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Routine Laboratory Biomarkers As Prognostic Indicators of Cardiac Sarcoidosis Outcomes

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Abstract. *Background:* Biomarkers to monitor disease activity and predict major adverse cardiac events (MACE) in CS have not been described previously. We aimed to identify biomarkers to predict MACE in cardiac sarcoidosis (CS). *Methods:* Patients (N=232) diagnosed with CS were retrospectively enrolled. Biomarkers including angiotensin-converting enzyme (ACE), N-terminal brain natriuretic peptide (NT-proBNP), troponin T, and creatinine levels were evaluated against a primary end point of left ventricular assist device implantation, heart transplantation, or death, and a secondary end point of cardiac hospitalization-free survival. *Results:* Troponin T (hazard ratio [HR], 1.06 per 0.01 ng/mL; *P*=.006), NT-proBNP (HR, 1.31 per 1,000 pg/mL; *P*<.001), and creatinine (HR, 4.02 per mg/dL; *P*=.01) were associated with the primary end point, even after adjusting for ejection fraction. NT-proBNP, B-type natriuretic peptide (BNP), creatinine, albumin, and calcium were associated with the secondary end point (*P*<.05). ACE levels were associated with presence of late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging (mean difference, 14.7; *P*=.03); 1,25 dihydroxyvitamin D (1,25-OHVit-D) was associated with uptake on cardiac ^{18}F-flurodeoxyglucose position emission tomography (FDG-PET, *P*=.03). *Conclusions:* Troponin T, NT-proBNP, and creatinine predict clinically significant outcomes in CS. ACE levels correlated with LGE on CMR, and 1,25-OHVit-D levels correlated with FDG-PET activity.

Key words: sarcoidosis, cardiac sarcoidosis, biomarkers, LVAD, heart transplant

1. Introduction

Sarcoidosis is an inflammatory condition of unknown cause characterized by noncaseating granulomas that may affect multiple organs. Cardiac sarcoidosis (CS) is characterized by the presence of non-necrotizing granulomatous lesions in any part of the heart, including the atria, ventricles, conduction system, pericardium, or coronary arteries (1-3). CS can present with congestive heart failure, conduction block, arrhythmias, and even sudden cardiac death (2, 4, 5). The prevalence of sarcoidosis varies on the basis of population demographics, but recent epidemiologic studies hint at a prevalence of 152 to 215 cases per 100,000 person-years, with an annual incidence of 11.5 in 100,000 (6, 7). The true prevalence of CS is unknown because it is likely underdiagnosed, but prevalence in the United States has been reported to be 3% to 5% of all patients with sarcoidosis (8, 9), with an autopsy-based study indicating more than a 27% incidence (10).

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Diagnostic criteria for CS have been proposed by the Japanese Circulation Society and the Heart Rhythm Society (8-11). Endomyocardial biopsy showing noncaseating granulomas is the gold standard for diagnosing CS, but this is an invasive procedure with low sensitivity because of the patchy distribution of sarcoid granulomas (12). Cardiac magnetic resonance (CMR) and ^{18}F-flurodeoxyglucose positron emission tomography (FDG-PET) studies are increasingly being utilized as noninvasive methods for diagnosing probable CS according to Heart Rhythm Society and Japanese Circulation Society criteria (12-15). Although these advanced imaging modalities can be used to facilitate diagnosis of CS and monitor disease activity (16), both CMR and FDG-PET are limited by cost and logistics. Radiation exposure is another potential limitation for FDG-PET imaging. Thus, identifying laboratory biomarkers to facilitate diagnosis, surveillance of disease activity, and prognosis for patients with CS is warranted.

Previously conducted studies have investigated a number of laboratory biomarkers and their association with CS. Angiotensin-converting enzyme (ACE) has been the most commonly used biomarker to study systemic sarcoidosis. Prior studies have shown that patients with sarcoidosis may have elevated ACE levels (17, 18). However, ACE levels are elevated in only about two-thirds of patients with sarcoidosis and are not specific for sarcoidosis, as elevated ACE levels are observed in other granulomatous diseases, such as tuberculosis and fungal infections (17-19). B-type natriuretic peptide (BNP) and N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP) levels have been shown to be elevated in patients with CS (17-21). High-sensitivity cardiac troponin T and troponin I concentrations have been shown to be elevated in patients with CS with associated diminished response to corticosteroid treatment (22). Despite this previous research, biomarkers of disease activity and prognosis for patients with CS have not been clearly identified. The aim of this study was to identify common biomarkers that could be used as tools to evaluate disease activity and predict outcomes in patients with CS.

2. Methods

The study was approved by the Mayo Clinic Institutional Review Board. All study patients provided written informed consent to allow the use of their health records for research purposes. No industry support was provided.

2.1 Patient Characteristics and Initial Diagnosis

We used a validated internal electronic health record search tool to retrospectively identify 232 patients, 18 years or older, who were diagnosed with CS and received care at Mayo Clinic, Rochester, between January 1, 1999, and December 31, 2017. Diagnostic criteria used to classify patients were based on the Heart Rhythm Society classification system (9). We included only patients diagnosed with "definite" or "probable" cardiac sarcoidosis.

The patients' demographic characteristics, symptoms at presentation, and relevant diagnostic tests including laboratory tests and imaging (transthoracic echocardiography, CMR or cardiac FDG-PET, or both), and cardiac implantable electrical device data were abstracted from the electronic medical record at the time of their initial evaluation at our institution.

2.2 Assessment of Laboratory Biomarkers

Patients underwent venous blood sampling to assess for biomarkers during their initial visit for evaluation of CS. The complete panel of biomarkers was not universally obtained at the initial visit, but important biomarkers analyzed included: ACE levels to assess sarcoid granuloma burden, as activated macrophages in granulomas produce ACE (18); erythrocyte sedimentation rate and C-reactive protein to assess the degree of inflammation; NT-proBNP and BNP as markers of congestive heart failure (20, 21); troponin T to assess for extent of myocardial damage secondary to CS involvement (22); 25 dihydroxyvitamin D (25-OHVit-D), 1,25 dihydroxyvitamin D (1,25-OHVit-D), and serum calcium, reflecting the ability of granulomas to produce 1α hydroxylase that induces the conversion of 25-OHVit-D to 1,25-OHVit-D with a subsequent increase in calcium absorption in the gut and calcium efflux from bones (2, 17); total protein and albumin as a marker of synthetic liver function and nutritional status; and serum creatinine as a marker of renal function. Baseline values across the entire cohort and stratified biomarkers based on results of particular imaging modalities were recorded and correlated to the outcomes.

End Points

The primary end point was a composite of left ventricular assist device implantation, heart transplantation, or death. The secondary outcome of this study was cardiac hospitalization-free survival. We also evaluated 2 relevant electrophysiologic end points, premature ventricular contraction burden and implantable cardioverter defibrillator discharges, in relation to biomarkers of interest.

2.3 Statistical Analysis

Comprehensive descriptive statistics for each laboratory variable are enumerated and values are expressed as mean±SD for parametric variables. A χ^2 regression analysis was used to determine the association between biomarkers and clinical variables of interest, namely the presence of late gadolinium enhancement (LGE) on CMR, FDG uptake on PET, premature ventricular contraction burden, left ventricular ejection fraction on presentation, presenting electrophysiologic abnormalities, and history of implantable cardioverter defibrillator discharge. Normal vs reduced left ventricular ejection fraction was stratified by using a value of 50%. Logistic regression was used to stratify outcomes of interest by biomarkers as continuous variables to identify the optimal cut point. A conventional receiver-operator curve was constructed by plotting sensitivity against 1-specificity, and the area under the curve was calculated for each model. Cox proportional hazard regression analysis was used to identify the relationship between biomarkers and the time-dependent primary composite outcome of left ventricular assist device implantation, heart transplantation, or death and secondary outcome of cardiac hospitalization-free survival. Kaplan-Meier analysis was used to stratify survival with respect to each laboratory biomarker.

3. Results

3.1 Clinical Characteristics

Among the 232 patients included in this study, 86 (37%) were women. Fifty-four (23%) of the 232 patients were diagnosed with definite CS, and 178 (77%) were diagnosed with probable CS. Many of these patients had multisystem sarcoidosis, including pulmonary sarcoidosis. Baseline characteristics are listed in Table 1. Patients in the definite vs probable CS group were more likely to have a history of atrial

Table 1. Baseline Patient Characteristics[a]

Characteristic	All Patients (N=232)	Definite CS (n=54)	Probable CS (n=178)	*P* Value
Age	63±12.81	50±13.33	55±12.54	.02
Sex				.51
Men	146 (63)	36 (67)	110 (62)	
Women	86 (37)	18 (33)	68 (38)	
Race				.37
Asian	3 (1)	1 (2)	2 (1)	
Black/African American	24 (10)	4 (7)	20 (12)	
White	195 (84)	47 (89)	148 (85)	
Hispanic	2 (1)	0 (0)	2 (1)	
Native American	1 (0.4)	0 (0)	1 (1)	
Other	1 (0.4)	1 (2)	0 (0)	
BMI	30.6±7.13	28.0±7.02	31.3±7.02	.004
Smoker				.50
Current	4 (2)	1 (2)	3 (2)	
Past	58 (25)	10 (20)	48 (28)	

Characteristic	All Patients (N=232)	Definite CS (n=54)	Probable CS (n=178)	*P* Value
None	162 (70)	40 (78)	122 (70)	
CAD				.60
None	149 (73)	40 (77)	109 (72)	
Mild	29 (14)	5 (10)	24 (16)	
Moderate	10 (5)	2 (4)	8 (5)	
Severe	15 (7)	5 (10)	10 (7)	
History of MI	16 (7)	4 (8)	12 (7)	.87
Diabetes mellitus				.82
None	189 (82)	45 (85)	144 (81)	
Type 1	1 (0.4)	0 (0)	1 (1)	
Type 2	41 (18)	8 (15)	33 (19)	
CKD				.16
Stage I-II	194 (85)	40 (75)	154 (87)	
Stage III	31 (14)	12 (23)	19 (11)	
Stage IV	3 (1)	1 (2)	2 (1)	
ESRD	1 (0.4)	0 (0)	1 (1)	
History of atrial fibrillation	51 (22)	18 (33)	33 (19)	.02
Previous ICD	144 (62)	40 (74)	104 (58)	.04
NYHA class				.03
I	56 (24)	8 (15)	48 (27)	
II	115 (50)	29 (54)	86 (48)	
III	52 (23)	12 (22)	40 (23)	
IV	8 (3)	5 (9)	3 (2)	

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; CS, cardiac sarcoidosis; ESRD, end-stage renal disease; ICD, implantable cardioverter-defibrillator; MI, myocardial infarction; NYHA, New York Heart Association.

[a] Values are mean±SD or number (percentage) unless indicated otherwise.

fibrillation (n=18, 33%; vs n=33, 19%; *P*=.02) and more likely to have previously undergone implantation of an implantable cardioverter defibrillator (n=40, 74%; vs n=104, 58%; *P*=.04). Patients with definite CS presented with a higher New York Heart Association heart failure classification *(P*=.03).

The laboratory biomarkers assessed in this study are shown in Table 2. Among the 13 biomarkers evaluated in this study, 3 were shown to significantly differ between the definite and probable CS groups. Erythrocyte sedimentation rate was significantly higher in patients with probable CS than definite CS (13.7 U/L vs 6.6 U/L; *P*=.001). Similarly, 25-OHVit-D levels were higher in the probable CS patient group (31.3 ng/dL vs 25.6 ng/mL; *P*=.04). NT-proBNP, however, was higher in patients with definite vs probable CS (3,200 pg/mL vs 1,100 pg/mL; *P*=.02).

3.2 Biomarker Associations With CMR and FDG-PET

Higher ACE levels were associated with the presence of LGE on CMR *(P*=.03) (Figure 1). On logistic regression, there was a nonsignificant association between ACE levels and the presence of LGE on CMR (area under the curve, 0.66; *P*=.06); however, at an optimum ACE threshold of 34 U/L (normal ACE levels based on Mayo Clinic laboratory assay is 16-85

Table 2. Biomarker Distribution by Cardiac Sarcoidosis Category[a]

Biomarker (No.)	Definite	Probable	*P* Value
ACE, U/L (146)	27.0±30.74	34.5±28.32	.22
ESR, mm/h (145)	6.6±9.31	13.7±14.03	.001
CRP, mg/L (67)	13.4±27.11	6.1±17.02	.38
hsCRP, mg/L (11)	25.8±30.31	8.8±9.47	.35
NT-proBNP,[b] pg/mL (107)	3.2±4.22	1.1±2.13	.02
BNP, pg/mL (33)	462.6±545.90	302.8±376.80	.46
Troponin T, ng/mL[c] (68)	6.7±19.82	1.2±2.29	.23
25-OHVit-D, ng/mL (58)	25.6±6.06	31.3±14.31	.04
1,25-OHVit-D, pg/mL (34)	53.5±24.35	55.9±19.51	.83
Serum calcium, mg/dL (161)	9.4±0.60	9.5±0.52	.30
Serum total protein, g/dL (113)	6.6±0.93	6.9±0.86	.26
Serum creatinine, mg/dL (217)	1.2±0.38	1.1±0.30	.06
Serum albumin, g/dL (122)	3.9±0.41	3.9±0.49	.92

Abbreviations: ACE, angiotensin-converting enzyme; BNP, brain natriuretic peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; hsCRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide; 25-OHVit-D, 25 dihydroxyvitamin D; 1,25-OHVit-D, 1,25-dihydroxyvitamin D.

[a] Values are mean±SD.

[b] Values ×1,000 pg/mL.

[c] Values ×0.01 ng/mL; 99th percentile upper reference limit, <0.01 ng/mL.

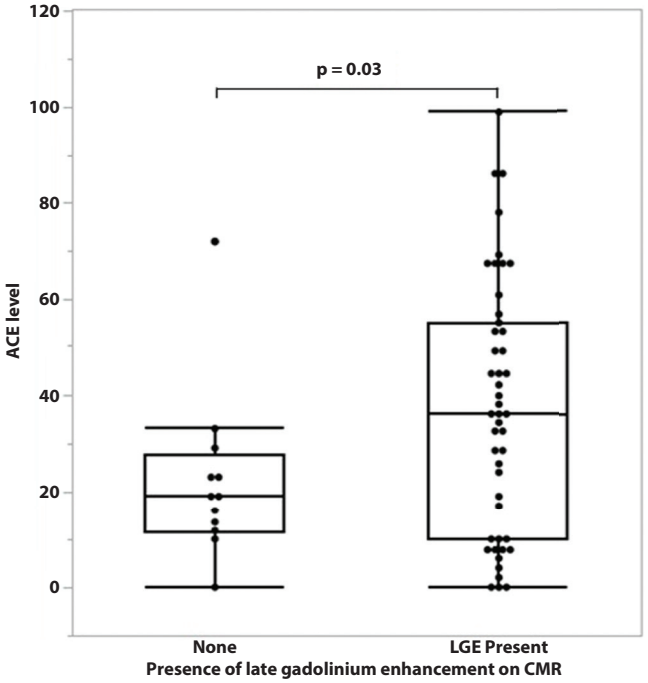

Figure 1. Evaluation of ACE Levels by the Presence of LGE on CMR. ACE levels were higher in patients with LGE present on CMR (37±26 vs 22±18; *P*=.03). ACE indicates angiotensin-converting enzyme; CMR, cardiac magnetic resonance; LGE, late gadolinium enhancement.

U/L), the sensitivity and specificity of the presence of LGE on CMR were 55.3% (95% CI, 40.1%-69.8%) and 91.7% (95% CI, 61.5%-99.8%), respectively.

On logistic regression analysis, 1,25-OHVit-D levels were associated with the presence of FDG uptake on cardiac PET scan (area under the curve, 0.80; *P*=.03). At an optimal threshold of 66 pg/mL, specificity was 100% and sensitivity was 55% for the association between 1,25-OHVit-D levels and FDG uptake on cardiac PET scan. Unlike the relation between ACE and LGE on CMR, ACE did not stratify cardiac PET scan results, although there was a general trend of increased ACE in patients with myocardial FDG uptake on PET scans as opposed to patients with no myocardial FDG uptake on PET scans (mean ACE, 41.4 SD 30 for PET+ vs 25.8 SD 16 for PET–; *P*=.12). None of the other biomarkers were associated with FDG uptake on cardiac PET scan *(P*= Nonsignificant for all).

3.3 Biomarkers and Outcomes

Table 3 depicts the prognostic significance of selected biomarkers in relation to the primary outcome of left ventricular assist device implantation, heart transplantation, or death. On univariate analysis, only troponin T (hazard ratio [HR], 1.06 per 0.01 ng/mL; *P*=.006), log-transformed NT-proBNP (HR, 2.3; *P*<.0001), creatinine (HR, 4.02; *P*=.01), and Modification of Diet in Renal Disease Study estimated glomerular filtration rate (MDRD eGFR [HR, 0.98]; *P*=.04) were associated with the primary end point. After adjustment for left ventricular ejection fraction, these associations remained significant (log-transformed NT-proBNP [HR, 2.4; *P*<.001]; troponin T [HR, 1.06 {CI, 1.02-1.11}; *P*=.005]; creatinine [HR, 4.2 {CI, 1.5-10.3}; *P*=.009]; and MDRD eGFR [HR, 0.98; *P*=.03]). These biomarkers of interest were further dichotomized by median values, and a Kaplan-Meier analysis was constructed (Figure 2). Both troponin values (detectable vs undetectable using fourth-generation troponin T assay) and NT-proBNP (dichotomized at 700 pg/mL) stratified long-term survival (*P*=.03 and *P*=.009, respectively). Neither creatinine (*P*=.16) nor MDRD eGFR (*P*=.15) stratified long-term outcomes when dichotomized. NT-proBNP, BNP, total serum calcium, serum

Table 3. Biomarker Association with LVAD Implantation, Heart Transplantation, or Death

Biomarker	Hazard Ratio (95% CI)	*P* Value
ACE, U/L	1.00 (0.98-1.02)	.75
ESR, mm/h	1.02 (0.99-1.04)	.21
CRP, mg/L	1.00 (0.97-1.02)	.79
hsCRP, mg/L	0.99 (0.86-1.08)	.96
NT-proBNP[a]	1.31 (1.15-1.48)	<.001
ln NT-proBNP pg/mL	2.35 (1.55-3.71_)	<.0001
BNP, pg/mL	0.99 (0.99-1.00)	.87
Troponin T[b]	1.06 (1.02-1.11)	.006
25-OHVit-D, ng/mL	0.99 (0.92-1.07)	.99
1,25-OHVit-D, pg/mL	0.96 (0.87-1.03)	.28
Serum calcium, mg/dL	1.15 (0.54-2.33)	.71
Serum total protein, g/dL	1.13 (0.71-1.90)	.63
Serum creatinine, mg/dL[c]	4.02 (1.41-9.94)	.01
MDRD eGFR, mL/min/1.73m^2	0.98 (0.95-1.00)	.04
Serum albumin, g/dL	0.78 (0.32-1.93)	.58

Abbreviations: ACE, angiotensin-converting enzyme; BNP, brain natriuretic peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; hsCRP, high-sensitivity C-reactive protein; LVAD, left ventricular assist device; NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide; 25-OHVit-D, 25 dihydroxyvitamin D; 1,25-OHVit-D, 1,25-dihydroxyvitamin D.

[a] Per 1,000 pg/mL change.

[b] Per 0.01 ng/mL change; 99th percentile upper reference limit, <0.01 ng/mL.

[c] Per 1 mg/dL change.

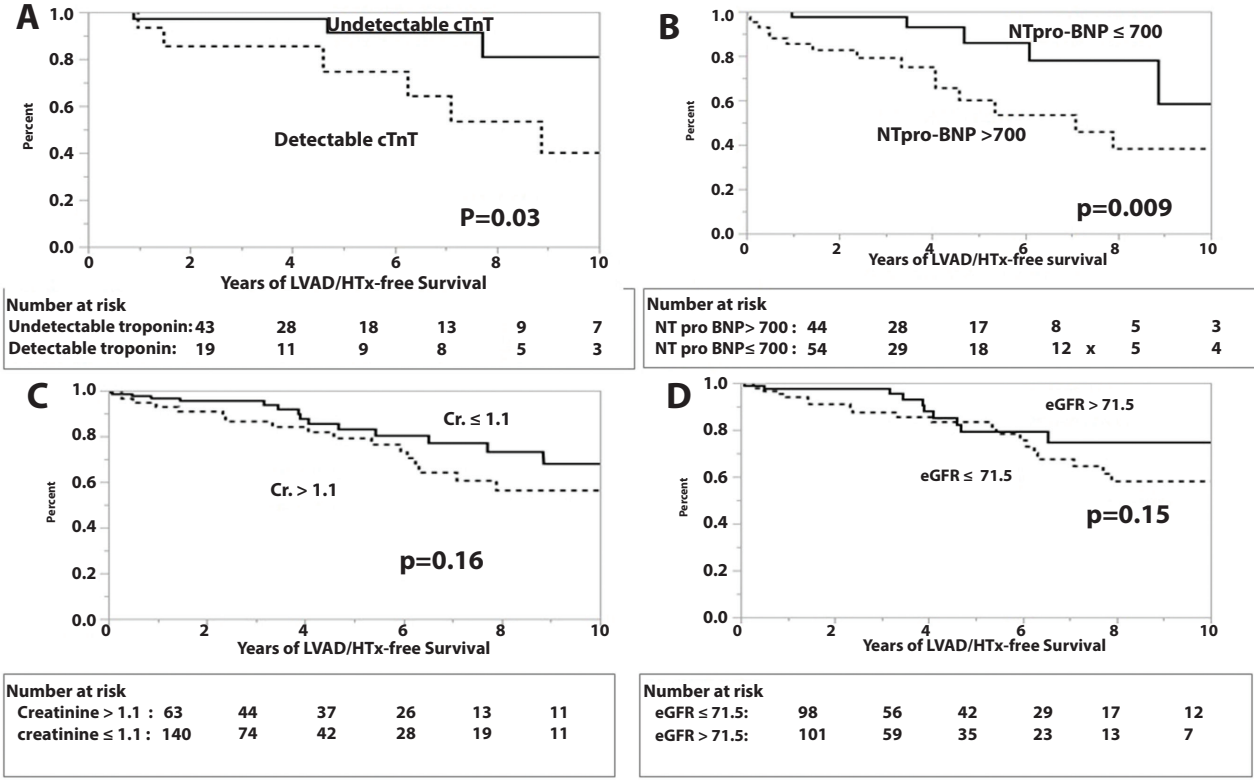

Figure 2. Kaplan-Meier Curves Stratifying LVAD Implantation/Heart Transplant-Free Survival Over Time. A and B, Detectable troponin T and NT-proBNP>700 pg/mL are associated with-event free survival (log-rank test, *P*=.03 and *P*=.009, respectively). C and D, Dichotomized serum creatinine levels and MDRD eGFR are not associated with event-free survival overtime (*P*=.16 and *P*=.15, respectively). Cr indicates creatinine; cTnT, cardiac muscle troponin T; HTx, heart transplant; LVAD, left ventricular assist device; MDRD eGFR, Modification of Diet in Renal Disease Study estimated glomerular filtration rate; NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide. (Central Illustration.)

creatinine, and serum albumin were all associated with the secondary end point of cardiac hospitalization-free survival (*P*<.05 for all, Table 4).

3.4 Biomarker Differences Between Groups

There was no association between troponin T or ACE levels and left ventricular ejection fraction on presentation (R^2=0.0004, *P*=.93) but, as expected, there was a relationship between left ventricular ejection fraction and NT-proBNP, albeit modest (R^2=0.14, *P*<.001; log NT-proBNP, R^2=0.23, *P*<.001). There was no significant difference in the percentage of patients with >10% premature ventricular contraction burden on Holter monitor or implantable cardioverter defibrillator discharges/antitachycardia pacing in patients with an implantable cardioverter defibrillator when stratified by ACE level, ESR, or troponin T level (Figure 3).

4. Discussion

We analyzed data from a large, single-center series of patients with CS to determine whether common biomarkers utilized in the diagnosis and management of CS could have a role in prognosis. We determined that elevated NT-proBNP levels, higher in patients with definite than probable CS, were associated with poor prognosis even after adjustment for left ventricular ejection fraction. We found that ACE levels, while not prognostic of long-term outcomes, were associated with LGE on CMR. Importantly, we determined that NT-proBNP, troponinT, serum creatinine, and MDRD eGFR were each associated with the composite end point of left ventricular assist device implantation, heart transplantation, or death when analyzed as continuous variables.

ACE level lacks adequate sensitivity and specificity and is therefore considered insufficient for the diagnosis of both systemic and cardiac sarcoidosis

Table 4. Univariate Analysis of Biomarkers and Cardiac Hospitalization-free Survival

Biomarker	Hazard Ratio (95% CI)	*P* Value
ACE, U/L	0.996 (0.98-1.01)	.41
ESR, mm/h	0.997 (0.98-1.01)	.77
CRP, mg/L	0.995 (0.97-1.01)	.58
hsCRP, mg/L	0.95 (0.82-1.05)	.11
NT-proBNP[a]	1.2 (1.13-1.27)	<.001
BNP, pg/mL	1.001 (1.000-1.002)	.02
Troponin T[b]	0.99 (0.92-1.03)	.75
25-OHVit-D, ng/mL	1.00 (0.97-1.03)	.96
1,25-OHVit-D, pg/mL	0.99 (0.96-1.03)	.73
Serum calcium, mg/dL	0.52 (0.33-0.81)	.004
Serum total protein, g/dL	0.85 (0.67-1.12)	.25
Serum creatinine, mg/dL[c]	2.05 (1.04-3.78)	.04
Serum albumin, g/dL	0.44 (0.23-0.84)	.01

Abbreviations: ACE, angiotensin-converting enzyme; BNP, brain natriuretic peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; hsCRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide; 25-OHVit-D, 25 dihydroxyvitamin D; 1,25-OHVit-D, 1,25-dihydroxyvitamin D.

[a] Per 1,000 pg/mL change.

[b] Per 0.01 ng/mL change; 99th percentile upper reference limit, <0.01 ng/mL.

[c] Per 1 mg/dL change.

(17-19, 23). Prior data have shown that ACE levels do not stratify active disease well relative to dormant disease in systemic sarcoidosis (17). Importantly, ACE levels have previously been shown to be associated with increased odds of all-cause mortality, cardiovascular mortality, and arrhythmogenic events such as ventricular arrhythmia, sudden cardiac death, or implantable cardioverter-defibrillator shock (15, 24). In one series, patients with LGE on CMR had a 10.8% annual incidence of death or ventricular arrhythmias compared with a 0.6% incidence for patients without LGE on CMR (15). Furthermore, extensive myocardial LGE on CMR has been associated with lack of improvement in left ventricular function even after corticosteroid treatment (25). Our data suggest that ACE levels correlate with LGE on CMR, and high ACE levels (>34 U/L) are more specific for CS-associated myocardial LGE, so they should prompt CMR imaging of patients being evaluated for possible CS. These data argue that ACE levels continue to be relevant in the management of CS.

4.1 N-Terminal Fragment of the Prohormone Brain Natriuretic Peptide

Previous studies have shown an association between higher NT-proBNP/BNP levels and CS, a result most likely due to the hemodynamic effects of the cardiomyopathy (2, 20, 21). However, we also identified that NT-proBNP levels were significantly higher in the definite than the probable CS cohort, possibly reflecting that patients with definite CS present with more advanced myocardial disease than patients with probable CS. Nevertheless, NT-proBNP was associated with the primary composite outcome in our study, irrespective of left ventricular ejection fraction, suggesting that NT-proBNP may serve as a prognostic biomarker for all patients with CS.

4.2 Troponin T

Although prognostic in a variety of disease states, the association between troponin T level and outcomes in CS is likely driven by the extent of myocardial injury from active inflammation or possibly subendocardial ischemia from previous vascular injury. Prior data have shown that high-sensitivity troponin T levels are frequently elevated in patients with newly diagnosed CS, correlate with disease

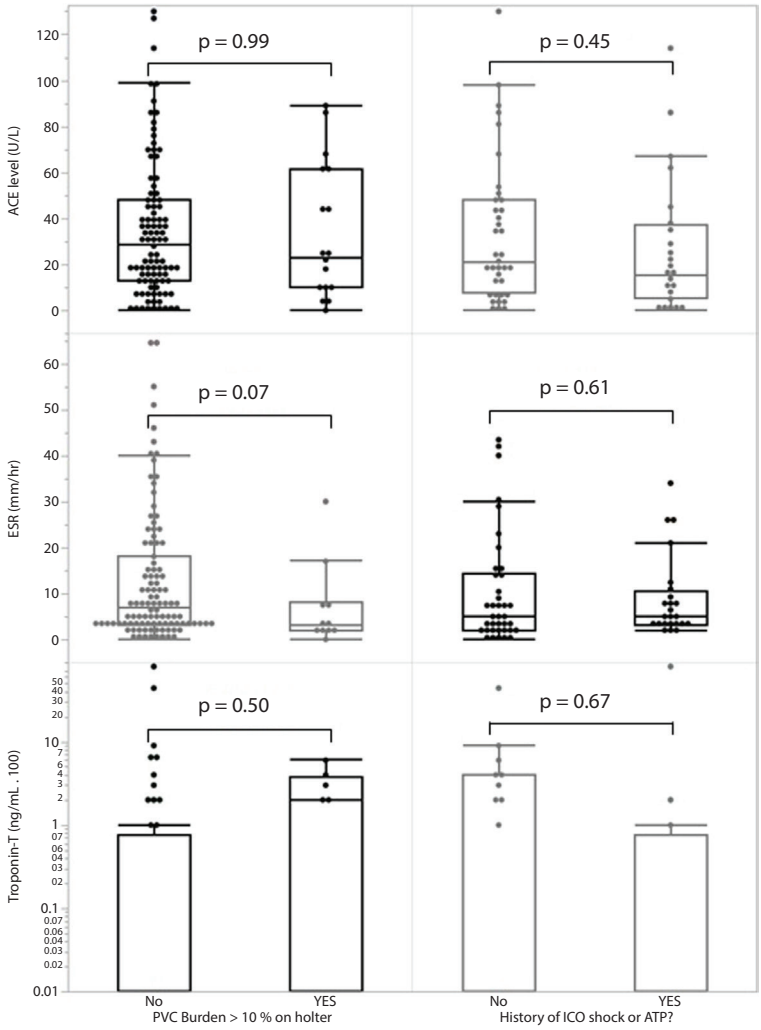

Figure 3. Association Between Biomarkers of Interest and PVC Burden and ICD Therapies. ACE, ESR, and troponin T levels did not correlate with the presence of >10% PVCs on 24-hour Holter monitoring (*P*=.99, *P*=.07, and *P*=.50, respectively) or with a history of ICD therapy (*P*=.45, *P*=.61, and *P*=.67, respectively). ACE indicates angiotensin-converting enzyme; ATP, antitachycardia pacing; ESR, erythrocyte sedimentation rate; ICD, implantable cardioverter defibrillator; PVC, premature ventricular contraction.

activity as seen on FDG-PET studies, and decrease with corticosteroid treatment (22, 23, 26, 27). Given the association with long-term outcomes observed in the present study, we extend the prior observations regarding utility as a prognostic biomarker in CS.

4.3 Serum Creatinine and MDRD eGFR

Higher serum creatinine, and in turn lower MDRD eGFR, has been shown in multiple studies to be associated with poor outcomes including cardiovascular events, cerebrovascular events, and mortality (28-30). The specific pathophysiologic mechanisms of how poor renal function relates to adverse cardiac events are complex and multifactorial, involving synergistic effects of comorbid conditions (such as hypertension, hyperlipidemia, diabetes mellitus, and smoking) and increased levels of inflammatory mediators in renal failure, atherosclerosis, and endothelial dysfunction (28, 29). Data in heart failure show that patients with reduced ejection fraction (both ischemic and nonischemic) and chronic kidney disease are at higher risk for adverse outcomes. Similarly, CS patients with poor renal function may also be at high risk for adverse

outcomes—not only from traditional cardiovascular risk factors but also from the added effects of metabolic abnormalities, sympathetic overactivity, repeated activation of the renin-angiotensin-aldosterone system, and volume dysregulation (31). The results of this study suggest that serum creatinine and MDRD eGFR can serve as a prognostic marker in patients with CS, likely due to similar pathophysiologic mechanisms and regardless of baseline ejection fraction.

4.4 Serum Calcium, Vitamin D, and Albumin in Association With Cardiac Hospitalization-Free Survival

Serum calcium and vitamin D levels have been shown to be elevated in sarcoidosis because of the presence of 25-hydroxyvitamin D_3-1α-hydroxylase enzyme in sarcoid granulomas, leading to the elevation of 1,25-OHVit-D levels which, in turn, increases calcium absorption. Therefore, high levels of activated vitamin D likely represent a marker of excess granulomatous inflammation, which in this study resulted in the observed association with FDG uptake on PET. Interestingly, although not described in the pathophysiology of CS, vitamin D has important immunomodulating effects, which could have a role in inflammatory conditions (32, 33). In our study, serum calcium and albumin emerged as significant biomarkers for the secondary end point of cardiac hospitalization-free survival. The prognostic influence of albumin is well stated in a number of disease states (34), not only through association with hepatic dysfunction but also with malnutrition. The association between serum calcium and hospitalization may reflect extent of inflammation, including active myocardial inflammation, which may result in worsening cardiomyopathy or ventricular arrhythmias.

4.5 Premature Ventricular Contraction Burden, Implantable Cardioverter Defibrillator Shocks, and Antitachycardia Pacing

We also assessed the importance of ACE level, ESR, and troponin T level in relation to increased premature ventricular contraction burden (>10%) or implantable cardioverter defibrillator shocks/antitachycardia pacing in our patient population. CS can cause various electrophysiologic abnormalities, including ventricular ectopy (5). High premature ventricular contraction burden (>10%) has been reported to induce cardiomyopathy (35), but on analysis ESR, ACE, and troponin T levels were not associated with increased premature ventricular contraction burden in our CS patient population. Furthermore, CS has been associated with arrhythmias requiring implantable cardioverter defibrillator shocks/antitachycardia pacing in patients with an implantable cardioverter defibrillator in place. However, these biomarkers did not correlate with an increased incidence of implantable cardioverter defibrillator discharges or antitachycardia pacing.

5. Limitations

The current study has several important limitations. First, this was a retrospective study of patients who were evaluated at a single tertiary referral institution, which limits the external generalizability. The modest sample size may affect the statistical conclusions of the study as well. Because of the retrospective nature of this study, there is significant risk of confounding factors in interpreting the results. Biomarker characterization was incomplete, as patients were not prospectively recruited, and thus the available panel of biomarkers was dependent on the treating clinician, potentially leading to ascertainment bias. Selection bias was also present, considering that some patients received advanced imaging tests (CMR and FDG-PET studies), whereas others did not. Also, some patients were receiving treatment for CS at the time of initial evaluation at our institution and others were not, which could have led to confounding of results. Furthermore, only patients with positive cardiac or extracardiac biopsies, or both, were included in the study, which could limit the generalizability of the results.

6. Conclusion

Biomarkers may have a role not only in management of CS but also in predicting patient outcomes. Important markers of disease activity may include ACE level, 1,25-OH vitamin D, and NT-proBNP, whereas troponin T, NT-proBNP, and creatinine are each associated with greater risk of left ventricular assist device implantation, heart transplantation, or death. While these data describe an important niche for these biomarkers in the evaluation of patients with CS, more data are needed to identify biomarkers with adequate diagnostic yield, effective correlation

with disease activity and response to immunosuppression, and association with long-term modifiable risk factors.

Abbreviations: ACE, angiotensin-converting enzyme, BNP, B-type natriuretic peptide, CMR, cardiac magnetic resonance, CS, cardiac sarcoidosis, FDG-PET, ^{18}F-flurodeoxyglucose positron emission tomography, LGE, late gadolinium enhancement, MDRD eGFR, Modification of Diet in Renal Disease Study estimated glomerular filtration rate, NT-proBNP, N-terminal fragment of the prohormone brain natriuretic peptide, 1,25-OHVit-D, 1,25 dihydroxyvitamin D, 25-OHVit-D, 25 dihydroxyvitamin D

Autor contribution: All authors takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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