"Prognosis of Cardiac Sarcoidosis Patients Treated with Steroid Therapy in the Modern Era in Japan"

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博士論文

Prognosis of Cardiac Sarcoidosis Patients Treated with Steroid Therapy in the Modern Era in Japan
(本邦におけるステロイド治療による心サルコイドーシスの予後に関する研究)

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内科病態学講座・循環器内科学分野

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Abstract

Background: Prognosis of Japanese steroid-treated patients with cardiac sarcoidosis (CS) and factors affecting it are not yet determined. ***Methods and Results:*** We examined 58 consecutive CS patients who were admitted to our hospital from April 2002 to March 2012 with a median follow-up period of 50 months to study their survival and the prognostic indicators of a composite endpoint including ventricular arrhythmias (VA), heart failure hospitalization, de novo device implantation and all-cause mortality. There was no significant difference in baseline clinical characteristics between patients according to their initial steroid dose. There were only two death events reported, and 5- and 10- years survival was 98% and 96% respectively. Composite endpoint-free survival was significantly better in patients with preserved left ventricular ejection fraction (LVEF) at baseline and after 1 year of steroid therapy, as well as in patients with no evidence of late gadolinium enhancement on cardiac magnetic resonance imaging (LGE-CMRI) ($P<0.001$, $= 0.03$, and < 0.01 respectively). Multivariate analysis revealed that independent markers of poor composite outcome include depressed LVEF at baseline (HR= 2.2, P=0.04), and after 1 year of treatment (HR=2.3, P=0.03), and VA at baseline (HR=2.9, P=0.02) ***Conclusions:*** The prognosis of Japanese CS patients is improving, and impaired baseline LVEF, unfavorable LVEF course, the presence of VA, and positive LEG-CMRI are independent predictors of poor outcome in this population.

Introduction

Sarcoidosis is a multisystem disease that is histologically characterized by non-caseating granuloma formation in various organs.[1)] Although sarcoidosis could affect any organ, including the lungs, skin, eyes, liver and lymphatics,[1,2)] cardiac involvement is the most important prognostic factor.[3,4)] The incidence of cardiac sarcoidosis (CS) has been reported to be ~2% among patients with sarcoidosis, however, previous autopsy studies demonstrated that cardiac involvement is relatively high (20~25%),[4,5)] which has been recently confirmed by cardiac imaging.[6)] Interestingly, CS is more common and seems to carry poorer prognosis in Japan, where cardiac involvement may be as high as 58% in Japanese patients with sarcoidosis[7,8)] and may be responsible for as many as 85% of deaths of Japanese patients with the disease.[8,9)]

CS frequently presents as asymptomatic cardiac involvement and is only evident by abnormalities on ECG, echocardiography or cardiac magnetic resonance imaging (CMRI).[2)] Clinically, CS commonly presents with congestive heart failure (CHF), often associated with a dilated cardiomyopathy (DCM)-like phenotype. CS also commonly presents with electrical abnormalities, including conduction disturbances,[4)] and serious ventricular arrhythmias (VA), that include both ventricular tachycardia (VT) and ventricular fibrillation (VF).[10)]

Although the etiology and exact pathophysiology of sarcoidosis, including cardiac involvement, are still not fully understood, the inflammatory nature of the disease resulted in offering corticosteroid treatment as a therapeutic option for patients with CS.[11-13] Despite the long term and frequent use of corticosteroid, there is still controversy about their proper timing,[3] proper dosing,[14] and their clinical efficacy, particularly in patients with advanced cardiac dysfunction [15,16] and VA[17-20] are not fully evaluated. Corticosteroid treatment favorably affects prognosis of CS patients, furthermore, significant improvement of prognosis of CS patients as compared to older registries that had lower rates of steroid use was also documented.[3,4,13] Steroid treatment became a cornerstone therapy for CS once cardiac involvement is strongly suspected or established, but in the last decade, no other agents, including immunosuppressive drugs, has been proved to be more effective in controlling inflammation in CS.

On the other hand, left ventricular (LV) systolic dysfunction, defined as a LV ejection fraction (LVEF) <50%, as documented with other forms of structural heart disease, was found to be a marker of poor prognosis in Japanese CS patients despite steroid treatment.[3] Furthermore, advanced LV dysfunction (LVEF <30%) in CS patients at time of presentation represented advanced LV remodeling that was irreversible after steroid treatment as compared to those with LVEF >30%, reflecting advanced myocardial scarring with little or no role of active inflammation at this stage.[21]

The latest study to address the prognosis of a Japanese steroid-treated CS population was the work of Yazaki et al. in 2001.[3] Since then, the increased use of novel and effective therapies for conditions such as VA, sudden cardiac death (SCD) and CHF, including drugs and devices, has greatly improved the prognosis and survival of patients in the context of various structural heart disease etiologies, and whether this will have similar impact on prognosis and survival of CS patients remains to be identified.

Therefore, it was our aim through this study to re-explore the natural history of Japanese steroid-treated CS patients, and to examine whether prognosis of this population has improved over time, and whether the prognostic markers of the disease have changed over the last decade.

Methods

Patient Selection

From 61 consecutive patients who were found to have a definite diagnosis of CS at Tohoku University Hospital between April 2002 and March 2012, we excluded 3 patients for not receiving steroid treatment upon diagnosis, and we included the remaining 58 steroid-treated patients in our analysis (figure 1). The reason of not using steroid upon diagnosis in these patients include refusal of receiving the drug by one patient and very limited myocardial involvement on CMRI with uneventful courses in the other two. The three patients are under close surveillance with uneventful courses on follow up. The clinical data of the 58 patients who were included in the analysis were obtained from the detailed database of cardiology department of Tohoku University Hospital, including demographic, clinical, laboratory, imaging, procedural and interventional data, both at time of primary presentation, as well as their follow-up data.

Diagnosis of Cardiac Sarcoidosis

The revised guidelines for diagnosis of cardiac sarcoidosis from the Japanese Ministry of Health and Welfare were used (table 1).[22] The diagnosis of CS was made either directly by endomyocardial biopsy or indirectly by clinical evidence of cardiac involvement on a background of biopsy-proven extra-cardiac sarcoidosis, using ECG findings and cardiac imaging tests that included echocardiography, scintigraphy and cardiac magnetic resonance imaging (CMRI).

Study Variables

I retrospectively examined the baseline clinical, laboratory, and imaging variables, of my population. CS patients were sub-divided according to their baseline loading prednisolone dose received upon diagnosis, and were categorized as those started on a dose ≤ 30 mg/day and those started on a dose of > 30 mg/day.

- Demographic and clinical data:

They include age, gender, presence of extra-cardiac sarcoidosis, heart rate (HR), New York Heart Association (NYHA) functional class. Electrical abnormalities were detected either by ECG monitoring during admission or later diagnostic evaluation with 12-lead ECG, Holter ECG, or device recording. VA in this study included sustained VT and aborted sudden cardiac death (SCD) due to VF, and the included beats of ventricular origin, at a rate of more than 100 beats/min,[23] that do not resolve spontaneously and/or last more than 30 seconds. Beats of ventricular origin not fulfilling these conditions were not included.

- Laboratory data:

Laboratory data included brain natriuretic peptide (BNP) level and soluble interleukin 2 receptor (IL-2R) level. Impaired BNP was defined as serum BNP level > 100 pg/ml. Both baseline BNP levels and levels after 1 year of starting steroid therapy were measured and reported, and their correlations with prognosis were individually evaluated.

- Imaging data:

1. Transthoracic echocardiography was performed to evaluate LV indices including LV end-diastolic and end-systolic diameters, left atrial dimensions, and LVEF. LVEF was measured by M-mode using Teichholz method and formula.[24] Modified Simpson's method (disc method) was used in the presence of LV dyssynchrony.[25] Impaired LVEF was defined as LVEF < 50%. Both baseline LVEF and LVEF after 1 year of starting steroid treatment were measured and reported, and their correlations with prognosis were individually evaluated.

2. CMRI was performed before starting corticosteroid therapy and after patients had been clinically stable after heart failure or arrhythmia. We used the standard protocol for cardiac MRI in our institution,[26] and ECG-gated magnetic resonance (MR) images were obtained in all patients during breath-holding on a 1.5-T imager (Magnetom Vision, Siemens Medical Solutions, Erlangen, Germany; Achiva, Philips Medical Systems, Best, The Netherlands) using a body array coil (Siemens) or a five-channel cardiac coil (Philips). To evaluate LV anatomy, cine MR images of the LV in one horizontal, one vertical long, and five short axis slices were obtained. Delayed contrast-enhanced MR images using inversion recovery-prepared gradient-echo sequence were acquired 10-15 minutes after the injection of gadopentetate dimeglumine (0.15 mmol/kg) in the same plane as cine imaging with the

Siemens Scanner or in 10 horizontal, 10 vertical long and 20 short axis slices with the Philips scanner. The acquisition parameters of the delayed contrast-enhanced MR images were 3.7-7.5/1.2-3.4; flip angle, 15°; field of view, 380 mm; matrix, 182-224 × 139-256; and slice thickness, 5 mm. The inversion time (200–300 milliseconds) was adjusted to null signal from normal myocardium. CMRI was performed in 37 out of the 58 CS patients, and prior device implantation was the reason for contraindication in the remaining 21 patients.

Study Endpoints

The primary endpoint was a composite outcome composed of VA, heart failure (HF) hospitalization, de-novo device therapy, and all-cause death. Secondary endpoints included the separate evaluation of VA, HF hospitalization, device therapy, and all-cause death, either studied in survival analysis, or studied in the process of describing their temporal trends following the initiation of steroid therapy in our CS population.

VA was previously defined and mode of detection reported. HF hospitalization was considered according to the index admission diagnosis in patients file as reported by first treating cardiologist. Only de-novo device implantation was considered because indications of later device management are confounded by issues unrelated to the natural history of CS, including management of system-related complications as well as battery exchange.

Statistical Analysis

Continuous variables were expressed as mean ± SD. Categorical data were presented as percentage and frequency. Differences between groups were compared by Student t-test (for normally distributed variables) and Mann-Whitney test (for non-normally distributed variables) for continuous variables. The chi-square test was used for categorical variables and the Fisher exact test for those instances in which the expected cell count was <5. Event rates of endpoints were expressed as unadjusted Kaplan-Meier estimates and a Cox proportional hazard test was used for univariate and multivariate analysis of the interaction between patient characteristics and study endpoints. All statistical tests were 2-tailed, and a P value <0.05 was considered to be statistically significant. All analysis was performed using SPSS software (version 18, SPSS, Chicago, Illinois).

Results

General Characteristics

The baseline clinical characteristics of the 58 patients with CS at presentation are shown in **table 2**. They were characterized by middle-age and more female, and 86% of them had extra-cardiac involvement of sarcoidosis, with only 17% of them having positive diagnostic cardiac biopsy. The prevalence of hypertension, diabetes mellitus, coronary artery disease and smoking was relatively low. No clinical or echocardiographic evidence of structural heart disease was noted in almost half of CS patients (49%), with 27% of patients showing a picture of dilated LV and cardiac dysfunction indistinguishable from the idiopathic form, and the remaining 24% showing isolated ventricular septal thinning that is characteristic of cardiac involvement in sarcoidosis. Most of the patients were in NYHA class I (52%) or II (29%), with less frequency of presenting with class III or IV (16% and 3% respectively).

Advanced heart block was the most common electrical abnormality encountered at baseline (41%), and VA collectively was the second most common electrical abnormality (31%), where NSVT was noted in 19% and VT/VF in 24%. Laboratory data were normal apart from modest elevation of BNP (325 pg/ml). Also echocardiographic parameters were within normal range with borderline mean LVEF (50 %). Importantly, LGE-CMRI at baseline examination was noted in 70% of the 37 CS patients tested. Other than prednisolone, drugs blocking the renin-angiotensin system, angiotensin converting enzyme inhibitors (ACE-Is) and angiotensin

receptor blockers (ARBs), were the most commonly used group of drugs in CS patients (57%) followed by beta blockers (BBs) in this population (46%). Amiodarone was administered to 7% of the patients in this cohort.

Steroid Treatment and Event Trend

The vast majority of our CS population (52 patients) received the conventional established prednisolone dose of 30 mg/day (either daily 30 mg or 60 mg every other day) or less, and only 6 patients were loaded with a prednisolone dose > 30mg/day.

As shown in **table 3**, there were no statistically significant differences in patients' characteristics between CS patients according to their initial prednisolone dose, apart from significantly higher levels of soluble Interleukin-2 receptor (IL-2R) levels among patients started on the higher dose. However, there was a uniform insignificant trend of more severe disease parameters in patients receiving a higher initial steroid dose, including higher incidence of VA, higher baseline BNP, lower LVEF and larger LV dimensions.

Figure 2 shows that there is a uniform trend of incident events in CS patients after starting steroid therapy as regards VA, HF hospitalizations, device therapy, and the primary composite endpoint (figures 2A, 2B, 2C, and 2D respectively), in the form of relatively high event rate at the outset of therapy, followed by steady state of relatively low event rate that continues across the first 3 years of therapy. Beyond the third-post treatment year, VA and device therapy remained

relatively low, while HF hospitalization and composite events showed a second rise of events.

Prognosis and Prognostic Indicators in CS patients

In the median follow-up period of ~50 months (18-120 months), and as shown in **table 4**, VA events, HF hospitalizations, and the composite endpoint occurred in 31%, 22% and 48% of CS patients respectively. Only two death events occurred in our population, the first of which occurred after 56 months, and the second after 75 months of follow-up respectively. Estimated 3-, 5- and 10-years survival was 100%, 98% and 96% respectively (**figure 3**).

Kaplan-Meier analysis in **figure 4** showed conventional prognostic indicators in patients with CS and their effect on outcome. Steroid-treated CS patients with baseline LVEF < 50% were shown to have significantly worse prognosis than those with preserved baseline LV systolic function, while a higher initial prednisolone dose >30 mg/day was not found to predict better event-free survival in CS patients as compared to regular dose of 30mg/day (**figures 4A and 4B,** P<0.001 and P=0.76 respectively).

As for novel predictors of prognosis studied in this research, a LVEF $\geq$ 50% after 1 year of steroid therapy was found to predict better prognosis in CS patients, while a normal BNP level < 100 pg/ml after 1 year of steroids did was not found to be similarly protective (**figures 5A and 5B,** P=0.03 and 0.24 respectively).

Figure 6 also shows the effect of another novel marker in this disease entity, which is the presence of LGE-CMRI at baseline, on the prognosis of CS patients in terms of both composite-endpoint and VA (**figures 6A and 6B** respectively), where it was found to be a significantly associated with poor composite event-free survival (P= 0.03). Although it did not reach statistical significance, there was a strong trend of higher VA events in patients with LGE-CMRI at baseline. Furthermore, the lack of LGE-CMRI at baseline carried a 100% negative predictive value of events, whether composite or VA, in steroid-treated CS patients, and as seen from two representative LGE-CMRI images of two CS cases in **figure 7**, where the first case with absence of LGE-CMRI (**figure 7A**) ran an uneventful course after starting steroid therapy as was the case with all cases with similarly negative LGE-CMRI at baseline. Patients with LGE-CMRI at baseline were at higher risk of events, particularly VA (**figure 7B**), despite steroid therapy.

Table 5 shows that univariate predictors of poor outcome in our population were the presence of VA at baseline (HR=2.4, P=0.02) and depressed 1 year post-steroid LVEF (HR 2.2, P=0.03). Adjusted multivariable analysis confirmed baseline VA (HR=2.9, P=0.02), and 1 year post-steroid LVEF (HR=2.3, P=0.03) as predictors of poor outcome, in addition to baseline LVEF (HR=2.2, P=0.04). LGE-CMRI was not included in the analysis due to lack of events in the negative arm.

Discussion

The main findings of the present study are; 1) Japanese steroid treated CS patients has favorable prognosis in the modern era, and 2) that depressed LVEF at baseline and on follow-up, the presence of VA, and the presence of LGE-CMRI at baseline are independent markers of poor prognosis in this population.

Prevalence and Diagnosis of CS

The prevalence of sarcoidosis, as well as the incidence of cardiac involvement are both relatively high in Japan,[2,27] reaching ~ 60% of sarcoidosis patients in some series.[8] This offers a unique chance to study various unstudied aspects of this disorder. Furthermore disease burden in Japanese patients seems to be particularly high, where cardiac involvement may be responsible for as many as 85% of deaths of Japanese patients with the disease.[8,9]

Although it was previously shown that the majority of western CS patients are young adults between the ages of 20~40 without a definite sex predominance,[5] the present study shows that the majority of the Japanese CS patients are middle-aged females, a consistent finding with the previous studies in Japan.[3,28] These results suggest some racial differences in demographic characteristics of CS patients that might extend to presentation and prognosis of the disorder. Most of the CS patients in the present study were diagnosed in conjunction with involvement of other organs, again, a consistent finding with the previous study in Japan.[29]

Most CS patients in the present study showed no evidence of structural cardiac abnormality when assessed by echocardiography with a similar prevalence rate as in western studies with 14~31% prevalence rate,[30,31] thus highlighting the limited sensitivity of echocardiography in this subset of CS patients.[32] In CS patients, the usual echocardiographic abnormality, if present, is a DCM-like phenotype (reduced LVEF and regional or global LV hypokinesia) that is difficult to distinguish from the idiopathic form,[2,27,32] which also was the case in the present study. Indeed, echocardiography has a low specificity for diagnosis of CS[32] and its main value lies in its ability to predict poorer prognosis of CS patients, as LV dilatation is an established predictor of mortality.[3] Although an appearance similar to hypertrophic cardiomyopathy (HCM) has been described in limited case series,[33] we did not come across any patient with such a phenotype in the present study.

Steroid Treatment and Events Trend

The optimal dose of steroid treatment in CS is not known or studied, and requires balancing the risk of side effects with the likelihood of response.[34] So using 30 mg/day as the cut-off point was based mainly upon consensus in the medical Japanese society of using no more than 30 mg day as a loading for CS, and supported by a single retrospective analysis stating that higher doses offers no additional benefit in terms of survival in Japanese CS patients.[3] That is why, compared to this older study, I reported marked decrease in the frequency of use of the larger

loading dose (> 30 mg/day) from 40% in the work of Yazaki et al.[3] to only 10% in this study despite continued lack of supportive evidence for superiority of such a higher dose. Although the obvious difference of the number between two groups is a limitation in this study, it was interesting to see that there is still some clinical trend to use it among patients with poorer presentations, as seen from the worse LV indices and significantly higher inflammatory burden, as evident by the significantly higher levels of soluble IL-2R levels, among patients chosen for such a starting dose.

Steroid treatment has also shown success in reducing various event rates after the early loading period, compared to very early high event rates during the loading period, after which event rates remained fairly low for around 3 years. The composite event rate, however, showed a second rise of event rate after the third year, mainly secondary to increase in HF events, which reflects the steadily progressive natural history of the disease when advanced heart failure and extensive myocardial fibrosis occur and the role of inflammation becomes minimal.[35] Although tachyphylaxis is well documented with topical steroids, no reports of a similar response with systemic use are yet reported,[36] and thus unlikely to be the cause of such a second rise of HF events.

Prognosis and Prognostic Indicators of Japanese CS Patients

In our study we came across only two death events, the first of which was just 4 months before

the fifth year of follow-up, and the second occurred between the sixth and seventh years of follow-up, and 3, 5, and 10-years survival were estimated to be 100%, 98% and 96% respectively, indicating very favorable survival and marked improvement in terms of mortality in Japanese CS patients in the modern era, as compared to a very similar Japanese steroid-treated CS cohort studied by Yazaki et al. in 2001, where 3, 5, and 10-years survival were estimated to be 82%, 75%, and 61% respectively.[3)] This may be explained by the increased use of evolving therapies targeting morbid conditions that accompany cardiac involvement in sarcoidosis patients, such as VA, SCD and HF. Increased use of protective agents might theoretically account for such improvement in survival, and this evident from increased use of angiotensin-converting enzyme inhibitors from 21% in the work by Yazaki et al.[3)] to 57% in this cohort. However, similar trends with other agents, especially beta-blockers, are not known due to lack of frequency of its use in the work of Yazaki et al.[3)]

More importantly is the prominent role of device therapy, where strong evidence from major trials in patients with ischemic heart disease and DCM, showed considerable survival benefits of implantable cardioverter- defibrillators (ICD),[37-39)] and cardiac resynchronization therapy (CRT), with or without defibrillator capabilities.[40-42)] This body of evidence resulted in recommending ICD as a class 1 indication for primary and secondary prevention of SCD due to VA in both European (ESC) and US (ACC/AHA) guidelines issued in 2005,[43,44)] and CRT was also recommended for use in patients with ischemic and dilated cardiomyopathy in US (ACC/AHA)

guidelines issued in the same year.[44] Furthermore, despite lack of specific statistics about their use in the work by Yazaki et al.,[3] the authors of that research reported limited use of ICD in their cohort, as compared to a considerable implantation rate in my study. Furthermore, they reported the total lack of any CRT device implantation in any patient in the cohort, supporting the possible interplay between device management and improved prognosis of CS patients in the modern era.

Due to improved prognosis and small number of events, we studied a primary composite endpoint including VA, HF hospitalization, de-novo device implantation and all-cause death as a surrogate of prognosis in CS patients. Independent predictors of poor outcome in our study included depressed LVEF at baseline and/or on follow-up, VA, and positive LGE-CMRI. LV systolic dysfunction is well-established as a marker of poor prognosis in various forms of structural heart disease, and is a well-established prognosticator in CS ptients.[3] This is explained by higher mortality, frequent heart failure hospitalization, and higher incidence of VA, [45-48] as was the case in our study. Interestingly, depressed LVEF on follow up and failure to improve after steroid therapy also predicted poorer prognosis. This is probably explained by higher myocardial scar burden that is irreversible with anti-inflammatory therapy, hallmarking more advanced disease. This marker has been recently verified to predict prognosis after primary revascularization in patients with acute myocardial infarction and in patients with advanced heart failure with CRT.[49-51]

The presence of sustained VT/VF on presentation predicted poorer outcome in CS, as the case with other forms of structural heart disease. VA itself is known to be the strongest predictor of subsequent VT/VF, as reported by secondary prevention studies of ICD.[52,53] Furthermore, we previously reported that CS patients with VA at presentation have more compromised LV function indices than those without, [54] and as mentioned earlier, this might add another reason for why such patients run a less favorable course.

LGE-CMRI significantly predicted poorer outcome in CS patients. This finding is also supported by the role of CMRI as a risk stratification method for adverse prognosis in various forms of structural heart disease, owing to its unique ability to accurately detect and delineate myocardial fibrosis, the presence and extent of which have become well established markers of poorer prognosis,[55-59] whether detected by histopathology[60] or LGE-CMRI,[57,58] and was even related to poor prognosis in the general population.[61]

The presence of LGE-CMRI at baseline was also specifically found to be linked to higher VA events in CS patients on follow up despite steroid treatment. Bello et al. reported that scar burden was a significant predictor of VT inducibility, whereas LVEF was not.[55] It has been recently shown that patients with advanced cardiomyopathy and ICD with proven myocardial fibrosis by LGE-CMRI have a high likelihood of appropriate ICD therapy.[62] Although scar-based-reentry has been thought to account for VA only in patients with ischemic cardiomyopathy, accumulating evidence suggests that reentry appears to play a major role in the

mechanism of sustained monomorphic VT in this patient population.[63] Furthermore, it has been recently demonstrated that programmed electrical stimulation predicts appropriate ICD therapy used for primary prevention of SCD only in patients with evidence of cardiac involvement on CMRI or positron emission tomography,[64] suggesting the possible importance of LGE-CMRI for risk stratification for VA and SCD in CS patients.

Importantly, patients without LGE-CMRI showed an uneventful course, and this perfect negative predictive value not only enforces its role in predicting adverse outcome in this population, but also stands out as a unique diagnostic criterion for CS in patients with extra-cardiac involvement. The present findings may be useful for the revision of the role of LGE-CMRI as a potential major diagnostic criterion for diagnosis of CS in the Japanese Ministry of Health and Welfare guidelines.[22]

Study Limitations

Several limitations should be mentioned for the present study. First, our study has the inherent limitations of retrospective analysis. Thus, the present findings should be confirmed in a future prospective study. Second, not all CS patients underwent CMRI test. This was inevitable as device implantation was the reason for contraindication in most cases without CMRI study. However, although not reported, the clinical characteristics and long-term prognosis were comparable between the patients who underwent CMRI study and those who did not, so the

present findings may not be biased in regarding this point. Third, the definitions of favorable LVEF and BNP courses were largely arbitrary due to lack of established definition for dynamic shifts in these variables. Fourth, evaluation of LVEF was mainly performed using Teichholz formula, which is known to have limitations and poor correlation with more recent modalities and methods in the presence of significant dyssynchrony or LV wall motion abnormalities; however, this was partially overcome in this study by using the modified Simpson's method in such in the presence of such conditions. Finally, the study was a single center experience, and was underpowered with little number of mortality events to be able to evaluate mortality as a separate endpoint. Thus, this point needs to be evaluated in a future study with a large number of patients in multi-center effort to be more informative and more representative of Japanese CS patients.

Conclusions

In the present study, we were able to demonstrate that a the prognosis of Japanese steroid-treated CS patients has improved in the modern era, and that the presence of VA, depressed LVEF at baseline and/or after 1 year of therapy, and LGE-CMRI are considered as independent predictors of poor prognosis in CS patients.

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Figure Legends

Figure 1. Flow Diagram for Study Population.

Figure 2. Temporal trends of Events in Steroid-treated Cardiac Sarcoidosis Patients.

There is uniform trend of an exceptional and brief high rate of cardiovascular events in the early post-treatment months, followed by a relatively low event rate within the first 3 post-treatment years. Some events continues to run a stable course extending beyond the third post-treatment year as with ventricular arrhythmias (2A), and device therapy (2C), while in the case of heart failure hospitalizations (2B) and composite events (2D), there is a trend of re-rise of event rate after the third post-treatment year.

Figure 3. Overall survival of Steroid-Treated Cardiac Sarcoidosis Patients.

Survival rates of cardiac sarcoidosis patients since the start of steroid treatment were 100% at 1 and 3 years, 98% at 5 years, and 96% at 10 years.

Figure 4. Traditional Prognostic Indicators and Composite Endpoint-Free Survival in Steroid-Treated Cardiac Sarcoidosis Patients.

Kaplan-Meier curves for composite endpoint-free survival in CS patients. (A) Patients with baseline LVEF $\geq$ 50% (blue line, n=38) had better event-free survival rate than patients with

baseline LVEF < 50% (red line, n=20) (P< 0.001)). (B) Composite endpoint-free survival was comparable between patients with conventional initial prednisolone dose ≤ 30 mg/day (blue line, n=52) and those with higher initial prednisolone dose > 30 mg/day (red line, n=6) (P=0.76).

Figure 5. Novel Prognostic Indicators and Composite Endpoint-Free Survival in Steroid-Treated Cardiac Sarcoidosis Patients.

Kaplan-Meier curves for composite endpoint-free survival in CS patients. (A) After 1 year of steroid therapy, patients with LVEF > 50% (blue line, n=33) had better event-free survival rate than patients with baseline LVEF < 50% (red line, n=25) (P= 0.03). (B) Patients with BNP < 100 pg/ml after 1 year of steroid therapy (blue line, n=43) had insignificant trend of better composite endpoint-free survival than patients with BNP > 100 pg/ml (red line, n=15) (P= 0.24).

Figure 6. Late Gadolinium Enhancement on Cardiac Magnetic Resonance Imaging and Prognosis of Steroid-Treated Cardiac Sarcoidosis Patients.

Kaplan-Meier analysis for prognosis of steroid-treated CS patients according to the presence of baseline LGE-CMRI. (A) Patients with no LGE-CMRI (blue line, n=11) had no reported composite endpoint events after steroid therapy as compared to significantly higher event rate in patients with positive LGE-CMRI (red line, n=26) (P< 0.01). (B) There were also no reported events of VA in CS patients without baseline LGE-CMRI (blue line, n=11), unlike multiple VA

events among the LGE-CMRI positive arm (red line, n=26), however, this trend did not reach statistical significance (P= 0.12)

Figure 7. Cardiac Magnetic resonance Imaging of Steroid-Treated Cardiac Sarcoidosis Patients.

CMRI depicting LV in short axis view of two steroid-treated CS patients. (A) Lack of LGE-CMRI in a 55 year old female patient with pulmonary sarcoidosis presenting with fatigue, premature ventricular beats, and positive cardiac gallium uptake at LV free wall, but with unremarkable course since the start of steroid treatment. (B) Evidence of LGE-CMRI in the sub-epicardial layer of the anterior LV wall (multiple small white arrows) in a 41 year-old male patient diagnosed with CS on the background of a pre-existing pulmonary sarcoidosis, presenting with recurrent sustained monomorphic VT despite steroid therapy.

Figure 1

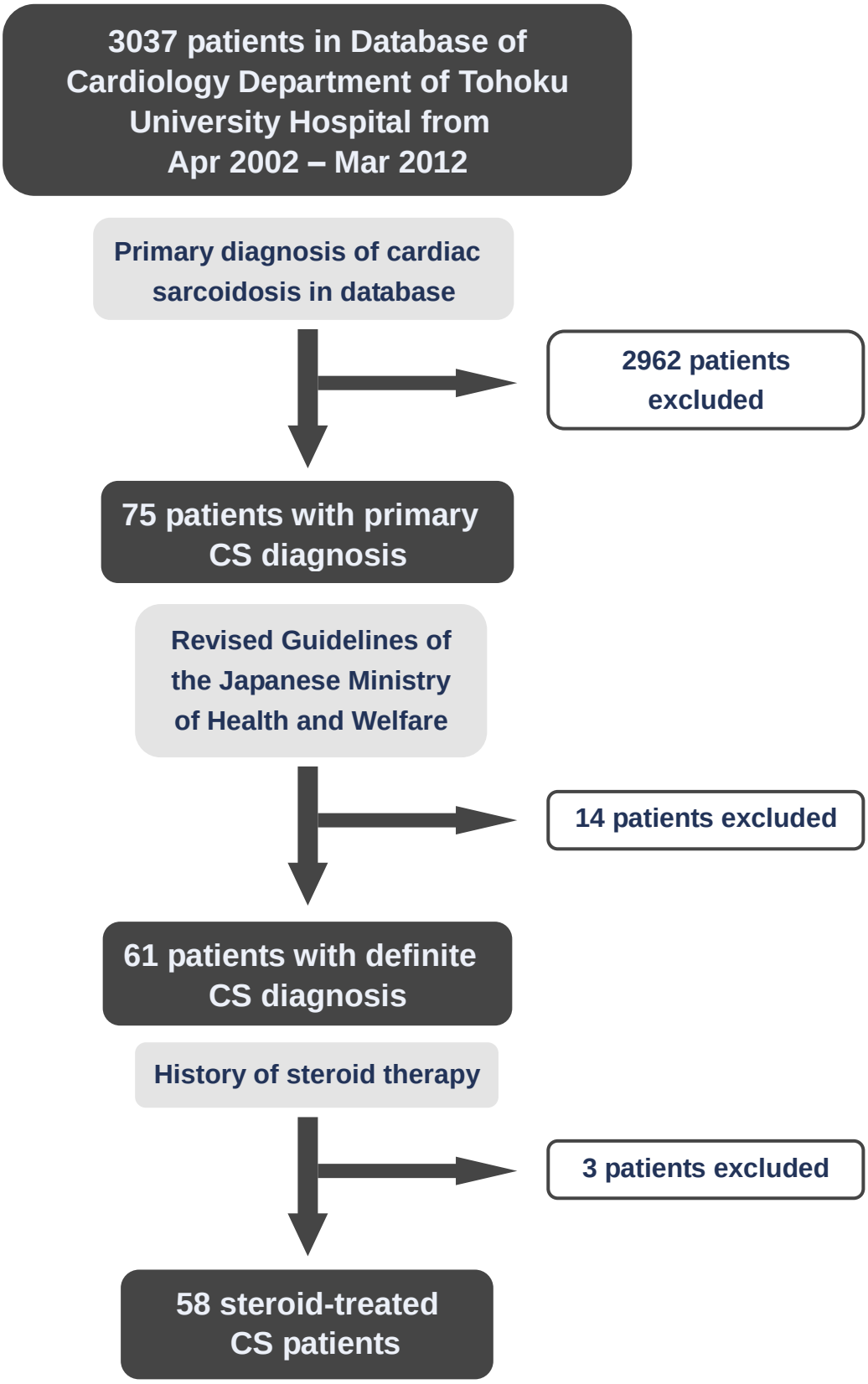

3037 patients in Database of Cardiology Department of Tohoku University Hospital from Apr 2002 – Mar 2012
Primary diagnosis of cardiac sarcoidosis in database
2962 patients excluded
75 patients with primary CS diagnosis
Revised Guidelines of the Japanese Ministry of Health and Welfare
14 patients excluded
61 patients with definite CS diagnosis
History of steroid therapy
3 patients excluded
58 steroid-treated CS patients

Figure 2

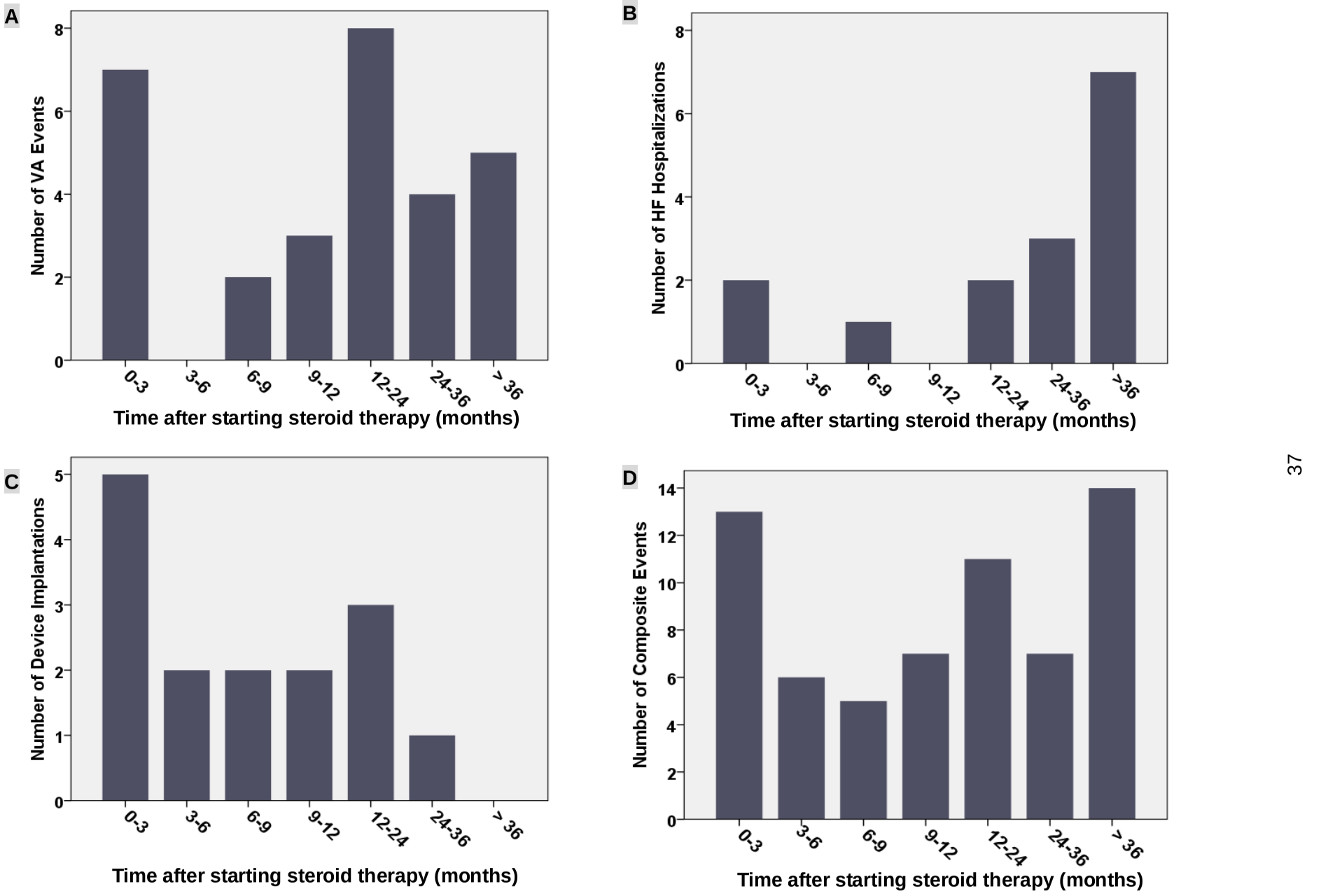
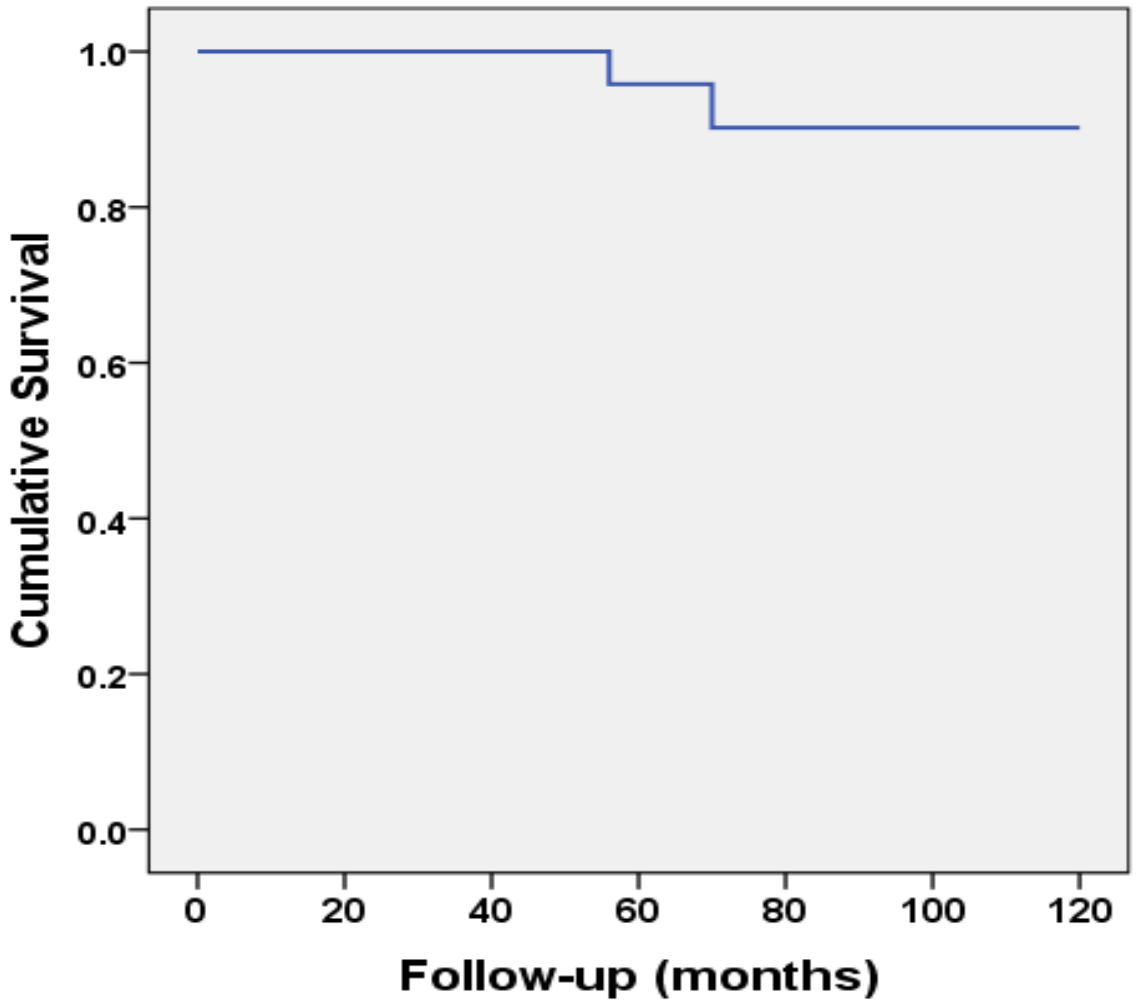

A
Number of VA Events
0
2
4
6
8
0-3
3-6
6-9
9-12
12-24
24-36
> 36
Time after starting steroid therapy (months)
B
Number of HF Hospitalizations
0
2
4
6
8
0-3
3-6
6-9
9-12
12-24
24-36
>36
Time after starting steroid therapy (months)
C
Number of Device Implantations
0
1
2
3
4
5
0-3
3-6
6-9
9-12
12-24
24-36
> 36
Time after starting steroid therapy (months)
D
Number of Composite Events
0
2
4
6
8
10
12
14
0-3
3-6
6-9
9-12
12-24
24-36
> 36
Time after starting steroid therapy (months)

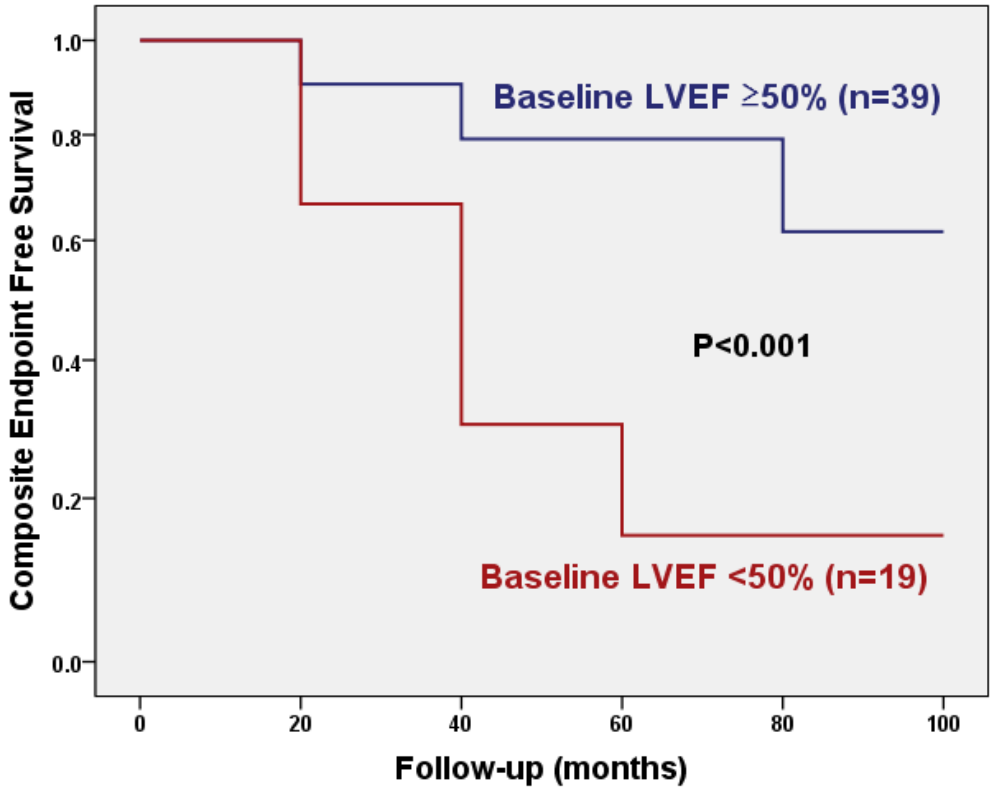
Figure 3



Months	20	40	60	80	100	120
Number at risk	58	48	34	19	11	5
Censored	10	14	14	7	6	5
Deaths	0	0	1	1	0	0
Cum. Survival	100	100	98%	96%	96%	96%

Figure 4

A


Composite Endpoint Free Survival
1.0
0.8
0.6
0.4
0.2
0.0
Baseline LVEF ≥50% (n=39)
P<0.001
Baseline LVEF <50% (n=19)
0
20
40
60
80
100
Follow-up (months)

B

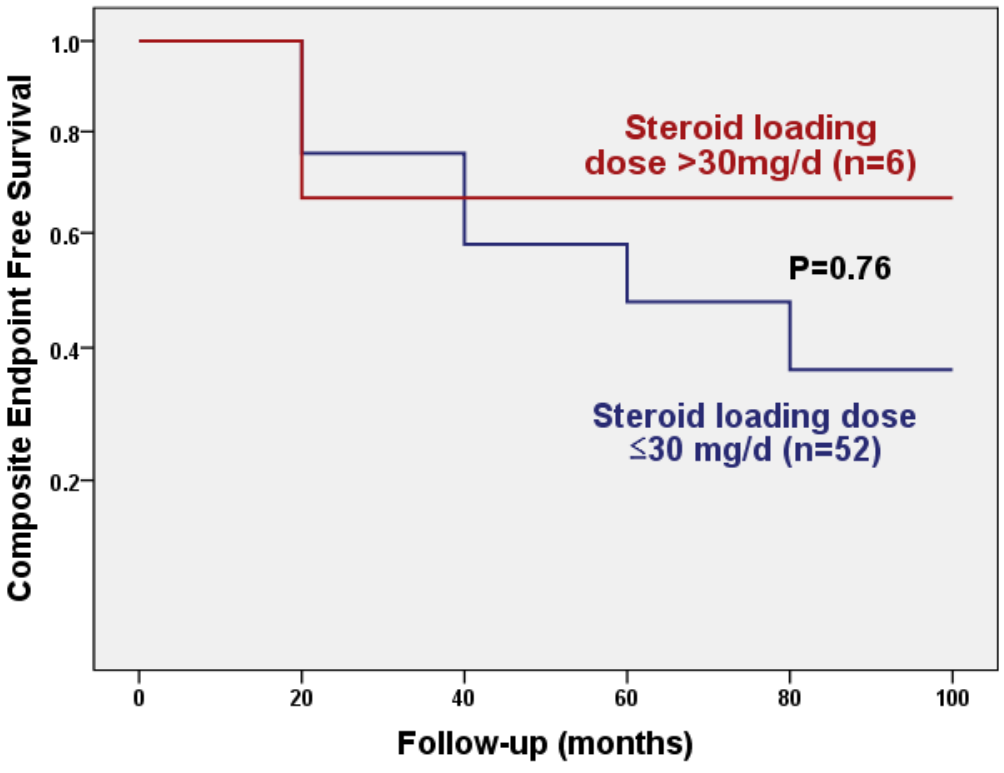
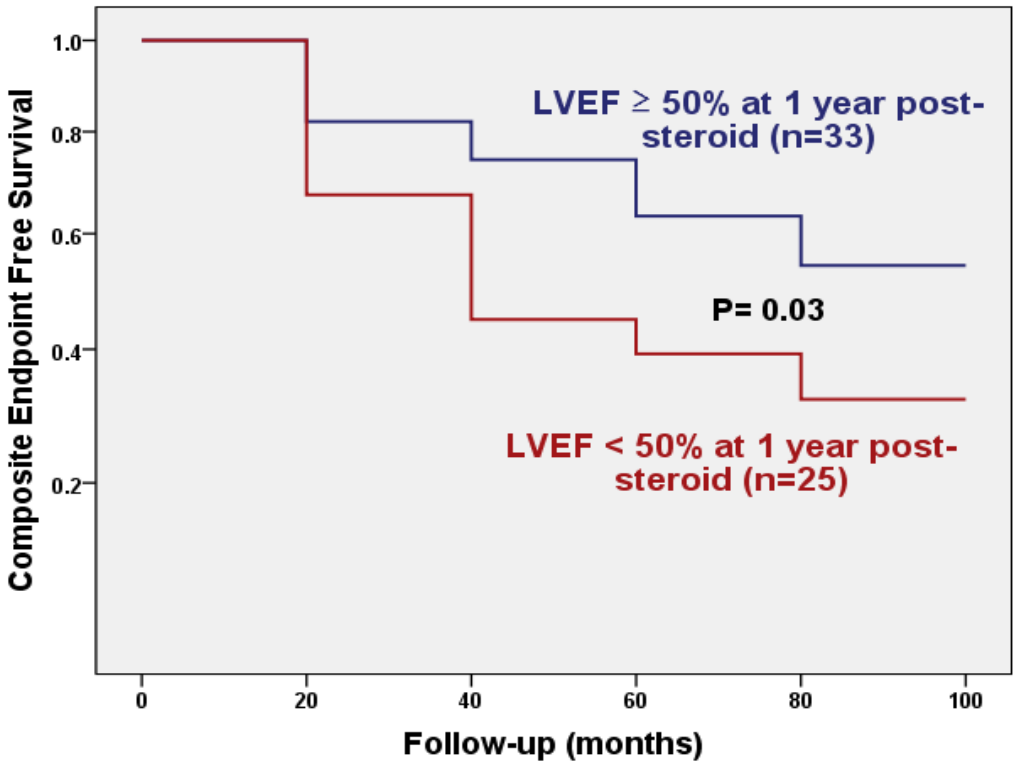

Composite Endpoint Free Survival
1.0
0.8
0.6
0.4
0.2
Steroid loading dose >30mg/d (n=6)
P=0.76
Steroid loading dose ≤30 mg/d (n=52)
0
20
40
60
80
100
Follow-up (months)

Figure 5

A


Composite Endpoint Free Survival
1.0
0.8
0.6
0.4
0.2
LVEF ≥ 50% at 1 year post-steroid (n=33)
P= 0.03
LVEF < 50% at 1 year post-steroid (n=25)
0
20
40
60
80
100
Follow-up (months)

B

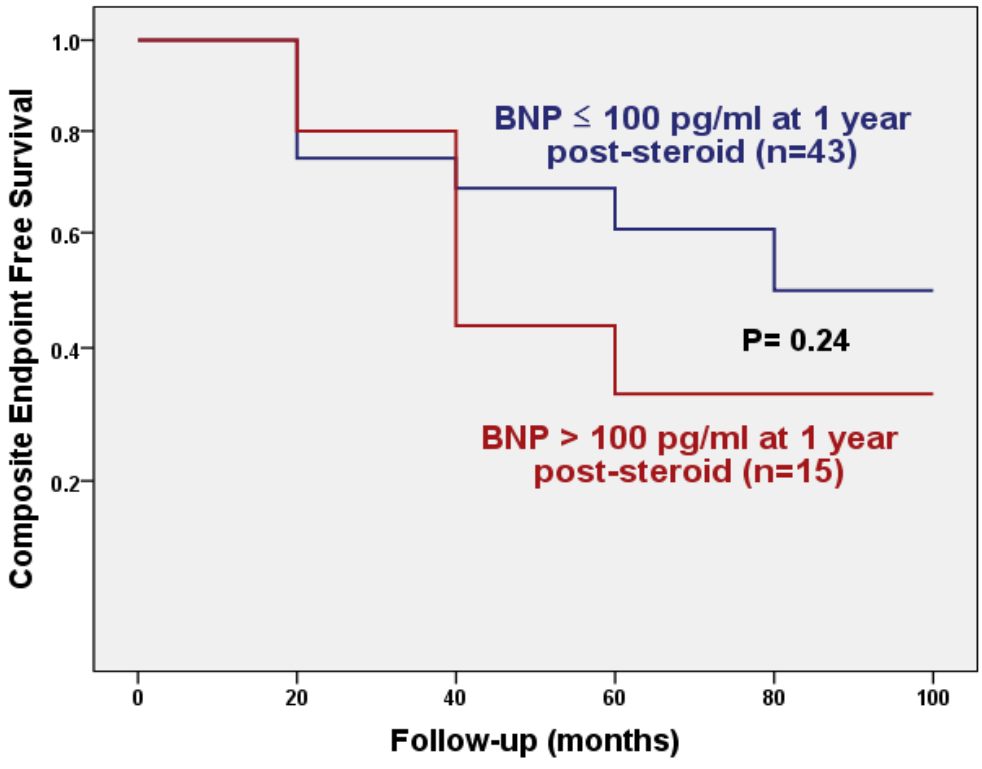
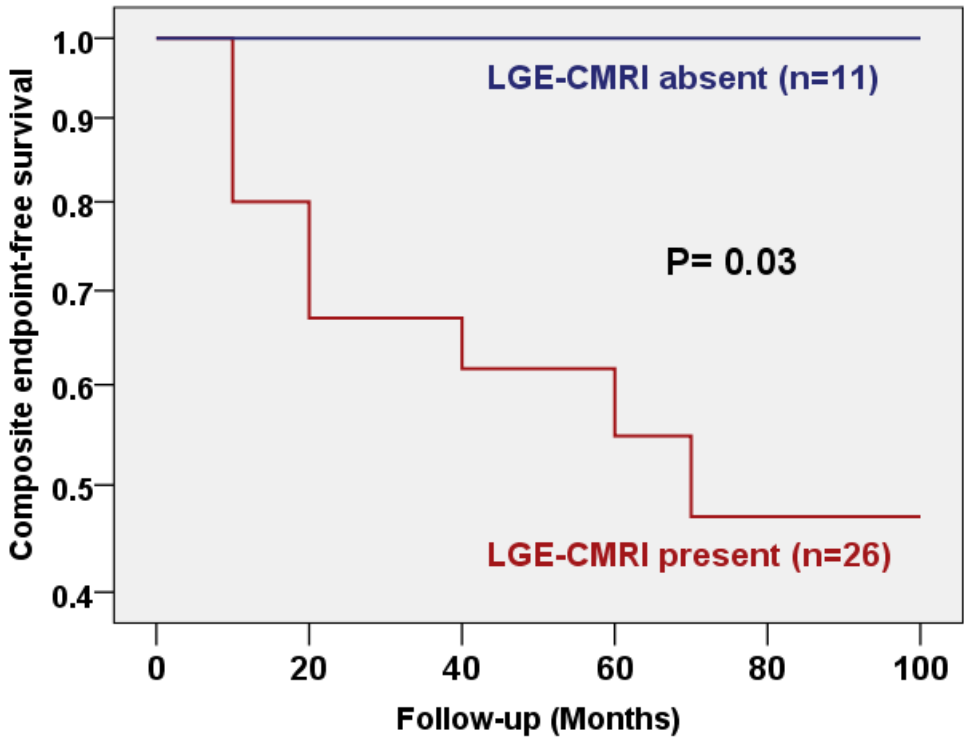

Composite Endpoint Free Survival
1.0
0.8
0.6
0.4
0.2
BNP ≤ 100 pg/ml at 1 year post-steroid (n=43)
P= 0.24
BNP > 100 pg/ml at 1 year post-steroid (n=15)
0
20
40
60
80
100
Follow-up (months)

Figure 6

A


Composite endpoint-free survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
LGE-CMRI absent (n=11)
P= 0.03
LGE-CMRI present (n=26)
0
20
40
60
80
100
Follow-up (Months)

B

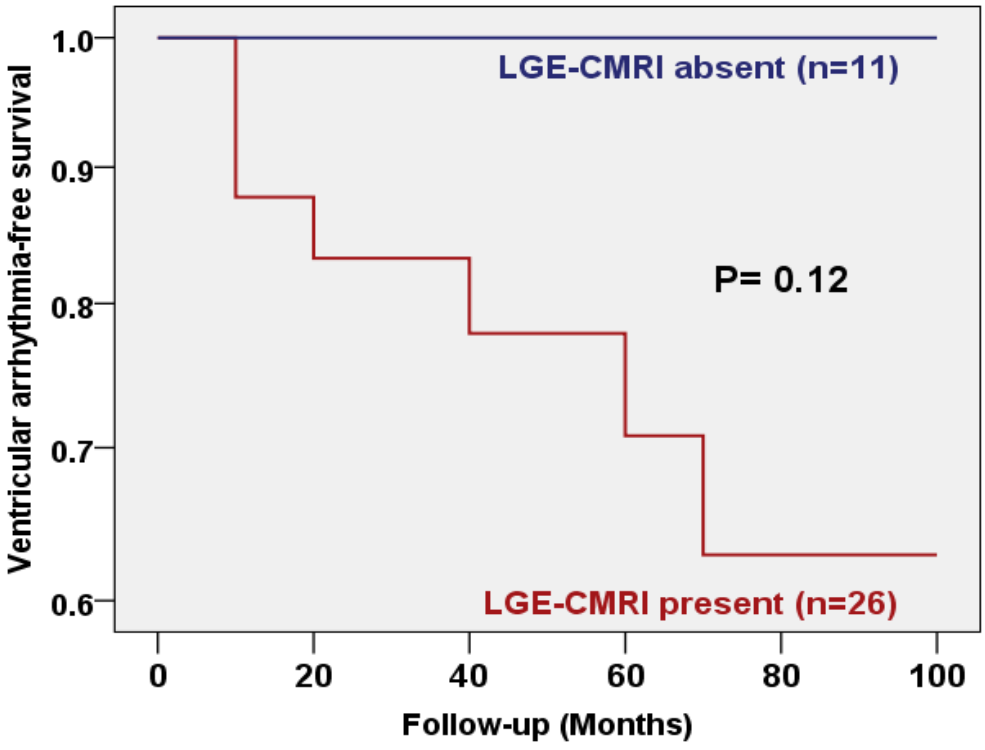
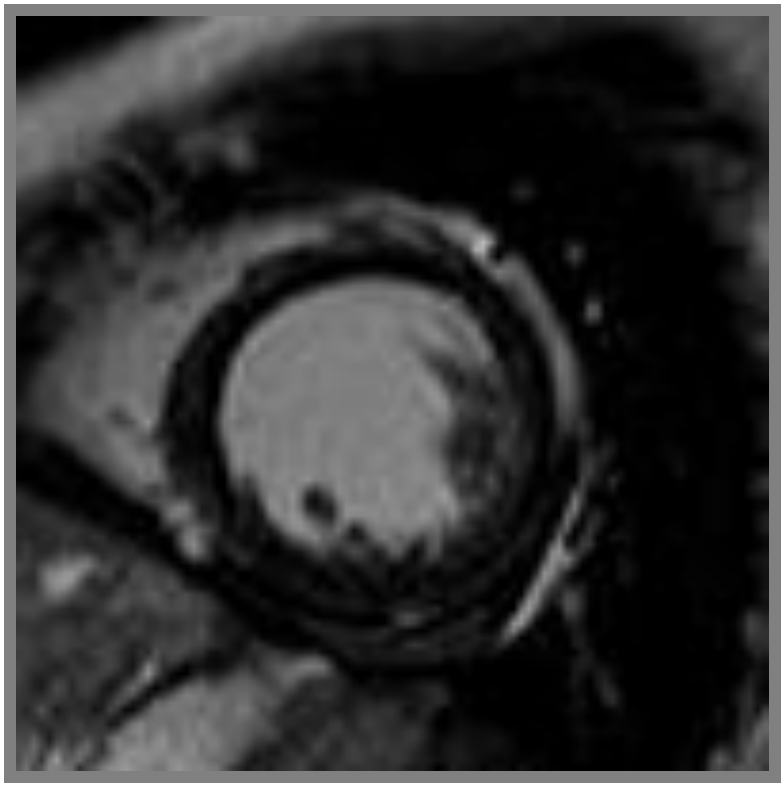

Ventricular arrhythmia-free survival
1.0
0.9
0.8
0.7
0.6
LGE-CMRI absent (n=11)
P= 0.12
LGE-CMRI present (n=26)
0
20
40
60
80
100
Follow-up (Months)

Figure 7

A



B

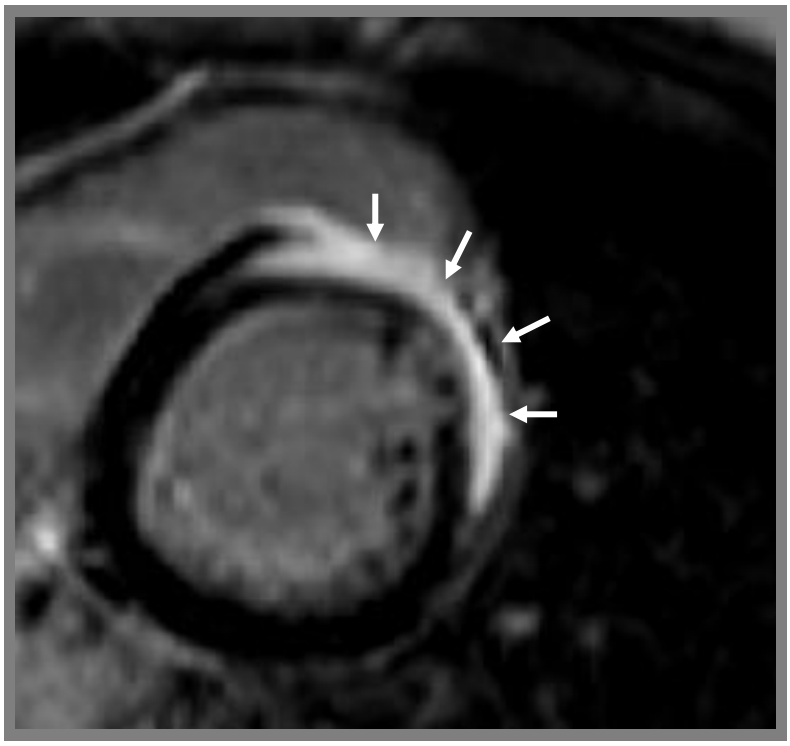


Table 1: Revised guidelines for diagnosing cardiac sarcoidosis 2006 (Japan Society of Sarcoidosis and Other Granulomatous Disorders)

1. Histologic diagnosis group

Cardiac sarcoidosis is confirmed when myocardial biopsy specimens demonstrate non-caseating epithelioid cell granuloma with histological or clinical diagnosis of extra-cardiac sarcoidosis

2. Clinical diagnosis group

Although myocardial biopsy specimens do not demonstrate non-caseating epithelioid cell granuloma, extra-cardiac sarcoidosis is diagnosed histologically or clinically and satisfies the following conditions and more than one in six basic diagnostic criteria

(1) More than 2 of 4 major criteria are satisfied

(2) One in 4 major criteria and more than 2 in 5 minor criteria are satisfied

Major Criteria

(a) Advanced AV block.

(b) Basal thinning of the interventricular septum.

(c) Positive cardiac 67Ga uptake.

(d) Depressed ejection fraction of the left ventricle (LVEF<50%).

Minor Criteria

(a) Abnormal ECG findings: Ventricular arrhythmias (VT, multifocal or frequent PVCs), CRBBB, axis deviation or abnormal Q-wave.

(b) Abnormal echocardiography: Regional abnormal wall motion or morphological abnormality (ventricular aneurysm, wall thickening).

(c) Nuclear medicine: Perfusion defect detected by 201Tl myocardial scintigraphy or 99Tc myocardial scintigraphy.

(d) Gd-enhanced MRI: Delayed enhancement of myocardium.

(e) Endomyocardial biopsy: Interstitial fibrosis or monocyte infiltration over moderate grade.

AV: atrioventricular; CRBBB: Complete right bundle branch block; ECG: electrocardiogram; MRI: magnetic resonance imaging; PVCs: premature ventricular contractions; VT: ventricular tachycardia

Table 2: Patients Characteristics at Baseline	
Variables	**All patients (n= 58)**
Age (years)	57±12
Gender (M/F)	15/43
Extra-cardiac sarcoidosis present	50 (86)
Hypertension	14 (24)
Diabetes mellitus	14 (24)
CAD	2 (3)
Dyslipidemia	23 (39)
Smoking	
Non-smoker	47 (81)
Ex-smoker	5 (9)
Current smoker	6 (10)
Cardiac phenotype (by echocardiography)	
Normal	28 (49)
DCM-like	16 (27)
Isolated septal thinning	14 (24)
Clinical data	
Heart rate (beats/min)	71±14
NYHA class	
I	30 (52)
II	17 (29)
III	9 (16)
IV	2 (3)
Electrical abnormalities	
Ventricular arrhythmias	18 (31)
Non-sustained VT	11 (19)
VT/VF	14 (14)
Advanced heart block	24 (41)
Sick sinus syndrome	1 (2)
AF	7 (12)
Supraventricular tachycardia	1 (2)
Laboratory data	
Hemoglobin (g/dl)	13±1.7
Serum creatinine (mg/dl)	0.8±0.3
Triglyceride (mg/dl)	138±72
Total cholesterol (mg/dl)	205±35
Brain Natriuretic Peptide (pg/ml)	325±515
Echocardiographic parameters	
LVEF (%)	50±16
LVDs (mm)	37±12
LVDd (mm)	52±8
LAD (mm)	35±6
Positive biopsy	10 (17)
LGE-CMRI (present/absent)	26/11
Drugs	
β-blockers	27 (46)
ACE-I/ARBs	33 (57)
Statins	17 (29)
Amiodarone	4 (7)

Results are presented as either mean±SD or number of patients (%).

ACE-I, Angiotensin converting enzyme inhibitors; AF, atrial fibrillation; ARBs, Angiotensin receptor blockers; BNP, brain natriuretic peptide; CAD, coronary artery disease; DCM, dilated cardiomyopathy; LAD, left atrial dimensions; LGE-CMRI, late gadolinium enhancement on cardiac magnetic resonance imaging; LVDs/LVDd, end-systolic/end-diastolic left ventricular dimensions; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; VF, ventricular fibrillation; VT, ventricular tachycardia.

The results on LGE-CMRI were obtained from 37 patients without device therapy.

Table 3: Patient Characteristics by Initial Steroid Dose			
Variables	**Steroid Dose ≤ 30 mg (n=52)**	**Steroid Dose > 30 mg (n= 6)**	**P-value**
Age (years)	57 ± 12	57 ± 12	0.29
Gender (M/F)	14/38	2/4	0.53
Advanced heart block	21 (40)	2 (33)	0.55
Ventricular arrhythmia	24 (46)	5 (83)	0.09
DCM-like phenotype	16 (30)	4 (66)	0.10
Heart rate (beats/min)	71 ± 13	77 ± 13	0.35
NYHA class			
I	27 (52)	4 (66)	
II	16 (30)	1 (17)	0.17
III	8 (16)	0 (0)	
IV	1 (2)	1 (17)	
IL2R	624 ± 287	1651 ± 1775	0.003
Baseline BNP (pg/ml)	236 ± 453	438 ±564	0.31
Favorable BNP course	38 (73)	5 (83)	0.51
Echocardiographic indices			
LVEF	50 ± 16	39 ± 12	0.14
LVDd (mm)	51 ± 8	58 ± 9	0.11
LVDs (mm)	36 ± 12	47 ± 9	0.08
Favorable LVEF course	32 (61)	1 (17)	0.04
LGE-CMRI (present/absent)	20/11	6/0	0.22

Results are presented as either mean±SD or number of patients (%).

Abbreviations as in table 2.

The results on LGE-MRI were obtained from 37 patients without device therapy.

Table 4: Event Rates in Japanese Steroid-treated Cardiac Sarcoidosis Patients						
Endpoints	Cumulative events					
	3 years		5 years		10 years	
	n	%	n	%	n	%
All-cause death	0	0	1	2	2	4
Ventricular arrhythmia	14	24	16	27	18	31
HF hospitalization	3	5	7	12	13	22
Composite events*	21	36	26	45	28	48

* Includes all-cause death, heart failure hospitalization, ventricular arrhythmia and device therapy

HF, heart failure

Table 5: Proportional Hazard Analysis of Prognostic Indicators of Composite Endpoints in Patients With Cardiac Sarcoidosis				
Variables	Univariate		Multivariate*	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Extra-cardiac sarcoidosis	0.71 (0.30-1.69)	0.45	--	--
Initial steroid dose > 30 mg/day	0.81 (0.26-2.57)	0.73	--	--
LVEF < 50%	2.09 (0.98-4.46)	0.06	2.27 (1.04-4.97)	0.04
VA at baseline	2.41 (1.14-5.07)	0.02	2.98 (1.17-7.59)	0.02
Unfavorable LVEF course	2.27 (1.06-4.86)	0.03	2.32 (1.07-4.99)	0.03
Unfavorable BNP course	1.40 (0.62-3.17)	0.41	1.43 (0.55-3.73)	0.45

* Adjusted for age, gender, presence of extra-cardiac sarcoidosis, initial steroid dose, hypertension, diabetes mellitus, and drug treatment

CI, confidence interval; HR, hazard ratio; other abbreviations as in table 2.