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Morbidity and Mortality in Sarcoidosis

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Abstract

Purpose of Review—Chronic sarcoidosis is a complex disease with numerous comorbid conditions and can be fatal in some cases. Recognizing causes of morbidity and mortality is important to effectively select treatments, manage symptoms, and improve outcomes. The purpose of this review is to examine emerging knowledge on morbidity and mortality in sarcoidosis.

Recent Findings—Approximately one to five percent of patients with sarcoidosis die from complications of sarcoidosis. Recent population studies indicate that mortality may be increasing over the past decade. The reasons behind these trends are unclear, but could include increasing incidence, detection rates, severity of disease, or age of the population. Morbidity of sarcoidosis is reflected by a trend of increased hospitalizations over recent years and increased use of healthcare resources. Morbidity can be caused by organ damage from granulomatous inflammation, treatment complications, and psychosocial effects of the disease. Recent studies are focused on morbidity related to cardiopulmonary complications, bone health, and aging within the sarcoidosis population. Last, sarcoidosis is associated with autoimmune diseases, pulmonary embolism, and malignancy; however, the underlying mechanisms linking diseases continue to be debated.

Summary—Morbidity in sarcoidosis is significant and multifactorial. Mortality is infrequent, but may be increasing over the years.

Keywords

Sarcoidosis; Epidemiology; Mortality; Prognosis; Aging; Comorbidity

Introduction

Although many patients with sarcoidosis resolve spontaneously, a significant proportion of patients have chronic or progressive disease with resultant morbidity. A small proportion of patients die from the disease. Morbidity and mortality can be due to both the disease and its treatments. Efforts have been made to determine prognostic factors for mortality and progressive disease in order to identify patients with a protracted clinical course, although it is not clear if earlier treatment is beneficial. Not all morbidities associated with sarcoidosis

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respond to immunosuppression, and understanding the underlying mechanisms may aid in better management of symptoms.

Mortality

Mortality rates in sarcoidosis range from less than one percent to eight percent depending on the care setting, severity of disease, and location, and appear to vary by age, ethnicity, and gender.[1–3] A population study of death certificates in the United States (U.S.) from 1988–2007 shows an age and sex-adjusted mortality rate of 4.32/1,000,000, with a majority of deaths (58.8%) occurring from underlying sarcoidosis. Mortality is highest in non-Hispanic blacks, women, and in ages over 55 years.[4] Similar rates of 4.2/1,000,000 deaths in people with sarcoidosis are seen in England's national death certificate data in 2008, and 2.3/1,000,000 with sarcoidosis as the underlying cause.[5] In Japan, age-adjusted mortality rates in the population are 0.1–0.2 per million.[6] The Black Women's Health Study shows age-adjusted mortality at 94 deaths per 10,000 person-years, 2.44 times higher than women without sarcoidosis.[7*] Almost one-fourth die from sarcoidosis-related causes. In the U.S. and Europe, death from sarcoidosis is primarily from respiratory involvement, while in Japan, mortality is usually attributed to cardiac involvement.[4,8]

Increasing mortality over the past decades has been suggested. Swigris, *et al.* shows an increased trend over a period of years, particularly in Blacks, women, and older populations.[4] Prior study in the U.S. shows an increase in mortality from 1.3 to 1.6/1,000,000 in men and 1.9 to 2.5/1,000,000 for women from 1979 to 1991.[9] In England, mortality rate has also increased.[10] However, questions remain whether these trends are related to increasing incidence or recognition of the disease, increased severity, coding differences, or reflective of an aging sarcoidosis population. A meta-analysis of earlier mortality studies found higher mortality in Blacks to be a factor of higher incidence in the black population, arguing against a higher case-fatality rate by race or ethnicity.[2] Current studies do not address these factors directly, and further evaluation is warranted.

Post-transplantation survival for lung, heart, and liver in patients with sarcoidosis is comparable to overall transplantation survival for each organ.[11] In lung transplantation, pulmonary hypertension, oxygen use, and African-American race are independent predictors of mortality for sarcoidosis patients on the waiting list.[12] Although long-term survival is similar to other lung diseases, mortality does appear higher within the first year, which may be related to increased primary graft dysfunction in sarcoidosis patients.[13,14,15*,16*] Data regarding heart transplantation survival are not uniform, with some centers reporting better or worse survival.[17] Similarly, it appears that liver transplant survival for sarcoidosis may be worse than for primary biliary cirrhosis or primary sclerosing cholangitis, but still favorable, and similar to other liver diseases.[18,19] Firm conclusions are limited by the rarity of heart and liver transplantation for sarcoidosis. Differences in survival may relate to the presence (or recurrence) of sarcoidosis in alternative organs, infection risk, or unknown immune factors related to graft dysfunction.

Morbidity

On an individual level, morbidity affects quality of life and function. The presence of dyspnea and the extent of concomitant morbidity predict anxiety and depression in sarcoidosis patients.[20*] In the U.S. population, hospitalizations of patients with sarcoidosis over the past ten years have increased significantly, but do not appear to be related to the primary diagnosis of sarcoidosis.[21**] This rise is particularly prominent in African Americans, women, and patients over 55 years, implying comorbid conditions, treatments, or evolving age are contributing to increasing morbidity.

Morbidity in sarcoidosis is largely related to the affected organ system(s), with pulmonary, cardiac, hepatic, neurologic, and ocular involvement often having the most severe consequences.[22] Frequency and morbidities of organ involvement are shown in Table 1. Multiple studies show that sarcoidosis tends to be more severe in black patients, whereas, white patients are more likely to have spontaneous resolution.[23,24] Japanese patients have a higher prevalence of cardiac and ocular disease than Western populations.[8] Last, lower socioeconomic status has been associated with more severe disease and new organ involvement.[24] The following focuses on the most recent advances in knowledge related to cardiopulmonary involvement, bone health, pain and fatigue.

Respiratory impairment

Pulmonary involvement can become symptomatic with dyspnea or cough. It is highly prevalent and can cause decline in lung function.[25] The clinical course can be acute, subacute, chronic, or progressive. Intermittent acute flares of disease (both during and after treatment), marked by decreased pulmonary function, symptoms, and exclusion of other respiratory causes, have also been described.[26*] Flares (or “exacerbations”) may respond to low-dose corticosteroids, although there are few studies guiding diagnosis and treatment.

Pulmonary fibrosis is a risk factor for mortality. Contrary to the belief that sarcoidosis is a benign disease, a recent retrospective study from France showed that sarcoidosis patients with pulmonary fibrosis have markedly decreased survival compared to the general population. Complications include long-term need for oxygen, progressive respiratory failure, bronchiectasis, pulmonary hypertension, pneumothorax, aspergillomas, pulmonary embolism, and infections.[27] Pathophysiologically, it is unknown if progressive fibrosis depends on granulomatous inflammation or is a result of alternative inflammatory or fibrotic mechanisms. Furthermore, questions remain whether the process is early or late stage.[28**] Research is necessary to determine whether and when immunosuppression may alter the clinical course. Generally, it is recommended that if accompanying granulomatous inflammation is suspected, immunosuppression should be initiated to prevent further organ damage.[28**]

Pulmonary hypertension (PH) is present in approximately 5–12% of unselected patients and up to 74% of patients awaiting lung transplantation.[29–31] Its presence has repeatedly been shown to be an independent predictor of mortality.[27,32] Mortality or transplantation rate is reported as 41% with a median survival of 5.3 years in a meta-analysis of sarcoidosis patients with PH.[33*] Treatment with pulmonary vasodilators may improve functional

parameters and hemodynamics, but it is not clear if it affects survival.[33*] The pathophysiology of PH in sarcoidosis is varied and can be due to granulomatous involvement of the heart, lungs, or vasculature, abnormal vaso-reactivity, porto-pulmonary hypertension, or compression by lymph nodes. It is more common in patients with pulmonary fibrosis or advanced lung disease, but can be present and severe in the absence of lung disease.[34,35] Recent study has shown that patients with an elevated pulmonary artery pressure in the absence of a high wedge pressure have an increased risk of mortality compared to those with PH related to left ventricular (LV) dysfunction.[32] Patients often have progressive dyspnea. Evaluation should be considered in patients with symptoms out of proportion to parenchymal disease, advanced lung disease, low diffusing capacity, and desaturation on six minute walk.[36] Because of its associated mortality risk, transplant evaluation should be considered in sarcoidosis-associated PH.

Cavitary Lung Disease and Mycetomas

Patients with chronic inflammation can develop pulmonary cavities with resultant mycetomas, most often caused by aspergillus.[37,38,39*] Aspergillus-related lung disease occurs in up to 1–2% of patients and is associated with poor outcomes.[40] The presence of a mycetoma may reflect the severity of pulmonary disease. It is speculated that aspergillomas may partially result from the structural abnormalities in the lung and/or an altered immune system due to sarcoidosis or immunosuppressives. Antifungals are typically utilized, as is surgery in selected cases. Mycetoma is often a contraindication to lung transplant due to high perioperative mortality, although in small series of patients, perioperative antifungals and bilateral transplantation may improve outcomes in highly selected patients.[41]

Cardiac

Granulomatous inflammation of the heart can cause ventricular or atrial arrhythmias, sudden death, or heart failure. Cardiac magnetic resonance imaging (MRI) and positron emission tomography (PET) scans are increasingly being used to diagnose cardiac sarcoidosis with better sensitivity and specificity.[42,43] Electrophysiology studies may also be helpful for risk stratification.[44]

Death due to cardiac reasons in sarcoidosis patients has been reported as 25% in the U.S, and higher in Japan.[4,45] The presence of sustained ventricular tachycardia (VT), severity of heart failure, and LV end-diastolic diameter predict sudden death.[45] Late gadolinium enhancement on cardiac MRI, indicating myocardial scar, is an independent predictor of death and potentially lethal cardiac events, superior to ejection fraction, left ventricular end-diastolic volume, or heart failure presentation in predicting adverse cardiac events.[46**,47] Similarly, focal uptake on cardiac PET has also been associated with higher risk of death or VT.[48**]

Treatment for cardiac sarcoidosis includes traditional treatment for heart failure and arrhythmias, as well as immunosuppressive medication in some cases. Implantable cardioverter-defibrillators (ICDs) are often considered, and placement depends on presence of arrhythmia, ejection fraction, and patient preference. Review of cardiac sarcoidosis

patients with ICDs shows efficacy, but also reports high rates of inappropriate shocks and device complications.[49**,50]

Pain and Fatigue

Pain and fatigue are becoming increasingly recognized as major comorbid conditions. Pain may reflect arthritis, myopathy (sarcoidosis or steroid-induced), small fiber neuropathy, or fibromyalgia syndrome. Fatigue is present in over 80% of patients and may be the main contributor to impaired quality of life.[51,52] The causes of fatigue are multifactorial and can include inflammation, treatments, or comorbidities. Given the association between sarcoidosis and sleep disorders, a sleep study is often recommended in the work-up of fatigue.[53**] Sarcoidosis patients also have decreased muscle strength and exercise capacity.[52,54] Fatigue does not respond well to immunosuppression and may actually be compounded by these medications. Exercise programs, stimulants, and behavioral therapy are currently being studied and may be beneficial in some patients.[55**,56,57*]

Bone Health

Osteoporosis and fracture risk are important complications of sarcoidosis and treatment. In one series, 20% of sarcoidosis patients had vertebral deformities that suggested fractures despite normal bone density, increasing to 32% after four years of follow-up with no change in bone density measurements.[58] These rates appear higher in comparable published population data. Increased markers of bone turnover suggest a potential alteration of bone remodeling, possibly related to cytokines from chronic inflammation.[59] Another study showed lower bone density in post-menopausal women with sarcoidosis compared to controls, regardless of treatment, highlighting the impact of age and sarcoidosis on bones.[60] The use of corticosteroids as treatment is also problematic, and may depend both on the duration and dose.[59,61] As for now, it is generally recommended that patients on chronic corticosteroids be strongly considered for osteoporosis prevention and treatment, and it may be prudent to assess bone health in all sarcoidosis patients based on the potential bone pathology associated with the disease. Further study on the role of bone density testing, biomarkers, and the influence of inflammation is warranted to better guide management algorithms.

Associated Diseases

Sarcoidosis has been associated with autoimmune diseases.[62,63*] It is important to note, however, that connective tissue diseases can cause a sarcoid-like reaction, and may not be concurrent separate diseases.[63*] Obesity in women has also been shown to be a pre-existing risk factor for the development of sarcoidosis and other autoimmune diseases, one potential connection for the associations.[64*]

It has long been debated whether there is a higher risk of cancer in sarcoidosis patients. Sarcoid-like reactions in malignancy and chemotherapy are well-described, making it difficult to discern two separate entities, particularly if temporally related. A recent population-based cohort study in patients with cancer supports the premise of a higher risk of malignancy. In this study, a history of hospitalization for sarcoidosis was associated with

higher incidence, worse prognosis, and excess mortality for six types of cancer.[65,66] Conversely, prior associations with cancers broach the idea that sarcoidosis is an immunologic response to a neoplasm.[67,68] The answers to these questions are far from clear, and continue to be discussed.

Three studies have shown a higher frequency of pulmonary embolism compared to the general population.[69,70,71] Results from decedent records may also imply pulmonary embolism as a potential contribution to mortality. The etiology of increased risk is unknown, but could reflect treatment effects, associated hypercoagulable disorders, shared mechanism, or a result of decline in mobility due to sarcoidosis-related morbidities.

Treatment-related Comorbidity

Treatments for sarcoidosis often include immunosuppressive medications that can have notable side effects and toxicities. All of the immunosuppressives contribute to increased susceptibility to infection.[27,37,72*,73] Higher use of corticosteroids has been linked to increased number of non-sarcoidosis-related emergency department visits compared to patients with lower cumulative corticosteroid exposure.[73]

There is continued controversy on whether corticosteroids may prolong the course of sarcoidosis, particularly in acute disease, limiting the benefit of early treatment in many cases.[74] Use of corticosteroids has been associated with higher mortality rates, even when accounting for stage (a proxy for severity) of disease.[2] Corticosteroid treatment has also been implicated in the development of recurrent flares.[26*] In theory, early use of corticosteroids may prevent natural clearance of an unknown antigen, perpetuating the granulomatous response. Conversely, earlier treatment in chronic sarcoidosis and pulmonary fibrosis may improve outcomes, highlighting the complexity of treatment decisions, and the importance of further research into prognostic indicators.[27]

Aging and Comorbidity in Sarcoidosis

Although sarcoidosis is commonly thought of as a disease of the young, almost 30% of patients in the ACCESS cohort were older than fifty, and epidemiologic studies report a second peak in incidence between 50 and 65 years.[8,22] It can also be speculated that improving treatments are prolonging survival, increasing the aging sarcoidosis population. In light of more recent evidence showing increased mortality and hospitalizations in older patients, understanding and managing comorbidity may be becoming increasingly important. [4,21**] Older sarcoidosis patients have more concomitant disease, more fatigue and anxiety at presentation, and are more prone to chronic disease.[75*,76**] Older patients may also have more obstructive lung disease, suggesting possibly more proximal airway involvement and increased functional impairment.[77*] Further, many sarcoidosis signs and symptoms overlap with age-related comorbidities, such as malignancy or atherosclerotic disease. Cognitive dysfunction or neurologic involvement can be confused for dementia. [75*,76**] The conglomeration of these factors may contribute to increased difficulty in diagnosis and management of older patients.

Conclusion

Mortality in sarcoidosis approximates five percent of cases, and may be increasing in the overall population. Morbidity from chronic sarcoidosis can be substantial and contribute to poor outcomes. Prospective studies are needed to further understand the contribution of disease complications, treatments, aging, and comorbid conditions to long-term morbidity and mortality in sarcoidosis.

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Abbreviations

ACCESS	A Case Control Etiologic Study of Sarcoidosis
ICD	Implantable cardioverter-defibrillator
LV	Left ventricular
MRI	Magnetic resonance imaging
PET	Positron emission tomography
PH	Pulmonary hypertension
U.S	United States
VT	Ventricular tachycardia

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Key Points

- Mortality and morbidity appear to be increasing over the years in the population, although the reasons for this are unclear, and could include increasing incidence or recognition of sarcoidosis, increased severity, or an aging sarcoidosis population.
- Understanding causes of morbidity and predictive factors for poor outcomes is important to determine appropriate management of symptoms and complications of sarcoidosis.
- Older patients with sarcoidosis are more likely to have chronic sarcoidosis, comorbid conditions, and side effects to treatments than younger patients, increasing the complexity of diagnosis and management in the aging population.

Table 1

Morbidity in sarcoidosis by organ.*

Organ (% [22])	Associated Morbidities
Lung (95%)	Decreased pulmonary function (restrictive or obstructive), pulmonary fibrosis, pulmonary hypertension, pulmonary embolism, intermittent flares/exacerbations, cavitary lung disease with mycetomas
Skin (excluding erythema nodosum) (15.9%)	Lupus pernio, maculopapular rash, nodules, plaques, alopecia, hypo/hyperpigmentation, scales, annular lesions
Non-Thoracic Lymph Nodes (15.2%)	Discrete, movable, nontender lymph nodes
Eyes (11.8%)	Uveitis, lacrimal gland enlargement, periorbital swelling, keratoconjunctivitis sicca, optic neuropathy (potentially leading to blindness), conjunctival nodules and follicles, dacryocystitis, retinal vasculitis
Liver (11.5%)	Cholestatic or obstructive liver disease, liver failure, cirrhosis, portal hypertension, abdominal pain, liver function abnormalities (most commonly, high alkaline phosphatase)
Erythema nodosum (8.3%)	Lofgren's syndrome (erythema nodosum, uveitis, lymphadenopathy)
Spleen (6.7%)	Abdominal pain/pressure or hematological abnormalities
Neurologic (4.6%)	Cranial nerve abnormalities or palsies, seizures, meningitis, peripheral neuropathy, pain, neuropsychiatric symptoms, endocrine abnormalities from pituitary or hypothalamic involvement, small fiber neuropathy
Bone Marrow (3.9%)	Hematological abnormalities (anemia, leukopenia, thrombocytopenia)
Parotid/Salivary Glands (3.9%)	Gland enlargement, painful swelling, xerostomia, facial palsy
Hypercalcemia/Hypercalciuria (3.7%)	Nephrolithiasis, high calcium levels, renal insufficiency
Ear/Nose/Throat (3.0%)	Hoarseness, sinusitis, rhinitis, Heerfordt's Syndrome (parotid swelling, uveitis, Bell's palsy)
Cardiac (2.3%)	Atrial or ventricular arrhythmia, sudden death, heart failure
Renal (0.7%)	Renal insufficiency, abnormal electrolytes
Bone/Joints (0.5%)	Joint pain, acute or chronic arthritis, peri-arthritis, synovitis, bone lesions/cysts, costochondral pain
Muscle (0.4%)	Muscle pain, weakness, tenderness, muscle nodules/masses, myositis, chronic myopathy
Gastrointestinal Tract	Dysphagia, bleeding, nausea/vomiting, pain, weight loss, obstruction, ulcers
Reproductive Organs	Masses
Constitutional	Fevers, fatigue, weight loss, night sweats, malaise

* Percentage of patients with organ involvement at presentation with sarcoidosis from the ACCESS study (n=736 sarcoidosis patients).[22] Organs without a percentage were not determined in the ACCESS study. (data from [22])