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EDITORIAL

Trends and Disparities Around Cardiovascular Mortality in Sarcoidosis: Does Big Data Have the Answers?

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Sarcoidosis is a multisystem inflammatory disorder of unknown cause characterized by the presence of nonnecrotizing granulomas. Sarcoidosis affecting the heart, termed cardiac sarcoidosis (CS), is challenging from a screening, diagnostic, and management perspective. A prevalence of 5% to 10% was reported in the largest case–control study among the general population with sarcoidosis but this is highly variable in different epidemiological studies.[1–3] In recent years, the increased awareness of the disease and the wider use of advanced imaging modalities such as cardiac magnetic resonance imaging and flurodeoxyglucose positron emission tomography have led to a significant increase in the reported prevalence of CS. The first presentation may be with high degree conduction abnormalities, ventricular arrhythmias, or heart failure. Not surprisingly, it is now reported to be the second most common cause of death among patients with sarcoidosis.[1]

See Article by Tan et al.

Given the rarity of CS, most of the literature on the incidence and prognosis has been derived from small, single-center retrospective studies with a likely selection bias. Indeed, there are few to no randomized controlled trials addressing CS or the use of heavy immunosuppressive treatments. To address this limitation, big data studies lend well to rare diseases by providing much larger sample sizes (numerator) with very large denominators. These secondary analysis studies have their own inherent weaknesses, are increasingly being used to make epidemiological and prognostic conclusions about cardiovascular morbidity and mortality in sarcoidosis and CS (Tables 1 and 2).

CURRENT STUDY

In this issue of the *Journal of the American Heart Association* (*JAHA*), Tan et al have taken up the challenge to describe the trends and disparities in cardiovascular mortality, excluding ischemic heart disease, among patients with sarcoidosis from 1999 to 2020 using the Centers for Disease Control and Prevention's Wide-Ranging Online Data for Epidemiologic Research database.[4] The authors calculated age-adjusted mortality rates (AAMR) per 1 000 000 individuals and determined how demographic and geographic factors affected it. They should be commended for demonstrating that AAMR (1) increased over the 22-year period, (2) was higher in women, (3) was higher in people with Black ancestry, (4) was highest in the 55- to 64-year-old cohort, (5) was highest in the South region, (6) was higher in urban regsions, specifically large

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Table 1. Secondary Database Studies on Cardiovascular Mortality in Sarcoidosiss

Study	Journal	Inclusion criteria	Patient cohort	Years studied	Name of database	Cohort size	Follow-up time	Outcomes
Tan et al 2024[4]	*Journal of the American Heart Association*	Age ≥25 y Cause of death: CVD (excluding IHD) with comorbid sarcoidosis	United States	1999–2020	Centers for Disease Control and Prevention's Wide-Ranging Online Data for Epidemiologic Research	3301 Cardiovascular deaths with comorbid sarcoidosis	22 y	AAMR increased from 0.53 (95% CI, 0.43–0.65) per 1 000 000 individuals in 1999 to 0.87 (95% CI, 0.75–0.98) per 1 000 000 individuals in 2020. AAMR was higher in women than men (0.77 [95% CI, 0.74–0.81] vs 0.58 [95% CI, 0.55–0.62]). AAMR was higher in Black ancestry than White ancestry (3.23 [95% CI, 3.07–3.39] vs 0.39 [95% CI, 0.37–0.41]). Highest percentage of mortality was observed in the 55–64 y age cohort in men (23.11%) and women (21.81%). South region had highest AAMR compared with other regions (0.78 [95% CI, 0.74–0.82]). AAMR was higher in urban regions than in rural areas (0.72 [95% CI, 0.69–0.74] vs 0.62 [95% CI, 0.56–0.68] per 1 000 000 individuals). Highest AAMR was seen in the large central metro region (0.90 [95% CI, 0.84–0.95] per 1 000 000 individuals). AAMR was highest in most vulnerable group vs least vulnerable group (social vulnerability index: 0.91 [95% CI, 0.79–1.03]) vs (0.61 [95% CI, 0.51–0.72]).
Casipit et al 2023[5]	*International Journal of Cardiology. Heart & Vasculature*	Hospitalized patients with sarcoidosis	United States	2018–2020	NIS database	36 864 Hospitalizations	Hospital admission	Concomitant heart failure was not an independent predictor of in-hospital mortality or LOS. Age (aOR, 1.04 [95% CI, 1.03–1.06]; $P \leq 0.001$) and arrhythmia burden (aOR, 2.08 [95% CI, 1.47–2.95]; $P \leq 0.001$), specifically VT and VF, were independently associated with in-hospital mortality among patients with sarcoidosis.
Dai et al 2022[6]	*Cardiovascular Digital Health Journal*	Patients with sarcoidosis admitted with acute HF	United States	2016–2019	NIS database	4659 Hospitalizations	Hospital admission	Comorbid arrhythmias, age, and fluid electrolyte disorders were the strongest factors in predicting in-hospital mortality.
Tan et al 2022[7]	*Journal of Cardiovascular Electrophysiology*	Hospitalized patients with sarcoidosis ≥18 with VT	United States	2022–2018	NIS database	3220 Hospitalizations	Hospital admission	Patients who had catheter ablation were younger, predominantly male, and White. Although not significant, in-hospital mortality was lower in catheter ablation (1.9% vs 6.6%, P=0.08). Catheter ablation procedure-related complications occurred in 9.1%. Predictors of in-hospital mortality in cohort with catheter ablation included congestive heart failure (OR, 13.2 [95% CI, 1.7–104.2]) and mild to moderate renal disease (OR, 3.9 [95% CI, 1.1–13.3]).
Taduru et al 2022[8]	*Indian Heart Journal*	Patients with CS	United States	2016–2017	NIS database	2420 Hospitalizations	Hospital admission	Most admissions occurred due to VT (12.8%), followed by myocarditis (9.9%) with a mean LOS of 7 d.The overall incidence of in-hospital mortality was 2.5%.
Higgins et al 2022[9]	*American Heart Journal*	Propensity-matched patients with CS and NICM with ICD	United States	April 1, 2010 and December 31, 2015	National Cardiovascular Data Registry ICD Registry	1638 CS and 8190 NICM	2y	Mortality following ICD implantation was similar in CS and NICM (9.0% vs 9.3%, P=0.72). Presence of heart failure (HR, 1.92 [95% CI, 1.44–3.22]), NYHA class III (HR, 1.68 [95% CI 1.16–2.45]), NYHA class IV (HR, 3.08 [95% CI, 1.49–6.39]), AF/flutter (HR, 1.66 [95% CI, 1.17–2.35]), chronic lung disease (HR, 1.64 [95% CI, 1.17–2.29]), creatinine >2.0 mg/dL (HR, 4.07 [95% CI, 2.63–6.30]), and paced rhythm (HR, 2.66 [95% CI, 1.07–6.59]) were predictors of increased 2-year mortality among patients with CS with ICDs.

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Table 1. Continued

Study	Journal	Inclusion criteria	Patient cohort	Years studied	Name of database	Cohort size	Follow-up time	Outcomes
Jackson et al 2022[10]	*Journal of Heart and Lung Transplantation*	Patients with CS and and non-CS undergoing OHT	United States	1987–2019	United Network for Organ Sharing Registry	63 947 Patients, which included 227 patients with CS	33 y	Patients with CS and non-CS had similar post-OHT survival (HR, 0.86 [95% CI, 0.59–1.3], *P*=0.446), odds of graft failure (HR, 0.849 [95% CI, 0.58–1.23], *P*=0.394), hospitalizations for infection, and posttransplant malignancy. Patients with CS had lower odds of rejection (OR, 0.558 [95% CI, 0.315–0.985], *P*=0.0444).
Gonen et al 2022[11]	*Journal of Clinical Medicine*	Patients with sarcoidosis and matched nonsarcoidosis controls	Israel	2000–2016	Database of Clalit Health Services	3750 Patients with sarcoidosis and 18 139 controls	15 y	Patients with sarcoidosis were also at increased risk for all-cause mortality compared with controls (multivariate model, adjusted HR, 1.93 [95% CI, 1.76–2.13]). Association between sarcoidosis and IHD was demonstrated by a multivariate analysis (aOR, 1.5 [95% CI, 1.36–1.66]).
Narasimhan et al 2021[12]	*Journal of the American College of Cardiology. Clinical Electrophysiology*	Patients with sarcoidosis ≥18 y and exclusion of IHD	United States	2005–2017	NIS database	803 557 Hospitalizations	Hospital admission	0.5% had SCA. Higher rates of SCA were noted in patients aged <40 y (OR, 1.012 [95% CI, 1.006–1.02]; *P*=0.001), Black individuals (OR, 1.63 [95% CI, 1.39–1.92]; *P*=0.001), and those with AF (OR, 1.69 [95% CI, 1.39–2.06]; *P*=0.001), heart failure, both HF with reserved ejection fraction (OR, 2.37[95% CI, 1.77–3.17]; *P*=0.001) and HF with preserved ejection fraction (OR, 1.88 [95% CI, 1.48–2.39]; *P*=0.001), Second-degree atrioventricular block (OR, 3.22 [95% CI, 1.32–7.86]; *P*=0.001), third-degree atrioventricular block (OR, 7.12 [95% CI, 4.38–10.57]; *P*=0.001), right BBB (OR, 2.59 [95% CI, 1.65–4.08]; *P*=0.001), left BBB (OR, 2.13 [95% CI, 1.13–4.02]; *P*=0.02), and fascicular blocks (OR, 2.75 [95% CI, 1.35–5.59]; *P*=0.005).
Larsson et al 2020[13]	*Sarcoidosis, Vasculitis, and Diffuse Lung Diseases*	Patients with sarcoidosis aged 20–65 y old with matched controls	Sweden	2007–2016	Swedish National Patient Register and Cause of Death Register	7828 Cases with sarcoidosis and 15 656 controls	Hospital admissions	Sarcoidosis was associated with increased mortality compared with controls (HR, 1.88 [95% CI, 1.56–2.26]) and the Swedish general population (standardized mortality ratio 1.75 [95% CI, 1.52–2.00]). Sarcoidosis was associated with increased hospital admissions for cardiomyopathy, heart failure, pulmonary embolism, and malignant neoplasm.
Jeon et al 2020[14]	*Sarcoidosis, Vasculitis, and Diffuse Lung Diseases*	Patients with sarcoidosis	Korea	2008–2015	National Health Insurance database	3259 New patients with sarcoidosis	8 y	The average annual incidence of sarcoidosis was 0.81 per 100000. The annual mortality rate was 9.26 per 1000 person-years. Mortality rate was significantly higher than those of the general population (standardized mortality rate, 1.91 [95% CI, 1.62–2.25]). The most common cause of death was cancer (41.7%), followed by respiratory disease (13.1%), sarcoidosis (13.1%), and heart disease (8.3%).

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Table 1. Continued

Study	Journal	Inclusion criteria	Patient cohort	Years studied	Name of database	Cohort size	Follow-up time	Outcomes
Yafasova et al 2020[15]	*Journal of the American College of Cardiology*	Patients with sarcoidosis ≥18 y and matched controls	Denmark	1996–2016	Danish nationwide registries	11 834 Patients with sarcoidosis and 47 336 controls	Median 8.2 y	All-cause mortality was higher in patients with sarcoidosis vs controls (10.88% [95% CI, 10.23%–11.55%] vs 7.43% [95% CI, 7.15%–7.72%]). Cardiac outcomes were higher in patients with sarcoidosis vs controls (HF, 3.18% [95% CI, 2.83%–3.57%] vs 1.72% [95% CI, 1.58%–1.86%]; composite of ICD implantation, ventricular arrhythmias, and cardiac arrest: 0.96% [95% CI, 0.77%–1.18%] vs 0.45% [95% CI, 0.38%–0.53%]; composite of pacemaker implantation, atrioventricular block, and sinoatrial dysfunction: 0.94% [95% CI, 0.75%–1.16%] vs 0.51% [95% CI, 0.44%–0.59%]; AF or flutter: 3.44% [95% CI, 3.06%–3.84%] vs 2.66% [95% CI, 2.49%–2.84%]).
Durugu et al 2020[16]	*Cureus*	Patients with sarcoidosis age ≥18 y without IHD	United States	2010–2014	NIS database	308064 Hospitalizations	Hospital admission	In-hospital mortality was higher in women (64% vs 36%; *P*<0.001). Women had higher rates of AF (59% vs 41%; *P*<0.001). Men had a higher burden of VT (55% vs 45%; *P*<0.001), more ICD (56% vs 44%; *P*<0.001), and cardiac resynchronization therapy defibrillator implantations (58% vs 42%; *P*=0.025) , and more endomyocardial biopsies (55% vs 45%; *P*<0.001).
Salama et al 2020[17]	*Cardiology Journal*	Hospitalizations with and without concomitant sarcoidosis	United States	2012–2014	NIS database	18013878 Hospitalizations (0.26% had sarcoidosis)	Hospital admission	Patients with sarcoidosis had more prevalent VT, VF, and SCA (VT: 2.29% vs 1.22%; *P*<0.001, VF: 0.25% vs 0.21%; *P*<0.001 and SCA: 0.72% vs 0.6% [*P*<0.001]). In unadjusted analysis, comorbidities were more common in sarcoidosis (diabetes: 31.6% vs 21.25%; *P*<0.001; hypertension: 65.2% vs 51.74%; *P*<0.001; chronic kidney disease: 21.09% vs 14.02%; *P*<0.001; HF: 24.87% vs 15%; *P*<0.001; acute coronary syndrome: 4.32% vs 3.35%; *P*<0.001)
Desai et al 2018[18]	*Annals of Translational Medicine*	Patients with sarcoidosis with and without arrhythmias	United States	2010–2014	NIS database	369285 Hospitalizations	Hospital admission	19.9% had arrythmias, which included a male preponderance. AF (10.97%) and VT (1.97%) were most common. The group with sarcoid-arrhythmia had significantly higher mortality (3.7% vs 1.5%; aOR, 2.06), mean hospital LOS (6.4 vs 5.2 d) and hospital charges ($64 118 vs $41 565) compared with the group without arrhythmia (*P*<0.001).
Patel et al 2018[19]	*Journal of the American Heart Association*	Patients with sarcoidosis without IHD	United States	2005–2014	NIS database	609051 Sarcoidosis hospitalizations	Hospital admission	The number of sarcoidosis hospitalizations increased from 2005 through 2014 (138 vs 175 per 100000; P_{trend}<0.001). Unadjusted in-hospital mortality decreased (6.5 to 4.9 per 100 sarcoidosis hospitalizations; P_{trend}<0.001). Black race was associated with increased risk of in-hospital mortality (OR, 1.21 [95% CI, 1.16–1.27]; *P*<0.001). HF (≈16%) and arrhythmias (≈15%) were the most common presentations. ICD placement was low (≈7.5 per 1000 sarcoidosis hospitalizations)
Guo et al 2017[20]	*Cardiology Journal*	Patients with CS	United States	2005–2011	NIS database	13045 Hospitalizations	Hospital admission	The annual admissions of CS increased from 1108 in 2005 to 2182 in 2011. The proportions of patients with CS with severe comorbidities, VT, VF, and HF all increased from 2005 to 2011. However, the in-hospital mortality rate declined (*P*=0.0462). Overall, in-hospital mortality was 2.3%.

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Table 1. Continued

Study	Journal	Inclusion criteria	Patient cohort	Years studied	Name of database	Cohort size	Follow-up time	Outcomes
Te et al 2017[21]	*International Journal of Cardiology*	Patients with sarcoidosis matched with controls (without structural heart disease)	Taiwan	2000–2004	National Health Insurance Research Database	2237 Patients with sarcoidosis and 2237 controls	Mean 11.4 y	Cohort with sarcoidosis had higher VT incidence (0.94% [85 per 100 000 person-years] vs 0.09% [8 per 100 000 person-years], HR, 12.7 [95% CI, 2.82–56.9]; *P*<0.001). Mortality and ICD implantation was similar between the 2 groups.
Jamilloux et al 2016[22]	*European Respiratory Journal*	Death certificates mentioning sarcoidosis	France	2002–2011	French Epidemiological Centre for the Medical Causes of Death	1662	10 y	AAMR was 3.6 per million and significantly increased over the study period (*P*=0.006). The in-hospital deaths were higher for sarcoidosis than general population (66.5% vs 49%). Sarcoidosis was most common underlying cause of death with main other mentions being chronic respiratory and CVDs. The overall observed/expected ratio was >1 for infectious disease, tuberculosis, and chronic respiratory disease, and <1 for neoplasms. There was a north–south gradient in AAMR at the country level. The mean age at death was 70.4 y (vs 76.2 y for the general population). The ratio (range) of women to men was 1.3 (0.9–1.8). Compared with the general population, sarcoidosis-related death before the age of 65 y was statistically more frequent among men (*P*=0.002) and was statistically more frequent for women aged ≥65 y (*P*<0.001).
Swigris et al 2011[23]	*American Journal of Respiratory and Critical Care Medicine*	Death certificates mentioning sarcoidosis	United States	1988–2007	National Center for Health Statistics	46 450 489 Deaths including 23 679 with sarcoidosis	20 y	AAMR was 4.32 per 1 000 000 population. AAMR for sarcoidosis increased 50.5% in women and 30.1% in men, with greatest increase in non-Hispanic Black patients. For any year, mortality rate was nearly 10-fold higher for non-Hispanic Black than White patients. Mortality rates rose most in decedents 55 y or older. Most common cause of death was sarcoidosis itself. Younger decedents with sarcoidosis and pulmonary fibrosis were more likely to be Black (*P*=0.001), and younger decedents with sarcoidosis (25–44y) were more likely than similarly aged decedents in the general population to have a cardiac cause (coded as ischemia or myocardial infarction, sudden cardiac death or arrhythmia, congestive HF, or cardiomyopathy) contributing to death. However, for most other age strata, sarcoidosis was protective against having a cardiac cause contribute to death.

AAMR indicates age-adjusted mortality rate; AF, atrial fibrillation; aOR, adjusted odds ratio; BBB, bundle-branch block; CS, cardiac sarcoidosis; CVD, cardiovascular disease; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter defibrillator; IHD, ischemic heart disease; LOS, length of stay; NICM, nonischemic cardiomyopathy; NIS, National Inpatient Sample Database; NYHA, New York Heart Association; OHT, orthotopic heart transplantation; OR, odds ratio; SCA, sudden cardiac arrest; VF, ventricular fibrillation; and VT, ventricular tachycardia.

Table 2. Strengths and Limitations of Secondary Database Studies

Strengths	Limitations
They are not confined to a single specialist center. Rather, they are nationally representative samples, thus reducing tertiary (Berkson selection) referral bias.	Human error in data entry and coding: misclassification bias is common in these retrospective databases.
	Selective inclusion and reporting of outcomes
	Granular variables, for example, details on medications such as immunosuppressants, biopsy data to establish diagnosis or causal details are unavailable
Large number of patients in a relatively rare disease with otherwise sparse data	Imaging data, for example details on cardiac magnetic resonance imaging and flurodeoxyglucose positron emission tomography scans, are not available.
Robust data on mortality and concomitant comorbidities	Diagnosis is not independently adjudicated, and there is no confirmation of sarcoidosis or cardiac sarcoidosis.
Many studies excluded patients with IHD, increasing chances that the majority of patients captured with cardiovascular comorbidities had suspected cardiac sarcoidoisis.	No information is available at the individual patient level. Follow-up after hospitalization not always possible.
	Time-dependent variables are not always available.
	Data are suppressed if a variable has <10 patient cases or death count is <20.
Secondary databases have been extensively validated and are more generalizable.	Most studies discuss in-patient cohorts who are sicker. Findings may not be applicable in an outpatient setting.
	IHD cases have been excluded in many studies. This might impact the applicability of the findings in patients with sarcoidosis with concomitant coronary disease.

IHD indicates ischemic heart disease.

central metro regions, and (7) was highest in most socioeconomic deprived populations (Table 1).[4–23]

This study seems to be an update on a similar large cohort study that analyzed the death certificates mentioning sarcoidosis in United States from 1988 to 2007 using the National Center for Health Statistics.[23] Given the first 3 conclusions are common in both adds validity to the methodology and results observed. Jamilloux et al also found that AAMR increased in the French population with sarcoidosis from 2002 to 2011.[22] With the advent of advanced imaging modalities and raised awareness, it is hardly surprising that patients with sarcoidosis and CS are increasingly being diagnosed and therefore AAMR is increasing too.

Tan et al give several hypotheses for the disparities observed in race on cardiovascular mortality in patients with sarcoidosis.[4] They postulate genetic susceptibility and health care inequalities due to socioeconomic status. Given their own study had highlighted the stark difference in mortality between highest social vulnerability group and lowest vulnerability group, had they also shown that the highest social vulnerability group had many more individuals from Black ancestry, the conclusion could have been drawn more easily. However, this is again a limitation of secondary big data studies where information is not always available at the individual patient level (Table 2). Similarly, exact or possible reasons for gender and geographical disparities are not given. However, their result is in keeping with other observational secondary database studies[16,22] (Table 1). One can safely conclude that though big data studies like this one benefit from large numbers in a rare condition, they lack the granularity to draw conclusions about cause (Table 2). Certainly, other studies have demonstrated an overlap of genetic cardiomyopathies and inflammation.[24–26]

Perhaps, another limitation of this specific study is that there is no comparison of cardiovascular deaths in a propensity-matched cohort without sarcoidosis. For example, secondary database studies from Sweden, Denmark, and Korea demonstrated that mortality was higher in patients with sarcoidosis when compared with cohorts without sarcoidosiss[13–15] (Table 1). However, Tan et al did demonstrate that cardiovascular mortality was highest in in 55- to 64-year-old patients with sarcoidosis, which is much younger than the >84-year-olds who had highest cardiovascular mortality in general population.[4] Alternatively, whether 55- to 64-year-old patients with sarcoidosis having highest cardiovascular mortality (22.33%) was statistically significant or not is not explored. Indeed, one can note that cardiovascular mortality in 45- to 54-year-olds was 19.60% and in 65- to 74-year-old was 20.45%. Overall, data support the conclusion that cardiovascular mortality in patients with sarcoidosis happens earlier than in the general population.

FUTURE DIRECTIONS

Does big data have all the answers? Probably not on the pathogenesis and causality of sarcoidosis. However, this study adds to growing literature of big data work in sarcoidosis and cardiac sarcoidosis, demonstrating that female sex, Black ancestry, younger age, higher social vulnerability status, and living in an urban area or the southern United States are associated with higher cardiovascular mortality in patients with sarcoidosis. Like other big data studies, this

is hypothesis-generating, which warrants future prospective studies and trials to be conducted to validate the findings and help develop preventative strategies in order to reduce mortality and health care burdens.

ARTICLE INFORMATION

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Disclosures

None.

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