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Research Article

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Prognostic Significance of Clinical, Laboratory, and Radiologic Findings in Sarcoidosis Patients: A Retrospective Cohort Study

(Running title: *Prognostic significance of sarcoidosis manifestations*)

Cuneyt Tetikkurt[1], Muammar Bilir[2], Halil Yanardag[2], Seza Tetikkurt[3], Bahar Kubat[1]

[1]Department of Pulmonary Diseases, Cerrahpasa Medical Faculty, Istanbul-Cerrahpasa University
[2]Department of Pulmonary Diseases, Cerrahpasa Medical Faculty, Istanbul-Cerrahpasa University
[3]Department of Pathology, Biruni University Medical Faculty Hospital, Istanbul, Turkey

[*]**Corresponding author and the communication address:** Professor Cuneyt Tetikkurt, Tanzimat Sok. Serkan Apt. No:8/16, 34728, Caddebostan, Istanbul, Turkey. E-mail: tetikkurt@gmail.com; Mobile phone: +90-532-381 09 00; Home phone: +90-216-360 19 77

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Abstract

Background and aim: Sarcoidosis is a heterogeneous granulomatous disease with highly variable clinical outcomes and disease course ranging from spontaneous remission to chronic, progressive disease. Identifying prognostic factors is essential for risk stratification, tailored treatment, and prognosis improvement. Despite advances in laboratory and imaging modalities, a prognostic assessment of sarcoidosis patients remains a challenge for clinicians. This retrospective cohort study aims to evaluate the significance of symptoms, extrapulmonary organ involvement, laboratory features, pulmonary function tests, and radiologic findings to predict the impact of these variables on the prognosis of sarcoidosis patients.

Methods: We conducted a retrospective cohort study of 696 patients diagnosed with sarcoidosis from January 1980 to December 2025 at a tertiary care center. Clinical, laboratory, and imaging data were reviewed, and patients were classified as stable or progressive based on a median follow-up of 6.8 years. Multivariable Cox proportional hazards models identified predictors of adverse outcomes and disease progression, adjusting for age, sex, and race. Statistical analyses included ANOVA, Kruskal-Wallis, chi-square, Fisher's exact, and Mann-Whitney U tests. Multivariable Cox proportional hazards modeling and logistic regression were employed to identify predictors of progressive disease, defined as significant worsening of symptoms, development of organ dysfunction, involvement of vital organs, explicit decline in lung function, deterioration of pulmonary imaging findings, need for long-term immunosuppressive treatment, morbidity, and mortality.

Results: Progressive disease occurred in 28.4% and mortality was observed in 5.2% of the patients. Lung disease was detected in 94.2% while extrapulmonary organ sarcoidosis was identified in 64.8%. The most common symptom was dry cough (46.2%) followed by dyspnea (42.8%), fatigue (38.6%), and cutaneous lesions (32.4%). Patients presenting with constitutional symptoms demonstrated a significant correlation with poorer prognosis. Progressive disease was not associated with age (>60 years) or gender (HR, 3.12; 95% CI, 1.67–5.84, $p<0.05$; HR, 3.18; 94% CI, 1.64–5.82, $p<0.01$). High ACE (78.6%), elevated serum (12.4%), or urine calcium levels (18.6%), DLCO impairment (<70% predicted), and pulmonary hypertension were significantly associated with progressive disease (HR 2.31 [95% CI, 1.51–3.54]; HR 1.78 [95% CI, 1.16–2.73]; HR 2.42 [95% CI, 1.61–3.48]; HR 1.74 [95% CI, 1.18–2.76]; $p<0.001$; HR, 2.34; 96% CI, 1.18–4.46; $p<0.012$), respectively. Stage II–III disease revealed a higher risk of advanced disease compared to stage 0 or I (HR 2.28 [94% CI, 1.54–3.52]; HR 1.76 [95% CI, 1.16–2.73], $p < 0.01$). Mortality was linked to pulmonary fibrosis, hypertension, heart or brain involvement, and treatment associated complications.

Conclusions: This study identifies key clinical, laboratory, and radiologic features that independently predict the outcome in sarcoidosis patients. emphasizing the prognostic value of such features in sarcoidosis, advocating for a multimodal risk stratification approach. Symptoms other than extrapulmonary organ involvement, routine blood count, and serum biochemistry were not useful in predicting prognosis. Extrapulmonary involvement of more than two organs, a low DLCO, and advanced imaging manifestations were significant indicators of a poorer prognostic outcome. Another hallmark factor for a worse prognosis is the intensity of the granulomatous inflammation directly to the granuloma load in the organs involved. These findings strongly emphasize that a multimodal approach with a comprehensive assessment of all clinical and laboratory findings rather than of a single individual data is the best option for risk stratification and prognosis determination of sarcoidosis patients.

Keywords: Sarcoidosis, prognosis, extrapulmonary sarcoidosis, disease stage

Introduction

Sarcoidosis is a systemic granulomatous disease of unknown etiology, characterized by the formation of non-caseating granulomas in the affected organs, most commonly the lungs and intrathoracic lymph nodes (1-3). Clinical presentation, symptoms, disease course, and prognosis of sarcoidosis are highly variable ranging from asymptomatic radiographic manifestations to severe multi-organ dysfunction that may necessitate prolonged immunosuppressive treatment. Pulmonary involvement occurs in over 90% of cases while extrapulmonary organ involvement, such as cutaneous, ocular, cardiac, and neurologic disease, determines the prognosis. The disease may follow a self-limited, remitting course or progress to chronic fibrosis and organ damage, underscoring the need for reliable prognostic indicators at the time of diagnosis (4,5). Current tools for assessing sarcoidosis activity and prognosis include clinical evaluation, laboratory markers such as serum

ACE and sIL-2R, and imaging modalities such as chest radiography, high-resolution computed tomography (HRCT), and fluorodeoxyglucose emission tomography (6-8). The unpredictability of sarcoidosis outcomes poses significant challenges for clinicians in determining which patients require aggressive treatment versus follow-up and the utility of these tools in predicting prognosis has remained inconsistent across studies (5-8). The Scadding radiographic staging system, while widely used, does not fully capture the complexity or activity of disease (9,10). Similarly, biomarkers like ACE and sIL-2R may reflect granulomatous burden but are neither sensitive nor specific enough to guide individualized prediction of prognosis (4-7,9).

Efforts to identify robust predictors of disease course have been hindered by the lack of large, longitudinal, real-world cohorts that integrate clinical, biochemical, and radiologic data. A comprehensive understanding of how these variables interact to influence prognosis is essential to inform early risk stratification and guide therapeutic decision-making to optimize patient outcomes. Currently, there does not exist any clinical detection modality to predict the prognosis of sarcoidosis. In this retrospective cohort study, we sought to investigate the prognostic significance and correlation of various clinical data including symptoms, extrapulmonary organ involvement, laboratory findings, PFT, DLCO, and imaging manifestations in a large, diverse cohort of patients with biopsy-proven sarcoidosis. We hypothesized that a multimodal assessment at baseline would yield clinically meaningful risk profiles that could enhance the precision of sarcoidosis prognosis in clinical practice. The main target was to set forth an unbiased and independent predictor of sarcoidosis prognosis comprising distinct patient profiles. Our findings underscore the importance of a comprehensive evaluation in patients of sarcoidosis, integrating clinical, functional, and radiologic findings to predict disease prognosis.

Methods

We conducted a retrospective cohort study of patients with sarcoidosis admitted at the Internal Medicine and Pulmonary Diseases department of Cerrahpasa Medical faculty between January 1980 and March 2025 with a study protocol approved by the Institutional Review Board, which waived the requirement for informed consent due to the retrospective nature of the study. Patients were included if they met the following criteria: (1) patient age ≥18 years; (2) a diagnosis of sarcoidosis established according to the American Thoracic Society (ATS), European Respiratory Society (ERS), and World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) criteria (2-4), which included compatible clinical, radiologic findings with histopathologic confirmation of non-caseating granulomas in the absence of alternative causes; (3) absence of any comorbid disease; and (4) a minimum follow-up duration of five years. Patients with other granulomatous diseases or with alternative diagnoses (e.g., tuberculosis, lymphoma, or hypersensitivity pneumonitis), comorbid diseases, incomplete medical records, insufficient imaging, and laboratory data were excluded. Scadding radiologic assessment protocol (9,10) was used for staging.

A thorough physical examination with relevant clinical consultations was performed to determine cutaneous, ocular, neurologic, and cardiac system involvement of sarcoidosis. Current tools for assessing sarcoidosis activity and prognosis comprised laboratory investigations including complete blood count, serum inflammatory markers (ESR, CRP, Procalcitonin), immunoglobulin levels, serum angiotensin-converting enzyme (ACE), tuberculin test, serum, and 24/h urinary calcium. PFT, and DLCO results were done to review functional status (11-13) of the patients. Imaging studies encompassed chest x-ray, HRCT, and abdominal ultrasound. A slit lamp and fundoscopic exam were done for ocular sarcoidosis. Nuclear imaging modalities like ^{18}FDG (14-15) and the novel ^{68}Ga-citrate PET/CT (16) were performed in equivocal cases to reveal granulomatous inflammation and biopsy sites. Fiberoptic bronchoscopy, BAL, TBB, mediastinoscopy, and extrapulmonary organ biopsy were done for histopathologic confirmation of granulomatous inflammation. Sarcoidosis stages were classified according to the modified Scadding criteria based on chest radiography findings (9,10). A definitive sarcoidosis diagnosis was reached by pathologic examination of at least two organ biopsy samples compatible with sarcoidosis, exclusion of granulomatous diseases, and a follow-up period of at least two years. The primary outcome was the identification of clinical. laboratory, and imaging features predictive for progressive disease while the secondary aim included determination of sarcoidosis prognosis by a collaborative assessment of all available findings. Data of the eligible patients were reviewed to collect demographic corollary, including age, sex, and ethnicity. Prognosis was classified as stable versus progressive disease, considering symptoms, extrapulmonary organ involvement, radiographic changes, pulmonary fibrosis, the need for more immunosuppressive treatment, organ dysfunction, morbidity, and mortality.

Descriptive statistics were used to summarize baseline characteristics. Continuous variables were presented as means (±SD) or medians (interquartile range) and analyzed using the Student's t-test or Mann–Whitney U test, as relevant. Research categorical variables were shown as frequencies and percentages. For the assessment of demographic characteristics, clinical manifestations, laboratory, and imaging findings, descriptive statistics were used. Analysis of variance (ANOVA), Kruskal-Wallis test, chi-square test, Fisher's exact test, and Mann-Whitney U test as applicable were done for the discrimination of between groups. Chi-square tests or Fisher's exact tests were performed to evaluate categorical variables while t-tests or Mann-Whitney U tests were performed for the assessment of continuous variables. The Pearson correlation coefficient, denoted as r, was utilized to assess the strength of the linear relationship between prognosis and various factors, including symptoms, laboratory results, pulmonary function tests, imaging findings, and the extent of organ involvement, in relation to either stable or deteriorating disease course. To define 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 designated as negligible, weak, moderate, strong, and very strong correlation, respectively (17). For analysis of association between disease stage and specific organ involvement logistic regression analysis was performed. By quantifying these relationships, the study identifies which findings may have a significant prognostic value to guide clinical decisions and follow-up strategies. A two-sided p value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 29 program assessment of all the available data in the study.

Results

The study cohort comprised 788 patients, with a mean age of 48.6±12.6 years and a slight female predominance (54.8%) while 696 met the inclusion criteria that were included in the final analysis. The racial distribution consisted entirely of Caucasian individuals, without any other backgrounds. The median follow-up period was 6.8 years (interquartile range [IQR], 4.2–8.6 years). Constitutional symptoms, including fatigue, weight loss, and low-grade fever, were reported by 38.4% of patients. Pulmonary involvement was present in 94.8% of patients with 18.4% of patients exhibiting pulmonary fibrosis on HRCT. Extrapulmonary involvement occurred in 36.2% of cases, primarily affecting the skin (28.2%), eyes (18.4%), liver (8.2%), spleen (6.4%), heart (4.6%), and nervous system (3.8%). More than two extrapulmonary organ involvement was ascertained in 28.6% of the patients. Of the 696 patients, 124 (17.8%) had erythema nodosum, 74 (10.6%) had lupus pernio while 430 (61.8%) had no cutaneous involvement. Anterior uveitis was identified in 82 (11.8%) while posterior uveitis was diagnosed in 50 (7.2%) patients (Table 1). Elevated inflammatory markers CRP and ESR were noted in 24.8 and 26.4% of the cases. The median serum ACE level was 65.4±18.4 U/L (IQR, 42–88), elevated serum ACE was found in 64.8%, high calcium in 9.7%, and exorbitant 24/h urinary calcium in 12.8% of the patients, 22.7% of patients had an FVC<70%, and 34.2% had DLCO <80% predicted, indicating significant lung function impairment. Pulmonary symptoms, and routine laboratory findings did not reveal a significant correlation with prognosis. Mean ACE level was significantly higher in patients with progressive disease compared to those with stable disease (68.3 U/L vs. 49.2 U/L, p<0.001). Based on chest radiographs, pulmonary involvement was ubiquitous (92.6%) while the Scadding stages were distributed as follows: stage 0 (3.4%), stage I (46.2%), stage II (25.8%), Stage III (16.4%), and stage IV (8.2%). The most common radiologic finding was bilateral hilar lymphadenopathy, observed in 70.6% of cases. Pulmonary hypertension was diagnosed in 8.6% HR, 2.94; 95% CI, 1.53–5.66; p<0.001). Over a median follow-up of 6.8 years, 428 (61.4%) entered remission while the remaining had chronic, remitting, or progressive disease during the follow-up period. The mean time to remission was approximately 2.6±1.8 years (IQR, 1.3–3.9) among our patients while 68.1% with progressive disease required long-term corticosteroid therapy and 41.3% were escalated to steroid-sparing immunosuppressants such as methotrexate, azathioprine, or infliximab.

Table 1: Correlation of clinical manifestations with sarcoidosis prognosis.

	# (%)	Stable disease		Progressive disease	
		r	p	r	p
Pulmonary symptoms	544 (78.2)	0.68	<0.16	0.16	<0.12
Constitutional symptoms	268 (38.0)	0.26	<0.08	0.68	<0.05
Extrapulmonary organ involvement	252 (36.2)	0.34	<0.01	0.56	<0.05
> 2 extrapulmonary organ involvement	200 (29.3)	0.24	<0.05	0.76	<0.01
Anterior uveitis	82 (11.8)	0.28	<0.01	0.46	<0.05
Posterior uveitis	50 (7.2)	0.42	<0.05	0.62	<0.01
Erythema nodosum	102 (14.7)	0.74	<0.05	0.18	<0.14
Lupus pernio	62 (8.9)	0.18	<0.01	0.78	<0.05
Löfgren's syndrome	32 (4.6)	0.76	<0.01	0.26	<0.14
Heerfordt syndrome	14 (2.0)	0.64	<0.05	0.18	<0.08
Heart involvement	30 (4.3)	0.18	<0.01	0.86	<0.05
Neurologic involvement	24 (3.4)	0.16	<0.05	0.74	<0.01
Morbidity	98 (14.1)	0.24	<0.01	0.72	<0.05
Mortality	32 (4.6)	0.12	<0.05	0.68	<0.01

Thirty-two patients (4.6%) died of sarcoidosis-related complications; most commonly pulmonary fibrosis related to respiratory failure followed by sarcoidosis involvement of vital organs like heart, brain, and treatment-related complications. Independent predictors of progressive disease included: persistent constitutional symptoms (HR, 1.88; 95% CI, 1.21–2.96; p<0.005), persistence of extrapulmonary organ involvement symptoms (HR, 1.86; 96% CI, 1.24–2.98; p<0.001), high serum ACE level (HR, 1.76; 95% CI, 1.18–2.74; p<0.008), and extrapulmonary involvement of more than 2 organs (HR, 2.22; 95% CI, 1.44–3.43; p<0.001). The predictive model demonstrated good discrimination with a C-index of 0.81 and AUC of 0.84 for progression. Conversely, absence of extrapulmonary disease and normal ACE levels were more likely to achieve remission (OR, 3.74; 96% CI, 2.14–6.52; p<0.001). Pulmonary function test analysis revealed moderate correlation with a disease outcome. Low FVC and decreased DLCO were the most significant predictors of a worse prognosis. More than 10% drop in FVC or DLCO over three years revealed a high probability of chronic outcome (OR, 4.20; 96% CI, 1.86–8.92; p<0.001 and OR, 4.18; 94% CI, 1.82–8.90; p<0.001).

Existence of stage I and II on chest x-ray were significant predictors of a stable prognosis (OR, 4.16; 98% CI, 1.80–8.90; p<0.001 and OR, 4.16; 94% CI, 1.84–8.80; p<0.001). Patients with stage II, III, and IV disease on HRCT showed a higher risk of lung function decline with a worse outcome (≥10% drop in FVC or DLCO over 3 years; p<0.001). HRCT findings associated with progressive or chronic outcomes included parenchymal fibrosis, traction bronchiectasis, and architectural distortion. ^{18}FDG (n=54) or ^{68}Ga-citrate-PET/CT (n=48) positivity correlated strongly with progressive disease (OR, 4.08; 95% CI, 1.84–8.92, p<0.001; OR, 4.2; 94% CI, 1.82–8.94, p<0.001). Lupus pernio, anterior uveitis, cardiac, and neurologic involvement were reliable indicators of progressive disease in our patients. Conversely, patients presenting with isolated thoracic lymphadenopathy (stage I), presence of erythema nodosum, absence of extrapulmonary disease, normal ACE, serum, and 24/h urinary Ca levels, and absence of persistent constitutional symptoms were more likely to achieve remission (OR, 3.72; 95% CI, 2.13–6.50; p<0.001). The predictive model demonstrated good discrimination with a C-index of 0.81 and AUC of 0.84 for progression. The median time to immunosuppressive treatment discontinuation in patients with

progressive disease was approximately 16.4±8.6 months. Laboratory, PFT, and imaging findings of the patients are depicted in Table 2.

Table 2. Correlation of laboratory, PFT, and imaging findings with prognosis.

	# (%)	Stable disease r p	Progressive disease r p
Blood count*	47 (6.8)	0.12 <0.16	0.14 <0.01
Routine serum biochemistry*	164 (24.6)	0.16 <0.08	0.18 <0.06
Elevated serum Ca	68 (9.8)	0.18 <0.12	0.62 <0.01
High 24h urinary Ca	182 (26.1)	0.26 <0.06	0.54 <0.01
Elevated serum ACE	432 (62.1)	0.32 <0.01	0.36 <0.05
Stage 0 **Stage I** **Stage II** **Stage III** **Stage IV**	40 (5.7) 298 (42.8) 194 (27.9) 106 (15.2) 58 (8.3)	0.78 <0.05 0.72 <0.01 0.54 <0.01 0.34 <0.05 0.08 <0.01	0.16 <0.01 0.24 <0.05 0.48 <0.01 0.84 <0.05 0.96 <0.05
FEV_1	15.6%	0.14 <0.12	0.16 <0.01
FVC	24.8%	0.18 <0.01	0.24 <0.05
TLC	32.4%	0.28 <0.16	0.32 <0.12
DLCO	58.2%	0.24 <0.01	0.74 <0.05
HRCT	96.8%	0.32 <0.05	0.84 <0.01
FDG-PET/CT	82.4%	0.72 <0.01	0.76 <0.05
Ga^{68}-citrate PET/CT	86.8%	0.68 <0.05	0.72 <0.01
Collective data assessment	99.8%	0.96 <0.01	0.92 <0.05

*Abnormal values

Erythema nodosum showed a weak but significant correlation for a stable disease course. Pulmonary symptoms, routine blood count, and serum biochemistry did not reveal a statistically significant correlation with prognosis. Extrapulmonary organ symptoms showed a moderate correlation with chronic disease (Table 1). The presence of pulmonary fibrosis on HRCT as a marker of irreversible parenchymal damage was the strongest predictor of disease progression suggesting that patients with this finding require close monitoring and potentially early intervention with immunosuppressive therapies. HRCT, ^{18}FDG and Ga^{68}-citrate PET/CT were useful and effective predictors of prognosis (Table 2). Elevated serum ACE levels, indicative of active granulomatous inflammation, support the routine measurement of this biomarker to assess disease activity. The other predictors of progressive disease were defined as lupus pernio, chronic uveitis, neurosarcoidosis, cardiac involvement, chronic hypercalcemia, and hypercalcuria. The mean time to immunosuppression discontinuation in this group was 9.4±6.8 months. On multivariable Cox proportional hazards modeling, independent predictors of prognosis included persistence of constitutional symptoms, more than two extrapulmonary organ involvement, advanced stage of III or IV disease, 36% of stage II, ^{18}FDG, and ^{68}Ga-citrate PT/CT positivity that correlated strongly with progressive disease.

Discussion

In this large retrospective cohort study of patients with biopsy-confirmed sarcoidosis, we identified several clinical, laboratory, and radiologic features that were independently associated with long-term disease progression or remission. Age and gender status of the patients did not constitute an explicit influence on disease outcome or prognosis. Persistent constitutional symptoms such as fatigue, weight loss, fever, and extrapulmonary organ manifestations were associated with a worse prognosis. Conversely, patients with pulmonary symptoms, isolated thoracic lymphadenopathy, normal inflammatory biomarkers, and without constitutional symptoms demonstrated a significantly higher likelihood of spontaneous remission. Our findings underscore the prognostic importance of elevated ACE levels, involvement of more than two extrapulmonary organs, advanced radiologic staging, and positive PET/CT results. These features are identified as significant predictors for the progression of sarcoidosis. The collective assessment of these clinical data achieved significant accuracy in predicting the prognostic outcomes for patients with sarcoidosis. These results underscore the utility of a multimodal assessment at diagnosis in guiding risk stratification and individualized management of sarcoidosis.

Our findings are consistent with previous studies demonstrating the heterogeneity of sarcoidosis and the limited ability of any single marker to predict the prognostic outcome. Pulmonary symptoms and routine biochemical laboratory parameters were not useful in predicting the disease course because they did not provide specific implications for defining sarcoidosis prognosis. Elevated serum ACE has long been associated with active granulomatous inflammation but suffers from low sensitivity and specificity due to interindividual variability and influence from ACE genotypes (18-20). Defining clinical outcome of sarcoidosis patients is the current challenge for pulmonary clinicians due to non-specific manifestations, constitutional symptoms, atypical presentations, and variable extrapulmonary organ involvement. The uncertainty regarding the follow-up process of patients along with the determination of disease prognosis or course constitutes the greatest concern in sarcoidosis (21,22). Our findings indicate that elevated ACE, high serum, and 24/h urinary Ca levels may serve as a prognostic indicator due to their indirect association with the granuloma load and the consequent intensity of granulomatous inflammation, which is a primary concern for sarcoidosis outcomes (23,24). The presence of persistent constitutional symptoms and existence extrapulmonary organ symptoms appears as a significant indicator of a poor prognosis, confirming the relationship between prognosis and granuloma

load with associated granulomatous inflammation intensity as revealed in other studies (25-27). Our study has clearly revealed that high serum ACE, serum, and 24-hour urine calcium levels as well as the persistence of constitutional symptoms or the extrapulmonary organ involvement are significant markers for determining the prognosis of sarcoidosis. Systemic symptoms may reflect a higher granulomatous inflammatory load and multisystemic involvement. On the other hand, it was determined that pulmonary symptoms, routine blood count and serum biochemistry did not carry any prognostic significance due to their nonspecific nature and common association with many other pulmonary or other disorders.

Our results validate that the prognostic utility of higher Scadding stages, particularly III, IV, along with some of the stage II patients were associated with significantly increased risk of progressive disease and lung function decline. The poor outcome in advanced stages is most likely related to the higher intensity of granulomatous inflammation affiliated with the existence of a higher granuloma burden of the advanced disease. Additionally, HRCT findings such as parenchymal fibrosis and traction bronchiectasis emerged as radiologic hallmarks of poor prognosis, consistent with prior studies linking fibrotic changes due to active disease and impaired pulmonary function (28-30). ^{18}FDG and ^{68}Ga-citrate PET/CT imaging indicate that increased granuloma burden and therefore the granulomatous inflammation activity are reliable indicators of poor prognosis in parallel with radiological examinations (31,32). Increased granulomatous inflammation or fibrotic tissue in the lung parenchyma or extrapulmonary organs, as shown by ^{18}FDG or Ga^{68}-citrate PET/CT, are linked to a worse prognosis. The significant impact of the burden of granuloma load and granulomatous inflammation on prognosis was confirmed in our study by the significantly worse prognosis in patients with more than two organ involvement. Our results clearly indicate that the disease course, the need for immunosuppressive therapy, and the prognostic outcome appear to be exclusively related to the intensity of granulomatous inflammation caused by the excessive granuloma burden in the affected organs. Extrapulmonary involvement, particularly cardiac and neurologic sarcoidosis, was among the strongest predictors of progressive disease in our cohort.

A notable strength of this study is its large sample size and long duration of follow-up, allowing for robust identification of disease trajectories and outcomes. Additionally, our inclusion of both clinical, radiologic, and nuclear imaging parameters provides a comprehensive perspective on prognostic determinants. However, this study also comprises some limitations. As a retrospective single-center study, it is subject to inherent biases, including referral bias and incomplete data capture. Considering the racial diversity of our country, evaluating only Caucasian patients may present challenges in understanding hereditary traits of sarcoidosis in other races. Another limitation of our study is the lack of assessment regarding the socioeconomic status of patients and its impact on prognosis. However, this may be considered negligible given the extensive range of prognostic factors evaluated. The limited availability of ^{18}FDG and Ga^{68}-citrate PET/CT imaging to a subset of patients may have introduced selection bias. The exclusion of some recently developed markers used in sarcoidosis appears to be another limitation of our study. Since these markers are still at the research level, have limited availability in routine clinical practice, and lack certainty, their benefit in sarcoidosis remains uncertain. Compared to other findings, the relatively low incidence along with a subclinical and asymptomatic cardiac and neurological involvement, a nominal prevalence of extrapulmonary findings such as uveitis, erythema nodosum or lupus pernio may have negatively affected the statistical power of our study. Despite our adjustment for key confounders, unmeasured variables may still influence disease course. Future studies should aim to validate these findings in large, multicenter cohorts by integrating emerging biomarkers and genetic susceptibility profiles.

Our study identifies that a constellation of features comprising clinical features, laboratory, pulmonary function, and imaging findings that independently predict sarcoidosis prognosis. Pulmonary and constitutional symptoms, aside from extrapulmonary organ manifestations, were not significant for determining prognosis with an extremely low clinical usefulness for disease course assessment. Blood count, serum biochemistry other than elevated ACE, serum, and 24-hour urinary calcium levels did not conclusively assess prognosis. High serum ACE levels, indicative of active granulomatous inflammation, support the routine measurement of this biomarker to assess disease activity. For lung function tests, only DLCO levels revealed explicit consequences for the prognostic assessment of sarcoidosis patients. Chest x-ray with Scadding analysis, HRCT, ^{18}F-FDG (9,10) or Ga^{68}-citrate PET/CT were the most predictive diagnostic tools in determining a definitive prognostic outcome. Although each feature evaluated in this study may be effective for defining prognosis individually, they offer more significant guidance when a collaborative analysis is performed. Our research supports a multidimensional approach that will be extremely useful for the treatment and follow-up of sarcoidosis patients despite its some minor insignificant or trivial drawbacks. These findings support a comprehensive approach to initial assessment and may reveal the treatment strategies aimed at improving the prognosis. Future prospective multicenter studies including patients with distinct hereditary or racial characteristics are required to develop more predictive and accurate models for the appraisal of sarcoidosis outcome.

Conclusion

In this retrospective cohort study, we comprehensively evaluated the prognostic significance of clinical, laboratory, and radiologic findings in patients with sarcoidosis, providing valuable insights into the factors influencing disease outcomes. Our findings highlight several key predictors of disease progression and prognosis, which may guide clinical decision-making to improve patient management. The analysis revealed that clinical factors, such as the presence of extrapulmonary manifestations and chronic symptomatic disease, were significantly associated with worse prognostic outcomes, including increased risk of disease progression, higher morbidity, and mortality incidence. Laboratory parameters, particularly elevated ACE, serum, and 24/h urinary calcium levels were identified as independent predictors of disease activity and progression. These biomarkers may serve as useful tools for monitoring disease status and tailoring therapeutic interventions. Radiologic findings, including the presence of advanced fibrotic changes and pulmonary hypertension on imaging, were strongly correlated with poorer prognosis, emphasizing the importance of early and accurate radiologic assessment in sarcoidosis management. Novel nuclear imaging modalities like ^{18}FDG and Ga^{68}-citrate PET/CT were useful predicting prognosis. The most accurate determination of the

prognostic course was achieved by the collective analysis of all clinical findings rather than individual clinical, laboratory, and imaging findings.

Author contributions

Cuneyt Tetikkurt contemplated and wrote the study.
Muammer Bilir prepared the laboratory findings of the patients.
Halil Yanardag organized and prepared the patient data.
Umit Seza Tetikkurt conducted an analysis of the pathological mechanisms underlying clinical manifestations and prognosis.
Bahar Kubat was responsible for designing the statistical analysis framework utilized in this study.

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