Main Paper Figures and Tables

Table 1. Clinical characteristics of all study population (n = 51) and by subgroup. Values are n (%) or mean ± S.D unless otherwise stated.

Characteristic	Total cohort (n=51)	CS by JMHW+ (n=33)	CS by JMHW– (n=18)	Patients with adverse events (n = 18)	Patients without adverse events (n = 33)
Age (yrs)	50.1 ±13	51.8 ± 13	46.8.±12	50.0 ± 12	50.1 ± 13
Age at diagnosis (yrs)	43 ± 13	44 ± 13	40 ± 13	43 ± 12	42 ± 14
Male sex (%)	31 (61)	21 (64)	10 (56)	14 (78)	11 (33)
Caucasian (%) **Afro-Caribbean (%)**	33 (65) 8 (16)	24 (73) 4 (12)	9 (50) 4 (22)	14 (78) 0 (0)	19 (58) 8 (24)
Symptoms (%) **- Chest pain** **- Dyspnoea** **- Palpitations** **- Syncope** **- Presyncope**	 19 (37) 27 (53) 24 (47) 10 (20) 11 (22)	 10 (30) 19 (58) 19 (58) 6 (18) 9 (27)	 9 (50) 8 (44) 5 (28) 4 (22) 2 (11)	 4 (22) 11 (61) 15 (83) 4 (22) 6 (33)	 15 (46) 16 (49) 9 (27) 6 (18) 5 (15)
Hypertension (%)	7 (14)	5 (15)	2 (11)	5 (28)	2 (6)
Hypercholesterolaemia (%)	9 (18)	7 (21)	2 (11)	4 (22)	5 (15)
Family history sarcoidosis (%)	6 (12)	1 (2)	2 (11)	0 (0)	3 (9)
Histologically confirmed (%) **Cardiac (EMB) sarcoidosis** **Extracardiac sarcoidosis**	 7 (14) 44 (86)	 7 (21) 25 (76)	 0 (0) 14 (78)	 5 (28) 14 (78)	 2 (6) 25 (76)
NYHA (%) **I** **II** **III** **IV**	 31 (61) 17 (33) 3 (6) 0 (0)	 20 (61) 10 (30) 3 (9) 0 (0)	 11 (61) 7 (39) 0 (0) 0 (0)	 1 (55) 5 (28) 3 (17) 0 (0)	 21 (64) 12 (36) 0 (0) 0 (0)
LV ejection fraction (%)	53 ±15	48 ± 16	62 ± 6	44 ± 14	58 ± 13
Clinical phenotype recorded at baseline (%) **- LVH** **- DCM** **- LVEF <50%** **- Decompensated heart failure** **- Conduction disease** **- CHB** **- Ventricular arrhythmia** **- Acute presentation**	 13 (25) 18 (35) 23 (45) 6 (12) 6 (12) 2 (4) 8 (16) 10 (20)	 8 (24) 19 (58) 23 (70) 6 (18) 19 (42) 1 (3) 7 (21) 9 (27)	 5 (28) 1 (6) 0 (0) 0 (0) 2 (11) 0 (0) 1 (6) 2 (11)	 3 (17) 12 (67) 13 (72) 5 (28) 6 (33) 1 (3) 5 (28) 8 (44)	 10 (30) 8 (24) 10 (30) 1 (3) 10 (30) 0 (0) 3 (9) 3 (9)
Serum ACE level (mg/ml)	35 ± 39	25 ± 30	52 ± 48	29 ± 32	38 ± 43
NT pro BNP (ug/ml)	52 ± 95	69 ± 112	20 ± 32	92 ± 112	30 ± 77
Immunosuppression at the time of scan **Corticosteroids** **Methotrexate** **Hydroxychloroquine** **Azathiaprine** **Mycophenalate mofetil (MMF)** **Cyclophosphamide**	19 (37) 16 3 4 2 2 1	14 (42)	7 (39)	8 (44)	13 (39)

Abnormal ECG	35	32 (97)	7 (39)	18 (100)	21 (64)
Basal thinning	21 (41)	19 (58)	3 (17)	10 (56)	12 (36)
Device therapy at study end **- Pacemaker** **- ICD** **- CRTD** **- ILR**	13 (25) 2 (4) 8 (16) 1 (2) 2 (4)	10 (32) 1 (3) 7 (21) 1 (3) 1 (3)	3 (17) 1 (6) 1 (6) 0 (0) 1 (6)	6 (33) 0 (0) 6 (33) 0 (0) 0 (0)	7 (21) 2 (6) 2 (6) 1 (3) 2 (6)

Hypertension is defined as a blood pressure persistently measuring greater than 140/90. Hypercholesterolaemia is defined as a total cholesterol measuring > 5mmol/L and low density lipoprotein (LDL) <3mmol/L. LVH is defined by a maximal LV wall thickness > 13mm. Dilated cardiomyopathy is defined by an LVEDD (% predicted) >112% and LVFS < 25%. The clinical phenotype describes the clinical characteristics noted at baseline. Immunosuppression was noted at the time of PET/MR scanning. Device therapy was noted at study end. ECG abnormalities were defined according to the JMHW criteria. ACE: angiotensin converting enzyme; BNP: brain natriuretic peptide; CHB: complete heart block; CRTD: cardiac resychronisation therapy with defibrillator; ECG: electrocardiogram; EMB: endomyocardial biopsy; ICD: implanted cardiovertor defibrillator; ILR: implantable loop recorder; LV: left ventricle; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricle ejection fraction on echocardiography; LVFS: left ventricle fractional shortening; LVH: left ventricular hypertrophy; NYHA: New York Heart Association.)

Table 2. Comparison of imaging abnormalities within the whole study population and according to subgroup categorization (JMHW criteria and by occurrence of an adverse event). Data is reported as frequencies (and percentages, %) or mean ± S.D unless otherwise stated.

Characteristic	Total cohort (n=51)	CS by JMHW+ (n=33)	CS by JMHW– (n=18)	P value	Patients with adverse events (n = 18)	Patients without adverse events (n = 33)	P value
Presence of LGE (%)	32 (63)	27 (82)	4 (22)	<0.05	17 (94)	14 (42)	<0.01
Cardiac PET findings (%) **- No abnormalities** **- Focal** **- Focal on diffuse** **- Diffuse**	28 (55) 19 (37) 17 (33) 11 (22) 4 (8)	20 (61) 11 (14) 14 (42) 6 (18) 2 (6)	8 (44) 8 (44) 1 (6) 5 (28) 2 (11)	0.27	13 (72) 3 (17) 10 (56) 3 (17) 2 (11)	15 (46) 16 (49) 7 (21) 8 (24) 2 (6)	0.06
RV FDG uptake	4 (8)	2 (3)	2 (11)	0.61	2 (11)	2 (3)	0.61
SUVmax:least avid ratio	1.71 ± 1.41	1.94 ± 1.69	1.29 ± 0.38	0.04	2.42 ± 2.15	1.33 ± 0.43	0.001
Extra-cardiac sarcoidosis on PET(%)	29 (57)	17 (52)	12 (67)	0.30	6 (33)	23 (70)	0.01
Extra-cardiac ± cardiac PET abnormality (%)	36 (71)	28 (85)	8 (44)	< 0.005	14 (78)	24 (73)	0.70
Hybrid PET/MR **- PET-/MR-** **- PET+/MR-** **- PET-/MR+** **- PET+/MR+**	 8 (16) 11 (22) 15 (29) 17 (33)	 3 (9) 14 (42) 10 (30) 16 (49)	 5 (28) 7 (39) 5 (28) 1 (6)	<0.05	 0 (0) 1 (9) 5 (33) 12 (71)	 8 (24) 10 (30) 10 (30) 5 (15)	<0.05

(JMHW: Japanese Ministry of Health and Welfare Guidelines; LGE: Late gadolinium enhancement, PET: Positron emission tomography; + represents the presence of an abnormality on either imaging technique, - represents the absence of an imaging abnormality).

Table 3. The diagnostic performance of PET and LGE in cardiac sarcoidosis.

Sensitivity, specificity and diagnostic odds ratio to evaluate the effectiveness of FDG-PET and LGE when performed alone versus utilising hybrid PET/MR when regressed against the JMHW guidelines as the reference standard (confidence interval).

	Sensitivity	Specificity	PPV	NPV	OR	AUC
Cardiac PET abnormality	60 (0.42-0.77)	56 (0.30 – 0.78)	71 (0.51 – 0.87)	44 (0.23 – 0.66)	1.92 (0.60 – 6.20)	0.58
Extra-cardiac ± cardiac PET abnormality	85 (0.68 – 0.95)	56 (0.31 – 0.78)	78 (0.61 – 0.90)	67 (0.38 – 0.88)	7 (1.85 – 26.5)	0.70
LGE on MRI	82 (0.65 – 0.93)	78 (0.52 – 0.94)	87 (0.70 – 0.96)	79 (0.46 – 0.88)	15.8 (3.80 – 65.2)	0.80

Hybrid PET/MR	94 (0.80 – 0.99)	44 (0.22 – 0.69)	76 (0.60 – 0.88)	80 (0.44 – 0.97)	12.4 (2.25 – 68.3)	0.70

(PPV: positive predictive value; NPV: negative predictive value; OR: diagnostic odds ratio; AUC: area under the curve; JMHW: Japanese Ministry of Health and Welfare Guidelines).

Table 4. Predictors of adverse events. Table 4A. Univariate Cox proportional hazards regression analysis of primary versus any adverse events. **Tables 4B – 4D.** Multivariate Cox Regression analyses for PET, LGE and PET and LGE versus adverse events having adjusted for LVEF (Tables 4B-C) and age, sex, LVEF and PET+ (Tables 4D). (Hybrid PET/MR has been excluded due to perfect prediction and the small sample size).

Table 4A.

Predictor	**Primary event**			**Any event**		
	Model Fit (Chi-Square (P Value))	**Hazard ratio (95% CI)**	**P Value**	**Model fit (Chi-square (P Value)**	**Hazard ratio (95% CI)**	**P Value**
Univariate variabl						
Age (years)	0.34 (0.55)	0.99 (0.95 – 1.03)	0.51	0.04 (0.84)	1.0 (0.96 – 1.03)	0.84
Male Sex	2.21 (0.14)	2.10 (0.77 – 5.71)	0.15	2.07 (0.15)	1.98 (0.77 – 5.09)	0.57
Initial LVEF %	5.78 (0.02)	0.97 (0.94 – 0.99)	0.02	5.61 (0.02)	0.97 (0.94 – 1.0)	0.02
History of VT	13.0 (<0.001)	5.67 (1.98 – 16.2)	0.001	13.2 (<0.001)	5.27 (1.96 – 14.1)	0.001
JMHW criteria +	7.01 (0.008)	9.44 (1.24 – 71.7)	0.03	5.70 (0.02)	5.04 (1.15 – 22.0)	0.03
Cardiac PET+ findings (%)	2.06 (0.15)	2.29 (0.72 – 7.32)	0.16	1.67 (0.20)	1.99 (0.69 – 5.74)	0.20
RV FDG uptake	1.85 (0.17)	2.75 (0.6 – 12.57)	0.19	1.56 (0.21)	2.53 (0.56 – 11.42)	0.23
Extra-cardiac sarcoidosis on PET(%)	4.39 (0.04)	0.34 (0.11 – 0.98)	0.05	6.70 (0.01)	0.28 (0.10 – 0.78)	0.02
Extra-cardiac + cardiac PET abnormality (%)	0.17 (0.68)	1.31 (0.36 – 4.69)	0.68	0.004 (0.95)	1.04 (0.33 – 3.22)	0.95
Presence of LGE (%)	8.10 (0.004)	10.63 (1.4 – 80.78)	0.02	9.11 (0.003)	11.7 (1.55 – 88.1)	0.02
RV LGE	21.2 (<0.001)	9.22(2.94 – 28.94)	< 0.001	19.1 (<0.001)	8.0 (2.65 – 24.1)	<0.001

(Overall model fit estimated using Chi-square (P value).

Table 4B. Multivariate analysis for a primary adverse event for PET after adjusting for LVEF.

Predictor	Hazard ratio (95% CI)	P Value
Initial LVEF %	0.97 (0.94 – 1.00)	0.03
Cardiac PET+ findings	2.07 (0.64 – 6.72)	0.23

Overall model fit estimated using Chi square: 7.07, p = <0.03.

Predictor	Hazard ratio (95% CI)	P Value
Initial LVEF %	0.96 (0.93 – 0.99)	0.007
Cardiac RV PET+ findings	5.84 (1.12 – 30.4)	0.036

Overall model fit estimated using Chi square: 8.72, p = 0.01.

Table 4C. Multivariate analysis for a primary adverse event for LGE after adjusting for LVEF

Predictor	Hazard ratio (95% CI)	P Value
Initial LVEF %	0.98 (0.95 – 1.01)	0.18
Presence of LGE	8.04 (1.02 – 63.8)	0.02

Overall model fit estimated using Chi square: 12.1, p = 0.002.

Predictor	Hazard ratio (95% CI)	P Value
Initial LVEF %	0.94 (0.91 – 0.98)	0.001
Presence of RV LGE	25.0 (6.00 – 104.1)	<0.001

Overall model fit estimated using Chi square: 24.6, p < 0.001.

Table 4D. Multivariate analysis for any adverse event

Predictor	Hazard ratio (95% CI)	P Value
Initial LVEF %	0.98 (0.95 – 1.02)	0.29
Age (years)	1.02 (0.98 – 1.06)	0.37
Sex	1.62 (0.58 – 4.52)	0.35
Cardiac PET+ findings (%)	1.94 (0.61 – 6.16)	0.26

Presence of LGE (%)	8.75 (1.07 – 71.26)	0.04

Overall model fit estimated using Chi square: 15.8, p = 0.008.

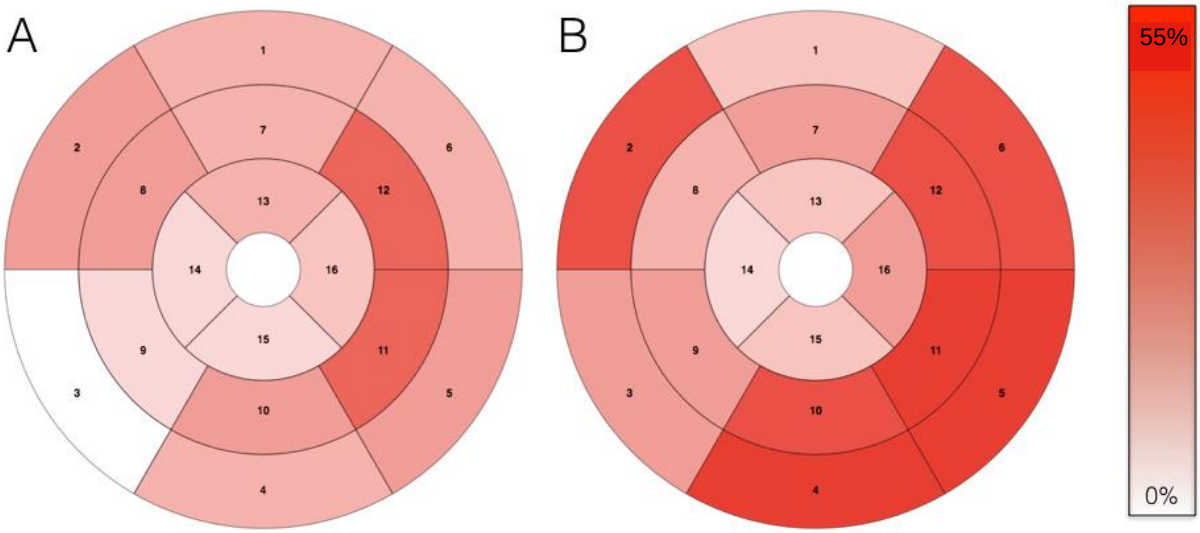
(CI: Confidence interval; FDG: fluorodeoxyglucose; JMHW+: fulfilment of the Japanese Ministry of Health and Welfare Guidelines; LGE: Late gadolinium enhancement; LVEF: Left ventricle ejection fraction measured by echocardiography; PET: Positron emission tomography; RV: Right ventricle; VT: Ventricular tachycardia; PET+ represents the presence of an abnormality on PET).

Figure Legends:

Figure 1: Regional distribution of FDG-PET uptake (Figure 1A) and of LGE (Figure 1B) in JMHW positive cardiac sarcoidosis group (n=33) according to AHA 16 segment model. The colour scale demonstrates an increasing proportion of segments (from 0 – 55%) with abnormal PET uptake (A) or the presence of LGE (B). This figure highlights the basal anteroseptum and inferolateral predominance of FDG uptake and LGE.

Figure 1A.

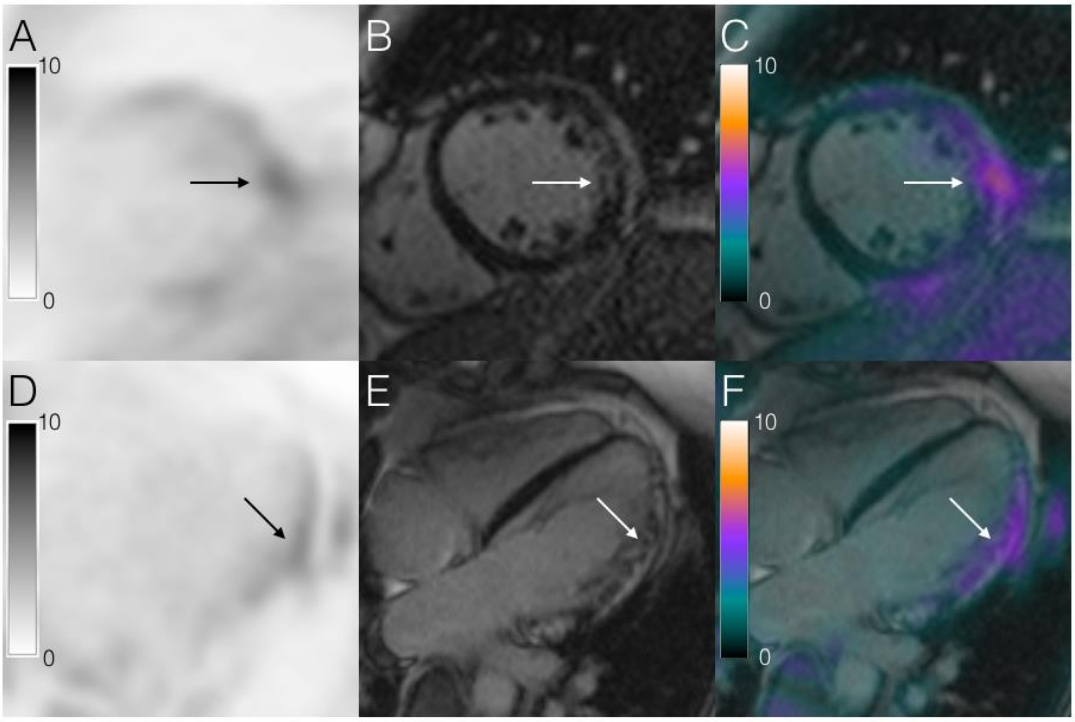
Figure 1B.



(AHA: American Heart Association; JMHW: Japanese Ministry of Health and Welfare; LGE: Late gadolinium enhancement; PET: Positron emission tomography)

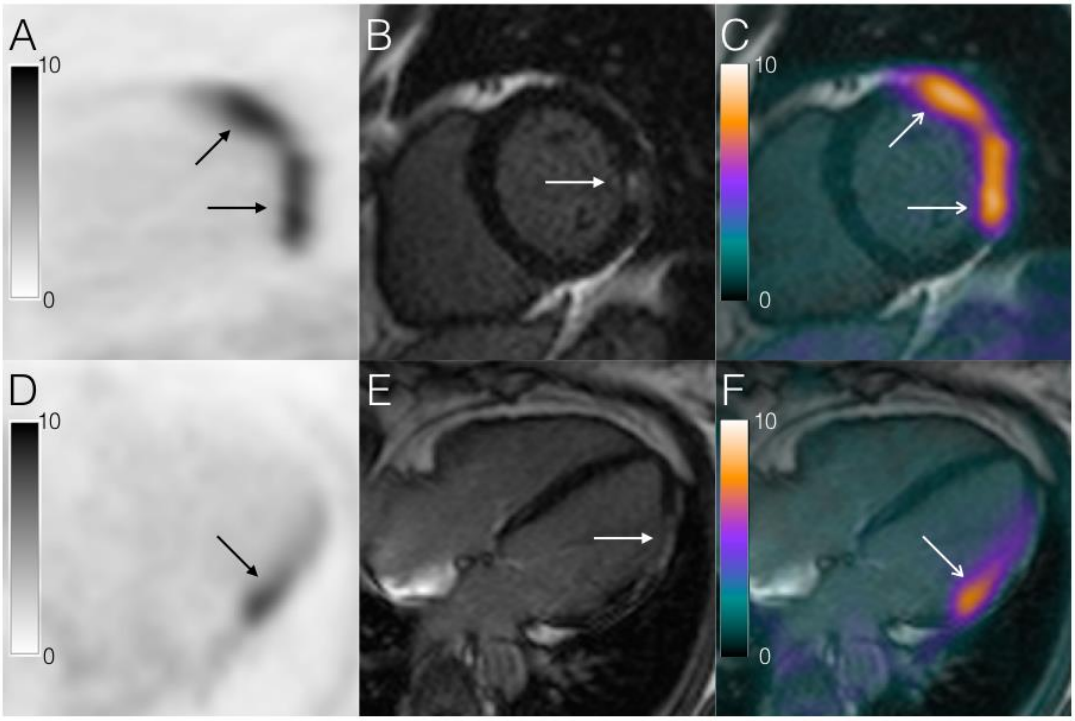
Figure 2. Hybrid imaging example of concordant LGE versus FDG uptake PET-MR images in a patient with biopsy-proven cardiac sarcoidosis. Figures 2A - F. Illustrate short and long axis imaging demonstrating a concordant pattern of overlying inflammation and LGE (fibrosis). Figures 2A and D are MIP images depicting lateral FDG uptake (arrow). Figures 2B and 2E demonstrate patchy epicardial and mid-

myocardial LGE (arrow) which when fused (Figures 2C and 2F) demonstrate overlying LGE and FDG uptake (arrow highlighting the area of abnormality).



(FDG: fluoro-deoxyglucose; LGE: Late gadolinium enhancement, MIP: maximum intensity projection; PET: Positron emission tomography)

Figure 3. Hybrid imaging example of discrete, independent, discordant regions of FDG uptake (regions of inflammation) and LGE (scar) in a patient with biopsy-proven cardiac sarcoidosis. Figures 3A-F illustrate short and long axis imaging demonstrating a discordant pattern of FDG uptake (acute inflammation) surrounding the presence of LGE (scar). Figures 3A and D are MIP images depicting lateral FDG uptake. Figures 3B and E demonstrate patchy epicardial and mid-myocardial LGE which when fused (Figures 3C and F) demonstrate discordant LGE and FDG uptake (the arrows highlight the area of abnormality).



(FDG: fluorodeoxyglucose; LGE: Late gadolinium enhancement, MIP: maximum intensity projection; PET: Positron emission tomography).

Figure 4. Kaplan Meier survival curves for all pre-specified end points. Figure 4A. Using the Log Rank statistical method, this graph demonstrates a worse survival as the number of abnormalities detected on PET or cardiac MRI imaging increases. Figure 4B. Demonstrates the adjusted survival analysis for imaging abnormalities and adverse event having adjusted for age, sex and LVEF using multivariate Cox regression analysis (Chi-square value 16.8, p = 0.01). It illustrates an adverse prognosis as subjects progress from PET positivity only, to LGE positivity and both PET/MR positivity.

Figure 4A.

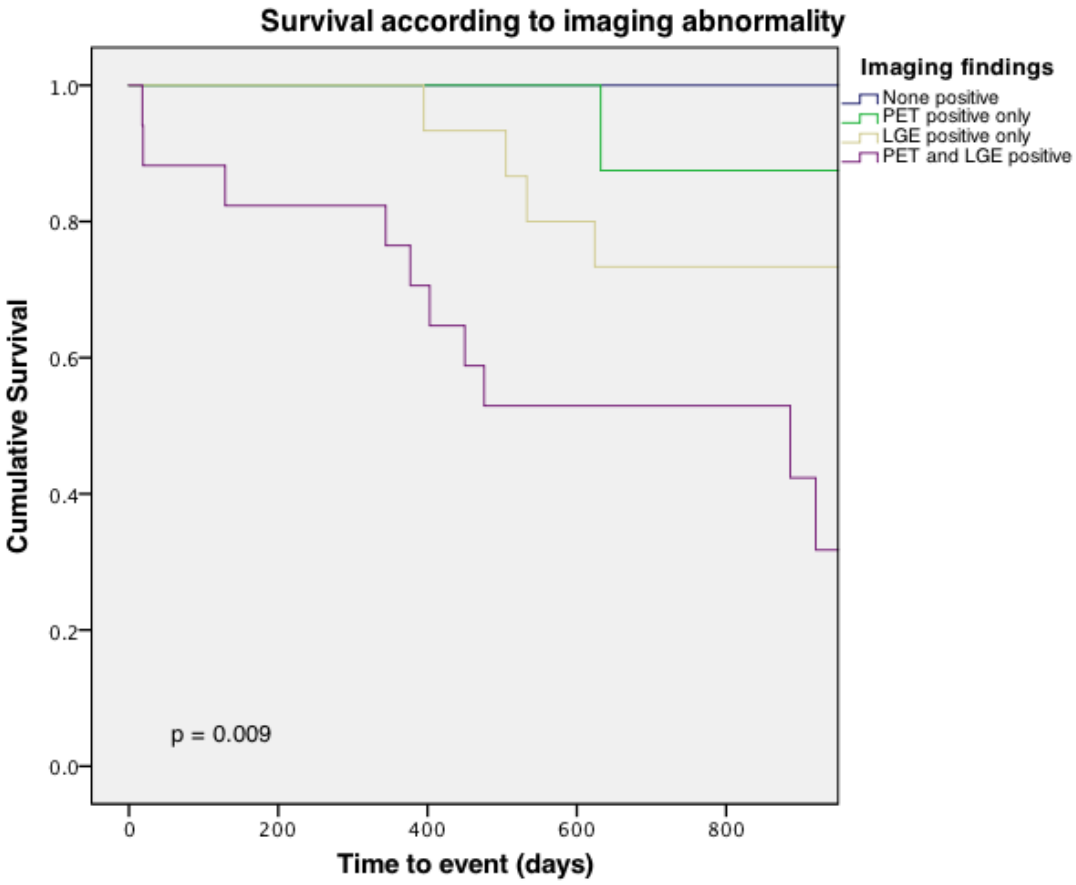
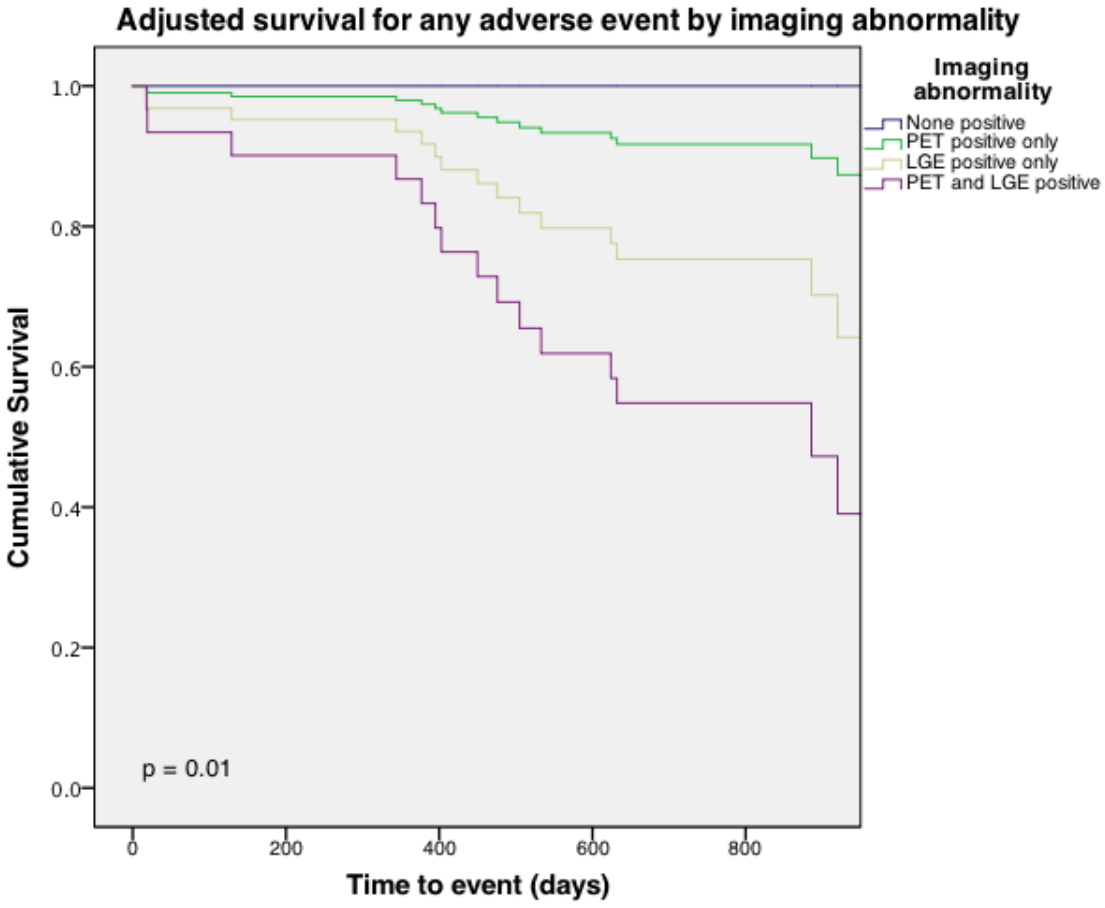

Survival according to imaging abnormality
Imaging findings
None positive
PET positive only
LGE positive only
PET and LGE positive
Cumulative Survival
1.0
0.8
0.6
0.4
0.2
0.0
p = 0.009
0
200
400
600
800
Time to event (days)

Figure 4B.


Adjusted survival for any adverse event by imaging abnormality
Imaging abnormality
None positive
PET positive only
LGE positive only
PET and LGE positive
Cumulative Survival
1.0
0.8
0.6
0.4
0.2
0.0
p = 0.01
0
200
400
600
800
Time to event (days)

(LVEF: Left ventricle ejection fraction; LGE: Late gadolinium enhancement; PET: Positron emission tomography).

Supplement:

Supplement Table 1. Revised Guidelines for Diagnosing Cardiac Sarcoidosis 2006 (Japan Society of Sarcoidosis and Other Granulomatous Disorders [4, 49]

<table>
<tr><th colspan="2">1. Histological Diagnosis Group</th></tr>
<tr><td colspan="2">Cardiac sarcoidosis is confirmed when myocardial biopsy specimens demonstrate non-caseating epithelioid cell granuloma with a histological or clinical diagnosis of extra-cardiac sarcoidosis</td></tr>
<tr><th colspan="2">2. Clinical Diagnosis Group</th></tr>
<tr><td colspan="2">Although myocardial specimens do not demonstrate non-caseating epithelioid cell granuloma, extra-cardiac sarcoidosis is diagnosed histologically or clinically and satisfies a combination of the following major and minor criteria:</td></tr>
<tr><td>1. 2 or more of major criteria are satisfied

OR

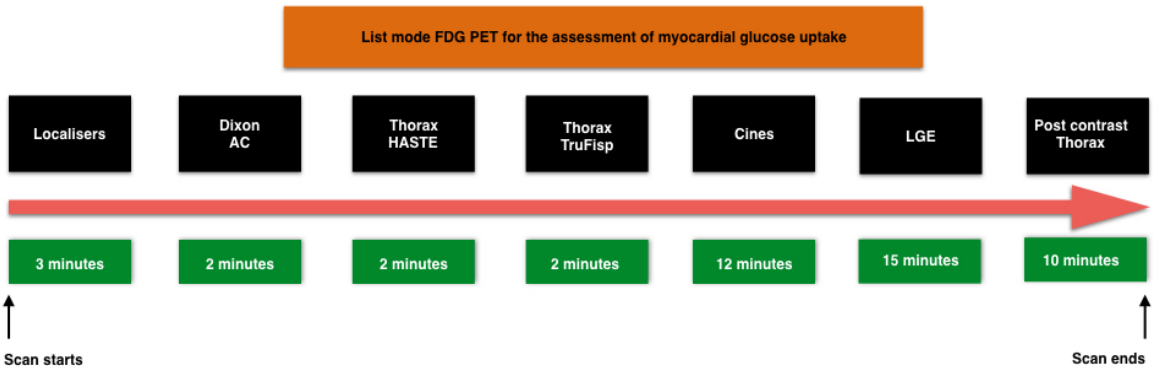
2. 1 of the major criteria and 2 or more of the minor criteria are satisfied</td><td>Major criteria
a) Advanced AV block
b) Basal thinning of the interventricular septum
c) Positive cardiac gallium (^{67}Ga) uptake
d) Left ventricular ejection fraction less than 50%

Minor criteria
a) Abnormal electrocardiogram findings including ventricular tachycardia (VT), multifocal or frequent premature ventricular contractions (PVCs), complete right bundle branch block (RBBB), axis deviation or pathological q-waves
b) Abnormal echocardiogram demonstrating: regional wall motion or morphological abnormality (ventricular aneurysm or unexplained wall thickening)
c) Nuclear medicine: perfusion defects detected by myocardial scintigraphy (^{201}Tl or ^{99}Tc sestamibi)
d) MRI: delayed gadolinium enhancement of the myocardium
e) Endomyocardial biopsy: interstitial fibrosis or monocyte infiltration greater than moderate grade</td></tr>
</table>

(AV: atrioventricular; PVCs: paired ventricular couplets; Tl: thallium; Tc: technetium; VT: ventricular tachycardia)

Supplement Figure 1: The hybrid PET-MR cardiac imaging protocol

Localisers and attenuation correction (AC) maps were initially acquired. PET acquisition was commenced in the background. Standard MR imaging sequences were subsequently acquired. These included half-Fourier acquisition single-shot turbo spin echo (HASTE) images, balanced steady-state free precession (bSSFP = cine) images and LGE two-dimensional inversion recovery turbo fast low-angle shot images).



(FDG: ^{18}F-fluorodeoxyglucose; PET: Positron emission tomography; AC: Attenuation correction; LGE: Late gadolinium enhancement).