Research Square

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Relation between relapse of abnormal fluorodeoxyglucose accumulation and cardiac dysfunction in cardiac sarcoidosis

Kiyota Kondo
Nagoya University Graduate School of Medicine Faculty of Medicin
ryota morimoto
ryota.morimoto0726@gmail.com

Nagoya University Graduate School of medicine
Kazumasa Unno
Nagoya University Graduate School of Medicine Faculty of Medicin
Shin Nagai
Nagoya University Graduate School of Medicine Faculty of Medicin
Asuka Nozaki
Nagoya University Graduate School of Medicine Faculty of Medicin
Chiaki Mizuno
Nagoya University Graduate School of Medicine Faculty of Medicin
Ryota Ito
Nagoya University Graduate School of Medicine Faculty of Medicin
Shotaro Komeyama
Nagoya University Graduate School of Medicine Faculty of Medicin
Shingo Kazama
Nagoya University Graduate School of Medicine Faculty of Medicin
Hiroaki Hiraiwa
Nagoya University Graduate School of Medicine Faculty of Medicin
Toru Kondo
Nagoya University Graduate School of Medicine Faculty of Medicin
Satoru Ohshima
Department of Cardiology, Nagoya Kyoritsu Hospital
Toyoaki Murohara
Nagoya University Graduate School of Medicine Faculty of Medicin

Research Article

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Abstract

Objective: Abnormal accumulation of fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) in the myocardium is a major criterion for a diagnosis and is commonly used for diagnosing cardiac sarcoidosis (CS). Once abnormal accumulation improves after immunosuppressive therapy, there is still a certain probability of relapse of FDG accumulation in the myocardium. However, whether the relapse contributes to subsequent cardiac dysfunction remains unclear. Methods: We retrospectively analyzed the data of patients with 41 CS who underwent serial ^{18}F-FDG-PET imaging at three timepoints: pretreatment ($T_{PET\text{-}0m}$), 6 months ($T_{PET\text{-}6m}$), and 12 months ($T_{PET\text{-}12m}$) post-intervention. Cardiac metabolic activity (CMA) was measured. Patients with a CMA reduction rate >70% in the initial 6 months of prednisolone (PSL) standard treatment and free fatty acid (FFA) value ≥0.8 before each PET imaging was enrolled. Patients with CMA-$T_{PET\text{-}12m}$/CMA-$T_{PET\text{-}6m}$ ≥1 and CMA-$T_{PET\text{-}12m}$ ≥50 constituted the relapse group. Results: The relapse and non-relapse groups included 6 (14.6%) and 35 (85.4%) patients, respectively. In the relapse group, subsequent changes in left ventricular ejection fraction did not significantly differ from those of the non-relapse group at 3-year follow-up. The rate of composite cardiac events showed no significant intergroup differences (log-rank, P=0.914). Conclusions: Relapse of abnormal FDG accumulation after immunosuppressive therapy occurred in 15% of patients. Relapse of FDG accumulation was not associated with subsequent cardiac dysfunction or cardiac events at the 3-year follow-up.

Introduction

Sarcoidosis is a systemic, chronic inflammatory disease characterized by noncaseating granulomas and subsequent tissue scarring of unknown etiology (1). Cardiac sarcoidosis (CS) is a fatal manifestation of systemic sarcoidosis, and approximately two-thirds of sarcoidosis-related deaths in Japan are attributed to cardiac involvement (2). Therefore, accurate early diagnosis and timely intervention are vital for managing CS. However, performing therapeutic management in CS can be challenging because of its nonspecific symptoms and the lack of a validated biomarker to reflect the disease status. In the 2016 update of the Japanese Circulation Society (JCS) regarding the diagnosis and treatment of CS, the major criterion for the diagnosis of CS included the use of 18F-fluoro-deoxyglucose positron-emission tomography (^{18}F-FDG-PET) to detect inflammatory lesions in the myocardium of patients with suspected CS (3). Thus, the role of ^{18}F-FDG-PET in diagnosing CS is well-established. However, its validity as a determinant of treatment efficacy and the prognostic role of serial quantitative evaluation of ^{18}F-FDG-PET are not standardized. Abnormal FDG accumulation in the myocardium has long been considered as a reflection of worsening inflammatory activity. A recent meta-analysis suggests that a lack of response on serial ^{18}F-FDG-PET is associated with adverse cardiac events (4); however, it was based on analyses from a small number of retrospective studies, and data regarding FDG relapse after immunosuppressive therapy and progression of myocardial damage in relapsed CS groups remain limited. Therefore, we examined the relationship between relapse of FDG accumulation and the subsequent change in cardiac dysfunction, and the rate of cardiac events during treatment with prednisolone (PSL).

Methods

Study population

We enrolled 70 patients with CS based upon JCS criteria who underwent serial ^{18}F-FDG-PET imaging between November 2016 and June 2021 at three timepoints: pre-treatment ($T_{PET\text{-}0m}$), 6 months after the intervention ($T_{PET\text{-}6m}$), and 12 months ($T_{PET\text{-}12m}$) post-intervention. A total of 41 patients met the inclusion criteria and were included in this study. Patients were excluded if they met one or more of the following criteria: (1) FFA value < 0.8 before one or more imaging examinations to exclude physiological accumulation as much as possible; (2) refusal of PSL intake; (3) follow-up period < 3 years. The study protocol was approved by the Ethics Committee of the Nagoya University Graduate School of Medicine (Nagoya, Japan; approval number, 2022 – 0277) and adhered to the principles of the Declaration of Helsinki. Participant consent was obtained using the “opt-out” method.

Cardiac PET acquisition protocol

All ^{18}F-FDG-PET scans were performed using a SIEMENS Biograph 16 (Siemens Healthineers, Erlangen, Germany). To inhibit physiological myocardial ^{18}F-FDG accumulation, patients were asked to follow a carbohydrate restricted/high-protein diet for 1 week, avoid vigorous exercise for 24 hours, and fast for at least 18 hours before each examination. FFA levels were measured immediately before ^{18}F-FDG injection to ensure that the fasting conditions were strictly adhered to. Patients weighing < 60 kg or > 60 kg were intravenously administrated 3.7 MBq/kg or 4.07 MBq/kg of ^{18}F-FDG, respectively. Image acquisition was initiated 1 hour after ^{18}F-FDG administration (5).

Cardiac PET data analysis protocol

Myocardial FDG uptake on fused ^{18}F-FDG PET/CT images was analyzed using GI-PET (AZE Ltd.). Although SUV_{max} has been reported to provide high sensitivity and specificity for diagnosing CS, it does not reflect the extent of myocardial inflammation. Therefore, cardiac metabolic activity (CMA), calculated as the FDG-positive myocardial volume multiplied by SUV_{mean}, was used as the primary measure of disease severity. The liver was used as an internal reference to define the threshold for abnormal myocardial FDG uptake. A 3-cm spherical volume of interest (VOI) was placed in the liver, and the threshold was calculated by the mean SUV + 1.5 standard deviations of the volume of interest in the liver. Myocardial voxels with SUV values above this threshold were considered FDG-positive, whereas those below the threshold were considered negative. Coronal and sagittal PET images with a slice thickness of 4 mm were reviewed to ensure complete myocardial coverage. SUV_{max}, SUV_{mean}, and CMA were calculated automatically (5).

Echocardiography

Comprehensive transthoracicechocardiography (EPIQ Elite; Philips Medical Systems, Best, Netherlands) was performed at the time of the initial diagnosis, the follow-up PET scan ($T_{PET\text{-}12m}$), and annual follow-up (i.e., T_{24m} and T_{36m}). Left ventricular ejection fraction (LVEF) was obtained using the modified Simpson's biplane method or the Teichholz method, when appropriate. Data were evaluated by a board-certified member of the Japanese Circulation Society (6).

Study design

Figure 1 summarizes the study design. After the diagnosis of CS, all patients were initially administered PSL at a dose of 30 mg/day. The dosage was tapered by 5 mg/month until the 6th month. After 6 months, ^{18}F-FDG-PET was performed a second time ($T_{PET\text{-}6m}$) to assess the abnormal FDG accumulation area (CMA-$T_{PET\text{-}6m}$). We defined "responders" as patients with a CMA reduction rate > 70% after immunosuppressive therapy, a criterion also used in the previous study (5). In this study, we analyzed patients in the "responders" to estimate the relapse of ^{18}F-FDG-PET findings and subsequent trends. All responders were maintained on 5 mg of PSL for 6 months. At the 12-month follow-up, ^{18}F-FDG-PET was performed a third time ($T_{PET\text{-}12m}$). Patients were considered to have a relapse if the FDG accumulation increased the CMA value, compared with the value at 6 months (i.e., CMA-$T_{PET\text{-}12m}$ > CMA-$T_{PET\text{-}6m}$), and the absolute value of CMA-$T_{PET\text{-}12m}$ was ≥ 50; otherwise, they were placed in the non-relapse group. We adopted the absolute value of CMA ≥ 50 because the 95% tile of the CMA-$T_{PET\text{-}6m}$ was 31.8, and ^{18}F-FDG-PET uptake was unequivocally positive on visual evaluation. The relapse and non-relapse groups subsequently continued treatment with 5 mg/day of PSL, and transthoracic echocardiography and laboratory measurements were performed at 2 and 3 years from baseline (i.e., T_{24m} and T_{36m}, respectively) to evaluate cardiac function. After FDG relapse was identified, no escalation of immunosuppressive therapy (e.g., intravenous steroids, methotrexate, or other steroid-sparing agents) was performed in any of the six patients. All patients continued prednisolone 5 mg/day without additional therapy. **(Fig. 1)**.

Study outcomes

The primary outcome was the change of LVEF in the transthoracic echocardiography index in the relapse and non-relapse groups. The secondary outcomes were (1) the proportion of patients who exhibited FDG relapse, (2) changes in the brain natriuretic peptide (BNP) levels of the analyzed patients, and (3) composite cardiovascular event rates of the relapse and nonrelapse groups within 3 years. Cardiovascular events were defined as heart failure (HF) hospitalization, sustained ventricular tachycardia (VT), or sudden cardiac death (SCD).

Statistical analysis

Continuous variables were expressed as the mean ± standard deviation if normally distributed or as the median and interquartile range if not normally distributed. Continuous variables were compared by using Student's *t*-test for parametric variables and the Mann–Whitney *U* test for nonparametric variables. Categorical variables were compared using the chi-squared test or Fisher's exact test, as appropriate. The value of each ^{18}F-FDG-PET (CMA) and echocardiography (LVEF and LVDd) parameter was analyzed using the Wilcoxon signed-rank test to determine the significance of the differences. Cox proportional hazards analysis was used to test the association between outcome events and metabolic responses (i.e., relapse vs nonrelapse). Statistical significance was set at $P < 0.05$. All statistical analyses were performed using the IBM SPSS version 29.0 (IBM Corporation, Armonk, NY, USA).

Results

Patient characteristics

The patients' characteristics are presented in **Table 1**. The mean age was 61.1 ± 8.7 years. Thirty-two (78.0%) of the patients were female. Implantable cardiac electronic devices were used in 27 (65.8%) patients. Fifteen (36.6%) patients received pacemaker implantation, seven (17.0%) received implantable cardioverter-defibrillator implantation, and five (12.2%) received cardiac resynchronization therapy implantation. Among the 41 patients, 6 underwent myocardial biopsy and 2 were diagnosed with CS based on pathological findings. Of the 39 patients, 23 and 14 were diagnosed with sarcoidosis by histological and clinical examination of extracardiac specimens, respectively, using the CS criteria. The remaining two (4.9%) patients had no evidence of extracardiac sarcoidosis but satisfied the criteria for isolated CS. The median BNP concentration was 57.4 pg/mL and the LVEF was 50.7%.

Study algorithm and patients' flowchart

Follow-up ^{18}F-FDG-PET was performed at 192.7 ± 41.8 days and 408.0 ± 64.1 days from the first ^{18}F-FDG-PET. Six of forty-one (14.6%) patients relapsed, whereas the remaining 35 (85.4%) did not relapse.

Characteristics of the patients in the relapse and non-relapse groups at baseline

The clinical data of all patients and comparisons between the relapse and non-relapse groups at baseline are summarized in **Table 2**. Including laboratory measurements, no significant differences in baseline characteristics were noted between the two groups.

Changes in CMA between the relapse and non-relapse groups

The time courses of quantitative metabolic volume, maximum standardized uptake value (SUV_{max}), and CMA in the relapse and non-relapse groups are summarized in Table 3. In the relapse group, CMA-$T_{PET\text{-}0m}$ was 349.3 [210.8–628.1], and no significant difference existed at baseline, when compared with the non-relapse group. CMA-$T_{PET\text{-}6m}$ markedly decreased; however, a substantial worsening of abnormal FDG

accumulation (CMA-$T_{PET-12m}$) occurred in the relapse group (median CMA 5.9 [0.0–44.7] at PET-6m and 162.1 [71.1–571.9] at PET-12m, P=0.028)

Representative cases in the relapse and non-relapse groups

Representative ^{18}F-FDG-PET computed tomography (CT) images are shown in **Figure 2**. The upper and lower panels show the PET findings for patients in the relapse and non-relapse groups, respectively. The CMA of patients in the relapsed group initially decreased from 283.9 to 11.8, and then relapsed to 834.7.

Changes in echocardiography and BNP measurements between the relapse and non-relapse groups

The changes in echocardiographic parameters are summarized in **Table 4** and **Figure 3**. **The variation rates of cardiac function or BNP levels did not significantly differ between the two groups.**

Kaplan–Meier survival curves of patients in the relapse and non-relapse groups

The median follow-up period for the study population was 1,522 days after baseline. During this period, 4 (9.8%) patients experienced sustained VT, 3 (7.3%) were hospitalized for HF, and no patients experienced SCD. Overall, 1 (16.7%) patient experienced HF hospitalization in the relapse group and 6 (17.1%) patients experienced the composite endpoint (4 patients had sustained VT and 2 patients had HF hospitalizations) in the non-relapse group. No significant difference existed between the two groups (log-rank, P=0.914) **(Figure 4)**.

Summary of the relapse group

Table 5 shows the details of the six patients in the relapse group: three of the six patients had relapses to a CMA ≥200, but none had worsening cardiac function in the echocardiography evaluation. No patient experienced worsening of AV block or ventricular arrhythmias during follow-up. When the patients relapse, 4 patients (67%) was focal type, 1 patient (17%) focal on diffuse type, 1 patient (17%) diffuse type. The abnormal accumulation was more likely relapsed at the basal anteroseptal walls. Moreover, 5 to 6 patients (83%) relapsed at the same part of T_{PET-0m}. Only Case 6 showed a decrease in LVEF from 64% to 51% and an increase in the BNP level from 30 to 93; however, these changes were not clinically problematic. Only patient 1 required hospitalization for HF 1,189 days after steroid induction; however, no rapid deterioration of cardiac function occurred during the course of the disease.

Discussion

The aim of this study was to estimate the therapeutic value of ^{18}F-FDG-PET in patients with CS who were prescribed PSL. We identified the following. First, relapse of abnormal FDG accumulation was detected in 15% of patients after a good response to the initial PSL therapy. Second, CMA relapse was not associated with subsequent cardiac dysfunction during 3-year follow-up when PSL at 5 mg/day was continued as the maintenance dose. Third, CMA relapse was not associated with subsequent composite cardiac events (i.e., SCD, sustained VT, or HF hospitalization).

Treatment of CS

PSL is widely accepted as a first-line drug for treating active myocardial inflammation in CS. In some facilities, PSL is discontinued after 1 year of therapy when no signs of disease activity exist (7). However, despite the lack of guidelines concerning the appropriate duration of the drug regimen and appropriate PSL maintenance dose, PSL was continued in many settings because the discontinuation of PSL was possibly associated with clinical outcomes and subsequent decline in cardiac function (8). The rate of symptomatic deterioration manifesting as chest discomfort and fatigue, although not associated with arrhythmia and/or cardiac dysfunction, is 36%–56% (9) (10) (11). A useful imaging modality is needed to determine the disease activity and the effectiveness of the treatment.

The relationship between ^{18}F-FDG uptake in the myocardium and cardiac events

Various studies have reported an association between abnormal FDG accumulation in the myocardium and the prognosis of CS. The relationship between the history of immunosuppressive drug introduction and course of treatment is unknown. Tuominen et al. (12) report that right ventricular uptake and CMA >900 MBq were significantly associated with cardiac events. However, Blankstein et al. (13) report that PET findings and prognosis are associated with right ventricular accumulation and cardiac events but not with accumulation in the left lateral wall. Kusano et al. (14) also detected that abnormal uptake of ^{18}F-FDG-PET in the heart was not prognostic; however, histological CS and increased LVEF were independent predictors of all-cause death. Few reports have demonstrated that abnormal FDG accumulation in the LV myocardium is directly related to prognosis.

Role of serial ^{18}F-FDG uptake in the myocardium after steroid therapy in relation to cardiac function and cardiac events

Quantitative analysis using PET may be therapeutically beneficial for guiding treatment responses (15). In a recent systematic review and meta-analysis, major adverse cardiac events increased when CS-related results revealed perfusion abnormalities and a lack of response to immunosuppressive therapy, based on serial PET imaging (4). Osborne (13) in 2014 and Shelke (16) in 2017 demonstrated that ^{18}F-FDG-PET findings were associated with LVEF improvement. Muser et al. (17) report that in serial PET imaging responders, defined as patients with a ≥25% decrease in lesion metabolic activity, correlated with changes in LVEF and incidence of cardiovascular events. However, their analyses were based on a small number of patients. PET is helpful when complementing the clinical evaluation of other modalities (15), although assessing cardiac risk by using only PET may be difficult. In fact, Rojulpote et al. (18), Yamamoto et al. (19), and the PRESTIGE study (5) enrolled more patients, compared with previous studies, and demonstrated no association between the response to immunosuppressive therapy and cardiac events **(Table 6)**.

Abnormal FDG accumulation in the heart as a metabolic abnormality

A shift in substrate dependence from fatty acids to glucose generally occurs in the failing myocardium (20), and FDG taken into the heart via glucose transporter (GLUT) becomes more prone to accumulation. Notably, pressure and volume loading, microcirculatory ischemia, and PSL can alter FDG permeability through the GLUT (21). Previous case report demonstrated that pathological evaluation of the whole heart 2 months after PET imaging showed strong abnormal FDG accumulation in the fibrotic area but not in the area of active inflammation (22). We must discuss the possibility that abnormal FDG accumulation on PET in patients with CS may not represent a significant clinical finding. If the relapse of abnormal FDG accumulation during immunosuppressive therapy is simply a metabolic abnormality but not associated with worsening cardiac function, it may not be used to guide treatment decisions. The influence of a variety of other factors on PET may need to be recognized (23).

The present study found that the subsequent decline in cardiac function was not observed for several years after the occurrence of a relapse, suggesting that additional evaluations, such as subjective symptoms and/or magnetic resonance imaging (MRI) and single-photon emission CT findings (24), should be considered for activity assessment rather than PET alone. An additional issue is that our study continued to use 5 mg of PSL as the maintenance dose. Wiefels et al. (25) reported that, when defining relapse as a 25% increase in the left ventricular SUV_{max}, the cardiac relapse rate after PSL discontinuation was 63%. No significant change occurred in the LVEF (47.6% ± 14.8 on PET 2 and 48.4% ± 14.4 on PET 3, P = 0.11), and no serious cardiac events occurred during a trial of therapy cessation. Thus, some patients with CS do not need an increased PSL dose; they can stop the maintenance dose when abnormal FDG accumulation occurs. Future studies are needed to determine which patient groups will no longer require steroid intervention.

Although PET is expected to be effective for determining a diagnosis, its prognostic value is not as high as that of MRI evaluation (26). The disease activity of CS after PSL treatment might be difficult to determine when evaluating with PET alone.

Study limitations

Our study has some limitations. First, this was a single-center, retrospective analysis on a small number of patients. Second, comprehensive simultaneous hybrid cardiac magnetic resonance (CMR)/^{18}F-FDG-PET imaging was useful for detecting active CS; however, hybrid CMR and myocardial perfusion were not used in this study (27) (28) . Third, this study failed to evaluate the effect that cardioprotective drugs prescribed to patients with CS have on cardiac function. Fourth, different definitions of relapse on ^{18}F-FDG-PET may have led to different results.

Conclusion

Relapse of abnormal FDG accumulation after introducing immunosuppressive therapy was detected in 15% of patients and was not related to subsequent cardiac dysfunction and cardiovascular events during the 3-year follow-up when PSL 5 mg/day was continued as the maintenance dose. Even if abnormal FDG

accumulation relapses, it may not be an immediate target for therapeutic intervention when subjective symptoms are not worsening and/or no abnormal findings of other modalities exist.

Declarations

Disclosures:

T.K. has received speaker fees from Abbott, Ono Pharma, Otsuka Pharma, Novartis, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, and Abiomed, and is supported by grant 20 K17112from Grant-in-Aid for Scientific Research. T.M. received lecture fees and unrestricted research grants from Bayer, Daiichi-Sankyo, Dainippon Sumitomo, Kowa, MSD, Mitsubishi Tanabe, Boehringer Ingelheim, Novartis, Pfizer, Sanofi-Aventis, Takeda, Astellas, Otsuka Pharma, and Teijin. All other authors have nothing to disclose.

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Data availability statement

No new data was generated or analyzed in support of this research

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Tables

Table 1 to 6 are available in the Supplementary Files section.

Figures

Figure 1

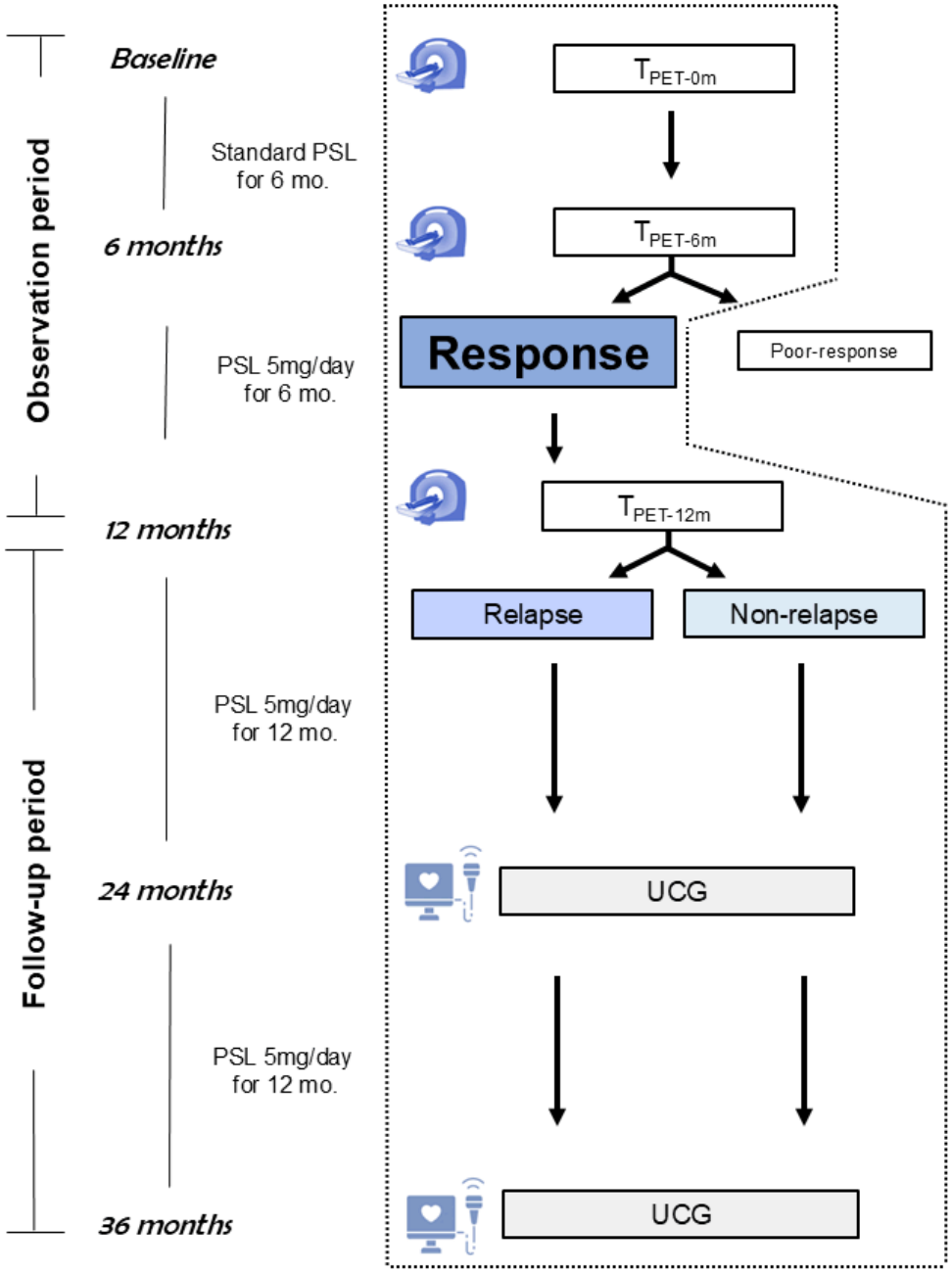


Figure 1

Study algorithm

The initial PSL dose was 30 mg/day and was tapered in increments of 5 mg/month for 6 months. A “responders” was a CMA reduction rate ≥70% after 6 months of PSL therapy. In this study, all responders were enrolled and continued on 5 mg of PSL for 6 months. At the 12-month follow-up, ^{18}F-FDG-PET was

performed a third time and patients were considered as experiencing a “relapse” if the FDG accumulation increased the CMA value, compared with the previous value at 6 months, and the absolute value of CMA was ≥50; otherwise, patients were placed in the non-relapse group. In this study, the patients in the relapse and non-relapse groups continued taking PSL at a dose of 5 mg/day as the maintenance therapy and no escalation of immunosuppressive therapy (e.g., intravenous steroids, methotrexate, or other steroid-sparing agents) was performed during the follow-up period. Changes in cardiac function from the time of enrollment to 3 years were investigated using echocardiography.

CMA: cardiac metabolic activity, **PSL:** prednisolone

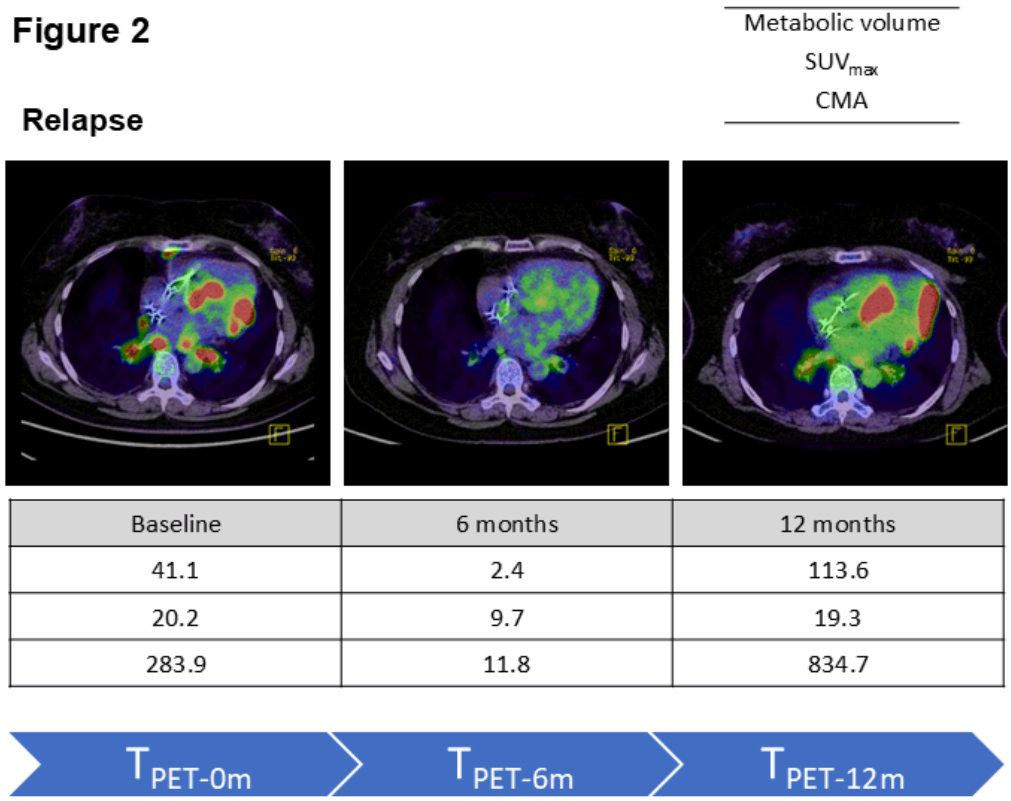


Figure 2

Representative cases of patients in the relapse and non-relapse groups

Upper panel: In the relapse group, the CMA initially decreases from 283.9 to 11.8 and then relapses to 834.7. Lower panel: The PET images of a patient in the nonrelapse group shows a marked response with

the complete resolution of the abnormal FDG accumulation in the myocardium after 12 months of PSL therapy.

SUV_{max}: maximum standardized uptake value, **CMA:** cardiac metabolic activity, **PET:** positron emission tomography

Figure 3

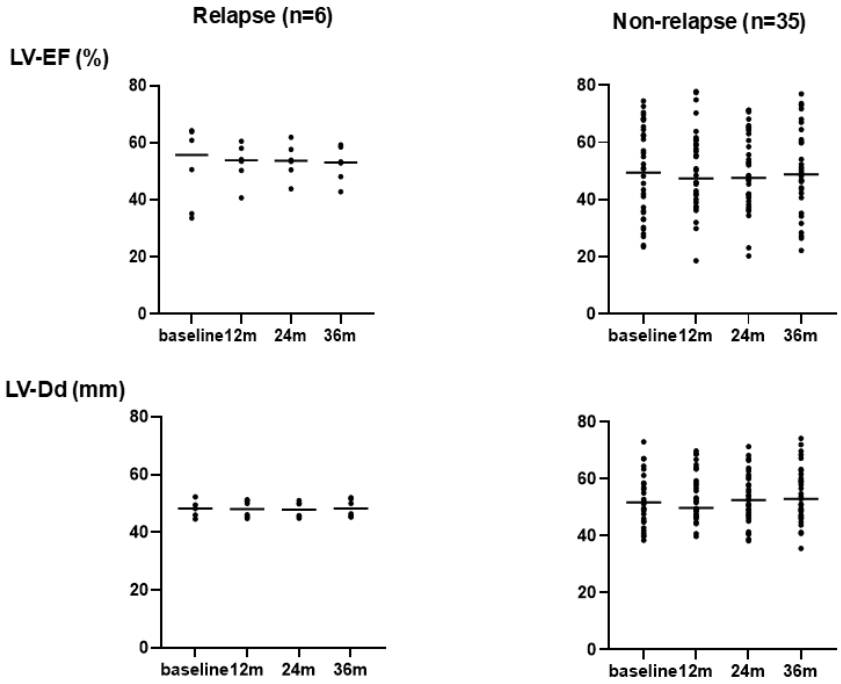


Figure 3

Changes in LVEF and LVDd over the 36-month PSL treatment period in the relapse (n=6) and non-relapse (n=35) groups

The two groups show no significant change in the LVEF and LVDd over the 36-month period.

LVEF: left ventricular ejection fraction, **LVDd:** left ventricular end-diastolic diameter

Figure 4

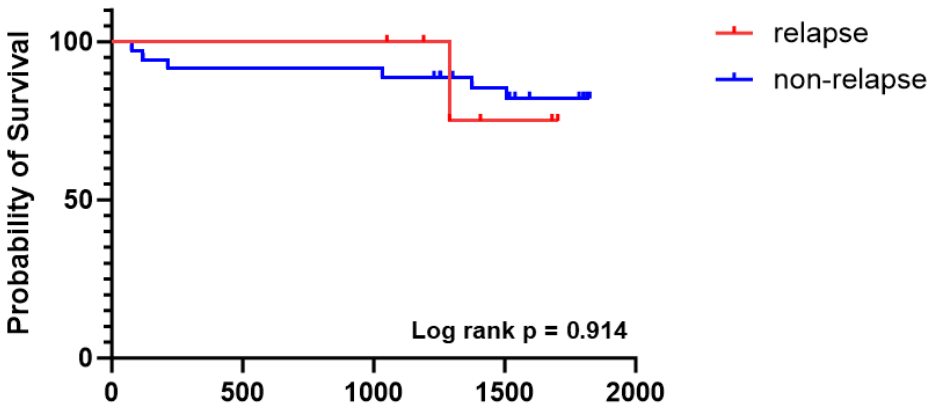


Figure 4

Kaplan–Meier survival curves of adverse cardiovascular events in the relapse and non-relapse groups

The median follow-up period for the study population was 1,522 days after baseline. During this period, 4 (9.8%) patients experienced sustained VT, 3 (7.3%) were hospitalized for HF, and no patient experienced SCD. Overall, 1 (16.7%) patient experienced HF in the relapse group and 6 (17.1%) patients experienced a composite endpoint (i.e., 4 patients had sustained VT and 2 patients had HFH) in the non-relapse group, and no significant difference existed between the two groups (log-rank, P=0.914).

VT: ventricular tachycardia, **HF:** heart failure

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1CSrelapse20260801.docx
- Table2CSrelapse20260801.docx
- Table3CSrelapse20260801.docx
- Table4CSrelapse20260801.docx
- Table5CSrelapse20260801.docx
- Table6CSrelapse20260801.docx