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### **Središnja medicinska knjižnica**

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# **Epidemiological Characteristics of Sarcoidosis Patients Hospitalized in the University Hospital for Lung Diseases "Jordanovac" in the period 1997- 2002**

**RUNNING TITLE:** Characteristics of Hospitalized Sarcoidosis Patients

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## **ABSTRACT**

*The aim of our study was to explore the characteristics of hospitalized patients with sarcoidosis concerning age, gender, clinical forms and staging, seasonality, geographical distribution, smoking habit and profession, familial clustering and mortality. We included 476 biopsy-proven sarcoidosis patients who were diagnosed at the University Hospital for Lung Diseases "Jordanovac" in the period from 1997-2002. Most of the patients (44%) were in the group of age between 20 and 40 years. The ratio of women to men was 1.4:1. The onset of the disease usually appeared in spring and summer, especially in the patients presenting with erythema nodosum, with majority of patients hospitalized in the period from May to August (51%). More patients came from urban, than from rural areas (1.5:1), and they were mostly nonsmokers (3.3:1). In 2% of sarcoidosis patients we found familial clustering. Although these data are biased regarding the selection of patients they give new insights into characteristics of sarcoidosis patients in Croatia.*

**Key words:** sarcoidosis, epidemiology, erythema nodosum

## **Introduction**

Sarcoidosis is a systemic multiorgan disease of unknown etiology<sup>1</sup>. It occurs most frequently among younger adults between 20 and 40 years of age and most of the studies show that it is more frequent among women<sup>2</sup>. Its clinical and histological representation does not depend on climatic conditions although the disease peaks with its clinical appearance in spring months<sup>3</sup>.

The epidemiological studies show great variability of results in which prevalence of sarcoidosis varies from 0.2 in Portugal to more than 50/100 000 in black people in USA, depending on the studied population and diagnostic methods used<sup>4</sup>. In the USA, sarcoidosis occurs 10-17 times more frequently among African Americans and Puerto Ricans than in white people. In Europe it is more frequent in the north than in the south. Sweden was once considered as the country with the highest incidence of 64/100000, but recent studies showed the incidence of about 19/100000. Spain with 1.2 and Italy with 0.5/100,000 have some of the lowest incidences in Europe<sup>5</sup>. The prevalence of sarcoidosis in Croatia is about 4.1/100,000 persons according to the National Registry data<sup>6</sup>. Profession or social status do not predispose to sarcoidosis although it is more frequent in non-smokers<sup>7</sup>.

In this article we have presented the patients hospitalized from 1997 to 2002 at the University Hospital for Lung Diseases "Jordanovac" in relation to age, gender, clinical forms and staging, seasonality, geographical distribution, smoking habit and profession, familial clustering and mortality.

## **Patients and methods**

The data available from case history documentation, with sarcoidosis as a discharge diagnosis from our hospital, for the period from 1997 until the end of 2002 were analyzed retrospectively. All medical history documents were analyzed in relation to age and gender, seasonal occurrence, geographical distribution, life style and familial occurrence of the disease. We found that in the period from 1997 until the end of 2002 sarcoidosis as discharge diagnosis was present in 711 cases representing 59.4% of all hospitalized patients for sarcoidosis in Croatia for the designated period of time. Since some patients were hospitalized more than once there were all together 476 persons who suffered from sarcoidosis. In all patients diagnosis was confirmed by histopathology of a biopsy samples recovered from sarcoidosis lesions. Family history data were analyzed for familial clustering

relating the family cases and non-family contacts, relation to living together, time elapsing between diagnoses of pairs. In all patients data were available for clinical forms and staging of the disease.

All statistical analyses were done using STATISTICA version 6 (StatSoft, Inc., Tulsa, USA). As it is almost impossible to define the population from which these patients were recruited as they come from different parts of Croatia no standardized prevalence was calculated. Statistical significance was set at  $p < 0.05$ .

## **Results**

### *Age and gender*

Among 476 patients, treated for sarcoidosis in the period from 1997 until the end of 2002 there were 276 women and 200 men. The ratio of women to men was 1.4:1 ( $p < 0.001$ ). Among the total number of patients treated for sarcoidosis, 206 patients were between 20 and 40 years of age, which represents 44%, with the peak between 35 and 39 years of age (20%) as shown in Figure 1. The increase in incidence of sarcoidosis was different in women and men with "second peak" between 50 and 54 years of age for woman and between 45 and 49 years of age for men, respectively. For all age groups the incidence was higher in women ( $p = 0.03$ ), except between 45 and 50 years of age when the incidence is higher in men (RR=1.551, 95% CI 1.225-1.956,  $p = 0.001$ ).

### *Clinical forms and staging*

Lung sarcoidosis was present in 370 (77.7%) and extra-pulmonary forms in 106 (22.3%) patients. In 41.6% (N=198) of patients radiographic stage I was confirmed, stage II in 39.7% (N=189), stage III in 18.1% (N=86), and stage IV in 0.6% of patients (N=3).

### *Seasonal occurrence*

Sarcoidosis patients were hospitalized throughout the whole year, but the highest rate was in May, June, July and August when 243 (51%, 95% CI 46.4%-55.6%) patients were treated with the rate ratio of 2.09 (95% CI, 1.743-2.497;  $p < 0.001$ ) compared to patients hospitalized during the rest of the year. The increase in the occurrence of the disease in spring and summer months showed the same pattern in women and men (rate ratio, women 2.035, 95% CI, 1.569-2.641, rate ratio, men 1.705, 95% CI, 1.236-2.346,  $p < 0.001$  for both; Figure 2). The seasonality of the occurrence was especially

pronounced in patients presenting with the erythema nodosum (rate ratio 4.333, 95% CI, 2.828-6.757,  $p < 0.001$ ). Erythema nodosum was found in 18.7% patients (N=89). The majority of patients (N=75) had EN in the period from April till August (81.3%).

#### *Geographical distribution*

Among the patients treated in our hospital for sarcoidosis, 282 persons were from urban areas while 194 were from rural areas. The ratio of urban to rural population is 1.5:1. The highest number of the persons affected was from Zagreb (N=142). It is difficult to establish their origin since Zagreb is a metropolis with a significant immigration of rural population in the last 10 years.

#### *Life style and profession*

There are numerous studies which discuss the correlation between sarcoidosis and non-smoking. Out of 476 patients in our sample 362 (76%) of them were non-smokers whereas 114 (24%) were smokers. The ratio of non-smokers to smokers in this sample was 3.3:1.

As for the professions, 2/3 of men did manual jobs (construction, drivers, fitters) while 1/3 did white-collar jobs. Among women there was roughly about the same number of white-collar jobs and housewives on one hand and jobs involving certain manual labor (cleaners, hair-dressers, shop-assistants) on the other. The number of smokers in men and women does not depend on profession. We found roughly about the same number of smokers among white-collar workers, manual workers and housewives.

#### *Familial clustering*

Among the patients treated in our hospital in the six-year period, we found familial occurrence within four families (mother and son, two sisters, a mother and a daughter, two brothers) which makes 2% of the total number of 476 patients. The occurrence of the disease in these cases was from 4 to 14 years apart and in three families it was pulmonary sarcoidosis in both family members but with different staging and/or additional organs affected. In one familial setting sarcoidosis affected different organs (mother, spleen; son, lungs). The age of onset was different in all but one family where two sisters had an onset of the disease at almost the same age (38 and 40 yrs) but 4 years apart.

## *Mortality*

Among all the patients hospitalized for sarcoidosis, two of them (0.42%) died, one at the age of 72 and the other at the age of 78. The cause of death was heart failure due to chronic cor pulmonale and respiratory failure, respectively.

## **Discussion**

Sarcoidosis is a systemic disease which occurs all around the world and among all nations. It is considered as an infrequent disease but numerous studies in the last twenty years provided evidence that sarcoidosis is significantly more frequent than previously thought<sup>8</sup>.

Sarcoidosis is the disease affecting mostly adults between 20 and 40 years of age. In literature we can find data on children affected by the disease, mostly between 9 and 15 years of age. The incidence in children below 15 years of age is between 0.06 and 1.02 per 100,000 children<sup>9,10</sup>.

The highest number of patients treated in our hospital was between 20 and 40 years of age which is in accordance with the findings in the literature. According to numerous studies in Japan and Scandinavia an increase in incidence in women after the age of 50, i.e. "the second peak", is repeatedly found<sup>11</sup>. The same was the case in our study for the age group between 50 and 54 years.

Sarcoidosis occurs in both sexes but according to the results of most of the studies it is more frequent in women. According to the published results the ratio of women to men in Japan is 3:1 and in Spain 2:1. In some countries sarcoidosis is almost equally frequent among both sexes<sup>12</sup>. Among patients treated at our hospital from 1997 until the end of 2002 the ratio of women to men was 1.4:1 which corresponds to our previously published results based on National Registry data<sup>6</sup>.

Studies from Finland and Japan in biopsy-proven cases of sarcoidosis show relatively high proportion of extra-pulmonary sarcoidosis (45-53.4%) which is substantially different from our series of patients (22.3%). In 41.6% of our patients radiographic stage I was confirmed, stage II in 39.7%, stage III in 18.1%, and stage IV in 0.6% of cases. Studies in Finland showed similar results (43.7% stage I, 42.6% stage II, 13.3% stage III, and 0.4% stage IV)<sup>13</sup>.

The proportion of patients presenting with erythema nodosum in our study was similar to the Finnish data (around 20%), as it was present in 18.7 % of cases<sup>14</sup>. Most often it occurs in the period from April till August (81.3%).

Many studies state more frequent occurrence of sarcoidosis from April to August and suggest some causative agent as trigger<sup>15</sup>. In England it is most frequent in the period from March to May, in Japan from April to August, in Spain from April to June and in Scandinavia from January to June<sup>16</sup>. Our results show similar pattern, even more pronounced in patients presenting with erythema nodosum.

Sarcoidosis has a variable incidence and prevalence depending on various environmental factors and numerous hypotheses about the causes of these differences have been suggested but none of them has been confirmed. One of them is that sarcoidosis is more frequent among people who are living or lived in childhood in rural households<sup>17</sup>. In our population, although it is more frequent among urban population, it might possibly be due to the significant migration of rural population to urban areas during the last war (1991-1995). According to data published by Đurić B.<sup>18</sup> in ex-Yugoslavia, more cases of sarcoidosis in urban areas were registered. This was explained by the fact that sarcoidosis was diagnosed more frequently in large medical centers.

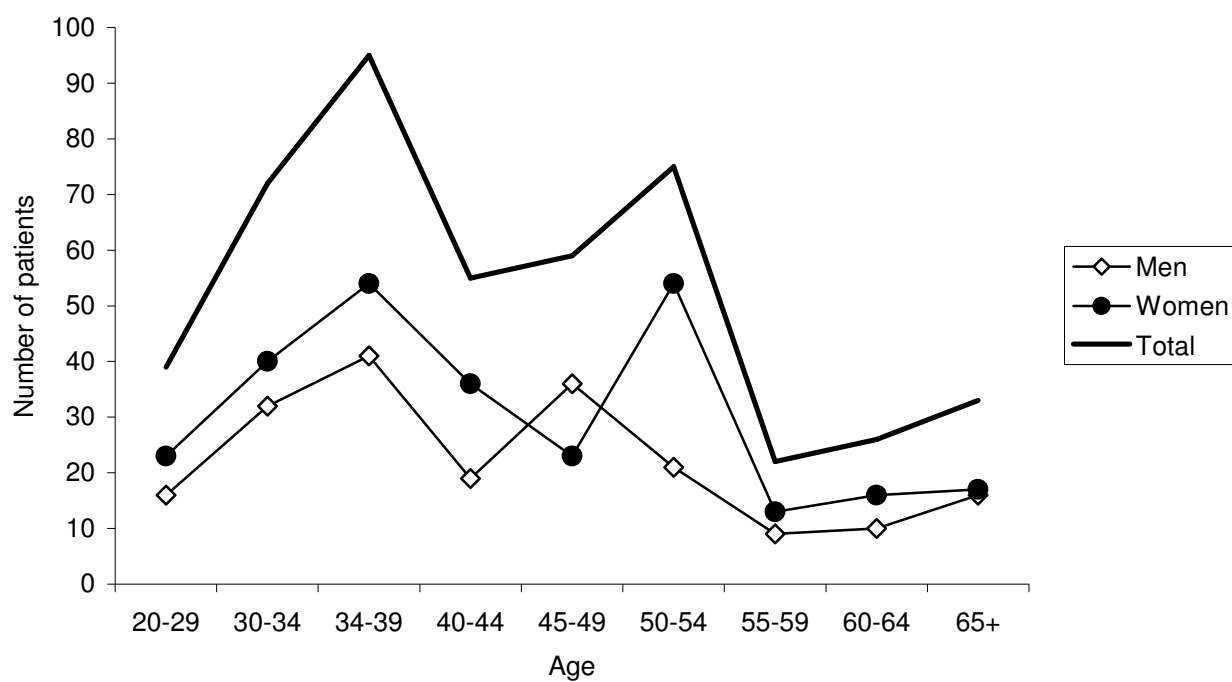
According to numerous studies sarcoidosis is mostly the disease of non-smokers which was also confirmed among our patients<sup>19</sup>. Profession and social status are not predisposing factors for the occurrence of sarcoidosis.

According to epidemiological studies in Japan (region Furano on the island of Hokkaido) and Finland, sarcoidosis frequently occurs within the family. Studies in Finland show familial clustering in 3.6% of patients, Hokkaido 4.3% and in Japan in 8.7%<sup>20</sup>. Among patients treated in our hospital familial clustering was recognized in 2% of our patients.

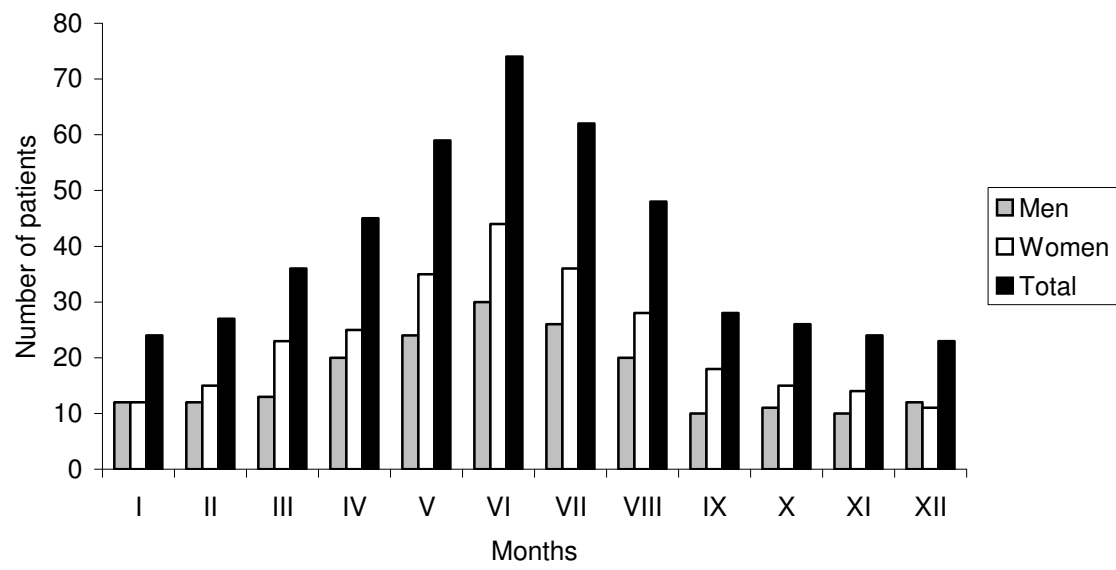
The mortality among sarcoidosis patients is 2–4%. The cause of death usually is respiratory failure, arrhythmias due to sarcoidosis of the heart, renal failure due to nephrocalcinosis or sarcoidosis of central nervous system<sup>21</sup>. The mortality rate in our series was substantially lower (0.42%) probably due to the fact that it represents only the hospital mortality rate and not the global mortality rate for sarcoidosis.

Although these data are biased regarding the selection of patients and chance of determining the populations they arrive from, they give new insights into epidemiologic characteristics of sarcoidosis patients in Croatia. They fill up the gaps regarding our already published data on the subject.





*Fig 1. Distribution of sarcoidosis by age and sex.*



*Fig. 2. Seasonal distribution of sarcoidosis.*

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## **EPIDEMIOLOŠKE OSOBINE BOLESNIKA SA SARKOIDOZOM HOSPITALIZIRANIH U KLINICI ZA PLUĆNE BOLESTI "JORDANOVAC" U RAZDOBLJU OD 1997-2002. GODINE.**

### **S A Ž E T A K**

Cilj naše studije bio je istražiti osobine hospitaliziranih bolesnika sa sarkoidozom prema dobi, spolu, kliničkom obliku, stadiju proširenosti, sezonskom pojavljivanju, geografskoj rasprostranjenosti, navikama pušenja, profesiji, obiteljskoj povezanosti i smrtnosti. Uključena su 476 bolesnika sa sarkoidozom dokazanom biopsijom u Klinici za plućne bolesti "Jordanovac" u razdoblju od 1997.-2002. godine. Većina bolesnika (44%) bila je u dobi između 20-40 godine života. Omjer muškaraca i žena je bio 1.4:1. Znakovi bolesti su se kod 51% bolesnika pojavljivali u proljeće i ljeto, posebno kod bolesnika koji su imali nodozni eritem. Više je bolesnika iz gradske nego seoske sredine (1.5:1), a više je bilo nepušača nego pušača (3.3:1). Kod 2% bolesnika sa sarkoidozom utvrdili smo obiteljsku povezanost. Premda su ovi podaci bazirani na selekciji bolesnika daju nam novi pogled na osobine bolesnika sa sarkoidozom u Hrvatskoj.