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Title page

-Full title of manuscript:

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

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-A short running head title:

Systemic score in Still's disease

Abstract

-Objectives: To evaluate the clinical usefulness of the systemic score in the prediction of life-threatening evolution in Still's disease. To assess the clinical relevance of each component of the systemic score in predicting life-threatening evolution and to derive patient subsets accordingly.

-Methods: A multicenter, observational, prospective study was designed including patients included in the GIRRCS (*Gruppo Italiano Di Ricerca in Reumatologia Clinica e Sperimentale*) AOSD-study group and AIDA (AutoInflammatory Disease Alliance) Network Still's Disease Registry. Patients were assessed if variables to derive the systemic score were available. The life-threatening evolution was defined as mortality, whichever the clinical course, and/or macrophage activation syndrome (MAS), a secondary hemophagocytic lymphohistiocytosis associated with a poor prognosis.

-Results: Totally 597 patients with Still's disease were assessed (age 36.6±17.3 years; male 44.4%). The systemic score, assessed as continuous variable, significantly predicted the life-threatening evolution (OR: 1.24, 95%CI:1.07–1.42; p=0.004). A systemic score ≥7 also significantly predicted the likelihood of a patient experiencing life-threatening evolution (OR: 3.36, 95%CI:1.81–6.25; p<0.001). Assessing the clinical relevance of each component of the systemic score, liver involvement (OR: 1.68, 95%CI:1.48–2.67; p=0.031) and lung disease (OR: 2.12, 95%CI:1.14–4.49; p=0.042) both significantly predicted life-threatening evolution. The clinical characteristics of patients with liver involvement and lung disease were derived, highlighting their relevance in multiorgan disease manifestations.

-Conclusion: The clinical utility of the systemic score was shown in identifying Still's disease at higher risk of life-threatening evolution in a large cohort. Furthermore, the clinical relevance of liver involvement and lung disease was highlighted.

Keywords

Still's disease; systemic juvenile idiopathic arthritis; adult-onset Still's disease; systemic score; macrophage activation syndrome.

Introduction

Still's disease is an inflammatory disorder typically manifesting with fever, arthritis, and salmon-colored skin rash affecting both children and adults [1,2]. It was formerly known as systemic juvenile idiopathic arthritis and adult-onset Still's disease, but multiple lines of evidence supported the concept of the Still's disease continuum, regarding genetic background, pathogenic findings by experimental murine disease models, clinical features, and clinical benefits to similar therapeutic strategies [1–3]. Concerning the pathogenesis of the disease, a multi-layer mechanistic model has been recently proposed at the crossroads of autoinflammatory and autoimmune disorders [3]. The consequent deregulated immune response leads to the development of Still's disease and its clinical features including cardinal manifestations, multi-organ involvement, and a typical hyperferritinemia [1,2]. Patients with Still's are variably treated with glucocorticoids (GCs), conventional synthetic disease modifying anti rheumatic drugs (csDMARDs), and biologic DMARDs (bDMARDs) [4,5]. Generally, in cases of failure of GCs or GC-dependence, csDMARDs or bDMARDs are administered to manage Still's disease [4,5]. Different patterns of disease course are recognized according to phases of flares and remission [1–3]. In addition, patients with Still's disease may be affected by the occurrence of life-threatening complications. The main concerning complication is macrophage activation syndrome (MAS), a secondary form of hemophagocytic lymphohistiocytosis (HLH) [6,7]. Patients with MAS are characterized by continuous high fever, hepatosplenomegaly, and marked hyperferritinemia, generally with the histological evidence of hemophagocytosis [6]. The development of MAS is associated with a poor prognosis, mainly in adult patients, due to the occurrence of cytokine storm syndrome, which is a hyperinflammatory state, together with multiorgan failure [7]. Prompt identification of MAS is therefore of crucial importance in facilitating the timely management of these patients with this life-threatening evolution. The clinical use of a systemic score has been suggested for identifying those patients at higher risk of MAS and mortality [8,9]. In fact, the systemic score may identify those patients at risk of a more severe outcome [8,9]. This prognostic tool was proposed by Pouchot et al. [8] to evaluate the systemic involvement of the disease by scoring the clinical manifestations of the patient clinical picture. It mainly evaluates the multi-organ involvement of Still's disease. In a previous retrospective study, we demonstrated that having higher systemic score values at the time of diagnosis was a predictor of subsequent poor outcomes associated with Still's disease-related mortality [9]. In addition, a score cut-off of 7.0 was derived to indicate patients with more aggressive disease [9]. Despite a

similar clinical picture at the beginning, a very different disease course is recognized in these high-scoring patients. This may indicate the importance of prognostic tools in identifying patients with more aggressive subsets of the disease, which could then guide the clinicians in applying additional resources in the care of these patients. Furthermore, following the identification of different clinical subsets, physicians could balance appropriate escalation of therapy to minimize exposure to iatrogenic harm and avoid unnecessary expenditures in patients with less severe disease. Thus, in this work, we aimed to evaluating the clinical usefulness of the systemic score in the prediction of life-threatening evolution in patients with Still's disease in a multicenter, observational, prospective study. We also assessed the clinical relevance of each component of the systemic score in predicting life-threatening evolution and derived clinical patient subsets accordingly.

Methods

Study design, patients, and settings

A multicenter, observational, prospective study was designed, including patients in the GIRRCS (*Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale*) AOSD-study group and the AIDA (AutoInflammatory Disease Alliance) Network Still's Disease Registry. Patients were included if specific variables for the derivation of systemic score, as detailed in Supplementary Table 1, were available to assess its predictive role in the emergence of a life-threatening evolution. The latter was defined as the development of MAS and/or mortality, whatever the clinical course. We also assessed the clinical relevance of each component of the systemic score in predicting the life-threatening evolution and derived patient subsets accordingly. Patients were assessed if an adequate follow-up of at least 12 months was available to evaluate different disease courses (detailed below). The GIRRCS AOSD-study group cohort is a national multicenter study involving rheumatologic units throughout Italy [9,10]. All units have extensive experience in management of Still's disease and in conducting observational studies. Furthermore, patients with Still's disease were selected from those included in AIDA Network Still's Disease Registry, an international, clinical, physician-driven, non-population, and electronic-based registry [11]. For centers included in both study groups, patients were considered only once to avoid duplication. Adult patients fulfilled the Yamaguchi criteria and/or Fautrel criteria and/or Cush criteria [12–14]. Pediatric patients fulfilled the International League of Associations for Rheumatology (ILAR) criteria for sJIA and/or the Pediatric Rheumatology INternational Trials Organization

(PRINTO) provisional criteria for sJIA [15,16]. Data of patients were recorded during the scheduled visits between January 2020 and June 2023. A flow-chart of the study design is reported in Figure 1.

The Ethics Committees of ASL1 *Avezzano-Sulmona-L'Aquila*, L'Aquila, Italy, (Ref. N. 0139815/16; 0095184/20) and 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 from all involved patients were collected. 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 when reporting the results (Supplementary Material 1).

Clinical work up

In all patients, other inflammatory diseases, malignancies, and infections were ruled out. The assessment at baseline excluded potential mimickers including infections, cancers, and other autoimmune or autoinflammatory diseases. We excluded infection by performing blood cultures and, in patients with MAS, bone marrow cultures, serology, PCR analyses, chest X-rays, and abdominal echography. We evaluated the possible differential diagnosis of malignancy using chest X-rays, abdominal ultrasound, and blood samples. Despite these exams, in the case of further suspicion, we added CT and/or PET/CT exams to the diagnostic workup. These additional investigations were mainly performed in adult patients, considering possible underlying hidden myelodysplastic syndrome or malignancy manifesting with a clinical picture similar to Still's disease. With regard to patients with possible hematologic cancers, we also performed bone marrow examination and lymph node biopsy. Other autoimmune diseases were excluded by blood tests, antinuclear antibodies, anti-citrullinated peptide autoantibodies, rheumatoid factor, and anti-neutrophil cytoplasmic antibodies, and for the exclusion of systemic vasculitides, we included tissue biopsy and arteriography in the workup. Finally, we evaluated, where appropriate, a possible differential diagnosis of autoinflammatory diseases by performing gene analyses according to clinical judgement.

Clinical variables to be assessed

The presence of the following clinical features, at the time of diagnosis, were recorded: fever, typical rash, arthralgia or arthritis, myalgia, lymphadenopathy, sore throat, splenomegaly, hepatomegaly or abnormal liver function tests, abdominal pain, sore throat, weight loss, and gastrointestinal symptoms. The diagnosis of pleural effusion or pleuritis, and lung parenchymal involvement was made by performing a chest radiograph or CT scan. After clinical examinations and chest radiographs, patients with clinical suspicion of pericarditis underwent echocardiography. Combining these features, each patient was also assessed by the systemic score [8,9]. This score assigns 1 point to each of 12 manifestations: fever, typical rash, pleuritis, pneumonia, pericarditis, hepatomegaly or abnormal liver function tests, splenomegaly, lymphadenopathy, leukocytosis > 15000/mm^3, sore throat, myalgia, and abdominal pain (maximum score: 12 points). More details of the systemic score are provided in Supplementary Table 1. Furthermore, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and ferritin were recorded at the time of diagnosis.

In addition, at the time of diagnosis and during each scheduled examination, each patient was assessed, where appropriate, for the presence of Still's disease-related complications including MAS, lung disease, thrombotic thrombocytopenic purpura, thrombotic microangiopathy, disseminated intravascular coagulopathy, respiratory distress syndrome, diffuse alveolar hemorrhage, pulmonary arterial hypertension, myocarditis, tamponade, constrictive pericarditis, endocarditis, shock, multiple organ failure, fulminant hepatitis, and amyloidosis, as suggested by the available literature [17–19]. MAS diagnosis was defined according to the diagnostic criteria proposed by the available literature [20–24]. Lung disease was defined as parenchymal lung involvement due to the disease, as previously reported [25,26]. In patients with a suspicion of lung involvement due to Still's disease, a chest CT scan was performed, and retrieved features codified according to the available literature in different main patterns of involvement: 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 [10,25,26].

The administration of therapies, GCs, csDMARDs, and bDMARDs, was also registered and categorized at the time of diagnosis and during follow-up, based on medications administered to each patient for the longest time-period, as previously described [27,28]. 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 [9,10,29]. As such, only patients with adequate prospective follow-up of at least 12 months were selected to enable identification of the different disease patterns. 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. A polycyclic pattern was defined by recurrent systemic flares with remission between the flares. A chronic pattern was defined as ≥ 1 episode of persistent symptoms lasting at least 12 months. Patients who died during follow-up were placed in the fourth group, which was categorized as death associated with Still's disease or its complications during the follow-up, whatever the clinical course.

Data sources, bias, and sample size

Relevant data were collected by reviewing clinical charts, which were stored in each of the involved centers, during the scheduled visits of each involved patient. All the data were fully anonymized before analysis. All data generated by the analysis is included in the body of the present work or uploaded as Supplementary Results. The Research Electronic Data Capture (REDCap) tool was employed to collect and store data for the AIDA Project, as detailed elsewhere [11].

Due to the observational design, this study may have been subject to a number of possible biases. We tried to minimize the main methodological problems by careful definition of each variable to be assessed. Furthermore, patients were removed if there was significant missing data considered to be meaningful for the analyses. Due to the "real-life" nature of our assessment, no specific sample size was estimated.

Statistical analysis

Initially, an explorative data analysis was carried out to explore the univariate frequency distributions of the categorical variables considered. The association between life-threatening evolution and components of the systemic score were tested using the χ^2 statistic to provide preliminary evidence of their possible association. Following this, the inferential part of the analysis was performed with two major goals. The first was to confirm the statistical significance of the systemic score in predicting life-threatening evolution using a larger cohort (n=597) than the previous validation study (n=100) [9]. There was no overlap between the cohorts of assessed patients in this and the previous validation study [9]. Although we did not estimate a specific target sample size, the available patient cohort permitted testing of the predictive role of the systemic score,

corroborating the results of the previous validation study [9]. Subsequently, an age- and sex-adjusted logistic regression using the Wald test was used to decide the statistical significance of the systemic score. The likelihood ratio test was performed, setting the type 1 error at 0.05, to assess the overall model fitting, which was found to be statistically significant ($p<0.001$). The second goal was to perform a risk profile assessment of the clinical variables used to calculate the systemic score on life-threatening evolution. Following this, ORs of specific components of the systemic score were estimated with the corresponding 95% confidence intervals (CIs) using the Woolf method. The continuous variable ORs were estimated using univariate logistic regressions. The analysis was performed using the statistical software STATA (StataCorp LLC, Copyright 1985-2021), version 17.

Results

Descriptive clinical characteristics of assessed patients with Still's disease

In this study, 597 patients with Still's disease were included and assessed (mean age 36.6 ± 17.3 years, male sex 44.4%), excluding from the analyses those with significant missing data (n=24), with inadequate follow-up (n=11), and presenting with MAS at the time of diagnosis (n=6), as shown in Figure 1. Among evaluated patients, 84 had a pediatric disease onset; patients of all ages were therefore assessed in our cohort. Histograms representing the percentages of evaluated patients according to age of onset are reported in Supplementary Figure 1.

As reported in Table 1, patient symptoms were mainly fever (100%), joint involvement (87.9%), including both arthralgia (84.1%) and arthritis (58.5%), and skin rash (66.1%). Multi-organ involvement was often observed, with lymphadenopathy in 49.6% of patients, hepatic involvement in 43.5%, and serositis, both pericarditis and pleuritis, in 16.5%. These patients were mostly treated with GCs (93.8%), csDMARDs was administered in 69.4%, and bDMARDs in 51.7%. Among the patients treated with bDMARDs, IL-1 inhibitors (anakinra and canakinumab) were mainly used (67.1%). An IL-6 inhibitor (tocilizumab) or TNF inhibitor was less frequently administered (29.4%, and 6.5%, respectively). These medications were given between 3 and 9 months (median 6 months) after the diagnosis of Still's disease in our cohort.

Regarding complications, MAS was reported in 13.1% of patients, whereas lung disease was reported in 6.9%. No other complications were recorded in addition to these. A mortality rate of 3.4% was registered in this cohort due to deaths related to Still's disease. Specifically, adult patients died due to multi-organ dysfunction associated with

uncontrollable MAS. No pediatric patients died during the follow-up period. Collectively, 89 patients out of 597 were codified as being in the life-threatening category (14.9%) due to MAS and/or mortality with any clinical course. The life-threatening evolution developed between 1 and 9 months (median 4 months) after the diagnosis of Still's disease in our cohort.

The systemic score as a predictor of life-threatening evolution in patients with Still's disease

To assess the prognostic role of the systemic score in our cohort of patients with Still's disease, multivariate logistic regression models were built on the likelihood of life-threatening evolution (MAS and/or mortality), as reported in Table 2. The value of the systemic score was assessed at the time of diagnosis of the disease to identify patients at higher risk of poor prognosis. The systemic score, assessed as continuous variable, was a significant predictor of life-threatening evolution (OR: 1.26, 95%CI: 1.11–1.42; p<0.001). Furthermore, in the multivariate analysis, the systemic score was a significant predictor of the life-threatening evolution in our cohort of patients with Still's disease (OR: 1.24, 95%CI: 1.07–1.42; p=0.004) when the model was adjusted for age, male sex, ESR, CRP, and ferritin. The latter features were added into the model as markers of disease severity. Considering the reported prognostic role of a systemic score of ≥ 7 on mortality in AOSD [9], systemic score was also tested as a dichotomy ("yes systemic score ≥ 7" / "no systemic score ≥ 7"). Patients characterized by a systemic score ≥ 7 had a significant higher probability of life-threatening evolution (OR: 3.64, 95%CI: 2.07–6.41; p<0.001). A systemic score ≥ 7 also significantly predicted the likelihood of life-threatening evolution in assessed patients (OR: 3.36, 95%CI: 1.81–6.25; p<0.001) when the model was adjusted for age, male sex, ESR, CRP, and ferritin. Thus, systemic score and its cut-off of ≥ 7, at the time of diagnosis, was found to be a prognostic clinical tool in delineating patients with a more aggressive subset of Still's disease characterized by a higher probability of life-threatening evolution.

We replicated this main analysis in the subset of pediatric patients considering the occurrence of MAS, as no deaths were registered (84 patients, of whom 21 developed MAS). Although not significant, a trend may be observed in the regression analysis of the systemic score as a predictor of life-threatening evolution (Supplementary Table 2). We also evaluated the predictive role of the systemic score on the different possible disease patterns. The systemic score predicted the mortality of our patients regardless of clinical course (Supplementary Table 3). Finally, we performed a multivariate

regression model to evaluate the impact of therapies, both csDMARDs and bDMARDs, on life-threatening evolution, but non-significant results were obtained (Supplementary Table 4). We also evaluated the impact of csDMARDs and bDMARDs on different disease courses by multinomial regression models. Both csDMARDs and bDMARDs were more frequently associated with polycyclic, chronic disease courses, and increased mortality when compared with the monocyclic pattern (Supplementary Table 5).

Lung disease and liver involvement significantly predicted the life-threatening evolution of Still's disease

In this study, a risk profile assessment was also performed on life-threatening evolution using the clinical variables used to calculate the systemic score. Male sex and arthritis were also included as variables, whereas fever was excluded as it was recorded in all patients. Univariate analyses suggested that liver involvement (p=0.012), abdominal pain (p=0.021), and lung disease (p=0.008) were significant predictors of life-threatening evolution in our cohort of patients with Still's disease when recorded at the time of diagnosis. Other clinical variables were not found to be significant predictors of life-threatening evolution. Based on these findings, an age- and male sex-adjusted multivariate logistic regression model was built accordingly. The presence of liver involvement (OR: 1.68, 95%CI: 1.48–2.67; p=0.031) at the time of diagnosis significantly predicted life-threatening evolution. Similarly, lung disease (OR: 2.12, 95%CI: 1.14–4.49; p=0.042) was found to be a predictor of life-threatening evolution in our cohort. Despite the trend, abdominal pain was not significantly associated with this outcome. These results are summarized in Table 3. Thus, within the variables included in the systemic score, liver involvement and lung disease appeared to be independently associated with life-threatening evolution in patients with Still's disease.

Clinical characteristics of patients with Still's disease characterized by lung disease and liver involvement

According to the previous results, the clinical characteristics of patients with liver involvement and lung disease were also derived. These findings are summarized in Table 4. Patients with liver involvement had more likely lymphadenopathy (OR: 1.80, 95%CI: 1.29–2.51; p=0.001) and splenomegaly (OR: 5.37, 95%CI: 3.74–7.72; p<0.0001). Furthermore, the presence of a form of serositis, both pericarditis (OR: 2.01, 95%CI: 1.29–3.13; p=0.001) and pleuritis (OR: 2.43, 95%CI: 1.55–3.80; p=0.001), was significantly associated with the presence of hepatic disease. In addition,

these patients with liver involvement were significantly burdened by lung disease (OR: 2.15, 95%CI:1.12–4.11; p=0.018).

Patients with lung disease had more likely sore throat (OR: 2.52, 95%CI: 1.21–5.24; p=0.010), lymphadenopathy (OR: 2.32, 95%CI: 1.17–4.57; p=0.013), splenomegaly (OR: 2.02, 95%CI: 1.07–3.83; p=0.028), and liver involvement (OR: 2.14, 95%CI: 1.12–4.11; p=0.019). Furthermore, patients with lung disease had an increased frequency of pericarditis (OR: 3.74, 95%CI: 1.91–7.32; p=0.001), pleuritis (OR: 6.52, 95%CI: 3.37–12.60; p=0.001), and abdominal pain (OR: 4.13, 95%CI: 2.05–8.30; p=0.001). Finally, patients with lung disease had a higher mortality rate (OR: 3.62, 95%CI: 1.15–11.41; p=0.019).

Discussion

In this study, the clinical usefulness of the systemic score, assessed at the time of diagnosis of Still's disease, was shown in identifying patients at higher risk of life-threatening evolution. We used data from a large cohort of patients from the GIRRCS AOSD-study group and the AIDA Network Still's Disease Registry. Furthermore, the assessment of components comprised in the systemic score highlighted the clinical relevance of liver involvement and lung disease, and patient subsets were derived accordingly. These features may indicate a subset of patients with more aggressive Still's disease who have a higher probability of life-threatening evolution. When compared with the previous validation study [9], the present study included a larger cohort of patients, thus numerically reinforcing the strength of our analysis. In addition, the previous evaluation was burdened by a retrospective study design and it only included adult patients. Conversely, we prospectively involved patients from all ages included in the GIRRCS AOSD-study group and AIDA Network Still's Disease Registry.

According to our results, higher values of the systemic score at the time of diagnosis strongly predicted life-threatening evolution, due to MAS and/or mortality, in Still's disease, allowing identification of a more severe patient subset. Our data may suggest that multi-organ involvement, assessed by systemic score at the time of disease diagnosis, is predictive of a more severe outcome and increased mortality in these patients [9,10,30]. Consequently, a clinical tool may be proposed for prompt identification of those patients who require careful management due to being frequently burdened by MAS and/or poor outcomes. Of note, the clinical variables needed to derive the systemic score are usually all included in the clinical work up of patients with suspected Still's disease. Clinicians could therefore have clinically relevant information

to inform future risk of poor outcomes at the time of disease diagnosis, allowing stratification of the patient clinical risk profile. Our data also highlighted the systemic score cut-off of ≥ 7 as predictive of life-threatening evolution of Still's disease. This threshold of the systemic score may be readily applied in clinical practice to identify those patients with a higher likelihood of a more severe clinical course and poor outcome. The importance of an accurate clinical evaluation and prognostication of patient clinical picture is therefore reinforced by our findings. The relevance of the multi-organ involvement of the disease is directly related to the development of a severe hyper-inflammatory state, which is linked to cytokine-induced tissue damage, acute-phase physiological changes, and aberrant immune cell-mediated responses [31,32]. As recently reported in points to consider about management of MAS [33], the timely recognition of the development of this complication is of crucial importance in improving the outcome of these patients, as the immunosuppressive therapeutic strategy could be simultaneously administered with diagnostic evaluations [33]. In addition, a large percentage of patients with Still's disease, both children and adults, may require admission to an intensive care unit due to MAS and associated multi-organ dysfunction [34–36]. Although intensive care procedures have improved the survival of critical care patients, a cohort of chronically critically ill patients has consequently emerged which is characterized by increased long-term morbidity and mortality, and greater utilization of healthcare resources [37]. Early identification of patients with Still's disease at higher risk of life-threatening evolution is therefore increasing required, highlighting the importance of prognostic tools such as the systemic score to improve outcomes over time.

When assessing the values of each component of the systemic score, our analysis showed the clinical relevance of liver involvement and lung disease in the context of multi-organ involvement in Still's disease. Both of these manifestations were predictors of life-threatening evolution. The presence of these features was linked with other multi-organ manifestations of patients. Both liver involvement and lung disease were associated with other clinical manifestations, suggesting a clinical patient profile to be managed.

Patients with Still's disease may have liver abnormalities such as hepatomegaly and increased hepatic enzyme values due to mild cytolysis [38]. During the disease course, liver function tests may correlate with disease activity and their persistent elevation may identify refractory patients [38]. Furthermore, prealbumin and albumin have been recently reported to be correlated with liver involvement and to negatively reflect the

disease activity of patients, possibly as part of the acute phase response [38]. However, a more severe involvement with substantial cytolysis and hepatic necrosis may occur in connection with a multi-organ failure syndrome [38,39]. Although liver involvement is frequently observed in Still's disease, it is quite heterogeneous. Non-specific histopathologic changes of liver involvement may be observed, also featuring hemophagocytosis [8,38]. Experimental models of HLH in association with the overproduction of cytokines have shown that hemophagocytosis may occur the in liver as well as in the bone marrow and lymph nodes [40,41]. Notably, patients with Still's disease and liver involvement have been reported to have an almost 6-fold higher risk of MAS than those without [29]. Furthermore, in a murine model of Still's disease, the excessive administration of ferritin induced liver inflammation, recapitulating the disease pathogenesis [42]. Liver dysfunction may also decrease procoagulant factor production, possibly precipitating disseminated intravascular coagulation, which may further complicate the management of these patients [18]. Taking together all of these observations, the importance of liver involvement in Still's disease may be suggested in connection with its life-threatening evolution, but the possible hepatoxicity of drugs administered to these patients must also be considered.

In our assessment, lung disease was also related to the life-threatening evolution of patients with Still's disease; however, unlike liver involvement, it also predicted mortality. Many studies have recently shown the association between lung disease, MAS, and a poor prognosis in patients with Still's disease [10,25,26,43]. A higher mortality rate has been reported in patients with Still's disease and lung involvement due to the occurrence of uncontrollable MAS [10,25,26,43]. Pulmonary disease has recently been associated with hyper-production of IL-1β, IL-6, IL-18, and IFN-γ supporting its relevance in the context of the pro-inflammatory burden of Still's disease and its evolution towards MAS [44,45]. Thus, the assessment of lung involvement appears to be of relevance in accurately stratifying the clinical risk profile of patients with Still's disease and their life-threatening evolution. In addition, considering the observed association with the use of both IL-1 and IL-6 inhibitors [25,26], lung involvement in Still's disease was proposed to develop due to a drug reaction with eosinophilia and systemic symptoms (DRESS) [46,47]. In this case, IL-1 and IL-6 inhibitors may act as antigens, or they may be presented by MHC class II to CD4+ T cells, leading to a Th2-predominant inflammatory response and predisposing to MAS and lung disease [47]. However, another possibility may be the "cytokine plasticity hypothesis" in which IL-1 and IL-6 inhibitors could change the cytokine inflammatory

environment by inducing IFN-γ–producing Th1 cells and/or IL-4–producing Th2 cells, consequently favoring MAS and lung disease [47]. Considering these findings, an accurate and continuous monitoring of the presence of lung disease should be carefully integrated into the management of patients with Still's disease by the assessment of clinical risk factors [48]. Furthermore, the role of pulmonary infections in possibly triggering the lung disease in these patients and favoring the evolution towards MAS remains to be fully elucidated.

Our assessment is affected by some limitations which limit the generalizability of the results. Although we assessed a combination of two large cohorts and only patients with a prospective follow-up were assessed, multicenter studies have some disadvantages regarding differences in clinical practice between centers, which may be a confounding factor in the interpretation of the derived findings. In addition, although Still's disease is more common in childhood, we assessed a majority of adult patients, suggesting that further studies in this patient subset are required. Furthermore, different therapeutic strategies were possibly applied in the management of patients with Still's disease in diverse involved centers according to multicenter study design. This may have an impact on both disease outcome and the development of life-threatening evolution in patients with Still's disease, demonstrating the need for specifically designed studies to address these issues. As the choice of specific medication to prescribe was left to the physicians in charge of the patients, patients with more severe disease may therefore have been more intensively treated, biasing the analyses on these features. In addition, the AIDA network is a worldwide international study which reflects differences in accessing some medications, thus limiting this kind of analysis on administered drugs. Finally, we did not specifically investigate laboratory features such as peripheral blood cytopenias, which have been recently assessed in other studies from the AIDA Network Still's Disease Registry [49,50]. Similarly, imaging-based differences in patients with Still's disease complicated or not by MAS have been previously investigated [51].

In conclusion, we have demonstrated the usefulness of the systemic score in recognizing those patients with Still's disease at higher risk of life-threatening evolution in a large cohort from the GIRRCS AOSD-study group and the AIDA Network Still's Disease Registry, thus providing a prognostic tool to be applied in clinical practice. In fact, the systemic score could be integrated into the management of Still's disease to appropriately identify patients at higher risk of life-threatening evolution and requiring a more careful management. Furthermore, the clinical relevance of liver involvement and lung disease was also highlighted for the multi-organ manifestations in patients,

and as major predictors of life-threatening evolution. Taking together these findings, a better clinical characterization and prognostication may improve the outcome of patients with Still's disease, paving the way for a more tailored management.

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Declarations

-Ethics approval and consent to participate:

The Ethics Committees of *ASL1 Avezzano-Sulmona-L'Aquila*, L'Aquila, Italy, (Ref. N. 0139815/16; 0095184/20) and 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 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:

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

-Competing interests:

The authors declare that they have no conflicts of interest for this work.

-Funding:

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-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.

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None.

Figure 1: Study Flow Chart

Table 1. Descriptive characteristics of assessed patients

Clinical characteristics	*597 patients*
Demographic features	
Age, years, mean ± sd	36.6 ± 17.3
Male sex, n (%)	265 (44.4)
Disease characteristics	
Fever, n (%)	597 (100.0)
Joint involvement, n (%)	525 (87.9)
Arthralgia, n (%)	502 (84.1)
Arthritis, n (%)	349 (58.5)
Skin Rash, n (%)	393 (66.1)
Sore throat, n (%)	333 (56.7)
Myalgia, n (%)	326 (55.3)
Lymphadenopathy, n (%)	293 (49.6)
Liver involvement, n (%)	257 (43.5)
Splenomegaly, n (%)	223 (37.7)
Pericarditis, n (%)	98 (16.5)
Pleuritis, n (%)	98 (16.5)
Abdominal pain, n (%)	75 (12.7)
Lung disease, n (%)	41 (6.9)
Systemic score, mean ± sd	5.2 ± 1.9
Systemic score ≥ 7, n (%)	73 (12.8)
MAS, n (%)	78 (13.1)
Laboratory markers	
CRP, mg/L, median (IQR)	40.0 (80.6)
ESR, mm/h, median (IQR)	72.0 (50.0)
Ferritin, ng/mL, median (IQR)	1319 (4074)
Ferritin ≥ 684 ng/mL, n (%)	505 (84.7)
Ferritin ≥ 1225 ng/mL, n (%)	393 (65.8)
WBC ≥ 15000 cells/mm^3, n (%)	369 (67.1)
Therapies	
GCs, n (%)	549 (93.8)
Low dosage of GCs, n (%)	254 (53.6)
csDMARDs, n (%)	406 (69.4)
bDMARDs, n (%)	298 (51.7)
Disease courses	
Monocyclic pattern, n (%)	251 (42.1)
Polycyclic pattern, n (%)	193 (32.2)
Chronic pattern, n (%)	133 (22.3)
Mortality, n (%)	20 (3.4)
Follow-up, years, median (IQR)	1.5 ± 0.3

Abbreviations: SD: standard deviation; IQR: interquartile range; CRP: C reactive protein; ESR: erythrocyte sedimentation rate; IQR: interquartile range; GCs: glucocorticoids; csDMARDs: conventional synthetic disease modifying anti rheumatic drugs; bDMARDs: biologic disease modifying anti rheumatic drugs

Table 2. Multivariate logistic regression models assessing the systemic score as predictor of life-threatening evolution in assessed patients.

Life-threatening evolution	OR	95%CI	p
Systemic score as predictor of life-threatening evolution			
Age and gender adjusted model			
Age	0.99	0.97-1.01	0.299
Male sex	1.09	0.68-1.76	0.719
Systemic score	**1.26**	**1.11-1.42**	**<0.001**
Age, gender, and laboratory markers adjusted model			
Age	0.99	0.98-1.01	0.530
Male sex	1.19	0.69-2.06	0.527
ESR	1.02	0.99-1.03	0.616
CRP	1.01	1.00-1.05	0.208
Ferritin	1.01	1.00-1.02	0.540
Systemic score	**1.24**	**1.07-1.42**	**0.004**
Systemic score ≥ 7 as predictor of life-threatening evolution			
Age and gender adjusted model			
Age	0.99	0.97-1.01	0.258
Male sex	1.04	0.64-1.69	0.858
Systemic score	**3.64**	**2.07-6.41**	**<0.001**
Age, gender, and laboratory markers adjusted model			
Age	0.99	0.98-1.09	0.433
Male sex	1.12	0.64-1.95	0.694
ESR	1.02	0.99-1.04	0.512
CRP	1.02	1.00-1.05	0.186
Ferritin	1.04	0.99-1.07	0.533
Systemic score ≥ 7	**3.36**	**1.81-6.25**	**<0.001**

Abbreviations: OR: odd ratio; 95%CI: 95% confidence interval; CRP: C reactive protein; ESR: erythrocyte sedimentation rate.

Footnote: ESR was assessed as mm/h, CRP as mg/L, and ferritin as ng/mL, respectively

Table 3. Univariate and multivariate regression analyses assessing systemic score components and life-threatening evolution

Life-threatening evolution	*506 patients without life-threatening evolution*	*89 patients with life-threatening evolution*	*Coefficient P values*
Univariate analyses assessing systemic score components and life-threatening evolution			
Male sex, n (%)	223 (43.9)	42 (46.7)	0.223/0.637
Arthritis, n (%)	295 (60.4)	54 (61.4)	0.026/0.872
Skin Rash, n (%)	331 (65.4)	62 (69.7)	0.609/0.435
Myalgia, n (%)	269 (53.7)	57 (64.1)	3.275/0.070
Liver involvement, n (%)	207 (41.3)	50 (55.6)	**6.293/0.012**
Sore throat, n (%)	278 (55.6)	55 (63.2)	1.752/0.186
Lymphadenopathy, n (%)	244 (48.7)	49 (54.4)	1.006/0.316
Splenomegaly, n (%)	189 (37.7)	34 (38.2)	0.012/0.910
Pericarditis, n (%)	78 (15.4)	20 (22.5)	2.495/0.114
Pleuritis, n (%)	78 (15.4)	20 (22.5)	2.683/0.101
Abdominal pain, n (%)	57 (11.4)	18 (20.2)	**5.368/0.021**
Lung disease, n (%)	29 (5.7)	12 (13.5)	**7.021/0.008**
WBC ≥ 15000 cells/mm^3, n (%)	309 (66.31)	60 (71.43)	0.845/0.358
Multivariate analysis assessing systemic score components and life-threatening evolution			
Life-threatening evolution	**OR**	**95%CI**	**p**
Age	0.99	0.98-1.01	0.231
Male sex	1.05	0.66-1.68	0.831
Liver involvement	1.68	1.48-2.67	**0.031**
Abdominal pain	1.69	0.91-3.11	0.094
Lung disease	2.12	1.14-4.49	**0.042**

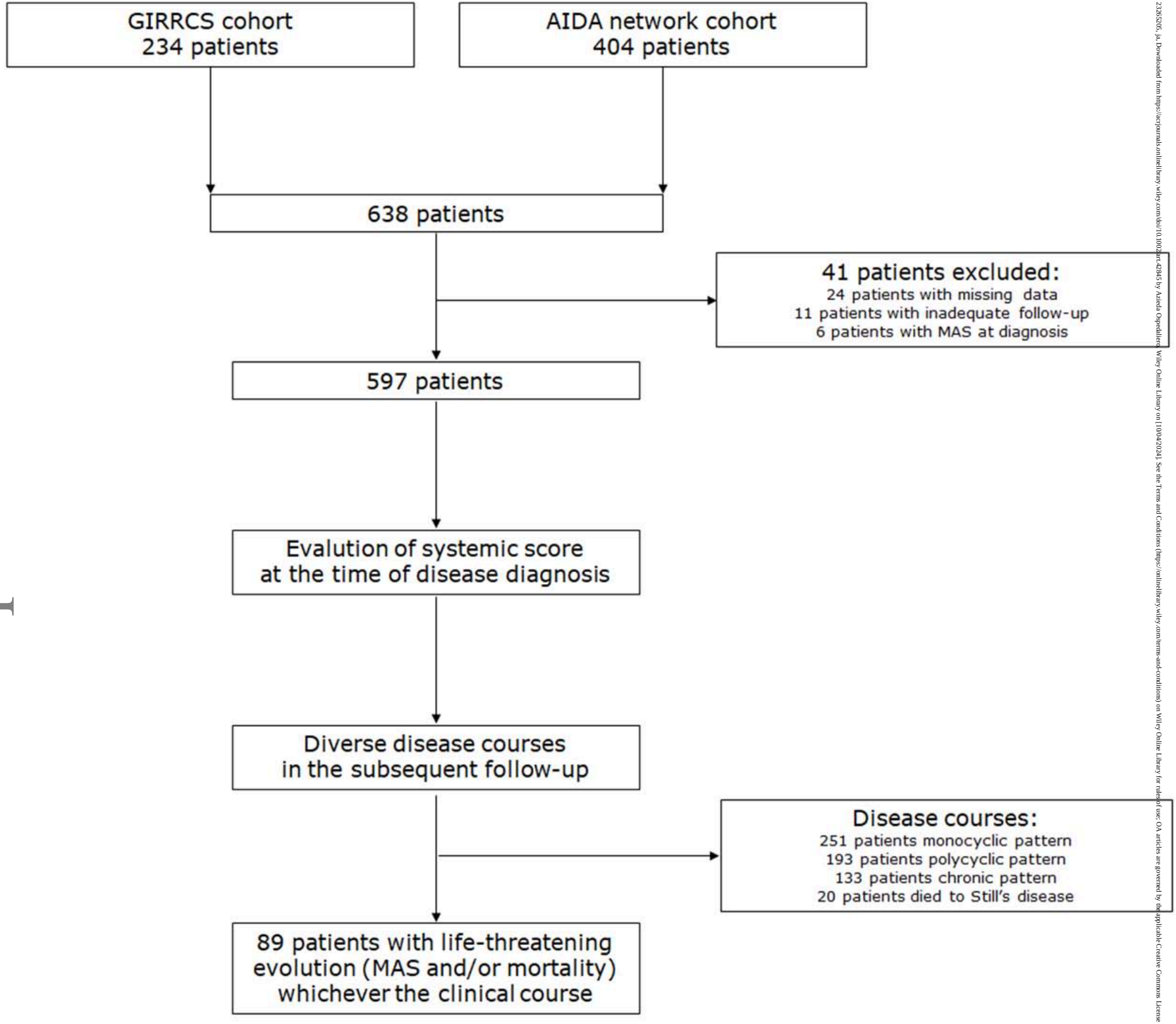
Abbreviations: OR: odd ratio; 95%CI: 95% confidence interval WBC: white blood cell count.

Table 4. Clinic risk profile of patients stratified according to liver involvement and lung disease

	OR	95%CI	p value
Liver involvement			
Skin Rash	0.96	0.68-1.36	0.189
Sore throat	1.20	0.86-1.68	0.269
Myalgia	1.43	1.03-1.99	**0.032**
Lymphadenopathy	1.80	1.29-2.51	**0.001**
Splenomegaly	5.37	3.74-7.72	**<0.0001**
Pericarditis	2.01	1.29-3.13	**0.001**
Pleuritis	2.43	1.55-3.80	**0.001**
Abdominal pain	1.09	0.67-1.77	0.733
Lung disease	2.15	1.12-4.11	**0.018**
WBC ≥ 15000 cells/mm^3	1.02	0.72- 1.47	0.884
Systemic score	1.75	1.56-1.97	**<0.0001**
ESR	1.01	0.99- 1.07	0.554
CRP	1.00	0.99-1.03	0.292
Ferritin	0.99	0.87- 1.07	0.585
Monocyclic pattern	0.98	0.71-1.38	0.944
Polycyclic pattern	1.16	0.81-1.64	0.412
Chronic pattern	0.78	0.51-1.15	0.200
Mortality	1.58	0.64-3.87	0.314
Lung disease			
Skin Rash	1.11	0.56-2.20	0.753
Sore throat	2.52	1.21-5.24	**0.010**
Myalgia	3.56	1.61-7.85	**0.001**
Lymphadenopathy	2.32	1.17-4.57	**0.013**
Splenomegaly	2.02	1.07-3.83	**0.028**
Pericarditis	3.74	1.91-7.32	**0.001**
Pleuritis	6.52	3.37-12.60	**0.001**
Abdominal pain	4.13	2.05-8.30	**0.001**
Liver involvement	2.14	1.12-4.11	**0.019**
WBC ≥ 15000 cells/mm^3	1.35	0.66-2.75	0.4124
Systemic score	2.27	1.83-2.83	**<0.0001**
ESR	0.99	0.98-1.09	0.902
CRP	1.01	0.99-1.05	0.629
Ferritin	1.00	0.99-1.07	0.548
Monocyclic pattern	1.40	0.74-2.67	0.301
Polycyclic pattern	0.77	0.38-1.58	0.482
Chronic pattern	0.49	0.189-1.28	0.139
Mortality	3.62	1.15-11.41	**0.019**

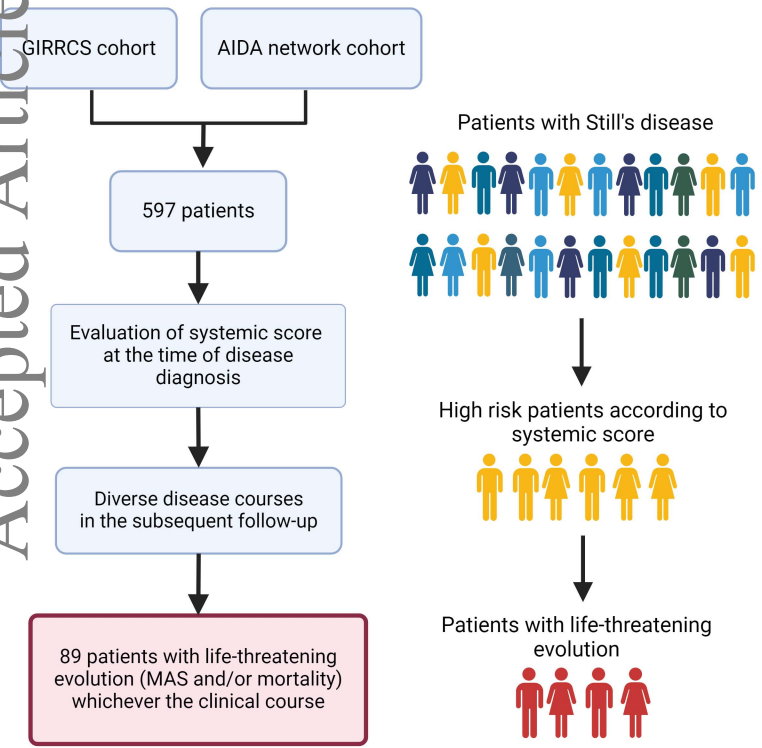
Abbreviations: OR: odd ratio; 95%CI: 95% confidence interval; CRP: C reactive protein; ESR: erythrocyte sedimentation rate; WBC: white blood cell count.

Footnote: ESR was assessed as mm/h, CRP as mg/L, and ferritin as ng/mL, respectively



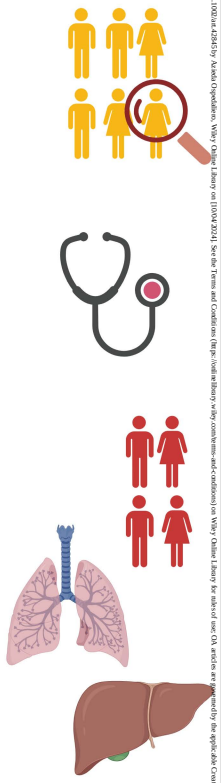
The Systemic Score May Identify Life-Threatening Evolution in Still's Disease

Study Design



Major Findings

- The systemic score may identify patients at higher risk of life-threatening evolution
- The systemic score is a prognostic tool to be readily applied in the clinical practice
- Lung disease and liver involvement both significantly predicted life-threatening evolution
- Lung disease and liver involvement may identify specific clinical subsets of patients



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