ORIGINAL ARTICLE

Association of high serum soluble interleukin 2 receptor levels with risk of adverse events in cardiac sarcoidosis

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Abstract

Aims   Although soluble interleukin 2 receptor (sIL-2R) is a potentially useful biomarker in the diagnosis and evaluation of disease severity in patients with sarcoidosis, its prognostic implication in patients with cardiac sarcoidosis (CS) is unclear. We sought to investigate whether sIL-2R was associated with clinical outcomes and to clarify the relationship between sIL-2R levels and disease activity in patients with CS.

Methods and results   We examined 83 consecutive patients with CS in our hospital who had available serum sIL-2R data between May 2003 and February 2020. The primary outcome was a composite of advanced atrioventricular block, ventricular tachycardia or ventricular fibrillation, heart failure hospitalization, and all-cause death. Inflammatory activity in the myocardium and lymph nodes was assessed by ^{18}F-fluorideoxyglucose positron emission tomography/computed tomography. During a median follow-up period of 2.96 (IQR 2.24–4.27) years, the primary outcome occurred in 24 patients (29%). Higher serum sIL-2R levels ($>$538 U/mL, the median) were significantly related to increased incidence of primary outcome (P = 0.037). Multivariable Cox regression analysis showed that a higher sIL-2R was independently associated with an increased subsequent risk of adverse events (HR 3.71, 95% CI 1.63–8.44, P = 0.002), even after adjustment for significant covariates. sIL-2R levels were significantly correlated to inflammatory activity in lymph nodes (r = 0.346, P = 0.003) but not the myocardium (r = 0.131, P = 0.27).

Conclusions   Increased sIL-2R is associated with worse long-term clinical outcomes accompanied by increased systemic inflammatory activity in CS patients.

Introduction

Sarcoidosis is a multisystemic inflammatory granulomatous disease,[1] and the presence of cardiac involvement can lead to congestive heart failure, atrioventricular block (AVB), ventricular tachycardia/ventricular fibrillation (VT/VF), and sudden cardiac death. Therefore, it is recognized as a key determinant of worse clinical outcomes in patients with sarcoidosis.[2,3] Although several reliable indicators of clinical outcome are available, such as left ventricular systolic function, and the extent of late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging in patients with cardiac sarcoidosis (CS) has been reported,[4,5] there are few serological biomarkers with unequivocally demonstrated prognostic value.

Several studies have identified that biomarkers such as serum angiotensin converting enzyme (ACE), soluble interleukin 2 receptor (sIL-2R) and lysozyme, and serum

amyloid A (SAA) are useful in the diagnosis of sarcoidosis.[6] ACE is derived from epithelioid granulomas; therefore, its activity is useful in supporting a diagnosis and monitoring disease activity in patients with systemic sarcoidosis; however, there is actually little evidence available that ACE activity is significantly different between active and inactive sarcoidosis or that it reliably correlates with disease severity and clinical outcomes.[7–9] On the other hand, SAA and lysozyme have been found to be elevated in patients with sarcoidosis and have been reported to be more sensitive markers than ACE for the diagnosis of sarcoidosis; however, these have a major problem of low diagnostic specificity.[10]

Serum sIL-2R is presumed to be able to serve as a marker of activity on T lymphocytes in patients with sarcoidosis.[11] Notably, sIL-2R is a more useful biomarker than ACE, C-reactive protein (CRP), and SAA for estimating the severity of lung lesions in patients with sarcoidosis.[12] Furthermore, sIL-2R is associated with the abnormal uptake of ^{18}F-fluorideoxyglucose in positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in patients with sarcoidosis.[13] However, it remains to be seen whether sIL-2R is associated with the severity and activity of disease in patients with CS. Accordingly, the aims of this study were to investigate whether sIL-2R was associated with clinical outcomes and to clarify the relationship between sIL-2R levels and disease activity evaluated by ^{18}F-FDG PET/CT in patients with CS.

Methods

Study design

This was a single-centre, observational, retrospective study that included consecutive patients who were admitted for a work-up of suspected CS and finally diagnosed with CS during the indexed hospitalization. CS was diagnosed based on the criteria specified in the guidelines of the Japanese Circulation Society.[14] Briefly, according to the guidelines, a definite diagnosis of CS was made on the basis of histopathological endomyocardial biopsy findings or clinical and/or histopathological findings meeting clinical cardiac criteria, with extracardiac involvement of at least one organ. The study protocol was approved by the Institutional Review Board of Hokkaido University Hospital for Clinical Research (018-0225). The investigation was carried out in accordance with the principles outlined in the Declaration of Helsinki.

Study population

We examined 101 consecutive patients with CS who were admitted to the Hokkaido University Hospital between May 2003 and February 2020. Patients who had no data of serum sIL-2R levels before initiation of immunosuppressive therapy (n = 18) were excluded. Ultimately, 83 patients were examined in this study (*Figure 1*).

Echocardiography

Echocardiographic examinations were performed during hospitalization. Left ventricular (LV) end-diastolic dimensions, LV end-systolic dimensions, and LV ejection fraction (LVEF), as calculated from apical 2-chamber and 4-chamber views using the biplane method of disks, were measured. The data were evaluated by two experienced cardiologists.

Blood tests

Venous blood samples were obtained to measure serum ACE, sIL-2R, CRP, and plasma B-type natriuretic peptide (BNP). Serum was obtained after at least 30 min of clotting by centrifugation at 3500 g for 5 min and was stored at −80°C until analysis. Serum sIL-2R levels were measured with an enzyme-linked immunosorbent assay (until November 2009: Kyowa Medex Co., Tokyo, Japan, from November 2009: Hitachi Chemical Diagnostics Systems Co., Tokyo, Japan). The normal ranges in both assays were 200–459 U/mL.

Cardiac magnetic resonance imaging procedure and analysis

Cardiac magnetic resonance imaging was carried out using a 1.5T whole-body scanner (Achieva, Philips Medical Systems, Best, the Netherlands) with a cardiac five-channel phased-array cardiac coil or a 3-T whole-body scanner (Achieva Tx, Philips Medical Systems) with a 32-channel

Figure 1 Flow diagram of the present study. CS, cardiac sarcoidosis; sIL-2R, soluble interleukin 2 receptor
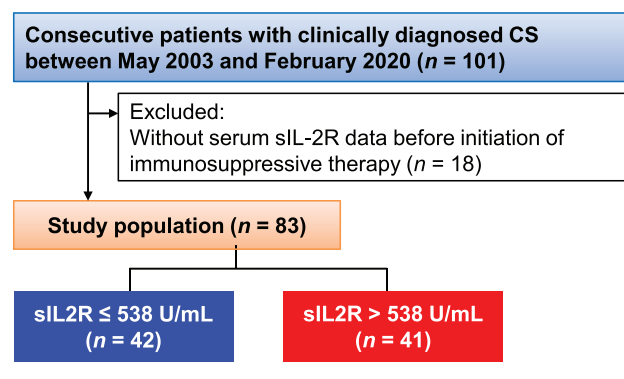
phased-array receiver torso-cardiac coil. Gadolinium-enhanced CMR imaging was performed 10–15 min after intravenous administration of 0.1 mmol/kg gadolinium diethylenetriamine penta-acetic acid (Magnevist, Bayer Yakuhin, Osaka, Japan) or gadobutrol (Gadovist, Bayer Yakuhin, Osaka, Japan). The LV short-axis images were obtained using a fast-field echo pulse sequence with inversion recovery with fat saturation or a phase-sensitive inversion recovery sequence. The optimal inversion time was selected to null the signal from normal myocardium using a Look-Locker sequence. Although 64 patients underwent CMR, we analysed 50 patients after excluding those without sufficient quality of imaging data to analyse CMR (*n* = 14).

We used commercially available software Ziostation2® (Ziosoft Inc., Tokyo, Japan) for quantitative analysis of LGE. The LGE was defined as the region with signal intensity ≥5 standard deviations (SD) above the mean CMR signal intensity of the normal remote myocardium.[15] The total amount of LGE was calculated as a percentage of the LV mass (%LGE).

Positron emission tomography imaging procedure and analysis

Positron emission tomography/CT imaging was acquired using a Gemini TF® PET/CT scanner (Philips Healthcare, Cleveland, OH) or a Biograph 64 TruePoint with TrueV® PET/CT scanner (Siemens Japan, Tokyo, Japan). Despite all patients undergoing a ^{18}F-FDG PET/CT scan, we analysed data from 73 patients after excluding those without sufficient quality of imaging data to analyse ^{18}F-FDG PET/CT (*n* = 10). All studied patients fasted for at least 18 h before ^{18}F-FDG PET/CT to suppress physiological myocardial ^{18}F-FDG uptake.[16] Eighteen patients received an injection with unfractionated heparin (UFH; 50 IU/kg, Mochida, Tokyo, Japan) alone, and 30 patients received a low-carbohydrate diet (LCD) alone. The remaining 25 patients received both UFH and LCD.

We used the METAVOL® software system (Department of Diagnostic Imaging, Hokkaido University, Sapporo, Japan) to analyse the maximal standard uptake value (SUV$_{max}$), cardiac metabolic volume (CMV), cardiac metabolic activity (CMA), lymph node metabolic volume (LyMV), and total lymph node glycolysis (TLyG) (*Figure 2*), as described previously.[17,18] The CMV was defined as the myocardium volume within the boundary determined by the FDG uptake threshold (SUV mean of blood pool × 1.5). The blood pool activity was measured in the descending aorta using a 1 cm spherical volume-of-interest. CMA was calculated by multiplying CMV by the SUV$_{mean}$.[19] The lymph node sarcoidosis lesions were evaluated using LyMV and TLyG. The LyMV was defined as the volume of the lymph node within the boundary determined by the FDG uptake threshold (SUV mean of blood pool × 1.5). TLyG was calculated by multiplying LyMV by the SUV$_{mean}$.

Clinical outcome

The primary outcome of interest was a composite of adverse outcomes, such as advanced AVB, VT/VF, heart failure hospitalization, and all-cause death. Ventricular arrhythmic events were defined as either emergency treatments for VF or sustained VT including appropriate implantable cardioverter defibrillator therapies (shock or anti-tachycardia pacing) or sustained VT with clinical symptoms and requiring admission. Advanced AVB was defined as AVB requiring permanent pacemaker implantation.

Statistical analyses

Continuous variables were presented as means ± standard deviations when normally distributed and as medians and interquartile ranges (IQR) when non-normally distributed. Comparisons of differences between the two groups (high and low sIL-2R levels) were performed using unpaired *t*-tests or Mann–Whitney *U* tests for continuous variables and by χ^2 tests or Fisher's exact tests for dichotomous variables, when appropriate.

The long-term cumulative incidence of the primary outcome was estimated using Kaplan–Meier curves, and a log-rank test was performed to assess significance according to sIL-2R value. To evaluate the influence of sIL-2R on the primary outcome, we constructed multivariable Cox proportional hazard models. Several studies have reported that multicollinearity exists among LVEF, %LGE, and other strong determinants of clinical outcomes in patients with CS.[5] Correspondingly, we observed a multicollinearity between CMV and %LGE (*r* = 0.64, *P* < 0.0001), and CMV and BNP (*r* = 0.50, *P* < 0.0001) in this study. Thus, we constructed three multivariable Cox proportional hazard models. Adjustments for age, LVEF, estimated glomerular filtration rate (eGFR), and BNP; age, eGFR, and %LGE; and age, LVEF, eGFR, and CMV were made in models 1, 2, and 3, respectively. Complete case analyses were applied in all multivariable models.

We performed a receiver operating characteristic (ROC) analysis to determine the optimal cut-off value of sIL-2R for adverse events.

Multivariable linear regression analysis was performed based on the variables achieving *P* < 0.10 in an univariable linear regression analysis, to explore the strongest independent determinants of sIL-2R. All tests were two tailed, and a value of *P* < .05 was considered statistically significant. All analyses were performed with Stata MP64 version 15 (StataCorp, College Station, TX).

Figure 2 Representative case of FDG PET/CT. (A) Original image of abnormal myocardial FDG uptake. (B) Voxel image of abnormal myocardial FDG uptake. (C) Volume-based image of abnormal myocardial FDG uptake. (D) Original image of lymph node FDG uptake. (E) Voxel image of lymph node FDG uptake. (F) Volume-based image of lymph node FDG uptake. CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography
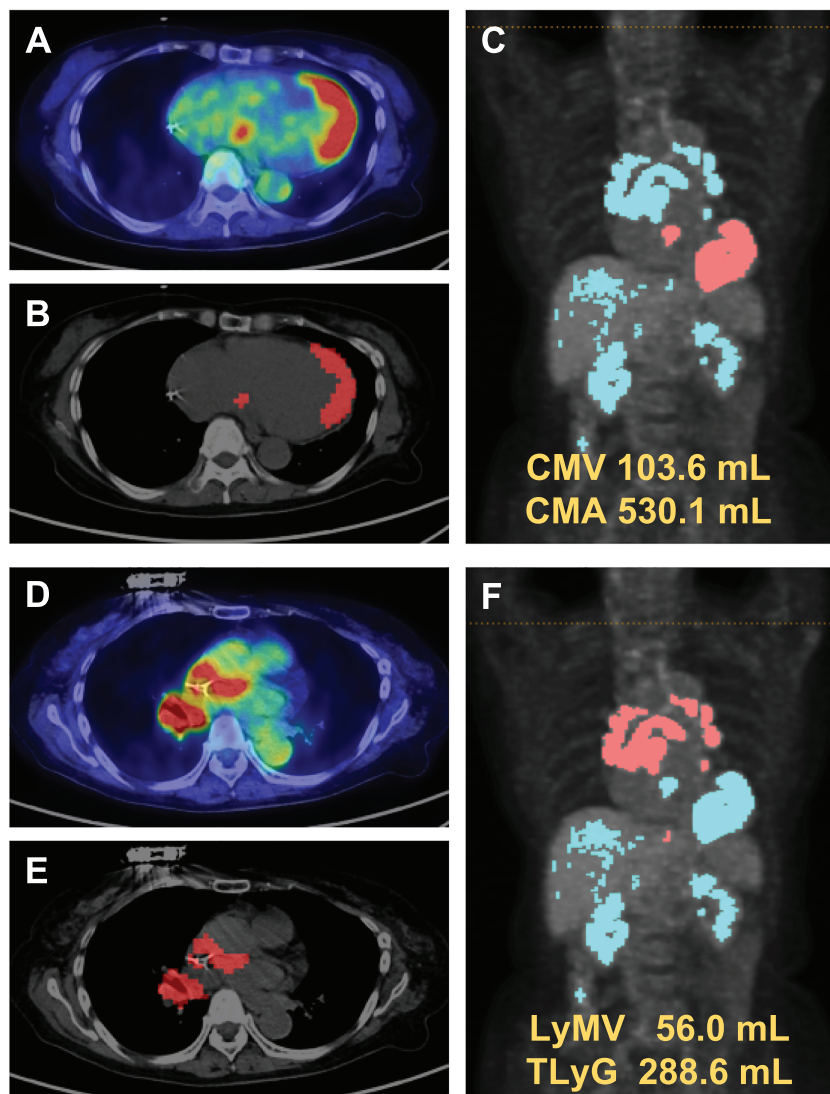
Results

Baseline characteristics

Baseline characteristics of all 83 studied patients are summarized in *Table 1*. Patients with a higher sIL-2R ($>$538 U/mL, the median) had a higher prevalence of diabetes mellitus, serum CRP, and ACE levels. There were no significant differences between the groups in terms of age, body mass index, prevalence of coronary artery disease, LVEF, plasma BNP levels, and use of oral medications.

Soluble interleukin 2 receptor levels and clinical outcomes

During a median follow-up period of 2.96 (IQR 2.24–4.27) years, the primary outcome occurred in 24 patients (29%), including 1 advanced AVB, 13 VT/VF, 5 hospitalizations for heart failure, and 5 all-cause deaths. Kaplan–Meier analyses showed that the primary outcome occurred more frequently in patients with higher sIL-2R levels than in those with lower sIL-2R levels ($P = 0.037$) (*Figure 3*). Notably, among the 24 patients with primary outcome, 12 patients developed an

Table 1 Baseline characteristics

Variable	Overall	Low sIL-2R ≤538 U/mL	High sIL-2R >538 U/mL	*P* value
Number	83	42	41	
Age (years)	61 (52–68)	60 (51–66)	63 (55–70)	0.91
Female	63 (76)	33 (79)	30 (73)	0.57
Body mass index (kg/m^2)	21.8 (20.2–24.2)	21.9 (21.1–24.2)	21.5 (20.1–23.9)	0.54
Organ involvement				
Lung	67 (81)	35 (83)	32 (78)	0.54
Skin	20 (24)	7 (16)	13 (31)	0.11
Eye	38 (46)	16 (38)	22 (54)	0.16
Number of involved organs	3.2 ± 1.5	3.0 ± 1.4	3.3 ± 1.6	0.50
Past history				
CAD	3 (4)	2 (5)	1 (2)	0.57
VT	7 (8)	6 (14)	1 (2)	0.052
Echocardiography				
LVEF (%) missing 6/83	44 (38–62)	43 (37–61)	50 (38–63)	0.46
LVDD (mm) missing 1/83	50 (45–57)	51 (46–58)	49 (45–55)	0.49
LVDS (mm) missing 2/83	34 (29–47)	36 (30–47)	34 (29–47)	0.82
IVS wall thinning missing 1/83	34 (41)	19 (46)	15 (37)	0.37
Laboratory data				
Haemoglobin (g/dL)	13.5 ± 1.5	13.3 ± 1.6	13.7 ± 1.5	0.24
CRP (mg/dL)	0.06 (0.04–0.19)	0.05 (0.02–0.08)	0.14 (0.06–0.34)	<0.001
eGFR (mL/min/1.73 m^2)	69.6 ± 17.9	69.3 ± 17.1	70.0 ± 18.8	0.86
BNP (pg/mL) missing 14/83	74 (28–179)	78 (28–180)	72 (18–170)	0.97
ACE (U/L) missing 1/83	15.2 (11.2–18.4)	12.6 (9.1–16)	17.4 (14.1–21.4)	<0.001
sIL2-R (U/mL)	538 (381–751)	389 (317–464)	751 (660–911)	<0.001
Medications				
ACE-inhibitors/ARBs	48 (58)	25 (60)	23 (56)	0.75
Beta-blockers	44 (53)	26 (62)	18 (44)	0.10
Immunosuppressive therapy	70 (84)	34 (81)	36 (89)	0.39
Amiodarone	11 (13)	9 (21)	2 (5)	0.03
CMR				
Missing 33/83				
LGE burden (%)	14.8 (4.4–24.6)	15.2 (3.3–25.4)	13.2 (5.3–22.5)	0.94
^{18}F-FDG PET/CT				
Missing 10/83				
FDG dose (MBq)	245.5 (216.6–276.3)	243.2 (217.5–292)	245.7 (215–268.9)	0.51
SUV$_{max}$	10.8 (7.9–13.6)	10.2 (6.8–13.6)	11.0 (8.8–13.8)	0.23
CMV (mL)	56.1 (10.4–104.5)	29.5 (8.1–95.0)	66.6 (23.5–134.4)	0.14
CMA (mL)	174.3 (41.2–411.1)	133.5 (28.2–411.1)	259.6 (75.9–411.5)	0.19
LyMV (mL)	56.0 (20.5–119.4)	30.8 (3.5–91.5)	80.1 (44.2–123.1)	0.004
TLyG (mL)	215.1 (78.0–500.8)	165.5 (13.1–411.9)	351.9 (162.5–552.9)	0.01

ACE, angiotensin converting enzyme; ARBs, angiotensin II receptor blockers; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CMA, cardiac metabolic activity; CMR, cardiac magnetic resonance; CMV, cardiac metabolic volume; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; FDG, fluorodeoxyglucose; IVS, interventricular septum; LGE, late gadolinium enhancement; LyMV, lymph node metabolic volume; LVDD, left ventricular end-diastolic diameter; LVDS, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; PET, positron emission tomography; sIL2-R, soluble interleukin-2 receptor; SUV, standardized uptake value; TLyG, total lymph node glycolysis; VT, ventricular tachycardia.
Continuous variables are presented as mean ± standard deviation if normally distributed and median (interquartile range) if not normally distributed. Categorical variables are presented as number of patients (%).

adverse event during within 1 year (10 VT/VF, 1 hospitalizations for heart failure, and 1 all cause death). Kaplan–Meier analysis showed that the primary outcome occurred more frequently in patients with higher sIL-2R levels than those with lower sIL-2R levels (*P* = 0.01). A multivariable Cox regression analysis revealed that a higher sIL-2R level was independently associated with an increased subsequent risk of adverse events, even after adjustments for age, BNP, eGFR, CMV, LVEF, and %LGE, which are known to be strong determinants of clinical outcomes in patients with CS (Model 1

[*n* = 65, Event = 19], HR 3.71, 95% CI 1.63–8.44, *P* = 0.002; Model 2 [*n* = 50, Event = 12], HR 3.48, 95% CI 1.34–9.08, *P* = 0.01; Model 3 [*n* = 68, Event = 20], HR 3.04, 95% CI 1.18–7.82, *P* = 0.02) (*Table 2*). Harrell's c-indices of the models 1, 2, and 3 were 0.79, 0.85, and 0.80, respectively. Based on ROC analysis, the optimal cut-off value of sIL-2R for the incidence of adverse events was 811 U/mL (sensitivity 45.8%, specificity 89.8%), and c-index was 0.65 (95% CI 0.50–0.80). The hazard ratio was 4.90 (95% CI 2.17–11.04, *P* < 0.001) when the sIL-2R was above 811 U/mL.

Figure 3 Survival analyses of long-term clinical outcomes of patients with cardiac sarcoidosis categorized by sIL-2R. (A) Composite of advanced atrio-ventricular block, VT/VF, heart failure hospitalization, and all-cause death. (B) All-cause death. (C) VT/VF. (D) Heart failure hospitalization. sIL-2R, soluble interleukin 2 receptor; VF, ventricular fibrillation; VT, ventricular tachycardia
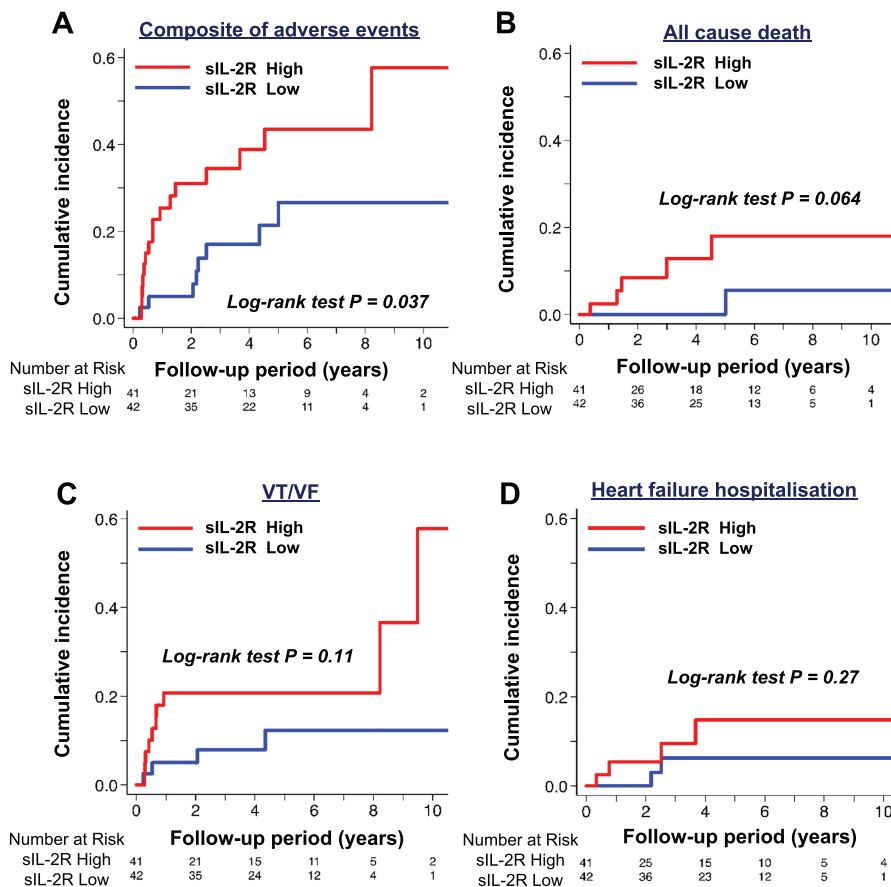
Relationships between serum soluble interleukin 2 receptor levels and clinical variables

The association between sIL-2R and variables of PET is shown in *Figure 4*. There was a modest positive correlation between sIL-2R levels and LyMV or TLyG ($r = 0.438$, $P = 0.00001$; $r = 0.346$, $P = 0.003$, respectively), whereas there was no significant correlation between sIL-2R and CMV or CMA ($r = 0.224$, $P = 0.06$; $r = 0.131$, $P = 0.271$, respectively). In the multivariable linear regression analyses, LyMV and TLyG were independent determinants of sIL-2R ($\beta = 2.50$, $P = 0.002$, $\beta = 0.41$, $P = 0.04$, respectively), even after adjustment for age and SUV$_{max}$ (*Table 3*).

Discussion

In the present study, we demonstrated that a higher serum sIL-2R level was significantly associated with subsequent worse clinical outcomes in patients with CS. Furthermore, sIL-2R levels were correlated to disease activities in lymph nodes rather than in the myocardium, as assessed by ^{18}F-FDG PET/CT, reflecting the systemic inflammatory activities of sarcoidosis.

Although the aetiology of sarcoidosis is unclear, it is thought that some antigens cause inflammation, which affects multiple organs.[20] This inflammation leads to the activation of monocyte-macrophages, which in turn release cytokines, such as tumour necrosis factor-α, interleukin-1 (IL-1), and interleukin-6 (IL-6).[21] These cytokines, mainly IL-1 and IL-6, stimulate the production of IL-2, which promotes T cell activation.[22] Finally, activated T cells release the 55-kDa protein, sIL-2R.[23] Eurelings *et al.* reported that sIL-2R was superior to ACE in screening for sarcoidosis (c-index = 0.91 vs. 0.68, sensitivity 88%, specificity 85%, cut-off value 3550 pg/mL) according to the analysis of 189 patients with suspected but unproven or unexcluded sarcoidosis.[24] Moreover, sIL-2R could be a more sensitive marker than lysozyme and ACE in patients with sarcoidosis who visited the dermatology clinic.[25] Notably, sIL-2R was significantly higher in patients with multiple organ involvements and parenchymal infiltrates,

Table 2 Cox proportional hazard model for composite of adverse events

| | Univariable | | | Multivariable | | | | | | | | |
| | | | | Model 1 | | | Model 2 | | | Model 3 | | |
Variable	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age	0.99	0.96–1.02	0.55	0.94	0.89–1.00	0.07	0.92	0.86–1.01	0.06	0.97	0.91–1.02	0.20
Female	1.02	0.40–2.58	0.97									
History of VT	1.82	0.42–7.94	0.42									
Amiodarone	1.88	0.70–5.06	0.21									
Immunosuppressive therapy	2.35	0.87–6.35	0.09									
LVEF (%)	0.97	0.94–0.99	0.02	0.97	0.92–1.01	0.13				0.98	0.95–1.01	0.23
eGFR (mL/min/1.73 m^2)	0.97	0.95–0998	0.03	0.94	0.91–0.99	0.008	0.93	0.88–0.98	0.01	0.94	0.90–0.98	0.002
CRP (mg/dL)	1.06	0.58–1.95	0.84									
Log BNP (pg/mL)	1.48	1.07–2.05	0.02	1.32	0.83–2.12	0.24						
Log sIL-2R (U/mL)	3.02	1.51–6.06	0.002	3.71	1.63–8.44	0.002	3.48	1.34–9.08	0.01	3.04	1.18–7.82	0.02
LGE burden (%)	1.05	1.02–1.09	0.003				1.06	1.02–1.10	0.005			
SUV$_{max}$	1.01	0.92–1.12	0.76									
CMV (mL)	1.01	1.00–1.01	0.02							1.01	1.00–1.01	0.01
CMA (mL)	1.00	1.00–1.002	0.07									
LyMV (mL)	1.00	1.00–1.01	0.04									
TLyG (mL)	1.00	1.00–1.002	0.17									

BNP, B-type natriuretic peptide; CI, confidence interval; CMA, cardiac metabolic activity; CMV, cardiac metabolic volume; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HR, hazard ratio; LGE, late gadolinium enhancement; LyMV, lymph node metabolic volume; LVEF, left ventricular ejection fraction; SUV, standardized uptake value; TLyG, total lymph node glycolysis; sIL2-R, soluble interleukin-2 receptor; VT, ventricular tachycardia.
Model 1: adjusted for age, left ventricular ejection fraction, estimated glomerular filtration rate and B-type natriuretic peptide. Model 2: adjusted for age, estimated glomerular filtration rate and late gadolinium enhancement burden. Model 3: adjusted for age, left ventricular ejection fraction, estimated glomerular filtration rate, cardiac metabolic volume.

Figure 4 Relationship between the respective covariates and sIL-2R. (A) CMV. (B) CMA. (C) LyMV. (D) TLyG. CMA, cardiac metabolic activity; CMV, cardiac metabolic volume; LyMV, lymph node metabolic volume; TLyG, total lymph node glycolysis
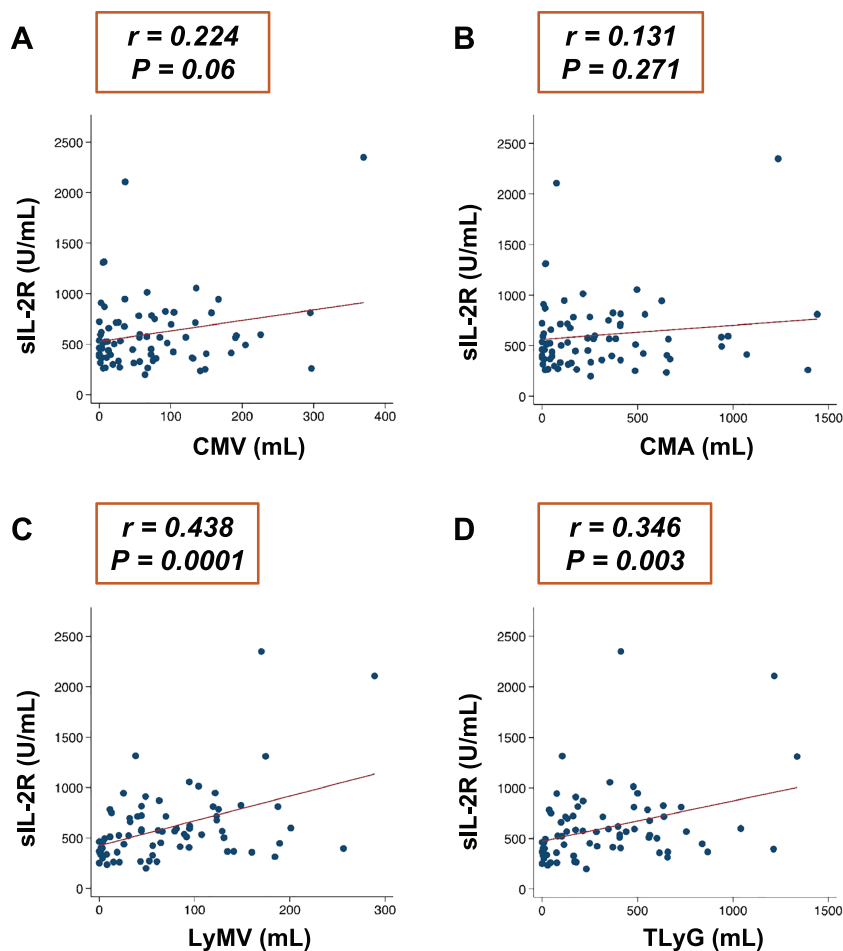
Table 3 Linear regression analyses for sIL-2R levels

| Variable | Univariable | | Multivariable | | | |
| | | | Model 1: LyMV | | Model 2: TLyG | |
	β coefficient	P value	β coefficient	P value	β coefficient	P value
Age	−16.79	0.006	−4.96	0.13	−5.88	0.09
LVEF (%)	3.22	0.56	Not selected		Not selected	
Haemoglobin (g/dL)	30.79	0.56	Not selected		Not selected	
CRP (mg/mL)	168.55	0.21	Not selected		Not selected	
eGFR (mL/min/1.73 m^2)	5.54	0.21	Not selected		Not selected	
BNP (pg/mL)	−0.14	0.74	Not selected		Not selected	
LGE (%)	−4.64	0.61	Not selected		Not selected	
SUV$_{max}$	16.19	0.048	−3.40	0.72	−2.77	0.81
CMV (mL)	1.03	0.06	Not selected		Not selected	
CMA (mL)	0.13	0.27	Not selected		Not selected	
LyMV (mL)	2.46	<0.001	2.50	0.002	-	
TLyG (mL)	0.39	0.003	-		0.41	0.04

BNP, B-type natriuretic peptide; CMA, cardiac metabolic activity; CMV, cardiac metabolic volume; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; LGE, late gadolinium enhancement; LyMV, lymph node metabolic volume; LVEF, left ventricular ejection fraction; SUV, standardized uptake value; TLyG, total lymph node glycolysis; sIL2-R, soluble interleukin-2 receptor.
Model 1: adjusted for age, maximal standard uptake value and lymph node metabolic volume. Model 2: adjusted for age, maximal standard uptake value and total lymph node glycolysis.

suggesting that sIL-2R could be an indicator of systemic disease activity.[25] In fact, there are several reports that sIL-2R is useful in assessing the severity of sarcoidosis, especially in pulmonary sarcoidosis.[12,26,27] Rothkrantz-Kos *et al*. revealed that sIL-2R appeared to be the best marker for estimating the severity of disease compared to ACE, high-sensitivity CRP, and SAA in patients with untreated pulmonary sarcoidosis.[12] Given its value in outcome prediction, sIL-2R would serve as a prognostic biomarker for progression and relapse in patients with sarcoidosis.[26,27]

Among sarcoidosis patients with no clinical indication for steroid treatment at the time of diagnosis, approximately 40% of those with a high level of sIL-2R had subsequent progression of disease, whereas those with a normal level of sIL-2R had no progression.[26] In addition, a high level of sIL-2R before initiation of infliximab, which is considered as a third-line therapeutic option for severe sarcoidosis, is significant predictor of relapse (HR 2.24, 95% CI 1.07 to 4.68).[27] Taking these results together, sIL-2R may further aid in the diagnosis and risk stratification of sarcoidosis compared with other markers such as ACE, lysozyme, and SAA.

To the best of our knowledge, this is the first report to examine the association between serum sIL-2R levels and adverse outcomes in patients with CS. A possible explanation for this association includes a significant correlation between levels of sIL-2R and LyMV or TLyG rather than CMV or CMA, as assessed by ^{18}F-FDG PET/CT. ^{18}F-FDG PET/CT is a useful modality in the diagnosis of CS and may be further associated with prognosis in patients with CS. Several studies have reported the usefulness of FDG uptake on PET/CT for risk stratification among patients with CS.[28,29] Blankstein *et al*. showed that the presence of abnormal FDG uptake on PET/CT, especially in the right ventricle, was significantly associated with VT/VF or death.[28] However, isolated sarcoid lesions in the right ventricle are relatively rare, suggesting that sarcoid lesions in the right ventricle follow left ventricular lesions and may be a more advanced stage of CS.[30,31] Ahmadian *et al*. demonstrated that CMA was independently associated with adverse events in patients with CS.[32] In contrast, Manabe *et al*. have reported that CMV and CMA, assessed with quantitative analysis of 18F-FDG PET/CT, were not significantly related to adverse events in such patients.[33] Therefore, whether quantitative measures of FDG volume intensity, such as CMV and CMA, are associated with adverse outcomes in patients with CS remains controversial. In addition, it should be noted that LGE on CMR imaging is associated with VT/VF, whereas FDG uptake in the myocardium was not associated with VT/VF.[34] In a study with 50 CS patients, 19% of the studied patients with positive findings in both LGE and PET and 21% of those with positive in LGE and negative in PET had subsequent VTVF events, whereas none of those with negative in LGE and positive in PET experienced VTVF events, indicating FDG uptake in the myocardium may not have additional prognostic value if CMR is available.[34] In addition, the most common mechanism of VT/VF is likely to be re-entrant arrhythmias associated with areas of scar tissue.[35] These findings indicate the limited prognostic implication of local inflammatory activity on the myocardium. In our study, we highlighted that sIL-2R was significantly associated with inflammation in the lymph nodes throughout the body as a reflection of systemic inflammatory activity but not with inflammation in the myocardium. Given the diagnostic and prognostic value of inflammatory activities in patients with CS, it would be important to evaluate systemic inflammation as well as inflammation in the myocardium. Collectively, elevated sIL-2R levels, which have an additive prognostic value to the extent of LGE, reflect a high level of systemic inflammation with advanced stage of CS.

Study limitations

There are several potential limitations of the present study that should be acknowledged. First, this was a single-centre study with a relatively small sample size, thereby limiting the ability to generalize the findings and the statistical power for detecting differences in negative data. Therefore, a larger-scale multicentre prospective study is warranted to confirm the relationship between sIL-2R levels and the subsequent adverse outcomes. Second, there was unavoidable bias in this study because 10 and 33 patients were excluded from the analyses of PET and CMR imaging, respectively. Third, we have constructed multivariable models with complete case analyses. Although Harrell's c-indices showed sufficient discriminative value in the multivariable models, the stability of the models might not be guaranteed. Fourth, because the optimal cut-off value of sIL-2R for the adverse events was derived from a relatively small number of study subjects, this cut-off value might not be able to generalize. Fifth, we did not assess the serial changes of sIL-2R levels and PET findings after immunosuppressive therapy; therefore, the association between the changes in sIL-2R levels and adverse events after immunosuppressive therapy is unclear. Sixth, although the Kaplan–Meier curve spreads quite early, suggesting that higher sIL-2R levels were associated with adverse events within a year rather than long-term events, we could not assess the association of higher sIL-2R levels with adverse events within a year because the number of adverse events in this duration were limited to 12. Finally, because patients without cardiac implantable electronic devices were not always monitored by 24 h electrocardiography, several ventricular arrhythmias might have been underestimated. Hence, the study endpoints regarding arrhythmic events were defined either as treatments for termination of VF or sustained VT including appropriate treatments with implantable cardioverter defibrillators or bradyarrhythmias requiring permanent pacemaker implantation.

Conclusions

A higher serum sIL-2R level before initiation of immunosuppressive therapy was associated with worse long-term clinical outcomes reflecting elevated systemic inflammatory activities in patients with CS. These findings suggest the importance of assessing sIL-2R as a surrogate marker for further risk stratification in these patients.

Conflict of interest

None declared.

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