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Clinical and radiological factors affecting progression in sarcoidosis

Olcay Aycicek[1], Ensar Cihat Emiroglu[1], Kadir Coban[1], Muge Erbay[2], Tevfik Ozlu[1], Funda Oztuna[1], Yılmaz Bulbul[1]

[1]Karadeniz Technical University Faculty of Medicine, Department of Chest Diseases, Trabzon, Turkey; [2]Karadeniz Technical University, Faculty of Medicine, Department of Allergy & Immunology Unit, Trabzon, Turkey

Abstract. *Background and aim:* To determine the clinical and radiological indicators of disease progression in a newly diagnosed patient with sarcoidosis. *Methods:* Data of patients diagnosed with sarcoidosis in our department between January 2014 and June 2022 were analyzed. The patients were divided into two groups: progression and non-progression. The groups were compared according to symptoms at the time of diagnosis, comorbidities, foci of extrapulmonary involvement, shape, size, density, localization of mediastinal lymph nodes, parenchymal findings, disease stage, and whether treatment was received at the beginning. *Results:* This study included 292 sarcoidosis patients. Forty-six patients progressed, and 46 (15.8%) progressed. It was observed that stage II patients progressed more than stage I patients (p<0,001). The mean time to progression was 38.05±30.45 months in stage I and 28±58 months in stage II. The progression rate was higher in patients with right upper paratracheal, subaortic-para-aortic, and subcarinal LAP (p=0.010, p=0.012, and p=0.020, respectively). A higher number of stations with LAP was associated with disease progression (p=0.017). The presence of parenchymal nodules (29/64.4%) and number of lobes with nodules were also associated with disease progression (p=0.027 and 0.022, respectively). The progression rate was 76.1% in the patients with treatment indications at the time of diagnosis (p<0.001).*Conclusions:* Disease stage is a prognostically important factor in the course of sarcoidosis, which was supported by the results of our study. Accordingly, it is important to closely follow up patients with high-stage sarcoidosis and identify patients with timely treatment indications.

Key words: sarcoidosis, progression, lymph node

Introduction

Sarcoidosis is a systemic granulomatous disease of unknown etiology. Although it may involve all organs, the intrathoracic lymph nodes and lungs are the most commonly affected areas. The staging of pulmonary sarcoidosis is based on posteroanterior chest radiographic findings. Sarcoidosis is classified as stages 0–4. At stage 0, the chest radiography findings were normal. Stage I, bilateral hilar lymphadenopathy without parenchymal findings; stage II, bilateral hilar lymphadenopathy with parenchymal findings; stage III, parenchymal findings without hilar lymphadenopathy; and stage IV, pulmonary fibrosis findings (1). Central and peripheral consolidations and band formations connecting these consolidated areas, subpleural infiltrative or wedge-shaped shadowing in the upper lobes, similar to pleuroparenchymal fibroelastosis, traction bronchiectasis, peripheral cysts, and honeycomb lung can be seen as fibrosis findings (2). Sarcoidosis has a variable clinical course. Although approximately 50% of patients

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Correspondence: Olcay Aycicek, Assist Prof
Karadeniz Technical University,
Faculty of Medicine, Department of Chest Diseases,
Trabzon, 61080, Turkey
E-mail: olcayaycicek@yahoo.com
ORCID: 0000-0002-0697-5680

recover with spontaneous remission, progression can be observed in the other half, which may lead to the development of conditions with high mortality rates, such as pulmonary fibrosis and hypertension (3,4). In stage IV patients with pulmonary hypertension, impaired pulmonary function tests, and pulmonary fibrosis rates of > 20%, the 5-year mortality rate can exceed 40% (5). The causes, mechanisms, and predictive factors for disease progression have not been fully elucidated, and no consensus prognostic markers have been identified. The ATS (American Thoracic Society) 2020 guidelines emphasize that studies are needed to determine which radiographic features predict disease progression (6). The detection of clinical, radiological, or laboratory markers predictive of disease progression will help physicians in the decision to start treatment earlier in high-risk patients or switch to alternative treatments to steroids, which is the first-line treatment. In our study, we aimed to determine the clinical and radiological indicators of disease progression in a newly diagnosed sarcoidosis patient, without going beyond routine tests.

Material and Method

This was a retrospective single-center study. The local ethics committee approved this study. The data of patients diagnosed with sarcoidosis, followed up, and treated in our department between January 2014 and June 2022 were analysed. Patients diagnosed with sarcoidosis but with incomplete data, those aged < 18 years, those lost to follow-up, and those with malignancy (due to the inability to differentiate sarcoid-like reactions from sarcoidosis) were excluded from the study. A Somatom device (Siemens, Forchheim, Germany) was used for computerized thorax tomography imaging. Sarcoidosis was diagnosed based on a joint statement by the American Thoracic Society, European Respiratory Society, and World Association of Sarcoidosis and Other Granulomatous Disorders: the presence of histologically confirmed non-caseating granulomas and exclusion of other possible granulomatous diseases or exclusion of clinical and other causes consistent with Löfgren's syndrome, Heerfordt's syndrome, or Löfgren's syndrome without histological confirmation (7). The patients were divided into two groups: progression and non-progression between the specified dates. The presence of at least one of the following three criteria was considered as progression [This British Thoracic Society (BTS) Clinical Statement 2019 was taken as the basis for progression criteria]; 1) aggravation of pulmonary symptoms or the emergence of new symptoms (cough, shortness of breath, chest pain, etc.) that cannot be explained by any other reason; 2) deterioration in lung function with at least a 10% decrease in Forced Vital Capacity (FVC) and at least a 15% decrease in diffusing capacity of the lungs for carbon monoxide (DLCO) or 4% or more decrease in oxygen saturation by pulse oximetry; and 3) worsening of radiological findings(8). The progression and non-progression groups were compared according to symptoms at the time of diagnosis; comorbidities; foci of extrapulmonary involvement; shape, size, density, and localization of mediastinal lymph nodes; parenchymal findings; disease stage according to posteroanterior (PA) chest X-ray and thoracic Computed Tomography (CT); and whether or not treatment was received at the beginning. Staging according to thoracic CT and PA chest radiography was performed according to the staging system (8).

Statistical analysis

The Kolmogorov-Smirnov test was used to test the normal distribution of continuous variables. Normally distributed data are expressed as mean±standard deviation. The Student's t-test was used to compare normally distributed data. The Mann-Whitney U test was used to compare non-normally distributed data. Discrete variables were compared using the chi-squared test. Parameters that were potential predictors of sarcoidosis progression were analysed using a logistic regression analysis. Multivariate logistic regression analysis was performed using the stepwise backward logistic regression (LR)method from predictive factors with a significance of ≤0.05 in univariate analysis. The Kaplan-Meier method was used to analyse the time to progression in patients with Stage I and II sarcoidosis. Data were analysed using the SPSS statistical software (version 13.01, serial number 9069728, SPSS Inc., Chicago).

Results

Between January 2014 and June 2022, 298 patients with sarcoidosis were diagnosed at our department. Three patients were excluded from the study due to loss to follow-up, and three patients were excluded due to lack of data. The inclusion criteria

were fulfilled, and 292 patients were included in this study. Of the patients, 223 (76.4%) were female and 69 (23.6%) were male, with a mean age of 49.81±12.02 years, 51.79±10.84 years for females and 43.42±13.41 years for males (p<0.001).

When staging was performed according to PA chest X-ray, 8 (2.7%) patients were stage 0, 201 (68.8%) were stage I, 82 (28.1%) were stage II, 1 (0.3%) was stage III, and no stage IV patients were found. Dyspnoea was the most common symptom among all patients (n=114 [39.0%]). Lymph node biopsy was performed in 243 patients (83.2%), lung parenchymal biopsy in 15 (5.1%), skin biopsy in 12 (4.1%), palate biopsy in one (0.3%), kidney biopsy in one (0.1%), spleen biopsy in one (0.3%), and adenoid biopsy in one (0.3%).18 (6.1%) were diagnosed based on bronchoalveolar lavage and clinical findings. Progression was observed in 46 patients (15.8%). All patients were Caucasians. A total of 290 patients were of Turkish origin, one patient was of Afghan origin, and one patient was of Georgian origin. Non-Turkish patients were included in the non-progressing group, and no statistical difference was found between the two groups in terms of pulmonary function test parameters. The demographic characteristics of the progressed and non-progressed groups are presented in Table 1.

Among the patients who progressed, 41 (89%) showed aggravation of pulmonary symptoms, 6 (13%) showed deterioration in lung function test results, and 28 (60,8%) showed worsening radiological findings. When the two groups were compared according to stage, it was observed that stage II patients progressed significantly more than stage I patients, according to both PA chest radiography and thoracic CT. Because the number of patients with stage 0, III, and IV disease was very low, statistical evaluation was performed by excluding these patients (Figure 1). According to PA chest radiography, 8 (2,7%) patients had stage 0 disease, one (0.3%) had stage III disease, and zero (0.0%) had Stage IV disease.

When staging was performed according to PA chest radiography, 42.2% of patients with stage I disease had stage II disease according to thoracic CT. However, when evaluated according to common intersection clusters, there was a significant difference in terms of progression between patients with stage I disease according to PA chest radiography and patients with stage II disease, whereas no statistically significant difference was found between patients with stage I disease according to thoracic CT and patients with stage II disease (p=0.44). When the stage according to thoracic CT was taken as the basis, there was a significant difference in terms of progression between patients with stage I disease according to PA chest radiography and those with stage II disease (p=0.09) (Figure 2).

The mean time to progression was 38.05±30.45 months in stage I and 28±58 months in stage II patients; no difference was found between the stages in terms of time to progression (p=0.371). When the progression time was evaluated by Kaplan-Meier analysis according to PA chest X-ray stage, the 1-year and 5-year progression rates were 26.3% and 73.7% in stage I and stage II, respectively, while these rates were 50% and 99.9%, respectively (Figure 3). The median time to progression was 32 months in stage I patients and 15 months in stage II patients, with no significant difference.

When a comparison was made according to the involved lymph node stations, the rate of progression was significantly higher in patients with right upper paratracheal LAP (lymphadenopathy (subaortic-para-aortic LAP) and subcarinal LAP (p=0.010, p=0.012, and p=0.020, respectively). A higher number of stations with LAP was significantly associated with disease progression (p=0.017). The presence of lymph node necrosis, lymph node homogeneity, lymph node diameter and density, and lymph node involvement was not significantly associated with progression (Table 2).

Parenchymal involvement was evaluated in the progression and non-progression groups. The presence of parenchymal nodules was significantly higher in the progressed group (29/64.4%), and the number of nodules was significantly associated with disease progression (p=0.027 and p=0.022, respectively). Other signs of parenchymal involvement, such as reticulation, consolidation, and ground glass, were not significantly associated with progression (Table 2). The progression rate was 76.1% in patients with treatment indications at the time of diagnosis, and 20.3% in those without treatment indications (p<0.001).

Logistic Regression Analysis was used to analyse factors affecting the risk of sarcoidosis progression. The results of the multivariate model showed that the risk of progression was 2.584 times higher in patients with stage II disease according to

Table 1. Comparison of demographic and clinical characteristics of the groups

	No Progression	**Progression**	**Total**	
	N=246 (84.2%)	N=46 (15,8)	N=292 (100.0%)	*p*
Gender				
Female	183 (74.4%)	40 (87.0%)	223 (76.4%)	*0.052*
Male	63 (25.6%)	6 (13.0%)	69 (23.6%)	
Age	49,70±12,255	50.41±10.784	49.81±12.021	*0.902*
Smoking Status				
Never Smoke	186 (76,5%)	37 (82,2%)	223 (77,4%)	*0.572*
Active Smoke	28 (11,5%)	3 (6,7%)	31 (10,8%)	
Dropped Out	29 (11,9%)	5 (11,1%)	34 (11,8%)	
Comorbidity				
No Comorbidity	141 (57,3%)	20 (43,5%)	161 (55,1%)	*0,084*
Symptoms				
Cough	27 (11,0%)	7 (15,2%)	34 (11,6%)	*0,425*
Dyspnoea	91 (37,0%)	23 (50,0%)	114 (39,0%)	*0,100*
Weight Loss	8 (3.3%)	2 (4.3%)	10 (3.4%)	*0.661*
Fatigue	28 (11,4%)	1 (2,2%)	29 (9,9%)	*0,060*
Arthralgia	28 (11,4%)	3 (6,5%)	31 (10,6%)	*0,439*
Chest Pain	35 (14,2%)	3 (6,5%)	38 (13,0%)	*0,125*
Extrapulmonary Involvement				
Abdominal Organ	10 (4,1%)	2 (4,3%)	12 (4,1%)	*0,592*
Skin	30 (12,2%)	10 (21,7%)	40 (13,7%)	*0,104*
Eye	17 (7,0%)	5 (10,9%)	22 (7,6%)	*0,263*
Other	17 (6,9%)	4 (8,7%)	21 (7,2%)	*0,431*
Ethnicity				
Caucasian	246 (100%)	46 (100%)	292 (100%)	-
Pulmonary Function Test Values				
FVC (%)	103,20±22,26	103,15±21,09	103,27±22,04	*0,969*
FEV1(%)	103,33±21,77	100,29±20,42	102,86±21,56	*0,408*
FEV1/FVC (%)	82,36±8,97	79,80±9,26	81,96±9,05	*0,097*
FEF_{25-75} (%)	87,44±32,18	85,17±43,66	87,10±34,09	*0,700*
PEFR (%)	90,09±24,55	86,59±30,72	89,54±25,58	*0,422*

Abbreviations: FVC: Forced Vital Capacity; FEV_1: Forced Expiratory Volume In 1 Second; $FEF_{25-75\%}$:Forced Mid-Expiratory Flow; PEFR: Peak Expiratory Flow Rate.

posteroanterior radiography than in those with stage I disease (p=0.038) (Table 3).

Discussion

One of the main findings of our study was that radiological stage II patients showed significantly more disease progression than did stage I patients. Staging according to PA chest radiography and orthoracic CT findings did not change the results. Some studies have reported a correlation between certain biomarkers and granulomatous inflammation, which is the main pathophysiological feature of sarcoidosis. These markers have been proposed to be indicators of disease progression. In patients with progressive sarcoidosis, some parameters have been

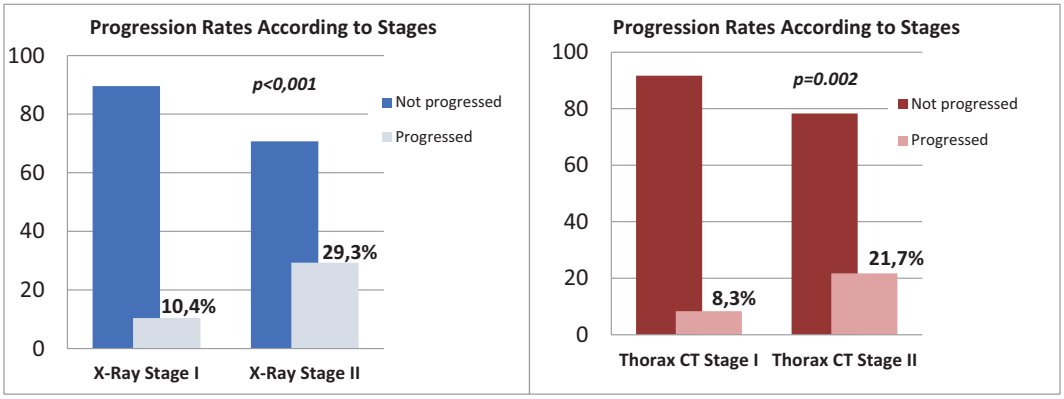


Figure 1. Progression rates according to stages.

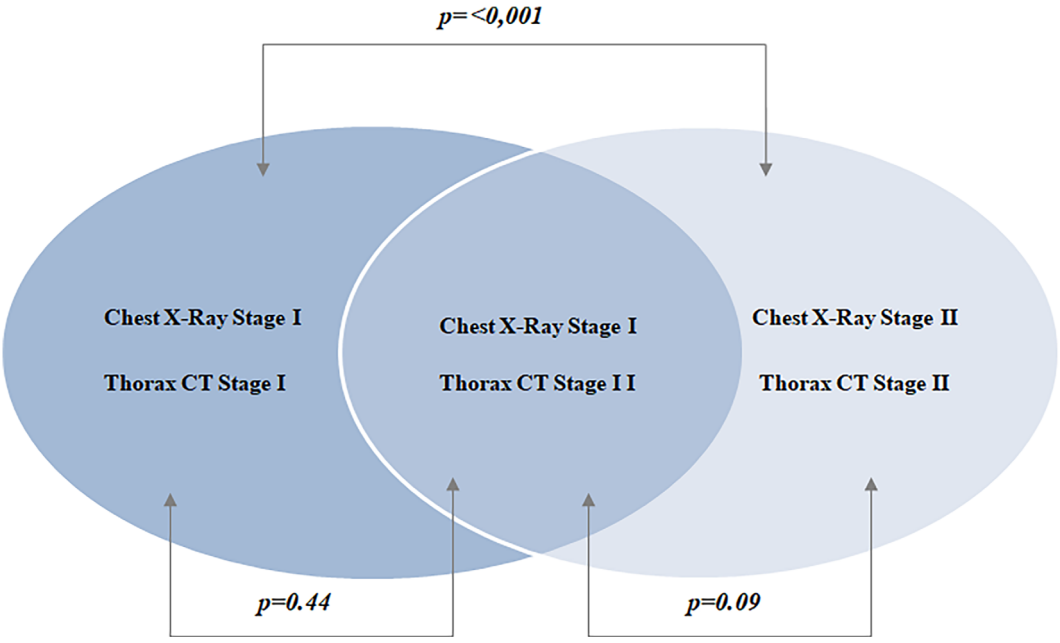
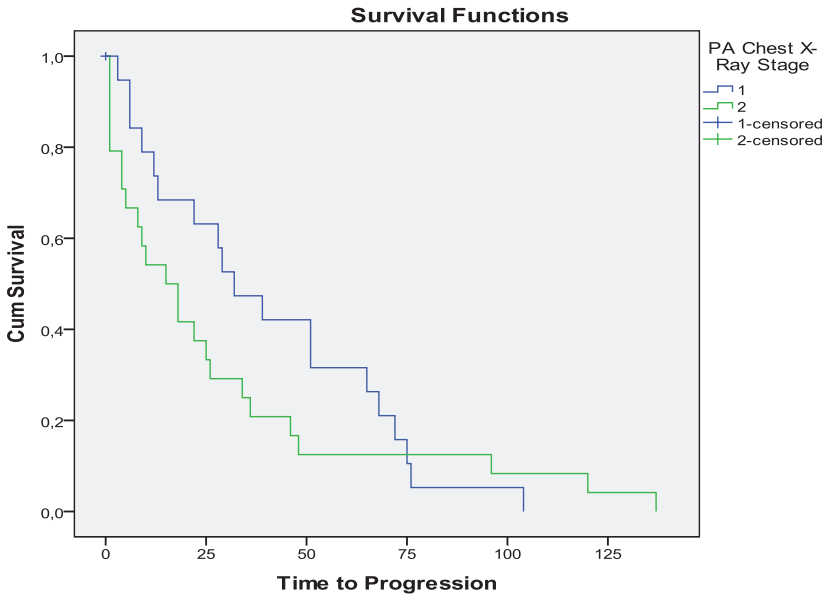


Figure 2. Staging of the cases according to X-ray and CT findings and comparison in terms of progression.

shown to be high or low in peripheral blood and BAL (Bronchoalveolar Lavage) fluid. For example, increased neutrophil levels in BAL fluid, high neutrophil-derived elastase and albumin values in BAL fluid, and increased tumour necrosis factor-α (TNF-α) and sIL-2R (soluble interleukin-2 receptor) have been associated with poor prognosis and chronicity (9-12). Increased levels of chitotriosidase secreted by activated macrophages and neutrophils have been associated with lung fibrosis and a poor prognosis (13). However, none of these biomarkers have been routinely used in our daily practice; it is not possible to check the levels of these markers in every center, and they are not included in the routine recommendations of the ATS/BTS guidelines (6,8). In our study, we aimed to determine the clinical and radiological indicators of disease progression in a newly diagnosed sarcoidosis patient, without going beyond routine tests. There are studies with a similar aim to our study, but designed differently and with similar and different results. For example, in a retrospective study by Casal et al. involving 277 patients with sarcoidosis that aimed to identify patients with a high probability of progression, age at the time of



PA Chest X-Ray	1-Year Progression Rate (%)	2-Year Progression Rate (%)	5-Year Progression Rate (%)	MPT (Months)	*p*
Stage I	26,3	42,1	73,7	32,0	*0,34*
Stage II	50,0	66,7	99,9	15,0	

Figure 3. Analysis of time to progression in sarcoidosis by the Kaplan-Meier Method for Stage I and II Cases. *Abbreviations:* MPT: Median Progression Time.

diagnosis was found to be the only factor associated with prognosis, and a one-year increase in age increased the risk of progression by 4% (14). In another study by Bilgin et al., no statistically significant difference was found in terms of age at diagnosis, laboratory values (leukocytes, lymphocytes, sACE, calcium, vitamin D, 24-hour urinary calcium, CRP, ESR), sex, smoking history, or extrapulmonary involvement (p>0.05).In this study, the most decisive factors in differentiating between good and poor prognosis groups were DLCO values at initial presentation, radiologic stage of the disease, and patient history of previous treatment (15). In our study, we did not observe any relationship between age, sex, smoking status, presence or absence of comorbidities, symptoms, extrapulmonary involvement, and disease progression. In another study by Silva et al. investigating prognostic factors at the time of diagnosis in the Portuguese population, chronic sarcoidosis patients and regressed patients were compared in terms of clinical, radiological, and laboratory characteristics, and factors predicting chronicity were tried to be determined. A positive correlation was found between chronic disease and impaired pulmonary function test values, radiological stage II, low CD4/CD8 ratio, and extrapulmonary disease, whereas a negative correlation was found between Löfgren syndrome and asthenia (16). Our evaluation criteria did not include the Pulmonary Function Test (PFT) and CD4/CD8 levels; however, in this study, we found that stage II patients progressed significantly more than stage I patients did. The rate of progression was also higher in patients with treatment indications at the time of diagnosis than in those without treatment indications (35.00% vs.76.1%, p<0.001). Sarcoidosis staging according to PA chest radiography has been used for a long time and remains valid. However, computed tomography is

Table 2. Comparison according to radiological characteristics.

	No Progression	Progression	Total	
	N=246 (84.2%)	N=46 (15,8)	N=292 (100.0%)	*p*
Lymph Node Involvement				
Right Upper Paratracheal	150 (63,3%)	37 (82,2%)	187 (66,3%)	***0,010***
Right Lower Paratracheal	190 (80,2%)	41 (91,1%)	231 (81,9%)	*0,061*
Left Upper Paratracheal	107 (45,1%)	22 (48,9%)	129 (45,7%)	*0,645*
Left Lower Paratracheal	138 (58,2%)	31 (68,9%)	169 (59,9%)	*0,175*
Subaortic/Para-Aortic	163 (68,8%)	40 (88,9%)	203 (72,0%)	***0,012***
Subcarinal	211 (89,0%)	45 (100,0%)	256 (90,8%)	***0,020***
Hilar LAP	213 (89,9%)	44 (97,8%)	257 (91,1%)	*0,147*
Bilateral Hilar LAP	167 (68,2%)	36 (78,3%)	203 (69,8%)	*0,160*
Extrapulmonary	13 (5,3%)	4 (8,7%)	17 (5,8%)	*0,322*
Number of Stations with LAP	6,00 (0,00-10,00)	8,00 (2,00-9,00)	6,00 (0,00-10,00)	***0,017***
Lymph Node Characteristics				
Necrosis	13 (8,5%)	1 (3,2%)	14 (7,6%)	*0,471*
Homogeneity	146 (86,4%)	27 (79,4%)	173 (85,2%)	*0,313*
Konglomere LAP	20 (11,9%)	1 (2,9%)	21 (10,4%)	*0,213*
LAP Small Diameter (mm)	18,00 (3,00-50,00)	20,00 (6,00-32,00)	19,00 (3,00-50,00)	*0,338*
Mean Density	52,35±16,06	50,94±16,42	52,09±16,07	*0,699*
Parenchyma Characteristics				
Nodule	114 (46,5%)	29 (64,4%)	143 (49,3%)	***0,027***
Reticulation	29 (11,8%)	8 (17,8%)	37 (12,8%)	*0,291*
Ground Frosted Glass	39 (15,9%)	10 (22,2%)	49 (16,9%)	*0,314*
Consolidation	23 (9,4%)	6 (13,6%)	29 (10,0%)	*0,413*
Number of Lobes with Nodules	2,00 (0,00-5,00)	3,00 (0,00-5,00)	2,00 (0,00-5,00)	***0,022***
Treatment				
Initial Treatment	50,00 (20,3%)	35,00 (76,1%)	85,00 (29,1%)	***<0,001***

Abbreviations: PA: Posteroanterior, CT: Computerized, LAP: Lymphadenopathy.

Table 3. Logistic regression analysis of the factors affecting the presence of progression

	Multivariate	
	OR (%95 CI)	*p*
PA x-Ray Stage	2,584 (1,055-6,327)	*0,038*
CT Stage	1,140 (0,256-5,070)	*0,864*
Right Upper Paratracheal	1,252 (0,269-5,837)	*0,775*
Subaortic/Paraaortic	1,195 (0,201-7,091)	*0,845*
Number of Stations with LAP	1,260 (0,842-1,885)	*0,261*
Presence of Parenchymal Nodule	1,578 (0,331-7,521)	*0,567*
Number of Lobes with Nodules	0,963 (0,716-1,294)	*0,801*

Abbreviation: OR: Odds Ratio.

more sensitive in detecting parenchymal lesions that cannot be seen on chest radiographs, especially in differentiating active inflammation from fibrotic changes (17). In a study of 351 sarcoidosis cases, Benn et al. found that CT scan features were inconsistent with the Scadding stage in approximately 40% of the cases (18). In a study of 30 patients by Koç et al., findings compatible with sarcoidosis were observed on CT in all patients with normal PA chest radiography, which led to a more advanced stage in many patients evaluated by CT (19). In addition, the Delphi consensus results emphasized that CT is more sensitive than chest radiography, and there is strong consensus that HRCT should be performed initially in sarcoidosis patients with evidence of

pulmonary involvement (20). In our study, 42.2% of the patients with stage I disease according to PA radiography were evaluated as stage II according to CT. However, according to our study, as shown in Figure 1, stage II patients progressed significantly more according to radiography than stage I patients. However, there was no significant difference in terms of progression between patients whose stage increased according to CT and those whose stage remained the same (p=0.44). In other words, our results suggest that the use of PA chest radiography in staging is sufficient to evaluate and predict disease progression. According to the Kaplan-Meier analysis, when the progression time was evaluated according to chest radiography stage, the 1-year progression rate was 26.3% and the 5-year progression rate was 73.7% in stage I patients, while these rates were 50% and 99.9% in stage II patients, respectively. However, there was no statistically significant difference between the median progression times (p=0.34). This result shows that the rate of progression is higher in stage II than in stage I, but the progression times of both stages are similar since diagnosis. In a study conducted in Brazil to determine the predictive features associated with the clinical course in the initial evaluation of sarcoidosis, the presence of parenchymal involvement, delayed diagnosis, dyspnoea, extrapulmonary involvement, and low FVC values were found to be related to the development of fibrotic disease and a 3-letter scoring system (A, B, and C) was developed based on the factors selected as a result of the study. The positive predictive values for A (≤ 1 point) and C (≥ 4 points) scores for persistent disease were 12.5% and 81.8%, respectively (21). In our study, we did not find an association between symptoms or extrapulmonary involvement and progression. However, the presence of nodular parenchymal involvement was significantly higher in patients with progressive disease (29/64.4%; p=0.027). We also found that the presence of nodules in more lobes (i.e., the extent of nodules) was associated with disease progression (p=0.022). Analyses of lymph node involvement and its characteristics were also important findings of this study. Our study showed that right upper paratracheal, subaortic/para-aortic, and subcarinal lymph node involvement was significantly associated with disease progression (p=0.010, p=0.012, and p=0.012, respectively). We also found that the number of involved lymph node stations was significantly higher in patients with disease progression (P =0.017). Because there are insufficient studies on this subject in the literature, these findings are an important reference for future research. When the multivariate model results of the factors affecting the risk of progression of sarcoidosis were analysed, it was found that the risk of progression was 2.584 times higher in patients with stage II disease according to posteroanterior radiography than in those with stage I disease (p=0.038). Disease stage is a prognostically important factor in the course of sarcoidosis, which was supported by the results of our study. Accordingly, it is important to closely follow up patients with high-stage sarcoidosis and identify patients with timely treatment indications. According to our study, advanced stage of the patient at the time of diagnosis, indication for treatment, involvement of unusual lymph nodes such as upper paratracheal, para-aortic-subaortic, a high number of involved lymph node stations, and nodular parenchymal involvement were effective factors for progression. The strength of our study is that it focused on determining which radiographic features predict disease progression, which is also underlined in the ATS (American Thoracic Society) 2020 guidelines(6). The limitations of this study are that it was retrospective, the number of patients in stages 0, III and IV was very few or none, it was a single-center study, the evaluation of these stages was incomplete due to the small number of patients and the difference in the number of patients between the progressed and non-progressed groups was large.

Conflict of Interest: Each author declares that he 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.

Availability of Data and Material: The corresponding author is responsible for the data and can contact the corresponding author.

Ethics Approval: The Local ethics committee has approved.

Consent to Participate: This study was conducted following the Declaration of Helsinki.

Consent for Publication: All authors declare that this article or any part of it has not been published in any other place, institution or organization. All authors have reviewed and approved the final manuscript. All authors have agreed to submit this manuscript to Medical Microbiology and Immunology.

Authors' Contributions: Authors' Contributions: The study design was developed by all authors. Data collection and analysis

were performed by OA, ECE, and KC, followed by a literature review conducted by ME and FO. The first draft of the manuscript was written by OA and YB. The first draft was edited by TO and FB, and the final manuscript was approved by all authors.

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