ORIGINAL REPORT

Organ Involvement and Treatment Response across Cutaneous Sarcoidosis Subtypes

Antonia SCHETT[1,2,3], Anna GABRIEL[3], Koray TASCILAR[2,4], Georg SCHETT[2,4], Carola BERKING[1,2], Wolfgang WENINGER[3], Michael STICHERLING[1,2*†] and Georg STARY[3,5,6*†]

[1]Department of Dermatology, Friedrich-Alexander-Universität (FAU) Erlangen-Nürnberg and Universitätsklinikum Erlangen, Erlangen, Germany, [2]Deutsches Zentrum Immuntherapie (DZI), Friedrich-Alexander-Universität (FAU) Erlangen-Nürnberg and Universitätsklinikum Erlangen, Erlangen, Germany, [3]Department of Dermatology, Medical University of Vienna, Vienna, Austria, [4]Department of Medicine 3 - Rheumatology & Immunology, Friedrich-Alexander-Universität (FAU) Erlangen-Nürnberg and Universitätsklinikum Erlangen, Erlangen, Germany, [5]CeMM – Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria, and [6]Christian Doppler Laboratory for Chronic Inflammatory Skin Diseases, Vienna, Austria

†These authors contributed equally to this work.

Cutaneous sarcoidosis presents with diverse morphologies, yet comparative data on systemic involvement, disease course and treatment response across subtypes remain limited. We conducted a 2-centre cross-sectional study including patients with histologically confirmed sarcoidosis identified through ICD codes, stratified into patients with and without cutaneous involvement and further by cutaneous subtype. Demographics, extracutaneous organ involvement, treatment response, clinical course and the organ leading to initial diagnosis were analysed. Among 125 patients (median age 53 years; 57% female), 99 had cutaneous sarcoidosis and 26 had no skin involvement. All major subtypes of cutaneous sarcoidosis were represented: plaque (39), papular (19), scar (15), subcutaneous (13) and lupus pernio (4); erythema nodosum (9) represented acute disease. Papular sarcoidosis (19) showed the mildest systemic involvement. Lymph nodes (64%) and lungs (48%) were most frequently affected with subtype-specific variation. Skin lesions led to diagnosis in 78% of cases. Remission with topical therapy was rare (11%), whereas systemic glucocorticoids (21%) and other immunosuppressants (37%) showed higher response rates; sirolimus (11%), hydroxychloroquine (10%) and TNF inhibitors (8%) were most effective. Relapse occurred in 40% and 46% required long-term systemic therapy. Cutaneous sarcoidosis subtypes differ markedly in systemic involvement, treatment response and disease course, supporting biological heterogeneity and the need for individualized management.

Key words: sarcoidosis; subtypes; organ involvement; immunosuppression.

Submitted Mar 11, 2026. Accepted after revision May 21, 2026

Published Jun 22, 2026.
DOI: 10.2340/actadv.v106.adv-2026-0482

Acta Derm Venereol 2026; 106: adv-2026-0482.

Corr: Michael Sticherling, Department of Dermatology, Friedrich-Alexander-Universität (FAU) Erlangen-Nürnberg and Universitätsklinikum Erlangen, Erlangen, Germany and Georg Stary, Department of Dermatology, Medical University of Vienna, Vienna, Austria. Emails: michael.sticherling@uk-erlangen.de; georg.stary@meduniwien.ac.at

SIGNIFICANCE

Cutaneous sarcoidosis often represents the earliest manifestation of systemic disease. Here, we show that distinct skin morphologies are associated with divergent systemic disease trajectories, ranging from largely skin-limited disease to extensive multiorgan involvement requiring prolonged systemic therapy. These findings establish dermatologic assessment as a clinically relevant stratification tool that may improve diagnostic evaluation, prognostication and therapeutic decision-making. Recognition of phenotype-specific disease patterns could enable more personalized management approaches and reduce unnecessary treatment. Our study further provides a framework for future investigations into the biological mechanisms underlying sarcoidosis heterogeneity and phenotype-guided therapeutic strategies.

Sarcoidosis is a rare multisystem granulomatous disease of unknown aetiology, defined by the presence of non-caseating granulomas (1). Current pathophysiological concepts suggest dysregulated T-cell activation, enriched Th17 cell responses, and metabolically reprogrammed macrophages. The latter produce TNF-α and, together with activated fibroblasts, drive granuloma formation (2). Diagnosis of sarcoidosis remains challenging due to its diverse clinical presentations, lack of reliable biomarkers and the requirement for histological confirmation (3).

The lungs are the most commonly affected organ, typically presenting with bilateral hilar lymphadenopathy and pulmonary micronodules, often accompanied by cough and dyspnoea (4, 5). Systemic symptoms, such as fever, fatigue and weight loss are frequent (4–6). Additional organ manifestations may include ocular, cutaneous and musculoskeletal disease, while neurologic, cardiac, renal and hepatic involvement occur less commonly (4). Treatment

options range from glucocorticoids and conventional immunosuppressants, like methotrexate (7), to targeted agents including tumour necrosis factor (TNF) and Janus kinase (JAK) inhibitors (8); however, efficacy data largely stem from small case series (9).

Cutaneous sarcoidosis occurs in up to one third of patients and represents the second most frequently affected organ system after the lymph nodes (10, 11). Skin lesions often precede systemic disease and may therefore carry diagnostic and prognostic relevance (12, 13). Clinical presentations of cutaneous sarcoidosis are highly variable. The most common morphologies – papules, plaques, nodules and subcutaneous lesions – account for the majority of cases (14). Less frequent variants include mucosal, nail or scalp involvement, and rare morphologies such as angiolupoid, psoriasiform or verrucous sarcoidosis (15).

Several clinical syndromes represent distinct cutaneous-systemic phenotypes, including Löfgren syndrome (16), Lupus pernio (16, 17), Heerfordt syndrome and the Blau syndrome (4). Sarcoidosis may also localize to previously injured skin, including scars and tattoos, and to predilection sites such as the scalp (18). Notably cutaneous involvement – particularly on the face – imposes a considerable psychosocial burden and can significantly impair quality of life (19).

Despite the clinical diversity of cutaneous sarcoidosis, comparative analyses of organ involvement, treatment response and prognosis across specific cutaneous subtypes have not been systemically undertaken. To address this gap, we examined a large cohort of patients with systemic sarcoidosis from 2 academic centres. Given the marked morphological heterogeneity of cutaneous sarcoidosis, we hypothesized that patterns and severity of systemic involvement as well as treatment response differ across subtypes. We also investigated how often cutaneous manifestations lead to the initial diagnosis of sarcoidosis.

MATERIAL AND METHODS

Study design and patients

This cross-sectional, 2-centre study included patients with sarcoidosis seen at the Departments of Dermatology of the Medical University of Vienna and the Friedrich Alexander University (FAU) Erlangen-Nürnberg. Individuals with cutaneous sarcoidosis who received topical or systemic treatment between January 2016 and July 2025 were identified via International Statistical Classification of Diseases (ICD-10) coding and histological databases. In addition, 26 patients without clinical evidence of cutaneous involvement but with treatment-requiring moderate pulmonary sarcoidosis were included as an exploratory comparator group to allow comparison of systemic organ involvement between patients with and without cutaneous sarcoidosis. These individuals were referred to the dermatology departments for systematic screening for potential skin manifestations. All cases had biopsy-proven noncaseating granulomas consistent with the diagnostic criteria for sarcoidosis defined by the American Thoracic Society (ATS), European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG). Histological evaluation was performed by board-certified pathologists or dermatopathologists. No formal power of calculation was performed due to the retrospective study design.

Exclusion criteria comprised insufficient documentation, which was defined as missing data in more than one key category (organ screening, disease duration, treatment history or follow-up, laboratory screening or photographic documentation) and lack of histological confirmation of sarcoidosis. To compare systemic disease burden, an additional control group of patients with noncutaneous sarcoidosis but histologically confirmed involvement of other organs was included.

The study complied with Good Clinical Practice and the Declaration of Helsinki and was approved by the local Institutional Review Board (IRB) (1529/2025). All participants provided informed consent according to CARE guidelines.

Clinical data collection

Demographic data (age, sex, body mass index) and disease-specific variables (disease duration, anatomical distribution, extent of skin involvement [localized, disseminated], extracutaneous organ manifestations [central nervous system, eyes, heart, kidneys, liver, lungs, lymph nodes, mucosal sites, musculoskeletal system, salivary glands, spleen] and leading organ at first diagnosis) were extracted from medical records and supported by structured patient telephone interviews. Lung involvement was classified according to Scadding staging; parenchymal lung disease (grade 2–4) was considered major organ involvement (1). Treatment history included topical glucocorticoids and tacrolimus, systemic glucocorticoids, conventional immunomodulators (hydroxychloroquine, dapsone), immunosuppressive drugs (mycophenolate mofetil, azathioprine, methotrexate, cyclosporine A) and targeted agents (sirolimus, Janus kinase inhibitors, tumour necrosis factor inhibitors). For all patients, the drug inducing remission, presence of relapse, comorbidities and need for chronic treatment (>1 year) were documented.

Classification of cutaneous sarcoidosis

Cutaneous phenotypes were defined according to clinical morphology following published criteria (20).

Plaque sarcoidosis was defined as indurated plaques >1 cm, ranging from flesh-coloured to erythematous or red-brown. Papules were discrete lesions measuring 0.1–1 cm. Subcutaneous sarcoidosis represented dermal or subdermal nodules. Scar sarcoidosis indicated granulomatous infiltration of scars, tattoos or sites of prior skin injury. Lupus pernio consisted of chronic infiltrative papulonodular or plaque-like lesions on cold-exposed facial areas. Erythema nodosum, a reactive sarcoidosis-associated skin manifestation, presented as painful, livid subcutaneous nodules on the lower extremities and was frequently associated with bilateral hilar lymphadenopathy and symmetric ankle arthritis (Löfgren's syndrome). Patients exhibiting multiple lesion types were classified according to the predominant clinical phenotype.

Assessment of systemic disease burden

The evaluation of systemic disease burden in sarcoidosis is challenged by the absence of a validated, organ-weighted severity score. While the WASOG Organ Involvement Instrument and the Sarcoidosis Diagnostic Score (SDS) allow standardized classification of organ involvement and estimation of diagnostic certainty, they do not quantify disease severity or activity (21). Other available tools focus on specific domains, such as cutaneous disease extent (CSAMI) or patient-reported outcomes (King's Sarcoidosis Questionnaire) (22, 23).

To enable comparative analyses of extracutaneous involvement across patient subgroups, we applied a pragmatic, study-specific Extracutaneous Organ Severity (ECOS) score. Major internal organs (lungs, heart, CNS, liver and kidneys) were weighted with 3 points; clinically relevant eye or musculoskeletal involvement with 2 points; and lymph nodes, spleen, salivary glands and mucosal surfaces with 1 point. Scores ranged from 1 (minimal) to 23 (maximum).

Laboratory evaluation

Baseline serum angiotensin converting enzyme (ACE) and soluble interleukin-2 receptor (IL-2R) concentrations were assessed in treatment naive patients only.

Statistical analysis

All data were pseudonymized. Statistical analysis was performed using GraphPad Prism version 9 (GraphPad Software, San Diego, CA, USA). Group comparisons involved one-way analysis of variance (ANOVA) for continuous variables and χ^2 or Fisher exact test for categorical variables. Relapse-associated factors were analysed using Wilcoxon rank-sum test for continuous/discrete variables and χ^2 or Fisher exact test for categorical variables as appropriate. Two-sided *p-values*<0.05 were considered statistically significant.

RESULTS

Patients' characteristics

A total of 125 biopsy-proven sarcoidosis patients were included (Vienna *n*=66, Erlangen *n*=59); 57% were female and the median age was 53 years [IQR 40–59] (**Table I**). The median disease duration was 4 years [IQR 2–4]. Cutaneous involvement was present in 99 patients (79.2%), while 26 patients (20.8%) had noncutaneous sarcoidosis.

Table I. Demographic parameters, comorbidities, disease duration and lesion localization across subgroups

	All N=125	No cutaneous N=26	All cutaneous N=99	Plaque N=39	Papular N=19	Sub-cutaneous N=13	Scar N=15	L. pernio N=9	E. nodosum N=9
Demographic characteristics									
Age (years), median (IQR)	53 (40;59)	50 (38;62)	49 (40;57)	48 (40;58)	57 (51;70)	48 (42;56)	42 (35;47)	44 (34;52)	45 (41;49)
Female, *N* (%)	71 (57)	11 (52)	60 (60)	20 (52)	11 (58)	10 (77)	11 (73)	3 (74)	5 (55)
BMI, median (IQR)	28 (24;32)	29 (26;31)	27 (24;32)	28 (25;33)	28 (24;33)	28 (25;32)	24 (24;30)	22 (20;25)	28 (27;32)
Coexisting conditions									
AH, *N* (%)	43 (34)	11 (42)	32 (32)	16 (41)	9 (47)	2 (15)	3 (20)	0 (0)	2 (22)
Metabolic, *N* (%)	50 (40)	12 (46)	38 (38)	18 (46)	4 (21)	5 (38)	3 (20)	2 (50)	1 (11)
Thyroid, *N* (%)	32 (26)	7 (27)	25 (25)	12 (31)	7 (37)	2 (15)	1 (7)	1 (25)	2 (22)
Lung, *N* (%)	39 (31)	7 (27)	32 (32)	8 (21)	1 (5)	2 (15)	0 (0)	1 (25)	0 (0)
Tumour, *N* (%)	7 (6)	2 (8)	5 (5)	4 (10)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)
DVT/Apoplex, *N* (%)	12 (10)	5 (19)	7 (7)	2 (5)	1 (5)	1 (8)	0 (0)	0 (0)	0 (0)
Disease-specific characteristics									
Disease duration, median (IQR)	4 (2;4)	6 (2;5;16)	3 (1;4)	4 (3;7)	1 (0;3;4)	2 (1;3)	3 (2;8)	6 (3;9)	1 (0;1;1.5)
Face lesions, *N* (%)	-	-	44 (44)	20 (51)	6 (32)	5 (38)	7 (47)	4 (100)	9 (100)
Trunk lesions, *N* (%)	-	-	26 (26)	9 (23)	13 (68)	1 (8)	1 (7)	0 (0)	0 (0)
Extremity lesions, *N* (%)	-	-	68 (68)	24 (62)	17 (89)	8 (62)	6 (43)	0 (0)	9 (100)
ACE (U/L), median (IQR)	47 (27;78)	39 (26;61)	52 (28;78)	45 (27;84)	59 (56;78)	59 (31;64)	48 (38;86)	91 (84;93)	47 (24;73)
IL-2R (U/ml), median (IQR)	1,098 (613;1,805)	905 (480;1,566)	1,215 (863;1,805)	1,079 (602;2,187)	1,215 (422;2,107)	1,196 (779;1,444)	887 (720;1,617)	1,107 (1,224;2,418)	1,103 (857;1,378)

Values are reported as the number of patients (*N*) and corresponding percentages (%). Coexisting conditions: "Metabolic" includes metabolic syndrome, hyperlipidaemia, hypercholesterolemia, and diabetes mellitus; "Lung" includes asthma and chronic obstructive pulmonary disease (COPD). "Thyroid" comprises active hypothyroidism, hyperthyroidism, and autoimmune thyroiditis; "Tumour" includes all malignant neoplasms. aHT, arterial hypertension; DVT = deep vein thrombosis. Reference ranges: angiotensin-converting enzyme (ACE), 20–70 U/L; soluble interleukin-2 receptor (sIL-2R), 378–2,114 pg/mL.

Among cutaneous cases, plaque sarcoidosis was the most frequent subtype (39%), followed by papular (19%), scar (15%), subcutaneous (13%), erythema nodosum (9%), and lupus pernio (4%). Demographic variables were comparable across all subtypes (**Table II**).

Organ severity differs between patients with and without cutaneous sarcoidosis

Patients without cutaneous involvement displayed a significantly higher overall disease burden (median ECOS 7 [IQR 3,7;9]) compared with individuals with skin disease (median ECOS 3 [IQR 1;6]; $p<0.0001$) (**Fig. 1**A). Within cutaneous subtypes, papular sarcoidosis exhibited the lowest organ severity ($p=0.019$) (Fig. 1B). Plaque sarcoidosis was associated with significantly higher systemic involvement than the papular subtype (median 3.5 vs. 0; $p=0.015$) (Fig. 1B).

Furthermore, the number of extracutaneous organs involved correlated strongly with the ECOS score. Notably, 58% of papular sarcoidosis cases showed isolated skin involvement without systemic disease (**Fig. 2**). In contrast, lupus pernio, scar sarcoidosis and subcutaneous sarcoidosis were frequently associated with multi-organ disease. Erythema nodosum was consistently accompanied by lymphadenopathy.

Patterns of systemic involvement

Across all forms of cutaneous sarcoidosis, involvement of lymph nodes (64%) and lung parenchyma with grade 2–4 affection (48%) were most frequent (**Table III**) (24). Musculoskeletal (14%) and ocular (7%) involvement were less common; cardiac, renal and CNS involvement each remained<5% (Table III).

Papular sarcoidosis showed markedly lower rates of lymph node involvement (26%) and lung involvement (21%), whereas other subtypes ranged from 60–100% and 38–75%, respectively. CNS involvement ($n=3$) occurred only in subcutaneous sarcoidosis and erythema nodosum ($p=0.04$) (Table III).

Remission and treatment outcomes

Spontaneous remissions were rare (3%) and topical therapies led to healing in only 11% of cases (**Table IV**). Most remissions were achieved with systemic glucocorticoids (21%) or systemic immunosuppressive drugs (37%). Sirolimus, hydroxychloroquine and tumour necrosis factor inhibitors were the most effective steroid-sparing agents. Methotrexate was widely used but contributed relatively little to remission, except in cases of erythema nodosum (Table IV). Subcutaneous lesions, lupus pernio and scar sarcoidosis were mainly resistant to treatment (Table IV).

Table II. Baseline characteristics of patients with cutaneous sarcoidosis stratified by relapse status

Characteristic	Overall *n*=95	No relapse *n*=54	Relapse *n*=41	*p*-value
Sex, *N* (%)				0.2
Male	40 (42)	26 (48)	14 (34)	
Female	55 (58)	28 (52)	27 (66)	
Age (years), median (IQR)	49 (40;58)	48 (41;56)	51 (40;60)	0.6
Body mass index (kg/m²), median (IQR)	27 (24;33)	27 (24;32)	29 (24;33)	0.4
Lung involvement, *N*(%)				0.019
0	48 (51)	33 (61)	15 (37)	
1	47 (49)	21 (39)	26 (63)	
Lymph node involvement, *N* (%)				0.7
0	34 (36)	19 (35)	15 (37)	
1	59 (62)	33 (61)	26 (63)	
n/a	2 (2)	2 (4)	0 (0)	
Eye involvement, *N* (%)				0.3
0	77 (81)	46 (85)	31 (76)	
1	17 (18)	8 (15)	9 (22)	
n/a	1 (1)	0 (0)	1 (2)	
Musculoskeletal involvement, *N* (%)				0.2
0	80 (84)	47 (87)	33 (80)	
1	13 (14)	5 (9)	8 (20)	
n/a	2 (2)	2 (4)	0 (0)	
Organ score, median (IQR)	3 (1;6)	1 (0;4)	4 (2;6)	0.017
Number of organs involved, median (IQR)	2 (1;3)	1 (0;2)	2 (1;3)	0.044
Use of prednisone, *N* (%)	50 (53)	25 (46)	25 (61)	0.2
Use of immunosuppressives, *N* (%)	48 (51)	23 (43)	25 (61)	0.10
Type of cutaneous sarcoidosis, *N* (%)				0.2
Plaque	37 (39)	22 (41)	15 (37)	
Papular	19 (20)	10 (19)	9 (22)	
Subcutaneous	12 (13)	5 (9)	7 (17)	
Scar	15 (16)	10 (19)	5 (12)	
Lupus pernio	3 (3)	0 (0)	3 (7)	
E. nodosum	9 (10)	7 (13)	2 (5)	

Values are presented as the number of patients (N) and corresponding percentages (%) or as median with interquartile range (IQR), as appropriate.
[a]Data available in 95/99 patients with cutaneous sarcoidosis.
[b]Group comparisons were performed using Pearson's chi-squared test, the Wilcoxon rank-sum test, or Fisher's exact test. 0, no; 1, yes; n/a, not applicable.

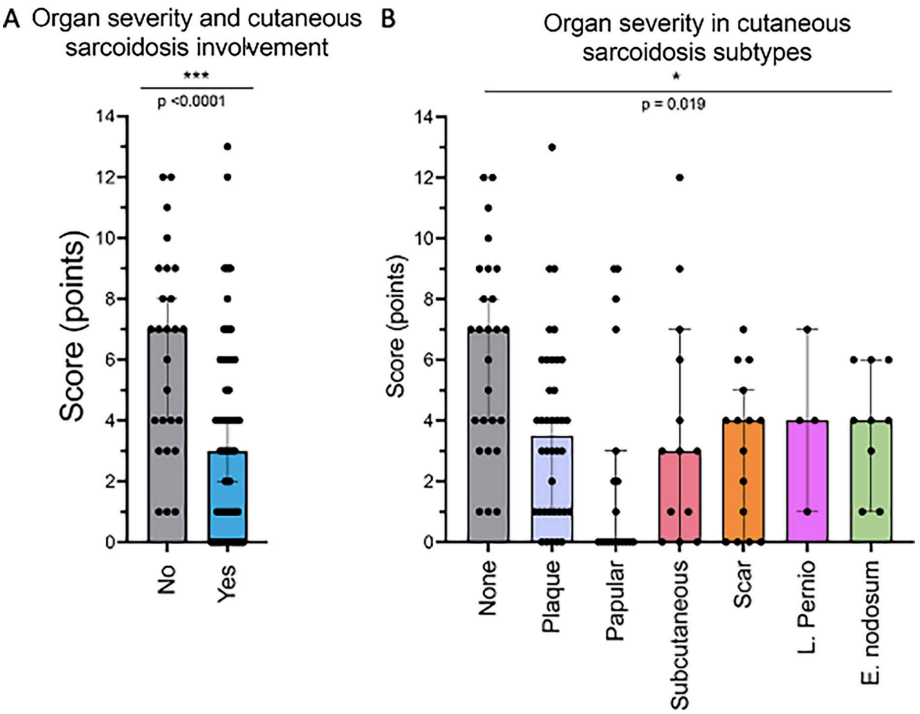

Fig. 1. Association between cutaneous involvement and systemic organ severity in sarcoidosis. (A) Patients with cutaneous sarcoidosis had a significantly lower systemic organ severity score compared to patients without cutaneous involvement (p<0.0001). Median organ severity scores were 7.0 [IQR 3.7–9.0] in patients without cutaneous involvement (n=26) and 3.0 [IQR 0.0–5.0] in patients with cutaneous sarcoidosis (n=99). (B) Among cutaneous sarcoidosis subtypes, papular sarcoidosis was associated with a significantly lower organ severity score compared to plaque-type sarcoidosis (p=0.019). Median [IQR] organ severity scores were 7.0 [3.7–9.0] (none, n=26), 3.5 [1.0–6.0] (plaque, n=39), 0.0 [0.0–3.0] (papular, n=19), 3.0 [0.5–6.5] (subcutaneous, n=13), 4.0 [0.0–5.0] (scar, n=15), 4.0 [1.7–6.2] (lupus pernio, n=4), and 4.0 [2.0–6.0] (erythema nodosum, n=9). Data are presented as median with interquartile range (IQR). Statistical significance was assessed using the Mann–Whitney U test (A) and ANOVA test with post hoc Bonferroni correction (B).

Skin disease as presenting manifestation

Cutaneous lesions led to the diagnosis of sarcoidosis in 78% of patients (**Fig. 3**A), underscoring the sentinel role of the skin. Erythema nodosum was an exception, as the diagnosis was often made on the basis of accompanying symptoms of Löfgren syndrome.

Relapse and need for chronic treatment

Relapses occurred in 40% of patients, most frequently in lupus pernio and least frequently in erythema nodosum (Fig. 3B). Relapse was associated with higher ECOS score, number of organs involved, and pulmonary disease (Table II). Long-term systemic treatment (>1 year) was required in 49% of patients – most notably in lupus pernio (100%), plaque sarcoidosis (61%) and subcutaneous sarcoidosis (61%) (Fig. 3C). Erythema nodosum (11%) and papular sarcoidosis (26%) showed the lowest need for chronic therapy (Fig. 3C).

DISCUSSION

In this large, cross-sectional, two-centre cohort, we identified distinct clinicopathological phenotypes of cutaneous sarcoidosis that differed markedly in systemic involvement, clinical course, and therapeutic response.

Papular sarcoidosis emerged as a predominantly cutaneous-limited disease with minimal systemic burden. More than half of papular cases displayed isolated skin involvement, which parallels molecular evidence describing a localized Th1-dominated

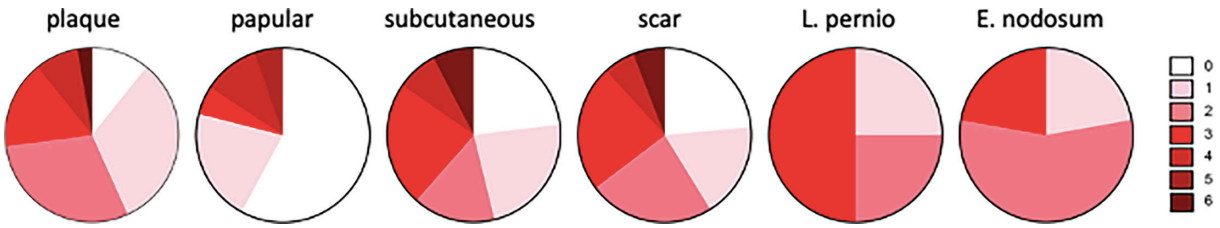

Fig. 2. Distribution of systemic organ severity across clinical subtypes of cutaneous sarcoidosis. Pie charts depict the distribution of total organ severity scores (range 0–6) within each subtype of cutaneous sarcoidosis. Increasing colour intensity corresponds to a higher systemic organ burden.

Table III. Organ involvement in patients with cutaneous sarcoidosis stratified by clinical subtype

	All N=99	Plaque N=39	Papular N=19	Subcutaneous N=13	Scar N=15	L. pernio N=4	E. nodosum N=9	*p*
Lymph nodes, *N* (%)	64 (64)	29 (74)	5 (26)	8 (61)	9 (60)	4 (100)	9 (100)	0.007
Lungs, *N* (%)	48 (48)	22 (56)	4 (21)	5 (38)	9 (60)	3 (75)	5 (56)	0.09
Musculoskeletal, *N* (%)	14 (14)	5 (13)	2 (11)	2 (15)	0 (0)	1 (25)	4 (44)	0.31
Eyes, *N* (%)	7 (7)	4 (10)	1 (5)	1 (8)	1 (7)	0 (0)	0 (0)	0.44
Kidneys, *N* (%)	5 (5)	1 (3)	2 (11)	2 (15)	0 (0)	0 (0)	0 (0)	0.29
Spleen, *N* (%)	5 (5)	3 (8)	0 (0)	1 (8)	1 (7)	0 (0)	0 (0)	0.77
Heart, *N*(%)	5 (5)	3 (8)	0 (0)	1 (8)	0 (0)	1 (25)	0 (0)	0.36
Liver, *N* (%)	4 (4)	2 (5)	1 (5)	1 (8)	0 (0)	0 (0)	0 (0)	0.87
CNS, *N* (%)	3 (3)	0 (0)	0 (0)	2 (15)	0 (0)	0 (0)	1 (11)	0.04
Mucosal tissue, *N* (%)	3 (3)	0 (0)	1 (5)	1 (8)	1 (7)	0 (0)	0 (0)	0.61
Salivary glands, *N* (%)	1 (1)	1 (3)	0 (0)	0 (0)	0 (0)	0 (0)	1 (11)	0.90

Values are reported as the number of patients (N) and corresponding percentages (%). Organs assessed include the lungs, liver, spleen, lymph nodes, central nervous system (CNS), muscles, and eyes. Differences in organ involvement between cutaneous subtypes were analysed using the chi-squared test; a significant difference was observed only for lymph node involvement (p=0.007), with the highest frequencies in lupus pernio, erythema nodosum, and plaque sarcoidosis.

granulomatous response with limited systemic cytokine activation and negligible fibrosis. Conversely, plaque sarcoidosis and lupus pernio were associated with more severe and often treatment-refractory systemic disease, consistent with increased TNF-α and IFN-γ signalling, extensive granulomatous inflammation, and higher risk of fibrosis. Scar sarcoidosis, arising in sites of prior trauma, aligns with the concept of an "immunocompromised district", characterized by altered local immune surveillance (25–28).

Our findings are consistent with those of GenPhenReSa and other large cohorts, which similarly report papular sarcoidosis as a benign musculoskeletal and cutaneous phenotype, whereas plaque disease and lupus pernio often indicate chronic systemic involvement, underscoring the prognostic relevance of classifying cutaneous subtypes (26, 29). Erythema nodosum, typically reflecting Löfgren syndrome, represented a distinct acute reactive granulomatous panniculitis rather than chronic granulomatous skin disease and was associated with an excellent prognosis.

Consistent with the literature (3, 26, 28), patients of our cohort with erythema nodosum achieved rapid remission under systemic glucocorticoids, with a median treatment duration of 1 year (0.1–1.5) compared with 4 years (2–4) in the overall cohort. Eighty percent remained relapse-free, and only two patients developed additional organ manifestations.

Approximately two-thirds of patients with cutaneous sarcoidosis had additional lymph node involvement and half displayed pulmonary parenchymal disease, underscoring the systemic nature of sarcoidosis even in the presence of skin manifestations. Importantly, ECOS score and pulmonary involvement were strongly associated with risk of relapse of cutaneous sarcoidosis. This supports current guidelines of the American Thoracic Society advocating thorough systemic evaluation in all patients presenting with cutaneous sarcoidosis (3).

Importantly, spontaneous and topical treatment-induced remissions were uncommon, highlighting the need for systemic treatment in most cases. Hydroxychloroquine, the mTOR inhibitor sirolimus and TNF-alpha inhibitors were the most effective steroid-sparing agents (7, 26), while methotrexate – although widely used – rarely induced remission in cutaneous

Table IV. Treatment outcomes and therapeutic approaches in patients with cutaneous sarcoidosis stratified by subtype

	All N=99	Plaque N=39	Papular N=19	Sub-cutaneous N=13	Scar N=15	L. pernio N=4	E. nodosum N=9
Outcomes							
Spontaneous rem., *N* (%)	3 (3)	0 (0)	0 (0)	3 (23)	0 (0)	0 (0)	0 (0)
Rem. by topical therapy, *N* (%)	11 (11)	4 (10)	2 (10)	1 (7)	3 (20)	0 (0)	1 (11)
Rem. by GCS, *N* (%)	21 (21)	6 (15)	5 (26)	1 (7)	2 (13)	0 (0)	7 (78)
Rem. by other systemic drugs, *N* (%)	37 (37)	17 (43)	7 (37)	4 (31)	6 (40)	2 (50)	1 (11)
- Sirolimus	11 (11)	7 (18)	2 (10)	0 (0)	2 (13)	0 (0)	0 (0)
- Hydroxychloroquine	10 (10)	3 (8)	1 (5)	3 (23)	1 (7)	2 (50)	0 (0)
- Tumour necrosis factor inhibitors	8 (8)	2 (5)	2 (10)	0 (0)	3 (20)	1 (25)	0 (0)
- Methotrexate	3 (3)	2 (5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (11)
- Janus kinase inhibitors	3 (3)	2 (5)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)
- Azathioprine	2 (2)	1 (3)	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)
- Dapsone	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (25)	0 (0)
- Mycophenolate	1 (1)	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)
No rem. / no treatment, *N* (%)	10 (10)	6 (15)	2 (10)	0 (0)	1 (7)	1 (25)	0 (0)
No rem. under treatment, *N* (%)	17 (17)	6 (15)	3 (16)	4 (31)	3 (20)	1 (25)	0 (0)

Values are presented as the number of patients (N) and corresponding percentages (%). The table summarizes the frequency of spontaneous remission, complete response to topical or systemic therapies, and lack of remission despite topical or systemic treatment. P-values were calculated using the chi-squared test and indicate significant differences in treatment responses between clinical subtypes.
GCS:glucocorticoids; JAKi:Janus kinase inhibitors; Rem.:remission; TNF-α-i:tumor necrosis factor-alpha inhibitors (adalimumab, infliximab, etanercept).

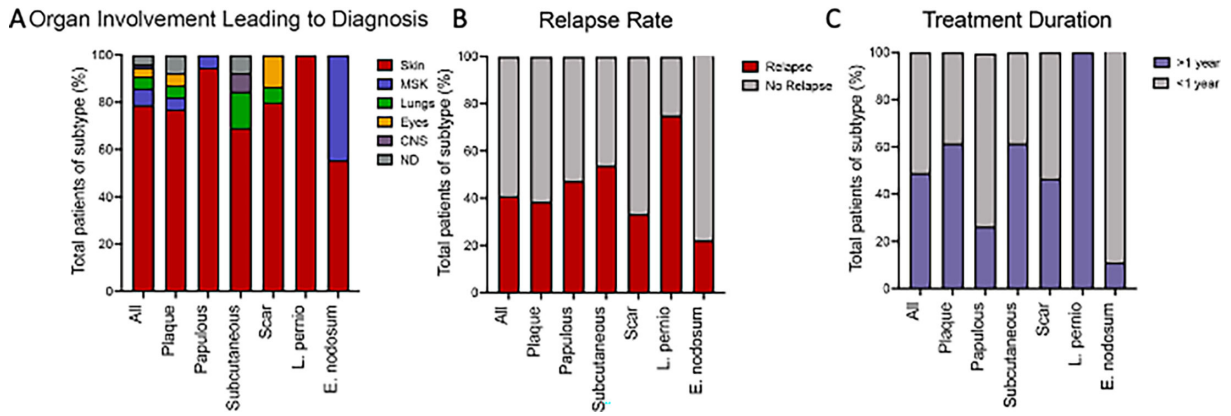

Fig. 3. Organ involvement leading to diagnosis, relapse rates, and duration of systemic therapy in subtypes of cutaneous sarcoidosis. (A) Organ manifestation that led to the initial diagnosis of sarcoidosis. (B) Relapse rate following completion of treatment. (C) Duration of systemic therapy (<1 year vs.>1 year). Percentages are calculated relative to the total number of patients within each clinical subtype.

sarcoidosis, which is in contrast to its established efficacy in pulmonary sarcoidosis (30).

Limitations include the retrospective design, potential selection bias due to inclusion of patients from two tertiary university referral centres, and centre-specific prescribing patterns, particularly given the exclusive use of mTOR inhibitors within a clinical trial and restricted application of Janus kinase inhibitors. In addition, some cutaneous sarcoidosis subgroups, particularly lupus pernio and subcutaneous sarcoidosis, were small in patient numbers, which may limit the robustness of subtype-specific analyses and generalizability. Nonetheless, the size of the cohort, comprehensive phenotyping, and uniform histological confirmation strengthen the robustness of the findings.

In summary, cutaneous sarcoidosis comprises clinically and biologically distinct subtypes that correlate with divergent systemic involvement and therapeutic requirements. Recognizing these phenotypes may refine diagnostic pathways and inform early treatment decisions. Prospective and molecularly annotated studies are needed to further delineate the mechanistic underpinnings of these phenotypes and to optimize individualized management strategies.

ACKNOWLEDGEMENTS

Funding sources: This work was funded by the FWF Austrian Science Fund [PAT 8019123] and LEO Foundation [LF-OC-24-001518] as well as a grant from the Ann Theodore Foundation Breakthrough Sarcoidosis Initiative (all to GSt). This work was also supported by the Federal Ministry of Economy, Energy and Tourism of Austria and the National Foundation for Research, Technology, and Development of Austria to the Christian Doppler Laboratory for Chronic Inflammatory Skin Diseases.

Data availability statement: Source data can be obtained from the first author upon request via E-mail to antonia.schett@uk-erlangen.de within 6 weeks. Patient data can only be shared in pseudonymized form. Otherwise, there are no restrictions to data access.

Ethics committee: Institutional Review Board (IRB) (1529/2025). The study complied with Good Clinical Practice and the Declaration of Helsinki and was approved by the local Institutional Review Board. All participants provided informed consent according to CARE guidelines.

The authors have no conflicts of interest to declare.

REFERENCES

1. Iannuzzi MC, Rybicki BA, Teirstein AS. . Sarcoidosis. N Engl J Med 2007; 357: 2153–2165. https://doi.org/10.1056/NEJMra071714
2. Krausgruber T, Redl A, Barreca D, Doberer K, Romanovskaia D, Dobnikar L, et al. Single-cell and spatial transcriptomics reveal aberrant lymphoid developmental programs driving granuloma formation. Immunity 2023; 56: 289–306. https://doi.org/10.1016/j.immuni.2023.01.014
3. Crouser ED, Maier LA, Wilson KC, Bonham CA, Morgenthau AS, Patterson KC, et al. Diagnosis and detection of sarcoidosis. An official American Thoracic Society clinical practice guideline. Am J Respir Crit Care Med 2020; 201: e26–e51. https://doi.org/10.1164/rccm.202002-0251ST
4. Sève P, Pacheco Y, Durupt F, Jamilloux Y, Gerfaud-Valentin M, Isaac S, et al. Sarcoidosis: a clinical overview from symptoms to diagnosis. Cells 2021; 10: 766. https://doi.org/10.3390/cells10040766
5. Mañá J, Rubio-Rivas M, Villalba N, Marcoval J, Iriarte A, Molina-Molina M, et al. Multidisciplinary approach and long-term follow-up in a series of 640 consecutive patients with sarcoidosis: cohort study of a 40-year clinical experience at a tertiary referral center in Barcelona, Spain. Medicine 2017; 96: e7595. https://doi.org/10.1097/MD.0000000000007595
6. Drent M, Lower EE, De Vries J. Sarcoidosis-associated fatigue. Eur Respir J 2012; 40: 255–263. https://doi.org/10.1183/09031936.00002512
7. Baughman RP, Valeyre D, Korsten P, Mathioudakis AG, Wuyts WA, Wells A, et al. ERS clinical practice guidelines on treatment of sarcoidosis. Eur Respir J 2021; 58: 2004079. https://doi.org/10.1183/13993003.04079-2020
8. Lower EE, Sturdivant M, Grate L, Baughman RP. Use of third-line therapies in advanced sarcoidosis. Clin Exp Rheumatol 2020; 38: 834–840.
9. Wang A, Singh K, Ibrahim W, King B, Damsky W. The promise of JAK inhibitors for treatment of sarcoidosis and other inflammatory disorders with macrophage activation: a review of the literature. Yale J Biol Med 2020; 93: 187–195.

10. Caplan A, Rosenbach M, Imadojemu S. Cutaneous sarcoidosis. Semin Respir Crit Care Med 2020; 41: 689–699. https://doi.org/10.1055/s-0040-1713130
11. Baughman RP, Teirstein AS, Judson MA, Rossman MD, Yeager H Jr, Bresnitz EA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med 2001; 164: 1885–1889. https://doi.org/10.1164/ajrccm.164.10.2104046
12. Costabel U, Guzman J, Baughman RP. Systemic evaluation of a potential cutaneous sarcoidosis patient. Clin Dermatol 2007; 25: 303–311. https://doi.org/10.1016/j.clindermatol.2007.03.008
13. Hanno R, Needelman A, Eiferman RA, Callen JP. Cutaneous sarcoidal granulomas and the development of systemic sarcoidosis. Arch Dermatol 1981; 117: 203–207.
14. Boch K, Langan EA, Zillikens D, Ludwig RJ, Kridin K. Evaluation of clinical and laboratory characteristics of patients with cutaneous sarcoidosis: a single-center retrospective cohort study. Front Med 2022; 9: 980507. https://doi.org/10.3389/fmed.2022.980507
15. Karadağ AS, Parish LC. Sarcoidosis: a great imitator. Clin Dermatol 2019; 37: 240–254. https://doi.org/10.1016/j.clindermatol.2019.01.005
16. Karakaya B, Kaiser Y, van Moorsel CHM, Grunewald J. Löfgren's syndrome: diagnosis, management, and disease pathogenesis. Semin Respir Crit Care Med 2017; 38: 463–476. https://doi.org/10.1055/s-0037-1602380
17. Baughman RP, Judson MA, Teirstein A, Lower EE, Lo K, Schlenker-Herceg R, et al. Chronic facial sarcoidosis including lupus pernio: clinical description and proposed scoring systems. Am J Clin Dermatol 2008; 9: 155–161. https://doi.org/10.2165/00128071-200809030-00003
18. Haimovic A, Sanchez M, Judson MA, Prystowsky S. Sarcoidosis: a comprehensive review and update for the dermatologist: part I. Cutaneous disease. J Am Acad Dermatol 2012; 66: 699. https://doi.org/10.1016/j.jaad.2011.11.965
19. Yeung H, Farber S, Birnbaum BK, Dunham J, Ogdie A, Patterson KC, et al. Reliability and validity of cutaneous sarcoidosis outcome instruments among dermatologists, pulmonologists, and rheumatologists. JAMA Dermatol 2015; 151: 1317–1322. https://doi.org/10.1001/jamadermatol.2015.2008
20. Karadağ AS, Parish LC. Clinical phenotypes of cutaneous sarcoidosis: a review. Clin Dermatol 2019; 37: 660–667.
21. Yeung H, Farber S, Birnbaum BK, Dunham J, Ogdie A, Baughman RP, et al. The WASOG sarcoidosis organ assessment instrument: an update of a previous clinical tool. Sarcoidosis Vasc Diffuse Lung Dis 2014; 31: 19–27.
22. Rosenbach M, Yeung H, Chu EY, Kim EJ, Payne AS, Takeshita J, et al. Reliability and convergent validity of the cutaneous sarcoidosis activity and morphology instrument for assessing cutaneous sarcoidosis. JAMA Dermatol 2013; 149: 550. https://doi.org/10.1001/jamadermatol.2013.60
23. Stjepanovic M, Mihailovic-Vucinic V, Gvozdenovic BS, Milin-Lazovic J, Belic S, Djurdjevic N, et al. King's Sarcoidosis Questionnaire (KSQ) - validation study in Serbian speaking population of sarcoidosis patients. PLoS One 2023; 18: e0273126. https://doi.org/10.1371/journal.pone.0273126
24. Belperio JA, Shaikh F, Abtin FG, Fishbein MC, Weigt SS, Saggar R, et al. Diagnosis and treatment of pulmonary sarcoidosis: a review. JAMA 2022; 327: 856–867. https://doi.org/10.1001/jama.2022.1570
25. Lo Schiavo A, Ruocco E, Gambardella A, O'Leary RE, Gee S. Granulomatous dysimmune reactions (sarcoidosis, granuloma annulare, and others) on differently injured skin areas. Clin Dermatol 2014; 32: 646–653. https://doi.org/10.1016/j.clindermatol.2014.04.012
26. Drent M, Crouser ED, Grunewald J. Challenges of sarcoidosis and its management. N Engl J Med 2021; 385: 1018–1032. https://doi.org/10.1056/NEJMra2101555
27. Zhang H, Costabel U, Dai H. The role of diverse immune cells in sarcoidosis. Front Immunol 2021; 12: 788502. https://doi.org/10.3389/fimmu.2021.788502
28. Monast CS, Li K, Judson MA, Baughman RP, Wadman E, Watt R, et al. Sarcoidosis extent relates to molecular variability. Clin Exp Immunol 2017; 188: 444–454. https://doi.org/10.1111/cei.12942
29. Schupp JC, Freitag-Wolf S, Bargagli E, Mihailović-Vučinić V, Rottoli P, Grubanovic A, et al. Phenotypes of organ involvement in sarcoidosis. Eur Respir J 2018; 51: 1700991. https://doi.org/10.1183/13993003.00991-2017
30. Kahlmann V, Janssen Bonás M, Moor CC, Grutters JC, Mostard RLM, van Rijswijk HNAJ, et al. First-line treatment of pulmonary sarcoidosis with prednisone or methotrexate. N Engl J Med 2025; 393: 231–242. https://doi.org/10.1056/NEJMoa2501443