

CLINICAL CHARACTERISTICS AND OUTCOMES OF HOSPITALIZED PATIENTS WITH HEART FAILURE AND SARCOIDOSIS: ANALYSIS OF THE NATIONWIDE READMISSIONS DATABASE 2010-2019

Short Title: Outcomes in heart failure and sarcoidosis

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ABSTRACT

BACKGROUND: Sarcoidosis is a multi-systemic granulomatous inflammatory disorder. In the setting of cardiac involvement, clinical manifestations include ventricular arrhythmias, high-grade atrioventricular block (AVB) and heart failure (HF). The impact of HF in patients with sarcoidosis has not been established from real-world data.

METHODS: Patients admitted with sarcoidosis from 2010-2019 were identified from the Nationwide Readmissions Database. Those with ischemic heart disease were excluded. Sarcoidosis patients without HF were propensity matched for age, gender and Charlson comorbidity index and compared to patients with HF. Clinical characteristics, length of stay (LOS), adjusted healthcare-associated costs (HAC), 90-day readmission and 90-day mortality was observed.

RESULTS: During the 10-year study period, 97,961 patients (median age 63 [54-71] years, 37.9% male) with a diagnosis of sarcoidosis were hospitalized (35.9% with HF and 64.1% without HF). On index admission, HF patients had a higher prevalence of AVB (3.3% vs 1.4%, $p<0.0001$), ventricular tachycardia (6.5% vs 1.3%, $p<0.0001$), ventricular fibrillation (0.4% vs 0.1%, $p<0.0001$) and atrial fibrillation (22.1% vs 7.5%, $p<0.0001$). The median LOS (4 [3-7] vs. 4[2-6] days, $p<0.0001$) was similar but median HAC (US\$ 9,954.5 [5,934.7-18,128.8] vs. 8,828.3 [5,303.1-15,384.9], $p<0.0001$) during the index admission were higher in HF patients.

The LOS and HAC were greater in HF patients on 90-day readmission. HF patients were significantly more likely to be re-admitted within 90 days [adjusted all-cause readmissions (HR [95% CI: 1.28 [1.25 – 1.31], $p<0.0001$), atrial fibrillation (HR 1.35 [1.05-1.75], $p=0.02$), acute HF (HR 10.77 [9.45 – 12.16], $p<0.0001$) and ventricular tachycardia/ventricular fibrillation (HR 2.55 [1.69 – 3.85], $p<0.0001$)]. Adjusted inpatient mortality at readmission was also higher in HF patients (5.1% vs. 3.8%, $p<0.0001$).

CONCLUSION: The presence of HF in hospitalized sarcoidosis patients is associated with an increased prevalence of conduction disorders, ventricular arrhythmias and atrial fibrillation. HF patients had greater costs, readmissions and mortality at 90-days.

KEY WORDS: sarcoidosis, cardiac sarcoidosis, heart failure, arrhythmia, healthcare associated costs, outcomes

What is known?

- 1) Cardiac involvement in sarcoidosis is associated with ventricular arrhythmias, high-grade atrioventricular block and heart failure
- 2) Retrospective small, single-center studies have reported relatively poor long-term survival outcomes for symptomatic cardiac sarcoidosis patients with reduced left ventricular ejection fraction

What the study adds?

- 1) Using a large real-world database, this study has demonstrated that heart failure in hospitalized sarcoidosis patients is associated with increased prevalence of arrhythmia, conduction disorders, cardiac implanted electronic devices, catheter ablations and cardiac transplantation.
- 2) Heart failure in hospitalized sarcoidosis patients leads to a significantly higher length of stay, healthcare-adjusted costs, 90-days readmissions and mortality following readmission.

INTRODUCTION

Sarcoidosis is a multisystem inflammatory disorder characterized by the presence of non-necrotizing granulomas(1). The annual incidence ranges from 2.3 to 11 cases per 100,000 individuals with the majority occurring between the ages of 25 and 40(2, 3). Cardiac involvement is present in 5-10% of cases, although autopsy data suggests a higher prevalence approximating 20-30%(4). In the absence of an endomyocardial biopsy demonstrating non-caseating granuloma, a clinical diagnosis of cardiac sarcoidosis (CS) can be made using diagnostic criteria established by guidelines such as the Japanese Ministry of Health and Welfare and the 2014 Heart Rhythm Society Consensus (HRS) document(5, 6). The prevalence of CS varies according to region and is reported as 1:100,000 in South Korea and Taiwan, 3.7:100,000 in Japan, and 150:100000 in Sweden and Canada(7-12). When present, clinical manifestations include high-grade atrioventricular block (AVB), ventricular arrhythmias, heart failure (HF) and sudden cardiac death (SCD)(13-16).

Historically, studies have reported relatively poor long-term survival outcomes for symptomatic CS patients with reduced left ventricular ejection fraction (LVEF), an independent predictor of adverse events(17, 18). However, in the era of advanced HF therapy, there is increasing 5-year survival rates(19, 20). Currently, most of the literature on the incidence and prognosis of sarcoidosis patients with HF has been derived from single-center retrospective studies(21).

There remains a lack of large-population real-world data on the prognosis of hospitalized sarcoidosis patients with HF. Accordingly, we used the National Readmission Database (NRD) to identify the characteristics and clinical outcomes of sarcoidosis patients with heart failure (sw-HF) and after propensity matching, compared these to sarcoidosis patients without heart failure (sw/o-HF).

METHODS

Database selection:

The NRD was developed by the Healthcare Cost and Utilization Project (HCUP) and sponsored by the Agency for Healthcare Research and Quality. The NRD data include inpatient care from all-payer hospitals and is the largest inpatient dataset in the United States of America (US)(22). It includes demographics, baseline characteristics including comorbidities, reasons for the admission, readmission days after the discharge, and reasons for the readmission. An advantage of utilizing these types of data is the ability to generate larger sample sizes for rarer diseases, for example CS, due to the large denominator as well as being representative of the US hospitalized population, reducing tertiary referral bias. This study was exempt from Institutional review board approval, given the use of deidentified, publicly available data.

Population selection:

Data on patients who were ≥ 18 years and admitted with sarcoidosis were abstracted from the NRD. Patients with presumed ischemic cardiomyopathy (ICM) were excluded from the data by removing those patients with a history of percutaneous coronary intervention (PCI) and/or coronary artery bypass grafting (CABG). The identification of admission for sarcoidosis (primary diagnosis) and the presence of HF from 2010 to 2019 were based on International Classification of Diseases- 9th and 10th Revision-Clinical Modification (ICD-9-CM and ICD-10-CM, respectively; **Supplemental Table 1 and Figure 1**. Heart failure presence was defined as a documented history of either systolic or diastolic HF. Due to heterogeneity among admitting centers in coding for this diagnosis, there was no uniformity with regards to LVEF cut off in defining systolic HF or what imaging modality was applied during diagnosis.

Initially, our study aimed to focus primarily on patients with ICD codes for CS. ICD-10 codes yielded very few CS patients from 2016-2019 (**Supplemental Table 2**: D8685 “sarcoid myocarditis”: 1252 hospitalizations). There were no ICD-9 codes specific for CS (for the years 2010-2015). Therefore, we changed the search strategy and after excluding patients with presumed ICM (ICD-10 codes 125.5 and 414), we identified all patients with extracardiac sarcoidosis plus HF. These patients were compared to matched cohort of sarcoidosis patients without HF.

Patients were followed up for 90-days from the point of discharge, with data limited to events within each calendar year. Those discharged from the months October to December were excluded due to 90-day follow-up not being available in these patients (**Figure 1**). Type of readmission (all-cause, atrial fibrillation [AF], ventricular tachycardia [VT], ventricular fibrillation [VF] and acute HF) were identified using the ICD-9-CM and ICD-10-CM codes (**Supplemental Table 3**). The presence of cardiac implanted electronic devices (CIED) was also recorded.

The primary payers were identified using the NRD database and categorized as Medicare/Medicaid, private insurance, and others. The medical costs of admission and readmission were calculated as adjusted medical costs, which were adjusted for the charge-to-cost ratio (provided by the HCUP) since the net medical costs included hospital bills for services such as wages, supplies, and utility that were different among the hospitals. The Charlson Comorbidities Index (CCI) was calculated using ICD-9-CM and ICD-10-CM codes (**Supplemental Table 5**)(23, 24).

Statistical analysis:

Descriptive statistics are presented as median (interquartile range; IQR) or number (%).

Propensity score matching with the nearest neighbor method (1:2) and a maximum caliber of 0.20 of the score was used for adjusting for potential confounders (that is, adjusted for sex, age,

and CCI) among the sw-HF and sw/o-HF. Comparisons between sw-HF and sw/o-HF were assessed using the χ^2 test for categorical variables. Continuous data normality was tested using Shapiro–Wilk W test; and compared using Mann–Whitney U for non-normal. For estimation for freedom from readmission, the log-rank test and the Cox proportional hazards regression models were used. For competing risks analysis, we used Fine-Gray model (Figures 2B-D). Logistic regression analysis was used to estimate the risk for in-hospital mortality at second admission. As per NRD rules, to prevent identification, some cases were excluded if cases with $n \leq 10$ in a particular hospital or area were present. The included variables for the Cox proportional hazards model and logistic regression analysis were age, sex, CCI, presence of comorbidities, and hospital bed size. Analysis was done using STATA v.15.1 (Stata-Corp). A two-tailed *a priori* $p < 0.05$ was regarded as significant.

RESULTS

Study population:

Over the 10-year period (2010-2019), a total of 175,349 patients met the inclusion criterion out of whom 97,961 patients were included in the study after propensity matching and exclusion of cases that could have been identified (**Figure 1**).

Baseline characteristics at time of index admission:

The baseline characteristics of patients are summarized in **Table 1**. Out of the matched population, 35,168 (35.9%) sarcoidosis patients had a history of HF, whereas 62,793 (64.1%) patients did not. The median [IQR] age of the whole cohort was 63 [54-71] years with a Charlson Comorbidity Index of 3 [2-4] and a female preponderance (62.1%).

HF patients had a significantly higher prevalence of AVB (3.3 vs. 1.4%, $p < 0.0001$), previous VT (6.5 vs. 1.3%, $p < 0.0001$), previous VF (0.4 vs. 0.1%, $p < 0.0001$) and AF (22.1 vs 7.5%, $p < 0.0001$). They had a similar, though statistically greater, median length of stay (LOS) (4 [3-7] vs. 4 [2-6] days, $p < 0.0001$) and higher median adjusted healthcare-associated costs (HAC) (US\$ 9,954.5 [5,934.7-18,128.8] vs. 8,828.3 [5,303.1-15,384.9], $p < 0.0001$) in the index admission when compared to those without HF.

On first admission, CIED were more common in HF patients (permanent pacemaker [PPM] 0.7 vs 0.5%, implantable cardioverter defibrillator 1.4 vs 0.3%, and Cardiac Resynchronization Therapy-Defibrillators (CRT-D) 0.8 vs 0.04%, all $p < 0.0001$). Moreover, a higher number of HF patients underwent catheter ablation (0.7 vs. 0.2%, $p < 0.0001$) or cardiac transplantation (0.07 vs 0.0%, $p < 0.0001$) during the index admission. Peripheral vascular disease, renal impairment, obesity and anticoagulation use were also more prevalent in patients with HF ($p < 0.0001$).

Conversely, cerebrovascular disease, chronic pulmonary disease, liver disease, diabetes and hypertension were more commonly observed in those without HF ($p < 0.0001$).

With regards to payment plans, Medicare/Medicaid insurance was more common (76.7 vs. 68.7%, $p < 0.0001$) among HF patients whereas private insurance use was less frequent (18.5 vs. 25.8%, $p < 0.0001$).

Comparison between patients with and without 90-day readmission:

Across both HF and non-HF sarcoidosis patients, those who were readmitted within 90-days had higher Charlson Comorbidity Index, longer LOS, higher HAC and greater use of anticoagulant therapy on index admission (**Table 2**). HF patients had a higher proportion of index admissions with VT/VF (1.5 vs. 0.3%, $p < 0.0001$), AVB (0.4 vs 0.3%, $p < 0.0001$, AF (1.9 vs. 0.8%, $p < 0.0001$) and cardiac arrest (0.06% vs 0.02%, $p = 0.003$) compared to those without HF (**Table 3A**). There was a greater proportion of HF patients undergoing 2nd admission within 90 days for, VT/VF, AF or acute HF (all $p < 0.0001$) compared to non-HF patients. (**Table 3B**).

Predictors of 90-day readmission:

On univariable Cox proportional hazard modelling, history of AVB (HR 0.87 [0.80-0.94], $p = 0.001$) and the presence of an existing CIED (HR 0.70 [0.57-0.85], $p = 0.001$) on index admission were associated with freedom from 90-days readmission. Increasing age, higher

Charlson Comorbidity Index and use of anticoagulant therapy were predictive of readmission.

Additionally, the presence of AF, chronic pulmonary disease, liver disease, diabetes, renal disease and coagulation defects were also predictors of 90-day readmission (**Table 4**).

The Kaplan-Meier curves in **Figure 2** demonstrate that HF patients had higher incidence of readmissions within 90-days when compared to non-HF patients. This was consistent for all-cause readmissions (HR 1.28 [1.25–1.31], $p < 0.0001$) as well as readmissions due to AF (HR 1.35 [1.05-1.75], $p=0.02$), acute HF (HR 10.77 [9.45–12.16], $p < 0.0001$) or VT/VF (2.55 [1.69–3.85], $p < 0.0001$) (**Figure 2A-D**).

Mortality, length of stay and cost of readmission:

Rates of in-hospital mortality on readmission was higher among HF patients (5.1 vs. 3.8%, $p < 0.0001$). On univariable analysis, the predictors of in-hospital mortality at readmission were HF presence (OR 1.24 [1.09-1.41], $p=0.001$), increasing age (OR 1.03 [1.02-1.03], $p < 0.0001$), male sex (OR 1.20 [1.06-1.35], $p=0.003$), higher Charlson Comorbidity Index (OR 1.14 [1.10-1.17], $p < 0.0001$) and presence of liver disease (OR 1.29 [1.06-1.57], $p=0.01$), (**Tables 5 and 6**).

Additionally, the median LOS (5 [3-8] vs. 4 [3-7] days, $p < 0.0001$) and HAC (US\$ 9,667.0 [5,626.6-18,076.6] vs. 9,087.1 [5,378.3-16,966.1], $p < 0.0001$) upon readmission were significantly higher in HF patients (**Table 5**).

DISCUSSION

This is the largest study of an inpatient cohort of propensity-matched sarcoidosis patients with and without HF and has several important findings. First, HF in patients with sarcoidosis was associated with a significantly greater prevalence of conduction disease, ventricular arrhythmias, atrial fibrillation and presence of CIEDs on index presentation. Second, the healthcare adjusted costs were significantly greater in sarcoidosis patients with HF compared to those without, both on index admission and on 90-day readmission. Third, at the time of readmission, LOS and in-patient mortality was greater among HF patients. Fourth, HF patients were more likely to be readmitted within 90 days for all causes, including acute heart failure, AF and VT/VF. Lastly, among HF patients with known AVB, a 90-day readmission was less likely than those without AVB, likely due to those with conduction disease receiving a CIED during the index admission.

Sarcoidosis and heart failure:

HF has an incidence of 240 per 1000 patient-years in sarcoidosis and 12 per 1000 patient-years in patients without sarcoidosis(25). The etiology is multifactorial and can be with reduced or preserved ejection fraction(26, 27). Symptomatic HF in these patients provokes a decline in functional capacity and quality of life which are important reasons for hospitalization(28).

While our study lacked the ability to focus solely on confirmed CS cases, there is likely to be a significant proportion of the sarcoidosis plus HF patients who do indeed have CS.

CS patients with or without LV systolic dysfunction are at greater risk of ventricular arrhythmias and high-grade AVB. However, those with LVEF <40% display the lowest survival rates(29). It is estimated that HF accounts for nearly a quarter of deaths in CS(30). We found that in sarcoidosis patients, HF presence was linked to increased prevalence of arrhythmias, conduction disorders and atrial fibrillation. This in turn translated to increased LOS, greater healthcare costs and increased mortality. Our results highlight the additional burden placed on the patient as well as healthcare systems with two major comorbidities. One of the cornerstones of sarcoidosis management is immunosuppressive therapy. However, the additional fluid retention associated with corticosteroids can be deleterious in HF. Furthermore, 2nd and 3rd line treatments such as Tumour Necrosis Factor alpha (TNF-a) inhibitors can be associated with worsening LVSD in rare cases(31). Therefore, not only does the combination of sarcoidosis and

HF encompass a group of CS patients at risk of arrhythmic SCD, the sarcoidosis treatments required can occasionally exacerbate acute HF episodes. While we compared sarcoidosis patients with and without HF, other investigators have examined hospital episodes for sarcoidosis patients with and without arrhythmias. *Desai et al* identified that those with arrhythmias had significantly higher mortality (3.7 vs. 1.5%), greater hospital LOS (6.4 vs. 5.2 days), and larger hospital charges (\$64,118 vs. \$41,565) in comparison to patients without arrhythmias ($p < 0.001$)(32). This emphasizes the need for robust anti-arrhythmic surveillance and management in patients with sarcoidosis.

Corticosteroids to improve outcomes in cardiac sarcoidosis:

A study conducted on 95 Japanese patients with CS demonstrated that HF severity was an important independent predictor of mortality with a 77% rise in death per increase in NYHA class. In this study, immunosuppression with corticosteroid therapy prior to the onset of systolic dysfunction led to improved clinical outcomes(33). *Kato et al* reported on 40 CS patients of whom half presented with high-grade AVB with preserved LV systolic function. Those treated with corticosteroids demonstrated improved survival(34). Similar findings were demonstrated in another Japanese study carried out on CS patients out of whom 31 experienced premature ventricular complexes (PVCs) and 14 participants suffered from non-sustained VT (NSVT). Participants having LVEF>35% demonstrated a significant reduction in PVCs and NSVT after

treatment with prednisolone(35). All these previous studies were retrospective small, single-center studies. Our study adds to the literature using a large real world readmissions database that HF in patients with sarcoidosis have worse outcomes.

Clinical indicators of inpatient mortality in Sarcoidosis:

Our findings demonstrate that HF, advancing age, male gender, higher Charlson Comorbidity Index and the presence of liver disease are predictors of in-patient mortality once a sarcoidosis patient is readmitted to hospital. Prior studies have reported increasing age to be an independent risk factor for inpatient mortality among sarcoidosis patients(36). Similar to our findings, female gender appeared to be a protective factor. A key demographic not examined in our study was ethnicity, due to limitations within the NRD database(37). However, across the US, Black patients are known to have poorer health outcomes compared to Caucasians, particularly among those with sarcoidosis, where Black ethnicity was linked to 21% increase in in-hospital mortality(36).

Strengths and limitations:

The major strengths of our study are the large number of patients who were not confined to a single specialist center. Instead, this is a nationally representative sample thus reducing tertiary referral bias. Another strength was the robust data obtained regarding HAC and LOS and

hospital readmissions which allowed us to assess the impact of clinical variables on the healthcare system. By excluding patients with ischemic heart disease, we increased the chances that the majority of patients captured with heart failure and sarcoidosis had suspected CS. However, in the absence of histological confirmation, compatible late gadolinium enhancement on cardiac magnetic resonance imaging (CMR) and suggestive uptake on ^{18}F -fludeoxyglucose positron emission tomography (FDG-PET), no CS diagnostic criteria could be met. Therefore, other overlapping diseases such as arrhythmogenic or LAMIN cardiomyopathy could not be excluded. Our study had several other limitations. We could not exclude misclassification bias which are inherent to such large databases. A key issue was the heterogenicity in labelling HF, as this included both systolic and diastolic presentations. Furthermore, the diagnosis and coding of sarcoidosis, particularly CS has been historically poor. While CS is mostly diagnosed using advanced imaging modalities such as CMR and FDG-PET, this information was not available from the NRD database and as such ICD codes were used. Information on the use of HF and immunosuppression therapies by sarcoidosis patients was unavailable and therefore the impact of such treatment on patient outcomes could not be evaluated.

Future Directions:

Given that we have demonstrated significantly worse mortality, cost and length of stay in sarcoidosis patients with heart failure, our study calls for screening for cardiac involvement in

those patients with systemic sarcoidosis or *de novo* presentation with HF in patients suspected to have isolated CS. This can be done using screening patient symptoms, 12-lead electrocardiogram, brain natriuretic peptide (BNP) levels and echocardiography(38, 39). In order to improve outcomes, we propose the early implementation of prognostically beneficial HF medications and device therapies where relevant, in this patient cohort.

Conclusion:

Heart failure in hospitalized sarcoidosis patients is associated with increased prevalence of arrhythmia, conduction disorders and a significantly higher length of stay, healthcare-adjusted costs, 90-days readmissions and mortality following readmission. Prospective studies are necessary to validate these findings and develop preventative strategies in order to reduce mortality and healthcare burdens.

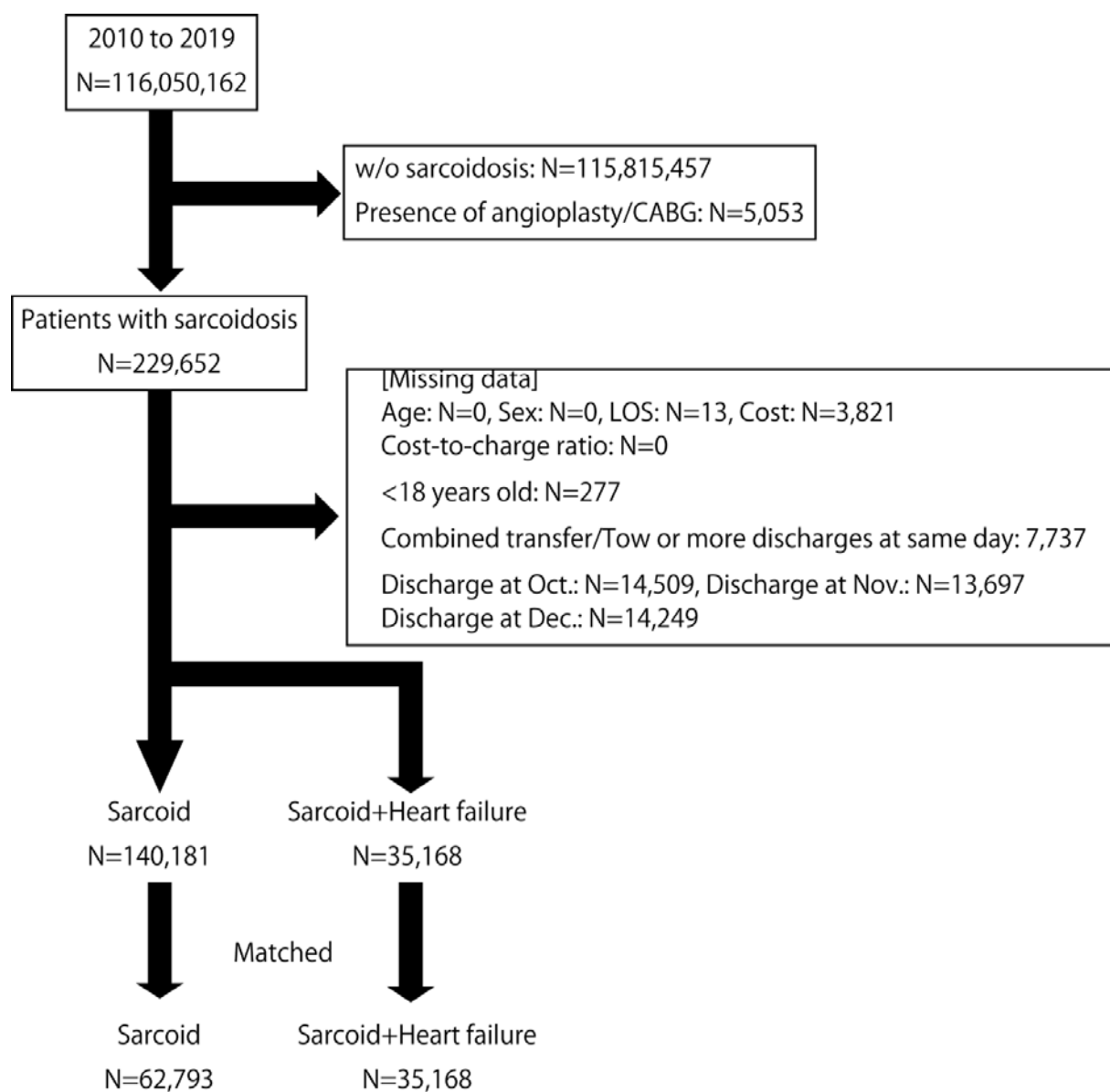
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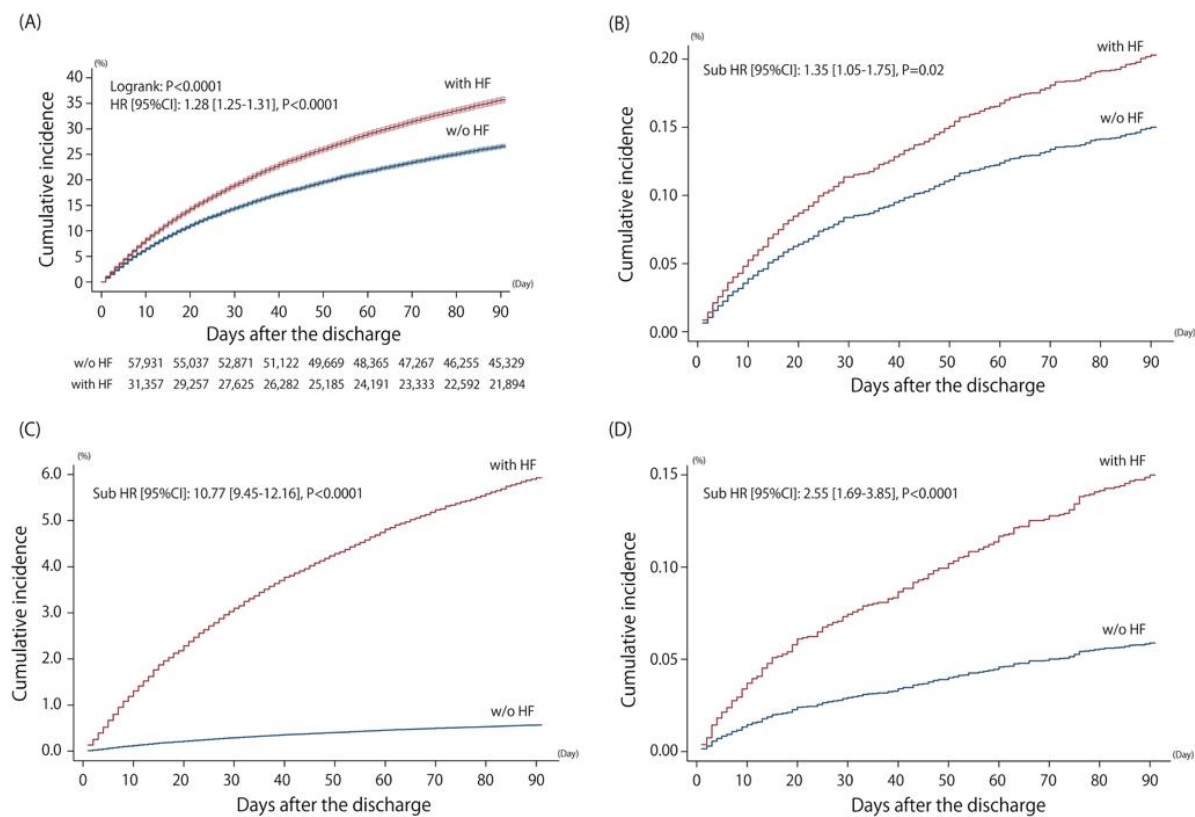
FIGURES

Figure 1 Inclusion Criteria Flow Chart



N=Number, LOS=Length of stay, HF=Heart failure

Figure 2 Kaplan-Meier Carve for 90 day readmission



(A) Readmission of All events

(B) Readmission of atrial fibrillation

(C) Readmission of heart failure

(D) Readmission of VT/VF

HF=Intracardiac echocardiography HR=Hazard ratio, CI=Confidence Interval

Shaded area indicates the 95% confidence interval.

The hazard ratio and 95%CI were adjusted for age, sex, Charlson comorbidity index, CHA2DS2-VASc score and presence of anticoagulation therapy, comorbidities and hospital bed size.

TABLES

Table 1 Clinical Characteristics at 1st admission

	All	w/o HF	with HF	P-value
Number, N (%)	97,961 (100.0)	62,793 (64.1)	35,168 (35.9)	-
Age, years	63.0 (54.0-71.0)	62.0 (53.0-71.0)	64.0 (55.0-73.0)	<0.0001
Male, N (%)	37,097 (37.9)	23,810 (37.9)	13,287 (37.8)	0.67
Charlson comorbidity index, points	3.0 (2.0-4.0)	2.0 (2.0-3.0)	3.0 (2.0-4.0)	<0.0001
Anti-coagulant therapy, N (%)	14,329 (14.6)	6,775 (10.8)	7,554 (21.5)	<0.0001
Length of stay, day	4.0 (2.0-6.0)	4.0 (2.0-6.0)	4.0 (3.0-7.0)	<0.0001
Healthcare associated cost, \$US				
Net value	32,952.0 (17,962-62,581)	31,594.0 (17,297.0-58,675.0)	35,723.5 (19,329.0-70,509.0)	<0.0001
Adjusted value	9,232.2 (5,519.2-16,290.9)	8,828.3 (5,303.1-15,384.9)	9,954.5 (5,934.7-18,128.8)	<0.0001
CIED implantation, N (%)				
PPM	539 (0.6)	289 (0.5)	250 (0.7)	<0.0001
ICD	629 (0.6)	155 (0.3)	474 (1.4)	<0.0001
CRT-P	≤50 (N/A)	≤10 (N/A)	≤40 (N/A)	<0.0001
CRT-D	301 (0.3)	25 (0.04)	276 (0.8)	<0.0001
Cardiac interventions, N (%)				
Catheter ablation	372 (0.4)	114 (0.2)	258 (0.7)	<0.0001
LVAD	≤110 (N/A)	≤10 (N/A)	≤110 (N/A)	<0.0001
Cardiac transplant	24 (0.02)	0 (0.0)	24 (0.07)	<0.0001
Comorbidities, N (%)				
Ventricular tachycardia	3,110 (3.2)	820 (1.3)	2,290 (6.5)	<0.0001
Ventricular fibrillation	247 (0.3)	91 (0.1)	156 (0.4)	<0.0001
Atrioventricular block	2,043 (2.1)	883 (1.4)	1,160 (3.3)	<0.0001
Atrial fibrillation	12,464 (12.7)	4,703 (7.5)	7,761 (22.1)	<0.0001
Cerebrovascular diseases	6,309 (6.4)	4,721 (7.5)	1,588 (4.5)	<0.0001
Chronic Pulmonary disease	46,501 (47.5)	30,136 (48.0)	16,365 (46.5)	<0.0001
Peripheral vascular diseases	8,165 (8.3)	3,931 (6.3)	4,234 (12.0)	<0.0001

Liver diseases	6,878 (7.0)	5,205 (8.3)	1,673 (4.8)	<0.0001
Diabetes	43,515 (44.4)	29,241 (46.6)	14,274 (40.6)	<0.0001
Renal diseases	31,545 (32.2)	18,677 (29.7)	12,868 (36.6)	<0.0001
Hypertension	61,106 (62.4)	45,170 (71.9)	15,936 (45.3)	<0.0001
Coagulation defects	1,104 (1.1)	680 (1.1)	424 (1.2)	0.08
Obesity	22,800 (23.3)	13,091 (20.9)	9,709 (27.6)	<0.0001
Hospital bed size, N (%)				
Small	12,805 (13.1)	8,272 (13.2)	4,533 (12.9)	
Medium	26,403 (27.0)	17,020 (27.1)	9,383 (26.7)	
Large	58,753 (60.0)	37,501 (59.7)	21,252 (60.4)	0.09
Primary payer, N (%)				
Medicare/Medicaid	69,987 (71.6)	43,071 (68.7)	26,916 (76.7)	
Private insurance	22,646 (23.2)	16,153 (25.8)	6,493 (18.5)	
Others	5,152 (5.3)	3,459 (5.5)	1,693 (4.8)	<0.0001

HF=Intracardiac echocardiography, N=Number, HAC=Healthcare associated cost

Table 2 Differences on index admission observed between patients with readmissions and those without readmissions at 90 days

	w/o HF			with HF		
	w/o readmission	with readmission	*P-value	w/o readmission	with readmission	*P-value
Number, N (%)	46,407 (73.9)	16,386 (26.1)	-	23,052 (65.6)	12,116 (34.5)	-
Age, years	62.0 (53.0-71.0)	62.0 (53.0-71.0)	0.02	64.0 (55.0-73.0)	64.0 (55.0-73.0)	0.004
				99% (35.0-90.0)	99% (34.0-90.0)	
Male, N (%)	17,520 (37.8)	6,290 (38.4)	0.15	8,731 (37.9)	4,556 (37.6)	0.62
Charlson comorbidity index, points	2.0 (2.0-3.0)	3.0 (2.0-4.0)	<0.0001	3.0 (2.0-4.0)	3.0 (2.0-5.0)	<0.0001
Anti-coagulant therapy, N (%)	4,307 (9.3)	2,468 (15.1)	<0.0001	4,318 (18.7)	3,236 (26.7)	<0.0001
Length of stay, day	3.0 (2.0-6.0)	4.0 (3.0-7.0)	<0.0001	4.0 (2.0-7.0)	5.0 (3.0-8.0)	<0.0001
CIED implantation, N (%)						
PPM	232 (0.5)	57 (0.4)	0.01	193 (0.8)	57 (0.5)	<0.0001
ICD	132 (0.3)	23 (0.1)	0.001	339 (1.5)	135 (1.1)	0.006
CRT-P	≤10 (N/A)	0 (0.0)	0.24	≤40 (N/A)	≤10 (N/A)	0.001
CRT-D	≤30 (N/A)	≤10 (N/A)	0.11	199 (0.9)	77 (0.6)	0.02
Cardiac interventions, N (%)						
Catheter ablation	95 (0.2)	19 (0.1)	0.02	181 (0.8)	77 (0.6)	0.12
LVAD	0 (0.0)	≤10 (N/A)	0.02	62 (0.3)	45 (0.4)	0.10

Cardiac transplant	0 (0.0)	0 (0.0)	-	≤30 (N/A)	≤10 (N/A)	0.07
Healthcare associated cost, \$US						
Net value	30,839.0 (16,981.0-57,239.0)	33,866.5 (18,264.0-62,888.0)	<0.0001	35,001.5 (18,946.0-69,885.0)	37,095.0 (20,172.5-71,774.0)	<0.0001
Adjusted value	8,639.4 (5,204.1-15,006.2)	9,383.5 (5,634.5-16,471.3)	<0.0001	9,797.2 (5,811.7-18,028.3)	10,289.3 (6,164.0-18,325.1)	<0.0001
Comorbidities, N (%)						
Ventricular tachycardia	609 (1.3)	211 (1.3)	0.81	1,508 (6.5)	782 (6.5)	0.75
Ventricular fibrillation	69 (0.2)	22 (0.1)	0.62	116 (0.5)	40 (0.3)	0.02
Atrioventricular block	674 (1.5)	209 (1.3)	0.10	819 (3.6)	341 (2.8)	<0.0001
Atrial fibrillation	3,296 (7.1)	1,407 (8.6)	<0.0001	4,877 (21.2)	2,884 (23.8)	<0.0001
Cerebrovascular diseases	3,662 (7.9)	1,059 (6.5)	<0.001	1,032 (4.5)	556 (4.6)	0.63
Chronic Pulmonary disease	22,419 (48.3)	7,717 (47.1)	0.007	10,372 (45.0)	5,993 (49.5)	<0.0001
Peripheral vascular diseases	2,810 (6.1)	1,121 (6.8)	<0.0001	2,725 (11.8)	1,509 (12.5)	0.08
Liver diseases	3,602 (7.8)	1,603 (9.8)	<0.0001	1,023 (4.4)	650 (5.4)	<0.0001
Diabetes	21,049 (45.4)	8,192 (50.0)	<0.0001	8,764 (38.0)	5,510 (45.5)	<0.0001
Renal diseases	13,127 (28.3)	5,550 (33.9)	<0.0001	7,784 (33.8)	5,084 (42.0)	<0.0001
Hypertension	33,363 (71.9)	11,807 (72.1)	0.69	10,385 (45.1)	5,551 (45.8)	0.17
Coagulation defects	473 (1.0)	207 (1.3)	0.009	271 (1.2)	153 (1.3)	0.48
Obesity	9,898 (21.3)	3,193 (19.5)	<0.0001	6,407 (27.8)	3,302 (27.3)	0.28

Hospital bed size, N (%)

Small	6,246 (13.5)	2,026 (12.4)		2,952 (12.8)	1,581 (13.1)	
Medium	12,616 (27.2)	4,404 (26.9)		6,175 (36.8)	3,208 (26.5)	
Large	27,545 (59.4)	9,956 (60.8)	<0.0001	13,925 (60.4)	7,327 (60.5)	0.72

Primary payer, N (%)

Medicare/Medicaid	30,977 (66.9)	12,094 (73.9)		17,231 (49.1)	9,685 (80.1)	
Private insurance	12,634 (27.3)	3,519 (21.5)		4,573 (19.9)	1,920 (15.9)	
Others	2,714 (5.9)	745 (4.6)	<0.0001	1,206 (5.2)	487 (4.0)	<0.0001

HF=Intracardiac echocardiography, N=Number, HAC=Healthcare associated cost

*We compared differences between the patients with event and those without event.

Table 3 Reasons for admission

(A) First admission

	w/o HF	with HF	P-value
VT/VF	208 (0.3)	527 (1.5)	<0.0001
Atrioventricular block	168 (0.3)	150 (0.4)	<0.0001
Atrial fibrillation	494 (0.8)	653 (1.9)	<0.0001
Acute Heart Failure	0 (0.0)	7,558 (21.5)	<0.0001
Cardiac arrest	14 (0.02)	21 (0.06)	0.003

(B) Second admission

	w/o HF	with HF	P-value
VT/VF	52 (0.3)	183 (1.5)	<0.0001
Atrioventricular block	≤10 (N/A)	13 (0.1)	0.17
Atrial fibrillation	140 (0.9)	213 (1.8)	<0.0001
Acute Heart Failure	367 (2.2)	2,307 (19.0)	<0.0001
Cardiac arrest	≤10 (N/A)	≤10 (N/A)	0.41

Values are shown as number (%).

Table 4 Predictors at 1st admission for readmission

	HR (95% CI)	P-value
Age	1.00 (1.00-1.00)	<0.0001
Male	0.98 (0.95-1.00)	0.07
Charlson comorbidity index	1.10 (1.09-1.11)	<0.0001
VT/VF	1.05 (0.98-1.12)	0.14
Atrioventricular block	0.87 (0.80-0.94)	0.001
Atrial fibrillation	1.06 (1.02-1.10)	0.001
Anti-coagulant therapy	1.47 (1.43-1.52)	<0.0001
Cerebrovascular diseases	0.85 (0.81-0.90)	<0.0001
Chronic Pulmonary disease	1.03 (1.01-1.06)	0.01
Peripheral vascular diseases	0.95 (0.91-0.99)	0.009
Liver diseases	1.11 (1.06-1.16)	<0.0001
Diabetes	1.14 (1.11-1.17)	<0.0001
Renal diseases	1.14 (1.11-1.18)	<0.0001
Hypertension	0.97 (0.95-1.00)	0.03
Coagulation defects	1.20 (1.08-1.33)	0.001
Obesity	0.88 (0.86-0.91)	<0.0001
Hospital bed size		
Small	(ref.)	-
Medium	1.02 (0.98-1.07)	0.23
Large	1.04 (1.00-1.08)	0.03

HF=Intracardiac echocardiography, HR=Hazard ratio, CI= Confidence Interval

Table 5 Differences between patients with HF and those without HF at readmission

	w/o HF	with HF	P-value
In-hospital death, N (%)	616 (3.8)	613 (5.1)	<0.0001
Length of stay, day	4.0 (3.0-7.0)	5.0 (3.0-8.0)	<0.0001
Healthcare associated cost, \$US			
Net value	32,838.0 (17,648.0-64,934.0)	34,885.0 (18,589.0-69,922.5)	<0.0001
Adjusted value	9,087.1 (5,378.3-16,966.1)	9,667.0 (5,626.6-18,076.6)	<0.0001

HF=Intracardiac echocardiography, N=Number, HAC: Healthcare associated cost

Table 6 Predictors of increasing LOS, HAC, and in-hospital death at readmission

	LOS		Adjusted HAC		In-hospital death	
	β	P-value	β	P-value	OR (95%CI)	P-value
HF	0.015	0.02	0.014	0.04	1.24 (1.09-1.41)	0.001
Age	0.009	0.14	0.002	0.71	1.03 (1.02-1.03)	<0.0001
Male	0.001	0.86	0.018	0.004	1.20 (1.06-1.35)	0.003
Charlson comorbidity index	0.023	0.002	0.017	0.02	1.14 (1.10-1.17)	<0.0001
Anti-coagulant therapy	-0.006	0.35	0.006	0.31	0.76 (0.65-0.89)	0.001
VT/VF	0.006	0.33	0.036	<0.0001	1.02 (0.75-1.38)	0.90
Atrioventricular block	0.027	0.65	0.020	0.001	0.81 (0.52-1.26)	0.35
Atrial fibrillation	0.009	0.14	0.004	0.51	1.09 (0.92-1.27)	0.32
Cerebrovascular diseases	0.012	0.048	0.0003	0.96	0.79 (0.61-1.03)	0.08
Chronic Pulmonary disease	-0.034	<0.0001	-0.042	<0.0001	0.91 (0.81-1.02)	0.11
Peripheral vascular diseases	-0.003	0.66	0.020	0.001	0.76 (0.62-0.94)	0.01
Liver diseases	0.010	0.11	0.022	<0.0001	1.29 (1.06-1.57)	0.01
Diabetes	0.001	0.85	-0.017	0.006	0.75 (0.66-0.84)	<0.0001
Renal diseases	0.019	0.007	0.008	0.27	0.87 (0.77-0.99)	0.04
Hypertension	-0.018	0.004	-0.035	<0.0001	0.86 (0.76-0.97)	0.02
Coagulation defects	0.023	<0.0001	0.018	0.002	1.40 (0.91-2.16)	0.13
Obesity	0.007	0.22	0.007	0.26	0.75 (0.64-0.88)	<0.0001
Hospital bed size						
Small	(ref.)	-	(ref.)	-	(ref.)	-
Medium	-0.001	0.91	-0.011	0.21	1.12 (0.92-1.37)	0.27
Large	0.042	<0.0001	0.038	<0.0001	1.17 (0.97-1.40)	0.11

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