

The incidence, comorbidity and mortality of sarcoidosis in Korea, 2008-2015: a nationwide population-based study

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ABSTRACT. *Background:* Few national level, population-based studies are present on the epidemiology of sarcoidosis and it is unclear whether these patients have higher mortality than the general population. The objective of this study was to investigate the nationwide epidemiology, comorbidity and mortality in sarcoidosis in Korea. *Material and Methods:* For the period between 2008 to 2015, we used the national population-based database operated by Rare Intractable Disease registration program in which patients' diagnosis are based on uniform criteria. All sarcoidosis patients were identified and followed-up using the National Health Insurance database to determine their incidence, comorbidity, mortality, causes of death and standardised mortality ratio (SMR). *Results:* During the study period, we identified 3,259 new sarcoidosis patients. The average annual incidence was 0.81 per 100,000. The annual mortality rate was 9.26 per 1,000 person-years. The mortality rate were significantly higher than those of the general population (SMR 1.91, 95% confidence interval 1.62-2.25). The major comorbidities of sarcoidosis patients were the diseases of the respiratory system (17.64%), heart (5.43%), eyes (4.27%) and cancer (2.3%). Mortality was higher in patients with lung involvement. Of the 84 deaths identified in this study from 2008-2013, the most common cause of death was cancer (41.7%), followed by respiratory disease (13.1%), sarcoidosis (13.1%) and heart disease (8.3%). *Conclusions:* We reported a nationwide incidence of sarcoidosis as 0.81 per 100,000 in Korea. The mortality of sarcoidosis patients was higher compared to the general population and the major causes of death were cancer, respiratory disease and sarcoidosis. Sarcoidosis patients with comorbid diseases showed increased mortality. (*Sarcoidosis Vasc Diffuse Lung Dis* 2020; 37 (1): 24-36)

KEY WORDS: sarcoidosis, incidence, comorbidity, mortality, cause of death

Abbreviation list:

ICD-10 = International Classification of Diseases, 10th revision,

RID = Rare Intractable Disease,

NHI = The National Health Insurance

CI = confidential interval

SMR = Standardised Mortality Ratio

INTRODUCTION

Sarcoidosis is an inflammatory disease characterized by non-caseating granuloma that generally affects the lungs, but can also involve various organs such as the liver, skin, eyes, heart and nervous system (1).

The incidence of sarcoidosis is known to vary according to race and region (2, 3). It is observed to be higher among African Americans compared to Caucasians (4, 5), and higher in northern European countries than southern countries. Although lower incidence has been reported in Asia (6-8), these studies were conducted based on a small population.

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The morbidity of sarcoidosis is associated with the extent of organ involvement and the diseases resulting from them (9-13). These comorbid conditions affect the prognosis of sarcoidosis in patients (14, 15), however the relationship between comorbidity of sarcoidosis and mortality has been poorly studied. Previous studies (14, 16, 17) that have investigated comorbidities in sarcoidosis were mostly hospital based where limited number of patients were available. The effect of comorbidity on mortality has rarely been researched specially in Asian countries where the incidence is relatively low.

Although sarcoidosis is usually a self-limited disease (18), it can be fatal when accompanied by organ failure, especially in the lungs, heart and nervous system (19, 20). However, it remains controversial whether sarcoidosis patients have a higher risk of mortality than the general population and only a few studies have investigated the causes of death (21-24). Also, though it reported that patients of Asian ethnicity have less severe symptoms (6), there is insufficient evidence if the severity and mortality of sarcoidosis differs according to race or region (9,19).

Previous epidemiological studies on sarcoidosis included only a small number of patients from a specific geographical areas (8, 22). In particular, the majority of mortality studies were cross-sectional in nature by using routinely collected administrative data rather than following-up patients, and were hospital-based instead of population-based (7, 25). Since few comorbidity and mortality studies followed-up sarcoidosis patients (23, 24), data from large-scale population-based nationwide studies are needed.

This study investigated the epidemiology, comorbidity, mortality and cause of death of sarcoidosis patients in Korea using Rare Intractable Diseases (RID) database linked with National Health Insurance (NHI) database which covers entire Korean population. To be registered in the RID program, which is run by the Korean government, patients must receive a physician-certified diagnosis based on uniform criteria. In this study, all sarcoidosis patients identified from the RID database were followed from 2008-2015 to determine their incidence, comorbidity and mortality.

MATERIALS AND METHODS

Data source

This study used claims data from the NHI database and registration data from the RID database. The Korean government implemented a national health insurance program for all citizens, which covers more than 50 million individuals. Each medical institution submits an electronic form including the diagnosis and treatments of all inpatients and outpatients to the NHI for claims of reimbursement. These data recorded in the NHI database contain information from the time of patients' diagnosis and thereafter, including the diagnosis, demographics, prescription history, surgical records and screening history. Patients' diagnostic information was recorded according to the International Classification of Diseases, 10th Revision (ICD-10).

Within this system, the NHI has established a registration program for rare intractable diseases (RIDs), including sarcoidosis, that provides copayment reduction to patients. To be registered in this RID program, specific diagnostic criteria need to be met and certified by a physician. Thus, the RID database allowed the current study to analyze reliable epidemiological features of sarcoidosis. We used this database to investigate the national incidence, mortality and causes of death of sarcoidosis in Korea.

Identification of sarcoidosis patients

Our study was based on data of all sarcoidosis patients registered in the RID program extracted from the NHI-RID database from January 2008 to December 2015.

All patients registered in the RID were identified and followed-up until 2015. Patients identified using the RID registration code (V111) combined with the ICD-10 codes (D860-D863, D868, D869) were included. The NHI diagnostic criteria for sarcoidosis(26) include noncaseating epithelioid cell granulomas detected microscopically from a histologic biopsy of pulmonary or suspected organ and a compatible clinical presentation as well as the finding from chest radiography. In making the diagnosis, other granulomatous diseases, such as silicosis, berylliosis, hypersensitivity pneumonitis etc., should be excluded.

Identification of comorbidity

In order to identify the comorbidity, we followed up the sarcoidosis patients using the NHI-RID database. From previous studies (6, 22, 23, 25, 27-30) we employed commonly related organ systems affected by sarcoidosis (neoplasm, respiratory disease, heart disease, renal disease, liver disease et al) as comorbidities for sarcoidosis, a list of which is provided in the supplementary material (Supplementary 1). We defined the comorbid disease as diagnosed code based on the ICD-10 codes for inpatient hospitalization and the comorbidities before diagnosis of sarcoidosis were excluded.

Identification of mortality and causes of death

To determine the mortality and causes of death, we linked patients' data to Statistics Korea. Statistics Korea is a government operated database established in 1981 that includes death certificates of all deceased persons in Korea. By law, death certificates must contain the cause of death issued by the attending physician at the time of death and recorded according to the ICD-10. Statistics Korea is supplemented by the NHI and the National Police Agency information to ascertain the cause of death when the diagnosis was uncertain. A 91% agreement rate has been reported (31) between the causes of death recorded in Statistics Korea and those confirmed through medical chart review. By using this database, we followed-up all sarcoidosis patients from 2008 to the end of 2013 to determine the causes of death.

The personal information of patients was protected and kept anonymous. Anonymous data linkage was processed by a third party organization. This study was approved by the Korea University.

Statistical Analysis

In this study, we calculated and stratified into different age bands sarcoidosis incidence, annual mortality and the standardised mortality ratio (SMR) from 2008-2015 and causes of death from 2008-2013.

We defined an incident case as a newly diagnosed sarcoidosis patient registered in the RID program in

the same year. Only patients identified as an incident patient during the study period were included in the numerator of this study. Annual incidence was calculated by dividing the number of total incident cases by the total population number as of July in the corresponding year. As prevalent cases may confound incident cases, we applied a 3-year washout period to exclude patients who had been diagnosed before they were registered in the RID program. The average age- and sex-specific incidences were calculated by dividing the number of cases in each age and sex group by the age- and sex-specific population and averaging these data from 2008-2015. We used the Poisson regression and Cochran-Armitage Trend Test to investigate the annual incidence trends. Incidence and mortality were calculated for each involved organ. As the RID program does not include diagnostic criteria for specific types of sarcoidosis, organ involvement type was determined by using ICD-10 codes. We classified organ involvement as lung, lymph nodes, skin and other organ (eyes, heart and nerves), based on the ICD-10 codes. When one person had multiple organ involvement, they were counted as separate cases.

All individuals with sarcoidosis were followed up till they were diagnosed with comorbidity, and then all individuals with each of the comorbidities were tracked till 2016 and at that point they were assessed for their vital status and the mortality was calculated. The comorbidity was presented as frequency (as a percentage), defined as the number of patients with specific comorbidity divided by the total number of sarcoidosis patients and it was also presented as an organ system. The mortality with each comorbidity was presented as the percentage of death among the sarcoidosis with comorbidity.

From the mortality data including causes of death obtained from Statistics Korea, the annual mortality rate was calculated by dividing the number of sarcoidosis patients who had died in the year by the person-years of sarcoidosis patients registered in RID. Person-years for patients were accumulated at the time of entry in this study until death. Mortality was compared to the general Korean population using SMR with 95% confidence interval (CI). The SMR is the ratio of observed deaths over expected deaths derived from the mortality of the total Korean population obtained from Statistics Korea data.

Survival data from Statistics Korea linked to the NHI-RID database were used in our survival analysis. We evaluated survival curves according to the Kaplan-Meier method. The date of initial registration in the database was considered the date of diagnosis. Patients were censored when a patient was alive at the time of last follow-up. A log-rank test was used to compare the cumulative survival of sarcoidosis patients by gender.

For all mortality cases, the causes of death were analyzed and presented by major disease classification. Causes of death were investigated for all sarcoidosis mortality cases using the Statistics Korea database between 2008 and 2013. We calculated the SMR by cause of death to compare cause-specific mortality between sarcoidosis patients and the general population.

RESULTS

Incidence

Table 1 shows the annual incidence of all sarcoidosis patients from 2008 to 2015. A total of 3,259 sarcoidosis patients were diagnosed. The incidence rate averaged during the study period at 0.81 per 100,000. The annual incidence showed a statistically significant increasing trend, with an increase of 1.03 cases per year on average. The male incidence rate was 0.64 per 100,000 and female incidence was 0.98 per 100,000 with a male:female ratio of 1:1.5. The age- and sex-specific incidence of sarcoidosis is displayed in Figure 1. Male patients exhibited a bimodal distribution, peaking at 30-39 years and again at 60-69 years, whereas females had a single peak at 50-59 years.

Our analysis of the distribution of organ involvement showed that lung involvement accounted for at most 60% (1,955 cases). 35.4% of patients (1,154 cases) exhibited involvement of the lymph nodes, 10.2% (332 cases) had skin involvement and 12.9% (421 cases) had other involvements, including eyes, heart and nervous system (Table 2).

Comorbidity and Mortality

The major comorbidities of sarcoidosis patients were the diseases of lungs (575 cases, 17.64%), heart

(177 cases, 5.43%), eyes (139 cases, 4.27%) and cancer (75 cases, 2.3%). Interstitial lung disease, chronic obstructive pulmonary disease, lung cancer and pneumonia were common comorbid respiratory disorders, while cardiomyopathy, ischemic heart disease and heart failure were common cardiac comorbidities. Iridocyclitis was the most common eye disease identified as comorbidity and colon and rectum cancer among malignancies, while chronic kidney disease and acute renal failure among renal disease. Among them, higher mortality was observed with pneumonia (63 deaths), chronic obstructive pulmonary disease (30 deaths), interstitial pulmonary disease (24 deaths), chronic kidney disease (13 deaths), acute renal failure (11 deaths), and lung cancer (7 deaths). Among patients with cardiac involvement, we identified mortality as 34.5% (25 deaths/ 73 patients) for patients with heart failure, 17.95% (7 deaths/ 39 patients) for patients with cardiomyopathy and 14.58% (7 deaths/ 48 patients) for patients with chronic ischemic heart disease.

The post-diagnosis survival of sarcoidosis patients is shown in Figure 2. We tracked 3,259 incident cases of sarcoidosis from diagnosis during a mean follow-up of 4.4 years, amounting to 15,119 person-years of observation. Women exhibited a slightly higher survival rate of 96.8%, while male survival was 93.4%.

The annual mortality rates are shown in Table 3. From 2008 to 2015, 140 of 3,259 patients with sarcoidosis died (78 males and 62 females). The annual mortality rate was 9.26 per 1,000 person-years, with a male and female annual mortality rate of 13.69 per 1,000 person-years and 6.58 per 1,000 person-years, respectively. The male: female ratio was 2.1:1. A high mortality rate of 38.43 per 1,000 person-years was observed among patients aged 0-19 years, after which mortality increased with increasing age, from 2.63 in the 20-39 year age group to 21.90 in the 60-79 year age group.

The age- and sex-specific SMRs for sarcoidosis are shown in Table 3. The mortality of sarcoidosis patients was significantly higher than the general population. The SMR was 1.91 (95% CI 1.62, 2.25), with a male SMR of 2.17 (95% CI 1.74, 2.71) and female SMR of 1.66 (95% CI 1.29, 2.12), indicating a higher mortality among males. Compared to the general population, the younger age groups of 0-19 years and 20-39 years exhibited significantly higher

Table 1. Incidence of sarcoidosis in Korea, 2008-2015

Year	Number of population	Incident cases			Incidence per 100,000/year		
	Total	Male	Female	Total	Male	Female	Total
2008	49,404,648	143	237	380	0.58	0.96	0.77
2009	49,656,756	132	230	362	0.53	0.93	0.73
2010	49,879,812	123	228	351	0.49	0.92	0.70
2011	50,111,476	148	242	390	0.59	0.97	0.78
2012	50,345,325	158	246	404	0.63	0.98	0.80
2013	50,558,952	182	253	435	0.72	1.00	0.86
2014	50,763,158	202	282	484	0.80	1.11	0.95
2015	50,951,719	195	258	453	0.77	1.01	0.89
Total		1,283	1,976	3,259	0.64	0.98	0.81

$$\text{incidence} = \frac{\text{incident cases}}{\text{total Korean populations}} \times 100,000$$

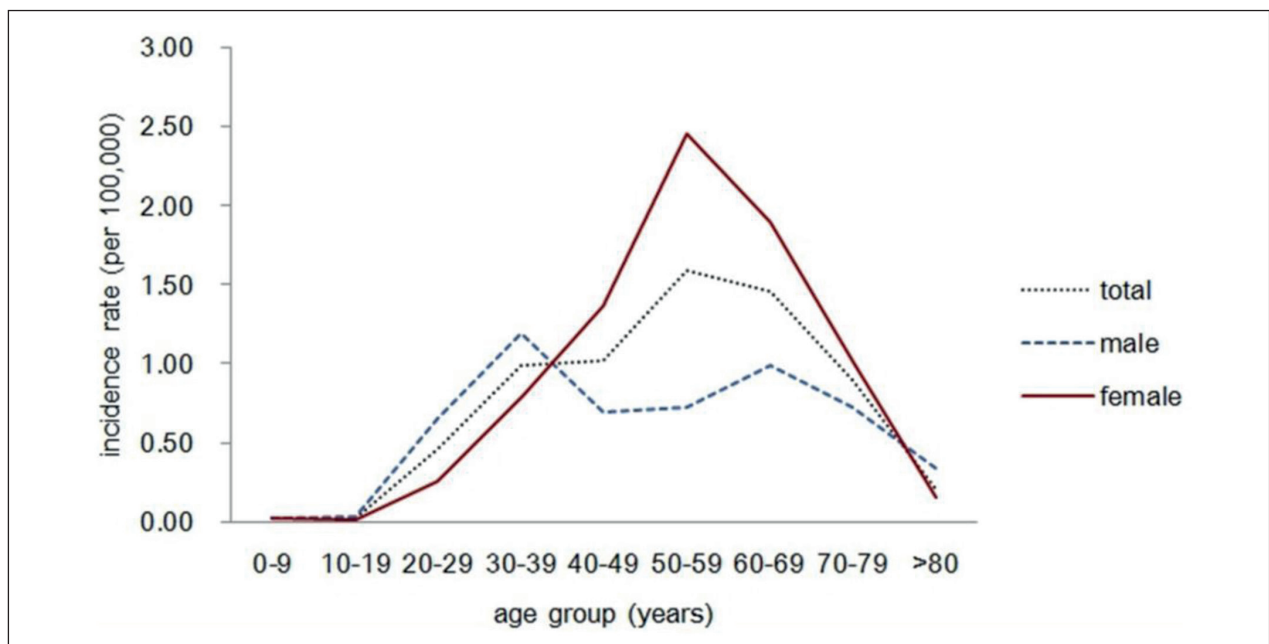


Fig. 1. Incidence of sarcoidosis by sex and age in Korea, 2008-2015. The vertical axis shows incidence rates by 100,000 people; the horizontal axis shows age in 10-year increments until the age of 80 years

SMRs of 240.83 and 3.74, respectively, while patients aged over 40 years had an SMR of 2.69.

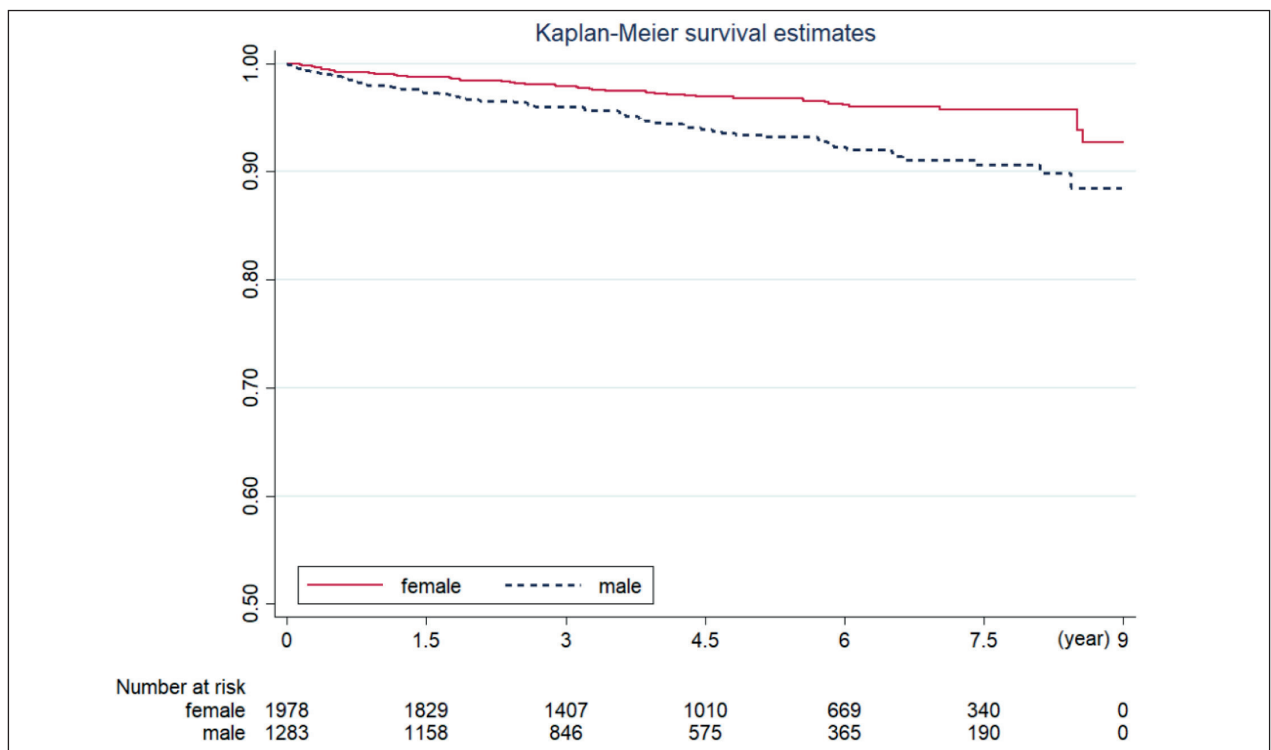
According to organ involvement, mortality was higher in sarcoidosis patients with lung involvement, at 8.30 per 1,000 person-years than in patients with other involvement including lymph nodes (6.91 per 1,000 person-years) and skin (3.12 per 1,000 person-years) (Table 2).

Cause of Death

Of the 84 deaths identified in this study from 2008-2013, the most common cause of death was neoplasms (35 deaths, 41.7%), followed by diseases of the respiratory system (11 deaths, 13.1%), sarcoidosis (11 deaths, 13.1%), and cardiac disease (7 deaths, 8.3%) (Table 4). Among the respiratory

Table 2. Incidence and mortality by distribution of organ involvement at the time of diagnosis among patients with sarcoidosis in Korea, 2008-2015

Site of lesion	Incidence		Mortality	
	No of patients(%)	Person-years	No of observed deaths(%)	Mortality rate (per 1000 person-years)
lung	1,955(60.0)	9,160	76(54.2)	8.30
lymph nodes	1,154(35.4)	5,356	37(26.4)	6.91
skin	332(10.2)	1,602	5(3.6)	3.12
eye, heart and nervous system	421(12.9)	2,314	16(11.4)	6.90
total	3,259		140	

**Fig. 2.** Survival curve of patients with sarcoidosis by gender. The vertical axis represents survival rate ; the horizontal axis represents years after diagnosis

diseases, 54.5% (6 cases) of patients had interstitial pulmonary disease.

DISCUSSION

In this nationwide population-based study, we identified 3,259 incident cases of sarcoidosis from

Table 3. The annual mortality and age-and sex-specific standardised mortality ratios (SMR) of sarcoidosis in Korea, 2008-2015

Age group	No of deaths/No of person			Annual mortality per 1000 person-years (95% confidence interval)			SMR (95% confidence interval)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
0-19	2/12	2/8	4/20	31.35 (7.84, 125.35)	49.64 (12.41, 198.48)	38.43 (14.42, 102.39)	160.74 (40.20, 642.70)	480.03 (120.06, 1900.00)	240.83 (90.39, 641.68)
20-39	6/580	5/317	11/897	2.31 (1.04, 5.15)	3.15 (1.31, 7.58)	2.63 (1.46, 4.75)	3.01 (1.35, 6.70)	5.91 (2.22, 15.74)	3.74 (2.01, 6.96)
40-59	30/456	22/1,174	52/1630	14.46 (10.11, 20.68)	3.90 (2.57, 5.92)	6.73 (5.13, 8.84)	3.02 (2.06, 4.44)	2.36 (1.54, 3.62)	2.69 (2.02, 3.58)
60-79	36/227	31/468	67/695	38.09 (27.47, 52.80)	14.66 (10.31, 20.85)	21.90 (17.23, 27.82)	1.72 (1.25, 2.38)	1.34 (0.93, 1.92)	1.53 (1.20, 1.94)
≥80	4/8	2/9	6/17	187.96 (70.54, 500.80)	57.11 (14.28, 228.37)	106.57 (47.88, 237.22)	1.85 (0.88, 3.89)	0.97 (0.44, 2.16)	1.31 (0.76, 2.25)
overall	78/1,283	62/1,976	140/3,259	13.69 (10.96, 17.09)	6.58 (5.13, 8.44)	9.26 (7.85, 10.93)	2.17 (1.74, 2.71)	1.66 (1.29, 2.12)	1.91 (1.62, 2.25)

$$\text{Annual mortality} = \frac{\text{total deaths with sarcoidosis}}{\text{The person-years of total sarcoidosis}} \times 100,000$$

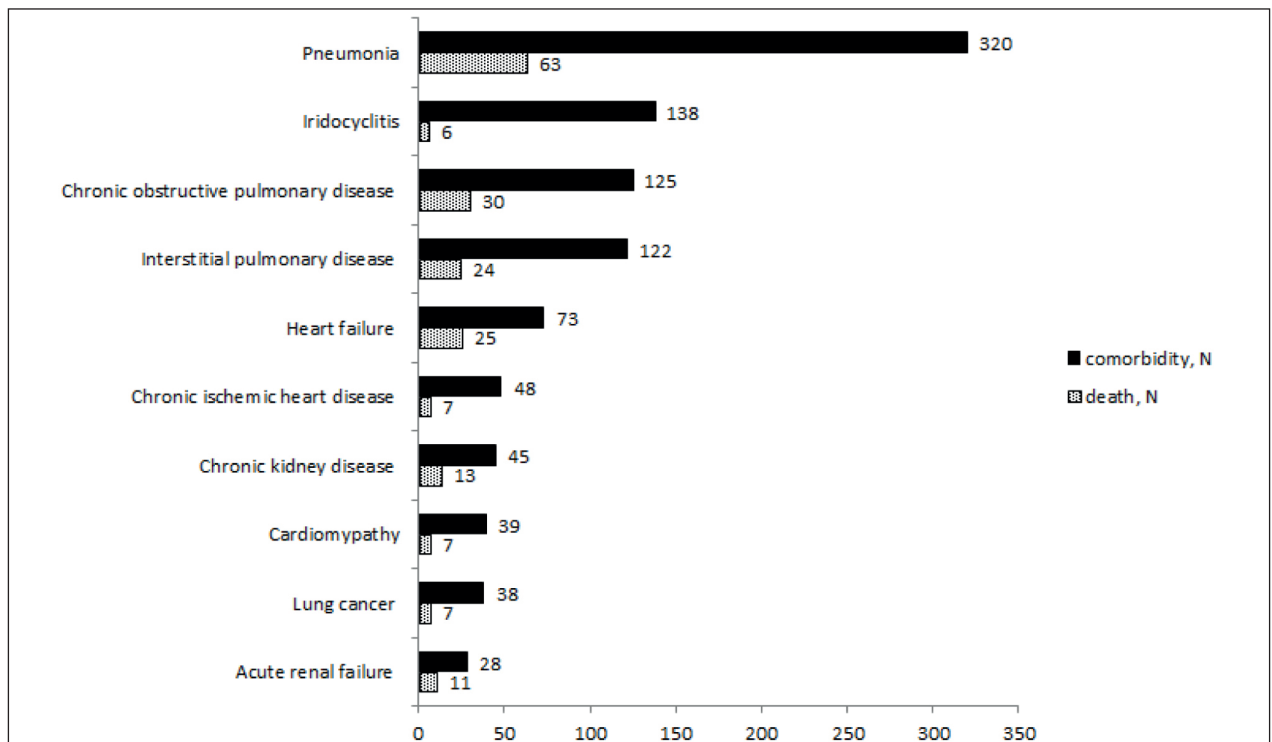


Fig. 3. Mortality associated with comorbidities in sarcoidosis in Korea, 2008-2015. The vertical axis represents comorbidities in sarcoidosis; the horizontal axis represents the number of comorbidity and death in sarcoidosis

Table 4. The cause of death among patients with sarcoidosis in Korea, 2008-2013

Condition (ICD-10 code)	No of observed deaths (%)		
	Male	Female	Total
Neoplasms (C00-D48)	16 (19.0)	19 (22.6)	35 (41.7)
Malignant neoplasms of colon (C18)	4 (4.8)	2 (2.4)	6 (7.1)
Malignant neoplasm of bronchus and lung (C34)	4 (4.8)	0 (0.0)	4 (4.8)
Malignant neoplasm of connective tissue of breast (C50)	0 (0.0)	4 (4.8)	4 (4.8)
Malignant neoplasm of bone and articular cartilage of other and unspecified sites (C41)	2 (2.4)	1 (1.2)	3 (3.6)
others	6 (7.1)	12 (14.3)	18 (21.4)
Disease of the respiratory system (J00-J99)	8 (9.5)	3 (3.6)	11 (13.1)
Pneumonia, organism unspecified (J18)	1 (1.2)	1 (1.2)	2 (2.4)
Other chronic obstructive pulmonary disease (J44)	2 (2.4)	0 (0.0)	2 (2.4)
Status asthmaticus (J46)	0 (0.0)	1 (1.2)	1 (1.2)
interstitial pulmonary disease (J84)	5 (6.0)	1 (1.2)	6 (7.1)
Sarcoidosis(D86)	5 (6.0)	6 (7.1)	11 (13.1)
Diseases of the circulatory system(I00-I99)	6 (7.1)	1 (1.2)	7 (8.3)
Acute myocardial infarction (I21)	1 (1.2)	0 (0.0)	1 (1.2)
Chronic ischemic heart disease (I25)	2 (2.4)	0 (0.0)	2 (2.4)
Acute myocarditis (I40)	1 (1.2)	0 (0.0)	1 (1.2)
Heart failure (I50)	1 (1.2)	1 (1.2)	2 (2.4)
Intracerebral hemorrhage (I61)	1 (1.2)	0 (0.0)	1 (1.2)
Diseases of the nervous system (G00-G99)	1 (1.2)	2 (2.4)	3 (3.6)
Encephalitis, myelitis and encephalomyelitis (G04)	0 (0.0)	1 (1.2)	1 (1.2)
Spinal muscular atrophy and related syndromes (G12)	1 (1.2)	0 (0.0)	1 (1.2)
Multiple sclerosis (G35)	0 (0.0)	1 (1.2)	1 (1.2)

2008-2015. The average annual incidence of sarcoidosis was 0.81 per 100,000. The average annual mortality rate was 9.26 per 1,000 person-years and the 5-year survival rate was 95.5%. Commonly associated comorbidities in sarcoidosis patients were the disease of lungs (575 cases, 17.64%), heart (177 cases, 5.43%), eyes (139 cases, 4.27%) and cancer (75 cases, 2.3%). It was also observed that the patients with these comorbidities show higher mortality.

Our study based on population-based data covering the entire population is less at risk of selection bias compared to surveys or hospital-based studies.

Also, incidence, mortality and survival rates were investigated in the same cohort during an 8-year follow-up period and so the entire mortality pattern and natural course of sarcoidosis could be understood. Similar with many existing reports (6, 32), the NHI diagnostic criteria for sarcoidosis used in our study required the identification of granulomas through histological findings, thus our findings are more comparable.

The incidence reported in this study is markedly lower than findings from the United States and Europe. The incidence of sarcoidosis in the United

Table 5. Comorbidities associated with sarcoidosis in Korea, 2008-2015

Disease Condition (ICD-10 code)	The number of comorbidity(%)		
	Male	Female	Total
Neoplasms			
Malignant neoplasm of bronchus, trachea and lung (C33~34)	19(0.58)	19(0.58)	38(1.17)
Malignant neoplasms of colon, rectosigmoid junction and rectum (C18~C20)	9(0.28)	15(0.46)	24(0.74)
Malignant neoplasm of connective tissue of breast (C50)	0(0)	9(0.28)	9(0.28)
Malignant melanoma of skin (C43)	1(0.03)	1(0.03)	2(0.06)
Disease of the respiratory system			
Pneumonia(J17, J18)	149(4.57)	171(5.25)	320(9.82)
Chronic obstructive pulmonary disease (J44)	64(1.96)	61(1.87)	125(3.84)
Interstitial pulmonary disease (J84)	61(1.87)	61(1.87)	122(3.74)
Pulmonary hypertension(I27.0, I27.2)	3(0.09)	5(0.15)	8(0.25)
Diseases of the circulatory system			
Heart failure (I50)	27(0.83)	46(1.41)	73(2.24)
Ischemic heart disease (I25)	20(0.61)	28(0.86)	48(1.47)
cardiomyopathy (I42)	18(0.55)	21(0.64)	39(1.20)
Acute myocardial infarction (I21)	11(0.34)	3(0.09)	14(0.43)
Stroke (I64)	7(0.21)	7(0.21)	14(0.43)
Intracerebral hemorrhage (I61)	4(0.12)	6(0.18)	10(0.31)
myocarditis (I40, I41.8)	2(0.06)	1(0.03)	3(0.09)
Diseases of the renal system			
Chronic kidney disease (N18)	25(0.77)	20(0.61)	45(1.38)
Acute renal failure (N17)	21(0.64)	7(0.21)	28(0.86)
Diseases of the Liver			
Hepatic failure(K72)	3(0.09)	6(0.18)	9(0.28)
Diseases of the nervous system			
Multiple cranial nerve palsies in sarcoidosis (G53.2)	3(0.09)	3(0.09)	6(0.18)
Encephalitis, myelitis and encephalomyelitis (G04)	3(0.09)	2(0.06)	5(0.15)
Spinal muscular atrophy and related syndromes (G12)	1(0.03)	0(0)	1(0.03)
Diseases of the musculoskeletal system			
Myositis in sarcoidosis (M63.3)	1(0.03)	3(0.09)	4(0.12)
Diseases of the eye and adnexa			
Iridocyclitis (H20, H22.1)	45(1.38)	93(2.85)	138(4.23)
Diseases of the skin			
erythema nodosum(L52)	0(0)	5(0.15)	5(0.15)

States is about 10.00 - 39.10 per 100,000(5, 22, 33), and that in Europe is 3.80 - 7.00 per 100,000 (24, 34, 35). Our findings are analogous with a Japanese study that reported an incidence of 1.01 per

100,000(6). In Asia, incidences have been reported ranging from 0.56-4.00 per 100,000(29, 36, 37), and the incidence of this study falls within this range. However, a direct comparison with these studies

may be difficult considering differences in methodology.

The incidence of sarcoidosis was 1.5 times higher in women. The female dominance observed in our study is comparable to other reports, in which incidence ranged from 1.22-2.08 times higher among women(6, 38). In males, the pattern of the age-specific incidence of sarcoidosis was biphasic, peaking twice at 30-39 and at 60-69 years of age, and monophasic in females, peaking at 50-59 years of age. Due to the preventive effect of female hormones, the peak of sarcoidosis among women is over fifty years of age (39).

In our study, lung and respiratory diseases were common comorbid disease with higher mortality. These findings are in line with previous studies that report common comorbidity as chronic pulmonary disease and obstructive pulmonary disease (14, 16, 17) and common cause of death as pneumonia, pulmonary fibrosis and obstructive airway disease (23, 25, 30) in sarcoidosis patients.

This study found that the 5-year survival rate after sarcoidosis diagnosis was 95.5%, which is comparable to the survival rate of 93.0% reported in a study of sarcoidosis in the UK (24). The annual mortality rate for patients with sarcoidosis was 9.26 per 1,000 person-years, which is similar to two previous studies that reported mortality rates of 9.40 per 1,000 person-years and 14.00 per 1,000 person-years (23, 24). Even though the incidence of sarcoidosis in Asia is much lower, our mortality and survival findings are similar to western countries.

Notably, the mortality of younger patients aged 20 years and under (38.43 per 1,000 person-years) was higher than adult patients aged 20 to 60 years (5.29 per 1,000 person-years). The main cause of deaths under 20 years of age were, systemic involvement of connective tissues, followed by breast cancer and heart failure. While skin melanoma accounted for all deaths under the age of 10 years. Though published data on the long-term prognosis of sarcoidosis in children are scarce, previous studies have found a poorer prognosis among young children with sarcoidosis (40, 41) associated with sequelae and progressive disease (42, 43). Our findings reflect the need for further detailed studies on the prognosis of sarcoidosis.

The SMR of sarcoidosis patients in this study was higher than the general population. There is a debate surrounding whether the mortality of sar-

coidosis is higher than the general population. Earlier (21, 22) no difference in mortality rates between sarcoidosis patients and the general population was reported, while some studies(23, 24) found a higher hazard ratio among sarcoidosis patients compared to the general population, which is similar to our results. In interpreting results, it should be taken into consideration that previous studies used hospital-based design which only included sarcoidosis patients followed up at hospitals, while our study used a population-based design in which all Korean sarcoidosis patients were followed with reliable SMR estimates.

Among organ involvement, lungs accounted for 60.0% of cases in our study (1,955 cases), which is consonant with previous studies from other countries (6, 28). Mortality was higher in lung involvement than with any other organ. This coincides with a previous study where pulmonary disease and upper respiratory mucosal involvement had unfavourable clinical courses compared to acute arthritis and bilateral hilar lymphadenopathy(19).

We found that cancer, respiratory disease and sarcoidosis were the main causes of death and these showed higher cause-specific SMRs compared to the general population. This finding is in line with several studies (10) that reported higher incidence of cancer among sarcoidosis patients. We reported that among the different types of cancer, colon and lung cancer were the most common causes of death. Our study also found that respiratory disease was also significant cause of death in sarcoidosis, with interstitial pulmonary disease in particular showing higher mortality. Consistent with our findings, one report (44) found interstitial lung involvement with pulmonary fibrosis and pulmonary hypertension were associated with increased mortality and another study reported that pulmonary fibrosis accounted for 9.0% of deaths (30).

In this study although cardiac involvement was relatively common among sarcoidosis patients, the deaths due to cardiovascular disease were low. In interpreting the cause of death in our study we should take into account the cause of death registration system in Korea, where the National Statistics Office registers the cause of death for each deceased patient as one single underlying disease. In this system, the cause of death of patients with underlying cardiovascular disease may be registered as immediate cause such as pulmonary embolism or as primary disease

such as sarcoidosis. In this case, cardiovascular diseases may not be recorded as underlying cause of death.

In order to identify the type of treatment for sarcoidosis patients, we searched the KoreaMed, domestic medical research database with the keyword "sarcoidosis" and identified 103 studies (3 case series and 100 case reports (supplementary 2)). Of the 260 patients with sarcoidosis, 162 (62.3%) were treated with steroids. In some of the patients in these studies, methotrexate (45-49), hydroxychloroquine (50, 51), and azathioprine (45, 52) were combined with steroids when multiorgan involvement was present such as lungs, eyes, muscles, liver, joints, and gastrointestinal tract and these results were similar to the standard treatment of sarcoidosis (53). In several cases, it has been reported that corticosteroids are effective in sarcoidosis treatment, but some studies report recurrences or steroid related complications due to long term use (54-57). In the literature, the effect of steroids for sarcoidosis still remains unclear.

The limitations of this study are as follows. First, because we used registration data, we were unable to identify detailed clinical features of sarcoidosis including clinical and radiological results. Second, ICD-10 code does not include information on specific organ involvement and therefore we could not determine the organ involvement separately for eye, heart and nervous system involved. Rather the patients invaded in eye, heart and nervous system were confirmed through comorbidity disease followed up in NHI database. Third, because we relied on government administrative cause of death data which includes one underlying cause, we could not investigate in detail the causes of death specifically designed for sarcoidosis patients. Therefore, sometimes it is difficult to distinguish whether designated cause of death was immediate cause or underlying disease. Finally, the use of ICD code registration data as diagnosis may raise questions concerning the diagnostic accuracy. However, the NHI provides uniform diagnostic criteria that must be followed in order to be registered in the RID and each diagnosis is reviewed at the healthcare institution before submission to the NHI to assure it meets the criteria. Through this process, we assumed that we maintained a high diagnostic reliability in this study.

CONCLUSION

This nationwide population-based study investigated the incidence, comorbidity, mortality and causes of death of sarcoidosis in Korea. The incidence of sarcoidosis was 0.81 per 100,000, which is lower than the United States and Europe, but similar with Japan. The annual mortality rate of 9.26 per 1,000 person-years and the survival rate of 95.5% were similar with previous studies. The mortality was significantly higher than the general population (SMR 1.91, 95% CI 1.62, 2.25) and was particularly high in younger age groups. The most common causes of death were cancer, sarcoidosis itself and respiratory diseases. Increased mortality was observed in sarcoidosis patients with comorbid diseases.

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Supplementary 1. Comorbidity list

Condition (ICD-10 code)

Neoplasms

Malignant neoplasms of colon (C18)

Malignant neoplasm of bronchus and lung (C34)

Malignant neoplasm of bone and articular cartilage of other and unspecified sites (C41)

Malignant melanoma of skin (C43)

Connective and soft tissue of other connective and soft tissue (C49)

Malignant neoplasm of connective tissue of breast (C50)

Disease of the respiratory system

Pneumonia in disease classified elsewhere (J17)

Pneumonia, organism unspecified (J18)

Other chronic obstructive pulmonary disease (J44)

Other interstitial pulmonary disease (J84)

Other interstitial pulmonary diseases with fibrosis(J84.1)

Primary pulmonary hypertension(I27.0)

Other secondary pulmonary hypertension(I27.2)

Diseases of the circulatory system

Acute myocardial infarction (I21)

Chronic ischemic heart disease (I25)

Acute myocarditis (I40)

Myocarditis in other diseases classified elsewhere (I41.8)

*D86.8+I41.8 : Sarcoid myocarditis

Heart failure (I50)

Cardiomyopathy(I42)

Intracerebral hemorrhage (I61)

Stroke, not specified as haemorrhage or infarction(I64)

Diseases of the renal system

Acute renal failure (N17)

Chronic kidney disease (N18)

Diseases of the Liver

Hepatic failure(K72, K72.0, K72.1)

Hepatic sclerosis(K74)

Diseases of the nervous system

Encephalitis, myelitis and encephalomyelitis (G04)

Spinal muscular atrophy and related syndromes (G12)

Multiple cranial nerve palsies in sarcoidosis (G53.2)

*D86.8+G53.2: Multiple cranial nerve palsies in sarcoidosis

Condition (ICD-10 code)

Diseases of the musculoskeletal system

Arthropathies in other specified diseases classified elsewhere(M14.8)

*D86.8+M14.8: Sarcoid arthropathy

Myositis in sarcoidosis (M63.3)

* D86.8+M63.3: Sarcoid myositis

Diseases of the eye and adnexa

Keratoconjunctivitis (H16.2)

Iridocyclitis (H20)

Iridocyclitis in other diseases classified elsewhere (H22.1)

* D86.8+H22.1: Iridocyclitis in sarcoidosis

Diseases of the skin

Erythema nodosum(L52)

Supplementary 2

no	Type of study	First author(year) (reference)	Subject (n)	Therapy
1	case series	Kim MS (2017)(1)	Sarcoidosis (99)	Systemic steroid treatment was initiated in 23.2% of cases.
2	case series	Lee SY (2009)(2)	Ocular sarcoidosis (22)	Of 22 patients, 20 patients(90.9%) was managed with topical, systemic or local steroid treatment.
3	case series	Kim TW (2008)(3)	Sarcoid uveitis (31)	Steroid therapy
4	case report	Lee CH (2018)(4)	Cardiac sarcoidosis presenting as complete atrioventricular block (1)	Steroid therapy
5	case report	Park H (2018)(5)	Cardiac sarcoidosis (1)	Corticosteroid therapy
6	case report	Choi SY (2017)(6)	Sarcoidosis of the nasal septum (1)	Steroid therapy
7	case report	Kim TK (2017)(7)	Pulmonary sarcoidosis that developed during the treatment of a patient with Crohn disease by using infliximab (1)	Infliximab was discontinued
8	case report	La YK (2017)(8)	Isolated leptomeningeal neurosarcoidosis (1)	Methylprednisolone
9	case report	Park SK (2017)(9)	Tumor necrosis factor alpha blocker-induced erythrodermic sarcoidosis in with juvenile rheumatoid arthritis (1)	The etanercept treatment was discontinued and changed to hydroxychloroquine and prednisolone to treat the underlying juvenile rheumatoid arthritis.
10	case report	Kang JH (2016)(10)	Sarcoidosis that developed after etanercept treatment of patients with ankylosing spondylitis (1)	Etanercept discontinued.

no	Type of study	first author(year) (reference)	Subject (n)	therapy
11	case report	Kim EH (2016)(11)	Splenic sarcoidosis concurrent with the ovarian cancer (1)	Prednisolone
12	case report	Kim HJ (2016)(12)	Sarcoidosis presenting with multiple lung parenchymal nodules (1)	The patient improved without any additional treatment
13	case report	Kim M (2016)(13)	Spinal cord neurosarcoidosis after cervical compressive myelopathy (1)	Methylprednisolone
14	case report	Lee JW (2016)(14)	Sarcoidosis that involved the lungs and mediastinal lymph nodes (1)	Systemic corticosteroid
15	case report	Sim JK (2016)(15)	Pulmonary sarcoidosis induced by adalimumab (1)	Discontinuation of adalimumab
16	case report	Cho NH (2015)(16)	Papillary thyroid carcinoma coexistent with thyroid sarcoidosis (1)	Radioiodine therapy and thyroid hormone therapy after thyroidectomy
17	case report	Hong SH (2015)(17)	Gastric involvement of pulmonary sarcoidosis (1)	Methylprednisolone
18	case report	Jeon JH (2015)(18)	Pulmonary sarcoidosis with mediastinal lymphadenopathy (1)	Oral prednisone
19	case report	Jeong DE (2015)(19)	Immune thrombocytopenia associated with sarcoidosis (1)	Intravenous immunoglobulin and oral steroid
20	case report	Kim BY(2015)(20)	Gastrointestinal sarcoidosis without pulmonary involvement (1)	Prednisolone, azathioprine

no	Type of study	first author(year) (reference)	Subject (n)	therapy
21	case report	Ohn J (2015)(21)	Nonspecific lesions of cutaneous sarcoidosis with venous leg ulcers (1)	Methylprednisolone, pentoxifylline, folic acid
22	case report	Park HS (2015)(22)	Hepatic sarcoidosis with Chronic Hepatitis B Virus infection (1)	Prednisolone
23	case report	Cho JW(2014)(23)	Neurosarcoidosis after uveitis (1)	Methyprednisolone
24	case report	Kim DH(2014)(24)	Solitary Cavernous sinus neurosarcoidosis (1)	Steroid treatment
25	case report	Kim HS(2014)(25)	Pulmonary sarcoidosis in a patient with breast cancer(1)	Because the patient did not complain of any respiratory symptom, her sarcoidosis was left untreated.
26	case report	Kwon DH(2014)(26)	Intramedullary spinal cord sarcoidosis (1)	Steroid therapy
27	case report	Park JS(2014)(27)	Isolated orbital sarcoidosis (1)	Oral steroid, methotrexate, azathioprine
28	case report	Byun CW(2013)(28)	Sarcoidosis characterized by erythema nodosum, bilateral hilar lymphadenopathy and polyarthralgia or polyarthritis (1)	Prednisolone
29	case report	Cho KH(2013)(29)	Pulmonary sarcoidosis with endobronchial nodular involvement (1)	Oral prednisolone
30	case report	Han EJ(2013)(30)	Muscular sarcoidosis (1)	Prednisolone
31	case report	Kim MH(2013)(31)	Sarcoidosis that developed after chemotherapy for ovarian cancer (1)	These lesions resolved spontaneously without treatment
32	case report	Kwon YS(2013)(32)	Cervical lymph node sarcoidosis (1)	Prednisolone

no	Type of study	first author(year) (reference)	Subject (n)	therapy
33	case report	Lee JH(2013)(33)	Ocular sarcoidosis with early axial spondyloarthritis (1)	Oral prednisolone, celecoxib, methotrexate
34	case report	Lee JK(2013)(34)	Orbital sarcoidosis presenting as diffuse swelling of the lower eyelid (1)	Pednisolone
35	case report	Jang JY(2012)(35)	Dermal and subcutaneous sarcoidosis (1)	Steroid treatment
36	case report	Kang SM(2012)(36)	Capecitabine-induced sarociodosis (1)	The discontinuation of capecitabine
37	case report	Lee IS(2012)(37)	Pleural sarcoidosis with lymph node and endobronchial involvement (1)	Prednisolone
38	case report	Lee JH(2012)(38)	Early-onset childhood sarcoidosis accompanied by incidentally noted enchondromatosis (1)	Oral prednisolone
39	case report	Lee JM(2012)(39)	Cardiac sarcoidosis presenting with complete atrioventricular block and sustained monomorphic ventricular tachycardia (1)	Systemic glucocorticoid
40	case report	Lee SJ(2012)(40)	Sarcoidosis combined with hepatic and peritoneal involvement (1)	Corticosteroids and methotrexate
41	case report	Min KD(2012)(41)	Muscular sarcoidosis (1)	Prednisolone
42	case report	Yoon H(2012)(42)	POEM Syndrome associated with sarcoidosis (1)	The patient was treated with Immunosuppression and dexamethasone
43	case report	Ahn SW(2011)(43)	Spinal cord neurosarcoidosis (1)	Corticosteroid, immunosuppressant, thalidomide
44	case report	Im MH(2011)(44)	Takayasu's arteritis combined with sarcoidosis, lymphoma or metastatic adenopathy (1)	Pprednisolone

no	Type of study	first author(year) (reference)	Subject (n)	therapy
45	case report	Kim YB(2011)(45)	Extensive systemic sarcoidosis with testicular involvement (1)	Corticosteroid
46	case report	Lee HJ(2011)(46)	Sarcoidosis occurred after treatment of tuberculous lymphadenitis (1)	Oral steroid
47	case report	Lee SH(2011)(47)	Sarcoidosis induced by adalimumab in Rheumatoid arthritis (1)	The patient was treated for sarcoidosis with prednisolone and methotrexate instead of adalimumab
48	case report	Lee YB(2011)(48)	Cutaneous and pulmonary sarcoidosis that was associated with interferon treatment for active chronic HCV infection (1)	Withdrawal of the interferon treatment and topical corticosteroid therapy for 2 weeks resulted in resolution of the cutaneous sarcoidosis.
49	case report	Park SY(2011)(49)	Development of sarcoidosis during tumor necrosis factor-alpha antagonist therapy (1)	The patients was treated for sarcoidosis with prednisolone instead of etanercept.
50	case report	Choi SC(2010)(50)	Morpheaform sarcoidosis (1)	Triamcinolone intralesional injection
51	case report	Han JY(2010)(51)	Sarcoidosis associated with acute tubular necrosis and pulmonary hemorrhage (1)	Prednisolone and hydroxychloroquine
52	case report	Kim DC(2010)(52)	Systemic sclerosis coincidence with sarcoidosis (1)	Corticosteroid therapy
53	case report	Kim SH(2010)(53)	Intramedullary sarcoidosis of cervical spinal cord (1)	Prednisolone
54	case report	Kim SH(2010)(54)	Neurosarcoidosis presenting as spinal nerve root pain of trunk (1)	Oral prednisolone
55	case report	Lee CH(2010)(55)	Hydrocephalus as a presenting manifestation of neurosarcoidosis (1)	The patients was performed ventriculoperitoneal shunt operation and administered corticosteroids.

no	Type of study	first author(year) (reference)	Subject (n)	therapy
56	case report	Lee KH(2010)(56)	Systemic sarcoidosis associated with early gastric cancer (1)	The patient was performed with endoscopic submucosal dissection
57	case report	Yang MY(2010)(57)	Pulmonary sarcoidosis (1)	Prednisolone
58	case report	Yun SE(2010)(58)	Diffuse subcutaneous sarcoidosis presenting as thickened extremities (1)	Corticosteroid treatment
59	case report	Cho HJ(2009)(59)	Isolated cardiac sarcoidosis (1)	Heart transplantation
60	case report	Choi HH(2009)(60)	Pulmonary sarcoidosis (1)	Prednisolone
61	case report	Choi KH(2009)(61)	A Nodular type of subcutaneous sarcoidosis (1)	The patient underwent marginal margin excision of the subcutaneous mass on the buttock, which involved the adjacent fascia on the operative field and refused steroid therapy.
62	case report	Kang MJ(2009)(62)	Cutaneous sarcoidosis presenting as multiple erythematous macules and patches (1)	Mild corticosteroids and 0.1% tacrolimus on the lesions
63	case report	Ko JK(2009)(63)	Neurosarcoidosis (1)	Intravenous methylprednisolone
64	case report	Park TS(2009)(64)	Sarcoidosis with pancytopenia as resulting from bone marrow involvement (1)	Oral prednisolone
65	case report	Chae DR(2008)(65)	Sarcoidosis presenting as a nasal cavity mass (1)	Methotrexate, prednisolone
66	case report	Hong YC(2008)(66)	Scar sarcoidosis (1)	Topical steroid
67	case report	Hong YS(2008)(67)	Primary sarcoidosis of the nasal cavity (1)	Steroid therapy
68	case report	Kang W(2008)(68)	Sarcoidosis presenting as a rectal polyp (1)	Conservative treatment

no	Type of study	first author(year) (reference)	Subject (n)	therapy
69	case report	Kim HK(2008)(69)	Pseudoalveolar sarcoidosis with unilateral pulmonary infiltration (1)	The patient improved without any treatment.
70	case report	Kim SJ(2008)(70)	Thyroid cancer combined with pulmonary sarcoidosis (1)	The patients was treated with thyroid hormones and followed up.
71	case report	You IC(2008)(71)	Sarcoidosis presented as multiple conjunctival and nasal mucosal nodule (1)	Triamcinolone intralesional injection and oral prednisolone
72	case report	Choi BY(2007)(72)	Ankylosing spondylitis accompanying sarcoidosis (1)	Conservative treatment for sarcoidosis and etanercept for ankylosing spondylitis
73	case report	Ji SG(2007)(73)	Pulmonary sarcoidosis which has similar finding of miliary tuberculosis (1)	Prednisolone
74	case report	Jo KW(2007)(74)	Graves' disease coexistent with pulmonary sarcoidosis (1)	Prednisolone
75	case report	Jung KS(2007)(75)	Sarcoidosis with chylothorax (1)	Prednisolone, sandostatin
76	case report	Kim KM(2007)(76)	Sarcoidosis presenting with thyroiditis (1)	Steroid therapy
77	case report	Kwok SK(2007)(77)	Sarcoidosis presented tenosynovitis (1)	Oral prednisolone
78	case report	Lee HJ(2007)(78)	Breast sarcoidosis (1)	Corticosteroid
79	case report	Lee JH(2007)(79)	Ethmoidal sarcoidosis (1)	Systemic corticosteroid
80	case report	Park BH(2007)(80)	Pulmonary sarcoidosis combined with neurosarcoidosis (1)	Prednisolone
81	case report	Chang HJ(2006)(81)	Exacerbation of pulmonary sarcoidosis after the cessation of interferon and ribavirin therapy for chronic hepatitis C (1)	The patient's sarcoidosis improved spontaneously and he continues to be monitored regularly without steroid therapy.

no	Type of study	first author(year) (reference)	Subject (n)	therapy
82	case report	Kim YJ(2006)(82)	Scar sarcoidosis of the eyelid (1)	Intralesional triamcinolone injectioni
83	case report	Do YS(2005)(83)	Sarcoidosis presented with myofasciitis (1)	The patient was given NSAID.
84	case report	Lee BH(2005)(84)	Sarcoidosis with cavitation and hepatic involvement (1)	Steroid treatment
85	case report	Ko DA(2004)(85)	Sarcoidosis, presented as recurrent eyelid masses (1)	Steroid therapy
86	case report	Kim JP(2003)(86)	Nodular type of muscular sarcoidosis (1)	Corticosteroid therapy
87	case report	Jang J(2001)(87)	Cardiac sarcoidosis (1)	Cardiac transplantation
88	case report	Choi JC(2000)(88)	Psoriasiform Sarcoidosis (1)	Intralesional injection of triamcinolone acetoneide
89	case report	Choi IK(1998)(89)	Sarcoid dactylitis (1)	Prednisolone, hydroxychloroquine
90	case report	Choi SH(1998)(90)	Neurosarcoidosis without systemic involvement (1)	Oral prednisolone
91	case report	Ju MS(1998)(91)	Sarcoidosis with cavitary nodule of the lung (1)	Steroid therapy
92	case report	Shin SJ(1998)(92)	Sarcoidosis involving skeletal muscle (1)	Prednisolone
93	case report	Kim GS(1997)(93)	Necrotizing sarcoid granulomatosis (1)	Because of spontaneously improved respiratory syptoms, the patients was not treated steroid therapy
94	case report	Lee SJ(1997)(94)	Sarcoidosis involving bone marrow, skin, uvea, joints and liver (1)	prednisolone
95	case report	Kim JW(1995)(95)	Sarcoidosis with bone involvement (1)	prednisolone
96	case report	Park HC(1995)(96)	Sarcoidosis with cardiac involvement (1)	lidocaine, oral prednisolone
97	case report	Cha MK(1994)(97)	Systemic sarcoidosis with cutaneous and subcutaneous involvement (1)	predinolone

no	Type of study	first author(year) (reference)	Subject (n)	therapy
98	case report	Uhm WS(1994)(98)	Pulmonary sarcoidosis (2)	steroid treatment
99	case report	Lee TH(1993)(99)	Ocular sarcoidosis (1)	corticosteroid therapy
100	case report	Kim YS(1991)(100)	Sarcoidosis involving the spinal dura (1)	steroid treatment
101	case report	Han JK(1989)(101)	Mediastinal and pulmonary sarcoidosis (1)	prednisolone
102	case report	Kim SJ(1989)(102)	Sarcoidosis (5)	Of 5 patients, 4 patients were treated the steroid therapy and the one patient was not treated the steroid therapy.

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