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Sarkoidozda Pulmoner Parankimal ve Ekstrapulmoner Tulumu Belirlemede Serum Anjiyotensin Konverting Enzimin Rolü

The Role of Serum Angiotensin Converting Enzyme for Predicting Pulmonary Parenchymal and Extrapulmonary Involvement of Sarcoidosis

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ÖZ

GİRİŞ ve AMAÇ: *Sarkoidoz günümüzde halen etiyolojisi bilinmeyen bir hastalıktır. Klinik tablo ve seyir hastalığın başlangıç yaşına, süresine, evresine ve yaygınlığına bağlı olarak değişmektedir. Klinik tabloyu ve seyri öngörebilecek biyomarkerların kullanılması hastalığın yönetiminde kolaylık sağlayacaktır. Çalışmamızda hematolojik ve biyokimyasal parametrelerle hastalığın evre ve yaygınlığı arasındaki ilişkiyi belirlemeyi amaçladık.*

YÖNTEM ve GEREÇLER: *2013-2018 yılları arasında kliniğimizde sarkoidoz tanısı konulan hastaların dosyaları retrospektif olarak incelendi. Hastaların demografik verileri, tanı sırasındaki klinik bulguları, evreleri, ekstrapulmoner tutulum olup olmadığı ve hemogram, eritrosit sedimentasyon hızı (ESR), C reaktif protein (CRP), serum kalsiyum (Ca) ve anjiotensin konverting enzim (ACE) düzeylerini içeren laboratuvar parametreleri kaydedildi. Hastalar akciğer parankim tutulumu ve ekstrapulmoner tutulumu olup olmamasına göre sınıflandırıldı. Akciğer parankim tutulumu olmayan evre 1 hastalar grup 1 ve akciğer parankim tutulumu olan evre 2 ve 3 hastalar grup 2 olarak sınıflandırıldı.*

BULGULAR: *Belirlenen tarihler arasında 121 sarkoidoz hastasının verilerine ulaşıldı. Hastaların 30 (%24.8)'u erkek, 91 (%75.2)'i kadın ve yaş ortalaması 50.71±11.76 idi. Grup 1'de 59 (%48,8) ve grup 2'de 62 (%51,2) olgu vardı. Hastaların 71 (%58,9)'de sadece akciğer tutulumu varken 50 (%41.3)'sinde akciğer ve akciğer dışı organ tutulumu birlikte vardı. Akciğer dışı organ tutulumu en sık eritema nodozum (EN)'du (%15,7). Grup 2 olgularda serum ACE değeri grup 1'den daha yüksekti (p =0,027). Akciğer ve akciğer dışı tutulumu olan olgularda serum ACE düzeyi akciğer dışı tutulum olmayanlara göre daha yüksekti (p =0,045). Bakılan diğer laboratuvar parametreleri gruplar arasında farklı değildi.*

TARTIŞMA ve SONUÇ: *Serum ACE düzeyi akciğer parankim tutulumunu ve ekstrapulmoner tutulumu göstermede faydalı olabilir.*

Anahtar Kelimeler: *Sarkoidoz, anjiotensin konverting enzim, pulmoner parankimal tutulum, ekstrapulmoner tutulum*

ABSTRACT

INTRODUCTION: *The clinical characteristics and course of sarcoidosis vary according to the age of onset, duration, stage, and extent of the disease. Biomarkers that can predict clinical characteristics and course will provide convenience in disease management. We aimed to determine relationships of hematologic and biochemical parameters with the stage and extent of the disease.*

METHODS: *The charts of sarcoidosis patients between 2013 and 2018 were retrospectively investigated. Demographic data, clinical findings at the time of diagnosis, stage, and extrapulmonary involvement were recorded together with complete blood count, erythrocyte sedimentation rate, serum C-reactive protein, calcium, and angiotensin converting enzyme (ACE) levels. Patients were classified according to the presence of pulmonary parenchymal and extrapulmonary involvement. Stage-1 patients with no pulmonary parenchymal involvement were in Group 1, and stage-2 and stage-3 patients with pulmonary parenchymal involvement in Group 2.*

RESULTS: *Of 121 sarcoidosis patients, 30 (24.8%) were male, 91 (75.2%) female. The average age was 50.71±11.76 years. 59 (48.8%) patients were in Group 1, and 62 (51.2%) in Group 2. Pulmonary involvement was present only in 71 (58.7%) patients. Extrapulmonary and pulmonary involvement was present in 50 (41.3%) patients. Most common extrapulmonary involvement was erythema nodosum (15.7%). Serum ACE level was higher in Group 2 than Group 1 (p=0.027) and in cases with pulmonary and extrapulmonary involvement both than those with pulmonary involvement only (p=0.045). No significant deviations were found between the groups regarding other laboratory parameters.*

DISCUSSION AND CONCLUSION: *The serum ACE level may be useful in showing both the pulmonary parenchymal and extrapulmonary involvements.*

Keywords: *Sarcoidosis, angiotensin converting enzyme, pulmonary involvement, extrapulmonary involvement.*

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INTRODUCTION

Sarcoidosis is a systemic disease with unknown etiology and characterized by non-caseating granulomas, involving all organs, mainly the lungs (1, 2). It is more commonly seen in females and between the ages of 20 and 40 years (3). Its prevalence changes with geographical location and race. The Scandinavian countries have the highest prevalence with 50-60/100.000 (4). In a study conducted in our country, the annual incidence was found to be 4/100.000 (5). Diagnosis is made by exclusion of other granulomatous disorders and histopathological identification of non-caseating granulomas in a patient meeting the clinical and radiological criteria of sarcoidosis (2). The clinical course is variable, related to factors such as age, ethnicity, disease duration, stage, and presence of extrapulmonary involvement (1, 5). Spontaneous resolution occurs in 2/3 of patients, and it is more common in Stage-1 patients, compared to Stage-2 and Stage-3 patients (6, 7). 30-50% of patients are asymptomatic at the time of diagnosis (8). Symptoms vary according to the involved organ in symptomatic patients. Cases with extrapulmonary involvement may present with non-respiratory symptoms, and in such cases, sarcoidosis may not come to mind at first. The frequency of symptoms varies according to the stage also. In Stage-1 cases, the clinical signs are observed less frequently compared to stages 2 and 3 (9, 10).

Variability of the clinical picture and course in sarcoidosis has led to the necessity of biomarkers in the initial assessment and follow-up of patients. Using biomarkers that can predict the stage and extensiveness of the disease will provide convenience in the management of the disease. In our study, we aimed to determine the relationships of hematologic and biochemical parameters with the stage and extensiveness of the disease.

MATERIALS AND METHODS

The data on the charts of the patients diagnosed with sarcoidosis at the Clinics of Chest Diseases in Adnan Menderes University between the years of 2013-2018 were evaluated retrospectively. Diagnosis of sarcoidosis was made by exclusion of other granulomatous disorders together with the identification of non-caseating granulomas in obtained samples or the presence of lymphocytosis and CD4/CD8 > 3.5 in bronchoalveolar lavage (BAL) in the patients meeting the clinical and radiological criteria of sarcoidosis (2, 11, 12). The demographic data, the symptoms at the time of admission, the physical findings, the pulmonary function test (PFT) parameters, the radiological stage, the erythrocyte sedimentation rate (ESR), the C reactive protein (CRP) level, the serum calcium (Ca) level, the urinary Ca and angiotensin converting enzyme (ACE) level, the hemogram results involving the white blood cell count (WBC), the hemoglobin (Hb) level, the neutrophil and lymphocyte counts, the neutrophil/lymphocyte ratio (NLR), the red cell distribution width (RDW), the mean corpuscular volume (MCV), the mean platelet volume (MPV), and the platelet distribution width (PDW) parameters were recorded. Patients who did not meet the diagnostic criteria or the investigated data of whom were incomplete were excluded from the study.

Pulmonary function tests were performed according to the ATS/ERS standards using a Jaeger MasterScope PC. Every measurement was repeated three times, and the best values were selected. Forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and FEV1/FVC were used as spirometric parameters (12). The recorded ESR, CRP, serum Ca, and hemogram parameters belonged to the peripheral blood at the time of diagnosis and the urinary Ca level was analyzed in the collected 24-hour urine. The chest x-ray findings were classified according to the Scadding staging system. According to this system, the patients with only bilateral hilar lymph node involvement and if present, paratracheal involvement were classified as stage 1, the patients with involvement of hilar lymph nodes and pulmonary parenchyma both were classified as stage 2, and the patients with involvement of pulmonary parenchyma only were classified as stage 3 (13). The stage-1 patients that involvement of pulmonary parenchyma was absent were categorized as Group 1, and the stage-2 and stage-3 patients with pulmonary parenchymal involvement were categorized as Group 2. The presence of hypercalcemia, hypercalciuria, erythema nodosum (EN), and uveitis, the occurrence of which cannot be

explained by other causes, or identification of granulomas in extrapulmonary tissue sampling were considered as extrapulmonary involvement. Approval of Ethics Committee of Adnan Menderes University was received for the study (Ethics Committee No: 2019/35).

Statistical Analysis

Statistical analyses were done using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA). The normality of the distribution of continuous variables was determined by the Kolmogorov Smirnov test. Descriptive statistics for quantitative variables were given as mean ± standard deviation for normally distributed variables and as median (25th - 75th percentiles) for non-normally distributed variables. Descriptive statistics for qualitative variables were given as frequency (%). Comparisons between quantitative variables were analyzed by conducting Student's t test or Mann Whitney U test. The dependence between qualitative variables was determined by chi-square analysis. $p < 0.05$ was considered statistically significant.

RESULTS

A total of 121 patients who met the criteria for inclusion in the study among 138 patients diagnosed with sarcoidosis were evaluated. 30 (24.8%) were male, and 91 (75.2%) were female. The mean age of all patients was 50.71±11.76 years. The mean age was 48.80±13 years in male patients, whereas 51.35±11.33 years in female patients (p=0.389). 59 (48.8%) patients were in stage 1, 59 (48.8%) patients were in stage 2, and 3 (2.5%) patients were in stage 3. The stage distribution of sarcoidosis patients was similar regarding gender (p=0.207). 54 (44.6%) patients were asymptomatic at the time of diagnosis. The most frequently met symptoms were cough (22.3%), fatigue (21.5%), and joint pain (19%). The symptoms of the patients were shown in Table 1. The symptoms of fatigue and dyspnea were found to be more common in stage-2 and stage-3 sarcoidosis patients (p=0.023 and p=0.042, respectively). The other symptoms had similar frequencies in all three stages (p>0.05).

Table 1. The symptoms of the sarcoidosis patients

Symptom*	n (%)
Cough	27 (22.3)
Dyspnea	18 (14.9)
Fatigue	26 (21.5)
Erythema nodosum	19 (15.7)
Joint pain	23 (19)
Visual impairment	6 (5)
Fever	3 (2.5)
**** Some patients had more than 1 symptoms***	

The most common findings found on physical examination of the patients were erythema nodosum (EN) (15.7%), peripheral lymphadenopathy (LAP) (7.4%), and uveitis (5.8%). The findings determined in the physical examination of the patients were shown in Table 2.

Table 2. The findings of physical examination in the sarcoidosis patients

Physical examination findings*	n (%)
Erythema nodosum	19 (15.7)
Uveitis	7 (5.8)
Peripheral lymphadenopathy	9 (7.4)
Arthritis	5 (4.1)
Hepatomegaly	1 (0.8)
**** Some patients had more than 1 physical examination findings***	

Among physical findings of the patients, arthritis was more common in the stage-1 patients compared to the stage-2 and stage-3 patients (p=0.025). The stages were not different from each other regarding the other physical examination findings (p>0.05). Only pulmonary involvement was present in 71 (58.7%) patients, whereas 50 (41.3%) patients had pulmonary and extrapulmonary involvement both. The most common extrapulmonary involvements were EN (15.7%), peripheral LAP (7.4%), uveitis (5.8), and hypercalciuria (5.8%), respectively. The results related to extrapulmonary involvement were shown in Table 3. The stages were not different from each other regarding extrapulmonary involvement (p>0.05).

Table 3. The extrapulmonary involvement in sarcoidosis patients	
Extrapulmonary involvement*	n (%)
Erythema nodosum	19 (15.7)
Subcutaneous nodule	3 (2.5)
Uveitis	7 (5.8)
Hypercalcemia	5 (4.1)
Hypercalciuria	7 (5.8)
Nephrolithiasis	1 (0.8)
Peripheral lymphadenopathy	9 (7.4)
Liver nodule	6 (5)
**** Some patients had more than 1 extrapulmonary involvement***	

The stage-1 patients with no pulmonary parenchymal involvement were classified as Group 1, and the stage-2 and stage-3 patients with pulmonary parenchymal involvement as Group 2; 59 patients were in Group 1, and 62 patients in Group 2. No significant differences were found among the groups regarding age, gender, smoking history, PFT parameters, and the frequency of extrapulmonary involvement ($p>0.05$). The symptom of fatigue was more common in Group 2, and the physical finding of arthritis was more common in Group 1 ($p=0.01$ and $p=0.025$, respectively). The serum ACE level was higher in Group 2 ($p=0.027$). The two groups did not have any significant difference regarding the ESR, CRP, serum Ca, urinary Ca, WBC, Hb, neutrophil, lymphocyte, NLR, RDW, MCV, MPV, and PDW values ($p>0.05$) (Table 4).

When the patients were categorized as those with pulmonary involvement only and those who had pulmonary and extrapulmonary involvement both, the two groups were found to be similar regarding age, gender, smoking history, PFT parameters, and radiologic staging ($p>0.05$). The presence of joint pain was found to be more common in the group with extrapulmonary involvement ($p=0.001$). The serum ACE level was found to be higher in the group that extrapulmonary involvement accompanied pulmonary involvement ($p=0.045$). The two groups were not significantly different from each other regarding the ESR, CRP, WBC, Hb, neutrophil, lymphocyte, NLR, RDW, MCV, MPV, and PDW values ($p>0.05$) (Table 5).

DISCUSSION

Sarcoidosis is characterized by various clinical pictures, and its course is variable. Patients manifest various clinical courses depending on the disease stage and the systems involved. The symptoms are met less frequently, and the prognosis is better in stage-1 patients (7, 13-15). In cases having extrapulmonary involvement together with pulmonary involvement, initial complaints may vary depending on the involved extrapulmonary sites. These cases may present with non-respiratory symptoms such as joint pain, visual impairment, swelling in various parts of the body, or palpitations. In such situations, sarcoidosis may not be considered as a preliminary diagnosis during the differential diagnostic processing.

In our study, when the stage-1 patients with no pulmonary parenchymal involvement were categorized as Group 1 and the stage-2 and stage-3 patients with pulmonary parenchymal involvement were categorized as Group 2, no significant differences were found to be present between the two groups regarding age, gender, smoking history, PFT parameters, and the frequency of extrapulmonary involvement. There are studies reporting that there were no differences between patients with and without pulmonary parenchymal involvement and among stage-1, stage-2, and stage-3 patients in terms of PFT parameters (16, 17). In the study conducted by Costabel et al., it was reported that PFT parameters were poorly correlated with the radiological findings (18).

In our study, the serum ACE level was found to be lower in Group 1 when compared to Group 2 ($p=0.045$). ACE is normally an enzyme responsible for blood pressure control and released from monocytes, macrophages, and pulmonary epithelial cell. In sarcoidosis patients, it is produced by active granulomas and shows the total granuloma burden. Its blood level is elevated in approximately 60% of patients (6, 19, 20). The use of ACE in diagnosis and prognosis is controversial. In the study conducted by Studdy et al., the sensitivity of ACE was found as 57%, the specificity as 90%, the positive predictive value as 90%, and the negative predictive value as 60% in the diagnosis of the disease (21). Various

Table 4. The demographic, functional, and laboratory data of the sarcoidosis patients with or without parenchymal involvement

Characteristic	Group 1	Group 2	p value
Patients n (%)	59 (48.8%)	62 (51.2%)	
Age	50.42±11.10	51.00±12.44	0.635
Gender			0.298
Female n (%)	47 (79.7%)	44 (71%)	
Male n (%)	12 (20.3%)	18 (29%)	
Smoking			0.418
Yes n (%)	15 (25.4%)	17 (27.4%)	
No n (%)			
Symptoms			
Cough n (%)	10 (17%)	17 (27.4%)	0.122
Dyspnea n (%)	6 (10.2%)	12 (19.4%)	0.122
Fatigue n (%)	7 (11.9%)	19 (30.7%)	0.010
Erythema nodosum n (%)	11 (18.6%)	8 (12.9%)	0.269
Joint pain n (%)	14 (23.7%)	9 (14.5%)	0.145
Fever n (%)	1 (1.7%)	2 (3.2%)	0.519
Physical examination			
Erythema nodosum n (%)	11 (18.6%	8 (12.9%)	0.269
Uveitis n (%)	4 (6.8%)	3 (4.8%)	0.472
Peripheral lymphadenopathy n (%)	6 (10.2%)	3(4.8%)	0.221
Arthritis n (%)	5 (8.5%)	0 (0%)	0.025
Hepatomegaly n (%)	0 (0%)	1 (1.6%)	0.512
Extrapulmonary involvement			0.181
Absent n (%)	31 (52.5%)	40 (64.5%)	
Present n (%)	28 (47.5%)	22 (35.5%)	
Pulmonary function tests			
FVC (L)	3.04±0.75	3.13±1.18	0.784
FVC (% pred)	100.96±14.25	94.29±22.11	0.185
FEV1(L)	2.29±0.67	2.36±0.9	0.941
FEV1 (%)	90.92±17.62	85.6±19.43	0.158
FEV1/FVC	78.5 (73.25-83.75)	78 (75-82)	0.883
ACE (U/L)	59.5 (44.25-75)	70 (47-116.5)	0.027
ESR (mm/h)	31 (20-48)	33 (20-57.2)	0.570
CRP (mg/L)	7.36±11.92	7.48±7.12	0.066
Serum Ca (mg/dl)	9.5 (9.3-9.77)	9.4 (9.1-9.8)	0.354
24-hour urine Ca (mg)	140.48±142.06	137.36±138.85	0.967
Hb (g/dL)	12.82±1.37	12.79±1.70	0.755
WBC ($\times 10^9$ /L)	7297.40±2345.62	7756.49±3251.60	0.520
Neutrophil ($\times 10^9$ /L)	4585.00±1836.69	5237.19±2510.65	0.114
Lymphocyte ($\times 10^9$ /L)	1910 (1155-2410)	1700 (1180-2405)	0.303
NLR	2.52 (1.87-3.21)	2.96 (2.06-4.12)	0.056
RDW (%)	14.79±2.60	14.35±1.65	0.876
MCV (fL)	82.05±7.02	83.84±6.21	0.307
MPV (fL)	10.16±1.03	10.12±1.11	0.824
PDW (%)	15.7 (13.2-16)	15.7 (13.55-16.2)	0.860

FVC, forced vital capacity; %pred., percent predicted; FEV1, forced expiratory volume in one second; ACE, angiotensin-converting enzyme; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; Ca, calcium; Hb, hemoglobin; WBC, white blood cell count; NLR, neutrophil/lymphocyte ratio; RDW, red cell distribution width; MCV, mean corpuscular volume; MPV, mean platelet volume; PDW, platelet distribution width.

Table 5. The demographic, functional, and laboratory data of the sarcoidosis patients with or without extrapulmonary involvement

Characteristic	Pulmonary involvement only	Pulmonary + extrapulmonary involvement	p value
Patients n (%)	71 (58.7%)	50 (41.3%)	
Age	50.25±11.08	51.38±12.75	0.589
Gender			0.394
Female n (%)	51 (71.8%)	40 (80%)	
Male n (%)	20 (28.2%)	10 (20%)	
Smoking			0.506
Yes n (%)	19 (26.8%)	13 (26%)	
No n (%)	52 (73.2%)	37 (74%)	
Symptoms			
Cough n (%)	15 (21.1%)	12 (24%)	0.437
Dyspnea n (%)	12 (16.9%)	6 (12%)	0.317
Fatigue n (%)	16 (22.5%)	10 (20%)	0.459
Joint pain n (%)	6 (8.5%)	17 (34%)	0.001
Fever n (%)	1 (1.4%)	2 (4%)	0.370
Parenchymal involvement			0.200
Absent n (%)	31 (43.7%)	28 (56%)	
Present n (%)	40 (56.3%)	22 (44%)	
Stage			0.408
1 n (%)	31 (43.7%)	28 (56%)	
2 n (%)	38 (53.5%)	21 (42%)	
3 n (%)	2 (2.8%)	1 (2%)	
FVC(L)	3.08±0.95	3.12±1.13	0.727
FVC (% pred)	96.45±20.34	97.62±18.72	0.745
FEV1(L)	2.27±0.77	2.41±0.88	0.497
FEV1 (%)	86.18±19.6	89.59±17.9	0.531
FEV1/FVC	78 (74-82)	77 (75-83.75)	0.543
ACE (U/L)	58.6 (43-75.5)	73.5 (46.5-99.25)	0.045
ESR (mm/h)	31.5 (17-47)	33.5 (20.75-55.75)	0.449
CRP (mg/L)	6.43±9.93	8.50±9.26	0.145
Hb (g/dL)	13.02±1.67	12.51±1.32	0.086
WBC ($\times 10^9$ /L)	7442.13±3107.42	7674.34±2523.27	0.591
Neutrophil ($\times 10^9$ /L)	4950.00±2234.95	4909.13±2260.15	0.992
Lymphocyte ($\times 10^9$ /L)	1740 (1155-2420)	1735 (1155-2402.5)	0.917
NLR	2.85 (1.93-3.45)	266 (1.96-3.71)	0.984
RDW (%)	14.61±2.21	14.49±2.07	0.920
MCV (fL)	83.88±6.53	81.84±6.65	0.175
MPV (fL)	10.16±1.06	10.11±1.10	0.607
PDW (%)	15.7 (13.5-16)	15.7 (13.15-16.2)	0.831

FVC, forced vital capacity; %pred., percent predicted; FEV1, forced expiratory volume in one second; ACE, angiotensin-converting enzyme; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; Hb, hemoglobin; WBC, white blood cell count; NLR, neutrophil/lymphocyte ratio; RDW, red cell distribution width; MCV, mean corpuscular volume; MPV, mean platelet volume; PDW, platelet distribution width.

results are present in the literature regarding ACE. In some studies, it was stated that the serum ACE level did not change according to the radiological stage and was not correlated with the severity of the disease (22-24). In the study by Lammi et al., the serum ACE level was reported to be higher in stage-

2 and stage-3 patients having parenchymal involvement when compared to those with no involvement of parenchyma (stage 0, 1) (16).

There are also publications in which the serum ACE level was recommended for following the course of the disease (25, 26). We have the opinion that the reason for such different results in the literature might have originated from different values of serum ACE due to ACE insertion/deletion (I/D) gene polymorphism. The serum ACE can have different values due to racial gene polymorphism (27). In our study, the serum ACE level was determined to be significantly higher in the stage-2 and stage-3 patient with parenchymal involvement when compared to those in stage-1. Since the prognosis is expected to be better in stage-1 cases compared to those in other stages, the result of our study suggests that the serum ACE level can predict the prognosis of the disease. The two groups did not have any significant difference regarding the other parameters such as ESR, CRP, serum Ca, urinary Ca, WBC, Hb, neutrophil, lymphocyte, NLR, RDW, MCV, MPV, and PDW, suggesting that these parameters cannot be used for the clinical course-related guidance.

Sarcoidosis can involve mainly the lungs, but also many other organs such as the skin, the eye, and the heart (28). The extrapulmonary involvement accompanying the pulmonary involvement is met in 30-50% of patients (29). In the ACCESS study, it was shown that extrapulmonary involvement was present in 50% of the patients (30). In our study, consistent with the literature, extrapulmonary involvement was present together with pulmonary involvement in 41.3% of the patients. The skin and the peripheral lymph nodes were determined as the most common extrapulmonary involvements. There are studies in the literature reporting that the most common sites of extrapulmonary involvement are the peripheral LAPs and the skin (31-33). Even though extrapulmonary involvement has been reported to be more common in females (3, 30, 33), its frequency was found to be similar in both genders in our study. There are also studies in the literature consistent with our study regarding gender (32-34).

It was shown in patients having extrapulmonary involvement accompanying pulmonary sarcoidosis that the symptoms were more severe and the daily life activities were limited (35). In our study, in the group with extrapulmonary involvement, joint pain was more common, and EN was present in all patients of the group. In the study conducted by Li et al., fatigue was reported to be more common in the group with extrapulmonary involvement, but no difference was found regarding other symptoms (32). In the study of Gvozdenovic et al., the symptoms of fatigue and dyspnea were found to be more common in the group with extrapulmonary involvement (35).

In our study, when the PFT parameters of patients having pulmonary only involvement were compared to those of the patients with both pulmonary and extrapulmonary involvement, no significant difference was determined to be present ($p>0.05$). Conducted studies have revealed similar results in the medical literature (5, 33, 34).

The serum ACE level was found to be higher in the group with both pulmonary and extrapulmonary involvement in our study. In the literature, different results have been reported regarding the serum ACE level in patients with extrapulmonary involvement. The serum ACE level has been reported to be elevated in cases with extrapulmonary involvement in some studies, whereas no difference has been reported in others (23, 32, 33). We have the opinion that this might also be related to the racial variability of serum ACE level due to the ACE gene polymorphism. Based on our results, we suggest that the serum ACE level is a parameter that can be used for prediction of extrapulmonary involvement and might be beneficial in the management of the disease.

EN is evaluated differently regarding extrapulmonary involvement. Some investigators consider EN as an extrapulmonary involvement (36, 37), whereas some others think that it is only a reaction, and do not consider EN as an extrapulmonary involvement (33, 38). In our study, when the statistical analysis was reperformed after exclusion of patients with EN, the serum ACE level was still found to be elevated in patients with

extrapulmonary involvement (p=0.006). This result suggests that the serum ACE level can serve as a guide in showing the extensiveness of the disease. The similarity of the ESR, CRP, serum Ca, urinary Ca, WBC, Hb, neutrophil, lymphocyte, NLR, RDW, MCV, MPV, and PDW values in both groups suggest that these parameters do not serve for guidance regarding extrapulmonary involvement. There are also studies in the literature reporting that no difference was determined between the groups with and without extrapulmonary involvement regarding CRP, ESR, and hemogram parameters (32, 33).

The retrospective nature of our study is the most important limitation. Clinical information were not systematically obtained and recorded. Thus, some of the pertinent data might not be available.

In conclusion, even though different results have been reported in the literature, in our study, the serum ACE level was found to be higher in the stages that pulmonary parenchymal involvement was present than those with no parenchymal involvement and higher in the patients with extrapulmonary involvement than those without extrapulmonary involvement. These results suggest that the serum ACE level can be useful in the prediction of disease severity and extensiveness. Since the serum ACE level might change depending on the ACE gene polymorphism, studies with genotype-corrected serum ACE levels are needed.

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