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Research Article

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Symptoms, Laboratory, and Imaging Manifestations of Sarcoidosis Across Disease Stages

(Running title:** Clinical features of sarcoidosis across stages**)

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Abstract

Background and aim: *Sarcoidosis is a diagnostic challenge with extremely variable manifestations across disease stages. The aim of this study is to provide a comprehensive review of clinical, laboratory, pulmonary, and extrapulmonary manifestations across stages to enlighten the disease pathogenesis. Another goal is to determine the incidence of clinical findings relevant to sarcoidosis stages.*

Methods: *576 patients were classified across disease stages in regard to symptoms, laboratory, and imaging findings. Exclusion criteria included patients with incomplete medical records, comorbid, or those diagnosed with alternative granulomatous diseases. Data were collected on patient symptoms, laboratory, and imaging manifestations. Analysis of variance (ANOVA), Kruskal-Wallis test, chi-square, Fisher's exact, and Mann-Whitney U tests were employed for statistical assessment.*

Results: *Lung disease was detected in 92.4% while extrapulmonary organ sarcoidosis was identified in 88.2% of the patients that virtually affected almost every organ system with an extremely wide profile of clinical manifestations. Extapulmonary organ sarcoidosis revealed the highest prevalance among stage II and III patients. A highly significant correlation was observed between these stages and the clinical, laboratory findings, and the incidence of extrapulmonary organ involvement. Stages 0, I, and IV displayed the lowest correlation with the prevalance of clinical, laboratory, and the extrapulmonary organ involvement manifestations.*

Conclusions

Pulmonary and extrapulmonsary organ manifestations revealed an exquisite incidence in stages II and III due to the higher intensity of granulomatous inflammation and the excessive granuloma burden. The prevalence was lowest in stages 0 and I relevant to the low intensity of granulomatous inflammation with a lesser granuloma load. Stage IV sarcoidosis displayed the same clinical profile associatively with the waning intensity of granulomatous inflammation that ultimately lead to fibrosis. The diverse array of clinical and laboratory profile of sarcoidosis is closely associated with the intensity of granulomatous inflammation and granuloma burden that may exhibit a marked variability with the disease stages.

Keywords: *Sarcoidosis, Diagnosis, Extrapulmonary sarcoidosis, Sarcoidosis stages.*

Introduction

Sarcoidosis is a complex multisystemic disorder characterized by the formation of non-caseating granulomas that can nearly affect any organ primarily the lungs resulting from an abnormal immune response to an unknown trigger, such as an infection or an environmental factor. Although the lungs are the exclusive site of granulomatous inflammation, extrapulmonary organ involvement may arise in approximately 60% of the patients (1-3). Sarcoidosis may emerge with a wide range of systemic, pulmonary or extrapulmonary organ manifestations that are extremely variable depending on the organs involved (2,4,5). Overall, patients are highly individualized due to the instability of clinical presentations or organ relevant symptoms. Genetic and hereditary factors may also play a significant role in the development of sarcoidosis manifestations influencing susceptibility, disease presentation, inconstancy, and prognosis (6-8).

Despite its relatively rare incidence, sarcoidosis remains an important diagnostic challenge for clinicians due to its wide-ranging clinical manifestations as any organ involvement may arise during the course of the disease that can mimic other lung or systemic disorders. Intensity of the granulomatous inflammation and granuloma burden in miscellaneous organs may vary across the distinctive stages of the disease, presenting a nuanced clinical picture. This retrospective study was conducted to evaluate the clinical profile and the extrapulmonary organ manifestations of sarcoidosis across disease stages. The second aim of this study was to reveal an accurate incidence of pulmonary and extrapulmonary organ involvement manifestations in different sarcoidosis stages to facilitate early diagnosis. Another objective was to shed light on the pathogenesis of sarcoidosis through specific organ relevance debouching in discrete stages. By effectively characterizing sarcoidosis manifestations this research will lead the clinicians in the accurate diagnostic pathway that will facilitate the diagnosis of sarcoidosis.

Methods

A retrospective cohort study was conducted at the Cerrahpasa Medical Faculty Internal Medicine Department. Medical records of 624 sarcoidosis patients admitted between 1974 and 2024 were reviewed. Patients were diagnosed with sarcoidosis based on clinical, radiological, histopathological, and follow-up findings. After incomplete medical or follow-up records were excluded, a total of 576 patients were included in the study. Data of the eligible patients were reviewed to collect demographic corollary, including age, sex, and ethnicity. The patients underwent a meticulous assessment for pulmonary symptoms such as well as the constitutional and extrapulmonary organ manifestations as well as the laboratory, imaging, and pathologic findings that may arise by sarcoidosis involvement.

A thorough physical examination with relevant clinical consultations were performed to determine dermatologic, ocular, neurologic, and cardiac system involvement. Laboratory investigations included complete blood count, serum inflammatory markers (ESR, CRP), immunoglobulin levels, serum angiotensin-converting enzyme (ACE), tuberculine test, serum, and 24/h urinary calcium. PFT and DLCO results were reviewed. Screening studies comprised chest X-ray, HRCT, and ultrasound. Nuclear imaging modalities like ^{18}FDG (9-12) and the novel ^{68}Ga-citrate PET/CT (13) were performed in equivocal cases to reveal granulomatous inflammation and biopsy sites. Fiberoptic bronchoscopy, BAL, TBB, mediastinoscopy, and extrapulmonary organ biopsy were done for final diagnosis. Disease stages were categorized according to the modified Scadding criteria based on chest radiography findings (14**)**. A definitive sarcoidosis diagnosis was reached by pathologic examination of at least two organ biopsy samples compatible with sarcoidosis, exlusion of granulomatous diseases, and a follow-up period of three years.

Continuous variables were presented as mean ± standard deviation while categorical variables were revealed as frequencies and percentages. Descriptive statistics were used for the assessment of demographic characteristics, clinical manifestations, laboratory, and imaging findings. Comparisons between groups were done by analysis of variance (ANOVA), Kruskal-Wallis test, chi-square test, or Fisher's exact test, and Mann-Whitney U test as applicable. Chi-square tests or Fisher's exact tests were employed to analyze categorical variables while t-tests or Mann-Whitney U tests were used for continuous variables. For correlation assessment, an r value $0.00 \leq r \leq 0.10$, $0.10 < r \leq 0.39$, $0.40 \leq r < 0.69$, $0.70 \leq r < 0.89$ and $0.90 \leq r \leq 1.0$ were considered as negligible, weak, moderate, strong, and very strong correlation, respectively (15). Logistic regression analysis was performed to evaluate the association between disease stage and specific organ involvement**.** SPSS 29 version was used for statistical assessment. Pertaining to the statistical analysis, a p-value less than 0.05 was considered statistically significant. For an explicit comparison of clinical, laboratory, and imaging data in regard to sarcoidosis stages, a mean r value was calculated to reflect the results in a more coherent and distinctive format as the correlation coefficient of stage II and III were in close range in all features of sarcoidosis revealing a high match while a mean r value was also calculated concerning stages 0, I, and IV because they displayed a similar low association with the disease attributes. Coefficients r_1 and r_2 designate the mean correlation of overall sarcoidosis manifestations across stages 0, I and II, III while r_3 defines the correlation of clinical features through stage IV patients.

Results

The mean age was 37.8 years (IQR 20-64) with 387 (67.2%) female and 189 (32.8%) male patients. Age distribution at the time of diagnosis was as follows: 23 (4%) patients aged 20 and under, 145 (25.2%) between 21-30, 180 (31.2%) between 31-40, 131 (22.7%) between 41-64 years. The mean duration of symptoms at presentation and disease from diagnosis was 14.2±6.8 months and 72±16.8 months (IQR 2-10 years), respectively. Distribution of patients across stages according to Scadding classification (6,7) were as follows: 74 (12.8%) had stage 0, 230 (39.9%) stage I, 182 (31.6%) stage II, 70 (12.2%) stage III and 20 (3.5%) stage IV while stage II was the most prevalent at admission. Of the 576 patients, 512 (88.8%) had extrapulmonary sarcoidosis. Incidence and statistical correlation of patient symptoms across sarcoidosis stages is shown in Table 1. Pulmonary involvement was observed in 532 patients (92.4%) at admission as the most frequently involved organ. Ninety-four (16.3%) patients were asymptomatic at the initial admission and were diagnosed with a coincidental chest x-ray examination. The most common pulmonary symptoms were dry cough and dyspnea that revealed a low correlation with disease stages. Constitutional symptoms did not reveal a significant correlation with disease stage. Extrapulmonary organ symptoms comprising specific cutaneous and ocular manifestations did not show a notable statistical association across stages. The highest prevalence in the number of organs involved was observed in stage II and III patients while it was significantly lower in stages 0 and I (Table 2). Multiple organ sarcoidosis was identified in 472 (81.9%) patients while 62 (10.8%) had more than three organ involvement.

Incidence of organ sarcoidosis is depicted in Table 3. The most frequently involved organ across stages was lung followed by thoracic lymph nodes, skin, and eye. Thoracic and peripheral lymph node sarcoidosis were identified in 342 (59.4%) and 198 (34.4%) of the patients, respectively. Cutaneous sarcoidosis was the most common extrapulmonary involvement detected in 190 (32.9%) of the patients. Of these, 112 (19.4%) had erythema nodosum, 28 had (4.9%), and 136 (23.9%) presented with non-specific lesions such as maculopapular rash, plaque-like, verrucous, or psoriatic lesions, subcutaneous nodules, and scar granulomas. Ocular disease was diagnosed in 172 (29.8%), liver sarcoidosis in 96 (16.7%), and splenic involvement in 48 (7.3%) patients. These organs revealed a high incidence of

Table 1: Incidence of symptoms among sarcoidosis patients at the initial setting.

Symptoms	Total (%)	Stage 0 (%)	Stage I (%)	Stage II (%)	Stage III (%)	Stage IV (%)	r_1	r_2	r_3	p
Asymptomatic	94 (16.3%)	28 (4.9%)	32 (5.6%)	24 (4.2%)	8 (1.4%)	6 (1.0%)	0.16	0.18	0.12	<0.24
Dry cough	198 (34.4%)	14 (2.4%)	26 (4.5%)	40 (6.9%)	56 (9.7%)	62 (10.8%)	0.24	0.28	0.46	<0.18
Dyspnea	102 (17.7%)	8 (1.4%)	12 (2.1%)	18 (3.2%)	28 (4.9%)	36 (6.3%)	0.18	0.42	0.58	<0.16
Malaise	118 (20.4%)	10 (1.7%)	18 (3.1%)	34 (5.9%)	48 (8.3%)	8 (1.4%)	0.22	0.38	0.34	<0.12
Fatigue	228 (39.6%)	24 (4.2%	38 (6.6%)	48 (8.3%)	56 (9.7%)	62 (10.8)	0.26	0.46	0.42	<0.20
Fever	58 (10.1%)	6 (1.0%)	8 (1.4%)	12 (2.1%)	14 (2.4%)	18 (3.1%)	0.28	0.28	0.24	<0.16
Weight loss	35 (6.1%)	1 (0.17%)	4 (0.69%)	8 (1.4%)	9 (1.6%)	13 (2.3%)	0.12	0.24	0.16	<0.18
Night sweats	42 (7.3%)	0 (0.0%)	6 (1.0%)	10 (1.74%)	12 (2.1%)	14 (2.4%)	0.16	0.18	0.14	<0.24
Weakness	46 (7.9%)	2 (0.0034%)	6 (1.0%)	8 (1.4%)	12 (2.1%)	18 (3.1%)	0.14	0.16	0.26	<0.05
Nonspecific skin lesions	86 (14.9%)	8 (1.4%)	12 (2.1%)	18 (3.1%)	38 (6.6%)	10 (1.7%)	0.18	0.36	0.18	<0.16
Specific skin lesions	120 (20.8%)	9 (1.6%)	14 (2.4%)	36 (6.3%)	51 (8.9%)	10 (1.7%)	0.48	0.62	0.54	<0.05
Ocular symptoms	134 (23.3%)	10 (1.7%)	18 (3.2%)	40 (6.9%)	54 (9.4%)	12 (2.1%)	0.42	0.56	0.32	<0.16
Uveitis	172 (29.8%)	12 (2.1%)	36 (6.3%)	52 (9.0%)	58 (10.1%)	14 (2.4%)	0.52	0.68	0.42	<0.05
Arthralgia	124 (%21.5)	9 (1.6%)	28 (4.9%)	34 (5.9%)	45 (7.8%)	8 (1.4%)	0.16	0.28	0.16	<0.24
Myalgia	50 (8.7%)	6 (0.01)	8 (1.4%)	22 (3.8%)	10 (1.7%)	4 (0.7%)	0.18	0.18	0.26	<0.18
Bone pain	49 (8.5%)	2 (0.35%)	7 (1.2%)	12 (2.1%)	20 (3.4%)	8 (1.4%)	0.12	0.24	0.12	<0.16
Parotid enlargement	28 (4.9%)	0 (0.0%)	2 (0.34%)	9 (1.6%)	14 (2.4%)	3 (0.53%)	0.18	0.62	0.28	<0.20
Facial paralysis	18 (3.1%)	0 (0.0%)	1 (0.17%)	6 (1.0%)	10 (1.7%)	1 (0.17%)	0.16	0.34	0.14	<0.24
Lofgren syndrome	98 (17.0%)	8 (1.4%)	16 (2.8%)	32 (5.6%)	40 (6.9%)	2 (0.34%)	0.86	0.84	0.42	<0.01
Neurologic symptoms	34 (5.9%)	2 (0.34%)	6 (0.10%)	10 (1.7%)	12 (2.1%)	4 (0.69%)	0.14	0.18	0.18	<0.15
Cardiac symptoms	30 (5.2%)	0 (0.0%)	4 (0.69%)	8 (1.4%)	12 (2.1%)	6 (1.0%)	0.18	0.12	0.16	<0.28

* Specific cutaneous lesions: erythema nodosum, lupus pernio

involvement across II and III stages with a prevalance for stages 0, I, and IV. Of the specific organ features, erythema nodosum and anterior uveitis displayed the highest prevalence (Table 1, 3) across stages. Cardiac (OR 2.5, 95% CI 1.5-4.2, p<0.01) and nervous system involvement (OR 2.1, 95% CI 1.2-3.7, p<0.05) were significantly more common in stages II and III (Table 3). CBC, ESR, and CRP showed abnormal results in a minority of patients without any significant correlation with disease stages. Immunoglobulin, liver, and renal function test values revealed pathologic results that did not show a significant association with stages. Tuberculine test was negative in 76.3% of the patients displaying a significant correlation with stages II and III (Table 4).

Table 2: Prevalence of extrapulmonary organ involvement across sarcoidosis stages.

Organs	Total	Stage 0 (%)	Stage I (%)	Stage II (%)	Stage III (%)	Stage IV (%)	r_1	r_2	r_3	p
One	104/576 (18.1%)	56/68 (82.4%)	22/76 (28.9%)	32/164 (19.5%)	8/58 (13.8%)	2/14 (14.3%)	0.92	0.98	0.96	<0.01
Two	314/576 (54.5%)	56/68 (82.4)	60/76 (78.9%)	138/164 (84.1%)	52/58 (89.7%)	8/14 (57.1%)	0.16	0.84	0.38	<0.05
Three	184/576 (31.9%)	8/68 (11.8%)	24/76 (31.6%)	102/164 (62.2%)	46/58 (79.3%)	4/14 (28.6%)	0.28	0.92	0.32	<0.01
≥ Four	62/576 (10.8%)	0/68 (0.0%)	6/76 (7.9%)	24/164 (31.4%)	30/58 (51.7%)	2/14 (14.3%)	0.34	0.82	0.24	<0.01

Table 3: Incidence of organ involvement across disease stages.

	Total (%)	Stage 0 (%)	Stage I (%)	Stage II (%)	Stage III (%)	Stage IV (%)	r_1	r_2	r_3	p
Lung	532 (92.4%)	48 (8.3%)	242 (42.0%)	142 (24.7%)	68 (11.8%)	32 (5.6%)	0.26	0.78	0.92	<0.05
Thoracic lymph nodes	342 (59.4%)	18 (3.1%)	162 (29.2%)	128 (22.2%)	28 (4.9%)	6 (1.0%)	0.32	0.68	0.86	<0.01
Extrathoracic lymph nodes	106 (18.4%)	10 (1.7%)	18 (3.1%)	28 (4.9%)	32 (5.6%)	8 (1.4%)	0.36	0.72	0.72	<0.01
Skin	190 (32.9%)	12 (2.1%)	28 (4.9%)	56 (9.7%)	70 /12.2%)	24 (4.2%)	0.28	0.82	0.24	<0.05
Eye	172 (29.8%)	14 (2.4%)	28 (4.9%)	42 (7.3%)	58 (10.1%)	30 (5.2%)	0.42	0.86	0.18	<0.01
Liver	96 (16.7%)	2 (0.35%)	8 (1.4%)	34 (5.9%)	42 (7.3%)	10 (1.7%)	0.24	0.54	0.12	<0.01
Spleen	48 (8.3%)	0 (0.0%)	2 (0.34%)	18 (3.1%)	24 (4.2%)	2 (0.34%)	0.18	0.46	0.10	<0.05
Kidney	24 (4.2%)	0 (0.0%)	1 (0.17%)	8 (1.4%)	12 (2.1%)	3 (0.52%)	0.16	0.70	0.10	<0.05
Parotid	32 (5.6%)	1 (0.17%)	3 (0.52%)	12 (2.1%)	14 (2.4%)	2 (0.35%)	0.32	0.68	0.24	<0.01
Upper respiratory tract	16 (2.8%)	1 (0.17%)	2 (0.34%)	5 (0.68%)	6 (0.01)	2 (0.35%)	0.12	0.64	0.08	<0.01
Heart	36 (6.3%)	0 (0.0%)	2 (0.35%)	14 (2.4%)	18 (3.1%)	2 (0.35%)	0.10	0.72	0.11	<0.01
Nervous system	34 (5.9%)	0 (0.0%)	2 (0.35%)	12 (2.1%)	16 (2.8%)	4 (0.69%)	0.12	0.76	0.12	<0.05
GIS	6 (1.0%)	0 (0.0%)	0 (0.0%)	2 (0.35%)	4 (0.70%)	0 (0.0%)	0.14	0.62	0.06	<0.05
Bone	18 (3.1%(	0 (0.0%)	1 (0.17%)	5 (0.87%)	9 (1.6%)	3 (0.52%)	0.11	0.42	0.04	<0.16
Joint	84 (14.6%)	4 (0.69%)	12 (2.1%)	28 (4.9%)	36 (6.3%)	4 (0.68%)	0.14	0.68	0.12	<0.05
Muscle	26 (4.5%)	1 (0.17%)	5 (0.87%)	8 (1.4%)	10 (1.7%)	2 (0.35%)	0.12	0.72	0.14	<0.05
Marrow	8 (1.4%)	0 (0.0%)	0 (0.0%)	2 (0.35%)	5 (0.87%)	1 (0.17%)	0.08	0.62	0.04	<0.05

Diagnosis was achieved by TTB in 251 (43.6%), lymph node biopsy in 82 (14.2%), skin punch biopsy in 78 (13.5%), mediastinoscopy in 56 (9.7%), liver biopsy in 17 (3.1%), parotid biopsy in 12 (1.9%), conjunctival biopsy in 10 (1.7%), and orbital biopsy in 8 (1.4%) patients. While sarcoidosis was diagnosed clinically in 62 (10.8%) patients, it was identified in 38 patients after an average follow-up of two years. Kveim test was positive in 76 (13.1%) patients. Laboratory and imaging findings of sarcoidosis with correlation across stages are denoted in Table 4. Lung function tests did not reveal a significant correlation with sarcoidosis stages. DLCO revealed substansially decreased levels in stages II, III, and IV. Thorax CT, ^{18}F-FDG and ^{68}Ga-citrate PET/CT significantly showed a noteworthy diagnostic correlation with stages II, III and IV. Kveim test had the highest diagnostic yield for all stages. BAL, TBB, and bronchial biopsy provided the most significant diagnostic rates in stage II and III disease. Lymph node and extrapulmonary organ biopsy yielded a similar diagnostic yield for stage II and III disease (Table 4). Clinical, laboratory, and imaging manifestations displayed a significant correlation with stage II and III disease while these features revealed a low correlation with stage 0, I, and IV sarcoidosis. A noteworthy

association was observed between stages II and III with a high incidence of extrapulmonary organ involvement (r: 0.72, p<0.01 and (r: 0.82, p<0.05), respectively. A statistically significant excess of more than two extrapulmonary organ involvement was defined during in these compared to other stages.

Table 4: Incidence of abnormal laboratory and imaging findings across sarcoidosis stages.

	Total* (%)	**Stage 0 (%)**	**Stage I (%)**	**Stage II (%)**	**Stage III (%)**	**Stage IV (%)**	**r_1**	**r_2**	**r_3**	**p**
CBC	30 (5.2%)	2 (2.7%)	8 (3.5%)	15 (6.5%)	4 (5.7%)	1 (5.0%)	0.24	0.18	0.14	<0.05
ESR, CRP	82 (14.2)	6 (8.1%)	20 (8.7%)	14 (7.7%)	6 (8.6%	1 (5.0%)	0.28	0.16	0.12	<0.05
Immunoglobulin	43 (7.5%)	2 (2.7%)	18 (7.8%)	16 (8.8%)	6 (8.6%)	1 (5.0%)	0.22	0.32	0.16	<0.05
LFT	57 (10.1)	3 (4.1%)	12 (5.2%)	28 (15.4%)	13 (18.6%)	1 (5.0%)	0.16	0.24	0.18	<0.01
RFT	33 (5.7%)	2 (2.7%)	6 (2.6%)	17 (9.3%)	6 (8.6%)	1 (5.0)	0.12	0.18	0.14	<0.01
Serum Ca	62 (10.8)	2 (2.7%)	10 (4.3%)	20 (10.9%)	11 (15.7%)	1 (5.0%)	0.18	0.52	0.24	<0.05
Serum ACE	**280 (48.6)**	**16 (21.6%)**	**94 (40.9%)**	**116 (63.7%)**	**50 (71.4%)**	**4 (20.0%)**	**0.26**	**0.74**	**0.24**	**<0.01**
Tuberculin test**	**348/456 (76.3)**	**10/74 (13.5%)**	**152/230 (66.1%)**	**124/182 (68.1%)**	**58 (82.9%)**	**4 (15.0%)**	**0.38**	**0.64**	**0.28**	**<0.01**
Restrictive PFT	**190/576 (32.9%)**	**2 (2.7%)**	**58 (25.2%)**	**84 (46.2%)**	**32 (45.7%)**	**14/14 (100.0 %)**	**0.14**	**0.42**	**0.78**	**<0.05**
Obstructive PFT	**82/576 (14.2)**	**4 (5.8%)**	**20 (7.4%)**	**38 (23.2%)**	**18 (32.8%)**	**2 (10.0%)**	**0.12**	**0.16**	**0.10**	**<0.16**
DLCO	**198/576 (34.4)**	**6 (8.1%)**	**54 (23.5%)**	**78 (42.9%)**	**46 (67.7%)**	**14/14 (100.0 %)**	**0.28**	**0.62**	**0.92**	**<0.01**
Thorax CT	**428/468 (74.3)**	**4 (5.4%)**	**186 (80.1%)**	**168 (92.3%)**	**60 (85.7%)**	**20 (100.0 %)**	**0.20**	**0.92**	**0.98**	**<0.01**
^{18}F-FDG PET/CT	**42/48 (87.5)**	**2 (4.2%)**	**4 (8.3%)**	**19 (39.6%)**	**16 (33.3%)**	**1 (2.1%)**	**0.28**	**0.86**	**0.54**	**<0.05**
Ga^{68}-citrate PET/CT	**49/54 (90.7)**	**4 (7.4%)**	**6 (11.1%)**	**24 (40.7%)**	**18 (44.4%)**	**2 (3.7%)**	**0.24**	**0.78**	**0.42**	**<0.01**
Kveim test	**62/86 (72.1)**	**3/10 (30.0%)**	**12/20 (60.0%)**	**21/24 (66.7%)**	**25/31 (87.5%)**	**0 (0.0%)**	**0.36**	**0.86**	**0.38**	**<0.05**
BAL CD_4/CD_8 >3.5	**196/448 (43.8)**	**12/54 (20.7%)**	**50/180 (42.3%)**	**104/152 (69.2%)**	**28/60 (46.1%)**	**2/18 (10.0%)**	**0.42**	**0.82**	**0.24**	**<0.01**
TBB	**192/428 (45.8)**	**8/42 (13.8%)**	**48/176 (19.1%)**	**108/164 (65.6%)**	**26/38 (68.4%)**	**2/8 (25.0%)**	**0.52**	**0.84**	**0.36**	**<0.01**
Bronchial biopsy	**148/342 (43.3)**	**4/32 (12.5%)**	**48/150 (32.0%)**	**76/128 (59.4%)**	**18/2 (69.2%)**	**2/6 (33.3%)**	**0.48**	**0.68**	**0.32**	**<0.05**
Lymph node biopsy	**78/224 (47.3)**	**2/18 (11.1%)**	**30/96 (31.3%)**	**32/84 (38.1%)**	**12/32 (37.5%)**	**0/4 (0.00%)**	**0.34**	**0.78**	**0.34**	**<0.05**
Other organ biopsy	**162/326 (49.7)**	**6/58 (10.3%)**	**12/64 (18.6%)**	**108/136 (79.4%)**	**33/54 (59.3%)**	**3/14 (21.4%)**	**0.42**	**0.72**	**0.28**	**<0.05**

***Negative tuberculin test**

Logistic regression analysis revealed a statistically higher incidence for (lymph node, cutaneous, and ocular involvement among stage II and III sarcoidosis patients. Lymph node, cutaneous, and ocular sarcoidosis revealed a statistically higher incidence in stage II and III sarcoidosis patients. Cardiac (OR 2.5, 95% CI 1.5-4.2, p<0.01), nervous system (OR 2.1, 95% CI 1.2-3.7, p<0.05) and other rare organ involvement were also significantly more common in these stages.

Discussion

Sarcoidosis is a systemic disorder characterized by noncaseiting granulomatous inflammation, predominantly affecting the lungs and the lymph nodes (1-3). However, its systemic nature often

leads to involvement of various extrapulmonary organs that can significantly impact disease presentation, prognosis, and management strategies (8-12). In this study, we comprehensively aimed to assess the clinical manifestations of sarcoidosis across disease stages that may highlight the diverse pathoenetic mechanisms of sarcoidosis. The present study provides an overall analysis of sarcoidosis profile along different stages. Our findings reveal a complex interplay between pulmonary and extrapulmonary manifestations of sarcoidosis across stages focusing on the need for a holistic approach for patient assessment. One notable aspect was variability of organ involvement across stages. In stages 0 and I, pulmonary manifestations predominated, often presenting with an asymptomatic or a mild respiratory symptom profile. Gradually waxing intensity of granulomatous inflammation in stages II and III had a significant impact on sarcoidosis profile and the organ involvement. We observed a higher incidence of extrapulmonary organ sarcoidosis in these stages suggesting a dynamic progressive status of granulomatous inflammation reaching its peak status. Clinical findings across disease stages highlighted the diverse pathoenetic mechanisms of sarcoidosis.

The clinical symptoms, abnormal laboratory profile, and the extrapulmonary organ involvement revealed a considerably lower incidence in stages 0 and I owing to the initial negligible or mild intensity of granulomatous inflammation that has not yet reached its full maturity along with a low granuloma burden. A similar outline was also detected in stage IV patients where active inflammation has gradually waned and evolved into fibrosis. In stages II and III this process can be explained by the the waxing intensity of granulomatous inflammation with the higher granuloma burden that has reached its peak. The decisive conclusion of our study is that the clinical outcome of sarcoidosis is directly associated with the intensity of granulomatous inflammation that may exhibit extreme instability between the stages. Extrapulmonary organ involvement which constitutes the hallmark of sarcoidosis is also exclusively associated with the intensity of granulomatous inflammation.

Constitutional and pulmonary symptoms did not reveal a significant correlation with sarcoidosis stages. This is probably relevant with the uncertainity of these symptoms in the differential diagnosis with other disorders (16-20) On the other hand, symptoms of extrapulmonary organ involvement, especially of the skin and eye such as erythema nodosum, lupus pernio, or uveitis revealed a significant statistical correlation with both diagnosis and stage of sarcoidosis. They are presumptively associated with the greater intensity of granulomatous inflammation and the high granuloma burden in these stages compared to stages 0, I, and IV. The third noteworthy corollary of our study is the higher incidence of extrapulmonary organ involvement that was much greater than the previously reported findings attributed to the noteworthy efficiency of the innovative laboratory techniques that may have increased the diagnostic yield (20-22). Higher prevalence of extrapulmonary and other rarely involved organs during stages II and III is relevant with the higher intesity of granulomatous inflammation and the associated excessive granuloma burden in these phases. Three or more extrapulmonary organ involvement detected in these stages can also be explained by the same pathogenetic mechanism.

Novel imaging modalities nuclear modalities ^{18}F-FDG (9,10) or Ga^{68}-citrate PET/CT (13) have contributed to the identification of organ sarcoidosis that can not be detected by the conventional procedures. These modalities have yielded higher diagnostic yield in regard to determination of granulomatous inflammation, identification of extrapulmonary organ sarcoidosis, and biopsy sites in stage II and III patients. Low incidence of distinctive clinical symptoms and laboratory manifestions in stages 0, I, and IV sarcoidosis patients is a another outstanding finding of our study. For stages 0 and I this finding is associated with the high intensity of granulomatous inflammation along with a greater granuloma load. For stage IV patients, the synergistic effect of gradually waning intensity granulomatous inflammation, waxing progressive fibrosis, and ongoing decline in granuloma burden is the mechanism for low prevalence or lack of clinical, laboratory, and extrapulmonary organ involvement manifestations.

Limitations of our study include its retrospective design and potential selection bias inherent to its single center study profile. The sample size and homogenous patient population may limit the generalizability of our findings. Different racial and genetic features may profoundly inflence the clinical findings and the extrapulmonary organ manifestations. Studies including greater number of individuals from different races with distinctive hereditary features may increase the power of statistical analysis. Another drawback of our study is the small number of stage IV patients that may have a negative impact on the statistical analysis. Because our study comprised some individuals since 1970, lack of current novel laboratory, and imaging modalities thereat may emerge as another negative impingement. Findings with cardiac, nervous, and other rarely involved organ systems may be misleading due to their low incidence. Future research endeavors should aim to validate our observations in larger, multicenter cohorts, and explore the novel diagnostic modalities for the assessment of our findings.

Given the limited specific data for clinical and laboratory manifestations of sarcoidosis across stages our study reveals significant conclusions that has not been reported previously. We have observed that every aspect of sarcoidosis including patient symptoms, organ involvement, abnormal laboratory, and imaging findings reveal a noteworthy correlation with the disease stage denoting the distinctive impact of granulomatous inflammation intensity of sarcoidosis. Clinical symptoms, abnormal laboratory findings, and extrapulmonary organ involvement manifestations have reached a highly significant incidence among stage II and III patients where the intensity of granulomatous inflammation and granuloma burden have the greatest impingement (23,24). The clinical, laboratory, and the imaging profile of sarcoidosis patients revealed equivocal results in the initial stages 0 and I where the impact of granulomatous inflammation has not yet reached its peak with a low granuloma load (25,26). The same clinical profile occurs in stage IV patients where the granulomatous inflammation has waned with a reduction of granuloma burden that has been replaced by progressive fibrosis leading to a distinctive and significant decrease or absence of clinical findings.

Conclusions

Our study provides valuable insights into the clinical manifestations of sarcoidosis across stages. Incidence of pulmonary or extrapulmonary organ involvement symptoms, laboratory findings and imaging manifestations was associated

with the current intensity of granulomatous inflammation of the disease. Prevalence of these pathologic clinical revelations was most frequent and intensive in stage II and III patients. This is associated in accordance with the higher intensity of granulomatous inflammation and the consequent greater granuloma burden compared to other stages. Symptoms of pulmonary and extrapulmonary organ involvement along with the associated abnormal laboratory and imaging profile revealed a much lower incidence in 0 and I stage. As the the initial or the onset phase of the granulomatous inflammation and the granuloma load that has not yet reached its peak confirms this notion. Moreover, detection of a similar clinical profile in stage IV patients where the intensity of granulomatous inflammation has progressively waned and that has evolved into definite fibrosis supports the lower incidence of such findings at thsi stage. Our study highlights the the clinical profile of sarcoidosis elucidating the significant correlation between disease stages, intensity of granulomatous inflammation, and the extent of clinical manifestations along with the comparative high incidence of abnormal laboratory findings in stages II and III. The intensity of granulomatous inflammation in sarcoidosis across disease stages is closely linked with the likelihood and extent of clinical manifestations along with the extrapulmonary organ involvement. Recognition of the existence of such a pathologic correlation will be the most significant step for the early and effective diagnosis of sarcoidosis to improve patient outcomes.

Author's contributions:

Emre Yanardag designed the patient findings and data of the study.

Cuneyt Tetikkurt contemplated and wrote the study.

Muammer Bilir prepared the laboratory findings of the patients.

Halil Yanardag analyzed the test results and performed the statistical analysis.

Conflicts of interest

All authors declare that they do not have any conflicts of interest associated with this study. Authors confirm that there does not exist any supporting or funding agencies for this research.

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