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Original Article

Comparison of long-term outcomes in patients with cardiac sarcoidosis treated with different immunosuppressive drugs

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Abstract: Background: We compared long-term clinical outcomes between patients with cardiac sarcoidosis (CS) who received no treatment (NT), steroid treatment (ST), disease-modifying anti-rheumatic drugs (DMARDs), or tumor necrosis factor alpha inhibitors (TNF). Methods: Patients from SSM healthcare system's data warehouse were identified using ICD codes. Inclusion criteria included at least 6 months of follow-up. Outcomes studied were heart failure (HF) admissions, ventricular tachyarrhythmias (VTA), and pacemaker/defibrillator placement. Statistical analysis included multivariate logistic regression and Kaplan-Meier curves. Results: We identified 198, 174, 66, and 19 patients in NT, ST, DMARDs, and TNF groups respectively. Mean age was 62.4, 60.2, 56, and 54.4 respectively. There was no significant difference in the rate of medical comorbidities including pulmonary sarcoidosis between the groups. Mean follow up was 92.3 months. Percent incidences of VTA were 17.5, 16.3, 12.5, and 5.6 (P 0.57) in the NT, ST, DMARDs and TNF groups respectively. DMARDs and TNF groups had a lower incidence of HF admission (43.9% and 36.8%) compared to NT and ST (59.1% and 59.2%). In the multivariate model, compared to NT group, the odds ratio for HF admission was 1.08 (CI: 0.70-1.65), 0.64 (0.36-1.14) and 0.45 (0.17-1.20) in the ST, DMARDs and TNF groups respectively. There was no significant difference in the rate of pacemaker/defibrillator placement between the groups. Conclusion: In this retrospective study from a large healthcare system, CS patients treated with DMARDs or TNF had a trend for lower incidence of HF admission than those on NT or ST.

Keywords: Cardiac sarcoidosis, heart failure, ventricular tachyarrhythmias, disease-modifying anti-rheumatic drugs, tumor necrosis factor alpha inhibitors

Introduction

Sarcoidosis is a multi-system granulomatous disorder, primarily affecting the lungs, and cardiac sarcoidosis (CS) is a rare manifestation that typically presents as an infiltrative cardiomyopathy, either in isolation or as part of systemic sarcoidosis [1]. Autopsy studies and systematic evaluations using magnetic resonance imaging (MRI) suggest that cardiac involvement occurs up to 30% of patients with systemic disease [2]. Patients with symptomatic CS and coexisting pulmonary involvement experience worse survival than other patients with extracardiac sarcoidosis [3, 4]. The three main manifestations of CS are ventricular arrhythmias, atrioventricular block, and heart failure (HF) [5, 6]. In patients with CS, the cardiomyopathy can manifest as either dilated cardiomyopathy with reduced left ventricular ejection fraction (LVEF) or as restrictive cardiomyopathy with normal LVEF. A common cause of mortality in patients with CS is sudden cardiac death secondary to ventricular arrhythmias [7-11].

The extreme heterogeneity in disease activity and long-term outcomes presents significant challenges in disease management. The decision to initiate treatment must be carefully balanced against the potential side effects of immunomodulatory therapies. Expert consensus recommends immunosuppressive therapy

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for symptomatic patients with CS, including those with heart failure (HF) due to left ventricular systolic dysfunction, heart block, or ventricular arrhythmias, provided there is evidence of active myocardial inflammation, as indicated by FDG-PET or myocardial histology. Because of the low event rate in observational studies of asymptomatic patients, treatment is often individualized, considering the risks and benefits, the burden of cardiac inflammation, and the extent of extracardiac inflammation [12, 13]. The goal of immunosuppressive therapy in CS patients is to control the inflammatory response and mitigate cardiac damage. Glucocorticoids have traditionally been the first-line therapy for CS, but their long-term use is associated with several adverse effects including infections, diabetes, weight gain, and osteoporosis [14]. Although corticosteroids are considered the first-line treatment for CS, several studies have shown that corticosteroid monotherapy leads to higher rates of relapse and disease progression [15-18]. As a result, glucocorticoid-sparing agents are increasingly used, either in combination with or as an alternative to glucocorticoids. These agents include disease-modifying anti-rheumatic drugs (DMARDs), most commonly methotrexate, and tumor necrosis factor-alpha inhibitors (TNF inhibitors). There is a paucity of data from randomized, placebo-controlled clinical trials specifically focused on CS. The addition of a glucocorticoid-sparing agent to glucocorticoid therapy has been shown to be helpful in minimizing glucocorticoid-related toxicities [14, 19, 20] and reducing disease activity, as measured by fluorodeoxyglucose (FDG) cardiac uptake [21-26]. Furthermore, long-term follow-up studies have reported a decreased risk of radiological relapse, improved LVEF, and reduced high-grade heart block or ventricular tachycardia, and sudden death [23]. However, the level of evidence to support different treatment approaches for CS is low, with multiple potential confounders and biases inherent in the available studies [27]. We aimed to compare the long-term clinical efficacy of the different immunosuppressive drug regimens in patients with CS from a large healthcare system database.

Methods

Data were obtained from Saint Louis University-SSM (SLU-SSM) healthcare system's Virtual Data Warehouse (VDW). SLU-SSM is a member site of the Health Care Systems Research Network (HCSRN) (www.hcsrn.org) and the VDW was created and is maintained per HCSRN specifications. The SSM healthcare system includes locations in Missouri, Illinois, Oklahoma, and Wisconsin. The VDW contains deidentified clinical data for over 5 million patients dating back to 2008. Because patients do not actively participate and all data is de-identified, all studies utilizing VDW data are approved as non-human subjects research by the Saint Louis University Institutional Review Board.

The inclusion criteria were based on the following key indicators: 1) Age: Patients aged 18 or older at the time of diagnosis. 2) Diagnosis of CS-related conditions: A new diagnosis of CS, identified through ICD-9 or ICD-10 codes, starting from 1/1/2011. 3) Healthcare Activity: Evidence of healthcare activity in the two years prior to and six months following the diagnosis to ensure patients primarily received care within the SLU-SSM healthcare system.

Exclusion criteria included: Patients with a history of ischemic cardiomyopathy or non-ischemic cardiomyopathy due to other etiologies other than CS, e.g. valvular heart disease, alcoholic cardiomyopathy, or cardiac amyloidosis (ICD codes provided in **Appendix 1**).

Medications were categorized into four groups based on prescription records: 1) No Treatment (NT): Patients who did not receive any prescription for corticosteroids, disease-modifying antirheumatic drugs (DMARDs), or tumor necrosis factor (TNF) inhibitors following their CS diagnosis. 2) Steroids (ST): Patients who were prescribed corticosteroids after their CS diagnosis. 3) DMARDs: Patients prescribed disease-modifying antirheumatic drugs (DMARDs), including methotrexate, hydroxychloroquine, and others, after the CS diagnosis. 4) TNF inhibitors: Patients who received TNF inhibitors such as infliximab or adalimumab following the CS diagnosis. Patients receiving both steroids and either DMARDs or TNF inhibitors were included in the DMARDs or TNF groups, respectively, based on the primary treatment. Prescriptions were tracked for medications filled following the CS diagnosis but prior to the studied outcomes to ensure the temporal sequence of treatment was accurately captured. The specif-

ic ICD codes and medication classes used to define each treatment group are detailed in **Appendices 1** and **2**. Outcomes were defined using the following indicators, all of which were identified through electronic chart review and ICD codes in the VDW: 1) Heart Failure (HF): Defined by inpatient admissions with a primary diagnosis of HF using ICD-9 and ICD-10 codes. 2) Pacemaker or Defibrillator Placement: Identified through procedure codes for pacemaker or defibrillator implantation. This includes relevant CPT and ICD-9/ICD-10 procedure codes. 3) Ventricular Tachyarrhythmia (VTA): Diagnosed based on specific ICD-9/ICD-10 codes for VTA. Detailed definitions for all ICD codes for outcome definitions are provided in **Appendices 1** and **3**.

Statistical analysis

Covariates included patient-level characteristics such as age at diagnosis, race, and the presence of comorbid medical conditions, which are critical in adjusting for confounding factors in the analysis. Detailed definitions for all covariates, are provided in **Appendices 1** and **3**.

Bivariate associations between treatment groups (NT, ST, DMARDs, and TNF) and outcomes (HF, VTA, device placement) were assessed using Student's t-tests for continuous variables and Chi-square or Fisher's exact tests for categorical variables. To examine the association between medication use and clinical outcomes, logistic regression models were used to estimate odds ratios for each outcome, adjusting for potential confounders such as age, race, and comorbidities. Kaplan-Meier survival curves were employed to compare the time to the occurrence of the study outcomes, and differences were assessed using the log-rank test. All statistical analyses were conducted using SAS v9.4 (Cary, NC), with a significance level set at an alpha of 0.05.

Results

Baseline characteristics are listed in **Table 1**. A total of 457 CS patients were identified with 198, 174, 66, and 19 patients in NT, ST, DMARDs, and TNF groups, respectively. The mean age was 62.4, 60.2, 56, and 54.4, respectively, and patients were predominantly female (65%). There were no major differences between patient groups in terms of baseline clinical comorbidities. There was no significant difference either in the prevalence of pulmonary sarcoidosis between groups.

Clinical outcomes are listed in **Table 2**. DMARDs and TNF groups had a significantly lower incidence of HF admissions (43.9% and 36.8%) compared to NT and ST (59.1% and 59.2%). There was no significant difference in the incidence of VTA, atrioventricular block or need for device placement between the groups. In the unadjusted logistic regression (**Table 3**), compared to NT group, DMARDs had significantly lower odds for HF admission (odds ratio [OR]: 0.54, confidence interval [CI]: 0.31-0.95) and VTA (OR: 0.39, CI: 0.16-0.94). TNF therapy showed a trend toward lower HF admissions (OR: 0.40, CI: 0.15-1.07). After adjusting for demographics and relevant comorbidities, there was a trend toward lower HF admissions in DMARDs (OR: 0.64, CI: 0.36-1.14) and TNF (OR: 0.45, CI: 0.17-1.2) groups (**Table 4**). There was no significant association between the remaining groups and HF admission. **Figures 1-4** show the survival analysis results for the study outcomes. Survival rates of patients using DMARDs or TNF were higher compared to NT or ST for HF admission (P 0.008) (**Figure 1**) and VTA (P 0.04) (**Figure 2**). There was no statistically significant difference for survival rates before pacemaker (**Figure 3**) or defibrillator implantation (**Figure 4**) between groups.

Discussion

In this retrospective study comparing treatment regimens in CS patients from a large healthcare system, the main findings were: 1) patients treated with DMARDs or TNF had longer survival before HF admissions and VTA; and 2) there was no difference between the groups in terms of survival free from the need for an intracardiac device placement.

As previously mentioned, most of the evidence for CS management is derived from retrospective trials which vary in quality, sample size, diagnostic criteria used and methods of assessing drug efficacy. In our multivariate logistic regression model, DMARDs and TNF did not reach statistical significance for the study outcomes, likely due to the relatively small sample size. Survival curves clearly show that DMARDs and TNF patients survived longer free of both

Table 1. Patient characteristics

Characteristic	Cardiac Sarcoidosis (n=457)	Medication Category				*p*-value
		No Treatment (n=198)	Steroids (n=174)	DMARD (n=66)	TNF (n=19)	
Age, mean ± SD (years)	60.3 ± 11.7	62.4 ± 10.5	60.2 ± 11.9	56.0 ± 13.5	54.4 ± 8.6	**<0.001**
Follow up, mean ± SD (months)	92.3 ± 39.4	90.3 ± 38.9	92.1 ± 37.2	96.3 ± 45.4	100.8 ± 43	0.56
Race/Ethnicity	--	--	--	--	--	0.45
White (%)	218 (47.7)	102 (51.5)	78 (44.8)	28 (42.4)	10 (52.6)	--
Other (%)	239 (52.3)	96 (48.5)	96 (55.2)	38 (57.6)	9 (47.4)	--
Sex	--	--	--	--	--	0.40
Female (%)	296 (64.8)	126 (63.6)	118 (67.8)	38 (57.6)	14 (73.7)	--
Male (%)	161 (35.2)	72 (36.4)	56 (32.2)	28 (42.4)	5 (26.3)	--
Smoker (%)	79 (17.3)	28 (14.1)	31 (17.8)	14 (21.2)	6 (31.6)	0.18
Diabetes (%)	152 (33.3)	75 (37.9)	57 (32.8)	13 (19.7)	7 (36.8)	**0.049**
Hypertension (%)	245 (53.6)	106 (53.5)	96 (55.2)	33 (50)	10 (52.6)	0.91
Dyslipidemia (%)	184 (40.3)	97 (49)	60 (34.5)	21 (31.8)	6 (31.6)	**0.01**
Sleep apnea (%)	99 (21.7)	46 (23.2)	33 (19)	14 (21.2)	6 (31.6)	0.51
Atrial fibrillation (%)	36 (7.9)	23 (11.6)	10 (5.7)	2 (3)	1 (5.3)	0.07
History of ICD (%)	20 (4.4)	12 (6.1)	5 (2.9)	2 (3)	1 (5.3)	0.39
History of pacemaker (%)	28 (6.1)	16 (8.1)	7 (4)	5 (7.6)	--	0.29
Lung sarcoidosis (%)	357 (78.1)	149 (75.3)	143 (82.2)	49 (74.2)	16 (84.2)	0.32
Skin sarcoidosis (%)	11 (2.4)	4 (2)	2 (1.1)	3 (4.5)	2 (10.5)	**0.048**
Eye sarcoidosis (%)	1 (0.2)	1 (0.5)	--	--	--	--
History of stroke (%)	42 (9.2)	15 (7.6)	22 (12.6)	4 (6.1)	1 (5.3)	0.28
History of MI (%)	13 (2.8)	4 (2)	6 (3.4)	3 (4.5)	--	0.61
CAD (%)	60 (13.1)	23 (11.6)	30 (17.2)	6 (9.1)	1 (5.3)	0.22
PVD (%)	28 (6.1)	14 (7.1)	13 (7.5)	1 (1.5)	--	0.24
Chronic lung disease (%)	166 (36.3)	65 (32.8)	71 (40.8)	20 (30.3)	10 (52.6)	0.13
Chronic kidney disease (%)	64 (14)	36 (18.2)	22 (12.6)	5 (7.6)	1 (5.3)	0.10

DMARD = disease-modifying anti-rheumatic drugs; TNF = tumor necrosis factor-alpha inhibitors; ICD = implantable cardioverter defibrillator; MI = myocardial infarction; CAD = coronary artery disease; PVD = peripheral vascular disease. Significant *p*-values are shown in bold.

HF admission and VTA. Our study results are consistent with the evidence from prior studies. In the study by Nagai et al. [28], weekly methotrexate (DMARDs) combined with low-dose steroids demonstrated significantly greater stabilization of LVEF, cardiothoracic ratio, and N terminal pro B-type natriuretic peptide levels, compared to steroid monotherapy. Another study by Rosenthal et al. [18] assessed the efficacy of methotrexate with or without adalimumab (TNF), concluding that the regimen effectively slowed disease progression, and discontinuation increased the risk of recurrent VTA. However, methotrexate did not show benefit in CS patients who did not respond to the initial steroid regimen, compared to redosing with steroids [29]. Vorselaars et al. [20] conducted a study comparing methotrexate to azathioprine, another potential immunomodulatory, as second line therapies for sarcoidosis and found that both had significant steroid-sparing potency and similar side effects, except for a higher infection rate with azathioprine. Anti-TNF therapy has not proven efficacy in all patients with congestive HF. In the ATTACH (Anti-TNF Therapy Against Congestive Heart Failure) trial, there was an association with high dose infliximab and worsening heart failure [30]. This study included patients with both ischemic and nonischemic heart failure, with a large proportion having noninflammatory forms of heart failure [30, 31]. In the study by Gilotra et al. of 38 patients, TNF treatment guided by FDG-PET imaging minimized corticosteroid use and effectively reduced cardiac inflammation without significant adverse effects on cardiac func-

Table 2. Clinical outcomes

Cardiac Outcome (%)	No Treatment (n=198)	Steroids (n=174)	DMARD (n=66)	TNF (n=19)	*p*-value
HF admission	117 (59.1)	103 (59.2)	29 (43.9)	7 (36.8)	**0.04**
Defibrillator implantation	8 (4.1)	11 (6.4)	4 (6.1)	2 (11.1)	0.41
Pacemaker implantation	17 (8.9)	11 (6.4)	5 (7.6)	1 (5.6)	0.87
Ventricular tachyarrhythmia	33 (17.5)	27 (16.3)	8 (12.5)	1 (5.6)	0.58
Right bundle branch block	12 (6.2)	17 (9.9)	5 (7.6)	1 (5.6)	0.61
Left bundle branch block	14 (7.1)	6 (3.5)	1 (1.5)	--	0.22
1st degree heart block	8 (4)	4 (2.3)	2 (3.1)	1 (5.6)	0.56
2nd degree heart block	6 (3.1)	1 (0.6)	2 (3)	--	0.25
Complete heart block	11 (5.8)	6 (3.5)	2 (3.2)	--	0.69

DMARD = disease-modifying anti-rheumatic drugs; TNF = tumor necrosis factor-alpha inhibitors; HF = heart failure. Significant *p*-values are shown in bold.

Table 3. Unadjusted logistic regression and survival analysis of cardiac outcomes for different immunosuppressive drugs

Sarcoid Medications	Heart Failure Admission (95% CI)	Defibrillator (95% CI)	Pacemaker (95% CI)	Ventricular Tachyarrhythmias (95% CI)
No Treatment	Ref	Ref	Ref	Ref
Steroids	1.00 (0.66-1.52)	0.69 (0.27-1.78)	**0.38 (0.17-0.86)**	0.76 (0.44-1.34)
DMARD	**0.54 (0.31-0.95)**	1.08 (0.37-3.14)	0.55 (0.21-1.45)	**0.39 (0.16-0.94)**
TNF	0.40 (0.15-1.07)	0.63 (0.08-5.24)	0.32 (0.04-2.48)	0.38 (0.08-1.70)

DMARD = disease-modifying anti-rheumatic drugs; TNF = tumor necrosis factor-alpha inhibitors. Significant *p*-values are shown in bold.

Table 4. Adjusted logistic regression of cardiac outcomes for different immunosuppressive drugs

Characteristic	Heart Failure Admission (95% CI)
No Treatment	Ref
Steroids	1.08 (0.70-1.65)
DMARD	0.64 (0.36-1.14)
TNF	0.45 (0.17-1.20)
Age	1.01 (0.99-1.03)
Diabetes	**1.56 (1.03-2.36)**
Dyslipidemia	1.20 (0.80-1.81)
CAD	1.05 (0.59-1.88)

DMARD = disease-modifying anti-rheumatic drugs; TNF = tumor necrosis factor-alpha inhibitors; CAD = coronary artery disease. Significant *p*-values are shown in bold.

tion. Four patients required inpatient heart failure treatment, and 8 had infections; 2 required treatment cessation [32]. The search continues for the ideal drug agent(s) which would achieve clinical remission while mitigating the need for high dose steroids. The role of cardiac magnetic resonance, in conjunction with FDG-PET, in prognosticating patients and guiding management is increasingly recognized [33, 34]. MAGiC-ART is an ongoing pilot trail that aims to enroll 28 patients with CS to compare the administration of an IL-1 blocker, anakinra, 100 mg daily on top of standard of care versus standard of care only [35].

Interestingly, in our study, NT group had a tendency for worse clinical outcomes, compared to DMARDs and TNF groups. That is counterintuitive as this group presumably had quiescent cardiac involvement. Possible explanations to this include that the diagnosis of active CS was missed in these patients, or they might have had subclinical disease that first manifested with clinical HF.

Our study has several limitations. The retrospective nature of the study has its inherent limitations. In addition, we had no data on the severity of extracardiac sarcoidosis. We could not confirm whether the treatment provided specifically targeted cardiac involvement or extracardiac disease, except for the temporal association between diagnosis and treatment. Specific dosing data for each treatment regi-

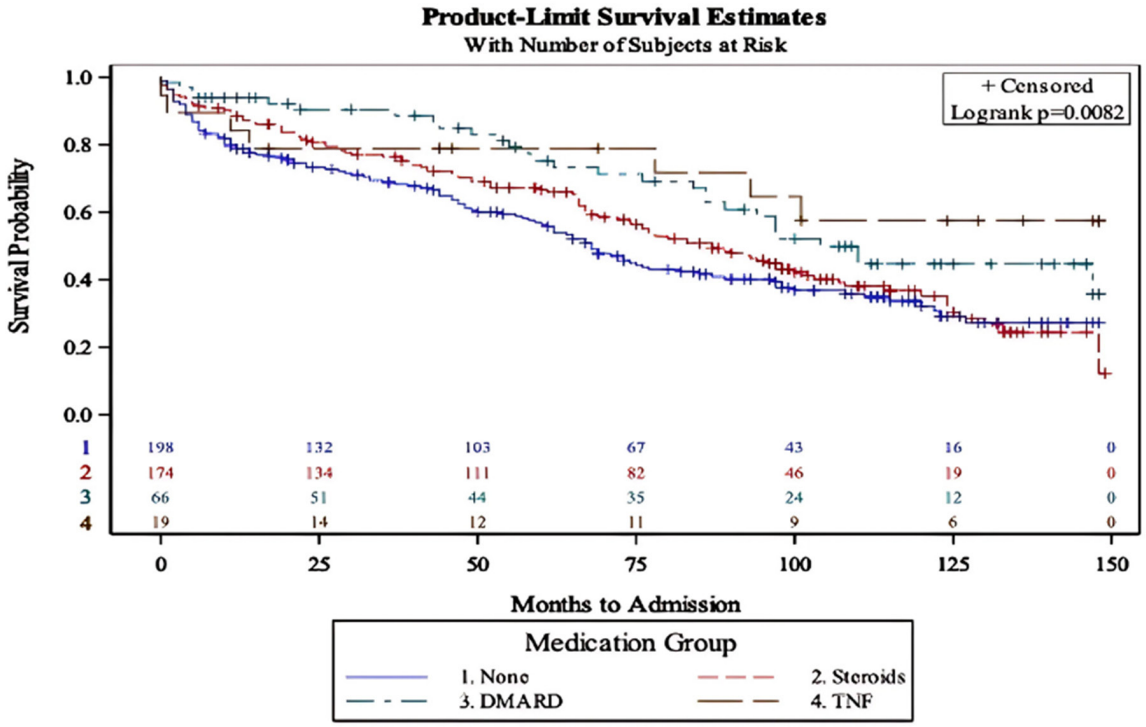

Figure 1. Kaplan-Meier curve for heart failure admission in no treatment (none), steroids, disease modifying anti-rheumatic drug (DMARD), tumor necrosis factor alpha inhibitors (TNF) groups.

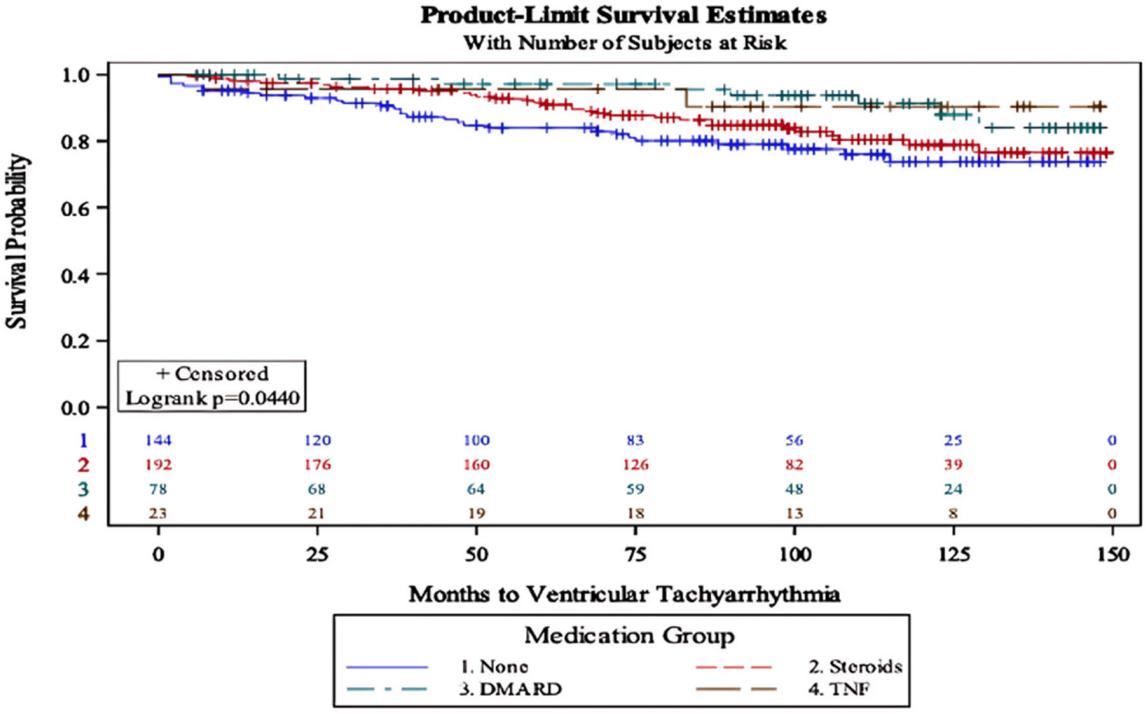

Figure 2. Kaplan-Meier curve for ventricular tachyarrhythmia in no treatment (none), steroids, disease modifying anti-rheumatic drug (DMARD), tumor necrosis factor alpha inhibitors (TNF) groups.

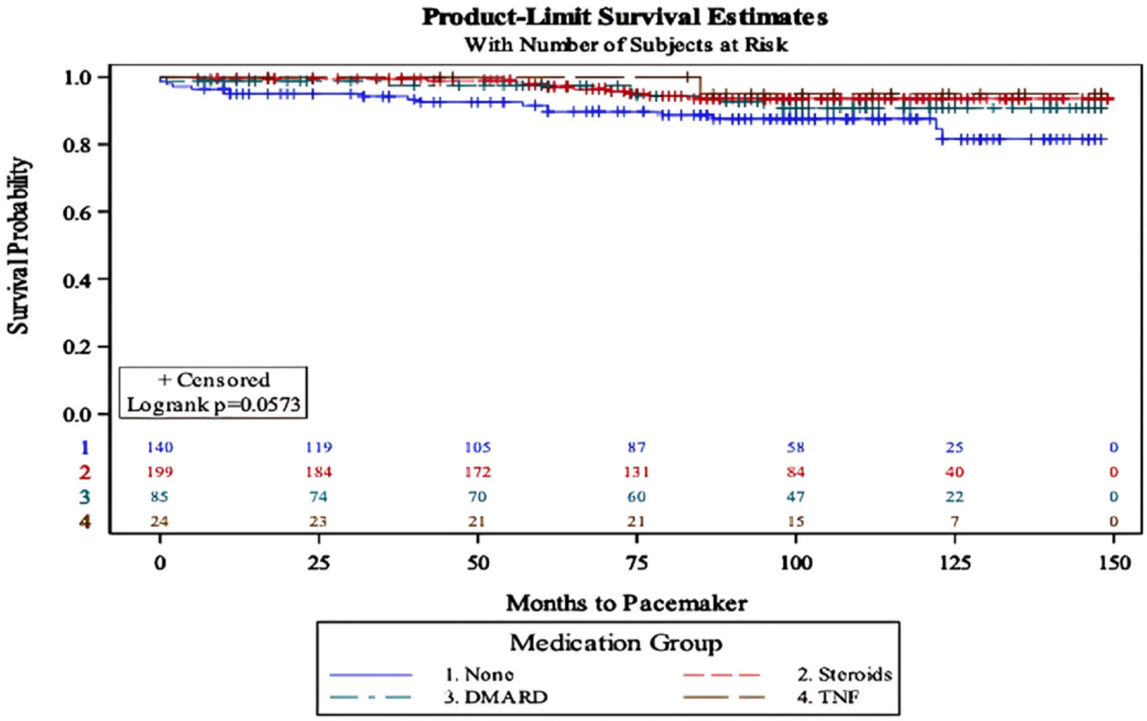

Figure 3. Kaplan-Meier curve for pacemaker implantation in no treatment (none), steroids, disease modifying anti-rheumatic drug (DMARD), tumor necrosis factor alpha inhibitors (TNF) groups.

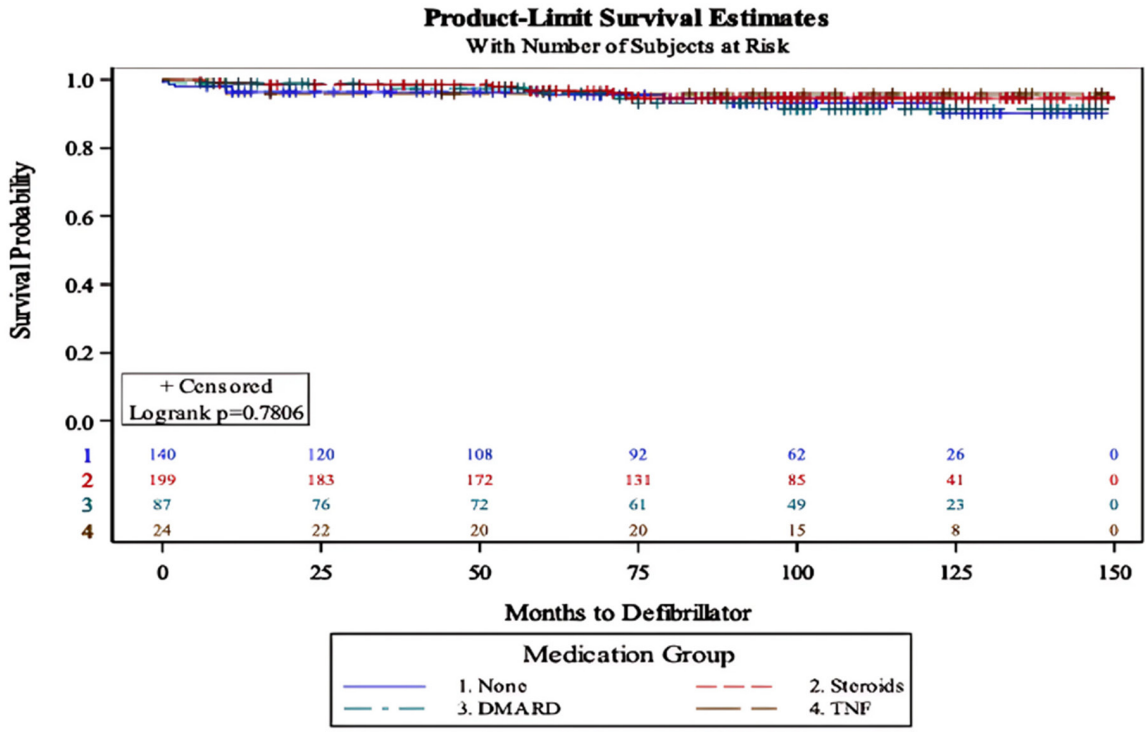

Figure 4. Kaplan-Meier curve for defibrillator implantation in no treatment (none), steroids, disease modifying anti-rheumatic drug (DMARD), tumor necrosis factor alpha inhibitors (TNF) groups.

men were unavailable, and dosing could impact the efficacy and tolerance of the different treatments. As the VDW data available is deidentified, we were not able to include mortality data in our analysis. Additionally, details of HF management, including in-hospital therapies, decongestion efficiency, and outpatient optimization of guideline-directed medical therapies, were unavailable, potentially affecting the course and future hospitalizations. The database, limited to the hospitals in the SSM network, excluded care received outside this system, leading to an underestimation of results, albeit partially mitigated by including only patients with a history of follow-up in our system. Lastly, the study could not evaluate other pertinent variables, such as the diagnostic criteria used for comorbid conditions and outcomes. Despite these limitations, there are significant strengths in this study with inclusion of a larger sample of patients with CS from multiple institutions across several states. This larger sample size enabled us to account for various comorbidities and their impact on hospital repeat admission rates. Data from multiple institutions also minimized the selection or referral bias inherent to single-institution studies.

Conclusion

In this retrospective study from a large healthcare system, CS patients treated with DMARDs or TNF compared to those on NT or ST had a 1) trend toward lower incidences of HF admissions and 2) longer survival rates free of HF admission and VTA.

Disclosure of conflict of interest

None.

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Appendix 1. ICD codes used to define diagnoses

Diagnosis	ICD9 Code(s)	ICD10 Code(s)	CPT Code(s)
Sarcoidosis	135	D869, D8685, D860, D861, D862, D863, D8681, D8682, D8683, D8684, D8685, D8686, D8687, D8689, D869	-
Non-ischemic cardiomyopathy	425.4 (exclude Pregnancy: 640-676, V22; Ischemic heart disease: 410-414; Valvular heart disease: 394-397; Alcoholism: 291, 303, 305.0-305.03, 571.0-517.3, 980, V113; Thyroid disease: 242-246; HIV/AIDS: 042; Amyloid: 277.3; Myocarditis: 422; Chemotherapy related: V073, V581, V662, V672)	I50 AND I42.0-I42.9	-
HFrEF	428.20, 428.21, 428.22, 428.23	I5020, I5021, I5022, I5023	-
HFpEF	428.30, 428.31, 428.32, 428.33	I5030, I5031, I5032, I5033	-
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.13, 404.91, 404.93, 425.4, 425.5, 425.7, 425.8, 425.9, 428, 428.0, 428.1, 428.220, 428.21, 428.22, 428.23, 428.30, 4283.1, 428.32, 4283.3, 428.40, 428.41, 428.42, 428.43, 428.9	I50.20, I50.22, 15030, I50.30, I50.32, I50.40, I50.42, I50.9, I11.0, I13.0, I13.2	-
Ventricular tachycardia or fibrillation	427.1, 427.41, 427.42	I472, I4901, I4902	-
Sudden cardiac arrest	427.5	I469, I462, I468	-
Pacemaker placement	37.70 to 37.73, 37.80 to 37.83, 00.50, 00.51	0JH604Z to 0JH607Z, 0JH634Z to 0JH637Z, 0JH804Z to 0JH807Z, 0JH834Z to 0JH837Z	33206 to 33208, 33225, 33249
ICD placement	37.94, 37.95, 37.96, 00.51, 00.50	0JH608Z, 0JH609Z, 0JH638Z, 0JH639Z, 0JH808Z, 0JH809Z, 0JH838Z, 0JH839Z, 0JH60FZ, 0JH63FZ, 02H43KZ, 02H60KZ, 02H63KZ, 02H64KZ, 02H70KZ, 02H73KZ, 02H74KZ, 02HK0KZ, 02HK3KZ, 02HK4KZ, 02HL0KZ, 02HL3KZ, 02HL4KZ, 02H40KZ, 02H40MZ, 02H44KZ, 02HN0KZ, 02HN3KZ, 02HN4KZ	-
Acute coronary syndrome	410.00, 410.01, 410.02, 410.10, 410.11, 410.12, 410.20, 410.21, 410.22, 410.30-410.32, 410.40, 410.41, 410.42, 410.50, 410.51, 410.52, 410.60-410.62, 410.70, 410.71, 410.72, 410.80, 410.81, 410.82, 410.90, 410.91, 410.92, 411.1, 411.8	I210, I2102, I2109, I2111, I2119, I2121, I2129, I213, I214, I219, I21A1, I21A9, I220, I221, I222, I228, I229	-
Right bundle branch block	426.4	I4510, I4519	-
Left bundle branch block	426.3	I447	-
1st Degree heart block	426.11	I440	-
2nd Degree heart block	426.13, 426.12	I441	-
3rd Degree heart block	426.0	I442	-
Fascicular block	426.51, 426.52, 426.53 426.54, 426.2	I4460, I4469, I450, I452, I453, I444, I445	-
Complete heart block	426.0, 426.10, 426.54	I44.2, I44.30, I45.3	-

ICD = Implantable cardioverter defibrillator; HFrEF = Heart failure with reduced ejection fraction; HFpEF = Heart failure with preserved ejection fraction.

Appendix 2. Medication group definitions

Drug class	Medications
Steroids	Prednisone
DMARD	Methotrexate, leflunomide, mycophenolate, cyclophosphamide, cyclosporine, hydroxychloroquine, or azathioprine
TNF inhibitors	Infliximab, adalimumab, golimumab, etanercept, certolizumab, pentoxifylline, or thalidomide

DMARD = disease-modifying antirheumatic drugs; TNF = tumor necrosis factor.

Appendix 3. ICD codes used for defining comorbidities

Comorbidity	ICD9 Code(s)	ICD10 Code(s)	CPT Code(s)
History of smoking	V15.82, 305.1	Z87.891, Z72.0, F17.20, F17.21	
Hypertension	401.0, 401.1, 401.9	I10	
Sleep apnea	327.20, 327.21, 327.23, 327.27, 327.29, 780.51, 780.53, 780.57	G47.30, G47.31, G47.33, G47.37, G47.39	
Atrial fibrillation	427.31	I48.91, I97790, I97.88, I97.89	
History of a stroke	431, 434, 438	I61, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I66, I69.1, I69.2, I69.3, I69.8, I69.9	
ICD Device	V45.02	Z95.810	
Pacemaker	V45.01	Z95.0	
Lung	135	D86.0 D86.2	
Skin	135 AND 782	D86.3	
Liver	135 AND 573.3	D86.9 AND D86.8 AND K75.3	
Eye	135 AND (360.11 or 364.10 or 364.3)	D86.83	
Central nervous system	321.4	D86.81	
Renal	135 AND 590	D86.84	
Ischemic cardiomyopathy	414.8	I25.5, I25.89, I25.9	
Prior stroke	V12.54	Z86.73	
Prior MI	MI4.12	I25.2	
Coronary artery disease	437.0, 440.9, 440.20, 413.9, 414.06, 411.1, 415.05, 414.01, 414.3, 414.4, 414.04, 437.0, 440.0, 414.8, 414.9, 447.9, 440.9	I25.10, I70.90, I17.79, I51.9, I25.9, I70.0, I67.2, I65.2, I25.799, I25.798, I25.790, I25.791, I25.709, I25.708, I25.700, I25.701, I25.84, I25.83, I25.119, I25.118, I25.110, I25.111, I25.119, I25.810, I72.09, I25.811, I25.759, I25.750, I25.751, I25.759, I70.209, K51.1, I78, I70.90, I67.2, G95.19, I27.0	
Diabetes mellitus	250.00, 250.01, 250.02, 250.03, 250.10, 250.11, 250.12, 250.13, 250.20, 250.21, 250.22, 250.23, 250.30, 250.31, 250.32, 250.33, 250.80, 250.81, 250.82, 250.83, 250.90, 250.91, 250.92, 250.93, 250.40, 250.41, 250.42, 250.43, 250.50, 250.51, 250.52, 250.53, 250.60, 250.61, 250.62, 250.63, 250.70, 250.71, 250.72, 250.73	E10.10, E10.11, E10.610, E10.618, E10.620, E10.621, E10.622, E10.628, E10.630, E10.638, E10.641, E10.649, E10.65, E10.69, E10.8, E10.9, E11.00, E11.01, E11.610, E11.618, E11.620, E11.621, E11.622, E11.628, E11.630, E11.638, E11.641, E11.649, E11.65, E11.69, E11.8, E11.9, E13.00, E13.01, E13.10, E13.11, E13.610, E13.618, E13.620, E13.621, E13.622, E13.628, E13.630, E13.638, E13.641, E13.649, E13.65, E13.69, E13.8, E13.9, E10.21, E10.22, E10.29, E10.311, E10.319, E10.3211, E10.3212, E10.3213, E10.3219, E10.3291, E10.3292, E10.3293, E10.3299, E10.3311, E10.3312, E10.3313, E10.3319, E10.3391, E10.3392, E10.3393, E10.3399, E10.3411, E10.3412, E10.3413, E10.3419, E10.3491, E10.3492, E10.3493, E10.3499, E10.3511, E10.3512, E10.3513, E10.3519, E10.3521, E10.3522, E10.3523, E10.3529, E10.3531, E10.3532, E10.3533, E10.3539, E10.3541, E10.3542, E10.3543, E10.3549, E10.3551, E10.3552, E10.3553, E10.3559, E10.3591, E10.3592, E10.3593, E10.3599, E10.36, E10.37, E10.37X1, E10.37X2, E10.37X3, E10.37X9, E10.39, E10.40, E10.41, E10.42, E10.43, E10.44, E10.49, E10.51, E10.52, E10.59, E11.21, E11.22, E11.29, E11.311, E11.319, E11.3211, E11.3212, E11.3213, E11.329, E11.3291, E11.3292, E11.3293, E11.3299, E11.3311, E11.3312, E11.3313, E11.3319, E11.3391, E11.3392, E11.3393, E11.3399, E11.3411, E11.3412, E11.3413, E11.3419, E11.3491, E11.3492, E11.3493, E11.3499, E11.3511, E11.3512, E11.3513, E11.3519, E11.3521, E11.3522, E11.3523, E11.3529, E11.3531, E11.3532, E11.3533, E11.3539, E11.3541, E11.3542, E11.3543, E11.3549, E11.3551, E11.3552, E11.3553, E11.3559, E11.3591, E11.3592, E11.3593, E11.3599, E11.36, E11.37, E11.37X1, E11.37X2, E11.37X3, E11.37X9, E11.39, E11.40, E11.41, E11.42, E11.43, E11.44, E11.49, E11.51, E11.52, E11.59, E13.21, E13.22, E13.29, E13.311, E13.319, E13.3211, E13.3212, E13.3213, E13.3219, E13.3291, E13.3292, E13.3293, E13.3299, E13.3311, E13.3312, E13.3313, E13.3319, E13.3391, E13.3392, E13.3393, E13.3399, E13.3411, E13.3412, E13.3413, E13.3419, E13.3491, E13.3492, E13.3493, E13.3499, E13.3511, E13.3512, E13.3513, E13.3519, E13.3521, E13.3522, E13.3523, E13.3529, E13.3531, E13.3532, E13.3533, E13.3539, E13.3541, E13.3542, E13.3543, E13.3549, E13.3551, E13.3552, E13.3553, E13.3559, E13.3591, E13.3592, E13.3593, E13.3599, E13.36, E13.37, E13.37X1, E13.37X2, E13.37X3, E13.37X9, E13.39, E13.40, E13.41, E13.42, E13.43, E13.44, E13.49, E13.51, E13.52, E13.59	

Dyslipidemia	272.0, 272.1, 272.2, 272.3, 272.4, 272.9, 272.5, 272.8	Z68.5, Z68.00, Z68.2, Z68.1, Z68.9, Z68.5, Z68.3, Z68.49, Z68.6
Peripheral vascular disease	443.89, 443.9, 443.81, 785.4, 440.20, 440.21, 440.22, 440.24, 440.29, 440.23, 440.4	I73.89, I73.9, I79.8, I96, I70.209, I70.219, I70.229, I70.269, I70.299, I70.25, I70.92
Chronic kidney disease	585.1, 585.2, 585.3, 585.4, 585.5, 585.6, 585.9	N18.1, N18.2, N18.3, N18.4, N18.5, N18.9
Chronic lung disease	416.8, 416.9, 490, 491.0, 491.1, 491.20-491.22, 491.8-492.0, 492.8, 493.00-493.02, 493.10-493.12, 493.20-493.22, 493.81, 493.82, 493.90, 493.91, 493.92, 494.0, 494.1, 495.0, 493.02, 493.10, 493.11, 493.12, 493.20, 493.21, 493.22, 493.81, 493.82, 493.90, 493.91, 493.92, 494.0, 494.1, 495.0	J40, J410, J41.1, J41.8, J42, J43.0, J431, J432, J438, J439, J44.0, J44.1, J45.20, J45.21, J45.22, J45.30, J45.31, J45.32, J45.40, J45.41, J45.42, J45.50, J45.51, J45.52, J45.901, J45.902, J45.909, J45.990, J45.991, J45.998, J47.0, J47.1, J47.9, J60, J61, J62.0, J62.8, J63.1, J63.2, J63.3, J63.4, J63.5, J63.6, J64, J65, J66.0, J66.1, J66.2, J66.8, J67.0, J67.1, J67.2, J67.3, J67.4, J67.5, J67.6, J67.7, J67.8, J67.9, I27.81, I27.82, I27.9, J68.4, J70.1, J70.3

ICD = Implantable cardioverter defibrillator; MI = Myocardial infarction.