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# Prognosis of sarcoidosis and factors affecting prognosis

*Bilge Bilgin[1], Mehmet Kursat Bilgin[2], Serhat Erol[3], Gokhan Celik[3], Ozlem Ozdemir Kumbasar[3]*
[1]Sakarya Training and Research Hospital, Department of Chest Diseases, Sakarya, Turkey; [2]Geyve State Hospital, Sakarya, Turkey; [3]Ankara University School of Medicine, Department of Chest Diseases, Ankara, Turkey

**Abstract.** *Introduction:* Sarcoidosis is a multi-system disease of unknown etiology characterized by non-caseating granulomatous inflammation. Determining the characteristics and prognosis of sarcoidosis cases and revealing the factors that may affect the prognosis are important for approach to patient. This study was planned to obtain prognosis data for our country and to determine the factors affecting the prognosis. *Patients and methods:* 188 patients, followed regularly for three years or more, admitted to Ankara University Faculty of Medicine, Department of Chest Diseases between 2012-2017 were evaluated retrospectively. Increased radiological findings, functional impairment and any of the clinical conditions requiring initiation/modification of treatment were accepted as progression. Clinical status of the patients at the last follow-up was defined as remission with treatment, spontaneous remission, stable disease, progression, chronic case and recurrence. Spontaneous remission and remission with treatment, regression, stable disease, and recurrence that followed without treatment and didn't cause symptom or functional impairment were accepted in good prognosis group. Progression, chronic cases that couldn't be followed without treatment and recurrence requiring treatment were included in poor prognosis group. *Results:* 58% of patients was accepted in good prognosis and 42% had poor prognosis group. During follow-up, spontaneous remission rate was 20.2%, pulmonary hypertension development rate was 10.6% and mortality rate was 4.25%. Low radiological stage, high spirometry and diffusion capacity values, being asymptomatic and having no previous treatment were associated with spontaneous remission and good prognosis. Increase in serum angiotensin converting enzyme and C-reactive protein and decrease in spirometry parameters and diffusion capacity values were associated with progression.

**Key words:** fibrosis, mortality, prognosis, pulmonary hypertension, sarcoidosis

## Introduction

Sarcoidosis is a systemic disease of unknown cause characterized by non-caseified granulamatous inflammation (1). It commonly presents with bilateral hilar lymphadenopathy (BHL), pulmonary infiltration and skin lesions. It usually affects young and middle aged adults (2).

Clinical picture and course may vary from patient to patient. In many asymptomatic patients, it is a apartially benign and selflimiting disease. In patients with major organ involvement, a chronic clinical picture requiring systemic treatment may be observed. There are studies on factors that can predict prognosis but no reliable prognostic algorithm has beeen developed for pulmonary sarcoidosis (3). Age, pulmonary fibrosis and pulmonary hypertension (PH) are main determinants of unfavorable prognosis in chronic pulmonary sarcoidosis (4, 5). However, there are inadequacies in identifying

Received: 25 May 2022
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Correspondence:
Bilge Bilgin, MD Specialist
Sakarya Training and Research Hospital, Department of Chest Diseases, Sakarya, Turkey
Phone: +90 544 241 1282
E-mail: bilged6@gmail.com

patients at risk of poor prognosis before they develop fibrosis or PH (6, 7).

The determination of the patient with poor prognosis will yield the following benefits:

- It will be easier to decide if the patient requires treatment.
- Patients and physicians will have more information on the risk of sarcoidosis associated morbidity and mortality.
- In patient not responding to steroid treatment, it will be easier to administer 2nd and 3rd line treatments and to develop novel treatment strategies.
- Patients requiring lung transplantation will be determined more clearly (4).

The aim of the present study is to obtain prognostic data and to determine factors predicting prognosis.

## Material and method

### *Patient selection and evaluation*

The files of patients followed with the diagnosis of sarcoidosis in Respiratory Diseases department of Ankara University, School of Medicine, between January 2012-December 2017 were reviewed retrospectively.

Patients over the age of 18, who were diagnosed with sarcoidosis according to ATS/ERS/WASOG criteria, followed for more than three years, and who has regular and reliable data were included in the present study (2).

Parameters evaluated were as follows: demographic characteristics (sex, age of diagnosis, duration of follow-up, smoking exposure), symptoms, radiological findings (chest radiography), laboratory findings (hemogram, calcium, C-reactive protein [CRP], erithrocyte sedimentation rate [ESR], serum angiotensin converting enzyme [sACE], vitamin D, 24 hour urine calcium), pulmonary function tests (PFT) (volume at 1st second of forced expiration [$FEV_1$], forced vital capacity [FVC], carbon monoxide diffucion capacity [DLCO]), as well as treatments administered and extrapulmonary organ involvement. PH possibility was assessed with echocardiographic criteria (pulmonary artery systolic pressure and tricuspid regurgitant velocity) according to 2015 PH guideline (8).

For follow-up, annual evaluation of patients were used. Annual follow-up parameters were determined to be sACE, CRP, ESR, pulmonary function tests ($FEV_1$, FVC, DLCO), changes in treatment, extrapulmonary organ involvement and radiological changes.

In the follow-up period, increase in radiological findings, functional impairment (in FVC≥10% or in DLCO≥15% reduction, newly developed hypoxemia which can not otherwise be explained), the presence of clinical conditions requiring the onset or alteration of treatment was regarded as progression. Returning to normal in all clinical, radiological and functional manifestations of sarcoidosis was accepted as remission.

Clinical condition of the patients at last follow-up evaluation was described as remission with treatment or spontaneous remission, stable disease, progression, chronic case or recurrence. Spontaneous remission or remission with treatment, regression, stable disease, recurrences not requiring treatment, and that do not produce symptoms or findings of organ impairment were evaluated in favorable prognosis group, while those with progression, chronic cases whose treatment can not be discontinued, and recurrences which requiring treatment were evaluated in poor prognosis group.

### *Statistical method*

SPSS version 17 (IBM Corporation, Armonk, NY, USA) was used for analysis. Statistical significance was set to a p-value <0.05. Data are expressed as mean ± SD or as median, depending on whether the data were normally distributed. Chi-square tests were used for comparisons of categorical values. Mann-Whitney U test and Kruskal Wallis Test was used to compare variables across groups with abnormally distribution and unpaired t-test and One Way Variance Analysis (ANOVA) for normally distributed variables. In the evaluation of categorical variables, Pearson Chi-Square Test, Fisher's Exact Test and continuous corrected chi-square tests were used.

Variables with P-value of<0.10 in univariate statistical analyses, were incorportaed in multivariate logistic regression analysis. The odds ratio of each variable was calculated with 95% confidence interval and Wald statistics.

Whether there was a significant difference in the measurements during progression compared to the beginning was evaluated with the dependent T test and Wilcoxon sign test. Whether there was significant difference between baseline and progression periods in terms of frequency of involvements was evaluated using McNemar test.

## Results

In the present study, among 394 patients who presented to Ankara University, School of Medicine, Respiratory Diseases Department between the dates of January 2012-December 2017 and who were diagnosed with sarcoidosis, files of 188 patients who were followed for at least for three years and who had regular and reliable data were reviewed.

Age of diagnosis, laboratory and PFT values are illustrated in Table 1.

Non smokers accounted for 72% (n=108) of female patients, while the corresponding rate was 34.2% (n=13) in male patients. The rate of smoking was higher in males (p<0.001). No significant relation was found between the history of smoking and radiological stage at first presentation (p=0.701).

**Table 1.** Age of diagnosis, initial laboratory and PFT values of the patients.

| | n | Descriptive statistics |
|---|---|---|
| **Age of Diagnosis (years)*** | 188 | 44.0 (20.0-67.0) |
| **Female** | 150 | 46 (20-67) |
| **Male** | 38 | 35 (22-61) |
| **Leukocyte*** | 188 | 6.7 (3.0-22.0) |
| **Lymphocyte*** | 188 | 1.4 (0.2-11.0) |
| **sACE*** | 188 | 61.5 (2.0-868.0) |
| **Calcium*** | 188 | 9.5 (6.8-15.2) |
| **Vitamin D*** | 150 | 15.0 (3.0-58.0) |
| **24 hour urine calcium*** | 188 | 184.5 (6.0-1548.0) |
| **CRP*** | 188 | 4.4 (0.1-77.0) |
| **ESR*** | 188 | 17.0 (1.0-70.0) |
| **$FEV_1$**,%predicted* | 188 | 87.0 (70.0-122.0) |
| **FVC**,%predicted** | 188 | 95.3±18.94 |
| **$FEV_1$/FVC**,%predicted* | 188 | 78.0 (38.0-113.0) |
| **DLCO**,%predicted* | 188 | 80.0 (20.0-129.0) |

* Datas; expressed as median (minimum – maximum) **Descriptive statistics presented as mean±standard deviation.

During their follow-up of at least 3 years, 83 (44.1%) of the patients were followed without treatment, 67 (35.6%) patients received only systemic steroids, 7 (3.7%) patients received only disease-modifying antirheumatic drugs (DMARDs), 30 (16%) patients received steroid and DMARD therapy, and only 1 patient received steroid DMARD and TNF-α inhibitors therapy.

Table 2 demonstrates information on demographic characteristics and clinical features.

In Table 3, stages at presentation and spirometry values are compared.

The median 5 years follow-up results of the patients are given in Table 4. 58% of patients was in favorable prognosis groups, while 42% was in poor prognosis group.

No statistically significant difference was found between favorable and poor prognosis group in terms of age of diagnosis, laboratory values (leukocyte,

**Table 2.** Some descriptive and clinical characteristics of patients.

| | (n=188) | (100%) |
|---|---|---|
| **Gender** | | |
| Female | 150 | 79.8 |
| Male | 38 | 20.2 |
| **Smoking History** | | |
| Non-smoker | 121 | 64.4 |
| Ex-smoker | 28 | 14.9 |
| Smoker | 39 | 20.7 |
| **Stage** | | |
| I | 53 | 28.2 |
| II | 103 | 54.8 |
| III | 3 | 1.6 |
| IV | 29 | 15.4 |
| **Extrapulmonary involvement** | | |
| Non | 94 | 50 |
| Eritema Nodosum (EN) | 14 | 7.4 |
| Lupus Pernio | 8 | 4.3 |
| Other Skin Involvements | 25 | 13.3 |
| Peripheral Lymphadenopathy | 23 | 12.2 |
| Joint | 19 | 10.1 |
| Eye | 13 | 6.9 |
| Liver | 10 | 5.3 |
| Heart | 2 | 1.1 |
| Neurological | 6 | 3.2 |
| Others | 22 | 11.7 |
| **Symptom status** | | |
| Asymptomatic | 39 | 20.7 |
| Pulmonary symptom | 100 | 53.2 |
| Extrapulmonary symptom | 49 | 26.1 |
| **PH** | 20 | 10.6 |
| **Previous history of treatment** | 76 | 40.4 |

**Table 3.** Functional values of patients according to initial radiological stages.

| | Stage 1 | Stage 2 | Stage 3-4 | p-value |
|---|---|---|---|---|
| **$FEV_1$,**%predicted | 92 (63-121)[b] | 90 (7-122)[a] | 62.5 (29-120)[a,b] | <0.001† |
| **FVC**,%predicted | 101.3±15.0[b] | 98.7±15.8[a] | 74.1±20.0[a,b] | <0.001$ |
| **$FEV_1$/FVC**,%predicted | 78.0 (62.0-95.0) | 79.0 (52.0-106.0) | 76,0 (38.0-113.0) | 0.189† |
| **DLCO**,%predicted | 86 (30-129)[b] | 82 (46-116)[a] | 52 (20-90)[a,b] | <0.001† |

† Kruskal test, $ One-Way ANOVA, a: The difference between Stage 2 and Stage 3-4 is statistically significant (p<0.05), b: The difference between Stage 1 and Stage 3-4 is statistically significant (p<0.001).

**Table 4.** Follow-up results of the patients.

| | n=188 |
|---|---|
| **Follow-up time (years)*** | 5 (3-8) |
| **Final Results**** | |
| Spontaneous remission | 38 (20.2%) |
| Remission with treatment | 17 (9.0%) |
| Progression | 38 (20.2%) |
| Chronic cases whose treatment can not be discontinued | 33 (17.6%) |
| Stable disease | 32 (17.0%) |
| Regression | 21 (11.2%) |
| Recurrences which requiring treatment | 8 (4.3%) |
| Recurrences not requiring treatment | 1 (0.5%) |
| **Progression**** | |
| No | 119 (63.3%) |
| Yes | 69 (36.7%) |
| **Type of progression**** | |
| Radiological | 22 (31.9%) |
| Radiological + other conditions requiring treatment | 20 (29.0%) |
| Other conditions requiring treatment | 16 (23.2%) |
| Functional | 5 (7.2%) |
| Radiological + functional | 5 (7.2%) |
| All | 1 (1.4%) |

* Datas; expressed as median (minimum – maximum) **Descriptive statistics presented as %.

**Table 5.** Comparison of favorable and poor prognosis group.

| | Favorable prognosis (n=109) | Poor prognosis (n=79) | p-value |
|---|---|---|---|
| **$FEV_1$,**%predicted | 92.0 (47.0-121.0) | 78.0 (7.0-122.0) | <0.001† |
| **FVC,**% predicted | 101.0±15.9 | 87.3±20.0 | <0.001‡ |
| **$FEV_1$/FVC,**% predicted | 78.0 (50.0-95.0) | 78.0 (38.0-113.0) | 0.326† |
| **DLCO,**% predicted | 86.0 (50.0-129.0) | 67.0 (20.0-99.0) | <0.001† |
| **Stage** | | | |
| I | 45 (41.3%) | 8 (10.1%) | <0.001† |
| II | 59 (54.1%) | 44 (55.7%) | |
| III | 1 (0.9%) | 2 (2.5%) | |
| IV | 4 (3.7%) | 25 (31.6%) | <0.001† |
| **Symptom** | | | |
| Asymptomatic | 35 (32.1%) | 4 (5.1%) | <0.001¥ |
| Pulmonary symptom | 42 (38.5%) | 58 (73.4%) | <0.001¥ |
| Extrapulmonary symptom | 32 (29.4%) | 17 (21.5%) | |
| **PH** | 0 (0.0%) | 20 (25.3%) | <0.001¶ |

† Mann Whitney U test, ‡ Student's t test, ¥ Pearson's chi-square test, ¶ Continuous corrected chi-square test

lymphocyte, sACE, calcium, vitamin D, 24 hours urine calcium, CRP, ESR), sex, smoking history and extrapulmonary involvement (p>0.05). In the poor prognosis group, the ratio of patients with history of previous treatment was higher than those in the good prognosis group (p<0.001), 47 (59.5%) of 76 patients who had previous history of treatment had a poor prognosis at follow-up. Of these, 15 were progressive, 27 were chronic cases whose treatment can not be discontinued and 5 had recurrences requiring treatment. Some descriptive and clinical characteristics of the patients according to favorable and poor prognosis groups are shown in Table 5.

Most decisive factor in differentiating poor and favorable prognosis groups were respectively DLCO at first presentation, radiological stage and previous history of treatment. There was inverse correlation between increase in DLCO level and poor prognosis (Odds ratio=0.944; 95% CI:0.929-0.969) (p<0.001). Rise in radiological stage increased the odds of poor prognosis by 2.053 fold (95% CI:1.224-3.445) (p=0.006). In patients who underwent treatment previously (before application to our department), the probability of poor prognosis increased by 2.293 fold (95% CI:1.102-4.771) compared to those with no previous treatment (p=0.026).

Spontaneous remission group is compared with other groups in Table 6.

No significant difference was found between spontaneous remission group and other outcomes groups with respect to age of diagnosis, sex, smoking history and extrapulmonary involvement (p>0.05). Among extrapulmonary involvements, EN, occurred at similar rates in spontaneous remission group and other groups. In spontaneous remission group, lupus pernio was not encountered while in other groups, it occurred at the rate of 5.3% (p=0.362).

Most decisive factors discriminating spontaneous remission group from other groups were respectively symptoms status, radiological stage at first presentataion and $FEV_1$/FVC ve DLCO values (Table 7).

**Table 6.** Comparison of the spontaneous remission group with other outcome groups.

| | Spontaneus remission (n=38) | Other outcome groups (n=150) | P-value |
|---|---|---|---|
| **Leukocyte** | 6.2 (3.2-10.7) | 6.8 (3.0-22.0) | 0.434† |
| **Lymphocyte** | 1.4 (0.8-3.2) | 1.3 (0.2-11.0) | 0.159† |
| **sACE** | 43.0 (2.0-117.0) | 64.5 (2.0-868.0) | **0.021**† |
| **Calcium** | 9.5 (8.7-13.0) | 9.5 (6.8-15.2) | 0.582† |
| **Vitamin D** | 18.5 (5.5-43.0) | 15.0 (3.0-58.0) | 0.078† |
| **24 hour urine calcium** | 114.5 (28.0-815.0) | 198.0 (6.0-1548.0) | **0.020**† |
| **CRP** | 4.1 (0.1-77.0) | 4.7 (0.2-56.0) | 0.301† |
| **ESR** | 16.0 (2.0-57.0) | 17.0 (1.0-70.0) | 0.563† |
| **$FEV_1$**,%predicted | 97.5 (75.0-121.0) | 85.0 (7.0-122.0) | <**0.001**† |
| **FVC**,%predicted | 103.6±14.8 | 93.2±19.3 | **0.002**‡ |
| **$FEV_1$/ FVC**,%predicted | 80.5 (62.0-95.0) | 78.0 (38.0-113.0) | **0.014**† |
| **DLCO**,%predicted | 88.0 (58.0-129.0) | 76.0 (20.0-116.0) | <**0.001**† |
| **Stage**<br>**I**<br>**II**<br>**III**<br>**IV** | 23 (60.5%)<br>15 (39.5%)<br>0 (0.0%)<br>0 (0.0%) | 30 (20,0%)<br>88 (58,7%)<br>3 (2,0%)<br>29 (19.3%) | <**0.001**† |
| **PH** | 0 (0.0%) | 20 (13.3%) | **0.015**¥ |

† Mann Whitney U test, ‡ Student's t test, ¥ Fisher's Exact Test, ¶ Continuous corrected chi-square test

**Table 7.** Most decisive factors discriminating spontaneous remission group from other groups.

| | Odds ratio | 95% confidence interval | Wald | P-value |
|---|---|---|---|---|
| **Pulmonary symptom** | 8.726 | 2.018-37.731 | 8.410 | **0.004** |
| **Extrapulmonary symptom** | 27.308 | 3.633-205.290 | 10.325 | <**0.001** |
| **Radiological Stage** | 9.383 | 2.389-36.855 | 10.287 | <**0.001** |
| **$FEV_1$/ FVC,**%predicted | 0.855 | 0.757-0.966 | 6.384 | **0.012** |
| **DLCO,**% predicted | 0.943 | 0.893-0.996 | 4.392 | **0.036** |

We evaluated patients with a sarcoid clinical activity classification (SCAC) system developed by Prasse et al., determined according to the type of disease onset and treatment need (9). According to the SCAC system, 19.1% (36) of the study cohort had acute sarcoidosis, whereas 152 patients (80.8%) had nonacute sarcoidosis. Fourteen patients (7.4%) were classified as having class 1 disease, 6 (3.1%) had class 2 disease, 16 (8.5%) had class 3 disease, 65 (34.5%) had class 4 disease, 14 (7.4%) had class 5 disease, and 73 (38.8%) had class 6 disease (Table 8).

Chest X-ray type II was found to predominate in all other classes except class 2; In class 2, patients with predominantly type I chest radiography were found. All patients in classes 1 and 2 were seen on chest x-ray types I and II. All of those with chest x-ray type III were seen in the group needed treatment with steroids for more than one period or long-term treatment lasting for more than 1 year (Table 8).

Predominantly patients with poor prognosis were found in classes 3 and 6 (Table 9).

Among 20 patients with PH, (10.6%) median age of diagnosis was found to be similar to that of overall patients, i.e. 43 (25-65). In this group, $FEV_1$, FVC and DLCO values were lower than mean values in overall patient group. Of patients with PH, 85% (n=17) was female, 15% (n=3) was male and 70% was nonsmoker. Sex ratio and smoking history was similar to that of overall patient group. At the time of presentation, 5% of patients was consistent with radiological stage I, 35% with stage II, 5% with stage III and 55% with stage IV. The rate of patients

**Table 8.** Proportional Distribution of Radiological Stage and Sarcoid Clinical Activity Classification Classes.

| Stage | Class 1 | Class 2 | Class 3 | Class 4 | Class 5 | Class 6 |
|---|---|---|---|---|---|---|
| **I** | 6(11.3%/42.9%) | 5(9.4%/83.3%) | 4(7.5%/25%) | 23(43.4%/35.4%) | 5(9.4%/35.7%) | 10(18.9%/13.7%) |
| **II** | 8(7.8%/57.1%) | 1(1%/16.7%) | 7(6.8%/43.8%) | 39(37.9%/60%) | 8(7.8%/57.1%) | 40(38.8%/54.8%) |
| **III** | - | - | 1(33.3%/6.2%) | - | - | 2(66.7%/2.7%) |
| **IV** | - | - | 4(13.8%/25%) | 3(10.3%/4.6%) | 1(3.4%/7.1%) | 21(72.4%/28.8%) |

Entries represent the number of patients followed in parentheses by the percentage of patients with a distinct radiological stage/percentage of patients in a distinct class.

**Table 9.** Proportional Distribution of Prognosis and Sarcoid Clinical Activity Classification Classes.

| | Class 1 | Class 2 | Class 3 | Class 4 | Class 5 | Class 6 |
|---|---|---|---|---|---|---|
| **Good prognosis** | 13(12%/92.9%) | 4(3.7%/66.7%) | 7(6.5%/43.7%) | 58(53.7%/89.2%) | 11(10.2%/78.6%) | 15(13.9%/20.5%) |
| **Poor prognosis** | 1 (1.2%/7.1%) | 2(2.5%/33.3%) | 9(11.3%/56.3%) | 7(8.7%/10.8%) | 3(3.8%/21.4%) | 58(72.5%/79.5%) |

Entries represent the number of patients followed in parentheses by the percentage of patients with a distinct prognose type/percentage of patients in a distinct class.

at stages III and IV was found to be higher and the rate of those in stage I was lower in this group than overall values. 90% of patients had pulmonary symptoms with no asymptomatic patients. The rate of previous treatment was found higher in PH group than all patients group (70% versus 40.4%). Right heart catheterization was performed in 4 of the patients who were diagnosed with PH according to echocardiography criteria, and sildenafil and bosentan were started during their follow-up.

In 36.7% of patients, progression was observed in a follow-up visit. In this visit, compared to baseline, sACE and CRP levels increased significantly (respectively p=0.029 and p=0.006). In PFT measurements, significant decrease was found (p<0.001). There was no significant difference between ESR value at baseline and progression time (p=0.325).

In the present study, aspergilloma was detected in 4 patients (1 male, 3 female). Mean age of diagnosis in these cases was 38.5. All were nonsmokers except one and all were consistent with radiological stage IV. One of our cases with aspergilloma died during follow-up and cause of death was respiratory failure.

In the present study, the rate of mortality was found to be 4.25% (7 cases, six of whom was female) 6 deaths were due to respiratory failure while one was associated with causes unrelated to sarcoidosis. Mean age of the patients with mortality was 50.7. At the time of presentation, 5 cases were consistent with radiological stage IV while the other two patients were diagnosed at stage I and II respectively. Only in male patient had extrapulmonary involvement (eye) accompany clinical picture. All of these cases had PH. Aspergilloma also was present in the male patient.

## Discussion

In an epidemiological study of sarcoidosis published in 2009 by Turkish Thoracic Society Clinical Problems Study Group, mean age of diagnosis was found 44±13 (17-90), mean age of male patients (38±12), was lower than females (48±13) (p<0.001) (10). In the present study, median age of diagnosis was 44 (20-67) with males being diagnosed at younger ages than female patients (46 versus 35) (P<0.001).

Female/male ratio in sarcoidois has been found to be 1.5:1 in USA (11) while in a large epidemiological study in Switzerland, no difference was found between genders (12). In a study in Sweden, it was observed at a higher rate in males than in females (13). In a study conducted with 100 patients in 2014 in our country, female/male ratio was 2.8 (14). In another study from Turkey, female/male ratio was 2.08 (15). As to the present study, the rate of female patients was 79.8%, with a female/male ratio of 3.94.

In ACCESS study, it was demonstrated that the incidence of sarcoidosis decreased by 35% in smokers (16). In two studies perfromed in Turkey in 2009 and 2014, it was established that respectively 73.4%

and 70% of sarcoidosis patients were non-smokers (10, 14). In our study, the rate of non-smokers was found 64.4%.

In a study conducted by Judson et al, it was established in two years of follow-up that in 50 out of 215 patients (%23) one or more new organ involvement was added to the clinical picture (17). In the present study, although there was an increase in the number of cases with skin, eye, cardiac and neurological involvement in the follow-up period compared to baseline in cases with progression, the difference was not statistically significant (p>0.05). During follow-up process of three years or more, 4 new cases of skin involvement, 1 eye, 2 liver, 1 cardiac and 2 neurological involvement developed. It was thought that the progress in organ involvement detected at the moment of diagnosis was more frequent than the addition of new extrapulmonary involvement.

Spontaneous remission was reported in around half of patients diagnosed with sarcoidosis within 2 years and in many remaining cases in 5 years. The probability of remission is lower after 5 years (18, 19). In the present study, spontaneous remisssion occurred in 20.2% of patients and remission with treatment in 9% of patients; 11.2% of patients experienced regression and 17% stable course. The reason why the rate of spontaneous remission and favorable prognosis was lower in the present study than other studies may be that as cases with longer than three years of follow-up were screened, the cases diagnosed before this time period and had remission were not included in the study while chronic cases with recurrence and progression were included, so a selection bias occured. In addition to this probable cause associated with method, the fact that our clinic is a reference center for intractable sarcoidosis cases may be another factor, 76 patients who had previous treatment history were referred to our department from other hospitals. In addition, patients wihout severe symptoms and who were followed without treatment may have been less enthusiastic for attending follow-up visits.

The specifity and sensitivity of sACE level in the diagnosis of sarcoidosis is low, but it may be beneficial in monitoring the course of the disease. High sACE levels reflect overall body granuloma load and correlates with the number of involved organs (20-23). In some studies, higher sACE levels have been reported in patients with active disease or chronic/progressive disease. However, some other studies reported negative correlation between them (24, 25). In the present study, sACE levels were similar between patients with good and poor prognosis (P=0.565) while in patients with spontaneous remission, sACE levels were found to be lower than other groups (P=0.021). During follow-up evaluation of patients with progression, sACE and CRP levels were established to increase compared to baseline levels (p=0.029 and p=0.006).

It has been demonstrated that radiological staging system has prognostic significance. Spontaneous remission occurs at the rate of 55-90% in stage I, 40-70% in stage II, and 10-30% in stage III. Stage IV is the one when irreversible fibrosis is observed (18, 20, 26). In a study with a recurrence rate of 18% during follow-up process, the incidence of recurrence was found to be higher in patients at higher stages compared to those at lower stage (p=0.04) (14). In another study, mortality rate was demonstrated to be higher in advanced stages (P=0.0043) (4). In our study, in poor prognosis group, at presentation, the ratio of stage I was lower and that of stage IV patients higher (p<0.001). It was established that radiological stage was the second leading factor in differentiating good/poor prognosis after DLCO and that each step increase in radological stage increased the odd of poor prognosis by 2.053 fold (p=0.006). In patients with spontaneous remission, radiological stages at baseline (60.5% stage I, 39.5% stage II) were found to be lower than other groups (P<0.001). It was established that rise in radiological stage increased the probability of not having spontaneous remission by 9.383 fold (p<0.001).

In a study comparing disease stage with functional status, statistically significant relation was found between advances in stage and decrease in $FEV_1$, FVC and DLCO (respectively p=0.007, 0.007 ve 0.01) (14). In this study, in the comparison between radiological stage at presentation and spirometry values, no significant difference was found between stage I and stage II with regard to $FEV_1$, FVC ve DLCO values. Although there was radiological parenchymal involvement in stage II, $FEV_1$, FVC and DLCO values were not different from those in stage I. However, in patients presenting at stage I and II, $FEV_1$, FVC and DLCO levels were found to be higher than those presenting at stage III-IV (P<0.01).

In ACCESS study, 2 years follow-up a group of 215 sarcoidosis patients, in about 80% of patients,

improvement or stable course was observed in $FEV_1$, FVC and radiological stage. As consistency between radiological stage and dyspnea level changes and FVC was low, changes in FVC were evaluated to be too inadequate to determine the course of disease (17). In a study including 452 patients, no relation could be demonstrated between spirometry values and mortality (4). In the present study, baseline $FEV_1$, FVC and DLCO levels were found higher in patients with good prognosis than those in the poor prognosis group (P<0.001). It was also observed that the most important factor discriminating good and poor prognosis was DLCO value (p<0.001). In addition, spontaneous remission group was found to have higher baseline $FEV_1$, FVC, $FEV_1$/FVC, DLCO values than other groups (p<0.05). Direct proportion was found between increase in $FEV_1$/FVC and DLCO levels and spontaneous remission (P=0.012-P=0.036). In patients with disease progression, $FEV_1$, FVC, $FEV_1$/FVC ve DLCO values were found to be decreased compared to baseline values (p<0.001).

It is thought that sarcoidosis patients who have sarcoidosis associated symptoms have worse prognosis than asymptomatic cases whose disease was detected incidentally (27). In a two year follow-up study, in patients with increase in dyspnea level, one or more new organ involvement was observed more commonly (P=0.013). In a cohort study carried out in 2019 with 660 sarcoidosis patients, 475 patients (73%) were symptomatic and 175 (27%) asymptomatic at the time of diagnosis. In symptomatic group, radiogical stage I disease occurred less commonly (P=0.041). In addition, the need for sarcoidosis treatment (P<0.01) and organ involvement (P<0.001) was found to be more common. At last follow-up visit, the rates of skin, eye and neurological involvement were found to be higher in the groups which were symptomatic at presentatation (28). In the present study, the ratio of asymptomatic patients was found lower and proportion of those presenting with pulmonary symptoms was higher in poor prognosis group (p<0.001). Altough extrapulmonary symptoms occurred more rarely in poor prognosis group, the difference was not significant (p>0.05). This finding may be due to the fact that patients may have described their extrapulmonary symptoms at a lower rate since pulmonary symptoms have become more severe. Likewise, in spontaneous remission group, the proportion of asymptomatic patients was found to be higher and that of patients with pulmonary symptoms was found to be lower (p<0.001). In multivariate logistic regression analyses, the probability of absence of spontaneous remission increased 8,726 fold (p=0.004) in cases with pulmonary symptoms and 27.308 fold in cases with extrapulmonary symptoms (p<0.001) compared to asymptomatic cases.

In a two year clinical follow-up study conducted with 215 patients, it was determined that of 95 patients who were not on steroids at baseline, 79% did not need any treatment during follow-up process. In addition of 110 patients who were on corticosterodis at baseline, in 47% treatment could not be discontinued (17). In another study with 337 patients, recurrence rate was found to be 74% in remission with treatment groups while it was 8% in spontaneous remission group (p<0.01) (29). In a study with 8207 sarcoidosis patients, mortality rate was found to be significantly higher in patients undergoing treatment at the time of diagnosis and within 3 months of diagnosis (30). In the present study, previous treatment rate was found to be higher in patients with poor prognosis compared to those with good prognosis (25.9% versus 60%) and in other groups compared to patients with spontaneous remission (0% versus 50.7%) (p<0.001). It was determined that in patients who underwent treatment before, the probability of poor prognosis increased 2.293 fold (p=0.026).

One of the most common complications of stage IV fibrotic lung disease is PH, which was reported in 5-15% of patients (31, 32). PH in sarcoidosis is associated with increase in mortality and morbidity (33). In a study including 313 patients, PH was detected in 34 patients (10.8%) and these patients were at more advanced ages and had more common respiratory dysfunction (p=0.001). In 17.6%, pulmonary fibrosis was impliacted for PH, in 35% cardiac sarcoidosis and in 14.7% cardiac involvement accompanying pulmonary fibrosis was incriminated for PH (34). In another study, PH was encountered in 12 of 212 patients (5.7%) and it was found to be associated with male sex, advanced radiological stage and hypoxemia (35). In two studies, PH was found significantly higher in women (36, 37). In a study with 50 sarcoidosis patients, in our country, PH prevalence was found to be 10%. In patients with PH, $FEV_1$ and FVC was found to be lower (p=0.005 and p=0.018). Although DLCO was lower in PH group, the difference was not found to be significant (p=0.23) (38). In the present study, age of diagnosis, smoking history and sex distribution was similar

in patients with PH (10.6%) and the other patients. It was also observed that among patients in whom PH developed radiological stages of III and IV were more common at the time of presentation and all of these patients presented with a pulmonary/extrapulmonary symptom. In addition, in PH group, $FEV_1$, FVC and DLCO values were found to be lower than mean values of the general patient group. The rate of PH was found to be higher in poor prognosis group than good prognosis group (0.0% versus 25.3%) and other outcome groups than spontaneous remission group (0% versus 13.3%) ($p<0.001$ and $p=0.009$).

Another complication of stage IV fibrotic lung disease is aspergilloma. Fungal colonization is a clinical picture that can occur in 11% of patients with fibrotic lung diseae (39). In a study including 427 patients, 10 patients with stage IV fibrotic cavitary sarcoidosis (2.3%) had chronic pulmonary aspergillosis in the form of aspergilloma and 7 of them were active smokers (40). In the study of Uzunhan et al, in a 25 years cohort, out of 3137 patients, 80 was found to have (2.6%) chronic pulmonary aspergillosis and of these patients 65(2%) completed the study. In the present study, aspergilloma was detected in 4 patients (1 male, 3 female) (2.1%). Mean age of diagnosis was 38.5. Only one of 4 patients had ever smoked and all cases were consistent with radiological stage IV. One of our cases died during follow-up process, but the cause of death was not aspergilloma associated complications, but respiratory failure.

Sarcoidosis associated mortality occurs in 1-5% of patients, the most common causes are respiratory failure, neurosarcoidosis and cardiac involvement (7, 20). This rate may be higher in different ethnic groups, different geographical regions, and in studies carried out with patients at more advanced stages. In two studies performed with patients at radiological stage IV mortality rates were found higher (respectively 11.3% and 20%) (3, 39). In the study of Kirkil et al, 42 out of 452 (9.3%) patients died and in 38 (8.4%) of these patients, the cause of death was reported to be respiratory failure associated with sarcoidosis (4). In our study, mortality rate was 4.25% (7 cases), 6 of which was female. The mean age of diagnosis was 50.7. At presentation, 5 of these cases was consistent with radiological stage IV and one was with stage I and another with stage II. Extrapulmonary involvement (eye) was observed only in male patients and PH was present in all cases. Male case also had aspergilloma. Of 7 deaths, 6 occurred on account of respiratory failure while one was not associated with sarcoidosis.

There are some limitations of the present study. The first one is that it was a retrospective study and 206 patients could not be included owing to lack of data at the medical records. Another limitation is the fact that as cases with longer than three years of follow-up within a certain time period were screened, cases diagnosed before this period and went into remission were not included in the study, while those who were diagnosed in the corresponding time period but were chronic, recurrent and progressive cases were included. Therefore, patients with poor prognosis may have been over represented in the present study.

In conclusison, being able to predict the course of disease in sarcodiosis is important for determining treatment need and preventing complications associated with unnecessary treatment. In the present study, it was established that radiological stage at the time of presentation, functional evaluation, symptom status and previous history of treatment are important in determining prognosis. In addition, it was demonstrated in follow-up evaluations, that increase in sACE and CRP values and decrease in spirometry parameters and DLCO were associated with progression of disease.

**Conflict of Interest:** Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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