Review Article

Sarcoidosis in the Middle East

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Abstract:

Sarcoidosis, a systemic granulomatous disease of unknown cause, has been described worldwide and in all populations with notable differences in clinical characteristics, organ involvement, disease severity, and prognosis among different ethnic and racial groups. While the exact prevalence of sarcoidosis in the Middle East is unknown, studies from various countries in the region have reported the clinical characteristics of affected patients, along with a few anecdotal reports. A search of the MEDLINE and Google Scholar databases was conducted for relevant English-language articles using the terms "sarcoidosis" and "Middle East" or "sarcoidosis" and "Arabs." Subsequently, the names of individual countries were used as search terms, replacing "Middle East." Overall, the clinical picture of patients with sarcoidosis in the Middle East is similar to that reported elsewhere; for example, the disease was more frequent among females and respiratory complaints were the predominant symptoms. Within the region, most patients from Oman were older and female, with arthralgia, hypercalcemia, and eye involvement being more common. Constitutional symptoms were frequent, especially among patients from Iran. Cough was more common among patients from Kuwait and Iran, while dyspnea was the predominant symptom for Saudi patients. Erythema nodosum was more common in the Turkish population. Clustering was seen in patients with Stage I and II of the disease in all countries except Oman. Apart from those in Iran, the prognosis of most patients from the Middle East was excellent.

Keywords:

Arabs, Middle East, sarcoidosis

Sarcoidosis, a systemic granulomatous disorder of unknown etiology, is seen all over the world and affects all individuals regardless of sex, race, and age, with a prevalence of about 4.7–64/100,000 people and an incidence of 1–35.5/100,000 people per year.[1] The lungs are involved in most patients, followed by the skin, liver, and eyes. Sarcoidosis may present either as an acute illness, also known as Löfgren's syndrome, or with a subacute onset. Pulmonary involvement varies from radiographic abnormalities in asymptomatic individuals to a progressive pulmonary disorder causing lung fibrosis and respiratory failure. Dyspnea and cough are the most common symptoms, followed by chest pain and wheezing. Fatigue is reported by >50% of sarcoidosis patients. Other constitutional symptoms include muscle pain, arthralgia, fever, weight loss, and headaches. Small-fiber neuropathy leading to peripheral pain and disturbances of sensation are particularly distressing symptoms.

The seasonal clustering and incidence of the disease among people in military, agricultural, or firefighting occupations suggests that exposure to common environmental agents can trigger the development of sarcoidosis; in contrast, sarcoidosis appearing in bone marrow or solid-organ transplant recipients raise the possibility of a transmissible agent or cell component.[2-4] Sarcoidosis is associated with a genetic risk profile made up of many variant genes linked to sarcoidosis susceptibility, phenotype, and prognosis.[1,2,5] These findings suggest that sarcoidosis results from the exposure of genetically susceptible individuals to specific, different, environmental organic, or inorganic agents.

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The incidence of sarcoidosis varies around the world. The highest rates are reported among Northern European and African-American individuals and lowest among those of Japanese origin. The clinical features of sarcoidosis usually follow a similar pattern. However, there is some diversity in terms of clinical characteristics, organ involvement, disease severity, and prognosis among patients of different ethnic and racial groups. Sarcoidosis in African-Americans appears to be more severe, while Caucasian Americans are likely to present with a milder form of the disease.[6,7] The disease shows a predilection for adults under the age of 40, peaking in those aged 20–29 years. However, in some Scandinavian countries, Japan, and the United States, there are reports of a fair percentage of older patients. In the Japanese population, there is a bimodal age distribution, with a male peak occurring at 20–29 years and a female peak occurring at 50–59 years; in contrast, a male peak at 30–39 years and female peak at 40–60 years has been described in the Arab population.[8-10] Familial incidence has been reported in 3.6%–9.6% of patients, indicating a possible recessive trait with incomplete penetrance.[11]

The Middle East refers to the region stretching from the Eastern Mediterranean to the Western side of the Indian subcontinent and from Turkey to the Arabian Peninsula in the South. While the prevalence of sarcoidosis in the Middle East is not yet fully known, it has been previously described in various populations in this region, especially among women.[12] Although data are not yet available from all Middle Eastern countries, this review presents all available relevant information in country-wise fashion before comparing the findings. However, it is important to note that the nonstandardized format of publications and variations in the reporting of symptoms and clinical signs can cause difficulties when making comparisons between countries. For example, fever, weight loss, and fatigue were grouped together in some reports as constitutional symptoms. In the same way, cough, dyspnea, and chest pain were often not reported separately but as respiratory symptoms. Moreover, the racial predilection, varied clinical presentation and the familial, geographic, climatic or occupational clustering of the disease also make it challenging to compare the nature of the disease between countries. The gradual decline in the incidence of tuberculosis in the region and the introduction of new diagnostic techniques also influence the reporting of the disease. In general, regional differences in the clinical characteristics of sarcoidosis in the Middle East are thus in part due to differences not just in genetic background and environment but also in the diagnosis and evaluation of pulmonary and extrapulmonary disease.[13]

The MEDLINE and Google Scholar databases were searched using the PubMed and Google search engines for all relevant English language articles using the terms "sarcoidosis" and "Middle East" or "sarcoidosis" and "Arabs." Finally, the names of individual countries in this region were used as search terms instead of "Middle East."

Sarcoidosis in the Middle East

Oman

In Oman, the clinical picture of patients with sarcoidosis appears to be similar to that reported elsewhere in the world.[14] The mean age was 52.90 ± 12.35 years (males: 52.78 ± 13.66 years; females: 52.90 ± 12.35 years). More than half (56.8%) of the patients were 40–60 years old. Cough was the predominant symptom (53%), followed by dyspnea (47%). Significant constitutional symptoms, such as fatigue (30.1%), fever (20.5%), and weight loss (10.8%), were also reported. The stage of the disease at presentation was almost evenly distributed, although more patients presented with Stage I (28%) and Stage III (24%) disease. Restrictive pulmonary function defects were reported in 43.7% of the patients, obstructive defects in 16.4%, and isolated diffusion defects in 21.9%. Serum angiotensin-converting enzyme (ACE) levels were high for 51.6% of the patients. Arthralgia was reported by 41.7% of the female patients and 4.3% of the male patients. Uveitis was present in 19.3%, erythema nodosum in 9.6%, and hypercalcemia in 15.7% of the patients. Only one patient (1.2%) had cardiac involvement, while the central nervous system and hepatic involvement was reported in 2.4% and 10.8% of the patients, respectively. Most of the patients (71.6%) received treatment for 3 years or less, with a good outcome reported in 94% based on radiology findings.

Kuwait

Sarcoidosis among patients of Arab descent in Kuwait was reported to occur more frequently at a relatively younger age (mean: 40.54 ± 12.47 years) and as usual among females (62.8%).[8] There was a peak incidence among males at 30–39 years, while a broader peak occurred at 40–60 years among the females. Cough was the predominant symptom (77.9%), followed by dyspnea (61.1%). Fever (27.4%) and weight loss (15.9%) were also common. The majority presented with Stage I (40.7%) or Stage II (46.9%) disease. Forced vital capacity (FVC) was significantly reduced (<50%) among 17.5% of the patients. Uveitis, erythema nodosum, and hypercalcemia were seen in 12.4%, 15%, and 5.3%, respectively. A total of 53 patients (51%) had a good prognosis, while the prognosis was intermediate or poor in 33 (32%) and 17 (17%) patients, respectively. Two patients (1.9%) died. Hypercalcemia was noted only in those with an inferior outcome. In a follow-up report, a good prognosis was reported for 74.4% of patients with Stage I, 40% of patients with Stage II, and 16.7% with

Stage III disease, with arthralgia identified as a predictor of good prognosis.[15]

In 1997, an earlier report of 18 Kuwaiti patients with ocular sarcoidosis was published.[16] Of these, 78% had only ocular involvement. Sole anterior uveitis was found in 28%, which was associated with intermediate uveitis in 55% and posterior uveitis in 16.6% of cases.[16] In 1991, in a study of 20 sarcoidosis patients, Diab *et al*. noted an older age group, more frequent constitutional symptoms, and the rarity of ocular and central nervous system involvement.[17] Most patients presented at an early stage, at either Stage I (55%) or Stage II (40%), with very few patients (5%) having Stage III disease.

Saudi Arabia

There are quite a few reports of sarcoidosis patients from Saudi Arabia from 1993 onward. Based on a study from the Dhahran Health Centre, the estimated prevalence of sarcoidosis in the Eastern region of Saudi Arabia was 13/100,000 people.[18] In 1993, Khan *et al*. reported that the disease was characterized among native Saudis in Riyadh by the presence of severe constitutional symptoms, relatively frequent eye involvement and Stage II disease at presentation.[19] From the Western region of Saudi Arabia, in a study of 21 patients over a period of 11 years, the mean age was 45 years and the most common presentations were cough (43%), dyspnea (43%), and joint pain (38%).[20] Most of the patients presented at Stage 1 (33%) or Stage 2 (43%) of the disease, with a favorable outcome in most patients (76%).

In a fairly recent retrospective study of 104 Arab patients from three Saudi Arabian centers, the main symptoms were dyspnea (76%), cough (72.1%), and weight loss (32.7%).[21] The peak incidence occurred at 41–50 years for males and 41–50 years for females, with a higher proportion of affected women above the age of 70 years. There was a significant impairment in FVC (<50%) in 17% of patients. Stage II disease was reported in 42.3%. In a more recent report from Eastern Saudi Arabia, the mean age was reported to be 44.5 ± 17 years, with the most common presentations being cough (48%), dyspnea (21%), and joint pain (18%). Hypercalcemia was reported in 6% and most patients had Stage I (39.4%) or Stage II (45%) disease. The outcome was favorable for most patients (85%).[18]

In Saudi Arabia, pulmonary hypertension (PHTN) was diagnosed among 20.8% of Arab sarcoidosis patients and was found to contribute to poor outcomes.[22] As with other areas, the majority (85%) were women. Lower pulmonary function test (PFT) parameters, low oxygen saturation at rest or after exercise, and higher frequencies of ground-glass opacities were seen in patients with PHTN compared to those without PHTN.

A study of Saudi patients with sarcoidosis showed that the average walking distance over a 6-min period was markedly reduced when compared to patients of other races.[23] In another study, the breathing patterns of Arab sarcoidosis patients during exercise showed a higher ratio of maximal tidal volume (V_{Tmax}) to inspiratory capacity (IC), even in the initial stages of the disease, when other tests were normal, such as a PFT.[24]

Iran

In a report of 392 cases over an 8-year period, sarcoidosis was more prevalent in Guilan compared to any other part of Iran, especially in the Western region and probably the Northern area as well.[25] Most reported clinical and radiological aspects of sarcoidosis seemed not to differ from other regions. However, while Löfgren's syndrome was a common feature, skin (12.3%) and eye (4.8%) involvement were less frequent. The mean age was 42.8 ± 9.8 years, with 63.5% of patients being female. The most common signs and symptoms were cough (77.3%), dyspnea (61.7%), weight loss (50%), fever (42.5%), fatigue (5%), and arthralgia (16.2%). Hypercalcemia was seen in 2.8% and erythema nodosum in 7.1%. Serum ACE levels were higher than normal in 77.4% of the patients. More than half of the patients (65.3%) had normal PFT results. Most of the patients (61.3%) had Stage I disease. Overall, 46.2% demonstrated significant improvement, either clinically, radiologically, or both.

In an earlier study of 310 sarcoidosis cases, the most common complaints were cough (59.6%), shortness of breath (37.4%), fever (28.7%), and chest pain (18.3%).[26] The prevalence of an obstructive pattern was less frequent than that of a restrictive pattern. About 83% had positive serum ACE levels. Overall, after a 20-year follow-up period, 44.9% experienced resolution of their symptoms while 31.2% continued to have active disease. Interestingly, there are many other isolated reports from Iran on different aspects of sarcoidosis including symptoms, genetics, rare presentations or treatment.

Turkey

Turkey lies mostly within Asia, with about 3% of the country falling in Europe, thus bridging the two continents. The estimated annual incidence of sarcoidosis in Turkey was calculated to be 4/100,000 people.[27] Demirkok *et al*. observed that the presentation of the disease showed significant seasonal variation, with symptoms most frequently manifesting in the spring (61.8%).[28] Familial sarcoidosis was reported in 1%. In another study of new cases of sarcoidosis occurring over a 2-year period, 67% of 293 cases were female.[29] The mean age of the study population was 44 ± 13 years, with males usually being a decade younger than females.

Pulmonary symptoms were found in 73.3% of the patients, most frequently cough (53.2%), followed by dyspnea (40.3%). Constitutional symptoms were seen in half of the patients, the most common being fatigue (38.6%), followed by weight loss (18.1%) and fever (13.3%). Erythema nodosum was seen in 17.1%. Most of the patients had Stage I or Stage II disease (51.9% and 31.7%, respectively).

In a report of 139 patients with sarcoidosis, ocular involvement was seen in 12.9%.[30] Although the majority of patients were female, ocular involvement was more common in men. The anterior segment was the most common area involved (67%) and conjunctival involvement was seen in 16.7%. In another retrospective study of 275 Turkish patients, respiratory symptoms were reported by 57.1% and constitutional symptoms by 42.5%.[31] Arthralgia was seen in 26.9%, ocular involvement in 10.8%, hepatomegaly in 12.7%, and hypercalcemia in 5.1%. In a meta-analysis of 27 articles from 1954 to 2000, including abstracts, a female predominance, and high incidence of erythema nodosum (18.95%) were noted among 1327 cases of sarcoidosis.[32]

Jordan

Sarcoidosis seems to be a rare disease in Jordan. In a report from 1995, the clinical features of sarcoidosis were described in 33 cases.[33] The disease was more common in females (69.7%) and 79% of patients were in their fourth or fifth decade. Cough was the predominant symptom (52%), followed by dyspnea (45%), arthralgia (24%), fever (12%), weight loss (12%), and fatigue (9%). The majority presented with Stage II (61%), followed by Stage I (30%) and Stage III (9%) of the disease. Hypercalcemia was seen in only one patient. The diagnosis of sarcoidosis was confirmed in all cases by tissue biopsies, of which 84.8% were taken from an intrathoracic site. The duration of the illness in 70% of the patients was <2 years. Most patients (72.7%) received oral corticosteroids. Another report noted the occurrence of sarcoidosis in two members of the same family.[34]

Lebanon

Certainly, information regarding the prevalence of sarcoidosis in Lebanon is lacking. However, a few case reports have been published on different aspects of the disease, including familial, oral, peritoneal, cardiac, and cutaneous disease and a case of sarcoidosis with a pulmonary embolism.[35-40] Myocardial involvement in one patient led to conduction abnormalities and was successfully treated with infliximab.[35] In two other reports, one patient with a pulmonary embolism was doubly heterozygous for methylenetetrahydrofolate reductase (MTHFR) gene polymorphisms and Factor V Leiden and homozygous for the D allele of the ACE gene, while the other had mutations in the MTHFR, Factor XIII, and Factor II genes.[38,41] In a study of 76 Lebanese patients with cutaneous sarcoidosis, systemic sarcoidosis was diagnosed among 29% of the patients, with the most frequent extracutaneous manifestation being lung sarcoidosis (73%).[40]

Syria

There are only a few isolated reports from Syria of patients with sarcoidosis of the scalp and bilateral lower limb paresis due to bone marrow sarcoidosis.[42,43]

Comparison of Sarcoidosis Cases in Middle Eastern Countries

Demographic characteristics

Worldwide, women are more likely to be affected by sarcoidosis, from 41% in India to 71% in Greece, with some sex differences in terms of clinical manifestations.[44] Moreover, females tend to be older and have more uveitis and cutaneous involvement than males.[45] In the Middle East, sarcoidosis was also more common among females, with a slightly higher percentage in Oman (72.3%), followed by Turkey (67%), Saudi Arabia (64.4%), Iran (63.5%), and Kuwait (62.8%) [Table 1]. Although an earlier study from Saudi Arabia reported a female predominance of 76%, this was among a series of only 21 patients.

Sarcoidosis typically presents in patients between 20 and 60 years of age. A study from United States in 2012 reported that the onset of the disease was approximately 10 years earlier in Americans of African origin when compared to others.[7] In general, the disease first occurs in younger people, with 18% of patients in Greece and 96% of those in the United Kingdom presenting between 20 and 40 years of age.[46] In contrast, patients from Oman were older (mean: 52.90 ± 12.35 years), while a younger onset was noted in Kuwait (mean: 40.54 ± 12.47 years). A study from Istanbul noted a younger age as well (mean: 40.2 ± 12.8 years); however, a more recent meta-analysis of Turkish patients indicated a higher age (mean: 44 ± 13 years). In Kuwait, the peak incidence of sarcoidosis among Arab males was found at 30–39 years, with a broader peak at 40–60 years among Arab females.

A familial clustering of sarcoidosis cases has been observed worldwide and occurs in approximately 3.6%–16% of patients.[11,46] In the Middle East, cases of sarcoidosis occurring among close family members were reported in Oman, Turkey, Jordan, and Lebanon. Despite estimates of familial sarcoidosis ranging from 1% to 3.7% in Middle Eastern countries, this may not be true as this information was not reported in most reports.

Table 1: Demographic profile of patients with sarcoidosis in the Middle East

Country	Saudi Arabia				Kuwait	Oman	Jordan	Iran		Turkey		
Region	Riyadh[19]	Western region[20]	Riyadh[21]	Eastern region[18]	Entire country[8]	Entire country[14]	Amman[33]	Tehran[26]	Northern region[25]	Entire country[32]	Istanbul[31]	Entire country[29]
Publication	1993	1999	2009	2011	2008	2016	1995	1994	2014	2004	2007	2011
Study period	-	1985-1996	1992-2007	1998-2008	-	-	1986-1992	1974-1993	2001-2009	1954-2000	1966-2004	2004-2006
n	20	21	104	33	-	83	33	310	392	1327*	275	-
Mean age	-	45.1	46.9±12.5	44.5±15	40.54±12.47	52.9±12.35	40-50	42	42.8±9.8	29.8-48.38	40.2±12.8	44±13
Females (%)	45	76	64.4	54	62.8	72.3	69.7	-	63.5	-	69	67
Tissue diagnosis (%)	95	95.2	-	100	83.9	61.4	100	-	31.4	-	98.9	90.4

*Meta-analysis of 27 articles

Symptoms

Constitutional symptoms

General constitutional symptoms of sarcoidosis are quite common, particularly at presentation; these include profound fatigue, malaise, anorexia, weight loss, fever with night sweats, sleep disturbances, and depression.[47] In particular, fatigue is highly prevalent among patients with sarcoidosis, especially women, and often interferes with activities of daily living. Symptoms of fatigue can persist for years and may be related to depression, sleep disturbances, socioeconomic factors, small-fiber neuropathy, or adverse effects of therapy.[48] Constitutional symptoms of sarcoidosis are more frequent in African-Americans and Asian Indians than in Caucasians.[49]

Certain constitutional symptoms were common in the Middle East, particularly among patients from Iran [Figure 1]. Overall, patients from Northern Iran (42.5%) and Kuwait (27.4%) most frequently reported fever. Weight loss was also more common in Iran (50%), followed by Saudi Arabia (32%). However, fatigue was seen only in 5% of patients from Iran, compared to 38.6% and 30.1% of patients from Turkey and Oman, respectively. In Saudi Arabia, 60% of native Saudis with sarcoidosis in Riyadh had weight loss and 40% had fever; nevertheless, it is important to bear in mind that this report comprised only 21 patients. Two later studies with a larger number of patients reported weight loss in 32.7% and 18% of Saudi patients, respectively.

Respiratory symptoms

Pulmonary involvement occurs at some point in nearly all patients with sarcoidosis and subclinical pulmonary disease may be present in patients with extrathoracic disease.[1] Dry cough, dyspnea, vague chest discomfort, exercise limitations, and wheezing are the most common symptoms.[50,51] Furthermore, patients with sarcoidosis are known to have a twofold increased risk of developing pulmonary emboli. As elsewhere, respiratory complaints were the predominant symptoms among sarcoidosis patients in the Middle East [Figure 2]. Cough was more common among patients from Kuwait (77.9%) and Iran (77.3%). Dyspnea was the predominant symptom in Saudi patients (76%).

Extrapulmonary involvement

Apart from the lungs, the skin and subcutaneous tissues are the next most commonly involved organ, affecting about 25% of sarcoidosis patients.[44] Cutaneous sarcoidosis presents with varied appearances. Erythema nodosum, a common manifestation, is neither clinically nor histologically diagnostic of the disease. In the Middle East, erythema nodosum was more common than other skin manifestations of sarcoidosis and was more frequent in the Turkish population (18.95%–29.1%) compared to

other countries like Iran (7.1%) and Oman (9.6%) [Table 2]. Nonerosive arthropathy is often chronic and troublesome and affects about 20% of patients worldwide.[52] Arthralgia was common in Oman (31.3%). Two earlier studies of 21 and 20 patients from Saudi Arabia reported the frequency of arthritis to be 43% and 45%, respectively.

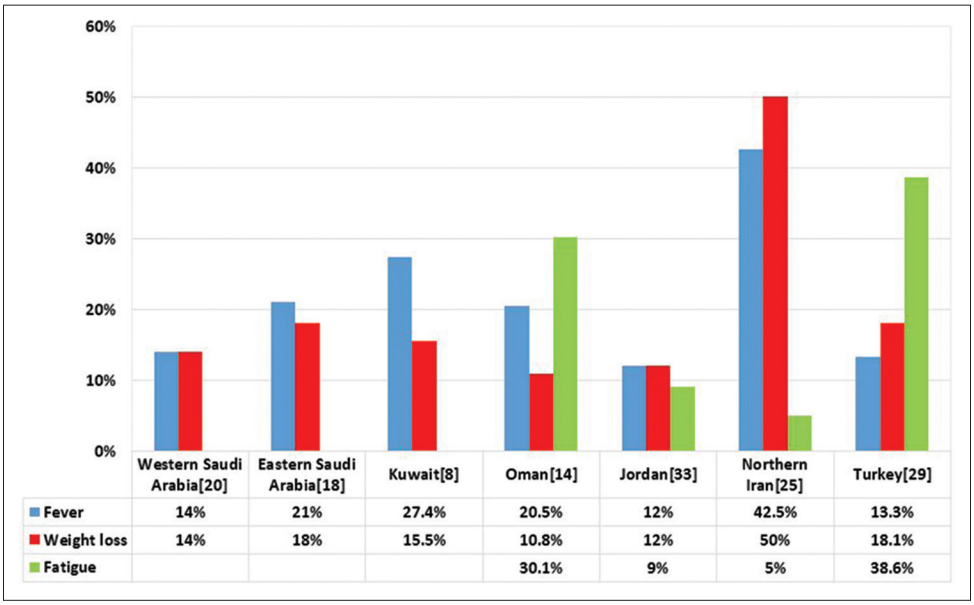


Figure 1: Constitutional symptoms in patients with sarcoidosis in the Middle East

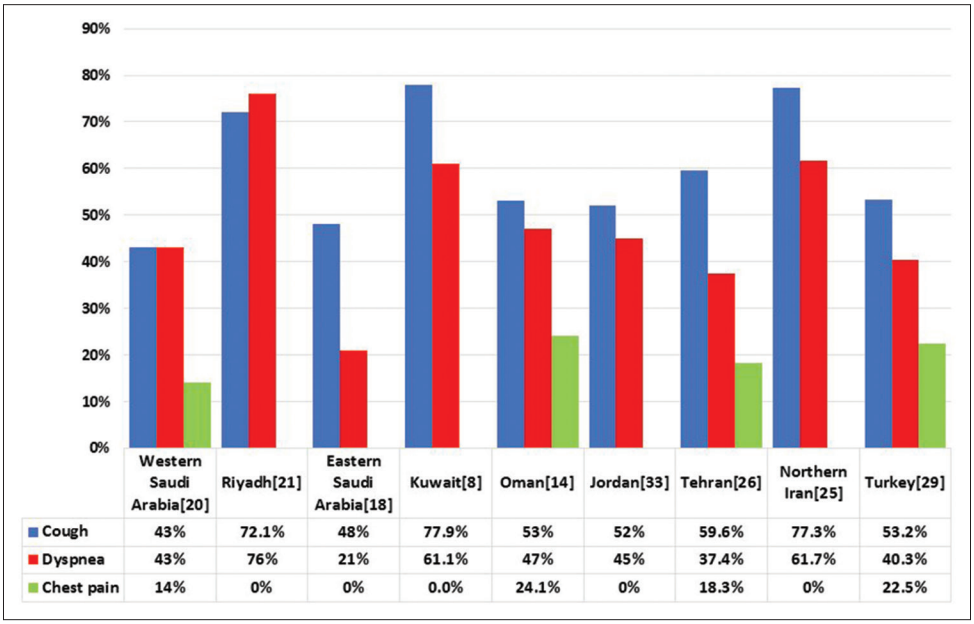


Figure 2: Respiratory symptoms in patients with sarcoidosis in the Middle East

Table 2: Extrapulmonary involvement in patients with sarcoidosis in the Middle East

Country	Saudi Arabia				Kuwait	Oman	Iran	Turkey		
Region	Riyadh[19]	Western region[20]	Riyadh[21]	Eastern region[18]	Entire country[8]	Entire country[14]	Northern region[25]	Entire country[32]	Istanbul[31]	Entire country[29]
Publication	1993	1999	2009	2011	2008	2016	2014	2004	2007	2011
Arthralgia (%)	45	43	-	18	16.8	31.3	16.2	-	26.9	20.8
Eye involvement (%)	25	5	9.6	12	12.4	19.3	4.8	-	10.8	-
Lymphadenopathy (%)	25	24	-	6	9.8	12	-	-	18.7	11.3
Skin involvement (%)	5	38	3.8	-	12.4	12	12.2	-	-	-
Erythema nodosum (%)	-	-	-	-	15	9.6	7.1	18.95	29.1	21.5

In Japan, up to 50% of sarcoidosis patients have uveitis whereas the frequency of this symptom is as low as 5% in Denmark.[44] Eye involvement was also found to be fairly common in patients from Oman (19.3%). Neurological involvement has been reported in 5%–26% of patients in the literature.[53] Two patients in Oman (2.4%) and one patient in Saudi (0.96%) had central nervous system involvement. Cardiac involvement was also documented in one patient each in Oman (1.2%) and Saudi Arabia (0.96%). The apparent rarity of cardiac and central nervous system involvement may partly be due to a bias in patient selection, as most studies were based in pulmonary clinics. Hepatic involvement, usually subclinical, is fairly common. Enzyme levels are occasionally raised and hepatic damage and cirrhosis is quite rare. Up to one-third of patients have hepatomegaly or a cholestatic pattern of liver function derangement, with nearly 10% of sarcoidosis patients having elevated serum aminotransferase and alkaline phosphatase concentrations.[6] In the Middle East, 8.6% of patients in Saudi Arabia, 10.8% in Oman, and 21% in Jordan had hepatic involvement.

Diagnostic workup

A diagnosis of sarcoidosis is confirmed by the presence of noncaseating granulomas in a tissue biopsy, together with compatible clinical and radiological evidence and the exclusion of other differential diagnoses.[49,51] In most countries in the Middle East, the diagnosis was made based on a biopsy specimen obtained mainly from an intrathoracic site, except in Iran, where it was mostly based on clinicoradiological data [Table 3]. In Oman, histopathological confirmation of the disease occurred in only 61.4% of cases, in comparison to rates of 83.9%–100% from adjoining countries. Worldwide, the reported incidence of sarcoidosis-associated hypercalcemia varies from 2% to 63%.[54] In the Middle East, hypercalcemia was seen more frequently in Omani patients (15.7%) compared to Iranian patients (2.8%). Tuberculin test results were negative for the majority of patients from Middle Eastern countries. However, serum ACE levels were elevated in 39.1%–77.4% of patients in this region. Nevertheless, the use of serum ACE levels as a potential diagnostic and prognostic biomarker of sarcoidosis is limited due to a lack of sensitivity and specificity and the influence of ACE gene polymorphisms.[46,55,56]

Disease staging

A common presentation of sarcoidosis is bilateral hilar lymphadenopathy on a chest radiograph, an incidental finding in an asymptomatic person or among those with respiratory symptoms and Stage I sarcoidosis. Patients from Japan generally present with Stage I disease, whereas Europeans and Americans usually present at a more advanced stage.[57,58] In the Middle East, Stage I disease was more common in Iran (61.3%), followed by Turkey (51.9%). In contrast, more patients presented with Stage II sarcoidosis in Jordan (61%), Kuwait (46.9%), and Saudi Arabia (38%–45%). A greater number of patients from Oman presented with a more severe form of the disease at Stage III (24%) or IV (12%). In Oman, patients were more or less evenly distributed between the different stages, while there was evidence of clustering at Stages I and II in other Middle Eastern countries [Figure 3].

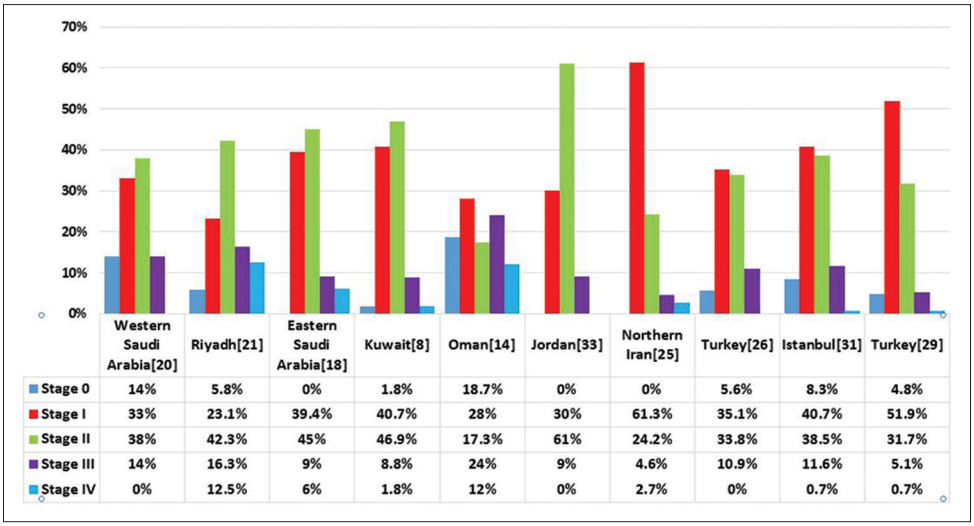
Pulmonary function and exercise capacity

Exercise capacity in individuals with sarcoidosis may be affected by lung involvement, muscle weakness, fatigue, and deconditioning. On a PFT, sarcoidosis patients can display normal, restrictive, or obstructive patterns; moreover, reduced diffusing capacity may be common.[59] Restrictive defects were the most common abnormalities reported from Oman, Kuwait, and Turkey, whereas 65.3% of patients from Iran had normal PFT results. Patients from the Middle East seem to have a reduced exercise tolerance, as evidenced by two studies from Saudi Arabia; one found walking distance over a 6-min period to be markedly reduced when compared with other races and the other noted the breathing of Saudi patients during exercise to have a higher V_{Tmax}: IC ratio.[23,24]

Table 3: Diagnostic workup for patients with sarcoidosis in the Middle East

Country	Saudi Arabia				Kuwait	Oman	Jordan	Iran	Turkey		
Region	Riyadh[19]	Western region[20]	Riyadh[21]	Eastern region[18]	Entire country[8]	Entire country[14]	Entire country[33]	Northern region[25]	Entire country[26]	Istanbul[31]	Entire country[29]
Publication	1993	1999	2009	2011	2008	2016	1995	2014	2004	2007	2011
Hypercalcemia (%)	10	14	7.9	6	5.3	15.7	3	2.8	6.6	5.1	-
High serum ACE levels (%)	-	73.3	-	46.7	-	51.6	-	77.4	-	52	39.1
Negative Mantoux test (%)	95	100	-	96	-	88.9	90.9	94.5	76.4	72	67
Histopathology (%)	95	95.2	-	100	83.9	61.4	100	31.4	-	98.9	90.4
Intrathoracic biopsy (%)	-	35	68.3	93.9	68.3	70.6	84.8	-	-	58.6	-

ACE=Angiotensin-converting enzyme



	Western Saudi Arabia[20]	Riyadh[21]	Eastern Saudi Arabia[18]	Kuwait[8]	Oman[14]	Jordan[33]	Northern Iran[25]	Turkey[26]	Istanbul[31]	Turkey[29]
Stage 0	14%	5.8%	0%	1.8%	18.7%	0%	0%	5.6%	8.3%	4.8%
Stage I	33%	23.1%	39.4%	40.7%	28%	30%	61.3%	35.1%	40.7%	51.9%
Stage II	38%	42.3%	45%	46.9%	17.3%	61%	24.2%	33.8%	38.5%	31.7%
Stage III	14%	16.3%	9%	8.8%	24%	9%	4.6%	10.9%	11.6%	5.1%
Stage IV	0%	12.5%	6%	1.8%	12%	0%	2.7%	0%	0.7%	0.7%

Figure 3: Disease staging at presentation among patients with sarcoidosis in the Middle East

End-stage lung disease

The prevalence of PHTN in sarcoidosis is between 5% and 79%, depending on the population studied.[50] The gender distribution of sarcoidosis patients with PHTN also varies globally, being more common among men in Japan and Europe and among women in the United States. In Saudi Arabia, PHTN was more common among female sarcoidosis patients, with an overall incidence of 20.8%. This condition was also reported to be associated with poor outcomes. Although many patients had pulmonary involvement and Stage III or IV disease, the exact number of patients with advanced lung disease and respiratory failure was not mentioned in other studies from the Middle Eastern region.

Prognosis

Siltzbach *et al*. reported an extraordinary parallel in the prognosis of sarcoidosis among different ethnic groups living in radically different environments and climates.[60] While the overall mortality rate in sarcoidosis cases can be as low as 0.5%, this may rise to 4.8% for those with severe lung disease requiring specialist care.[44] The clinical course of sarcoidosis varies, with the disease resolving spontaneously within 2 years for half of all patients, but potentially persisting for up to 5 years in other cases.[1] Determining the prognosis of a patient requires the assessment of serial changes in symptoms, pulmonary function, and imaging. However, there is no clear overall measure combining these variables, each of which is often reported in isolation, thereby limiting their significance.[50] As reported in other regions of the world, the prognosis of sarcoidosis patients in the Middle East was excellent. A good outcome or resolving/stable disease was noted in 94% of cases in Oman, 93.3% in Saudi Arabia, and 83% in Kuwait. However, a good prognosis was recorded in only 45.7% of Iranian patients. In a study from Kuwait, improved initial lung function values, the presence of arthralgia, and an early stage of the disease were found to be predictive of a good prognosis, whereas sex, age, ethnicity, and the presence of fever, weight loss, or erythema nodosum did not influence patient outcomes.[15]

Limitations

The major limitation of this report on the clinical presentation of sarcoidosis in the Middle East is probably the nonstandardized format of publications and variations in the reporting of symptoms and clinical signs leading to selection, reporting, and sampling biases. Many studies from this region were not explicit in defining the constitutional or respiratory symptoms. Although a few tools for defining organ involvement or clinical presentation are available, none of the scanned studies used any. No clear guidelines on an overall measure for assessing the prognosis exist and the reports present the progress differently. There is significant variation in the region in terms of economy, access to health care, and diagnostic tools which adds to the difficulty in comparing the clinical presentation in different countries. Moreover, the studies reported vary over a long period of time including patients from 1950's to the present. Better imaging techniques, increased awareness of the disease, and improvement in the general health-care systems would have influenced the reporting of the clinical data and the prognosis. In addition, the racial predilection and the familial, geographic, climatic, or occupational clustering of the disease also influence the incidence in different countries.

Conclusion

Overall, the clinical picture of patients with sarcoidosis in the Middle East appears to be similar to that reported

elsewhere in the world. In most cases, the diagnosis of sarcoidosis was made based on biopsy specimens sourced mainly from intrathoracic sites. Sarcoidosis was more common in females. Patients from Oman tended to be older females, with arthralgia, hypercalcemia, and eye involvement being more common. Constitutional symptoms were frequent, especially in patients from Iran. As elsewhere, respiratory complaints were the predominant symptoms, with cough being most common in patients from Kuwait and Iran while dyspnea was most frequently observed in Saudi Arabia. Erythema nodosum was more common in the Turkish population. Clustering was seen at Stage I and II disease in all countries except Oman. The relative rarity of cardiac and central nervous system involvement is worth noting; however, this is probably due to a bias in patient selection as most studies were based in pulmonary clinics. As with studies conducted elsewhere, the prognosis of patients from this region was excellent, apart from those reported in Iran.

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Conflicts of interest
There are no conflicts of interest.

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