Analysis of Age Distribution and Disease Presentation of 1269 Patients with Sarcoidosis

Sarkoidoz Tanılı 1269 Hastanın Yaş Dağılımı ve Hastalık Prezentasyonuna Göre İncelenmesi

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ABSTRACT

Objective: While the incidence of sarcoidosis peaks between 20 and 39 years, it is comparatively low in elderly subjects. We sought to determine whether there are age-dependent differences in the demographic and laboratory characteristics of patients with sarcoidosis.

Materials and Methods: We retrospectively collected information from our database using the International Classification of Disease (ICD) diagnostic code D86 between 2008 and 2014. Patients were divided into three groups: 20–39 years old (Group 1), 40–59 years old (Group 2), and 60–80 years old (Group 3).

Results: A total of 3988 patients with code of D86 were included in the study. After the exclusion of non-eligible patients, the number of cases in Groups 1, 2, and 3 were 276, 641, and 352, respectively. The groups were compared according to demographic characteristics, ICD diagnostic codes, and laboratory parameters. The ratio of female patients was significantly higher in Group 3 than in Groups 1 and 2 (p=0.000). There was no difference in diagnostic codes of the ICD subgroups between groups (p=0.19). While the level of blood-urea nitrogen was significantly higher in Group 3 patients than in other groups (p=0.000), serum angiotensin-converting enzyme (ACE) values were found to be significantly low in Group 3 (p=0.010). The mean ACE values did not differ between females and males (50.8±39.3 and 59.1±45.5 mg/dL, respectively) (p=0.18).

Conclusion: The majority of patients with sarcoidosis were female in all age groups and pulmonary sarcoidosis was the most common presentation of the disease. Elderly patients (≥60 years) with sarcoidosis had lower serum ACE levels than younger patients.

Keywords: Age groups, gender, ICD codes, sarcoidosis

ÖZ

Amaç: Sarkoidoz insidansı 20 ve 39 yaşları arasında pik yapmakta iken, yaşlı olgularda görece düşüktür. Çalışmamızda, sarkoidoz hastalarının demografik ve klinik özelliklerinde yaşa bağlı değişiklikler olup olmadığını belirlemeyi amaçladık.

Gereç ve Yöntem: Hastane veritabanımızı kullanarak 2008 ve 2014 yılları arasında, Uluslar arası Hastalık Sınıflama (ICD) tanı kodu D86 olan hastalara ait verileri, retrospektif olarak topladık. Hastalar yaş aralığına göre üç gruba ayrıldı: 20-39 yaş (Grup 1), 40-59 yaş (Grup 2) ve 60-80 yaş (Grup 3).

Bulgular: ICD tanı kodu D86 olan toplam 3988 hasta çalışmaya alındı. Uygun olmayan hastalar çalışma dışı bırakıldıktan sonra vaka sayıları Grup 1, 2 ve 3'de sırasıyla 276, 641 ve 352 oldu. Gruplar, demografik özellikleri, ICD tanı kodları ve laboratuar parametrelerine göre karşılaştırıldı. Kadın hasta oranı Grup 3'de Grup 1 ve 2'ye göre anlamlı oranda yüksekti (p=0,000). ICD tanı kodu alt kırılımlarına göre gruplar arasında farklılık yoktu (p=0,19). Kan üre azotu düzeyi Grup 3'de anlamlı oranda yüksek iken (p=0,000), serum anjiyotensin-konverting enzim (ACE) değerleri anlamlı oranda düşük bulundu (p=0,010). Kadın ve erkeklerde ortalama ACE düzeyleri arasında fark yoktu (sırasıyla, 50,8±39,3 ve 59,1±45,5mg/dL) (p=0,18).

Sonuç: Tüm yaş gruplarında sarkoidoz hastalarında kadın oranı daha yüksek olup, akciğer sarkoidozu en sık saptanan prezentasyon şekli idi. Yaşlı hastalarda (≥60 yaş) gençlere göre serum ACE düzeyleri daha düşük bulundu.

Anahtar Kelimeler: Yaş grupları, cinsiyet, ICD kodları, sarkoidoz

Introduction

Sarcoidosis is an idiopathic, systemic granulomatous disease that primarily affects the lungs and lymphatic system [1]. It can occur in patients of both sexes and all age and ethnic groups [1-4]. However, the peak incidences are in adults between 20 and 39 years old, though in Scandinavian countries and Japan there is a second peak in females over 50 [1, 2]. Females are more affected than males [1, 2].

Presentation of sarcoidosis is variable and the value of diagnostic tests is low [1]. Given the insufficient data on the disease incidence and different prevalence rates among countries there is a lack of understanding of the disease's epidemiology [1, 4]. Because most patients with sarcoidosis are middle-aged, a limited number of studies include elderly patients (≥70 years of age) [5].

The present study was conducted in a tertiary hospital. The primary aim was to determine whether there are differences in demographic characteristics and laboratory findings between young, middle-aged and elderly patients with sarcoidosis.

Materials and Methods
Study design: A retrospectively observed cohort.

Study population: Subjects treated between 2008 and 2014 at a Turkish education and research hospital.

Patient inclusion criteria: Patients with the D86 International Classification of Disease (ICD) diagnostic code (see below) who were treated in a hospital between 1 January 2008 and 31 December 2014 were included in the study.

ICD sarcoidosis codes: ICD D86.0: Pulmonary sarcoidosis; the diagnosis of sarcoidosis is established by histopathological findings and lung parenchyma involvement.

ICD D86.1: Lymph node sarcoidosis; the diagnosis of sarcoidosis is established by histopathological findings and mediastinal lymph node involvement.

ICD D86.2: Pulmonary sarcoidosis together with lymph node sarcoidosis; the diagnosis of sarcoidosis is established by histopathological findings and lung parenchyma and mediastinal lymph node involvement.

Patient exclusion criteria: Patients with an ICD diagnostic code of D86.8 (Sarcoidosis, of other and combined areas; the diagnosis of sarcoidosis is not established by histopathological findings in extrapulmonary organs) and D86.9 (Sarcoidosis, undefined; to investigate suspicion of sarcoidosis but unproven histopathologically) and/or those who had no laboratory findings recorded in hospital the online data-based system were excluded.

Data: Patients' demographics (age, sex) were recorded upon admittance to the out-patient
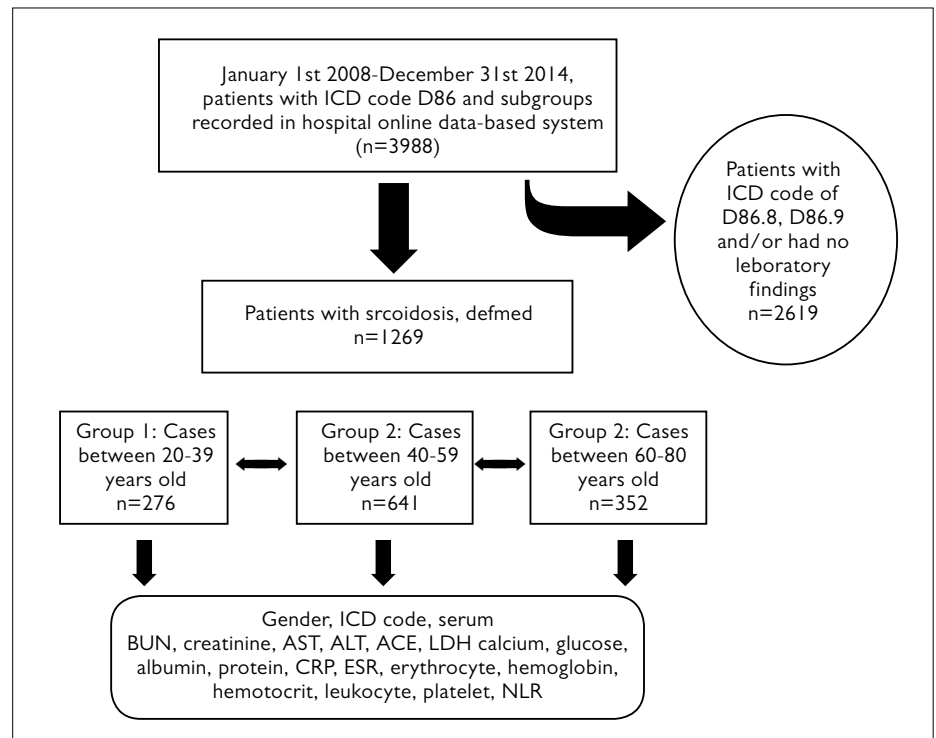
Figure 1. Study flow chart
ACE: angiotensin-converting enzyme; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood-urea nitrogen; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ICD: International Classification of Diseases; LDH: lactate dehydrogenase; NLR: neutrophil-lymphocyte ratio

clinic. All laboratory results were gathered from our hospital online database (HIS: Hospital Information System). Hemogram parameters included counts for erythrocytes, leukocytes, and platelets; neutrophil-lymphocyte ratio (NLR); hemoglobin; hematocrit; and erythrocyte sedimentation rate (ESR). Biochemistry values included levels of C-reactive protein (CRP), glucose, blood-urea nitrogen (BUN), creatinine, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), calcium, and angiotensin-converting enzyme (ACE).

Calculations: NLR was calculated by neutrophil over lymphocyte count.

Patients were classified into three groups according to age. Groups 1, 2, and 3 included patients between 20–39, 40–59, and 60–80 years old, respectively.

Statistical analysis
Descriptive statistics (age, sex, ICD diagnostic codes, hemogram, and biochemistry values) are described as frequencies, percentages, mean values, and standard deviations (SDs). Chi-square tests were performed for between-group comparisons of categorical variables. We used t-tests and One-Way ANOVAs to compare continuous variables between groups. A p

value <0.05 was considered significant. All statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS) software version 20 (IBM Corp.; Armonk, NY, USA).

The study was approved by the local Ethics Committee of the Institution and was conducted in accordance with the ethical principles stated in the Declaration of Helsinki. Because the study was conducted retrospectively, a patient approval form was not required.

Results
A total of 3988 subjects with an ICD code for sarcoidosis were treated during the study period. After excluding patients with D86.8 and D86.9 ICD codes and those who lacked sufficient laboratory parameters, 1269 patients remained (Figure 1). Of these patients, 872 (68.7%) were female and 397 (31.3%) were male. The mean age was 50.9±13.6 (20–87years old); the age distribution of all patients is shown in Figure 2. After we excluded patients over 80, Groups 1 (20–39 years old), 2 (40–59 years old), and 3 (60–80 years old) included 276, 641, and 352 cases, respectively (Figure 3).

The ratio of female patients in Group 3 (76%) was significantly higher than in Groups 1 (52%) and 2 (71%) (p=0.000) (Figure 4). The numbers of patients with lymph node sarcoidosis
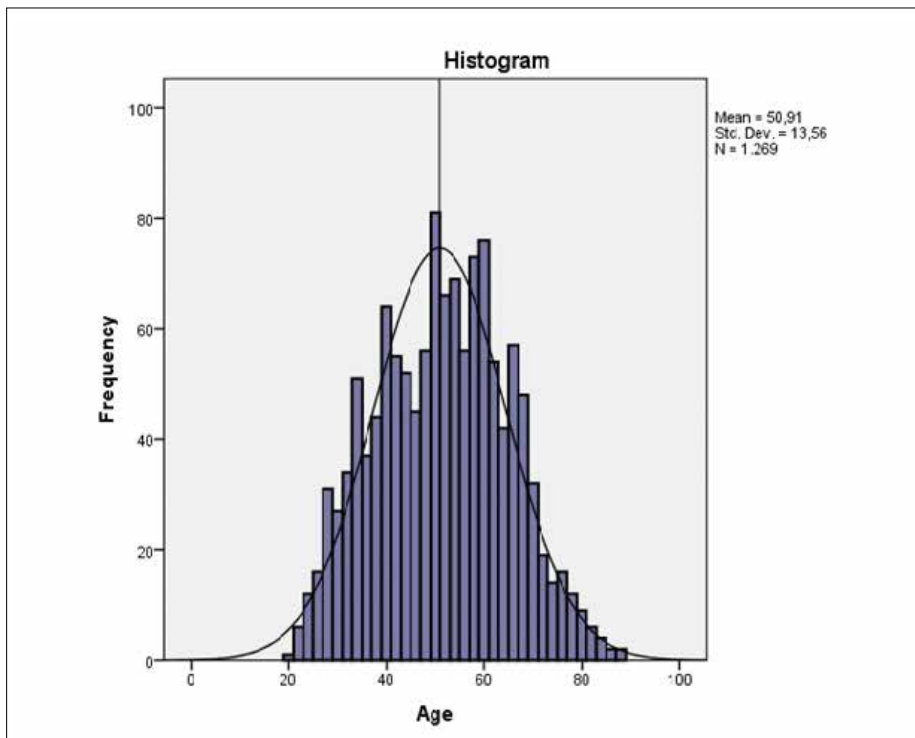
Figure 2. Patient age distribution
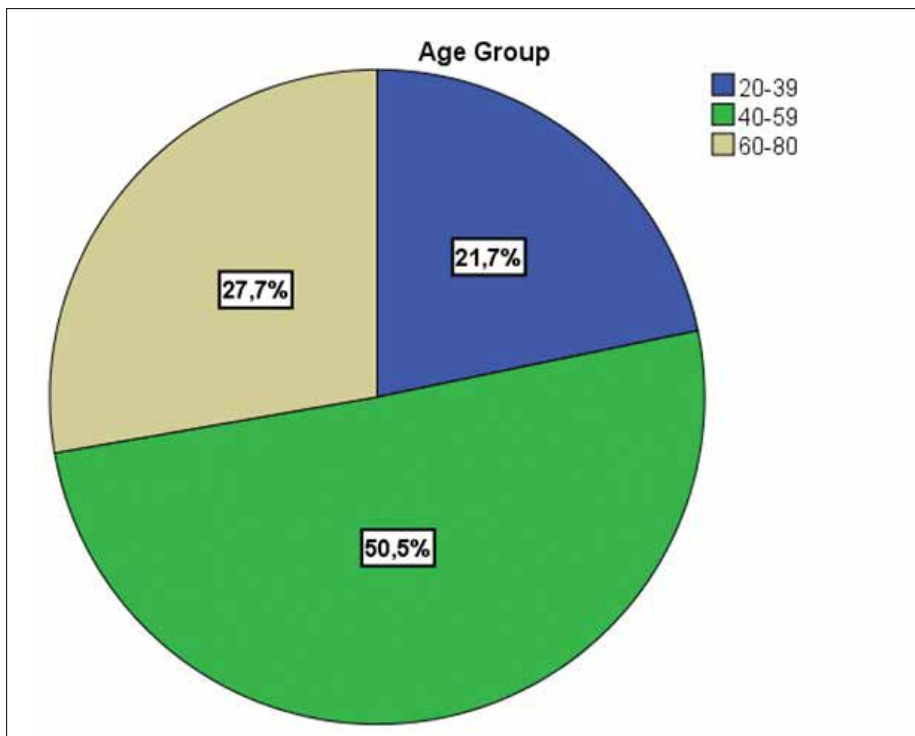
Figure 3. Age groups distribution

(D86.1) in Group 1, 2, and 3 were 47, 112, and 65, respectively. Thirty-six cases had pulmonary sarcoidosis together with lymph node sarcoidosis (D86.2) in Group 1, 71 cases in Group 2, and 57 cases in Group 3. Pulmonary sarcoidosis (D86.0) was the most frequent code in each group. Groups 1, 2, and 3 included 193, 458, and 230 patients, respectively (Figure 5). There

was no difference in the ratio of diagnostic codes of the ICD subgroups between groups (p=0.19).

Groups were compared according to laboratory parameters. Complete blood cell count and NLR were not different between groups

(p=0.41). The level of BUN was significantly higher in Group 3 patients than in other groups. Conversely, serum ACE values were significantly lower in Group 3 (Table 1). The mean ACE value was 50.8±39.3 in females and 59.1±45.5 in males for all patients (p=0.18). Also, there was no association between sex and ACE levels in any group (Table 2).

Discussion
Our results show that elderly patients with sarcoidosis (≥60 years) are more likely to be female and have a lower serum ACE level compared to young and middle-aged patients.

Gender is important for many epidemiological and clinical characteristics, including sarcoidosis treatment options and prognosis [2]. Many autoimmune diseases are more common in females, and sarcoidosis is no exception [6]. Environmental factors, hormones, genetic effects, occupational exposures, drugs, smoking, and vitamin D insufficiency have been hypothesized as factors influencing the growing prevalence of autoimmune diseases in females [7]. As the incidence of sarcoidosis is higher in females, it is thought to be associated with hormones; however, different results have been reported. A study of Black females with a 14-year follow-up period failed to find an association between the incidence of sarcoidosis and age menarche, age menopause and parity [8]. Another report found that the incidence of sarcoidosis increased after the first year of parity [9]. We observed that the majority of our patients with sarcoidosis were female in all age groups, suggesting that sex hormone levels may affect sarcoidosis presentation. Demonstrating possible hormone effects in disease pathogenesis may identify alternative approaches for disease treatment.

Sarcoidosis incidence is known to have a second peak in patients older than 50, and several studies have shown that the female ratio is higher among older patients [2-4, 10, 11]. On the other hand, the number of studies including elderly patients is very limited due to the low incidence of sarcoidosis among elderly subjects. In one study, of the 30 patients ≥70 years old, 70.3% were female [12]. In another study that included 30 cases ≥65 years and 70 younger subjects, the ratio of female patients was found to be significantly higher in the older group (83.3% vs 50%) [5]. A multicenter Turkish study reported that sarcoidosis was the most common interstitial disease; 53% were female and 75% were ≤50 years old [13]. The most comprehensive epidemiological research in Turkey included 293 patients with sarcoidosis and was published in 2009. The num-
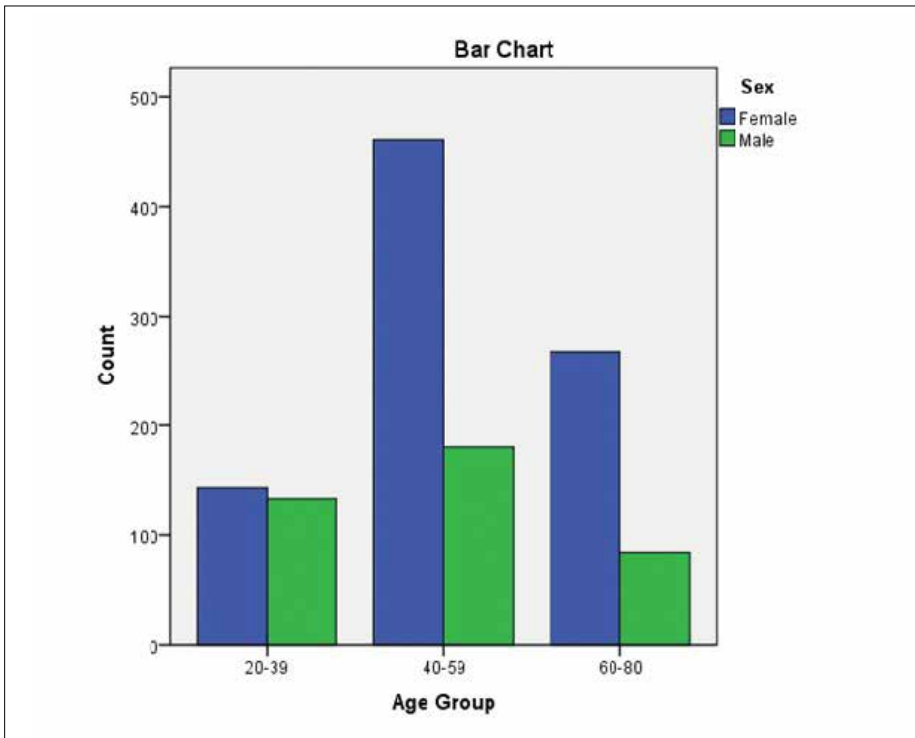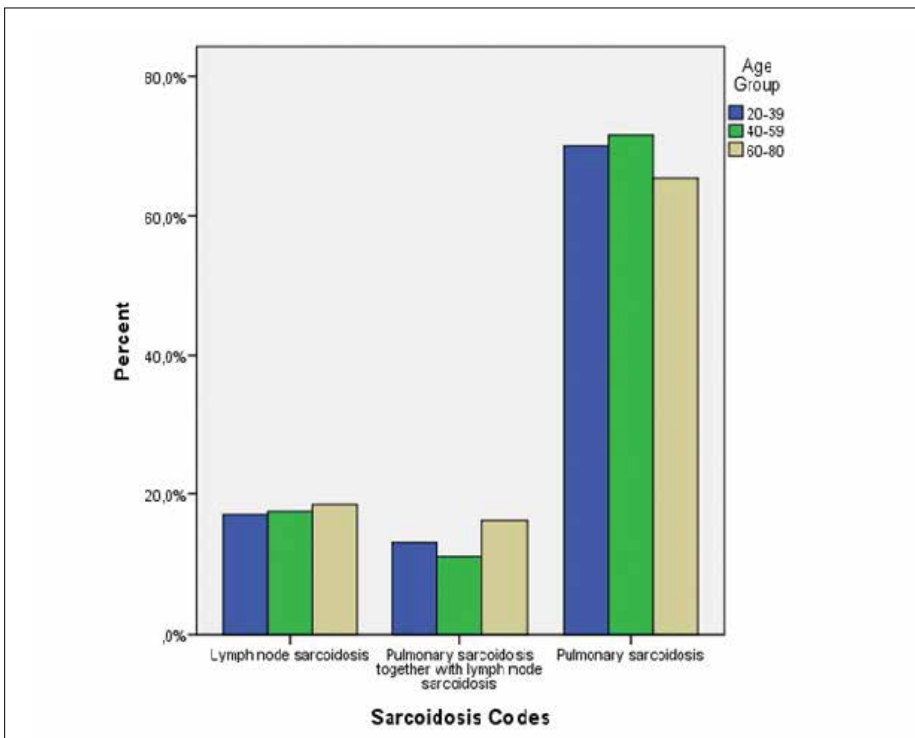
Figure 4. Sex-ratio in age groups

Figure 5. Sarcoidosis codes distribution in age groups

ber of cases ≥70 years of age in that investigation was 8 (2.7%), of which 7 were female [14]. Our results are in accordance with the findings of these limited studies.

When we evaluated patients according to ICD diagnostic codes, we did not observe signifi-cant differences in terms of the distributions between Groups 1, 2, and 3. In each group, the most common code was pulmonary sarcoidosis (D86.0) followed by lymph node sarcoidosis (D86.1). In a previous study of 736 patients with sarcoidosis, lung involvement was the most common [95%], and the lymph node involve-

ment rate was 15.2% [15]. In a Polish epide-miological study, the D86.0 ICD diagnostic code was dominant, accounting for more than 75% of all cases [16].

Angiotensin-converting enzyme is synthesized by sarcoid granulomas. Although ACE is not specific for sarcoidosis, it is used as a diagnostic and prog-nostic marker because its serum concentration is high in 60%–70% of patients depending on dis-ease extent and activity [2, 17]. Although some researchers report that there is no difference regarding ACE activities between sexes [2, 18], one Turkish study reported there were more females and serum ACE levels were significantly lower among patients over 50 years of age with sarcoidosis [3]. We found a significant decrease in serum ACE values among patients ≥60 years. Nonetheless, ACE levels did not differ according to sex in the subgroup analysis. Unfortunately, the relationship between ACE levels and disease activity could not be evaluated.

As there is dysregulation of calcitriol excre-tion by activated macrophages and granulomas, hypercalcemia can occur in 2%–10% of patients with sarcoidosis [1]. Even though it was previ-ously reported that the presence of hypercalce-mia increases after 45 years of age [19], another study did not find differences in calcium values among elderly patients (≥65 years) [5]. We did not find a significant difference in serum calcium levels between groups.

The NLR has emerged as a new marker of inflammation [20, 21]. It can be easily calculated from a routine complete blood count and is determined by dividing the absolute neutro-phil count by the number of lymphocytes. In a Turkish study that compared sarcoidosis and control groups, neutrophil count, NLR and CRP were significantly higher, and lymphocytes were significantly lower in the sarcoidosis group [20]. Additionally, Dirican et al. [21] concluded that a higher NLR (≥2) was detected in patients with sarcoidosis and that this was more frequent in patients with extrapulmonary involvement. We assessed whether NLR varied with age in our cohort but did not find a significant difference between the groups.

Among the other laboratory findings, only serum BUN levels were found to be signifi-cantly higher in Group 3. This variation might be associated with patient age and the presence of chronic disease.

The most important limitation of this study is its retrospective design. However, we believe that the study provides valuable information

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Table 1. Group comparison according to laboratory parameters

Parameters	Group 1 (n=276) Mean±SD	Group 2 (n=641) Mean±SD	Group 3 (n=352) Mean±SD	p*
Leukocyte count	7.9±3.0	7.4±2.5	7.3±2.7	0.22
Erythrocyte count	4.7±0.4	4.7±0.5	4.6±0.5	0.13
Hemoglobin (mg/dL)	13.1±1.4	13.1±1.6	13.0±1.5	0.80
Hematocrit (%)	39.3±3.9	39.4±4.6	38.9±4.0	0.52
Platelet count	257.0±71.2	262.1±79.2	254.6±66.7	0.62
NLR	3.3±2.5	2.9±2.0	3.2±2.4	0.41
ESR (mm/h)	38.6±32.0	33.6±25.4	41.5±28.8	0.22
CRP (mg/dL)	22.6±32.2	12.9±17.3	14.7±18.7	0.32
Glucose (mg/dL)	97.4±23.9	114.5±48.7	113.5±39.0	0.07
BUN (mg/dL)	12.5±5.1	13.7±4.3	18.6±10.0	0.000
Creatinine (mg/dL)	0.8±0.1	0.8±0.2	0.8±0.3	0.08
Albumin (mg/dL)	3.9±0.5	3.9±0.4	3.8±0.5	0.66
Total protein (mg/dL)	7.8±0.7	7.6±0.5	7.5±1.2	0.19
Calcium (mg/dL)	9.7±0.8	9.6±0.7	9.5±0.8	0.49
AST (mg/dL)	24.5±9.3	24.3±12.3	20.5±6.9	0.05
ALT (mg/dL)	29.5±17.6	27.8±17.3	28.9±17.0	0.08
LDH (mg/dL)	212.3±61.8	246.3±119.7	199.5±37.8	0.09
ACE (mg/dL)	67.0±56.6	52.8±36.9	42.3±31.4	0.010

ACE: angiotensin-converting enzyme; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood-urea nitrogen; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase; NLR: neutrophil-lymphocyte ratio; SD: standard deviation
*: One-Way ANOVA test

Table 2. ACE levels according to sex between groups

ACE level	Group 1 (n=276) Mean±SD	Group 2 (n=641) Mean±SD	Group 3 (n=352) Mean±SD
Sex			
Male	40.8±9.9	72.0±49.9	58.7±47.1
Female	56.1±32.8	69.1±41.4	47.3±39.3
p*	0.28	0.87	0.11

ACE: angiotensin-converting enzyme
* Independent samples t-test

for assessing the age-related characteristics of patients with sarcoidosis. Secondly, detailed clinical and radiological evaluations could not be performed because the data were retrieved from our hospital's online database. Therefore, a possible relationship between disease status and age could not be evaluated. Lastly, this study was carried out at a single center.

On the other hand, the number of publications describing elderly patients with sarcoidosis is small, and the ones we found assessed limited numbers of patients. We did not find any other studies with a comparable sample size in this age group in the published literature. We think that our findings can guide the design of future studies.

In conclusion, it was detected that the majority of patients were between 40 and 59 years old. Female dominance was marked for sarcoidosis presentation in all age groups. It may be helpful to note that lung involvement is common and that elderly patients with sarcoidosis may have lower serum ACE levels than younger patients during the follow-up period.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Süreyyapaşa Chest Diseases and Thoracic Surgery Education and Research Hospital (Decision Number-Date: 3 /22.01.2015).

Informed Consent: Written informed consent was not obtained from patients due to the retrospective nature of this study.

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