Finally, the administration of both IL-1 or IL-6 inhibitors was not associated with the presence of parenchymal lung involvement.

Conclusion: The clinical characteristics of patients with Still's disease and lung involvement were described in the AIDA network. We also provided a clinical profile of patients with parenchymal lung involvement considering its prognostic relevance. Although providing a clinical landscape of these patients, further studies are needed to fully clarify this issue.

Keywords

Still's disease; systemic juvenile idiopathic arthritis, adult-onset Still's disease; lung involvement; prognosis

Introduction

Still's disease, formerly known as systemic juvenile idiopathic arthritis and adult-onset Still's disease, is an inflammatory disorder usually manifesting with high spiking fever, arthritis, and evanescent skin rash in association with a typical hyperferritinemia [1]. Both children and adults may be affected according to a disease continuum across all ages [2,3]. Still's disease is induced by an aberrant inflammatory response involving a deregulated activity of innate and adaptive arms of the immune system, at the crossroads of autoinflammatory and autoimmune disorders [4]. The inflammatory mechanisms behind the disease provide the rationale for the administration of immunosuppressive agents [5]. Consequently, glucocorticoids (GCs), conventional synthetic disease modifying anti rheumatic drugs (csDMARDs), and biologic DMARDs (bDMARDs) are administered to manage these patients according to the phases of activity and the clinical response [6,7]. Despite the different possible disease courses, Still's disease may be characterized by a potential life-threatening evolution due to the occurrence of severe complications [1-4]. These patients may be indeed burdened by the occurrence of macrophage activation syndrome (MAS), which is a secondary form of hemophagocytic lymphohistiocytosis [8,9]. In this context, recent lines of evidence have increasingly reported the clinical relevance of the development of parenchymal lung involvement in Still's disease in addition to the presence of pleuritis, which is the most common studied pulmonary finding so far [10-16]. Parenchymal lung involvement appears to be another complication associated with a poor prognosis, which has been increasingly raised the attention of the scientific community [10-16]. Although at the beginning it could be subtle, lung involvement may present with dyspnoea, tachypnoea, and cough. Differently from adults, children with Still's disease and parenchymal lung involvement may be characterized by peculiar clinical features including acute erythematous clubbing, and atypical skin rash [10-14]. Histologically, this manifestation seems to be related with features of pulmonary alveolar proteinosis and/or lipoid pneumonia [10,11]. Pulmonary alveolar proteinosis is a lung disease related to surfactant accumulation within the alveoli mainly resulting from decreased clearance than increased production whereas lipoid pneumonia is due to the abnormal presence of lipid-containing products. In Still's disease, these histological findings were described in children but not in adults so far [10,11]. In addition, preliminary reports of lung involvement in Still's disease could be linked this complication to anaphylactic reaction to bDMARDs, both interleukin (IL)-1 and IL-6 inhibitors [10-14]. Moreover, the occurrence of parenchymal lung involvement in Still's disease has increasingly

corresponded with the use of inhibitors of IL-1 and IL-6, and many patients with this manifestation have a history of exposure to these drugs [10,11]. Based on these findings, a potential contribution of bDMARD exposure has been recently suggested in increasing the risk of development of the parenchymal lung involvement in these patients [10,11]. Also, two possible pathogenic explanations have been lately proposed, namely drug reaction with eosinophilia and systemic symptoms (DRESS) hypothesis and/or cytokine plasticity hypothesis, in deregulating the immune response towards the occurrence of such manifestation [17]. These hypotheses have different clinical implications, since DRESS typically requires drug continuation, whereas the cytokine-plasticity hypothesis suggests instead that interventions that counter pathogenic T cell skewing could be therapeutic [17]. Consequently, clinical concerns are increasingly raised about the occurrence of lung involvement in Still's disease, thus suggesting the need of further studies to fully elucidate this issue also considering the management of these patients.

On these bases, in this work, we aimed to assess the clinical characteristics of patients with Still's disease and lung involvement. In addition, possible associated factors with parenchymal lung involvement were evaluated in a multicenter observational study.

Methods

Patients, variables to be assessed and study design

A multicenter observational study was arranged assessing consecutive patients with Still's disease characterized by the lung involvement among those included in the AIDA (AutoInflammatory Disease Alliance) Network Still's Disease Registry. This is an international, clinical, physician-driven, non-population, and electronic-based dataset involving both children and adults [18-22]. In all patients, other inflammatory diseases, malignancies, and infections were ruled out as elsewhere better detailed [8,15,23]. Specifically, after having excluded all these possible alternative causes, especially the infectious ones comprising COVID-19, the patients were codified with lung involvement as we previously performed [15,16].

Still's disease-lung involvement was defined according to the presence of pleuritis, parenchymal features, acute respiratory distress syndrome (ARDS), and/or pulmonary arterial hypertension. In the patients with the suspicion of parenchymal lung involvement, a chest CT scan was performed, and retrieved features codified according to the available literature in different main patterns: i. multilobar, predominantly peripheral septal thickening, parahilar and/or anterior upper lobes with or without

adjacent ground glass opacities; ii. crazy-paving; iii. peripheral consolidations; iv. peribronchovascular consolidations, and iv. predominantly ground-glass opacities [10,11,15]. The CT scans were locally red, and we collected what reported in the clinical chart of patients and data included in the registry. ARDS was defined according to what reported in clinical charts of patients and available literature [24]. Patients were codified as having ARDS if CT scans showed that the acute exudative lesions were not randomly distributed but had a gravitationally dependent gradient, with more consolidation in the postero-basal regions [25]. Pulmonary arterial hypertension was defined according to what reported in the registry and available literature [26]. Considering the "real-life" nature of our study, a measurement bias may indeed occur in the collection of these data, which we tried to minimize by a careful definition of those findings to be collected. CT scans of chest were not available in all patients; CT scans were mainly performed in adult patients since considered a routine workup in the context of fever of unknow origin requiring advanced diagnostic tests [27]. In patients without CT scan, the identification of the lung involvement was based on chest X-ray and clinical observations collecting what recorded in patient clinical chart. This difference may also reflect the diversities in healthcare utilization and access which could be encountered in a worldwide study like AIDA network.

In addition, at the time of assessment, the following parameters were registered: fever, typical or atypical skin rash, arthralgia or arthritis, myalgia, lymphadenopathy, sore throat, splenomegaly, hepatomegaly or abnormal liver function tests, abdominal pain, and sore throat. These clinical signs were combined to derive the systemic score [23]. Furthermore, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and ferritin, were recorded. In addition to lung involvement, each patient was assessed, where appropriate, for the presence of Still's disease-related complications, including MAS which was codified according to the diagnostic criteria proposed by the available literature [23,28]. The administration of therapies, GCs, csDMARDs, and bDMARDs, was also registered and categorized based on medications administered to each patient as previously described [8,15,23]. In case of sequential therapy, the drug administered for the longest time was considered. In the subsequent follow-up, according to the disease course, patients were categorized into four groups: either one of three clinical patterns (monocyclic, polycyclic, chronic) or death, whichever the course [25]. Specifically, a monocyclic pattern was defined as a single episode lasting > 2 months but < 12 months, followed by sustained remission through the whole follow-up period

without any medication [29]. This definition was used to codify patients achieving and maintain the clinical remission.

Data of patients were recorded during the scheduled visits between January 2020 and January 2024. Relevant data were collected by reviewing clinical charts, which were stored in each of the involved centers. Due to the "real-life" nature of our study, no specific sample size was estimated.

The Ethics Committee of *Azienda Ospedaliero-Universitaria Senese*, Siena, Italy, (Ref. N. 14951; NCT05200715) approved the study, which was performed according to the Good Clinical Practice guidelines and the latest Declaration of Helsinki. Written informed consent were collected from all patients. Clinical data were kept in accordance with the EU General Data Protection Regulations (GDPR), or other counterparts, on the processing of personal data and the protection of privacy (2016/679/EU). We followed the STROBE checklist in reporting the results.

Statistical analysis

Initially descriptive statistics were provided of the collected data. Dichotomous variables were expressed as percentage, whereas continuous variables as mean and standard deviation (SD) or median and range interquartile (IQR) based on their distribution. After that, clinical characteristics of patients were compared, according to the presence of parenchymal lung involvement, by either parametric or non-parametric t-tests for continuous variables, and Chi-squared test for categorical ones. Moreover, regression analyses were exploited to characterise patients with parenchymal lung involvement. The selection process of variables to be included in these models started by a univariate analysis of each item. Any variable having a significant univariate test was selected as a possible candidate for the multivariate analysis. Conversely, variables were excluded from the model if not significant unless a clinical relevance. At the end of this multistep process of deleting and refitting, age- and sex-adjusted multivariate models were built, providing OR estimations about the clinical risk profile of patients with the parenchymal lung involvement. Thus, multiple multivariate models were built considering the results of the univariate analysis but also the clinical relevance of some variables, possible confounders, and the number of patients with parenchymal lung involvement. Exploratively, univariate analyses were also exploited for ARDS; multivariate models were not built on this feature due to the number of patients with this complication. In all the analyses, the systemic score was assessed without the items "pleuritis" and "pneumonia" to avoid redundancy in the calculations. All these analyses were performed

considering the findings included in the registry at the time-point of data extraction. Due to the relatively simple study design, few retrieved missing data were managed by exclusion 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.

Results

Descriptive statistics of assessed patients with lung involvement

At the time of data extraction in February 2024, 413 patients were included in the AIDA network in total; out of these 16.0% were pediatric patients. In this study, 90 patients with Still's disease and lung involvement were thus assessed among those included in the AIDA network (mean age 36.3 ± 17.8 years, 35.6% male sex). All these patients were considering to be "active" according to the physicians in charge of their management. Among them, 13.3% of patients were paediatrics. Considering the time from the beginning of symptoms to the diagnosis, a mean duration was estimated to be 1.2 ± 0.8 years [median 6 months (range 3 months – 18 months)]. These patients with lung involvement mainly showed pleuritis in 72.2% of cases, parenchymal features in 34.4%, ARDS in 9.5%, and pulmonary arterial hypertension in 2.3%. The coexistence of parenchymal lung involvement and pleuritis was reported in 13 patients, the coexistence of ARDS and pleuritis in 4 patients. Parenchymal lung involvement and ARDS were simultaneously observed in 2 patients. Pulmonary arterial hypertension was reported in 2 patients without other lung features. Concerning the subset of paediatrics, 9 patients showed pleuritis, 6 parenchymal lung involvement, and 1 ARDS. CT scans of chest were available in 62 out of 90 patients, all patients with parenchymal lung involvement and ARDS underwent this diagnostic procedure. In patients without CT scan, the diagnosis of lung involvement was based on chest X-ray and clinical observations collecting what reported in patient clinical chart. Representative images of lung involvement are presented in Figure 1. Considering other main clinical characteristics, patients had arthralgia (83.3%), fever (80.0%), skin rash (62.2%), and liver involvement (50.0%). In this cohort, a significant increase of inflammatory markers was also observed ESR 81.6 ± 30.2 mm/h, and CRP 19.0 mg/L (IQR 34.6), and ferritin 1926.0 (IQR 11112.0) ng/ml. Furthermore, analysing therapies, 91.9% patients were treated with GCs, 69.3% with csDMARDs, and 63.6% with bDMARDs (mainly anti-IL1 and anti-IL-6). In regard to IL-1 inhibitors, 29 patients were specifically treated with anakinra whereas 17 with canakinumab. No anaphylactoid reactions were

described to bDMARDs before our assessment of the lung involvement in these patients with Still's disease. Moreover, 20.0% of these patients had MAS. Additional descriptive characteristics are reported in Table 1.

After that we focused on patients characterised by parenchymal lung involvement. Comparing clinical features of patients with parenchymal lung involvement than others, some differences were retrieved. Specifically, higher rate of sore throat (parenchymal lung involvement: 80.6% vs no parenchymal lung involvement: 49.2%, p=0.006) and pericarditis (parenchymal lung involvement: 45.8% vs no parenchymal lung involvement: 19.4%, p=0.02) was observed in these patients. Furthermore, patients with parenchymal lung involvement showed higher values of systemic score (parenchymal lung involvement: 7.3 ± 2.2 vs no parenchymal lung involvement: 6.3 ± 2.1, p=0.034) and an increased percentage showed a systemic score ≥ 7 (parenchymal lung involvement: 75.9% vs no parenchymal lung involvement: 51.7%, p=0.038). In all these analyses, the systemic score was assessed without the items "pleuritis" and "pneumonia" to avoid redundancy in the calculations. No other differences were retrieved analysing other clinical features, laboratory markers, and disease patterns. Finally, no significant differences were retrieved in terms of administered therapies, GCs, cs-, and bDMARDs.

Associated clinical factors with the parenchymal lung involvement

In our cohort, both univariate and multivariate regression models were built to evaluate patient clinical characteristics associated with the presence of parenchymal lung involvement in order to exploit a clinical risk profile. In univariate analyses, pericarditis (OR: 3.52, 95%CI: 1.26-9.83, p=0.017) and sore throat (OR: 4.31, 95%CI: 1.54-12.04, p=0.005) were significantly associated with the parenchymal lung involvement. Furthermore, the systemic score, at the time of evaluation, resulted significantly associated with presence of parenchymal lung involvement assessed both as continuous (OR: 1.28, 95%CI: 1.01-1.62, p=0.039) or dichotomic variable (systemic score ≥ 7) (OR: 2.93, 95%CI: 1.09-7.93, p=0.034). Based on the results of univariate analyses but also clinical relevance, clinical features were selected to build age- and sex-adjusted multivariate models. The latter were also built taking into consideration the number of assessed patients with parenchymal lung involvement. To date, sore throat (OR: 5.08, 95%CI: 1.73-14.93, p=0.03) and pericarditis (OR: 4.18, 95%CI: 1.39-12.52, p=0.01) were significantly associated with the parenchymal lung involvement. Furthermore, higher values of systemic score, assessed as continuous variable (OR: 1.27, 95%CI:

1.00-1.62, p=0.04), was associated with the presence of parenchymal lung involvement. Finally, the administration of both IL-1 or IL-6 inhibitors did not result to be associated with the presence of parenchymal lung involvement. These findings are reported in Table 2.

ARDS in patients with Still's disease

Eight patients were characterised by the presence of ARDS (5 female, mean age 38.4 ± 20.7); 6 out of these showed a concomitant MAS. All patients with ARDS had fever with a mean systemic score of 7.2 ± 3.1 in association with increases inflammatory markers: ESR 71.2 ± 13.5 mm/hr, CRP: 33.0 (108.5) mg/L, and ferritin 5250.0 (11523.0) ng/ml. All these patients were treated with GCs in combination with csDMARDs and bDMARDs, mainly IL-1 inhibitors. In these patients, univariate analyses were also exploited with explorative purposes considering the low number of patients. In univariate analyses, the occurrence of MAS resulted to be significantly associated with the presence of ARDS (OR: 16.0, 95%CI: 2.9-88.9, p=0.002). These findings are reported in Supplementary Table S1.

Discussion

In this study, assessing patients included in the AIDA network, we provided a clinical landscape of the lung involvement in Still's disease. In addition, associated factors with the parenchymal lung involvement were also analysed to provide a risk profile considering its emergent clinical relevance.

The most common patient feature of lung involvement was the presence of pleuritis in our assessment, followed by parenchymal features, ARDS, and less frequently pulmonary arterial hypertension. Pleuritis is an organ manifestation of patients with Still's disease, as reported in available cohorts [15,30-32]. This feature may be asymptomatic or may be recognised in the context of the life-threatening evolution of Still's disease [4,5]. In fact, in addition to other clinical factors, pleuritis is included in the systemic score which is a clinical tool to prognosticate the patients with Still's disease according to their possible higher risk of life-threatening evolution and poor prognosis [23].

In our cohort, almost 35.0% of patients with Still's disease showed the parenchymal lung involvement. The latter is an emerging cause of clinical concern in managing patients with Still's disease since it is associated with a poor prognosis in both children and adults [10-16]. To better describe these patients, we exploited a clinical risk profile

assessing potential associated factors with such manifestation. We retrieved that sore throat and pericarditis were associated with the presence of the parenchymal lung involvement. In Still's disease, sore throat is mainly related to cricoarytenoid joints inflammatory involvement and/or aseptic non-exudative pharyngitis. However, it could also indicate a possible infection in triggering the inflammatory process [33,34] and, although not fully clarified yet, the development of the parenchymal lung involvement. Pericarditis also predicted the presence of parenchymal lung involvement; this is a clinical feature which commonly accompanies the pleuritis during Still's disease. In addition, the smoking habit is associated with the presence of serositis considering both pleuritis and pericarditis [35]. This finding may suggest a possible common shared risk factor with parenchymal lung involvement to be carefully considered mostly in managing adult patients with Still's disease [35]. In fact, smoking habit may be a confounding factor in this context since represented in adult ages but not in paediatrics. Our analysis also showed that higher values of the systemic score and its cut-off ≥ 7 could be associated with the presence of parenchymal lung involvement. This is a prognostic clinical tool which identifies those patients with Still's disease at higher risk of life-threatening evolution [36,37]. In fact, the systemic score accurately discriminates a subset of patients with a poor prognosis over time, due to an increased risk of severe complications [36,37]. Differently from what previously reported [10,11], MAS appeared to be not associated with the parenchymal lung involvement and not a predictive factor of its presence in our cohort. However, we assessed all patients with lung involvement considering different pulmonary features which could be all associated with the occurrence of MAS. In addition, we did not show the association between the administration of bDMARDs and the parenchymal lung involvement. In this context, the first reports highlighted that anaphylactic reaction to bDMARDs could induce the development of parenchymal lung involvement also advocating suggestive pathogenic hypothesis [10,11,17]. These findings were not confirmed in our cohort. According to the "real-life" design, the therapies were not systematically administered limiting our analysis on this feature. In any case, considering their therapeutic relevance in Still's disease [38,39], further studies are needed to fully clarify this issue and the most appropriate administration of bDMARDs in these patients with lung involvement or at high risk of developing these manifestations. In fact, it remains to be established the most appropriate therapeutic management of patients with Still's disease and parenchymal lung involvement. Finally, further studies are needed to evaluate the long-

term consequences of parenchymal lung involvement towards a possible fibrotic evolution as recognised in other inflammatory diseases.

In our cohort, we also described 10% of patients with ARDS, a life-threatening condition characterized by poor oxygenation and "non-compliant" lungs [40]. This condition is usually associated with capillary endothelial injury, pulmonary artery vasoconstriction, and diffuse alveolar damage [41]. Once developed, these patients could be at higher risk of mortality since usually occurring in the context of multi-organ dysfunction and requiring intensive care admission [40,41]. Therefore, although less frequent, patients with Still's disease and lung involvement should be carefully managed in regard to possible ARDS occurrence. However, additional studies are necessary to entirely clarify the issue of ARDS and its predictive factors in Still's disease considering that is mainly described in case reports so far.

This study is no without limitations in reducing the generalizability of the results. Although we studied a large cohort of patients, multicenter studies may have some weaknesses due to the disparities in clinical practice between centers and access to healthcare resources, which could be even more evident in a worldwide registry as the AIDA Network. Furthermore, as AIDA network is an observational study, pulmonary function tests, lung biopsies, and specific biomarkers for parenchymal lung involvement (i.e., S100A8/A9, IL-18) were not collected. Furthermore, in our study, we did not evaluate the presence of HLA-DRB1*15 haplotypes. In a previous study, the DRESS-type reactions associated with parenchymal lung involvement were observed among patients with Still's disease treated with IL-1 or IL-6 inhibitors and were related to HLA-DRB1*15 haplotypes [42]. Our study was designed before the emergence of these features about parenchymal lung involvement, it involved mainly adults [10,11,42], and we registered what reported in the clinical patient charts and the relative details included in the registry. In addition, we did not evaluate recently synthetized red-flags and risk factors in pediatric patients [43]. This issue may suggest the need for future studies comparatively assessing pediatric and adult patients. Finally, in the present evaluation, we did not specifically investigate particular imaging-based differences, since they were previously described [44,45]. In addition, although reported in the description of the cohort, smoking habit and obesity were not added in the main analysis to avoid overlaps with previous studies specifically designed to investigate these features and their prognostic impact in patients with Still's disease [35,46]. Furthermore, studies with a longer follow-up are needed to entirely evaluate the possible fibrotic evolution of the parenchymal lung disease and its impact on disease

course of patients and their management. Taking together all these observations, our study should be considered as providing the basis for further specific designed studies to entirely investigate the clinical concerns about the parenchymal lung involvement in patients with Still's disease.

In conclusion, the clinical characteristics of patients with Still's disease and lung involvement were described in the AIDA network. We also provided a clinical profile of patients with parenchymal lung involvement considering its prognostic relevance. Sore throat, pericarditis, and systemic score resulted to be associated with the parenchymal lung involvement. Although providing a clinical landscape of these patients, further studies are needed to fully clarify this issue. In fact, it remains to be established the most appropriate management of patients with Still's disease and lung involvement as well as the long-term consequences of these manifestations.

Declarations

-Ethics approval and consent to participate:

The Ethics Committee of the *Azienda Ospedaliero-Universitaria Senese*, Siena, Italy (Ref. N. 14951; NCT05200715) approved the study, which was performed according to the Good Clinical Practice guidelines and the latest Declaration of Helsinki. Written informed consents for involved patients were collected. Clinical data are kept in accordance with the EU General Data Protection Regulations (GDPR), or other counterparts, on the processing of personal data and the protection of privacy (2016/679/EU).

-Consent for publication:

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

-Availability of data and material:

De-identified patient-level data can be available upon reasonable and pertinent research request to the AIDA network scientific committee via the corresponding author.

-Competing interests:

The authors have declared no conflicts of interest.

-Funding:

No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

-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:

From the International AIDA (AutoInflammatory Diseases Alliance) Network and from the Autoinflammatory Diseases Working Group of the Italian Society of Rheumatology (SIR).

This research is supported (not financially) by the European Reference Network (ERN) for Rare Immunodeficiency, Autoinflammatory and Autoimmune Diseases (RITA) of the authors of this publication [Antonio Vitale, Valeria Caggiano, Jurgen Sota, Elena Bargagli, Laura Calabrese, Pietro Rubegni, Carla Gaggiano, Maria Tarsia, Verónica Gómez-Caverzaschi, Micol Frassi, Paolo Sfriso, Claudia Fabiani, Maria Antonietta Mazzei, Alberto Balistreri, Bruno Frediani, Luca Cantarini] belong to institutes that are members of the ERN RITA [Azienda Ospedaliero-Universitaria Senese of Siena; Hospital Clínic of Barcelona; Spedali Civili of Brescia; University of Padua].

References

1. Ruscitti P, Cantarini L, Nigrovic PA, McGonagle D, Giacomelli R. Recent advances and evolving concepts in Still's disease. Nat Rev Rheumatol. 2024 Feb;20(2):116-132. doi: 10.1038/s41584-023-01065-6. Epub 2024 Jan 11. PMID: 38212542.

2. Ruscitti P, Natoli V, Consolaro A, Caorsi R, Rosina S, Giancane G, Naddei R, Di Cola I, Di Muzio C, Berardicurti O, Iacono D, Pantano I, Rozza G, Rossi S, De Stefano L, Balduzzi S, Vitale A, Caso F, Costa L, Prete M, Navarini L, Iagnocco A, Atzeni F, Guggino G, Perosa F, Cantarini L, Frediani B, Montecucco C, Ciccia F, Cipriani P, Gattorno M, Giacomelli R, Ravelli A. Disparities in the prevalence of clinical features between systemic juvenile idiopathic arthritis and adult-onset Still's disease. Rheumatology (Oxford). 2022 Oct 6;61(10):4124-4129. doi: 10.1093/rheumatology/keac027. PMID: 35078234; PMCID: PMC9536787.

3. Vitale A, Caggiano V, Lopalco G, Mayrink Giardini HA, Ciccia F, Almaghlouth IA, Ruscitti P, Sfikakis PP, Tufan A, Dagna L, Giacomelli R, Hinojosa-Azaola A, Ragab G, Direskeneli H, Fotis L, Sota J, Iannone F, Morrone M, de Brito Antonelli IP, Dagostin MA, Iacono D, Patrone M, Asfina K, Alanazi F, Di Cola I, Gaggiano C, Tektonidou MG, Kardas RC, Kucuk H, Campochiaro C, Tomelleri A, Navarini L, Berardicurti O, Martín-Nares E, Torres-Ruiz J, Mahmoud AAA, Alibaz-Oner F, Kourtesi K, Tarsia M, Sfriso P, Makowska J, Govoni M, La Torre F, Maggio MC, Monti S, Del Giudice E, Emmi G, Bartoloni E, Hernández-Rodríguez J, Gómez-Caverzaschi V, Maier A, Simonini G, Iagnocco A, Conti G, Olivieri AN, De Paulis A, Lo Gullo A, Viapiana O, Wiesik-Szewczyk E, Erten S, Ogunjimi B, Carubbi F, Tharwat S, Laskari K, Costi S, Triggianese P, Karamanakos A, Conforti A, Frassi M, Sebastiani GD, Gidaro A, Mauro A, Balistreri A, Fabiani C,

Frediani B, Cantarini L. Still's disease continuum from childhood to elderly: data from the international AIDA Network Still's disease registry. RMD Open. 2023 Dec 1;9(4):e003578. doi: 10.1136/rmdopen-2023-003578. PMID: 38053457; PMCID: PMC10693888.

4. Giacomelli R, Ruscitti P, Shoenfeld Y. A comprehensive review on adult onset Still's disease. J Autoimmun. 2018 Sep;93:24-36. doi: 10.1016/j.jaut.2018.07.018. Epub 2018 Aug 1. PMID: 30077425.

5. Feist E, Mitrovic S, Fautrel B. Mechanisms, biomarkers and targets for adult-onset Still's disease. Nat Rev Rheumatol. 2018 Oct;14(10):603-618. doi: 10.1038/s41584-018-0081-x. PMID: 30218025; PMCID: PMC7097309.

6. Di Cola I, Cipriani P, Ruscitti P. Perspectives on the use of non-biological pharmacotherapy for adult-onset Still's disease. Expert Opin Pharmacother. 2022 Oct;23(14):1577-1587. doi: 10.1080/14656566.2022.2126764. Epub 2022 Sep 22. PMID: 36124816.

7. Di Cola I, Ruscitti P. The latest advances in the use of biological DMARDs to treat Still's disease. Expert Opin Biol Ther. 2024 Jan-Feb;24(1-2):63-75. doi: 10.1080/14712598.2024.2307340. Epub 2024 Feb 4. PMID: 38284774.

8. Ruscitti P, Iacono D, Ciccia F, Emmi G, Cipriani P, Grembiale RD, Perosa F, Emmi L, Triolo G, Giacomelli R, Valentini G. Macrophage Activation Syndrome in Patients Affected by Adult-onset Still Disease: Analysis of Survival Rates and Predictive Factors in the Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale Cohort. J Rheumatol. 2018 Jun;45(6):864-872. doi: 10.3899/jrheum.170955. Epub 2018 Apr 15. PMID: 29657144.

9. McGonagle D, Ramanan AV, Bridgewood C. Immune cartography of macrophage activation syndrome in the COVID-19 era. Nat Rev Rheumatol. 2021 Mar;17(3):145-157. doi: 10.1038/s41584-020-00571-1. Epub 2021 Feb 5. PMID: 33547426; PMCID: PMC7863615.

10. Saper VE, Chen G, Deutsch GH, Guillerman RP, Birgmeier J, Jagadeesh K, Canna S, Schulert G, Deterding R, Xu J, Leung AN, Bouzoubaa L, Abulaban K, Baszis K, Behrens EM, Birmingham J, Casey A, Cidon M, Cron RQ, De A, De Benedetti F, Ferguson I, Fishman MP, Goodman SI, Graham TB, Grom AA, Haines K, Hazen M, Henderson LA, Ho A, Ibarra M, Inman CJ, Jerath R, Khawaja K, Kingsbury DJ, Klein-Gitelman M, Lai K, Lapidus S, Lin C, Lin J, Liptzin DR, Milojevic D, Mombourquette J, Onel K, Ozen S, Perez M, Phillippi K, Prahalad S, Radhakrishna S, Reinhardt A, Riskalla M, Rosenwasser N, Roth J, Schneider R, Schonenberg-Meinema D, Shenoi S, Smith JA, Sönmez HE, Stoll ML, Towe C, Vargas SO, Vehe RK, Young LR, Yang J, Desai T, Balise R, Lu Y, Tian L, Bejerano G, Davis MM, Khatri P, Mellins ED; Childhood Arthritis and Rheumatology

Research Alliance Registry Investigators. Emergent high fatality lung disease in systemic juvenile arthritis. Ann Rheum Dis. 2019 Dec;78(12):1722-1731. doi: 10.1136/annrheumdis-2019-216040. Epub 2019 Sep 27. Erratum in: Ann Rheum Dis. 2022 Feb;81(2):e35. PMID: 31562126; PMCID: PMC7065839.

11. Schulert GS, Yasin S, Carey B, Chalk C, Do T, Schapiro AH, Husami A, Watts A, Brunner HI, Huggins J, Mellins ED, Morgan EM, Ting T, Trapnell BC, Wikenheiser-Brokamp KA, Towe C, Grom AA. Systemic Juvenile Idiopathic Arthritis-Associated Lung Disease: Characterization and Risk Factors. Arthritis Rheumatol. 2019 Nov;71(11):1943-1954. doi: 10.1002/art.41073. Epub 2019 Oct 1. PMID: 31379071; PMCID: PMC6817389.

12. Wobma H, Arvila SR, Taylor ML, Lam KP, Ohashi M, Gebhart C, Powers H, Case S, Chandler MT, Chang MH, Cohen E, Day-Lewis M, Fishman MP, Halyabar O, Hausmann JS, Hazen MM, Lee PY, Lo MS, Meidan E, Roberts JE, Son MBF, Sundel RP, Dedeoğlu F, Nigrovic PA, Casey A, Chang J, Henderson LA. Incidence and Risk Factors for Eosinophilia and Lung Disease in Biologic-Exposed Children With Systemic Juvenile Idiopathic Arthritis. Arthritis Care Res (Hoboken). 2023 Oct;75(10):2063-2072. doi: 10.1002/acr.25129. Epub 2023 May 18. PMID: 37038961; PMCID: PMC10524230.

13. Lerman AM, Mahmud SA, Alfath Z, Langworthy BW, Hobday PM, Riskalla MM, Binstadt BA. HLA-DRB1*15 and Eosinophilia Are Common Among Patients With Systemic Juvenile Idiopathic Arthritis. Arthritis Care Res (Hoboken). 2023 Oct;75(10):2082-2087. doi: 10.1002/acr.25132. Epub 2023 May 15. PMID: 37052526; PMCID: PMC10524250.

14. Huang Y, Sompii-Montgomery L, Patti J, Pickering A, Yasin S, Do T, Baker E, Gao D, Abdul-Aziz R, Behrens EM, Canna S, Clark M, Co DO, Collins KP, Eberhard B, Friedman M, Graham TB, Hahn T, Hersh AO, Hobday P, Holland MJ, Huggins J, Lu PY, Mannion ML, Manos CK, Neely J, Onel K, Orandi AB, Ramirez A, Reinhardt A, Riskalla M, Santiago L, Stoll ML, Ting T, Grom AA, Towe C, Schulert GS. Disease course, treatments, and outcomes of children with systemic juvenile idiopathic arthritis associated lung disease (SJIA-LD). Arthritis Care Res (Hoboken). 2023 Sep 10. doi: 10.1002/acr.25234. Epub ahead of print. PMID: 37691306.

15. Ruscitti P, Berardicurti O, Iacono D, Pantano I, Liakouli V, Caso F, Emmi G, Grembiale RD, Cantatore FP, Atzeni F, Perosa F, Scarpa R, Guggino G, Ciccia F, Barile A, Cipriani P, Giacomelli R. Parenchymal lung disease in adult onset Still's disease: an emergent marker of disease severity-characterisation and predictive factors from Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale (GIRRCS) cohort of patients. Arthritis Res Ther. 2020 Jun 22;22(1):151. doi: 10.1186/s13075-020-02245-5. PMID: 32571407; PMCID: PMC7310010.

16. Ruscitti P, Bruno F, Berardicurti O, Acanfora C, Pavlych V, Palumbo P, Conforti A, Carubbi F, Di Cola I, Di Benedetto P, Cipriani P, Grassi D, Masciocchi C, Iagnocco A, Barile A, Giacomelli R. Lung involvement in macrophage activation syndrome and severe COVID-19: results from a cross-sectional study to assess clinical, laboratory and artificial intelligence-radiological differences. Ann Rheum Dis. 2020 Sep;79(9):1152-1155. doi: 10.1136/annrheumdis-2020-218048. Epub 2020 Jul 21. PMID: 32719039; PMCID: PMC7456556.

17. Binstadt BA, Nigrovic PA. The Conundrum of Lung Disease and Drug Hypersensitivity-like Reactions in Systemic Juvenile Idiopathic Arthritis. Arthritis Rheumatol. 2022 Jul;74(7):1122-1131. doi: 10.1002/art.42137. Epub 2022 May 29. PMID: 35413159; PMCID: PMC9367674.

18. Vitale A, Della Casa F, Lopalco G, Pereira RM, Ruscitti P, Giacomelli R, Ragab G, La Torre F, Bartoloni E, Del Giudice E, Lomater C, Emmi G, Govoni M, Maggio MC, Maier A, Makowska J, Ogunjimi B, Sfikakis PP, Sfriso P, Gaggiano C, Iannone F, Dagostin MA, Di Cola I, Navarini L, Ahmed Mahmoud AA, Cardinale F, Riccucci I, Paroli MP, Marucco EM, Mattioli I, Sota J, Abbruzzese A, Antonelli IPB, Cipriani P, Tufan A, Fabiani C, Ramadan MM, Cattalini M, Kardas RC, Sebastiani GD, Giardini HAM, Hernández-Rodríguez J, Mastrorilli V, Więsik-Szewczyk E, Frassi M, Caggiano V, Telesca S, Giordano HF, Guadalupi E, Giani T, Renieri A, Colella S, Cataldi G, Gentile M, Fabbiani A, Al-Maghlouth IA, Frediani B, Balistreri A, Rigante D, Cantarini L. Development and Implementation of the AIDA International Registry for Patients With Still's Disease. Front Med (Lausanne). 2022 Apr 7;9:878797. doi: 10.3389/fmed.2022.878797. PMID: 35463015; PMCID: PMC9021753.

19. Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H, Kashiwazaki S, Tanimoto K, Matsumoto Y, Ota T, et al. Preliminary criteria for classification of adult Still's disease. J Rheumatol. 1992 Mar;19(3):424-30. PMID: 1578458.

20. Fautrel B, Zing E, Golmard JL, Le Moel G, Bissery A, Rioux C, Rozenberg S, Piette JC, Bourgeois P. Proposal for a new set of classification criteria for adult-onset still disease. Medicine (Baltimore). 2002 May;81(3):194-200. doi: 10.1097/00005792-200205000-00003. PMID: 11997716.

21. Martini A, Ravelli A, Avcin T, Beresford MW, Burgos-Vargas R, Cuttica R, Ilowite NT, Khubchandani R, Laxer RM, Lovell DJ, Petty RE, Wallace CA, Wulffraat NM, Pistorio A, Ruperto N; Pediatric Rheumatology International Trials Organization (PRINTO). Toward New Classification Criteria for Juvenile Idiopathic Arthritis: First Steps, Pediatric Rheumatology International Trials Organization International Consensus. J Rheumatol. 2019 Feb;46(2):190-197. doi: 10.3899/jrheum.180168. Epub 2018 Oct 1. PMID: 30275259.

22. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, He X, Maldonado-Cocco J, Orozco-Alcala J, Prieur AM, Suarez-Almazor ME, Woo P; International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004 Feb;31(2):390-2. PMID: 14760812.

23. Ruscitti P, Cipriani P, Masedu F, Iacono D, Ciccia F, Liakouli V, Guggino G, Carubbi F, Berardicurti O, Di Benedetto P, Valenti M, Triolo G, Valentini G, Giacomelli R. Adult-onset Still's disease: evaluation of prognostic tools and validation of the systemic score by analysis of 100 cases from three centers. BMC Med. 2016 Dec 1;14(1):194. doi: 10.1186/s12916-016-0738-8. PMID: 27903264; PMCID: PMC5131497.

24. ARDS Definition Task Force; Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012 Jun 20;307(23):2526-33. doi: 10.1001/jama.2012.5669. PMID: 22797452.

25. Gattinoni L, Pesenti A. The concept of "baby lung". Intensive Care Med. 2005 Jun;31(6):776-84. doi: 10.1007/s00134-005-2627-z. Epub 2005 Apr 6. PMID: 15812622.

26. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, Carlsen J, Coats AJS, Escribano-Subias P, Ferrari P, Ferreira DS, Ghofrani HA, Giannakoulas G, Kiely DG, Mayer E, Meszaros G, Nagavci B, Olsson KM, Pepke-Zaba J, Quint JK, Rådegran G, Simonneau G, Sitbon O, Tonia T, Toshner M, Vachiery JL, Vonk Noordegraaf A, Delcroix M, Rosenkranz S; ESC/ERS Scientific Document Group. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022 Oct 11;43(38):3618-3731. doi: 10.1093/eurheartj/ehac237. Erratum in: Eur Heart J. 2023 Apr 17;44(15):1312. doi: 10.1093/eurheartj/ehad005. PMID: 36017548.

27. Haidar G, Singh N. Fever of Unknown Origin. N Engl J Med. 2022 Feb 3;386(5):463-477. doi: 10.1056/NEJMra2111003. PMID: 35108471.

28. Fardet L, Galicier L, Lambotte O, Marzac C, Aumont C, Chahwan D, Coppo P, Hejblum G. Development and validation of the HScore, a score for the diagnosis of reactive hemophagocytic syndrome. Arthritis Rheumatol. 2014 Sep;66(9):2613-20. doi: 10.1002/art.38690. PMID: 24782338.

29. Cush JJ, Medsger TA Jr, Christy WC, Herbert DC, Cooperstein LA. Adult-onset Still's disease. Clinical course and outcome. Arthritis Rheum. 1987 Feb;30(2):186-94. doi: 10.1002/art.1780300209. PMID: 3827959.

30. Gerfaud-Valentin M, Jamilloux Y, Iwaz J, Sève P. Adult-onset Still's disease. Autoimmun Rev. 2014 Jul;13(7):708-22. doi: 10.1016/j.autrev.2014.01.058. Epub 2014 Mar 19. PMID: 24657513.

31. Kalyoncu U, Solmaz D, Emmungil H, Yazici A, Kasifoglu T, Kimyon G, Balkarli A, Bes C, Ozmen M, Alibaz-Oner F, Erten S, Cagatay Y, Cetin GY, Yilmaz S, Yildiz F, Pamuk ON, Kucuksahin O, Kilic L, Yazisiz V, Karadag O, Koca SS, Hayran M, Akar S, Aksu K, Akkoc N, Keser G, Gonullu E, Kisacik B, Onat AM, Soy M, Inanc N, Direskeneli H, Sayarlioglu M, Erken E, Turgay M, Cefle A, Ertenli I, Pay S. Response rate of initial conventional treatments, disease course, and related factors of patients with adult-onset Still's disease: Data from a large multicenter cohort. J Autoimmun. 2016 May;69:59-63. doi: 10.1016/j.jaut.2016.02.010. Epub 2016 Mar 9. PMID: 26970681.

32. Zhao M, Wu D, Shen M. Adult-onset Still's disease with neurological involvement: a single-centre report. Rheumatology (Oxford). 2021 Sep 1;60(9):4152-4157. doi: 10.1093/rheumatology/keaa899. PMID: 33369675.

33. Gremese E, Tolusso B, Bruno D, Alivernini S, Ferraccioli G. Infectious agents breaking the immunological tolerance: The holy grail in rheumatoid arthritis reconsidered. Autoimmun Rev. 2022 Jun;21(6):103102. doi: 10.1016/j.autrev.2022.103102. Epub 2022 Apr 19. PMID: 35452849.

34. Berkun Y, Padeh S. Environmental factors and the geoepidemiology of juvenile idiopathic arthritis. Autoimmun Rev. 2010 Mar;9(5):A319-24. doi: 10.1016/j.autrev.2009.11.018. Epub 2009 Nov 22. PMID: 19932890.

35. Ruscitti P, Di Cola I, Berardicurti O, Conforti A, Iacono D, Pantano I, Rozza G, Rossi S, De Stefano L, Balduzzi S, Vitale A, Caso F, Costa L, Prete M, Navarini L, Atzeni F, Guggino G, Perosa F, Cantarini L, Frediani B, Montecucco C, Ciccia F, Giacomelli R, Cipriani P. Impact of smoking habit on adult-onset Still's disease prognosis, findings from a multicentre observational study. Clin Rheumatol. 2022 Mar;41(3):641-647. doi: 10.1007/s10067-021-05929-8. Epub 2021 Oct 11. Erratum in: Clin Rheumatol. 2022 Nov;41(11):3597. PMID: 34636022.

36. Ruscitti P, Masedu F, Vitale A, Caggiano V, Di Cola I, Cipriani P, Valenti M, Giardini HAM, Parente de Brito Antonelli I, Dagostin MA, Lopalco G, Iannone F, Maria M, Almaghlouth IA, Asfina KN, Ali HH, Ciccia F, Iacono D, Pantano I, Mauro D, Sfikakis PP, Tektonidou M, Laskari K, Berardicurti O, Dagna L, Tomelleri A, Tufan A, Kardas RC, Hinojosa-Azaola A, Martín-Nares E, Kawakami-Campos PA, Ragab G, Tharwat Hegazy M, Direskeneli H, Alibaz-Oner F, Fotis L, Sfriso

P, Govoni M, La Torre F, Maggio MC, Montecucco C, De Stefano L, Bugatti S, Rossi S, Makowska J, Del Giudice E, Emmi G, Bartoloni E, Hernández-Rodríguez J, Conti G, Olivieri AN, Lo Gullo A, Simonini G, Viapiana O, Wiesik-Szewczyk E, Erten S, Carubbi F, De Paulis A, Maier A, Tharwat S, Costi S, Iagnocco A, Sebastiani GD, Gidaro A, Brucato AL, Karamanakos A, Akkoç N, Caso F, Costa L, Prete M, Perosa F, Atzeni F, Guggino G, Fabiani C, Frediani B, Giacomelli R, Cantarini L. The systemic score may identify life-threatening evolution in Still's disease: data from the GIRRCS AOSD-study group and the AIDA Network Still's Disease Registry. Arthritis Rheumatol. 2024 Mar 18. doi: 10.1002/art.42845. Epub ahead of print. PMID: 38499989.

37. Ruscitti P, Masedu F, Vitale A, Di Cola I, Caggiano V, Di Muzio C, Cipriani P, Valenti M, Berardicurti O, Navarini L, Iacono D, Pantano I, Mauro D, Ciccia F, Rossi S, De Stefano L, Monti S, Bugatti S, Montecucco C, Caso F, Costa L, Prete M, Perosa F, Iagnocco A, Atzeni F, Guggino G, Giardini H, Antonelli IPB, Almaghlouth IA, Asfina K, Direskeneli H, Alibaz-Oner F, Sevik G, Tufan A, Sfikakis PP, La Torre F, Hinojosa-Azaola A, Martín-Nares E, Torres-Ruiz J, Ragab G, Maggio MC, Makowska J, Del Giudice E, Bartoloni E, Emmi G, Govoni M, Lo Gullo A, Lopalco G, Simonini G, Fotis L, Ogunjimi B, Tharwat S, Frediani B, Maier A, Carubbi F, Dagna L, Erten S, Gidaro A, Hernández-Rodríguez J, Sfriso P, Fabiani C, Giacomelli R, Cantarini L. Derivation and validation of four patient clusters in Still's disease, results from GIRRCS AOSD-study group and AIDA Network Still Disease Registry. RMD Open. 2023 Nov;9(4):e003419. doi: 10.1136/rmdopen-2023-003419. PMID: 37989322; PMCID: PMC10660445.

38. Giacomelli R, Caporali R, Ciccia F, Colafrancesco S, Dagna L, Govoni M, Iannone F, Leccese P, Montecucco C, Pappagallo G, Pistone G, Priori R, Ruscitti P, Sfriso P, Cantarini L; Expert Panel. Expert consensus on the treatment of patients with adult-onset still's disease with the goal of achieving an early and long-term remission. Autoimmun Rev. 2023 Dec;22(12):103400. doi: 10.1016/j.autrev.2023.103400. Epub 2023 Jul 22. PMID: 37482365.

39. Ruscitti P, McGonagle D, Garcia VC, Rabijns H, Toennessen K, Chappell M, Edwards M, Miller P, Hansell N, Moss J, Graziadio S, Feist E. Systematic review and meta-analysis of pharmacological interventions in adult-onset Still's disease highlights the beneficial role of biologic DMARDs. J Rheumatol. 2024 Feb 1:jrheum.2023-0995. doi: 10.3899/jrheum.2023-0995. Epub ahead of print. PMID: 38302170.

40. Matthay MA, Zemans RL, Zimmerman GA, Arabi YM, Beitler JR, Mercat A, Herridge M, Randolph AG, Calfee CS. Acute respiratory distress syndrome. Nat Rev Dis Primers. 2019 Mar 14;5(1):18. doi: 10.1038/s41572-019-0069-0. PMID: 30872586; PMCID: PMC6709677.

41. Fan E, Brodie D, Slutsky AS. Acute Respiratory Distress Syndrome: Advances in Diagnosis and Treatment. JAMA. 2018 Feb 20;319(7):698-710. doi: 10.1001/jama.2017.21907. PMID: 29466596.

42. Saper VE, Ombrello MJ, Tremoulet AH, Montero-Martin G, Prahalad S, Canna S, Shimizu C, Deutsch G, Tan SY, Remmers EF, Monos D, Hahn T, Phadke OK, Cassidy E, Ferguson I, Mallajosyula V, Xu J, Rosa Duque JS, Chua GT, Ghosh D, Szymanski AM, Rubin D, Burns JC, Tian L, Fernandez-Vina MA, Mellins ED, Hollenbach JA; Drug Hypersensitivity Consortium; INCHARGE Consortium. Severe delayed hypersensitivity reactions to IL-1 and IL-6 inhibitors link to common HLA-DRB1*15 alleles. Ann Rheum Dis. 2022 Mar;81(3):406-415. doi: 10.1136/annrheumdis-2021-220578. Epub 2021 Nov 17. PMID: 34789453; PMCID: PMC10564446.

43. Wobma H, Bachrach R, Farrell J, Chang MH, Day-Lewis M, Dedeoglu F, Fishman MP, Halyabar O, Harris C, Ibanez D, Kim L, Klouda T, Krone K, Lee PY, Lo MS, McBrearty K, Meidan E, Prockop SE, Samad A, Son MBF, Nigrovic PA, Casey A, Chang JC, Henderson LA. Development of a Screening Algorithm for Lung Disease in Systemic Juvenile Idiopathic Arthritis. ACR Open Rheumatol. 2023 Oct;5(10):556-562. doi: 10.1002/acr2.11600. Epub 2023 Sep 8. PMID: 37688362; PMCID: PMC10570670.

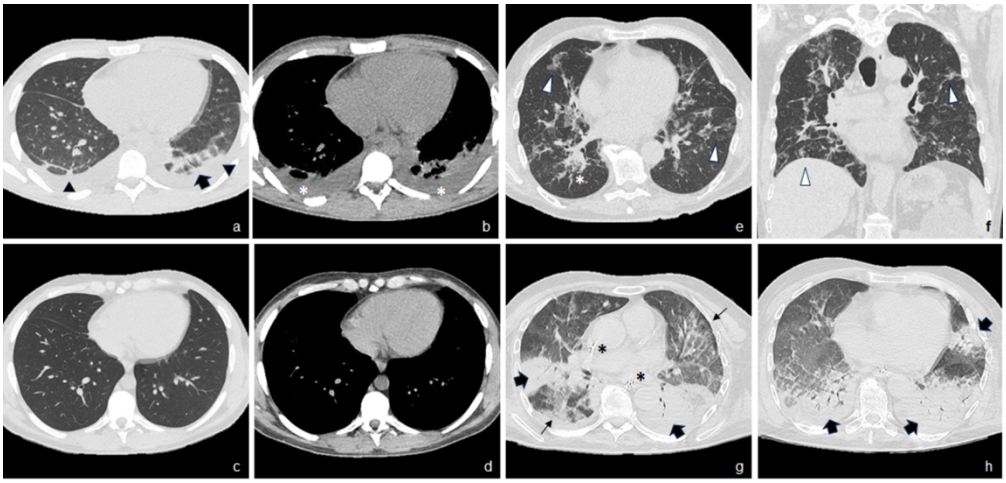
44. Di Cola I, Bruno F, Berardicurti O, Monti R, Conforti A, Di Sibio A, Pavlych V, Masciocchi C, Barile A, Cipriani P, Ruscitti P. Evaluating the multivisceral involvement on adult-onset Still's disease to retrieve imaging-based differences in patients with and without macrophage activation syndrome: results from a single-centre observational study. Clin Rheumatol. 2021 Oct;40(10):3971-3978. doi: 10.1007/s10067-021-05727-2. Epub 2021 Apr 14. PMID: 33855668.

45. Wang R, Li T, Ye S, Tan W, Zhao C, Li Y, de Bao C, Fu Q. Macrophage activation syndrome associated with adult-onset Still's disease: a multicenter retrospective analysis. Clin Rheumatol. 2020 Aug;39(8):2379-2386. doi: 10.1007/s10067-020-04949-0. Epub 2020 Mar 4. PMID: 32130578.

46. Di Cola I, Iacono D, Pantano I, Mauro D, Vitale A, Caso F, De Stefano L, Prete M, Navarini L, Ciaffi J, Ursini F, Costa L, Perosa F, Montecucco C, Cantarini L, Frediani B, Ciccia F, Giacomelli R, Cipriani P, Ruscitti P. Clinical characteristics of obese patients with adult-onset Still's disease. Data from a large multicentre cohort. Joint Bone Spine. 2023 Sep;90(5):105576. doi: 10.1016/j.jbspin.2023.105576. Epub 2023 Apr 18. PMID: 37080283.

Figure legend.

Figure 1. Patients with AOSD may exhibit different pattern of lung involvement. Usually, it consists of pleural effusion or transient pulmonary infiltrates. Images from A to D show the axial views of a patient with a transient pulmonary lung involvement. Notably, thick black arrows show a focal consolidation (high density area with preserved air bronchogram). White asterisks highlight bilateral pleural effusion. Black arrowheads show patchy areas of atelectasis. Images C and D show full recovery at 1 month CT follow-up. However, pulmonary lung involvement may become life threatening possibly progressing to acute respiratory distress syndrome (ARDS). Images from E to H show the evolution of a patient with Still's disease to ARDS. Images E and F show the early presentation of lung involvement in patients with bilateral patchy areas of ground glass opacities (GGOs) (white arrowheads), which appear confluent in some cases (image E: white asterisk). After 2 weeks, the patient was admitted to intensive care unit for ARDS. Images G and H show bilateral dense consolidations (thick black arrows), GGOs and intralobular septal thickening in a «crazy-paving» pattern (thin black arrows). Given the patient's poor condition, central venous catheter and nasogastric tube were placed (black asterisks).



73x35mm (600 x 600 DPI)

Table 1. Clinical descriptive characteristics of assessed cohort of Still's disease and comparisons between patients with and without parenchymal lung involvement.

Clinical characteristics	90 assessed patients	59 without parenchymal lung involvement	31 with lung parenchymal involvement	p-value
Demographic features				
Male sex (%)	35.6	33.9	38.7	0.652
Age, years, mean ± SD	36.3 ± 17.8	36.6 ± 18.1	35.7 ± 17.5	0.813
BMI, median (IQR)	20.9 (18.2)	21 (20.1)	19.8 (16.8)	0.974
Smoking habit (%)	20.0%	18.6%	22.6%	0.459
Clinical characteristics				
Fever (%)	80.0	81.4	77.4	0.782
Arthralgia (%)	83.3	79.7	90.3	0.245
Arthritis (%)	42.2	35.6	54.8	0.115
Skin Rash (%)	62.2	57.6	71.0	0.257
Atypical rash (%)	28.4	26.3	32.3	0.624
Sore throat (%)	60.0	49.2	80.6	**0.006**
Pericarditis (%)	36.7	19.4	45.8	**0.021**
Liver involvement (%)	50.0	49.2	51.6	1.000
Splenomegaly (%)	38.9	37.3	41.9	0.820
Lymphadenopathy (%)	52.2	47.5	61.3	0.269
Myalgia (%)	61.1	54.2	74.2	0.073
Abdominal pain (%)	20.0	15.3	29.0	0.166
Systemic score, mean ± SD	6.6 ± 2.2	6.3 ± 2.1	7.3 ± 2.2	**0.034**
Systemic score ≥ 7 (%)	59.8	51.7	75.9	**0.038**
MAS (%)	20.0	18.6	22.6	0.782
Laboratory markers				
ESR, mm/h, mean ± SD	81.6 ± 30.2	85.0 ± 31.2	74.6 ± 27.4	0.189
CRP, mg/dL, median (IQR)	19.0 (34.6)	24 (52.0)	15.3 (15.4)	0.431
Ferritin, ng/ml (IQR)	1926.0 (11112.0)	2300.0 (14272.0)	1861.0 (9337.8)	0.171
Leucocytosis ≥ 15,000 mm^3 (%)	73.3	72.9	74.2	1.000
Therapies				
Glucocorticoids (%)	91.9	92.9	90.0	0.691
csDMARDs (%)	69.3	71.9	64.5	0.479
Methotrexate (%)	51.1	55.9	41.9	0.268
bDMARDs (%)	63.6	59.6	71.0	0.357
IL-1 inhibitor (%)	51.1	45.8	61.3	0.188
Duration of IL-1 inhibitor therapy, months, median (IQR)	12.5 (20.5)	11.7 (18.5)	13.0 (21.6)	0.758
IL-6 inhibitor (%)	15.6	13.6	19.4	0.545
Duration of IL-6 inhibitor therapy	14.5 (25.0)	17.0 (27.0)	9.8 (18.0)	0.345
Disease patterns and outcome				
Monocyclic pattern (%)	44.2	44.6	43.3	1.000

Chronic pattern (%)	9.4	10.7	6.9	0.710
Polycyclic pattern (%)	23.5	23.2	24.1	1.000
Mortality (%)	2.2	1.7	3.2	1.000

Abbreviations: BMI: body mass index, MAS: macrophage activation syndrome, SD: standard deviation, IQR: range interquartile, ESR: erythrocyte sedimentation rate, CRP: C reactive protein, csDMARDs: conventional synthetic disease modifying anti rheumatic drugs, bDMARDs: biologic disease modifying antirheumatic drugs, IL: interleukin.
Bold font highlights significant results.

Table 2. Regression analyses exploiting the clinical risk profile of parenchymal lung involvement in assessed cohort of patients with Still's disease

Clinical Variables	OR	95% CI	p-value
Parenchymal lung involvement			
Univariate analyses			
Age	0.98	0.97-1.02	0.810
Male sex	1.23	0.50-3.03	0.651
Fever	0.77	0.27-2.28	0.658
Arthralgia/arthritis	2.14	0.55-8.33	0.273
Skin Rash	1.78	0.71-4.56	0.217
Atypical rash	1.33	0.51-3.47	0.555
Sore throat	4.31	1.54-12.04	**0.005**
Pericarditis	3.52	1.26-9.83	**0.017**
Liver involvement	1.10	0.46-2.63	0.824
Splenomegaly	1.22	0.50-2.95	0.668
Lymphadenopathy	1.75	0.72-4.25	0.214
Myalgia	2.43	0.94-6.30	0.069
Abdominal pain	2.27	0.79-6.50	0.126
Systemic score*	1.28	1.01-1.62	**0.039**
Systemic score ≥7**	2.93	1.09-7.93	**0.034**
MAS	1.27	0.44-3.67	0.658
ESR	0.99	0.97-1.00	0.189
CRP	0.99	0.99-1.00	0.438
Ferritin	1.02	0.97-1.06	0.376
Leucocytosis ≥ 15,000 mm^3	1.07	0.40-2.87	0.894
Glucocorticoids	0.69	0.14-3.32	0.646
csDMARDs	0.71	0.28-1.80	0.472
Methotrexate	0.57	0.24-1.37	0.209
IL-1 inhibitor	1.88	0.77-4.55	0.164
IL-6 inhibitor	1.53	0.48-4.89	0.473
Monocyclic pattern	0.95	0.39-2.32	0.907
Chronic pattern	0.62	0.12-3.27	0.571
Polycyclic pattern	1.05	0.37-3.02	0.924
Mortality	1.90	0.12-31.46	0.654
Multivariate analysis			
Age	0.99	0.97-1.03	0.959
Male sex	1.09	0.40-2.99	0.870
Sore throat	5.08	1.73-14.93	**0.003**
Pericarditis	4.18	1.39-12.52	**0.011**
Multivariate analysis			
Age	0.99	0.97-1.02	0.741

Male sex	1.05	0.41-2.74	0.916
Systemic score	1.27	1.02-1.62	**0.047**
MAS	0.87	0.27-2.76	0.812
Multivariate analysis			
Age	1.01	0.98-1.03	0.871
Male sex	1.21	0.48-3.04	0.692
IL-1 inhibitor	2.04	0.81-5.13	0.130
IL-6 inhibitor	1.74	0.51-5.97	0.377

Abbreviations: OR: odds ratio, CI: confidence interval, MAS: macrophage activation syndrome, ESR: erythrocyte sedimentation rate, CRP: C reactive protein, csDMARDs: conventional synthetic disease modifying anti rheumatic drugs, bDMARDs: biologic disease modifying antirheumatic drugs, IL: interleukin.

*systemic score assessed as continuous variables; **systemic score assessed as dichotomic variable. Bold font highlights significant results.