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Systemic phenotype of sarcoidosis associated with radiological stages. Analysis of 1230 patients

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Abbreviations: WASOG, World Association of Sarcoidosis and Other Granulomatous Disorders; BHL, Bilateral hilar adenopathies; PI, Pulmonary infiltrates; ENT, ear, nose, and throat; CT, computed tomography; OCCC, oculo-cardiac-central nervous system-cutaneous

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ABSTRACT

Background: To analyze the association between Scadding radiological stages of sarcoidosis at diagnosis and the disease phenotype (epidemiology, clinical presentation and extrathoracic involvement) in one of the largest cohorts of patients with sarcoidosis reported from southern Europe.

Methods: The SARCOGEAS-Study Group includes a multicenter database of consecutive patients diagnosed with sarcoidosis according to the WASOG 1999 criteria. Extrathoracic disease at diagnosis was defined according to the 2014 instrument and the clusters proposed by Schupp et al.

Results: We analyzed 1230 patients (712 female, mean age 47 yrs.) who showed the following Scadding radiologic stages at diagnosis: stage 0 (n = 98), stage I (n = 395), stage II (n = 500), stage III (n = 195) and stage IV (n = 42). Women were overrepresented in patients presenting with extrathoracic/extrapulmonary disease, while the diagnosis was made at younger ages in patients presenting with BHL, and at older ages in those presenting with pulmonary fibrosis (q values < 0.05). Multivariable adjusted analysis showed that patients presenting with pulmonary involvement (especially those with stages II and III) had a lower frequency of concomitant systemic involvement in some specific extrathoracic clusters (cutaneous-adenopathic/musculoskeletal, ENT and neuro-ocular/OCCC) but a higher frequency for others (hepatosplenic), in comparison with patients with extra-pulmonary involvement (stages 0 and I). The presence of either BHL or fibrotic lesions did not influence the systemic phenotype of patients with pulmonary involvement.

Conclusions: The key determinant associated with a differentiated systemic phenotype of sarcoidosis at diagnosis was interstitial pulmonary involvement rather than the individual Scadding radiological stage.

1. Introduction

Sarcoidosis is a systemic granulomatous disease that affects adults older than 50 years-old in more than half the cases [1] with a slight predominance in women (female: male ratio 1.2 to 1.5:1) and an estimated prevalence ranging between 1 and 40 cases per 100,000 individuals [2]. The most commonly involved organs are the lungs, the lymph nodes, the skin and the eyes [3]. Since sarcoidosis may mimic a wide variety of processes, the diagnosis is established when clinical and radiologic findings are supported by histologic evidence of non-caseating granulomas [4]. Although the natural history of sarcoidosis is highly variable, spontaneous remission may occur in up to two thirds of patients, while the remaining cases may follow a chronic and progressive disease course or may even present with life-threatening features [5]. This clinical heterogeneity led to the need to define clusters of patients presenting with homogeneous clinical patterns with a similar prognostic outcome (sarcoidosis phenotypes) [6].

Since > 90% of patients with sarcoidosis are diagnosed due to thoracic involvement, thoracic X-ray has played a key diagnostic role for decades. In 1961, Karl Wurm and Guy Scadding [6] proposed a simple X-ray staging classification, which was the first historical attempt at sarcoidosis phenotyping. Since then, the Scadding staging has been used with no modifications, even after the introduction of CT, which is clearly superior for evaluating parenchymal pulmonary involvement. However, CT is mainly carried out in patients with respiratory symptomatology (suggestive of pulmonary sarcoidosis), and is not always available in some clinical settings. In contrast, chest X-ray remains a key diagnostic tool in sarcoidosis, probably due to its simplicity and availability in non-specialized medical settings such as primary care. Several studies have analyzed the correlation between the radiological stages and the disease phenotype [6], but no large studies have analyzed how the Scadding radiological stages are linked to the clinical presentation of sarcoidosis in southern Europe.

This study analyzed the association between the Scadding radiological stage findings at diagnosis and the disease phenotype (epidemiology, clinical presentation and extrathoracic patterns of involvement) in one of the largest cohorts of patients with sarcoidosis reported from southern Europe.

2. Methods

2.1. Patients

The SARCOGEAS-Study Group was founded in 2015 with the aim of collecting a large series of patients with sarcoidosis from 36 Spanish hospitals with substantial experience in the management of systemic autoimmune diseases. Both incident (new) and prevalent (already-diagnosed) cases were retrospectively included. Incident cases ($n = 67$) were defined as those included during the first study visit or within the previous 12 months. Patients were included at the time of fulfillment of the classification criteria for sarcoidosis proposed by the American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) 1999 statement on sarcoidosis [7]: a) clinical or radiologic findings consistent with sarcoidosis, such as pulmonary disease, uveitis, mediastinal bilateral hilar lymphadenopathy (BHL), or erythema nodosum; b) tissue biopsy with histologic evidence of non-caseating granulomas; c) absence of other causes of granulomatous disease. Patients lacking the histopathological criteria (b) were included if they presented at least one of the following features: elevated serum angiotensin-converting enzyme, organ-specific abnormal uptake on gallium-67 citrate scintigraphy, elevated lymphocyte count or elevated CD4/CD8 ratio in bronchoalveolar lavage fluid, or active extrathoracic involvement classified as highly probable according to the WASOG extrathoracic classification [8,9]. The study was conducted in accordance with the amended Declaration of Helsinki. The Clinical Research Ethics Committee of the coordinating center (HCB2016/0181) approved the protocol, and written informed consent was obtained from patients with current follow-up.

2.2. Variables

Variables were retrospectively collected at the diagnosis of sarcoidosis, defined as the date of the first positive histopathological result or, in non-biopsy-proven cases, the date of the clinical diagnosis of sarcoidosis confirmed by the attending physician.

Epidemiological variables included age, gender, country of birth, ethnicity (classified according to FDA) and previous/concomitant associated disease collected according to previous definitions [10]. Clinical presentation patterns were classified as acute or non-acute onset following the definitions used by Prasse et al. [11]; asymptomatic cases were classified apart. Extrathoracic involvement at diagnosis was defined according to the 2014 WASOG organ assessment instrument, including only the clinical scenarios classified as highly probable or at least probable [9]. Clinical patterns of extrathoracic involvement were evaluated as follows: 1) frequency (patients with at least one extrathoracic organ involved), frequency of multisystemic involvement (patients with ≥2 extrathoracic organs involved) and mean number of organs involved, 2) individual organ-by-organ WASOG involvements; 3) anatomically-guided clustering of WASOG organs (cutaneous-adenopathic, hepatosplenic, ENT, musculoskeletal, renal and neuro-ocular clusters); and 4) extrathoracic clusters proposed by Schupp et al. [12] (musculoskeletal-cutaneous, oculo-cardiac-central nervous system-cutaneous-OCCC- and abdominal clusters). The use of extrathoracic clustering was based on statistical requirements (taking into account the large number of extrathoracic organs involved, most of which had frequencies < 10%) rather than for immunopathogenic reasons. Initial therapeutic management was classified as the need for systemic therapy (first-line use of oral/intravenous glucocorticoids, immunosuppressive agents and/or biological agents), and need for aggressive systemic therapy (first-line use of immunosuppressive agents and/or biological agents) following the definitions proposed by Inoue et al. [13]. Scadding radiographic stages were evaluated in all cases with available chest X-ray at diagnosis, and were defined as stage 0 (normal), stage I (BHL without pulmonary infiltrates -PI-), stage II (BHL plus PI), stage III (PI without BHL) and stage IV (extensive fibrosis with distortion or bullae) [14].

2.3. Statistical analysis

Descriptive data are presented as mean and standard deviation (SD) for continuous variables and numbers and percentages (%) for categorical variables. Comparisons were made taking into account the presence or absence in the Scadding classification of the following three determinants: presence of thoracic involvement (Yes/No), BHL (Yes/No) and pulmonary involvement (Yes/No; an additional comparison was made with fibrosis [Yes/No]) (Supplementary Fig. 1). The Chi-square test was used to study the association between Scadding subsets and the main epidemiological, clinical, extrathoracic and therapeutic variables. One-way ANOVA tests were used to compare continuous variables. Q-values, adjusted *P*-values for multiple comparisons, were computed using the false discovery rate (FDR) correction. Multinomial logistic regression analyses, with the scadding thoracic stages as the dependent variable, adjusted for the main epidemiological and clinical baseline characteristics (age, gender, ethnicity and clinical presentation patterns) were used to analyze the association between the Scadding system and the disease phenotype. Individual organ WASOG involvements were not included in the adjustment in order to avoid multicollinearity. The odds ratios (ORs) and their 95% confidence intervals (CI) were calculated. All significance tests were two-tailed and values of $q < 0.05$ were considered significant. Scadding thoracic stages were subclassified according to the presence or absence of BHL, pulmonary involvement or fibrosis (Supplementary Fig. 1). All analyses were conducted using the R V.3.2.3 for Windows statistical software package (https://www.R-project.org/).

3. Results

Of the 1245 patients included in the cohort, information about X-ray baseline Scadding staging was not available in 15. Therefore, 1230 patients were finally analyzed (712 women, mean age at diagnosis of 47 years, 81% biopsy-proven); 1124 (91%) patients were classified as White, and 1063 (86%) were born in Spain (Table 1). Scadding radiologic stage at diagnosis consisted of stage 0 in 98 (8%) patients, stage I in 395 (32%), stage II in 500 (41%), stage III in 195 (16%) and stage IV in 42 (3%) patients. Eight hundred and sixty seven (70%) patients had involvement in at least one WASOG extrathoracic site (extrathoracic disease), with a mean of 1.2 (SD 1.2) organs involved; the most frequent extrathoracic sites included the skin (35%), extrathoracic lymph nodes (18%), liver (13%) and ocular (10%); 409 (33%) patients had involvement in at least 2 extrathoracic organs (multisystemic disease). No significant differences were found in the distribution of the Scadding stages between prevalent and incident cases ($p = .129$) or between cases with or without a biopsy-proven diagnosis ($p = .137$). Therapies administered included oral glucocorticoids in 565 (46%) patients, together with immunosuppressive agents in 89 (7%) and biological agents in 13 (1%) due to severe clinical presentations (Table 1).

Supplementary Table 1 summarizes the main epidemiological, clinical and therapeutic features of patients according to each Scadding stage. Epidemiologically, age at diagnosis and gender distribution were clearly linked with the Scadding stage, with younger mean ages being reported for stages I and II, and a predominance of affected women in stages 0 and I.

With respect to extrathoracic patterns of involvement, the highest frequencies of the organ-by-organ WASOG involvements are reported in stage 0 (skin, liver, spleen, ENT, nervous system and bone marrow), stage I (salivary glands, bone/joint) and stage IV (extra-thoracic lymph node, eye, kidney, calcium-vitamin D and heart) (Fig. 1). With respect to WASOG clusters, the highest frequencies are reported in stage 0 for cutaneous-adenopathic, hepatosplenic and neuro-ocular clusters, in stage I for ENT and musculoskeletal clusters, and in stage IV for the

Table 1
Main features at the time of diagnosis in 1230 patients with sarcoidosis and available information about radiological Scadding stages.

Variables	Patients (n = 1230)
Gender (women)	712 (57.9)
Mean age (years)	47.3 ± 15.3
Ethnicity	
White	1124 (91.4)
Latin American	56 (4.6)
Asian	18 (1.5)
Other	32 (2.6)
Born in Spain	1063 (86.4)
Associated diseases	263 (21.4)
Scadding radiological stage	
0	98 (8)
1	395 (32.1)
2	500 (40.7)
3	195 (15.9)
4	42 (3.4)
Clinical presentation patters	
Acute onset	223 (18.1)
Non-acute onset	877 (71.3)
Asymptomatic diagnosis	130 (10.6)
Extrathoracic phenotype	
a) Global WASOG	
Extrathoracic disease	867 (70.5)
Multisystemic involvement	409 (33.3)
Number of involved organs (mean ± SD)	1.2 ± 1.2
b) Organ by organ WASOG	
Skin	437 (35.5)
Extra-thoracic lymph node	226 (18.4)
Eye	124 (10.1)
Liver	166 (13.5)
Spleen	95 (7.7)
Salivary glands	62 (5)
ENT	27 (2.2)
Bone/Joint	79 (6.4)
Muscle	16 (1.3)
Kidney	52 (4.2)
Calcium-Vitamin D	93 (7.6)
Nervous system	80 (6.5)
Heart	24 (2)
Bone marrow	54 (4.4)
c) WASOG clusters	
Cutaneous-adenopathic	604 (49.1)
Hepatosplenic	212 (17.2)
ENT	84 (6.8)
Musculoskeletal	93 (7.6)
Renal	118 (9.6)
Neuro-ocular	187 (15.2)
Others	76 (6.2)
d) Schapp's clusters	
Abdominal cluster	244 (19.8)
OCCC cluster	250 (20.3)
Musculoskeletal-cutaneous cluster	472 (38.4)
Histopathological confirmation	992 (80.7)
Therapeutic management	
Need for therapy	590 (48)
Aggresiveness of therapy	95 (7.7)
Drugs	
Glucocorticoids	565 (45.9)
Immunosuppressive agents	89 (7.2)
Biological agents	13 (1.1)

renal cluster (Fig. 2). The three Schapp's extrathoracic clusters are overrepresented in stage 0. Therapeutic management also correlated with Scadding stages: patients with stage IV had the highest frequencies of both need for and aggressiveness of therapy, while patients with stage I had the lowest frequencies.

3.1. Systemic phenotype in thoracic involvement

According to baseline Scadding stages, 1132 (92%) patients showed evidence of thoracic involvement (stages I to IV) while the remaining 98 (8%) presented with sarcoidosis limited to extrathoracic organs (stage 0). Patients with thoracic involvement were diagnosed at a younger age (q = 0.005), were less frequently women (q = 0.007) and had a lower frequency of skin (54% vs 34%, q = 0.001) and nervous system (q = 0.008) WASOG involvements in comparison with patients with extrathoracic involvement (Table 2). With respect to systemic clusterization, patients with thoracic involvement presented a significantly-lower frequency of the cutaneous-adenopathic (45% vs 75%, q < 0.001) and neuro-ocular (14% vs 24%, q = 0.032) WASOG clusters, and a lower frequency of the OCCC (19% vs 31%, q = 0.032) and cutaneous-musculoskeletal (37% vs 56%, q = 0.001) Schupp extrathoracic clusters (Table 2). Multivariable analysis confirmed the lower frequency of extrathoracic disease in all thoracic stages in comparison with the extrathoracic stage, especially for the cutaneous-adenopathic WASOG cluster, but also for the hepatosplenic/abdominal (for stage I), neuro-ocular/OCCC (for stages II and III) and renal (for stage III) systemic clusters (Table 3).

3.2. Systemic phenotype in pulmonary involvement

Among the 1132 patients with thoracic involvement, 395 (35%) showed isolated thoracic lymphadenopathy (stage I) and 737 (65%) showed interstitial pulmonary disease (stages II, III and IV). Patients with pulmonary involvement had a significantly-lower frequency of skin (43% vs 29%, q < 0.001) and salivary glands (3% vs 8%, q = 0.005) WASOG involvements and a significantly-higher frequency of liver WASOG involvement (16% vs 8%, q = 0.004) in comparison with patients with stage I. With respect to systemic clusterization, patients with pulmonary involvement presented a significantly-lower frequency of the cutaneous-adenopathic (42% vs 56%, q < 0.001) and ENT (5% vs 10%, q = 0.004) WASOG clusters, and of the cutaneous-musculoskeletal (32% vs 46%, q < 0.001) Schupp cluster (Table 2). Multivariable analysis confirmed the lower frequency of extrathoracic disease in all pulmonary stages in comparison with stage I, and a similar systemic phenotype in stages II and III consisting of a lower frequency of involvement in the cutaneous-adenopathic/musculoskeletal, ENT and OCCC clusters and a higher frequency in the hepatosplenic cluster (Table 3).

Two sensitive studies were additionally performed in patients with pulmonary involvement (stages II, III and IV). The first consisted of analyze the influence in systemic phenotype of concomitant thoracic adenopathies: no statistically-significant differences were detected both in the univariate (Supplementary Table 2) and the multivariable (Supplementary Table 3) analysis. The second consisted of analyze the influence of pulmonary fibrosis (stage IV), that was associated with an older age of diagnosis (55 years vs 47 years in stages II/III, q < 0.001) and a higher use of systemic therapy (81% vs 49%, q = 0.002), with no statistically-significant differences being detected in the systemic phenotype both in the univariate (Supplementary Table 2) and the multivariable (Supplementary Table 3) analysis.

4. Discussion

Due to the clinical heterogeneity of sarcoidosis, various studies have tried to delineate phenotypic subgroups that could predict the outcome of an individual patient and, therefore, help physicians decide on a specific therapeutic approach and/or the need for referral to highly-specialized healthcare settings [11,15,16]. The first historical attempt at a phenotypical staging of sarcoidosis was proposed by Karl Wurm in 1960 [17], and modified by Guy Scadding in a seminal 1961 publication [14], a classification that relied entirely on the results of the chest radiograph depicting the involvement of the lungs and hilar lymph nodes. However, studies of the correlation between the Scadding classification and the sarcoidosis phenotype have found heterogeneous results. In 1961, Scadding himself found that some extrathoracic

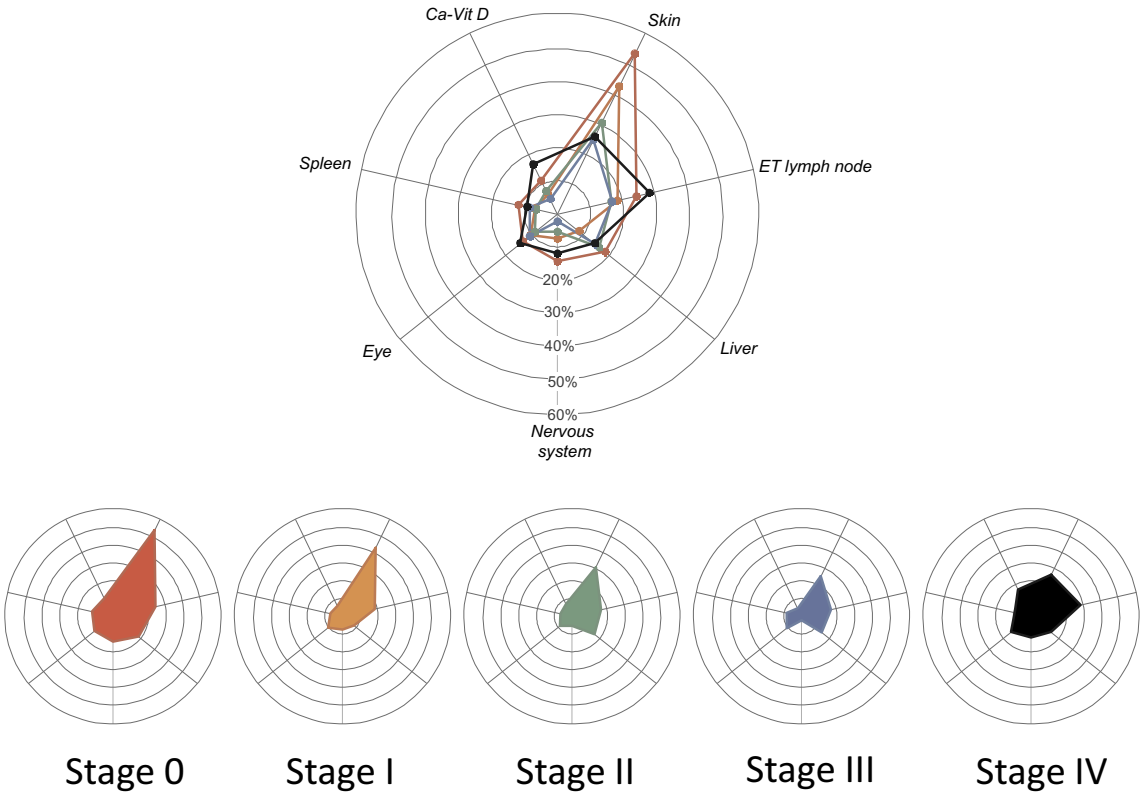

Fig. 1. Radar plots of the frequencies of the seven most-frequent WASOG extrathoracic organs involved in our cohort (skin, extrathoracic lymph nodes, liver, nervous system, eye, spleen and calcium/vitamin D) for Scadding radiological stages. Each point represents the relative frequency of Scadding radiological stage for the corresponding extrathoracic organ. Each circle inside the radars corresponds to an increase of 10%. Central circle compares the five Scadding stages according to the frequency of involvement of the seven most-frequent WASOG extrathoracic organs involved (stage 0 = red, stage I = orange, stage II = green, stage III = blue, stage IV = black). Peripheral circles on the five arms of the central circle depicts individual radar plot for each Scadding radiological stage. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

features were unrelated to radiographic patterns [14], and further studies found a poor correlation with disease severity, pulmonary function tests or the need for treatment [18–21]. In contrast, other studies have reported a positive correlation with ethnicity and gender [22], respiratory symptoms [23], pulmonary function tests [24–26], high-resolution CT (HRCT) scores [24], bronchial granuloma density [23], the prognosis [27,28] and diagnostic delay [29]. In this study, we found a differentiated epidemiological profile, extrathoracic patterns of involvement and initial therapeutic management, although the phenotype was principally associated with the presence or absence of pulmonary involvement rather than with the individual Scadding stage. Our results suggest that sarcoidosis phenotyping is improved when thoracic organs are analyzed separately rather than when patients are clustered according to individual Scadding stages, because this classification includes organs with a contradictory prognosis (and therefore, a contradictory therapeutic management) whose involvement is mixed among different stages.

Patients with sarcoidosis limited to extrathoracic organs at diagnosis (Scadding stage 0) accounted for 8% of our total cohort, with nearly 50% of patients presenting with the isolated involvement of only one extrathoracic organ. These patients showed a specific phenotype characterized by a predominant involvement of women diagnosed at older ages with an enhanced frequency of all organ-specific extrathoracic involvements (except for muscular and renal) (Fig. 2), an unsurprising finding since, in these patients, sarcoidosis was diagnosed based on extrathoracic disease. However, we found a significantly-enhanced prevalence of skin and nervous system involvements. In fact, a recent study [30] has reported that isolated skin sarcoidosis was the most common extrathoracic presentation of sarcoidosis in patients with Scadding stage 0, and other studies have reported that skin or neurological features were the first sign of the disease in nearly 50% of cases [31,32]. Although this subset of patients will first be seen by the corresponding specialist, referral to a multidisciplinary unit for an active search for underlying systemic involvement may be recommended, since more than half the patients presenting with extrathoracic sarcoidosis may have at least one second organ involved; an enhanced work-up searching for concomitant silent cutaneous, musculoskeletal, ocular, cardiac and neurological involvements should be recommended in these patients.

Patients with Scadding stage I represented one third of our patients, and also showed a specific phenotype predominantly involving women diagnosed at younger ages and presenting a specific extrathoracic pattern (predominant involvement of the skin, joints and lymph nodes). This clinical cluster is highly suggestive of Löfgren syndrome, which is mainly reported in European countries in 30–50% of patients with sarcoidosis [33–35], while the frequency reported in US and Indian studies [36,37] is < 5%. Sarcoidosis should be included prominently in the differential diagnosis of patients presenting with isolated BHL [29], especially those with concomitant fever, erythema nodosum and/or arthritis. Since spontaneous resolution rates range between 55% and 90% [38], an initial follow-up of these patients could be made in non-specialized settings with symptomatic therapy, waiting for spontaneous resolution in a few weeks. In these patients, an enhanced extrathoracic screening is recommended due to the increased risk of presenting concomitant ENT, neuro-ocular and cardiac involvements, while a presentation with concomitant hepatosplenic involvement is infrequent.

Our results also showed the key role of pulmonary involvement in the disease phenotype of sarcoidosis at diagnosis, since the largest number of significant variables among all the univariate comparisons

	Scadding stages	Stage 0	Stage I	Stage II	Stage III	Stage IV
	Number of patients	n = 98	n = 395	n = 500	n = 195	n = 42
General	Extrathoracic involvement (overall), %	100%	78.2%	64.8%	57.4%	61.9%
	Systemic involvement (at least 2 involv), %	52%	34.7%	31%	26.2%	35.7%
	Number of involved organs, mean	1.8	1.3	1.1	1.0	1.5
WASOG individual organs	Skin, %	54.1%	43%	30.8%	25.1%	26.2%
	Extra-thoracic lymph node, %	24.5%	18.5%	16.8%	16.9%	28.6%
	Eye, %	13.3%	10.4%	8.6%	10.8%	14.3%
	Liver, %	18.4%	8.4%	16.2%	14.4%	14.3%
	Spleen, %	12.2%	7.1%	6.8%	8.7%	9.5%
	Salivary glands, %	7.1%	7.8%	3.4%	2.6%	4.8%
	ENT, %	4.1%	2.8%	1.4%	2.1%	2.4%
	Bone/Joint, %	7.1%	8.1%	5 5%	6.7%	4.8%
	Muscle, %	1%	1%	1.4%	1.5%	2.4%
	Kidney, %	3.1%	5.3%	4%	2.6%	7.1%
	Calcium-Vitamin D, %	11.2%	6.6%	7.8%	5.1%	16.7%
	Nervous system, %	14.3%	7.6%	5.4%	2.1%	11.9%
	Heart, %	3.1%	1.5%	1.6%	2.6%	4.8%
	Bone marrow, %	5.1%	5.1%	4.6%	2.6%	2.4%
WASOG clusters	Cutaneous-adenopathic, %	75.5%	56.2%	43.6%	37.9%	38.1%
	Hepatosplenic, %	25.5%	13.2%	18.6%	17.4%	19%
	ENT, %	9.2%	10.1%	4.6%	4.6%	7.1%
	Musculoskeletal, %	8.2%	9.1%	6%	8.2%	7.1%
	Renal, %	13.3%	9.6%	9.6%	6.2%	16.7%
	Neuro-ocular, %	24.5%	17%	13%	11.3%	21.4%
	Others, %	8.2%	6.3%	6.2%	4.6%	7.1%
Schupp's clusters	Abdominal, %	26.5%	17%	21%	18.5%	23.8%
	OCCC, %	30.6%	23.3%	17.2%	15.4%	28.6%
	Musculoskeletal-cutaneous, %	56.1%	46.3%	33%	28.7%	31%

Fig. 2. Heat map summarizing the frequency distribution of the main extrathoracic variables (extrathoracic involvement, systemic extrathoracic involvement, WASOG individual organs, WASOG clusters and Schupp clusters) in each individual Scadding stage. For each cell, the value corresponds to the relative frequency by row. For each row, the relative frequencies have been ordered: the darkest color indicates the highest frequency and the lightest color the lowest frequencies.

made between the different Scadding stages was found when patients were divided according to the presence or absence of pulmonary involvement. In contrast, the presence or absence of BHL played a weak role in driving significant phenotypic differences when pulmonary involvement was present (Supplementary Fig. 2). Previous studies reported that radiological enlargement of thoracic lymph nodes appeared to have no additional value in relation to functional pulmonary impairment [21], and some authors have even suggested merging these two stages [29]. Although no prospective studies have confirmed a differentiated prognosis between patients presenting with stage II or stage III, the benign prognosis of adenopathic involvement [39] suggests that the presence of BHL should not influence the prognosis of non-fibrotic pulmonary sarcoidosis.

Stage IV (radiological evidence of lung fibrosis) was the least-frequently found stage at diagnosis (3% of our cohort) and was associated with an older age at diagnosis. Little is known about the characterization of this subset of patients at disease diagnosis, and they may be patients who were diagnosed late or who have more-rapidly progressing lung disease; in fact, a prolonged delay in the disease diagnosis has been reported in patients with higher Scadding stages [29]. In addition, our results suggest an enhanced presence of extrathoracic disease, and although the differences were not significant in the multivariate analysis (probably due to the small number of patients), the heat map of frequencies of extrathoracic patterns of involvement clearly showed a differentiated scenario compared with the other pulmonary stages (II and III) (Fig. 1); an enhanced work-up searching for concomitant extrathoracic involvements should be recommended in these patients.

Logically, the main limitation of any clinical study using X-ray-based diagnostic tests is the poor agreement between HRCT and conventional thoracic X-ray findings. Although a significant correlation between the thoracic X-ray score and the total HRCT score has been reported [24], CT, and especially HRCT [40], has a higher sensitivity than chest X-ray in detecting subtle parenchymal abnormalities in the early stages of pulmonary disease, suggesting that some patients classified as stage I might have been stage II; however, subtle infiltrates are often associated with an excellent long-term prognosis [7,41] and may even have a spontaneous resolution, suggesting asymptomatic transitory pulmonary involvement. It would be of interest to specifically analyze the correlation between X-ray and CT findings in future studies (including outcomes), although it should be taken into account that most patients with stages 0 and I (and even some with stage II) probably did not have a CT scan at diagnosis due to the lack of significant respiratory symptoms. Other limitations inherent to the retrospective design include the lack of pre-defined radiological criteria and a central process for X-ray reading (making it impossible to evaluate Kappa interrater reliability in our study). There is no doubt of the utility of thoracic X-rays in primary care and other non-specialized healthcare settings when sarcoidosis is clinically suspected, since it is a key tool

Table 2
Epidemiological, clinical, extrathoracic and therapeutic features of patients with sarcoidosis according to the presence or absence of thoracic involvement in Scadding radiological staging.

Definition	Extrathoracic disease	Thoracic disease	*Q value*	Thoracic no pulmonary	Pulmonary	*Q value*
Scadding stages	0	I, II, III, IV		I	II, III, IV	
Number of patients	(*n* = 98)	(*n* = 1132)		(*n* = 395)	(*n* = 737)	
Epidemiological features						
Gender (women)	72 (73.5)	640 (56.5)	**0.007**	241 (61)	399 (54.1)	0.086
Mean age (years)	52.1 ± 16.7	46.8 ± 15.1	**0.005**	46.2 ± 15	47.2 ± 15.2	0.465
Clinical presentation patters			0.332			0.812
Acute onset	15 (15.3)	208 (18.4)		77 (19.5)	131 (17.8)	
Non-acute onset	77 (78.6)	800 (70.7)		273 (69.1)	527 (71.5)	
Asymptomatic diagnosis	6 (6.1)	124 (11)		45 (11.4)	79 (10.7)	
Extrathoracic phenotype						
a) Global WASOG						
Extrathoracic disease	96 (98)	771 (68.1)	< **0.001**	309 (78.2)	462 (62.7)	< **0.001**
Multisystemic involvement	51 (52)	358 (31.6)	< **0.001**	137 (34.7)	221 (30)	0.227
Number of involved organs (mean ± SD)	1.8 ± 1.1	1.2 ± 1.2	< **0.001**	1.3 ± 1.1	1.1 ± 1.2	**0.028**
b) Organ by organ WASOG						
Skin	53 (54.1)	384 (33.9)	**0.001**	170 (43)	214 (29)	< **0.001**
Extra-thoracic lymph node	24 (24.5)	202 (17.8)	0.255	73 (18.5)	129 (17.5)	0.820
Eye	13 (13.3)	111 (9.8)	0.500	41 (10.4)	70 (9.5)	0.812
Liver	18 (18.4)	148 (13.1)	0.332	33 (8.4)	115 (15.6)	**0.004**
Spleen	12 (12.2)	83 (7.3)	0.242	28 (7.1)	55 (7.5)	0.912
Salivary glands	7 (7.1)	55 (4.9)	0.579	31 (7.8)	24 (3.3)	**0.005**
ENT	4 (4.1)	23 (2)	0.484	11 (2.8)	12 (1.6)	0.439
Bone/Joint	7 (7.1)	72 (6.4)	0.992	32 (8.1)	40 (5.4)	0.220
Muscle	1 (1)	15 (1.3)	1	4 (1)	11 (1.5)	0.812
Kidney	3 (3.1)	49 (4.3)	0.842	21 (5.3)	28 (3.8)	0.453
Calcium-Vitamin D	11 (11.2)	82 (7.2)	0.349	26 (6.6)	56 (7.6)	0.812
Nervous system	14 (14.3)	66 (5.8)	**0.008**	30 (7.6)	36 (4.9)	0.200
Heart	3 (3.1)	21 (1.9)	0.776	6 (1.5)	15 (2)	0.812
Bone marrow	5 (5.1)	49 (4.3)	0.992	20 (5.1)	29 (3.9)	0.642
c) WASOG clusters						
Cutaneous-adenopathic	74 (75.5)	530 (46.8)	< **0.001**	222 (56.2)	308 (41.8)	< **0.001**
Hepatosplenic	25 (25.5)	187 (16.5)	0.083	52 (13.2)	135 (18.3)	0.086
ENT	9 (9.2)	75 (6.6)	0.579	40 (10.1)	35 (4.7)	**0.004**
Musculoskeletal	8 (8.2)	85 (7.5)	1	36 (9.1)	49 (6.6)	0.295
Renal	13 (13.3)	105 (9.3)	0.408	38 (9.6)	67 (9.1)	0.881
Neuro-ocular	24 (24.5)	163 (14.4)	**0.032**	67 (17)	96 (13)	0.200
Others	8 (8.2)	68 (6)	0.649	25 (6.3)	43 (5.8)	0.881
d) Schapp's clusters						
Abdominal cluster	26 (26.5)	218 (19.3)	0.242	67 (17)	151 (20.5)	0.295
OCCC cluster	30 (30.6)	220 (19.4)	**0.032**	92 (23.3)	128 (17.4)	0.072
Musculoskeletal-cutaneous cluster	55 (56.1)	417 (36.8)	**0.001**	183 (46.3)	234 (31.8)	< **0.001**
Therapeutic management						
Need for therapy	39 (39.8)	551 (48.7)	0.242	174 (44.1)	377 (51.2)	0.085
Aggresiveness of therapy	15 (15.3)	80 (7.1)	**0.020**	21 (5.3)	59 (8)	0.227

Q values were calculated as estimates of the multiple-testing-corrected false discovery rate (FDR). In bold, statistically significant (Q < 0.05) differences between groups.

that provides a prompt diagnostic suspicion of a disease often diagnosed late (almost one half of patients with sarcoidosis required at least four physician visits until diagnosis) [29]. However, specific characterization of interstitial lung disease by pulmonary functional tests and HRCT are better tools than the Scadding stages for delineating distinct pulmonary phenotypes to predict the prognosis or therapeutic response in patients with sarcoidosis in future studies.

In summary, we found that pulmonary involvement depicted by the Scadding radiological stages was associated with a differentiated systemic phenotype at diagnosis in patients with sarcoidosis from Southern Europe, with a lower frequency of systemic disease except for an enhanced risk of concomitant abdominal involvement (liver, spleen). In contrast, patients without pulmonary involvement had a higher frequency of systemic disease, especially an enhanced risk of concomitant cutaneous/musculoskeletal features (Löfgren's phenotype) and cephalic extrathoracic involvements (ENT, ocular, neurological). These patterns of associations may help physicians enhance or decrease the suspicion of a specific extrathoracic involvement during the diagnostic work-up according to the thoracic organs involved in the chest X-ray, making it a useful approach in all types of clinical settings (especially primary care). The results highlight the protean phenotypic expression of sarcoidosis at diagnosis, both intra- and - extra thoracically.

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Author contributions

All authors listed have contributed sufficiently to the project to be included as authors. Authors' contributions were the next. Conception and design: RPA, PBZ, LP and MRC; acquisition of data: all authors; analysis and interpretation of data: RPA, PBZ, BK and MRC; statistical analysis: BK; drafting the article or revising it critically for important intellectual content: all authors; final approval of the version published: all authors. MRC had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analysis. BK takes responsibility for the statistical analysis.

Table 3
Association between Scadding radiological staging and phenotypic clusters.

Definition	Extrathoracic	Only BHL	BHL + PI	Only PI	Lung fibrosis
Scadding stage	0	I	II	III	IV
Number of patients	(*n* = 98)	(*n* = 395)	(*n* = 500)	(*n* = 195)	(*n* = 42)
Extrathoracic disease	Ref	0.08 [0.02–0.32]	0.04 [0.01–0.16]	0.03 [0.01–0.12]	0.03 [0.01–0.15]
Multisystemic involvement	Ref	0.47 [0.30–0.75]	0.40 [0.25–0.63]	0.32 [0.19–0.54]	0.54 [0.25–1.15]
WASOG clusters					
Cutaneous-adenopathic	Ref	**0.42 [0.25–0.71]**	**0.25 [0.15–0.42]**	**0.19 [0.11–0.33]**	**0.21 [0.09–0.48]**
Hepatosplenic	Ref	**0.48 [0.27–0.85]**	0.83 [0.48–1.44]	0.89 [0.47–1.68]	0.85 [0.33–2.19]
ENT	Ref	1.49 [0.67–3.31]	0.65 [0.28–1.51]	0.66 [0.24–1.78]	0.87 [0.22–3.55]
Musculoskeletal	Ref	1.27 [0.55–2.90]	0.91 [0.39–2.13]	1.37 [0.54–3.45]	1.19 [0.29–4.90]
Renal	Ref	0.74 [0.36–1.51]	0.64 [0.31–1.30]	**0.39 [0.16–0.93]**	1.07 [0.37–3.09]
Neuro-ocular	Ref	0.63 [0.36–1.11]	**0.45 [0.25–0.79]**	**0.37 [0.19–0.72]**	0.83 [0.33–2.06]
Others	Ref	0.92 [0.38–2.20]	0.79 [0.33–1.89]	0.61 [0.21–1.72]	0.75 [0.18–3.20]
Schupp's clusters					
Abdominal	Ref	**0.53 [0.31–0.92]**	0.68 [0.40–1.15]	0.60 [0.33–1.09]	0.76 [0.32–1.81]
OCCC	Ref	0.73 [0.44–1.22]	**0.46 [0.28–0.77]**	**0.41 [0.22–0.74]**	0.86 [0.38–1.94]
Musculoskeletal-cutaneous	Ref	0.67 [0.42–1.07]	**0.39 [0.24–0.62]**	**0.30 [0.18–0.51]**	**0.36 [0.16–0.80]**
Extrathoracic disease		Ref	0.52 [0.38–0.71]	0.38 [0.26–0.55]	0.44 [0.22–0.87]
Systemic involvement		Ref	0.85 [0.64–1.12]	0.68 [0.46–0.99]	1.16 [0.59–2.31]
WASOG clusters					
Cutaneous-adenopathic		Ref	**0.60 [0.46–0.80]**	**0.46 [0.32–0.66]**	0.51 [0.25–1.02]
Hepatosplenic		Ref	**1.79 [1.21–2.65]**	**1.95 [1.18–3.20]**	1.82 [0.75–4.40]
ENT		Ref	**0.42 [0.25–0.73]**	**0.43 [0.20–0.92]**	0.56 [0.16–1.97]
Musculoskeletal		Ref	0.73 [0.43–1.23]	1.10 [0.58–2.07]	0.97 [0.27–3.40]
Renal		Ref	0.88 [0.55–1.41]	0.54 [0.27–1.09]	1.43 [0.57–3.62]
Neuro-ocular		Ref	0.71 [0.48–1.04]	0.59 [0.35–1.01]	1.30 [0.57–2.95]
Others		Ref	0.88 [0.50–1.55]	0.68 [0.30–1.54]	0.88 [0.24–3.23]
Schupp's clusters					
Abdominal		Ref	1.29 [0.91–1.84]	1.15 [0.72–1.82]	1.44 [0.66–3.16]
OCCC		Ref	**0.64 [0.46–0.89]**	**0.56 [0.35–0.89]**	1.17 [0.56–2.43]
Musculoskeletal-cutaneous		Ref	**0.58 [0.44–0.77]**	**0.45 [0.31–0.67]**	0.55 [0.27–1.13]

Values are represented as ORs [95% Cis] for the multinomial logistic regression analyses adjusted for age, gender, ethnicity and clinical presentation patterns. In bold, statistically significant associations between the Scadding system and the disease phenotype. BHL: bilateral hilar adenopathies; PI: pulmonary infiltrates; Ref: reference.

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Declaration of Competing Interest

None.

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