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ORIGINAL ARTICLE

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Clinical valuables related to resolution of complete or advanced atrioventricular block after steroid therapy in patients with cardiac sarcoidosis

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Abstract

Background: Prediction of atrioventricular block (AVB) resolution after steroid therapy in patients with cardiac sarcoidosis (CS) is difficult.

Methods: We identified 24 patients with CS and complete or advanced AVB receiving steroid therapy. AVB resolution was assessed by reviewing surface electrocardiogram and the percentage of ventricular pacing required on subsequent device interrogation reports.

Results: AVB resolution was noted in eight (33%) patients 1 year after receiving steroid therapy. Univariate Cox regression analysis demonstrated that left ventricular ejection fraction (LVEF) (hazard ratio [HR] 1.07, 95% confidence interval [CI] 1.01-1.14, $P = .016$), interval from recognized AVB to start of steroid therapy (HR 0.98, 95% CI 0.95-0.99, $P < .001$), and lysozyme (HR 1.51, 95% CI 1.12-2.19, $P = .013$) were significantly associated with resolution of AVB. Combination of area under the curve (AUC) of each variable that was significantly related to resolution of AVB (AUC, 0.969; 95% CI 0.921-1.000, $P < .001$) was tended to be higher compared with each variable alone.

Conclusions: A shorter interval from recognition of AVB to start of steroid therapy, higher LVEF, and higher lysozyme levels were significantly associated with resolution of AVB after steroid therapy in patients with CS. The combination of each variable could be able to distinguish patients with resolution of AVB from those without.

KEYWORDS

atrioventricular block, cardiac sarcoidosis, immunosuppression therapy, inflammation

1 | INTRODUCTION

Sarcoidosis is a heterogeneous multisystem granulomatous disease of unknown etiology.[1,2] Although symptomatic cardiac involvement is noted in 5% of the patients with systemic sarcoidosis,[2] the mortality rate for cardiac sarcoidosis (CS) is >67% among patients with sarcoidosis.[3]

Atrioventricular block (AVB) can be the first presentation of sarcoidosis in any organ.[4,5] A national registry in Finland showed that Mobitz type II second-degree AVB or third-degree AVB was observed in 44% of the patients with CS.[6] In addition, advanced AVB may lead to syncope and sudden death.[7,8] The involvement of the basal septum by granulomas may be related to AVB in patients with CS.[9,10] Immunosuppression therapy using corticosteroids is standard therapy to suppress the inflammatory activity in patients with CS and advanced AVB.[2,11] A previous systematic review reported that recovery of atrioventricular nodal function and resolution of AVB occurred in 47.4% of the patients after steroid therapy.[12] Conversely, as previous studies reported limited data and statistical validation to precisely identify whether resolution of AVB occurs after steroid therapy, it is difficult to predict the resolution of AVB.[7,12,13] Therefore, device therapy was recommended in a recent expert consensus for patients with CS and advanced AVB.[2] However, device-related complications (ie, lead failure and device infection) were occasionally observed.[14,15] If resolution of AVB after steroid therapy could be predicted accurately, unnecessary device implantation may be avoided. In this observation study, we assessed the frequency of resolution of AVB in patients with CS and AVB after steroid therapy. In addition, we sought to identify clinical factors associated with resolution of AVB after steroid therapy.

2 | MATERIAL AND METHODS

2.1 | Study population

From January 2006 to December 2017, a total of 24 CS patients with complete or advanced AVB were retrospectively analyzed. Thirteen (54%) patients were diagnosed with CS before 2015 using criteria based on guidelines.[16] All patients received corticosteroid therapy after diagnosis. Medical treatment and an indication of electronic implantable device therapy were performed according to the latest Japanese guidelines at the diagnosis. Blood tests, electrocardiography (ECG), cardiac echocardiography, and cardiovascular magnetic resonance imaging (MRI) including late gadolinium enhancement (Gd-MRI) were assessed before corticosteroid therapy. Angiotensin-converting enzyme (ACE) and lysozyme levels were measured using standard methods in the clinical laboratory (normal values: ACE 6.6-21.4 U/L; lysozyme 5.0-10.2 μg/mL). Left ventricular ejection fraction (LVEF) was measured by the modified Simpson method. Gallium-67 (Ga) scintigraphy and/or ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) were also used to assess the disease activity. All patients were instructed to eat a low-carbohydrate meal and then fast for at least 18 h before 18-F-FDG injection.[16] FDG uptake in the heart was defined as focal 18-F-FDG uptake present in at least one segment.[10] In addition, the maximum standardized uptake value (SUVmax) was used for semiquantitative analysis of 18-F-FDG uptake. This study was approved by the Scientific and Ethical Committee of the Kitasato University School of Medicine and complies with the Declaration of Helsinki. The study subjects provided their informed consent or were informed of the study by information posted at our institution. This study was performed in accordance with relevant guidelines and regulations.

2.2 | Steroid therapy protocol and clinical follow-up

Corticosteroid therapy was started during hospitalization in addition to other conventional treatment for heart failure (HF). Corticosteroid therapy was performed according to the general worldwide consensus statement.[17] The initial dosage was 30 mg/d of prednisone for 4 weeks for all patients except for one, who was treated with steroid pulse therapy (1000 mg/d for 3 days and 30 mg/d for 25 days). The steroid dose was gradually decreased by 5-10 mg/d every 2-4 weeks until the maintenance dose of 5-10 mg/d.

Resolution of complete or advanced AVB was assessed by reviewing the surface ECG and the percentage of ventricular pacing required on subsequent device interrogation reports.[18] If conduction was present at device interrogation, atrioventricular delays were extended as much as possible, and if conduction was absent, shorter physiological atrioventricular delays were selected.[19] The review of ECG follow-up continued for 1 year.

2.3 | Statistical analysis

Continuous variables are expressed as median with interquartile range, and differences in means were evaluated using the Mann–Whitney *U*-test. Categorical variables are expressed as the number of subjects and proportion, and differences in means were assessed using the chi-square test. To explore the association between resolution of AVB and covariables, univariate Cox proportional hazard models were evaluated. Cut-off points for the significant continuous variables in the Cox proportional hazard models were determined by receiver-operating characteristic (ROC) analysis. In the Kaplan–Meier analysis, event times were measured from the time of start of corticosteroid treatment to the resolution of AVB.

All probability values were two-tailed, and $P < .05$ was considered statistically significant. All statistical analyses were performed with R software (Version 3.5.2; R Foundation for Statistical Computing, Vienna, Austria) and JMP Version 13 (SAS Institute, Cary NC, USA).

3 | RESULTS

3.1 | Baseline characteristics

The patients' baseline characteristics are shown in Table 1. Resolution of AVB was achieved in eight (33%) patients. Interval of treatment from diagnosis of AVB to start of steroid therapy was significantly shorter in patients with resolution of AVB than in those without. The proportion of patients who received ACE inhibitors (ACEIs) or angiotensin II receptor blocker (ARB) was lower in patients with resolution of AVB than those without. The reasons for receiving ACEIs or ARB were reduced LVEF (n = 12), HF (n = 2), and hypertension (n = 3). Serum ACE was not significantly different between the two groups, whereas lysozyme levels were significantly higher in patients with resolution of AVB than in those without. LVEF was significantly higher in patients with resolution of AVB than in those without. A total of 17 (71%) patients received pacemaker, and six (25%) patients were implanted with an implantable cardiac defibrillator with left ventricular (LV) lead because of LV dysfunction and HF. There was no history of sustained ventricular arrhythmias and LVEF > 35% at pacemaker implantation among patients with a pacemaker. However, LVEF decreased and LVEF < 35% at steroid therapy in 3/17 patients after implantation.

Imaging test findings before corticosteroid therapy are shown in Table 2. Ga scintigraphy was performed in all patients, and Ga uptake in the heart was observed in 11 (45.8%) patients, whereas FDG-PET was performed in 16 (66%) patients, and FDG uptake at heart was observed in all patients. Although FDG uptake around the AV node was not present in two patients without AVB resolution, the SUVmax was not significantly different between the two groups. Gd-MRI was performed in nine (37.5%) patients, and myocardial late enhancement was present in all patients. Around the AV node, late enhancement was observed in almost all (8/9; 88.9%) patients except for one with no evidence of resolution of AVB.

TABLE 1 Patient characteristics before steroid therapy

Parameters	Total n = 24	Resolution of AVB n = 8	No resolution of AVB n = 16	*P*-value
Age (years)	69 (56-73)	63 (50-70)	71 (61-76)	0.177
Male	6 (25.0)	3 (37.5)	3 (18.8)	0.317
Positive histology	12 (50.0)	4 (50.0)	8 (50.0)	>0.999
Extracardiac organ involvement				
Lung	18 (75.0)	8 (100.0)	10 (62.5)	0.046
Skin	4 (16.7)	1 (12.5)	3 (18.8)	0.699
Eye	5 (20.8)	3 (37.5)	2 (12.5)	0.155
Type of AVB				
Complete AVB	19 (79.3)	6 (75.0)	13 (81.3)	0.722
Advanced second-degree AVB	5 (20.1)	2 (25.0)	3 (18.8)	-
Interval from recognition of AVB to start of steroid therapy (days)	98 (39-1057)	40 (21-59)	518 (55-2257)	0.003
Medical treatment at initiation of steroid therapy				
ACEI or ARB	17 (70.8)	3 (37.5)	14 (87.5)	0.011
Beta-blocker	15 (62.5)	3 (37.5)	12 (75.0)	0.074
Diuretics	8 (33.3)	1 (12.5)	7 (43.8)	0.126
Laboratory data at initiation of steroid therapy				
BNP (pg/ml)	159 (63-256)	98 (52-159)	204 (69-367)	0.188
Calcium (mg/dl)	9.1 (9.0-9.6)	9.6 (8.7-9.9)	9.3 (9.0-9.4)	0.580
CRP (mg/dl)	0.12 (0.04-0.28)	0.20 (0.12-0.33)	0.10 (0.03-0.19)	0.141
ACE (U/L)	12.0 (7.9-16.2)	13.9 (11.3-21.3)	11.0 (5.4-15.8)	0.168
Lysozyme (μg/ml)	8.4 (7.0-11.4)	11.3 (8.3-13.0)	7.7 (6.9-9.5)	0.032
TTE data before steroid therapy				
LV end-diastolic diameter (mm)	54.0 (45.3-59.5)	53.0 (44.5-57.5)	54.5 (46.5-63.0)	0.560
LVEF (%)	46.5 (34.0-61.5)	57.5 (53.5-64.5)	36.0 (31.8-54.0)	0.020

Note : Categorical variables are shown as numbers (percentages), and continuous variables are shown as medians (25th–75th percentiles).

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AVB, atrioventricular block; BNP, brain natriuretic peptide; CRP, C-reactive protein; EF, ejection fraction by the modified Simpson; LV, left ventricular; TTE, transthoracic echocardiography.

TABLE 2 Imaging test findings

Parameters	Total	Resolution of AVB	No resolution of AVB	*p*-value
Performed ^{67}Ga scintigraphy	n = 24	n = 8	n = 16	
Positive Ga uptake at heart	11 (45.8)	5 (62.5)	6 (37.5)	0.247
Performed ^{18}F-FDG-PET	n = 16	n = 6	n = 10	
FDG uptake at heart	16 (100.0)	6 (100.0)	10 (100.0)	-
SUVmax at heart	7.3 (4.3-13.0)	12.3 (5.3-16.4)	6.7 (3.9-9.3)	0.129
FDG uptake at AV node area	14 (87.5)	6 (100.0)	8 (80.0)	0.242
SUVmax at AV node area	7.2 (4.3-10.6)	9.4 (4.7-14.5)	5.9 (2.8-9.3)	0.175
Performed Gd-MRI	n = 9	n = 4	n = 5	
Myocardial late enhancement	9 (100.0)	4 (100.0)	5 (100.0)	-
Late enhancement at AV node area	8 (88.9)	4 (100.0)	4 (80.0)	0.343

Note : Categorical variables are shown as numbers (percentages), and continuous variables are shown as medians (25th–75th percentiles).

Abbreviations: AV node, atrioventricular node; FDG-PET, fluorodeoxyglucose positron emission tomography; Gd-MRI, gadolinium-enhanced cardiac magnetic resonance imaging; SUV, standardized uptake value.

TABLE 3 Univariate Cox proportional hazard analysis for resolution of AVB

Parameters	Hazard ratio	95% CI	*p*-value
Age (per 1 year)	0.97	0.92-1.03	.289
Male	2.23	0.53-9.38	.272
Complete AVB	0.74	0.15-3.68	.715
Interval from recognition of AVB to steroid therapy (per 1 day)	0.98	0.95-0.99	<.001
Received ACEI or ARB	0.16	0.04-0.68	.012
Received beta-blocker	0.27	0.07-1.16	.078
LVEF (per 1%)	1.07	1.01-1.14	.016
LV end-diastolic diameter (per 1 mm)	0.97	0.89-1.04	.364
BNP (per 1 pg/ml)	0.99	0.99-1.00	.281
ACE (per 1 U/L)	1.06	0.96-1.16	.226
Lysozyme (per 1 μg/mL)	1.51	1.12-2.19	.013
Positive Ga uptake	2.22	0.53-9.31	.275
SUVmax at heart (per 1)	1.20	0.99-1.47	.061

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AVB, atrioventricular block; BNP, brain natriuretic peptide; CI, confidence interval; CRP, C-reactive protein; EF, ejection fraction by the modified Simpson; LV, left ventricular; SUV, standardized uptake value.

3.2 | Multivariate analysis and prediction score for resolution of AVB

Univariate Cox proportional hazard analysis demonstrated that a shorter interval from recognition of AVB to start of steroid therapy, received ACEI or ARB treatment, higher LVEF, and higher lysozyme levels were associated with resolution of AVB (Table 3). Results of ROC curve analysis and cut-off point of each variable significantly associated with resolution of AVB were shown in Figure 1. The combination of each variable had higher AUC compared with each predictor alone; however, the difference of each variable and model was not statistically significant (Figure 2).

3.3 | Timing of resolution of AVB and outcome

After steroid therapy, the resolution of AVB occurred within 1 month (Figure 3). In one patient who received steroid pulse therapy, the resolution of AVB was observed after 11 days of beginning of steroid

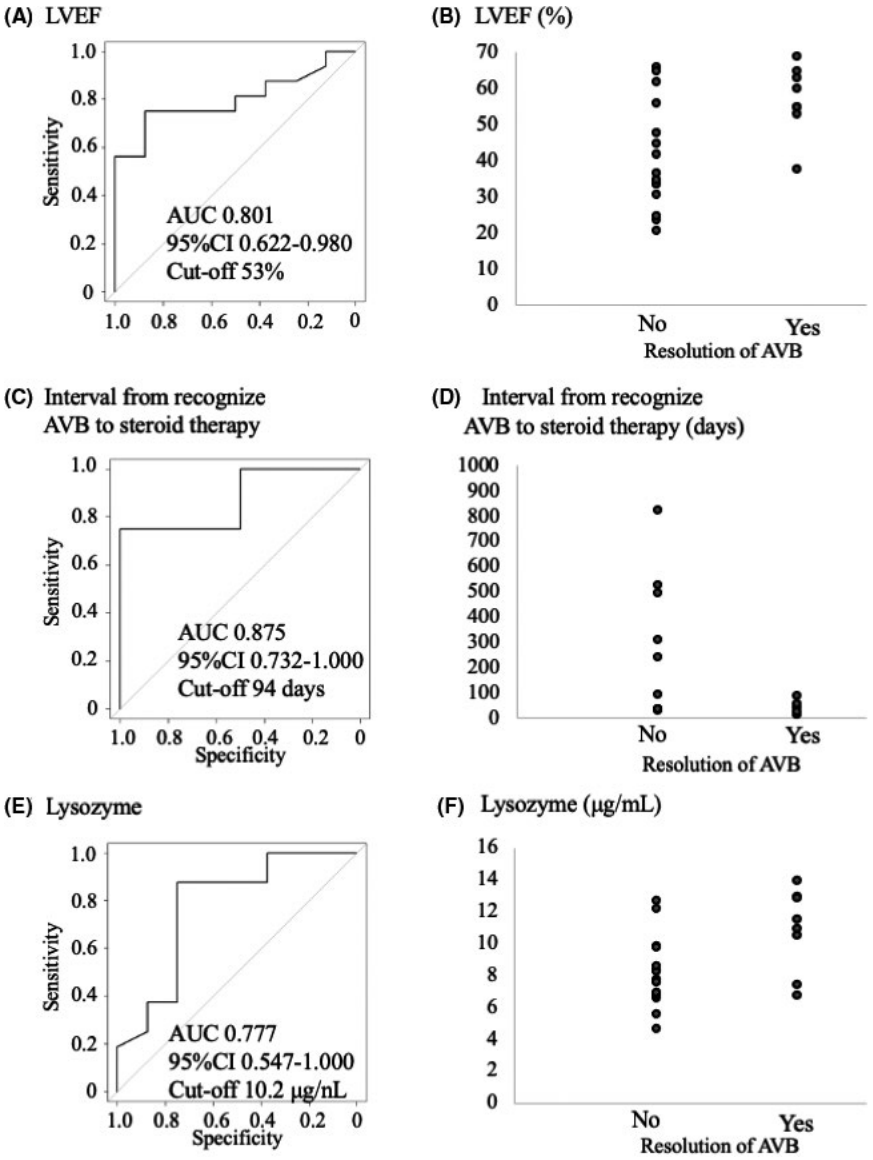


FIGURE 1 Receiver-operating characteristic analysis and scatter diagram of each variable, which significantly associated with resolution of atrioventricular block in univariate analysis. AUC, area under the curve; AVB, atrioventricular block; CI, confidence interval; LVEF, left ventricular ejection fraction

therapy. Recurrence of AVB occurred in one patient after 6 months from AVB resolution.

4 | DISCUSSION

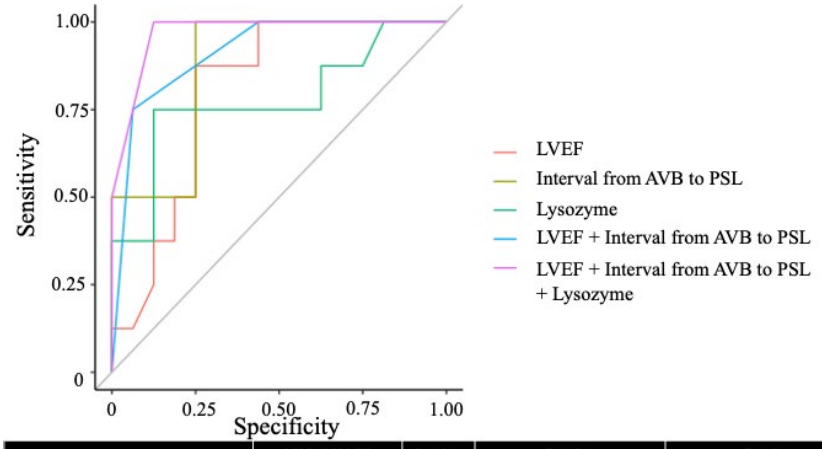
Resolution of AVB occurred in 33% patients with CS and complete or advanced AVB following steroid therapy. A shorter interval from recognition of AVB to start of steroid therapy, higher LVEF, and higher lysozyme levels were significantly associated with resolution of AVB after steroid therapy. The combination of each variable could be able to distinguish patients with resolution of AVB from those without.

4.1 | LV function and geometry and resolution of AVB

Several previous studies have reported that there are significant differences in the clinical characteristics between patients with resolution of AVB and those without AVB resolution.[7,13,20] Yodogawa et al[7] showed that resolution of AVB occurred in 7/15 (47%) patients with complete or advanced AVB after steroid therapy. Patients with resolution of AVB exhibited higher LVEF and a higher prevalence of advanced AVB compared with those without. In the present study, LVEF was also higher in patients with resolution of AVB. LV dysfunction and remodeling occurs due to progression of myocardial damage due to CS.[18] Therefore, these results suggest that steroid therapy before progression of myocardial damage is important for the resolution of AVB.

4.2 | Inflammatory activity of CS and resolution of AVB

The mechanism involved in the resolution of AVB after steroid therapy is considered to be the suppression of the inflammatory activity of CS.[9] Orii et al demonstrated that resolution of AVB occurred in patients who increased T2-weighted signal on cardiac MRI and cardiac FDG



	AUC (95%CI)	P-value	P-value (vs LVEF+Interval from AVB to PSL)	P-value (vs LVEF+Interval from AVB to PSL+Lysozyme)
LVEF	0.801 (0.622-0.980)	0.008	0.185	0.068
Interval from AVB to PSL	0.875 (0.732-1.000)	<0.001	0.591	0.130
Lysozyme	0.777 (0.537-1.000)	0.010	0.337	0.088
LVEF + Interval from AVB to PSL	0.914 (0.810-1.000)	<0.001	ref	0.186
LVEF + Interval from AVB to PSL + Lysozyme	0.969 (0.921-1.000)	<0.001		ref

FIGURE 2 Comparison of area under the curve for the variables associated with resolution of atrioventricular block. The combination of each variable had higher area under the curve compared with each predictor alone; however, the difference of each variable and model was not statistically significant. AUC, area under the curve; AVB, atrioventricular block; CI, confidence interval; LVEF, left ventricular ejection fraction; PSL, steroid therapy [Colour figure can be viewed at wileyonlinelibrary.com]

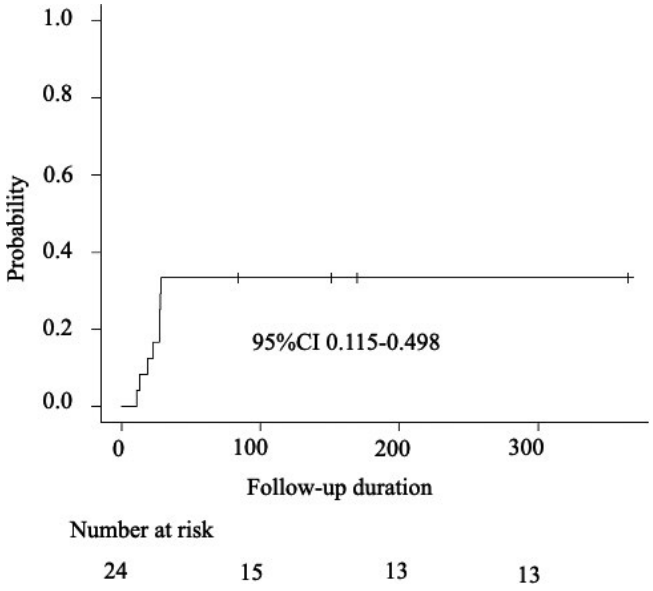


FIGURE 3 Kaplan–Meier analysis for the cumulative rate of resolution of atrioventricular block (AVB) 1 year from the commencement of steroid therapy. Resolution of AVB is noted within 1 month

uptake in the septum.[13] These results are in accordance with those of our study. FDG uptake around the AV node was present in all patients with resolution of AVB. However, FDG uptake around the AV node was also shown in some patients without resolution of AVB, whereas there was no significant difference in the frequency of FDG uptake around the AV node between patients with resolution of AVB and those without. Therefore, inflammatory activity in septum evaluated by FDG-PET might not be a sufficient indicator to be used as a predictive factor.

In the present study, serum lysozyme levels were higher in patients with resolution of AVB than those without. Both monocytes and tissue macrophages contain high a degree of lysozyme activity. Because granulomatous reactions such as sarcoidosis are characterized by the accumulation of macrophages in tissue granulomas, serum lysozyme levels might reflect activity of sarcoidosis.[21] Specifically, lysozyme activity is only higher in patients with sarcoidosis and in earlier phases and subsequently falls with the development of fibrosis.[21] Therefore, high serum lysozyme levels might reflect an early inflammatory state whereby AVB could improve with steroid therapy in CS patients.

4.3 | Appropriate interval from onset AVB to steroid therapy

Although several reports have recommended early diagnosis and immunosuppression therapy in patients with CS, it is unclear by when steroid therapy should start following the onset of cardiac symptoms.[8,18,22,23] Padala et al[18] showed that resolution of AVB only occurred in patients treated with steroid therapy within 1 month from diagnosis of CS. These results were similar to our results showing that steroid therapy was recommended within <94 days of recognized AVB. However, in Padala et al's[18] report, the interval from therapy was not determined from the onset of AVB recognition but from the initial diagnosis of CS. The timing of diagnosis was often different from appearance of AVB in patients with CS.[23] Thus, the interval from recognized AVB to start of steroid therapy, which we used in our study, could be a more appropriate parameter. From the present study, both early diagnosis of CS and steroid therapy are needed in patients with recognized AVB.

4.4 | Limitations

There are several limitations of this study. First, ours was a single-center retrospective observational study, and only patients with AVB were enrolled. The results of the present study are limited by the small sample size and the small number of events assessed. Therefore, there were some concerns about selection bias, inclusion of incomplete data, and limited statistically power. Further prospective studies involving larger populations are warranted. Second, in the present study, although Ga scintigraphy was performed for all patients, FDG-PET and Gd-MRI were not performed for all patients. The sensitivity of FDG-PET and Gd-MRI for detecting inflammatory activity in CS is better than that of Ga scintigraphy.[24] Thus, the assessment of inflammatory activity in CS might have been inadequate in some patients.

5 | CONCLUSIONS

In the present study, resolution of AVB was observed in 33% patients with CS and AVB after steroid therapy. Shorter interval from recognition of AVB to start of steroid therapy, higher LVEF, and higher lysozyme levels were significantly associated with resolution of AVB after steroid therapy. The combination of each variable that was significantly associated with resolution of AVB could be able to distinguish patients with resolution of AVB from those without. Further prospective studies validating this scoring system are warranted.

CONFLICT OF INTERESTS

Authors declare no conflict of interests for this article.

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