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Research paper

Right ventricular longitudinal strain on CMR predicts ventricular arrhythmias and mortality in cardiac sarcoidosis

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ABSTRACT

Background: Right ventricular (RV) dysfunction and late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMR) are associated with ventricular arrhythmias (VA) and mortality in cardiac sarcoidosis (CS). However, image resolution limits the detection of RV LGE. Global longitudinal RV strain (RVS) correlates to RV scar on electroanatomical mapping and RV function.
Objective: We evaluated the association between RVS on CMR and VA/death (combined-primary-endpoint (CPE)) in patients with CS.
Methods: RVS and RV LGE on MRI were retrospectively compared to variables known to predict outcomes in 66 patients with CS. Outcomes were obtained from electronic medical records and implantable cardioverter defibrillator (ICD) interrogations over median [IQR] 3.7[1.7, 6.3] years. Cox proportional hazard models were used to evaluate survival. Harrell's C-statistic was used to compare variables in risk prediction models.
Results: 62.1 % of patients were male, with a mean age [SD] of 52.3 [9.6] years and left ventricular ejection fraction (LVEF) of 51.1[17.5]%. 9 patients with the primary endpoint were more likely to be Caucasian ($p = 0.01$) with prior VAs ($p = 0.002$), be on anti-arrhythmic drugs ($p = 0.001$) with an ICD ($p = 0.002$). In multivariable analyses adjusted for age, race, and history of VA, RVS (1.18 [1.05–1.31], $p = 0.004$), RV EDVI (1.08 [1.01, 1.14], $p = 0.02$), and LV LGE (1.07[1.00, 1.13], $p = 0.04$) predicted the CPE. Risk prediction models including RVS (Cstatistic 0.94), outperformed those including RV and LV LGE (0.89–0.92).
Conclusion: RVS on CMR was the best predictor of VA and mortality in CS.

1. Introduction

Sarcoidosis is a granulomatous disease that can affect any organ, including the lungs, skin, lymphatics, central nervous system, and heart (cardiac sarcoidosis [CS]) [1]. CS is characterized by infiltrating granulomas resulting in myocardial inflammation and fibrosis, which has been linked to the incidence of ventricular arrhythmias (VA) [1]. Late gadolinium enhancement (LGE) on cardiac magnetic resonance imaging (CMR) can identify the presence of myocardial fibrosis in CS and has been shown to predict VAs and cardiovascular mortality in patients with CS [1]. As such, LGE represents a non-invasive risk stratification tool that can help identify those at risk for VAs and sudden cardiac death (SCD) in CS. Current guidelines list a class IIA recommendation for consideration of device therapy in patients with CS, LVEF ≥35 %, and "extensive" LGE burden on CMR for prevention of sudden cardiac death (SCD) [2]. However, the lack of precise quantification of "extensive" LGE limits the clinical application of LGE in this patient population.

Prior studies have suggested that right ventricular (RV) scar in CS may identify patients with advanced stage of disease and may identify those at highest risk for VAs and sudden cardiac death (SCD), independent of ventricular function [3–5]. In addition, several studies have shown that the presence of RV LGE may predict poor outcomes in patients with CS [6–9]. However, evaluation of RV LGE is technically challenging because of the partial volume effect and the thinness of the

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RV wall, which limits accurate user quantification of LGE [10–12]. This limitation is supported by prior studies that suggest that RV LGE poorly correlates to RV scar burden by electroanatomic mapping (EAM) [11,12]. Given the prognostic significance of RV involvement in CS, alternative non-invasive modalities that can assess RV scar burden are necessary. Feature tracking-based RV strain (RVS) analysis on CMR has been validated as a measure of RV scar burden and RV function in arrhythmogenic right ventricular dysplasia (ARVD) [13]. In this study, we sought to determine the association between RVS, the incidence of VAs, and cardiovascular outcomes in patients with CS and compare it to other known predictors of outcomes in CS.

2. Methods

2.1. Patient population

In this retrospective study, 66 patients with probable or definite CS defined by the 2014 Heart Rhythm Society (HRS) expert consensus statement [14] and had undergone CMR imaging between 2000 and 2017 were included. Detailed clinical and demographic information on our cohort has been previously described [15]. The Johns Hopkins Institutional Review Board approved the study.

2.2. CMR image acquisition

CMR images were obtained on 1.5-T magnetic resonance imaging units (GE Medical Systems, Waukesha, Wis; or Avanto, Siemens, Erlangen, Germany) as previously described [15]. Cine images in the short axis (SA) and long axis planes were acquired using a balanced, steady-state free precession sequence (repetition time/echo time/flip angle [TR/TE/FA] 2.4/1.2/50–75 degrees, matrix 256–192, resolution 1.3 × 1.3.8 mm^3, a field of view 30–36 cm, temporal resolution ≤40 ms, slice thickness 6-8 mm). LGE imaging was obtained 10 to 18 min after injection of 0.2 mmol/kg of gadolinium (gadopentetate dimeglumine or gadobutrol; Bayer Healthcare Pharmaceuticals, Montville, NJ). Images were visually analyzed for the presence or absence of LGE.

2.3. CMR and strain analysis

RVEF, LVEF, RV, and LV end-systolic volumes (ESV) and end-diastolic volumes (EDV) were measured with CVI42 (Circle Cardiovascular Imaging; Client Version 248, Server Version 258; Calgary, Alberta, Canada). ESV and EDV measurements were indexed for body surface area (EDVI, ESVI). For right ventricular analysis, we measured longitudinal strain in 4-chamber views using Multimodality Tissue Tracking (MTT) software (MTT Version 6.0.4725, Toshiba Medical Systems Corporation, Tokyo, Japan, as described previously [13,16]. Semi-automated endocardial and epicardial contours were drawn at peak diastole, and the software automatically propagated these borders throughout the cardiac cycle. The quality of the contours was visually verified and manually adjusted if necessary by one reader (BV). The software calculated strain by tracking individual pixel motion within the region of interest. By convention, longitudinal strain is reported as a negative value when two points moved closer together from diastole to systole. Therefore, the more negative the RVS, the greater RV segmental deformation.

The presence of RV LGE was visually assessed by experienced readers. In patients with LV LGE, the extent of LGE in the LV was quantitatively assessed using Qmass 7.4 software (Medis, Leiden, The Netherlands). LGE regions were determined using a threshold signal intensity of 5 standard deviations (SDs) above the mean signal intensity of remote normal myocardium [17].

2.4. Clinical follow up and outcomes

Outcomes were obtained by review of electronic medical records and cardiac implantable electronic device interrogations. A VA event was defined as sustained ventricular tachycardia, ventricular fibrillation, SCD, unheralded syncope, or any appropriate ICD therapy [15]. To assess the effect of RVS on future events, a combined primary endpoint of ventricular arrhythmia (VA), and cardiovascular death were used.

2.5. Statistical analyses

Continuous data were presented as mean ± SD, whereas categorical variables were presented as counts with percentages. Comparison between groups was performed using a *t*-test for continuous, normally distributed variables and Wilcoxon rank-sum tests for continuous, non-normally distributed data. Chi-squared tests were used to compare discrete data between groups.

Hazard ratios (HR) were calculated using Cox proportional hazards regression and presented with 95 % confidence intervals (CIs). Risk prediction models adjusted for age, sex, and race were created, and Harrell's C statistic was used to compare variables in risk prediction models. The net reclassification improvement (NRI) of RVS to demographic and MRI parameters (including LV LGE and RV LGE)was calculated as a continuous variable and reported using 2-sided *p*-values. Cutoffs that optimized sensitivity and specificity were chosen. Kaplan-Meier curves were constructed to evaluate the variables of interest. For time to event analysis, the date of the initial CMR was time "zero." All statistical comparisons were 2-tailed with a *p*-value <0.05 considered statistically significant. All analyses were performed using the STATA software system (version 13, StataCorp, College Station, TX).

3. Results

3.1. Baseline characteristics

A total of 393 patients were referred for CMR evaluation of CS at Johns Hopkins Hospital (Baltimore, MD) between January 1st, 2000, and June 23rd, 2017. Among these, 66 patients met HRS criteria for diagnosis of CS and had appropriate CMR imaging for analysis. Patients excluded either had no follow up information, or missing data/images. Table 1 summarizes the baseline demographic and clinical characteristics of the patients included in the study. The mean age ± SD was 52.3 ± 9.6 years; 62.1 % were male, and 48.5 % of patients were Caucasian. A total of 5 patients (7.5 %) had a history of VAs, 56.1 % of patients were on beta-blocker therapy, 21.2 % were on anti-arrhythmic drug (AAD) therapy, and 40.9 % of patients had an ICD. 10.6 % of patients had

Table 1
Baseline characteristics

	All patients (n = 66)	VA and death + (n = 9)	VA and death- (n = 57)	p Value
Age (y) mean ± SD	52.3 ± 9.6	52.6 ± 15.4	52.2 ± 8.5	0.51
Male n (%)	41 (62.1)	7 (77.8)	34 (59.7)	0.3
Caucasian n(%)	32 (48.5)	8 (88.9)	24 (42.1)	**0.01**
Conduction disease n(%)	4 (6.06)	0 (0)	4 (7.02)	0.41
Hx of CAD n(%)	7 (10.6)	2 (22.2)	5 (8.77)	0.22
Hx of VA n(%)	5 (7.58)	3 (33.3)	2 (3.51)	**0.002**
CHF n(%)	27 (40.9)	5 (55.6)	22 (38.6)	0.34
Beta blockers n (%)	37 (56.1)	5 (55.6)	32 (56.1)	0.97
ICD n(%)	27 (40.9)	8 (29.6)	19 (70.4)	**0.002**
AAD n(%)	14 (21.2)	6 (66.7)	8 (14.0)	**<0.001**

Values are mean ± SD, n (%), or median (range).
VA = ventricular arrhythmias, Hx = history, CAD = coronary artery disease, CHF = congestive heart failure, Hx = history,
AAD: Anti-arrhythmic drug therapy; CD: conduction disease; SS: systemic sarcoidosis.
Items in bold represent values reaching statistical significance (p<0.05).

comorbid CAD, and 40.9 % had congestive heart failure.

3.2. CMR characteristics

The CMR characteristics are listed in Table 2. The mean LVEF was 51.1 % ± 17.5, and the mean RVEF was 41.1 % ± 15.7. The mean LV LGE burden was 8.89 ± 10.8 % of LV mass, whereas RV LGE was present in 16.7 % of patients. The mean RV global longitudinal strain (RVS was −21.7 ± 7.9. RV EDVI, RV ESVI, RV LGE and RVS were significantly different in those who developed VA from those who did not. Fig. 1 highlights the LV and RV LGE on CMR in a patient who suffered a VA event, compared to a patient who did not develop the primary combined outcome. Fig. 2 provides the corresponding strain images for the patients with and without a VA event.

3.3. Clinical management and outcomes

The median follow-up period was 3.7 [1.7,6.3] years. During the follow-up period, 9 patients developed the combined primary endpoint of VAs and cardiovascular (CV) death, and the mean time to event was 1511 ± 1093 days. More specifically, 6 patients developed VA and 3 patients died. No patients were lost to follow-up. Patients who developed the combined endpoint were more likely to be Caucasian ($p = 0.01$), have a history of VAs ($p = 0.002$), be on AAD therapy ($p < 0.001$) and have an ICD in place ($p = 0.002$).

3.4. Association between RV Global Longitudinal Strain (RVS) and clinical events

Table 3 summarizes the association between CMR parameters and clinical outcomes using Cox proportional hazards ratios. In univariate analysis, RV EDVI (HR 1.03 [95 % CI][1.02,1.05], $p < 0.001$), RV ESVI (1.03 [1.02,1.06], $p < 0.001$), LV LGE burden (1.06 [1.00,1.12], $p = 0.04$) and RVS (1.12 [1.03–1.21], $p = 0.006$) were associated with the combined primary endpoint, whereas LV EDVI, LV ESVI, LVEF, RVEF and RV LGE were not. In multivariable risk prediction models adjusted for age, race, and history of VAs, LV LGE burden (1.07 [1.00, 1.13], $p = 0.04$), RVS (1.18[1.05, 1.31], $p = 0.004$) and RV EDVI (1.05 [1.02, 1.09], $p = 0.004$) were significant predictors of the combined primary outcome, whereas RV LGE was not ($p = 0.06$) (see Table 3). Compared to adjusted models that combined clinical variables, CMR parameters (C statistic 0.84), LV LGE (0.89) and RV + LV LGE (C statistic 0.92), the addition of RVS resulted in a significantly improved fit (C statistic 0.94). The addition of RVS to models with demographic parameters(age, race, and history of VA), MRI parameters (RV EF, RV EDVI, LV EF) and LV LGE improved risk prediction model based on net classification index as subjects with events had 88.9 % increased probability of events with RVS, and in subjects without events, 86.0 % had decreased probabilities of events. The overall net reclassification improvement with RVS was 1.50 ± 0.36, $p < 0.0001$ when added to demographic, MRI parameters and LV LGE. Similarly, the addition of RVS to models with demographic parameters, MRI parameters and RV LGE had net reclassification improvement of 1.43 ± 0.36, $p < 0.0001$ as subjects with events had 88.9 % increase probability of events and subjected without events had 82.5 % had decreased probability of events.

Based on these results, the RVS cutoff of −18.9 was identified as the optimal discriminator for the purposes of our study (sensitivity 77.8 %, specificity 77.2 %). Fig. 3 highlights the improved fit with RVS (AUC 0.85) when compared to LV LGE (AUC 0.67) in predicting future events. Based on Kaplan-Meier analysis, future VA and all-cause mortality risk were higher in patients with RVS > −18.9 (less negative strain reflecting worse function) ($p = 0.009$) as seen in Fig. 4.

Table 2
CMR characteristics.

	All patients (n = 66)	VA and death + (n = 9)	VA and death - (n = 57)	p Value
LV EDVI (ml/m2)	75.4 ± 20.4	67.8 ± 13.8	76.6 ± 21.1	0.36
LV ESVI (ml/m2)	37.7 ± 19.3	36.1 ± 20.0	37.9 ± 19.4	0.8
LV EF (%)	51.1 ± 17.5	49.0 ± 23.1	51.5 ± 16.7	0.89
RV EDVI (ml/m2)	81.4 ± 30.3	119.4 ± 53.1	75.4 ± 19.8	**0.003**
RV ESVI (ml/m2) mean ± SD	49.0 ± 29.2	84.9 ± 58.1	43.4 ± 16.3	**0.009**
RV EF (%)	41.1 ± 15.7	33.5 ± 19.4	42.3 ± 14.9	0.17
LV LGE presence n(%)	57 (86.3)	9 (100)	48 (84.2)	0.2
LV LGE burden mean (%) ± SD	8.87 ± 10.8	13.5 ± 11.9	8.14 ± 10.5	0.11
RV LGE presence n (%)	11 (16.7)	4 (44.4)	7 (12.3)	**0.02**
RVS (% per unit length) mean ± SD	21.7 ± 7.9	13.5 ± 6.0	23.0 ± 7.35	**0.001**

Values are mean ± SD, n (%), or median (range).
LV: left ventricle; EDV: end-diastolic volume, EF: ejection fraction, LGE: late gadolinium enhancement, RVS: right ventricular global longitudinal strain.
Items in bold represent values reaching statistical significance ($p<0.05$).

4. Discussion

This study evaluated the association between RV global longitudinal strain (RVS) on CMR and incidence of VA and mortality in a cohort of patients with CS. We demonstrate that RV ESVI, RV EDVI, LV LGE burden and RVS predict the primary outcome on univariate analysis. In multivariable analyses adjusted for age, race, and history of VA, LV LGE burden (1.07 [1.00, 1.13], $p = 0.04$), RVS (1.18[1.05, 1.31], $p = 0.004$) and RV EDVI (1.05 [1.02, 1.09], $p = 0.004$) were significant predictors of the primary outcome. Risk prediction models that included RVS (C-statistic 0.94) were superior to those that included RV LGE and LV LGE (0.92). In addition, addition of RVS demonstrated improved prediction of risk in models with demographic parameters (age, race, and history of VA), MRI parameters (RV EF, RV EDVI, LV EF), and LV LGE burden (NRI 1.49 ± 0.36, $p < 0.0001$) and models with demographic parameters, MRI parameters and RV LGE (NRI 1.43 ± 0.36, $p < 0.0001$). An RVS threshold of −18.9 was chosen to optimize the sensitivity (77.8 %) and specificity (77.2 %) of the model to accurately screen patients with CS at risk for VA and CV death.

VA and SCD is often a presenting symptom of CS [1,18,19]. In our study, the overall event rate for the primary outcome was 13.6 % which is similar to prior studies that have shown overall event rates up to 18% [20]. Therefore, identifying those at increased risk for VAs may help improve outcomes in patients with CS. Scar formation within the myocardium due to granulomatous inflammation is thought to be the primary substrate of VAs in patients with CS [21,22]. Whereas LV scar is patchy, RV scar tends to be confluent with all segments affected with equal frequency [1]. Prior studies have shown that the presence of LV LGE on CMR correlates to the presence of myocardial fibrosis and is predictive of VA and adverse cardiovascular events in patients with CS [1]. A meta-analysis including ten studies of patients with CS demonstrated that the presence of LGE was predictive of VAs in those with LVEF >50 % [5]. As a result, current guidelines list a class IIA recommendation for consideration of device therapy in patients with CS, LVEF ≥35 %, and evidence of scar on CMR to prevent sudden cardiac death (SCD) [2]. However, the lack of precise quantification of the LGE burden needed for risk stratification limits the ability to clinically identify who would benefit most from device therapy. In a study evaluating the safety and efficacy of ICD therapy in patients with CS, those with moderately reduced LVEF (38 % ± 15) or those with secondary prevention indications were more likely to receive appropriate ICD therapies [23]. However, there are still high rates of inappropriate shocks (24 %) and

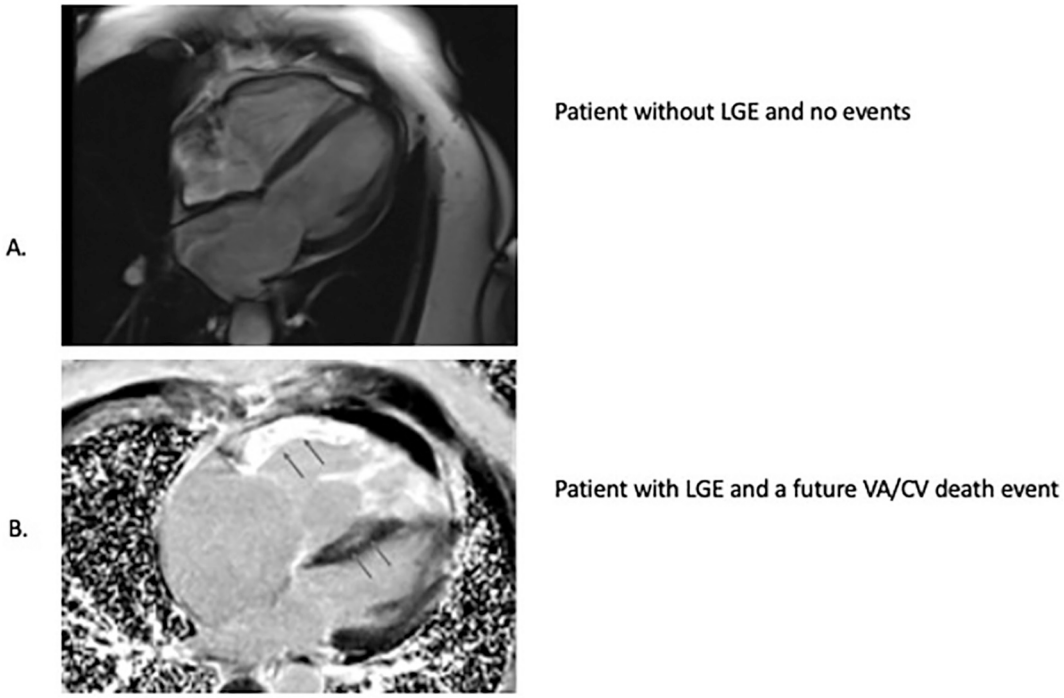

Fig. 1. LGE predicts adverse cardiovascular events in patients with cardiac sarcoidosis
Legend: Fig. A highlights the 4-chamber view of a patient without evidence of LGE on CMR and who did not develop a future VA/CV death event. Fig. B highlights LGE in both the LV and RV of a patient who developed a future VA/CV death event. (VA = ventricular arrhythmia, CV = cardiovascular).

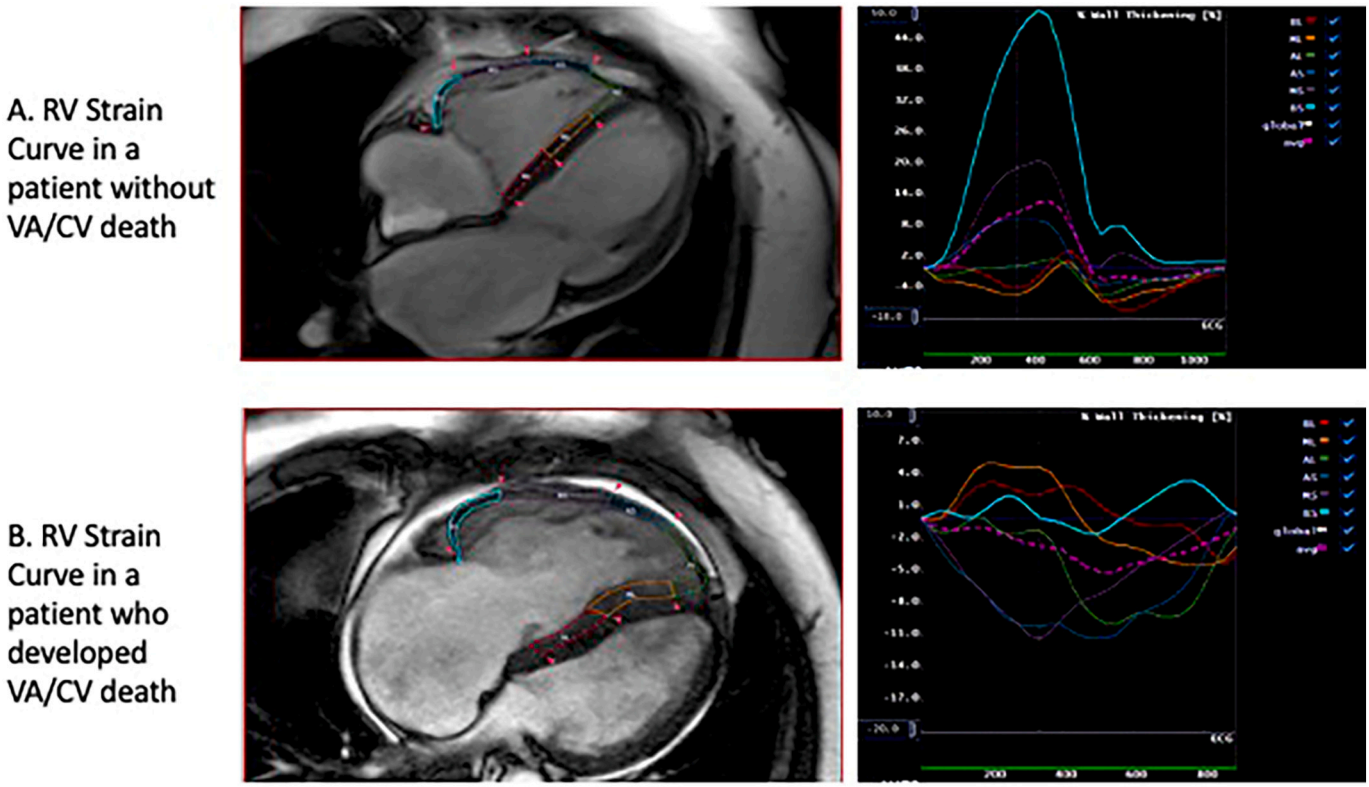

Fig. 2. Right ventricular global longitudinal strain predicts adverse cardiovascular events in patients with cardiac sarcoidosis
Legend: This figure compares and contrasts the strain images/curves of patients who did and did not develop a VA/CV death event. Fig. A shows the 4-chamber CMR image of a patient who did not develop a future event and the corresponding normal strain curves of the individual segments of the RV wall and the global longitudinal strain curve as well. This is contrasted by Fig. B which highlights the diminished strain in different segments of the RV wall and the overall diminished global longitudinal strain (BL: basolateral, ML: midlateral, AL:anterolateral, AS: anteroseptal, MS: midseptal, BS: basalseptal).

Table 3
Univariable and multivariable predictors of the primary endpoint
Univariable analysis

Univariable analysis			
	HR	95 % CI	p value
LV EDVI (ml/m2)	0.98	0.94–1.01	0.22
LV ESVI (ml/m2)	1	0.96–1.03	0.87
LV EF (%)	0.99	0.95–1.02	0.49
RV EDVI (ml/m2)	1.03	1.02–1.05	**<0.001**
RV ESVI (ml/m2) mean ± SD	1.03	1.02–1.06	**<0.001**
RV EF (%)	0.96	0.92–1.00	0.06
LV LGE burden mean ± SD	1.06	1.00–1.12	**0.04**
RV LGE presence	3.67	0.97–13.9	0.06
RVS (per %)	1.12	1.03–1.21	**0.006**

Multivariable analysis[a] (LV LGE only)			
	HR	95 % CI	p value
Age	1.04	0.96–1.12	0.38
Caucasian	5.05	0.59–43.6	0.14
Hx of VA	8.73	1.79–42.7	**0.007**
LV LGE burden	1.07	1.00–1.13	**0.04**
C statistic = 0.83.			

Multivariable analysis[a] (RV LGE only)			
	HR	95 % CI	p value
Age	1.06	0.98–1.16	0.15
Caucasian	6.6	0.71–61.5	0.1
Hx of VA	6.63	1.32–33.2	**0.02**
RV LGE	4.7	0.92–24.0	0.06
C statistic 0.84.			

Multivariable analysis[a] (RVS only)			
	HR	95 % CI	p value
Age	1.08	1.00–1.17	0.045
Caucasian	20.5	1.63–258	**0.02**
Hx of VA	2.91	0.53–16.0	0.22
RVS	1.18	1.05–1.31	**0.004**
C statistic 0.88.			

Multivariable analysis[a] (CMR parameters)			
	HR	95 % CI	p value
Age	1.02	0.94–1.11	0.58
Caucasian	4.29	0.47–39.0	0.2
Hx of VA	4.91	0.64–37.6	0.13
LV EF (%)	0.98	0.92–1.04	0.53
RV EDVI (ml/m2)	1.03	1.00–1.06	**0.04**
RV EF (%)	1	0.93–1.08	0.97
C statistic = 0.84			

Multivariable analysis[a] (CMR parameters + LV LGE ± RV LGE).			
	HR	95 % CI	p value
Age	1.02	0.93–1.12	0.61
Caucasian	7.01	0.37–131.9	0.19
Hx of VA	8.13	0.70–94.7	0.09
LV EF (%)	1.01	0.95–1.08	0.74

(*continued on next page*)

Table 3 (*continued*)

Multivariable analysis[a] (CMR parameters + LV LGE ± RV LGE).			
	HR	95 % CI	p value
RV EDVI (ml/m2)	1.06	1.02–1.11	**0.01**
RV EF (%)	1.06	0.97–1.15	0.17
LV LGE burden	1.24	1.06–1.45	**0.007**
RV LGE	5.03	0.77–32.6	0.09
C statistic = 0.92			

Multivariable analysist[a] (CMR parameters + LV LGE ± RVS)			
	HR	95 % CI	p value
Age	1.03	0.93–1.14	0.55
Caucasian	244	1.09–54,804	**0.05**
Hx of VA	0.65	0.02–24.5	0.82
LV EF (%)	1.03	0.96–1.12	0.4
RV EDVI (ml/m2)	1.08	1.01–1.14	**0.02**
RV EF (%)	1.11	1.00–1.24	0.06
LV LGE burden	1.23	1.04–1.45	**0.01**
RVS	1.37	1.03–1.84	**0.03**
C statistic = 0.94			

[a] Models are adjusted for age, sex, and history of ventricular arrhythmias.

device complications (18 %) in patients with CS and implanted ICDs. Therefore, it remains crucial to accurately identify patients with CS who would benefit most from ICD therapy.

Some studies have suggested that a threshold effect of RV involvement may be a particularly high-risk feature that could identify those who would benefit most from device therapy [3,7]. Isolated RV involvement tends to be rare. Additionally, RV involvement is typically associated with more extensive LV scar burden [3,7,24,25]. In post-mortem studies of SCD patients with CS, RV involvement was present in up to 65 % of patients [18,26–29]. In a study of VT ablation in CS, patients who developed arrhythmia almost universally exhibited confluent RV scarring [21]. In the study by Velangi et al., RV dysfunction was linked to all-cause mortality but not associated with VAs [30]. In contrast, other studies have shown that RV dysfunction has been linked to appropriate ICD shocks in patients with CS [31]. As designated by perfusion and metabolism defects on FDG-PET, active inflammation in the RV has also been linked with a significantly higher rate of adverse events, including VAs [4,32,33]. In contrast, other studies suggest that scar detected by CMR and not active inflammation were predictive of VAs [34,35]. Given the conflicting data, future studies delineating the role of CMR and FDG-PET in risk stratification are necessary.

Although RV LGE has been used as a surrogate for RV scar burden, evaluation of RV LGE is also technically challenging [10–12]. However, feature tracking-based RVS has been shown to correlate to RV scar in patients with ARVC and can be used as an objective measure of RV function in CS [36]. In our cohort, RV LGE was present in 16.7 % of patients which falls in the broad range of the presence of RV LGE (5.5–48 %) in prior studies [8,30]. In our study, the presence of RV LGE was not a significant predictor of the primary outcome. This finding contrasts with prior studies that suggest that RV LGE is associated with adverse outcomes, and may reflect either the technically challenging nature of accurately identifying RV LGE [3,8,30,37,38]. Consistent with prior studies, LV LGE burden remained a significant predictor of the primary outcome [1]. However, decreased RVS was the best predictor of outcomes based on overall fit in multivariable models. Based on these results and the known technical challenges associated with RV LGE, RVS may prove to be a better risk stratification tool in patients with CS. In studies evaluating the role of global longitudinal strain (GLS) by transthoracic echocardiogram in CS, GLS aided in diagnosing CS [39,40], and the degree of strain linearly correlated to LGE burden on CMR

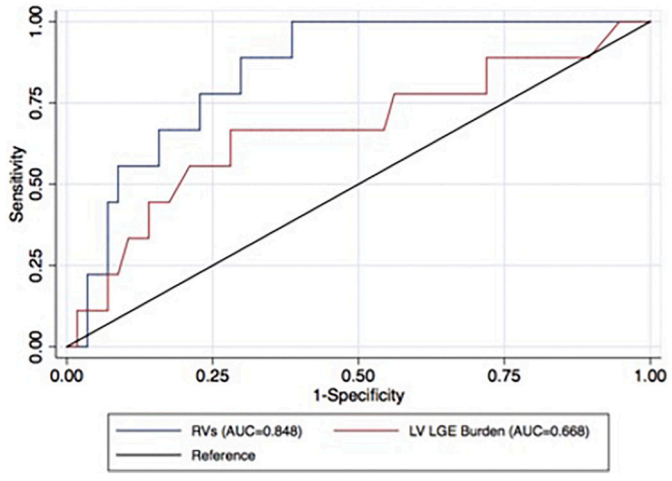

Fig. 3. ROC curve comparing RVS and LV LGE in predicting adverse cardiovascular events in patients with cardiac sarcoidosis
Legend: this figure highlights the improved fit achieved with RVS as opposed to LV LGE in models predicting future VA events and CV death in patients with CS.

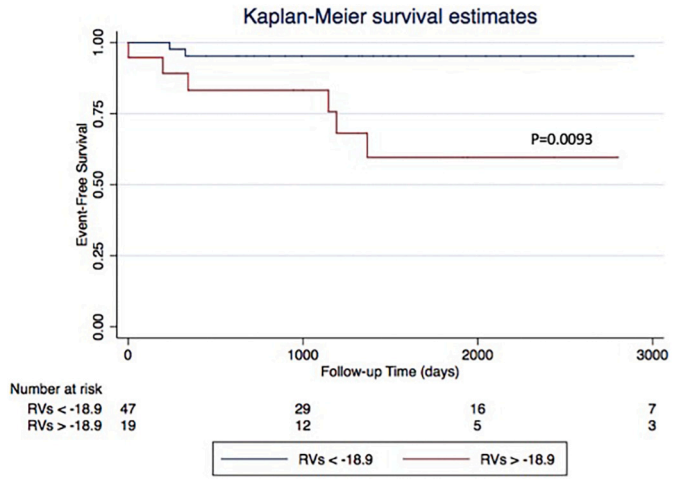

Fig. 4. Kaplan-Meier SURVIVAL CURVES BASED on RVS
Legend: The overall mortality in patients with CS and decreased global longitudinal strain (RVS) (with a chosen cutoff of −18.9 %) is significantly higher than in patients without abnormal global longitudinal strain (RVS).

[36,40–42]. In addition, GLS by TTE correlated to adverse outcomes such as VA and death [36,40–42]. Although TTE can identify RVS, CMR provides the added benefit of identifying LGE, RVS, and RVEF and can also distinguish between the inflammatory, edematous and fibrotic phases of CS with high sensitivity and specificity [43,44], and can therefore serve as a comprehensive aid in diagnosis and risk stratification of patients with CS.

In the 2017 ACC/AHA/HRS Guideline for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death, extensive LGE is a criterion for ICD implantation in patients with LVEF >35 % [2]. The results of our study suggest that RVS by CMR may be a valuable risk stratification tool in identifying patients with CS who would benefit from ICD therapy. Future large, prospective studies evaluating the role of RVS, LGE, and other CMR and PET parameters are necessary to validate these findings.

4.1. Limitations

The retrospective nature of our study, modest sample size, and limited follow-up duration limits the generalizability of our study. The overall number of clinical endpoints was low, which limits the ability to compare different CMR parameters. In addition, the cohort is limited to patients referred to a tertiary academic medical center which introduces the possibility of selection or referral bias. In addition, the difference in C-index between models containing LV LGE, RV LGE and RVS was minimal and the clinical relevance for this remains to be evaluated in future prospective studies. Although in our study, RV LGE did not predict the combined primary end-point, it must be noted that the scans were performed over a long period of time during which the resolution of LGE imaging and the ability to mitigate the limitations of RV LGE detection has evolved inducing variability in the data. Therefore the utility of RV LGE must be evaluated in future studies. Another limitation is that we have limited data on the severity of pulmonary involvement and the degree of pulmonary hypertension within the cohort. The data on right ventricular systolic pressure by TTE was incomplete within the cohort and represents a limitation as the presence of pulmonary hypertension can worsen GLS and increase cardiovascular events in patients with CS. Finally, given that a significant portion of patients in our cohort had prior ICD, were on AAD therapies, or had heart failure diagnoses, it is unclear if RVS is a predictor of outcomes in a primary prevention group.

5. Conclusion

In this retrospective study of patients with CS, global longitudinal strain as assessed by CMR was the best predictor of ventricular arrhythmias and overall mortality. Future prospective studies are necessary to determine the relationship between RV strain and outcomes in patients with CS.

Abbreviations

CS	cardiac sarcoidosis
VA	ventricular arrhythmias
CMR	cardiac magnetic resonance imaging
RVS	Right ventricular global longitudinal strain
LGE	late gadolinium enhancement
LV	left ventricle
RV	right ventricle
EDVI	End diastolic volume index
ESVI	End systolic volume
ICD	implantable cardioverter-defibrillator

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Disclosures

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CRediT authorship contribution statement

BV, TZ, EX, SZ, NG, DRO, JACL, and JC designed the study. BV, TZ, EZ, SZ acquired the data. BV, TZ, EX, SZ, NG, DRO, JACL, and JC analyzed and interpreted the data. BV, TZ, EX, SZ, NG, DRO, JACL, and JC were major contributors to writing the manuscript. BV, TZ, EX, SZ, NG, DRO, JACL, and JC provided substantial revisions to the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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