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PREVALENCE OF CARDIAC SARCOIDOSIS AND CARDIOVASCULAR OUTCOMES: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Cardiac sarcoidosis is a rare inflammatory condition where immune cells form granulomas in different parts of the heart and may lead to manifestations such as heart failure, ventricular arrhythmias, and death. The aim of this systematic review is to synthesize evidence of prevalence and outcomes in patients with cardiac sarcoidosis. This study seeks to contribute to the paucity of literature in this area. **Methods:** Adhering to PRISMA 2020 Statement guidelines, a systematic review was conducted through June 15, 2022. PubMed, Cochrane Central, and Embase were used to locate original studies including cohorts and case controls. The following keywords were used: Cardiac, Sarcoidosis, Heart, Arrhythmia, Mortality, and Heart Failure. The data were entered into a shared spreadsheet which was presented in a tabulated format. All statistical analysis was conducted in SPSS v.23. **Results:** Out of the 1284 studies originally located through the systematic search, a total of 6 were included in this systematic review. Of the 18,194,709 participants, 128,921 had cardiac sarcoidosis. The three most commonly reported comorbidities were hypertension (n=32,287, 63.8%), diabetes mellitus (n=14,758, 31.1%) and ischemic heart disease (n=1,565, 3.4%). Reported outcomes included heart failure (n=30,096, 23.4%), mortality (n=2,398, 2.9) and ventricular tachycardia (n=1,111, 2.4%). **Conclusion:** Cardiac sarcoidosis while rare occurs in around 10% of patients with sarcoidosis. When isolated to only the heart, various effects such as arrhythmias, conduction abnormalities, heart failure, and death can occur. The etiology of the disease is believed to be either environmental or infection. So far, immunosuppression in combination with steroid therapy has proven to be of benefit for immediate improvement in outcomes. Larger-powered clinical studies are required to denote the most valuable imaging modalities, therapies, and long-term prognostic outcomes in patients.

KEYWORDS: Cardiac; Sarcoidosis; Prevalence; Vascular; Systemic.

INTRODUCTION

Sarcoidosis is a multisystem granulomatous disease with an unknown etiology typified by the presence of noncaseating granulomas in the involved organs.[1] The estimated prevalence of sarcoidosis is 10 to 40 out of 100,000 persons in Europe and the United States with a cumulative higher prevalence in African Americans compared to Caucasians (10-17:1).[1] It is reported that sarcoidosis is more common in women as compared to men; any tissue in the body may be involved as a sequala.[1] The most commonly involved organs include lymph nodes, lungs, skin, central nervous system, and

the eyes.[2] In nearly 50% of patients that have acute presentations, a constellation of bilateral lymphadenopathy, erythema nodosum, and polyarthralgia may be seen. A majority of patients present with chronic respiratory symptoms in addition to constitutional symptoms.[2][3]

The exact pathophysiology of sarcoidosis has not been fully elucidated yet but it is a widespread belief that immunologic reactions against novel antigens in genetically susceptible individuals are not uncommon.[4] The antigens are phagocytosed by macrophages and are presented to CD+ T helper cells. Thereby, the secretion of interferon-γ (INF-γ) and interleukin-2 (IL-2) leads to the activation of type-1 T-helper cells (Th1). These cells play a critical role in mediating the immune response by augmenting the production of inflammatory cytokines.[5] The major histocompatibility gene complex (MHC) encodes the human leukocyte antigen (HLA) system, which is associated with sarcoidosis.[6] Furthermore, the CD4+ T-cell response is linked to the HLA genes and cardiac involvement in the disease.[7] When granulomas begin to form as a consequence of the immunological response, those granulomas that are located in the heart may progress to scar formation, which ultimately leads to fibrosis.[5]

On reviewing the histopathology, the classic presentation of cardiac sarcoidosis (CS) may show non-caseating granulomas.[8] There is often multifocal involvement with CS, which can progress from edema to inflammation, and fibrosis. However, the most commonly involved site is the left ventricle in the interventricular septum and the papillary muscles.[9] Once CS progresses, it may eventually lead to increased granulomas with macrophages, that have a lymphocyte predominance. This may be correlated to worsened patient outcomes. It is pertinent to note that pulmonary manifestation of sarcoidosis is seen in around 90% of patients, with CS occurring as a rare anomaly, with an estimated prevalence of 5-10%.[10] Due to the insidious presentation of sarcoidosis, it is imperative to monitor patients that present with CS-like manifestations which include (i) heart failure manifesting as orthopnea and dyspnea or with presentations of (ii) coronary vasculitis including myocardial infarction and angina.[11]

The aims and objectives of this systematic review are to perform a synthesis of prevalence studies comprising patients with CS, that present with comorbidities and report cardiovascular outcomes. The current data from this study will add to the scarce literature addressing clinical and prognostic outcomes of CS.

METHODS

Following the PRISMA Statement 2020 guidelines, original studies including clinical trials, cohorts, and case series that comprised patients reporting cardiac sarcoidosis were included.[12] The studies were required to report the prevalence of CS among the included population, gender (male/female), and comorbidities including diabetes mellitus, hypertension, and ischemic heart disease. The data were systematically entered into a preplanned spreadsheet by all authors as the following: *i)* author, year, *ii)* study type, *iii)* patients with sarcoidosis, *iv)* age in years, *v)* gender (male), *vi)* comorbidities (diabetes mellitus, hypertension, ischemic heart disease), *vii)* mortality, *viii)* heart failure and *ix)* ventricular tachycardia. The patients were adults (aged >18 years), of any gender, and were diagnosed with cardiac sarcoidosis defined *as the rare inflammatory condition where immune cells form granulomas in different areas of the heart that can lead to manifestations such as ventricular arrhythmias, heart failure, and death.*[13] Case reports, letters, and reviews were excluded in this review; non-English studies were excluded as well.

Three databases were searched including PubMed, Embase, and Cochrane Central from inception until June 15, 2022. A manual search of the reference lists was additionally conducted to locate any omitted studies (umbrella). The following search terms were utilized across the databases: "Cardiac, Sarcoidosis, Heart, Arrhythmia, Mortality, Heart Failure." No date restrictions were applied.

All authors reviewed the titles and abstracts of the studies during the screening phase. During the full-text reviewal phase, the first three authors assessed the studies independently with a fourth author present for any disagreements. All studies were stored in EndNote X9 (Clarivate Analytics) – a bibliographic management tool. The methodology was quantitative analytical where the proportion of patients presenting with the various symptoms was computed for numerical values. Statistical Package for Social Sciences (SPSS v.23) was used for all statistical analyses.

RESULTS

In total, 1,284 studies were identified from all databases. Of these 127 were duplicates and were thereby removed for further processing. During the screening phase, a total of 1,157 studies were screened of which 1,116 were excluded. 41 full-text studies were retrieved and sought for eligibility. Of these 35 studies were removed as they did not meet the inclusion criteria; in the inclusion phase, a total of 6 studies were added (**Figure 1**).

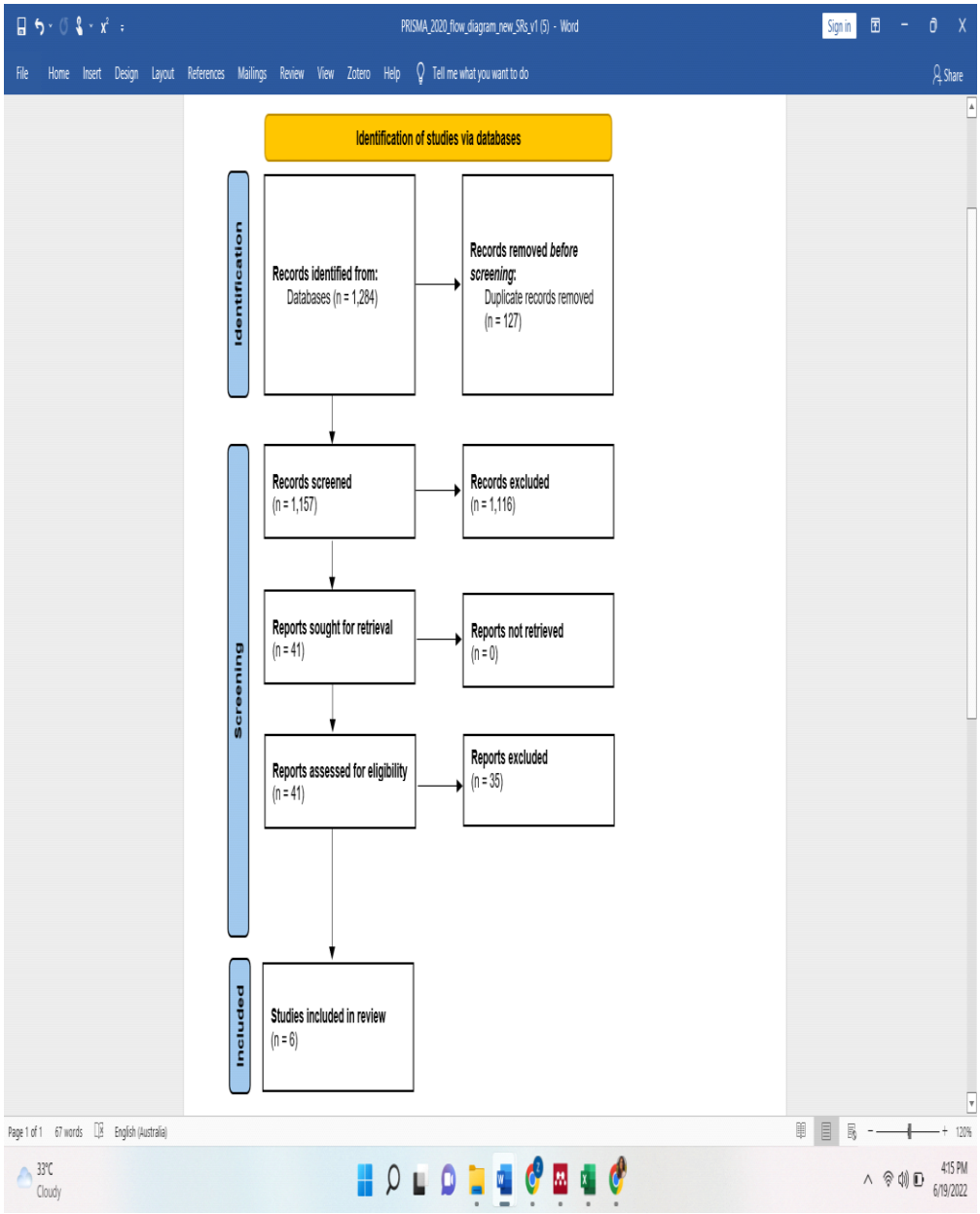

Figure 1. PRISMA Flowchart Depicting Study Selection Process.

Etinger and colleagues' (2021)[14] retrospective cohort study pooled a total of 23,849 patients of which 3,993 (16.74%) had CS. The mean age of CS patients was 56 years (SD=15.2), whereas 35.3% of them were male. Hypertension was reported in 50.7% of CS patients (P<0.001). Reported outcomes included 17.8% of people with mortality (P<0.001) and 10.9% with heart failure (P<0.001).[14] Salama et al.'s (2020)[15] national inpatient sample database cohort study pooled a total of 18,013,878 patients of which 46,289 had CS with a mean age of 58.2 years (SD=13.6). Of these, 35.8% were males. Reported comorbidities included diabetes mellitus (31.6%, P<0.001), hypertension (65.2%, P<0.001), and ischemic heart disease (3.4%, P<0.001). Outcomes included 24.9% CS patients with heart failure (P<0.001), and 2.3% with ventricular tachycardia (P<0.001).[15] Philips et al. (2014)[16], in their prospective cohort study, pooled 57 patients of which 15 had CS. The mean age was 44.3 years (SD=1.2), and 80% were males; reported comorbidities included ischemic heart disease (33.3%) (P<0.001) and hypertension (40%) (P=0.003). 33% patients had heart failure (P<0.05) and 33% had ventricular tachycardia (P<0.05).[16] A case-control study by Zeron and colleagues[17] pooled 436 patients of which 50% had CS, with a mean age of 47.1 years (SD=15.9%). On noting comorbidities, 14.7% had diabetes mellitus (P=0.014). Mortality was reported in 12.8% of the patients (P<0.001).[17] National inpatient sample cohort study by Ungprasert et al., 2019[18] pooled 156,110 patients of which 50% had CS, with a mean age of 58.6 years. Mortality was reported in 2.1% of patients (P=0.32) and heart failure was reported in 23.18% of the patients (P=0.02).[18] Nordenswan et al. (2021)[19], in their nationwide cohort study, pooled 379 patients of which 92.6% had CS. The mean age of patients was 51 years with 29.3% of them being males. On noting

comorbidities, 10% had diabetes mellitus (P=0.755), 22% had hypertension (P=1), and 3% had ischemic heart disease (P=1). Heart failure was reported in 15% of patients (P<0.001) and ventricular tachycardia was reported in 13% of participants (P=0.557).[19] The characteristics of included studies are listed in Table 1.

In summary, a total of 6 studies were included. The studies pooled in a total of 18,194,709 patients of which 128,921 (0.71%) had CS. The reported comorbidities included *i)* diabetes mellitus, where 14,758 (31.1%) CS patients of 47,427 reported it; *ii)* hypertension where 32,287 (63.8%) CS patients of 50,648 reported it; *iii)* ischemic heart disease where 1,565 CS patients of 46,655 (3.4%) reported past occurrence. Reported outcomes were *i)* mortality, where 2,398 (2.9%) of 82,266 CS patients died, *ii)* heart failure, where 30,096 (23.4%) of 128,703 reported heart failure outcomes due to CS, and *iii)* ventricular tachycardia where 1,111 (2.4%) of 46,655 CS patients reported outcomes.

DISCUSSION

In this systematic review, we included a total of 128, 921 patients with CS. The most commonly reported comorbidity among the patients was hypertension (63.8%), followed by diabetes mellitus (31.1%) and ischemic heart disease (3.4%). On noting the reported outcomes, around one-fourth of the patients presented with heart failure (23.4%), whereas mortality (2.9%) and ventricular tachycardia (2.4%) were additional adverse outcomes reported in the patient group.

Current literature suggests that the etiology of CS is unknown, but that the inciting event ends in granuloma formation, which either resolves or progresses to fibrosis.[3] There are three major events, including the initial exposure to an antigen; secondly, acquired cellular immunity using antigen-presenting cells and T lymphocytes, and lastly, the immune effector cells that lead to non-specific inflammatory responses.[3] The characteristic lesion of sarcoidosis is compact, discrete, noncaseating epithelioid cell granuloma. The granuloma comprises many differentiated lymphocytes and phagocytes.[20] Environmental and infectious agents have been implicated as potential antigens, which primarily trigger helper inducer T cells leading to the formation of granuloma lesions. In the early phase of the disease, sarcoid infiltrates consist of CD4 positive T cells, T helper type 1 responses, and mononuclear phagocytes.[3] In the later phase, the cytokine profile shifts to a T helper type 2 response that has inflammatory effects resulting in tissue scarring.[3] Moreover, high concentrations of interleukin 6 are present in the circulation after disease onset and before treatment; however immunosuppressive therapy reduces the concentration. IL-6 is central in maintaining inflammation and induces the proliferation of T cells.[3]

CS is common and occurs in over 20% of patients with systemic sarcoidosis, however, the true prevalence remains unknown.[21][22] It is likely underestimated since many individuals with CS present with either subclinical disease or nonspecific symptoms. Moreover, around 25% of CS cases are isolated – without extracardiac involvement – and therefore the absence of extracardiac sarcoidosis does not fully exclude CS.[22] The clinical presentation spans from incidentally discovered CS to syncope, heart failure, and sudden death.[23] Patients who have extracardiac sarcoidosis and who lack one or more of the signs and symptoms of CS that serve as indications for advanced treatment may or may not benefit from further immediate evaluation.[9] However, serial (i.e., annual) cardiac examinations and electrocardiograms are currently recommended to detect the development of CS.[24] To diagnose CS, clinicians require appropriate suspicious and integrated pathological/clinical data with results of advanced cardiac imaging. The diagnostic certainty ranges from definite to probable (>50%).[25] In patients with extracardiac sarcoidosis, the characteristics of cardiac magnetic resonance imaging (CMR) or 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) are utilized to establish the diagnosis of CS.[26] In most cases, an endomyocardial biopsy is often not required. However, in the absence of biopsy-proven disease or when the acquired data is inconclusive, integrated data from FDP-PET and CMR imaging are useful in establishing the occurrence of CS.[26]

When considering the prognosis and outcomes of CS, these currently require further deliberation for immediate and long-term follow-ups. For instance, a cohort of 157 patients with CS that had a median follow-up of 7 years ascertained that the 10-year survival rate of CS was 90%.[27] Baseline factors that are associated with mortality include older age, abnormal pulmonary function tests, high degree atrioventricular block, and a below 40% left ventricular ejection fraction.[27] Baseline factors that are associated with cardiac relapse consist of left heart failure, wall motion abnormalities, and kidney involvement.[27]

Sarcoidosis can be widespread or limited to the involvement of only a single system at a time.[28] Many asymptomatic cases may be discovered by chest radiography which may or may not progress to clinically symptomatic disease. However, the clinical manifestations of sarcoidosis depend on the location and profusion of granulomas. CS is associated with noncaseating granulomas that can involve many heart structures such as the right/left atrium, right ventricle, left ventricular free wall, basal ventricular septum, and papillary muscles.[29] The pathologic features are divided into three histological stages: edema, granulomatous infiltration, and fibrosis that leads to post-inflammatory scarring. The pathological samples of the myocardium involved with CS reveal numerous lymphocytes located at the border of granulomas.[29] A dense band of collagen fibers, fibroblasts, and proteoglycans tend to encase this aggregate of inflammatory cells.[29]

When considering the first line of treatment for CS, corticosteroids are commonly utilized. Management of patients with probable or definite CS consists of monitoring and managing underlying cardiovascular risk factors, imploring heart failure therapy, managing asymptomatic valvular dysfunction, administering immunosuppressive therapies, managing arrhythmias and possibly opting for device therapy (i.e., a pacemaker or implantable cardioverter-defibrillator (ICD)).[30] A meta-analysis that combined results from 10 original studies ascertained prednisone (20-60 mg/day) is effective for CS – another trial that used methylprednisolone (10-15 mg/kg/day for 3 days) noted efficacy for CS.[31] In a Japanese cohort study, a higher dose of prednisone (54 mg/day) did not lead to better survival.[32] Notably, the combination of corticosteroids with other immunosuppressive agents may be an essential combination to improve outcomes. Moreover, tumor necrosis factor antagonists (adalimumab and infliximab) are viable options for refractory sarcoidosis. A randomized controlled trial employing infliximab for patients that had refractory sarcoidosis showed improvement in extrapulmonary disease as well.[33] Moreover, ongoing clinical trials registered with clinicaltrials.gov seek to explore viable therapies for CS. Interleukin-1, which is the prototypical pro-inflammatory cytokine is involved in virtually every acute process, however, the drug has never been evaluated as a potential therapeutic for CS.[34] An ongoing phase 2 trial employs Anakinra in a randomized clinical trial setting.[34] Another phase 3 intervention, a randomized clinical trial seeks to assess whether low dose Prednisone in combination with Methotrexate is as effective as standard dose Prednisone, and seeks to assess outcomes on quality of life and toxicity.[35] Another randomized, placebo-controlled open-label cohort in phase 2 randomized patients with CS to receive namilumab or placebo every 4 weeks for 30 weeks post the initial dosing period.[36] The trial also requires the continuation of background therapy without any change to oral corticosteroid intake or immunosuppressive therapy.[36]

A permanent pacemaker is also valuable for high-degree atrioventricular blocks even in cases where immunosuppression reversed the heart block to reduce the risk of future events. If there is an indication for pacemaker implantation, an implantable cardiac defibrillator (ICD) and a pacemaker both ought to be considered.[37] The ICD devices are either single, two, or three leads that are capable of cardiac resynchronization therapy.[38] For end-stage CS, heart transplantation is a viable strategy. Heart transplantation has been performed in 10% of 110 patients with CS in a study from Finland with a median follow-up of 6.5 years.[9] In this follow-up period, 10 patients died of cardiac causes, 11 patients underwent transplantation, and another 11 patients suffered an aborted sudden cardiac death. Heart failure at presentation predicted a poor outcome with a 10-year transplantation-free cardiac survival of only 53%.[9]

Table 1: Characteristics of included studies.

Sr. No.	Author, Year	Study Type	Patients with Sarcoidosis	Age in Years	Gender (Male)	Comorbidities (DM, HTN, IHD)	Mortality	Heart Failure	Ventricular Tachycardia	Authors' Takeaway
1	Etinger et al., 2021[14]	Retrospective Cohort Study	3,993 (16.74%) out of 23,849	56 (SD=15.2)	1,411 (35.3%)	HTN=2,026 (50.7%); (P<0.001)	710 (17.8%); P<0.001	434 (10.9%); P<0.001	NA	Sarcoidosis was independently associated with heart failure, and both of the factors were associated with mortality
2	Salama et al., 2020[15]	National Inpatient Sample Database, Cohort Study	46,289 (0.26%) out of 18,013,878	58.2 (SD=13.6)	16,556 (35.8%)	DM=14,626 (31.6%); P<0.001; HTN=30179 (65.2%); P<0.001; IHD=1551 (3.4%); P<0.001	NA	11,510 (24.9%); P<0.001	1,059 (2.3%); P<0.001	Sarcoidosis was linked to increased prevalence rates of ventricular tachyarrhythmia, which can impact disease morbidity and mortality
3	Philips et al., 2014[16]	Prospective Cohort Study	15 (26.32%) out of 57	44.3 (SD=1.2)	12 (80%)	IHD=5 (33.3%); P<0.001; HTN=6 (40%); P=0.003	NA	5 (33%); P<0.05	5 (33%); P<0.05	Patients of older age, with associated cardiovascular comorbidities, and ventricular conduction abnormalities should raise the suspicion of cardiac

										sarcoidosis
4	Zeron et al., 2018[17]	Case-Control Study	218 (50%) out of 436	47.1 (SD=15.9)	76 (35%)	DM=32 (14.7%); P=0.014	23 (12.8%); P<0.001	NA	NA	Higher rates of comorbidities were found in patients with sarcoidosis; these included hepatic, respiratory, autoimmune, and neoplastic in origin
5	Ungprasert et al., 2019[18]	Nationwide Inpatient Sample, Cohort Study	78,055 (50%) out of 156,110	58.6	28,646 (36.7%)	NA	1665 (2.1%); P=0.32	18,093 (23.18%); P=0.02	NA	Patients hospitalized with sarcoidosis were associated with significantly higher risks of several cardiac comorbidities including conduction abnormalities, cardiomyopathy, and atrial fibrillation
6	Nordenswan et al., 2021[19]	Nationwide Cohort Study	351 (92.6%) out of 379	51	103 (29.3%)	DM=34 (10%); P=0.755; HTN=76 (22%); P=1; IHD=9 (3%); P=1	NA	54 (15%); P<0.001	47 (13%); P=0.557	Overall, cardiac sarcoidosis presented with less extensive myocardial injury as compared to other conditions such as giant cell myocarditis in the cohort; the key prognostic indicator was the extent of myocardial injury and not the histopathologic diagnosis

CONCLUSION

Cardiac sarcoidosis is a rare entity and occurs in around 5-10% of all sarcoidosis cases. When isolated to the heart only, it is associated with conduction anomalies, arrhythmias, heart failure, and mortality. Since the etiology is believed to stem from an infection or environmental contributors, it is imperative to note contributing factors such as comorbidities that may lead to adverse outcomes. In patients with a high index of suspicion of cardiac sarcoidosis, the clinical symptoms at onset ought to be noted and diagnostic testing such as cardiovascular magnetic resonance imaging and positron emission tomography ought to be utilized. In addition to clinical presentation, comorbidities and treatments such as immunosuppressive therapies in combination with corticosteroids play a vital role in predicting immediate outcomes. Future studies are needed to assess factors contributing to cardiac sarcoidosis, treatment advancements, and prognosis for CS patients.

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