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ORIGINAL RESEARCH

Heart Failure, Atrioventricular Block, and Ventricular Tachycardia in Sarcoidosis

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BACKGROUND: Sarcoidosis is a granulomatous disease usually affecting the lungs, although cardiac morbidity may be common. The risk of these outcomes and the characteristics that predict them remain largely unknown. This study investigates the epidemiology of heart failure, atrioventricular block, and ventricular tachycardia among patients with and without sarcoidosis.

METHODS AND RESULTS: We identified California residents aged ≥21 years using the Office of Statewide Health Planning and Development ambulatory surgery, emergency, or inpatient databases from 2005 to 2015. The risk of sarcoidosis on incident heart failure, atrioventricular block, and ventricular tachycardia were each determined. Linkage to the Social Security Death Index was used to ascertain overall mortality. Among 22 527 964 California residents, 19 762 patients with sarcoidosis (0.09%) were identified. Sarcoidosis was the strongest predictor of heart failure (hazard ratio [HR], 11.2; 95% CI, 10.7–11.7), atrioventricular block (HR, 117.7; 95% CI, 103.3–134.0), and ventricular tachycardia (HR, 26.1; 95% CI, 24.2–28.1) identified among all risk factors. The presence of any cardiac involvement best predicted each outcome. Approximately 22% (95% CI, 18%–26%) of the relationship between sarcoidosis and increased mortality was explained by the presence of at least 1 of these cardiovascular outcomes.

CONCLUSIONS: The magnitude of risk associated with sarcoidosis as a predictor of heart failure, atrioventricular block, and ventricular tachycardia, exceeds all established risk factors. Surveillance for and anticipation of these outcomes among patients with sarcoidosis is indicated, and consideration of a sarcoidosis diagnosis may be prudent among patients with heart failure, atrioventricular block, or ventricular tachycardia.

Key Words: atrioventricular block ■ cardiac sarcoidosis ■ cardiomyopathy ■ sarcoidosis ■ ventricular tachycardia

Sarcoidosis is a multisystem granulomatous disease that primarily affects the lungs, although cardiac involvement is common, morbid, and underrecognized.[1–3] Improvements in diagnostic imaging and increased disease awareness have led to a marked increase in the incidence of cardiac sarcoidosis in recent years,[1] although diagnosis remains difficult because of the heterogeneous clinical manifestations of cardiac sarcoidosis, including heart failure (HF), high-grade atrioventricular block, and ventricular tachycardia (VT). Examinations of death certificates suggest that cardiac events may be the leading cause of mortality among those with the disease.[4]

Identification of patients with sarcoidosis at elevated risk of cardiac involvement is paramount to prevent the high morbidity associated with progressive myocardial infiltration, particularly because the initial evidence of cardiac involvement can be sudden cardiac death.[5] Investigation of risk factors for adverse cardiac manifestations in systemic sarcoidosis is often limited by small sample sizes, typically arising only from 1 tertiary medical center at a time, raising concerns about appropriate extrapolation to the general population.[6–8]

We therefore sought to leverage data from every inpatient, emergency department, and ambulatory surgical encounter in California coupled with

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CLINICAL PERSPECTIVE

What Is New?

- Sarcoidosis was the strongest identified predictor of heart failure, atrioventricular block, and ventricular tachycardia among all investigated risk factors in a large administrative data set of ambulatory surgery, emergency, or inpatient encounters from 2005 to 2015.
- Among those with sarcoidosis, each outcome was most strongly predicted by the presence of other cardiac pathology present in cardiac sarcoidosis, while conventional cardiovascular risk factors strongly predicted each outcome among those without sarcoidosis.
- Over 20% of the heightened risk of death among those with sarcoidosis was explained by the presence of at least 1 of these cardiac outcomes.

What Are the Clinical Implications?

- These findings highlight the importance of considering a sarcoidosis evaluation when an individual presents with unexplained heart failure, atrioventricular block, or ventricular tachycardia.
- Careful surveillance and anticipation of these potentially avoidable complications is critical in patients with sarcoidosis.

Nonstandard Abbreviations and Acronyms

OSHP	DOffice of Statewide Health Planning and Development

ascertainment of mortality using the Social Security Death Index to investigate the epidemiology of HF, atrioventricular block, and VT among patients with sarcoidosis.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. This community-based prospective cohort study investigated sarcoidosis as a risk factor for HF, atrioventricular block, VT, and death among all California residents ≥21 years of age who received care in a California ambulatory surgery unit, emergency department, or inpatient hospital unit between January 1, 2005, and June 30, 2015, using the Office of Statewide Health Planning and Development (OSHPD) California State Ambulatory Surgery Databases, Emergency Department Databases, and State Inpatient Databases. The individual OSHPD databases specific to healthcare setting and calendar year were merged using an encrypted unique patient identifier to capture repeated visits for a given patient. Outpatient death was ascertained by linking each subject to the Social Security Death Index until December 31, 2013, the last available date in our data set, and inpatient deaths were identified in the OSHPD database. Patients were not involved in the design or conduct of this research.

Follow-up began at the first healthcare encounter for each participant and ended at incident diagnosis of the given outcome of interest (HF, atrioventricular block, VT, and death in separate analyses) or at the end of follow-up. Last available follow-up date for mortality-related analyses was December 31, 2013; last available follow-up for all other outcomes was June 30, 2015. Patients with residence outside of California or with missing visit date information were excluded, as well as subjects with prevalent HF, atrioventricular block, or VT in respective analyses (defined as carrying the diagnosis at the first recorded encounter).

We recorded demographic data, including age, sex, race, and income at each healthcare encounter. Race and Hispanic ethnicity are reported separately in OSHPD, and race was coded as either White or "other" for the vast majority of individuals with Hispanic ethnicity. Therefore, those with Hispanic ethnicity were treated as a distinct group that superseded the coded race. Income level was categorized using the median household income for the patient's zip code; observations with missing data had the value carried forward from the most recent encounter, and those patients without any income data over the study period were excluded. Up to 29 *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes and 17 Current Procedural Terminology codes were provided for each encounter. The specific codes used for covariates and each outcome variable are described in Table S1.

If sarcoidosis was present at any time, the patient was considered to have sarcoidosis for the entirety of follow-up. Heart failure was considered present whether it was initially coded as acute or chronic, and systolic or diastolic. Atrioventricular block was defined as a diagnosis of Mobitz II second-degree atrioventricular block or third-degree atrioventricular block. The VT outcome was defined as sustained VT or ventricular fibrillation. Dichotomous medical comorbidities were accumulated at each healthcare encounter and carried forward over time.

Statistical Analysis

Continuous variables with a normal distribution are presented as mean±SD and compared using Student *t* tests. Non–normally distributed continuous variables

Table. Characteristics of Patients With Sarcoidosis Stratified by the Presence or Absence of Incident HF, Atrioventricular Block, or VT

	HF			Atrioventricular Block			VT		
	Sarcoidosis With Incident HF (n=629)	Sarcoidosis Without Incident HF (n=16 850)	*P* Value	Sarcoidosis With Incident Atrioventricular Block (n=58)	Sarcoidosis Without Incident atrioventricular Block (n=19 221)	*P* Value	Sarcoidosis With Incident VT (n=152)	Sarcoidosis Without Incident VT (n=19 022)	*P* Value
Age, mean years ± SD	65.1±14.0	57.6±13.3	<0.01	65.2±14.3	58.5±13.6	<0.01	62.4±13.1	58.5±13.6	<0.01
Female	387 (62%)	10 853 (64%)	0.14	31 (53%)	12 291 (64%)	0.10	88 (58%)	12 195 (64%)	0.11
Race/Ethnicity			0.01			0.06			0.07
White	327 (52%)	8803 (52%)		32 (55%)	9961 (52%)		70 (46%)	9873 (52%)	
Black	236 (38%)	5550 (33%)		16 (28%)	6483 (34%)		67 (44%)	6372 (34%)	
Asian or Pacific Islander	<15	545 (3)		<15	614 (3)		<15	618 (3)	
Hispanic	37 (6)	1489 (9)		<15	1611 (12)		<15	1643 (9)	
Other	16 (3)	463 (3)		<15	512 (3)		<15	516 (3)	
Hypertension	413 (66)	7886 (47)	<0.01	36 (62)	9492 (49)	0.05	102 (67)	9372 (49)	<0.01
Diabetes mellitus	262 (42)	4101 (24)	<0.01	16 (28)	5112 (27)	0.86	46 (30)	5040 (27)	0.29
Coronary artery disease	212 (34)	1364 (8)	<0.01	<15	2171 (11)	<0.01	60 (39)	2088 (11)	<0.01
Obesity	117 (19)	2346 (14)	<0.01	<15	2766 (14)	0.61	22 (14)	2737 (14)	0.98
HF	…	…		36 (62)	2100 (11)	<0.01	84 (55)	1984 (10)	<0.01
High-degree atrioventricular block	24 (4	55 (0.3%)	<0.01	…	…		<15	102 (1)	<0.01
VT	46 (7)	117 (1)	<0.01	<15	88 (0.5)	<0.01	…	…	
Median household income	$62 845 ($23 349)	$65 432 ($25 700)	0.01	$66 364 ($19 519)	$64 958 ($25 529)	0.68	$64 865 ($27 326)	$64 977 ($25 457)	0.96
Alcohol dependence	<15	250 (1)	0.45	<15	291 (2)	0.90	<15	287 (2)	0.26
Tobacco use	130 (21)	2902 (17)	0.03	<15	3379 (18)	0.27	22 (14)	3350 (18)	0.31

Values are n (%) or mean±SD. In accordance with the regulations governing use of deidentified Office of Statewide Health Planning and Development data, no details regarding cells of <15 patients are allowed. HF indicates heart failure; and VT, ventricular tachycardia.

are presented as medians with interquartile ranges and compared using the Wilcoxon rank-sum test. Categorical variables were compared using the chi-square test. Adjusted person-time incidence rates by sarcoidosis for HF, atrioventricular block, VT, and death were estimated and compared using Poisson models with log follow-up time as an offset. Adjusted cumulative incidence curves by sarcoidosis status were estimated by the complement of the survival functions obtained from a Cox model for each outcome after stratifying by sarcoidosis status and adjusting for the selected covariates centered on their sample-wide means, so that both curves represent a comparable, typical patient in each group. The associations of sarcoidosis with HF, atrioventricular block, and VT were estimated using Cox models, first unadjusted, then adjusted for all covariates, with $P<0.01$ in single predictor Cox models. In these models, we included baseline demographic characteristics and modeled medical comorbidities as time-dependent covariates. Log-log survival plots were created for each model, which were widely separated and essentially parallel in those with and without sarcoidosis in each plot. Finally, we performed separate tests for interaction by each one of several covariates identified a priori as potential effect modifiers of the relationship between sarcoidosis and each outcome using the fully adjusted Cox proportional hazards models.

To ease interpretation of these results, race was dichotomized as White versus non-White, and age was dichotomized as <60 years of age or ≥60 years of age. Sensitivity analyses were performed for the atrioventricular block and VT outcomes, excluding those with a pacemaker or implantable cardioverted defibrillator before or during the study period. For mediation analyses, we repeated analyses using pooled logistic regression instead of Cox models, and we calculated the "proportion of effect explained" as the percentage reduction in the adjusted pooled logistic regression coefficient after additional adjustment for either HF, atrioventricular block, or VT, with a 95% CI obtained using seemingly unrelated regressions.[9]

Analyses were performed using Stata version 14 (StataCorp, College Station, TX) and SAS 9.4 (SAS Institute, Cary, NC). A 2-tailed $P<0.05$ was considered statistically significant.

This study was approved by the University of California, San Francisco Institutional Review Board (number 17-23686). In accord with regulations governing use of OSHPD data, no details for cells of <15 patients are reported.

RESULTS

After application of our exclusion criteria, 22 381 964 total patients were included in our analyses (Figure S1). Of these, 19 762 (0.09%) had a diagnosis of sarcoidosis. The number of outpatient surgery encounters, emergency department encounters, and hospitalizations among those with and without sarcoidosis are described in Table S2. Patient follow-up is described in Table S3, and a description of cardiac device implantation among subjects is described in Table S4. Characteristics of patients with sarcoidosis who did and did not develop HF, atrioventricular block, and VT are shown in Table.

Heart Failure

The incidence rate of HF was 240 per 1000 patient-years in patients with sarcoidosis and 12 per 1000 patient-years in those without sarcoidosis ($P<0.001$). After adjusting for age, sex, race/ethnicity, hypertension, diabetes mellitus, coronary heart disease, obesity, atrioventricular block, VT, alcohol abuse, tobacco use, and income, those with sarcoidosis had a substantially higher risk of developing HF than the rest of the population (Figure 1). After adjustment for those same covariates, sarcoidosis exhibited the highest relative risk of HF (hazard ratio [HR], 11.2; 95% CI, 10.7–11.7) of any established risk factor for the disease that was measurable in this data set (Figure 2). Atrioventricular block and VT were the strongest predictors of incident HF in those with sarcoidosis, while conventional cardiovascular risk factors exhibited the highest HRs in those without sarcoidosis (Figure 3).

Atrioventricular Block

The incidence of atrioventricular block was 229 per 1000 person-years in those with sarcoidosis versus 1 per 1000 person-years in those without sarcoidosis ($P<0.001$). After adjusting for age, sex, race/ethnicity, hypertension, diabetes mellitus, coronary heart disease, HF, VT, obesity, income, alcohol abuse, and tobacco use, those with sarcoidosis exhibited a substantially increased risk of atrioventricular block (Figure 1). Sarcoidosis was associated with a stronger relative risk for atrioventricular block (HR, 117.7; 95% CI, 103.3–134.0) than any other measured covariate (Figure 2). Among those with sarcoidosis in the atrioventricular block cohort, 22 (2.1%) received a pacemaker, and 62 (6.0%) received an implantable cardioverter defibrillator during study follow-up. Sensitivity analyses excluded 129 individuals with a cardiac device implanted before or during the study period demonstrated a similarly elevated risk of atrioventricular block among those with sarcoid (HR, 99.45; 95% CI, 84.86–116.55). After multivariable adjustment, those with HF and VT exhibited the highest relative risk of atrioventricular block among those

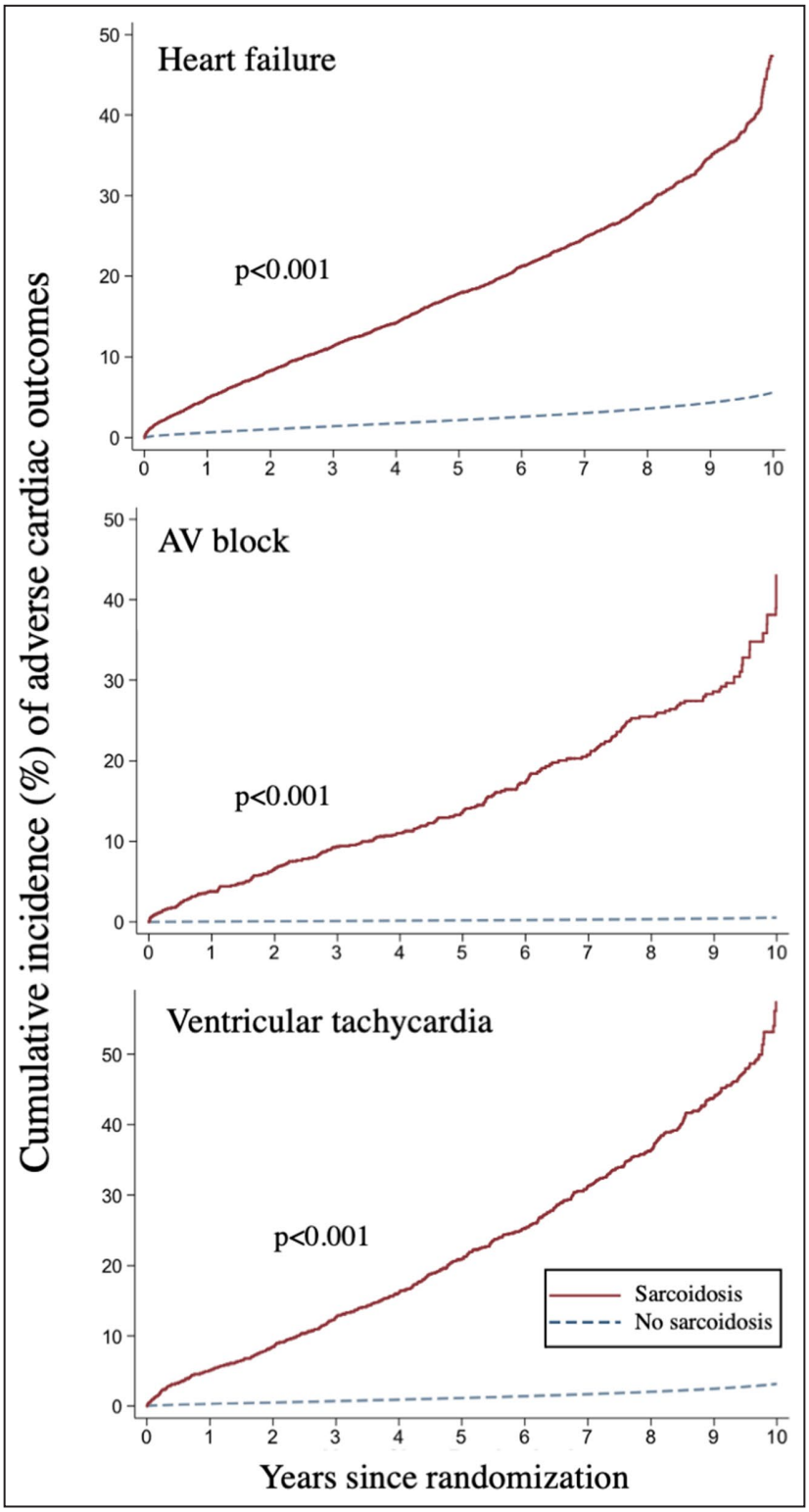

Figure 1. Cumulative incidence of heart failure, atrioventricular block, and ventricular tachycardia stratified by the presence or absence of sarcoidosis. Each curve was generated under a proportional hazards assumption, and was adjusted for age, sex, race/ethnicity, hypertension, diabetes mellitus (in the heart failure model), coronary artery disease, obesity (in the heart failure model), heart failure (in the atrioventricular block and ventricular tachycardia models), atrioventricular block (in the heart failure and ventricular tachycardia models), and ventricular tachycardia (in the heart failure and atrioventricular block models), income (in the heart failure model), and tobacco use (in the heart failure model).

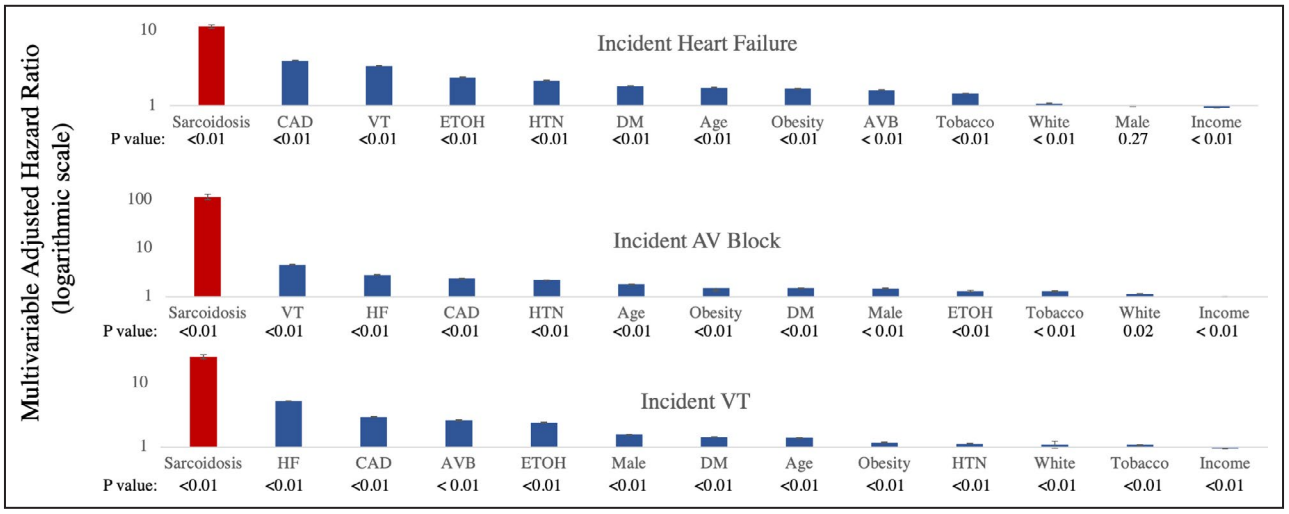

Figure 2. Association of sarcoidosis and other risk factors with incident heart failure, atrioventricular block, and ventricular tachycardia.

Age is dichotomized to ≥60 years vs <60 years. White race was used as a comparison group to all other races/ethnicities combined. Income was analyzed in $10 000 increments. Hazard ratios are presented on a logarithmic scale. Y error bars denote 95% CIs. AVB indicates atrioventricular block; CAD, coronary artery disease; DM, diabetes mellitus; ETOH, history of alcohol abuse; HF, heart failure; HTN, hypertension; and VT, ventricular tachycardia.

with sarcoidosis, while conventional cardiovascular risk factors were associated with the highest risk of atrioventricular block in those without sarcoidosis (Figure 3).

Ventricular Tachycardia

The rate of VT among those with sarcoidosis was 225 per 1000 patient-years compared with 4 per 1000 patient-years in those without sarcoidosis (P<0.001). After adjusting for age, sex, race/ethnicity, hypertension, diabetes mellitus, coronary heart disease, obesity, HF, atrioventricular block, income, alcohol abuse, and tobacco use, patients with sarcoidosis experienced a significantly increased risk of VT (Figure 1), and sarcoidosis was found to be the most potent predictor of VT (HR, 26.1; 95% CI, 24.2–28.1) among all covariates examined (Figure 2). Among those with sarcoidosis in the VT cohort, 10 (0.2%) received a pacemaker, and 470 (10.1%) received an implantable cardioverter defibrillator during study follow-up. Sensitivity analyses excluding 203 subjects with cardiac devices implanted before or during the study period demonstrated a similar risk of VT among patients with sarcoidosis (HR, 26.49; 95% CI, 22.83–30.72; P<0.001). After multivariable adjustment, HF and atrioventricular block were the most important risk factors for VT among those with sarcoidosis, while again conventional cardiovascular risk factors were associated with risk of VT among those without sarcoidosis (Figure 3).

Death and Heart Transplantation

Of the 21 710 858 individuals with follow-up until the end of 2013 (last date of available Social Security Death Index data for this cohort), 575 436 (2.7%) died. The rate of death among those with sarcoidosis was 19 per 1000 patient-years compared with 7 per 1000 person-years in those without sarcoidosis (P<0.001). After adjustment for potential confounders, those with sarcoidosis demonstrated a 2.29 times (95% CI, 2.14–2.46) increased risk of death compared with those without sarcoidosis (P<0.001). In mediation analysis, attenuation of that heightened mortality risk after adjustment for HF, atrioventricular block, and VT suggested that 22% (95 CI, 18%–26%) of the increased risk for death among patients with sarcoidosis was explained by the presence of at least 1 of those 3 cardiovascular conditions.

During the study period, heart transplantation was performed in 57 (0.29%) subjects with sarcoidosis and 5110 (0.02%) subjects without sarcoidosis. After adjusting for age, sex, race/ethnicity, hypertension, diabetes mellitus, coronary heart disease, obesity, heart failure, atrioventricular block, VT, income, alcohol abuse, and tobacco use, sarcoidosis was a stronger relative risk factor for heart transplantation (HR, 14.94; 95% CI, 7.09–31.48; P<0.001) than other examined covariates, exceeding the relative risk of HF (HR, 3.83; 95% CI, 3.31–4.41; P<0.001). Among those who developed HF during the study period, those with sarcoidosis (HR, 5.10; 95% CI, 3.90–6.68) were at greater risk of requiring heart transplantation compared with those without sarcoidosis.

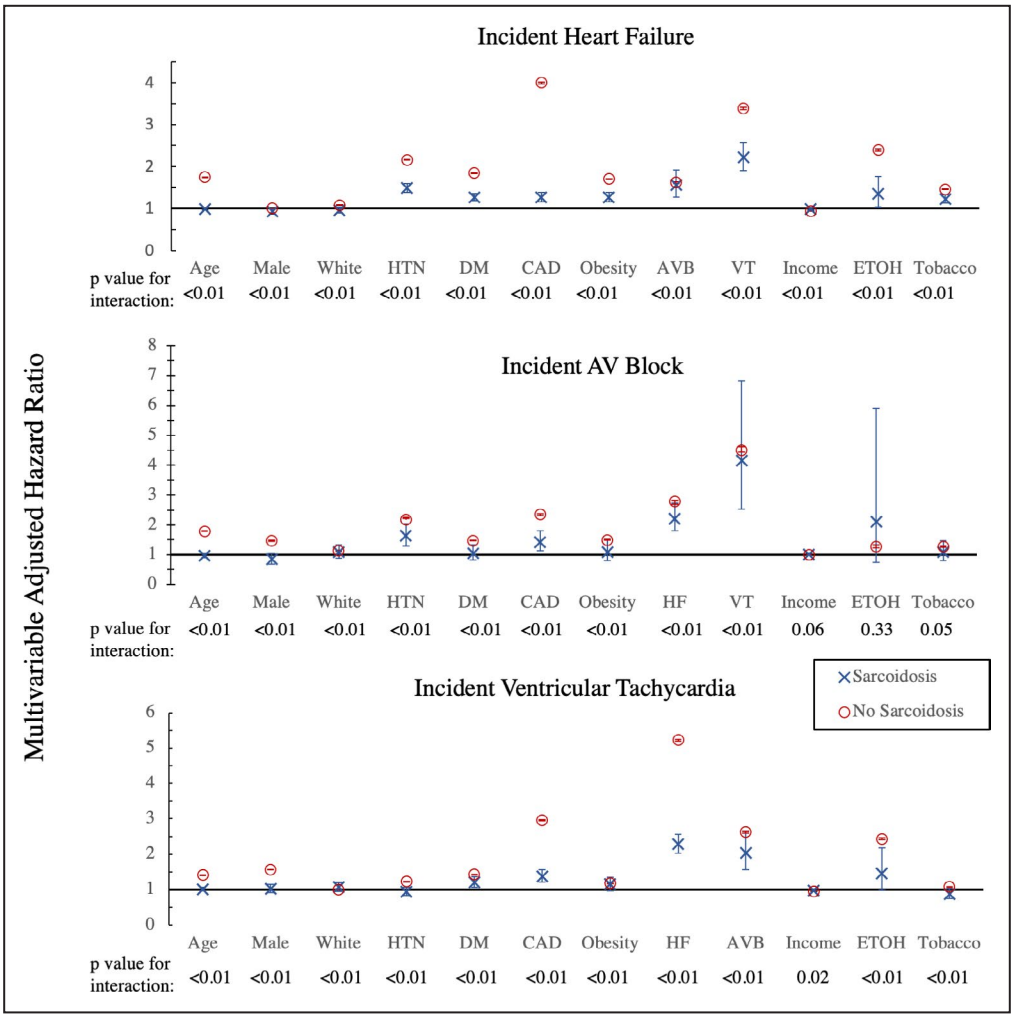

Figure 3. Multivariable adjusted hazard ratios for predictors of incident heart failure, atrioventricular block, and ventricular tachycardia among patients with and without sarcoidosis. Age was dichotomized to ≥60 years vs <60 years. White race was used a as a comparison group to all other races/ethnicities combined. Income was analyzed in $10 000 increments. Y error bars denote 95% CIs. CIs in subjects with no sarcoidosis were narrow and may be contained entirely within the marker. AVB indicates atrioventricular block; CAD, coronary artery disease; DM, diabetes mellitus; ETOH, history of alcohol abuse; HF, heart failure; HTN, hypertension; and VT, ventricular tachycardia.

DISCUSSION

Sarcoidosis exhibited the strongest relative risk for HF, atrioventricular block, and VT than any other established risk factor in this administrative data set of nearly every California resident receiving care in a hospital, emergency room, or outpatient surgery center. Each of these outcomes was most strongly predicted by the presence of other cardiac pathology consistent with infiltrative sarcoidosis, while conventional cardiovascular risk factors were more powerful predictors of each outcome among those without sarcoidosis. Furthermore, over 20% of the heightened risk of death among patients with sarcoidosis was explained by the presence of at least 1 of these cardiac outcomes.

Sarcoidosis is a relatively rare disease, with a reported prevalence between 0.10% and 0.16% in the US population.[10,11] Growing evidence demonstrates that sarcoidosis frequently has an unrecognized causative role in the development of HF, atrioventricular block, and VT.[3,12] A previous analysis suggested that cardiovascular manifestations are responsible for about a third of all hospitalizations in those with the disease, but as repeated hospitalizations among the same individual could not be distinguished from individual hospitalizations for a given person in that analysis, it has previously been difficult to quantify the risk of these outcomes among the population.[11] Compared with the great majority of research on the subject that arises from single, and often tertiary, medical centers, our current population-based,

administrative data set–driven analysis includes a substantial number of patients with a sarcoidosis diagnosis.[6–8,13,14] By leveraging the complete populations of all those seeking inpatient-related care over more than a decade, we were able to study the relative importance of sarcoidosis as a risk factor itself compared with other conventional risk factors and illustrate relative differences in risks for these outcomes within the sarcoidosis population as well as compared with the general population.

The etiology of HF in sarcoidosis is likely multifactorial.[5] Direct cardiac involvement of sarcoidosis, such as with granulomatous infiltration of myocardium, can result in fibrosis and progressive systolic and diastolic dysfunction.[14] In the general population, HF is known to substantially reduce physical functioning and quality of life, is one of the most important causes of hospitalizations, and in severe cases can have a prognosis that is worse than many stage IV cancers.[15] Combined with previous literature, our findings highlight the particularly high risk for developing HF among those with sarcoidosis. Indeed, the relative risk of sarcoidosis outstripped other important HF risk factors, including coronary disease and hypertension. The most important risk factors for HF among those with sarcoidosis were atrioventricular block and VT, suggesting that the presence of either of these conditions should heighten suspicion for concurrent HF or the future development of HF.

Unlike with HF, there has traditionally been less of a focus on predicting atrioventricular block in the general population. No therapies other than pacemakers are available for this disease, although prompt immunosuppression can uniquely prevent and reverse atrioventricular block secondary to cardiac sarcoidosis.[16,17] Regardless, those with atrioventricular block and pacemakers exhibit significant reductions in both quality of life and longevity.[18] Sarcoidosis was a particularly strong risk factor for atrioventricular block, and once again other manifestations of cardiac sarcoidosis proved to be the most predictive of atrioventricular block in those with sarcoidosis. That atrioventricular block itself was also an especially important predictor of both HF and VT suggests that pacemaker implantation alone is not sufficient to address the underlying pathology in patients with sarcoidosis presenting with atrioventricular block. Chronic right ventricular pacing increases ventricular desynchrony and worsening of ventricular function, and these data may suggest that a biventricular pacing device may be useful in these subjects. A His lead may be another approach to minimize right ventricular pacing–induced HF, but the utility in sarcoidosis and the theoretical risk of lead-induced injury leading to progression and loss of capture at that site may limit applicability.[19,20] One small retrospective study reported that those with cardiac sarcoidosis who received cardiac resynchronization therapy did not demonstrate improvement in ventricular function,[21] but no prospective study has investigated this important question. Given the associated risk of VT also observed in previous cohort studies, our data support the recent Expert Consensus Guidelines on Diagnosis and Management of Cardiac Sarcoidosis, which treat atrioventricular block in the setting of sarcoidosis as warranting consideration of implantable cardioverter-defibrillator (Class IIA recommendation).[22]

Sarcoidosis was identified as the strongest risk factor for incident VT, with a relative hazard higher than HF and the presence of coronary artery disease. Again, other manifestations of cardiac sarcoidosis (namely HF and atrioventricular block) were potent predictors of VT in those with sarcoidosis, emphasizing the importance of considering a primary prevention implantable cardioverter-defibrillator when either of those is present in a patient with sarcoidosis.

Several additional risk factors were identified in those with sarcoidosis. Medical comorbidities traditionally associated with development of HF, namely, hypertension, diabetes mellitus, coronary artery disease, and obesity remained significant, albeit less potent, predictors of new HF in the sarcoidosis population. Male sex was an independent risk factor for developing atrioventricular block and VT, but not HF, in those with sarcoidosis.

Patients with sarcoidosis experienced a significantly higher risk for overall mortality and heart transplantation than those without the disease. Our mediation analyses suggested that any cardiac manifestation of sarcoidosis (namely, HF, atrioventricular block, or VT) statistically explained 22% of the increased risk of death that was observed. These data have important and direct clinical applications. First, in those with a diagnosis of sarcoidosis, clinicians should have a high suspicion for the presence of cardiac involvement. Immunosuppression can potentially treat all of each of these cardiac manifestations of the disease,[17,23,24] while supportive medications, pacemakers, and implantable cardioverter-defibrillators (the latter 2 generally working in tandem as part of 1 device) can prove to be lifesaving.[22] In addition, these data demonstrate the importance of considering an evaluation for sarcoidosis when an individual with HF, atrioventricular block, or VT presents without any other explanation for their disease.

Limitations

OSHPD relies on physician coding; however, coding for the types of covariates and outcomes used in the current analysis has been shown to exhibit high

specificity with variable sensitivity.[25–29] Importantly, limited sensitivity would be expected only to decrease power and should not lead to spurious false-positive results. In fact, research using similar methods has proven valuable, and similar use of such administrative data sets is now an accepted approach for large population studies.[30–32] Some potentially relevant confounders and mediators are not directly captured by *ICD-9* codes, such as specific diets or levels of activity; however, we adjusted for demographic information, tobacco use, and obesity, which may parallel and even directly reflect many of these unmeasured factors. The location of sarcoidosis was unable to be obtained due to limited *ICD-9* coding for organ-specific sarcoidosis involvement. We were unable to comment on information gleaned from outpatient encounters; however, the death data used here included total mortality regardless of the location of death. In addition, by capturing patients treated in ambulatory procedural units, emergency departments, and inpatient settings, we likely studied the most clinically relevant episodes of HF, atrioventricular block (of note, any pacemaker implantation would have been detected), and VT and certainly captured those responsible for the majority of healthcare usage. We were not able to examine the role of immunosuppression, a hallmark of sarcoidosis treatment. However, such treatment would be expected to reduce each of these outcomes rather than increase their risk, again likely resulting in a reduction in power or underappreciation of the raw risk of each outcome in the presence of sarcoidosis. Indeed, the importance of recognizing these 3 outcomes specifically among patients with sarcoidosis and the importance of considering a diagnosis of sarcoidosis in patients with these cardiac manifestations is that immunosuppression may be particularly useful.[33–35] Prior or ongoing surveillance for cardiac involvement among those with sarcoidosis was not available. As with any observational study, we cannot exclude residual or unmeasured confounding as an explanation for our results. In the hopes of addressing this, we adjusted for conventionally recognized mediators and confounders in as exhaustive a fashion as possible and as appropriate. Because broad screening for sarcoidosis is not a normal part of clinical practice, the magnitude of the observed effects is inferred from patients seeking care who received a sarcoidosis diagnosis attributable to clinically evident disease, perhaps inflating the proportion with the outcomes observed.

In conclusion, sarcoidosis is a potent risk factor for HF, atrioventricular block, and VT, exceeding the hazard posed by other well-established risk factors. Among those with sarcoidosis, each outcome was predicted most strongly by the presence of the other 2 outcomes, while established risk factors were relatively less potent compared with those without sarcoidosis. The presence of HF, atrioventricular block, or VT accounts for >20% of sarcoidosis-associated death. These findings highlight the need for careful surveillance and anticipation of these potentially avoidable complications in patients with sarcoidosis and suggest that HF, atrioventricular block, or VT in the absence of an identifiable cause should arouse suspicion for the disease.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S4
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. ICD-9 and CPT Codes for each covariate.

Covariate	ICD-9 Code or CPT Code
Sarcoidosis	135.xx
Heart failure	402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.1, 425.4, 425.5, 425.7, 425.8, 425.9, 428.x
Hypertension	401.x, 402.x, 403.x, 404.x, 405.x, 437.2
Diabetes mellitus	249.X, 250.X, 790.2-790.29, 791.5, 791.6, V458.5, V539.1, V654.6
Coronary artery disease	36.01-36.09, 36.1X, 410-410.92, 411.0, 411.1, 411.8, 411.89, 412, 413.X, 414.X, 429.7, V458.2
Obesity	278.0-278.03
High-grade AV block	426.12, 426.0
Ventricular arrhythmias	427.41, 427.42
Alcohol dependence	291-291.9, 303, 303.0-303.03, 303.9-303.93, 305.0-305.03, 790.3, 980.0
Tobacco use	305.1, 649.0, 989.84, V15.82
Permanent pacemaker	33206, 33207, 33208, 33210, 33211, 33212, 33213, 33221, 33216, 33217, 33224, 33225, 93279, 93280, 93281, 93288, 93294, V4501, V4509
Implantable cardioverter defibrillator	33230, 33231, 33240, 33248, 33270, 33271, 93282, 93283, 93284, 93295, 93289, V4502
Heart transplantation	V42.1

Table S2. Encounters among those with and without sarcoidosis.

	Sarcoid (n=64,668)	No Sarcoid (n=109,495,633)
Number of Emergency Department encounters	19,647	59,807,213
Number of outpatient surgery encounters	9,500	20,814,720
Number of Hospitalization encounters	35,521	28,873,700

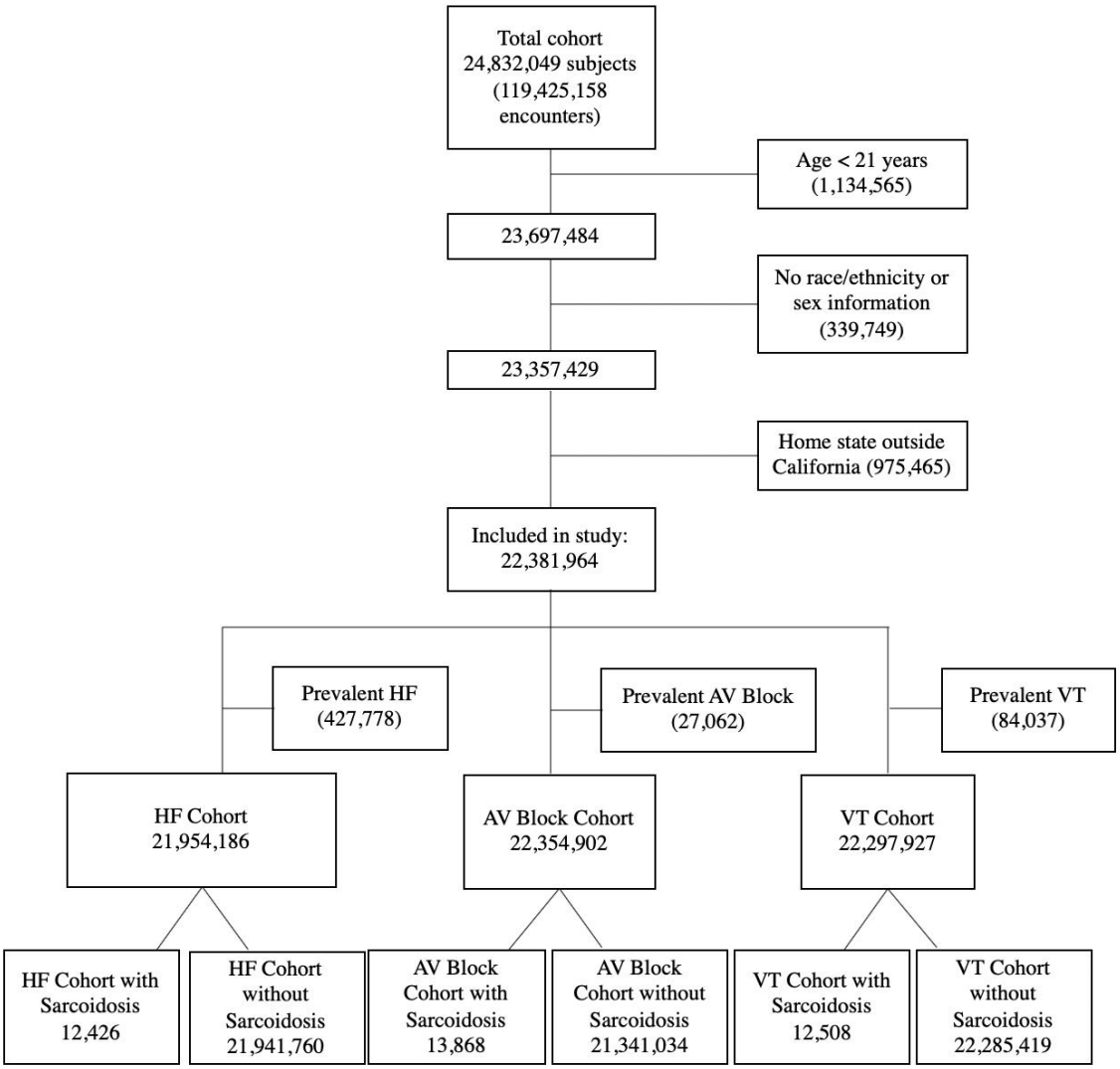
Table S3. Follow-up for each clinical outcome in the cohort.

	Median follow-up (Interquartile range), years	Follow-up range, years
Heart failure	3.01 (1.02-5.66)	0.003 -10.49
AV block	3.68 (1.53-6.20)	0.003 -10.48
VT	3.52 (1.20-6.35)	0.003 -10.49

Table S4. Cardiac device implantation in each cohort.

	Sarcoidosis		No Sarcoidosis	
	Pacemaker	Implantable cardioverter defibrillator	Pacemaker	Implantable cardioverter defibrillator
Heart failure	6 (0.08%)	35 (0.4%)	39,561 (0.04%)	40,953 (0.04%)
AV block	17 (1.7%)	8 (0.8%)	57,205 (0.05%)	375,840 (0.4%)
VT	10 (0.2%)	466 (10%)	58,562 (0.06%)	264,903 (0.3%)

Figure S1. Determination of Study Population for Incident HF, AV block, and VT Cohorts.



Flowchart identifying subjects in the OSHPD database included in incident HF, AV block, and VT analyses.