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Can the Sarcoidosis Health Questionnaire predict the long-term outcomes in Japanese sarcoidosis patients?

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ABSTRACT

Rationale: The Sarcoidosis Health Questionnaire (SHQ) is the first sarcoidosis-specific health status questionnaire ever developed. Worse health status, as evaluated by the SHQ, may indicate higher risk for deterioration in the following 5 years.

Objectives: To evaluate the association between SHQ scores and deterioration defined clinically at 5-year follow-up.

Methods: 122 patients with biopsy-supported sarcoidosis completed the SHQ and underwent evaluation with respect to organ involvement, chest radiograph, electrocardiogram, serum biomarker measurements, pulmonary function tests, and echocardiogram. Of these 122, 88 (72.1%) were available for pulmonary, cardiac, and non-pulmonary, non-cardiac deterioration assessment during the following 5 years.

Measurements and main results: Five-year deterioration was observed in 20 patients (23%). The SHQ total score was significantly associated with 5-year deterioration, after adjusting for cardiac involvement at baseline, with adjusted odds ratio (OR) of 0.54 (95% confidence interval [95% CI], 0.29–0.99). The association of the total SHQ with 5-year outcome was not significant when adjusted for left ventricular ejection fraction (LVEF) at baseline (adjusted OR, 0.61 [0.32–1.16]), whereas LVEF was significantly associated with 5-year outcome (adjusted OR, 0.92 [0.86–0.99]). The association between total SHQ score and 5-year deterioration was marginal when adjusted for baseline usage of systemic corticosteroid (CS)/immunosuppressive (IS) agents (adjusted OR, 0.58 [0.31–1.10]), whereas systemic CS/IS usage significantly predicted 5-year deterioration (adjusted odds ratio [OR], 3.46 [1.12–10.7]). There was a marginal correlation between the total SHQ and LVEF (rho = 0.19, p = 0.07) and a weak association between the total SHQ and systemic CS/IS usage (rho = −0.23, p = 0.03). The Physical Functioning domain scores of the SHQ were significantly associated with 5-year deterioration (adjusted OR, 0.45–0.51).

Conclusions: Worse health status, as assessed by the SHQ score, can be a risk factor for 5-year deterioration of sarcoidosis, although usage of the CS/IS at baseline and lower LVEF at baseline are more predictive of 5-year deterioration.

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Abbreviations list

ACCESS	A Case-Control Epidemiologic Study of Sarcoidosis
BHL	bilateral hilar lymphadenopathy
CES-D	Center for Epidemiologic Study-Depression
CI	confidential interval
COS	clinical outcome status
CS	corticosteroid
DF	Daily Functioning
EF	Emotional Functioning
^{18}F-FDG PET	^{18}F-fluorodeoxyglucose positron emission tomography
IS	immunosuppressive agent
KSQ	King's Sarcoidosis Questionnaire
LVEF	left ventricular ejection fraction
MCID	minimal clinically important difference
MRC	Medical Research Council
OR	odds ratio
PF	Physical Functioning
PFT	pulmonary function test
PRO	patient-reported outcome
SAT	Sarcoidosis Assessment Tool
SF-36	Medical Outcomes Study 36-item short form
SGRQ	St. George's Respiratory Questionnaire
SHQ	Sarcoidosis Health Questionnaire
WASOG	World Association of Sarcoidosis and Other Granulomatous Disorders

1. Introduction

Sarcoidosis is a chronic and multisystem granulomatous disease of unknown etiology that can involve almost any organ system [1]. The disease has a highly variable clinical outcome [2,3] and often impairs the health status of patients [4]. The correlation between physician assessment of sarcoidosis and patient self-assessment is relatively low. In consequence, patient-reported outcome (PRO) measures of sarcoidosis patients can reflect aspects of the disease that are divergent from objective measurements.

The Sarcoidosis Health Questionnaire (SHQ) was developed by Cox and colleagues in the United States as the first questionnaire specifically focused on the health status of sarcoidosis patients [5,6]. Later, our group developed and validated a Japanese version of the SHQ. However, no previous study has evaluated whether the SHQ can predict outcomes in sarcoidosis patients.

The objective of this study is to evaluate the association between health status, as assessed by the SHQ, and long-term deterioration of sarcoidosis. We hypothesize that worse health status is associated with higher frequency of deterioration. We also evaluated the associations between other PRO indices and objective variables, and deterioration.

2. Methods

2.1. Study population

One-hundred twenty-two consecutive patients with biopsy-supported sarcoidosis who visited the Kyoto Central Clinic between June and December 2009 were enrolled in our previous study for validation of a Japanese version of the SHQ [6]. Grounds for exclusion were: 1) age < 18 years; 2) presence of an active neoplasm; 3) failing to complete the questionnaire, or 4) no active organ involvement of sarcoidosis when filling out the questionnaire. Of these 122, 88 (72.1%) were available for 5-year follow-up and were analyzed in the present study. All patients provided written informed consent to participate in the prospective study approved by the ethics committees of Kyoto University Hospital (approval No. E679) and Kyoto Central Clinic.

2.2. Patient-reported outcomes

All patients completed the Japanese versions of the SHQ [4,6], the generic Medical Outcomes Study 36-item short form (SF-36) [7,8], and the respiratory-specific St. George's Respiratory Questionnaire (SGRQ) [9,10], to evaluate their health status at the time of enrollment (baseline). The SHQ consists of 29 items and three domains: Daily Functioning (DF), Physical Functioning (PF), and Emotional Functioning (EF). Each item was scored on a 7-point scale, and scores were calculated for each domain and for the total test by dividing the sums of the

Deterioration during five-year follow-up (the long-term deterioration)
One or more of *pulmonary*, *cardiac*, and *non-pulmonary and non-cardiac* deteriorations.

Pulmonary deterioration: either of 1) – 2)
1) %FVC < 80%, and an absolute decline in %FVC from baseline >10%.
2) Hypoxia at rest and/or on exertion that needs a new commencement of LTOT, or an increase in oxygen through LTOT to keep the percutaneous oxygen saturation ≥ 88% at rest and/or on exertion.

Cardiac deterioration: either of 1) – 2)
1) LVEF < 50%, and an absolute decline in LVEF from baseline >10%.
2) New implantation of permanent cardiac pacemaker.

Non-pulmonary and non-cardiac deterioration: either of 1) – 2)
1) Development/worsening of central nervous system involvement.
2) Any organ system involvement with objective evidence of disease worsening, that needs the induction/augmentation of systemic therapy (e.g. skin lesion, polyarthritis)

Fig. 1. Definition of deterioration. *Systemic therapy is systemic corticosteroid or immunosuppressive agent. Abbreviation: LTOT, long-term oxygen therapy.

Table 1
Demographics, organ involvement, radiographic stage, serum biomarkers, pulmonary function tests, echocardiogram, and treatment at enrollment (baseline).

Number	All enrolled patients	Available for 5-year follow-up
	122	88
Age, years	56.8 ± 15.5	55.8 ± 14.1
Male	48 (39)	35 (40)
Duration of disease, months	108.9 ± 86.2	112.4 ± 82.9
Number of organ systems involved	1.8 ± 0.8	1.8 ± 0.8
Pulmonary involvement	98 (80)	68 (77)
Cardiac involvement	27 (22)	23 (26)
Ocular involvement	58 (48)	42 (48)
Skin involvement	26 (22)	23 (26)
Radiographic stage, 0/I/II/III/IV	37/31/33/14/5	31/18/23/13/3
0/I/II/III/IV	(31/26/28/12/4)	(35/20/26/15/3)
Serum biomarkers		
ACE, IU/L	17.2 ± 6.5	17.2 ± 6.7
sIL-2R, IU/mL	639.9 ± 507.5	676.7 ± 565.3
Pulmonary function tests		
FVC, % predicted	105.8 ± 18.5	107.1 ± 16.8
FEV_1, % predicted	105.8 ± 21.0	106.0 ± 18.7
DLCO, % predicted	85.1 ± 17.2	85.1 ± 16.9
Echocardiogram		
LVEF, %	68.1 ± 11.4	67.9 ± 8.3
PASP, mmHg	29.4 ± 5.9	29.2 ± 5.8
Treatment		
Systemic CS or IS	26 [23]	20 [23]

Data represent mean ± standard deviation or number (percentage).
Abbreviations: SD, standard deviation; ACE, angiotensin-converting enzyme; sIL-2R, soluble interleukin-2 receptor; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; DLCO, diffusion capacity for carbon monoxide; LVEF, left ventricular ejection fraction; PASP, pulmonary arterial systolic pressure; CS, corticosteroid; IS, immunosuppressive agent.

scores by the numbers of items. Higher scores indicate better health status on the SHQ and SF-36, but worse health status on the SGRQ. Dyspnea at baseline was self-evaluated using the Japanese version of the Medical Research Council (MRC) dyspnea scale, in which a higher score indicates a worse status [11]. Depressive symptoms at baseline were also self-evaluated by the Japanese version of the Center for Epidemiologic Study-Depression scale (CES-D, 20-item version), in which a higher score indicates more severe depression [12,13].

2.3. Clinical variables

Baseline clinical variables obtained on all patients and included in this analysis were organ involvement, chest radiograph, electrocardiogram, serum biomarkers (angiotensin converting enzyme activity, and soluble interleukin-2 receptor), pulmonary function tests (PFTs) [14,15], and echocardiogram [16]. The extent of organ involvement was assessed by the ACCESS (A Case-Control Epidemiologic Study of Sarcoidosis) Organ Involvement Index [17]. Chest radiographs were classified according to standard radiographic staging: stage 0, normal; stage I, bilateral hilar lymphadenopathy (BHL); stage II, BHL with pulmonary infiltrates; stage III, pulmonary infiltrates without BHL; and stage IV, advanced pulmonary fibrosis [18]. Serum angiotensin converting enzyme activity and soluble interleukin-2 receptor were measured by Kasahara's method [19] and chemiluminescence enzyme immunoassay, respectively.

2.4. Outcome variables

Evaluations at the 5-year follow-up after baseline included physician assessments, PFTs, and echocardiograms, but did not include any PRO measures. The long-term outcome was determined for this analysis from data during 5-year follow-up. Deterioration is defined in Fig. 1. All evaluations and decisions about treatment after baseline were made blinded to PRO indices at baseline.

2.5. Statistical analysis

Clinical features and patient-oriented outcomes were summarized using mean (standard deviation) and number (percentage) as appropriate. Logistic regression was used to evaluate the association between SHQ scores, other PRO indices, and clinical variates with long-term deterioration. Candidate co-variates for multivariate models were identified based on the results of univariate analyses with $P < 0.05$. Since the number of patients with long-term deterioration was still small (20 with 5-year deterioration), only two variates were included in each model simultaneously. To overcome this paucity of outcome events, forward stepwise logistic regression analysis (removal from the model with $P \geq 0.2$, and addition to the model with $P < 0.1$) was performed. Individual domain scores of the SHQ (DF, PF, and EF domains) were also analyzed in the same manner as were the SHQ total scores. Subgroup analyses were performed for the two subgroups: the subgroup of patients with lung involvement at baseline, and that of patients without cardiac involvement at baseline.

Lungs are the most common involved organ system. Cardiac involvement was associated with both of worse prognosis and worse PRO measures in sarcoidosis [20,21]. In these subgroup analyses, multivariate analyses were not performed because of the small numbers of patients with deterioration (15 and 11, respectively). All data analyses were performed using STATA/IC 14.2 for Mac (Stata Corp., Lakeway, TX, USA). For all analyses, a $P < 0.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics and patient-reported outcome (PRO) measures

Clinical features and patient-reported outcomes at the time of enrollment are shown in Tables 1 and 2. Histograms of the SHQ scores are shown in Fig. 2.

3.2. Associations of the SHQ scores with long-term outcome

Of 88 patients at the 5-year follow-up, 20 (23%) had five-year deterioration; this included pulmonary deterioration in two (2%), cardiac in nine (10%), and non-pulmonary, non-cardiac in nine (10%) patients. In univariate analysis, the total SHQ score was associated with 5-year deterioration: OR, 0.52 (0.28–0.94) (Table 3) (Fig. 2A). Total SHQ score was associated with 5-year deterioration after adjustment for cardiac involvement at enrollment, with adjusted OR of 0.54 (0.29–0.99) (Table 4, *Model 1*). The association of the total SHQ with 5-year outcome was not significant when adjusted for LVEF at baseline (Table 4, *Model 2*), and marginal when adjusted for the usage of systemic CS or IS at enrollment (Table 4, *Model 3*). There was a marginal correlation between the total SHQ and LVEF at baseline (rho = 0.19, p = 0.07) and a weak association between the total SHQ and systemic CS/IS usage at enrollment (rho = −0.23, p = 0.03). When the SHQ total scores, cardiac involvement, the usage of systemic CS or IS, and LVEF were entered into a forward stepwise logistic regression, none of these baseline indices were associated with 5-year deterioration (Table 4, *Model 4*).

Among the SHQ domain scores, DF and PF scores were associated with 5-year deterioration in univariate analysis: DF with OR, 0.56 (0.33–0.96), and PF with OR, 0.48 (0.27–0.85) (Table 3) (Fig. 2B). PF

Table 2
Patient-oriented outcomes at baseline.

Number	All enrolled patients	Available for five-year follow-up
	122	88
SHQ		
Daily Functioning [1–7]	4.7 ± 1.0	4.7 ± 1.0
Physical Functioning [1–7]	5.4 ± 1.0	5.4 ± 0.9
Emotional Functioning [1–7]	4.8 ± 1.0	4.8 ± 1.0
Total [1–7]	4.9 ± 0.9	4.9 ± 0.8
SF-36		
Physical functioning [0–100]	79.2 ± 20.9	80.5 ± 20.5
Role-physical [0–100]	77.1 ± 27.0	79.2 ± 24.8
Bodily pain [0–100]	71.9 ± 26.7	74.2 ± 24.4
General health perceptions [0–100]	50.0 ± 19.7	49.5 ± 19.7
Vitality [0–100]	52.2 ± 23.1	53.4 ± 22.3
Social functioning [0–100]	78.6 ± 24.1	80.5 ± 22.7
Role-emotional [0–100]	77.7 ± 25.7	78.1 ± 25.7
Mental health [0–100]	66.6 ± 20.5	67.1 ± 21.4
SGRQ		
Symptoms [0–100]	39.8 ± 20.6	39.1 ± 20.3
Activity [0–100]	29.7 ± 24.9	27.6 ± 23.9
Impact [0–100]	14.6 ± 14.6	13.6 ± 14.0
Total [0–100]	23.4 ± 16.3	22.1 ± 15.4
MRC [1–5]	1.8 ± 0.8	1.5 ± 0.8
CES-D [0–60]	12.8 ± 9.3	11.6 ± 8.4

Data represent mean ± standard deviation.
The numbers in square brackets represent the theoretical score ranges.
Better status is indicated by higher scores on the SHQ and SF-36, and by lower scores on the SGRQ, MRC, and CES-D.
Abbreviations: SHQ, Sarcoidosis Health Questionnaire; SF-36, Medical Outcomes Study 36-item short form; SGRQ, St. George's Respiratory Questionnaire; MRC, Medical Research Council; CES-D, Center for Epidemiologic Study-Depression Scale.

scores of the SHQ were significantly associated with 5-year deterioration after adjustment for cardiac involvement at enrollment, the usage of systemic CS or IS at enrollment, and with baseline LVEF, respectively (Table 5, *Model 1 to 3*). No other domain score was associated with 5-year outcome in multivariate models, with the marginal association of the DF scores adjusted after cardiac involvement at enrollment (adjusted OR, 0.59 [0.34–1.00]). In the forward stepwise logistic regression model including the SHQ PF scores, cardiac involvement, the usage of systemic CS or IS, and LVEF, the SHQ PF scores was the only significant predictor for 5-year deterioration with adjusted OR of 0.48 (0.26–0.90). The SHQ PF scores were significantly associated with SF-36 physical functioning domain (rho = 0.570, $p < 0.0001$), SGRQ total scores (rho = −0.714, $p < 0.0001$), and MRC dyspnea scale (rho = −0.436, $p < 0.0001$).

Of 68 patients who had lung involvement at enrollment and were available for 5-year follow-up, 15 (22%) had 5-year deterioration, including 2 (2%) with pulmonary deterioration, 7 (10%) with cardiac deterioration, and 6 (9%) with non-pulmonary, non-cardiac deterioration. In univariate analysis, total SHQ score was marginally associated with 5-year deterioration: OR, 0.51 (0.26–1.02) (Table 6) (Fig. 2C). The PF domain score was significantly associated with 5-year deterioration in this subgroup: OR, 0.45 (0.24–0.86) (Table 6).

Of 65 patients who did not have cardiac involvement at enrollment, and were available for 5-year follow-up, 11 (17%) had five-year deterioration; this included pulmonary deterioration in 2 (3%), cardiac in 1(2%), and non-pulmonary, non-cardiac in 8 (12%). In univariate analysis, total SHQ score was associated with 5-year deterioration: OR, 0.40 (0.18–0.93) (Table 6) (Fig. 2D). The PF domain score was also associated with 5-year deterioration in this subgroup: OR, 0.49 (0.24–0.98) (Table 6).

4. Discussion

In our cohort of well-characterized patients with sarcoidosis, the total SHQ score was associated with outcome after 5 years. This association is independent of cardiac involvement at baseline, while it is marginal and not significant after adjusting for the baseline usage of systemic CS/IS and LVEF, respectively. The Physical Functioning domain score is also associated with 5-year deterioration even after adjustment for these other confounders. These findings suggest that worse health status on the SHQ can be a risk for long-term deterioration in sarcoidosis patients.

Evaluation of outcomes in sarcoidosis patients has not been standardized thus far [20]. Sarcoidosis is a multisystem disease that can affect different organs with different severities and activities [2,3,20]. An objective assessment of a single organ system cannot reflect other organ system lesions or systemic symptoms. There has been also no blood biomarker established as a comprehensive index for disease activity in sarcoidosis [20,22–24]. The World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) recently defined the clinical outcome status (COS) based on examinations 5 years after diagnosis [3]. However, WASOG COS would not be appropriate in this study because our patients were enrolled at various phases of the disease course and were reevaluated not at 5 years after diagnosis, but at 5 years after enrollment. We, thus originally defined “deterioration” for this study to evaluate the 5-year outcome after baseline.

The SHQ is the first disease-specific PRO instrument for sarcoidosis. Multidisciplinary properties of the SHQ were shown in Cox's original study and our previous one [5,6]. On the other hand, some limitations of the SHQ have been described. The SHQ is supposed to be almost entirely based on the SF-36 and contains standalone items for ocular, skin, and pulmonary involvement [25]. Indeed, the generic health status measured by the SF-36 was also associated with long-term outcome in our study. Additionally, the minimal clinically important difference (MCID) has not been established for the SHQ [26]. The King's Sarcoidosis Questionnaire (KSQ) and the Sarcoidosis Assessment Tool (SAT), two assessments recently developed to overcome these limitations, have been validated as new sarcoidosis-specific PRO instruments [26,27]. Both the KSQ and the SAT have several modules that reflect specific aspects of sarcoidosis, such as fatigue and skin involvement [26,27], and an MCID has been established for the latter [26]. The predictive properties of the KSQ and the SAT should be evaluated and compared to the SHQ in future studies.

Of the PRO measures evaluated in this cohort, the MRC dyspnea scale and the CES-D tended to be associated with outcome, whereas the SGRQ was not. Dyspnea can be associated with both pulmonary and cardiac involvement, and also with fatigue in sarcoidosis [28]. Depressive symptoms have an association with organ involvement other than pulmonary and cardiac, such as muscles, nerves and bones [29]. On the other hand, the SGRQ is more specific for respiratory diseases. Although the SGRQ significantly correlates with the SHQ [5], the SHQ is superior in differentiating the number of organ systems involved [5]. In addition, any PFT parameters were not associated with outcome in this study. This may be because respiratory specific indices cannot predict worsening of extrapulmonary organ involvement. Another possible reason is that pulmonary deterioration was seen only in two patients (2%).

Among the three domains of the SHQ, the scores from the PF domain were the strongest predictor for 5-year deterioration. The PF domain was significantly associated with the SF-36 physical functioning (PF) subscale, the SGRQ score and dyspnea. The original report as well as our previous study also showed stronger associations of the PF domain with the SGRQ score, dyspnea, and physiological measurements, compared to the other SHQ domains [5,6]. However, the SF-36 PF subscale, the SGRQ score or any physiological measurement other than

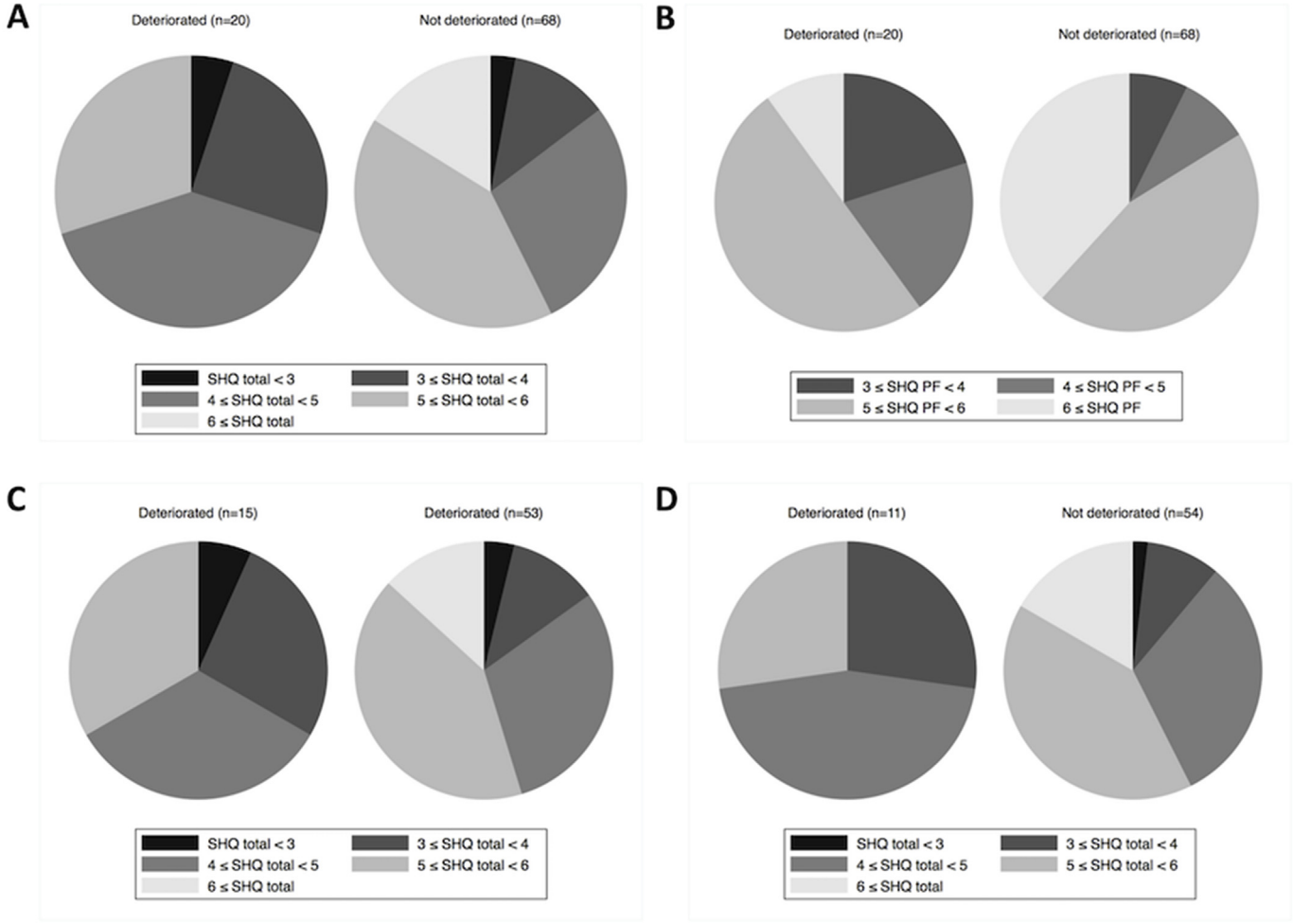

Fig. 2. Distributions of the scores of the Sarcoidosis Health Questionnaire by five-year deterioration. Higher SHQ total and Physical Functioning domain scores represent better health status. A. Five-year deterioration in all patients (n = 88) and SHQ total scores. B. Five-year deterioration in all patients (n = 88) and SHQ Physical Functioning domain scores. C. Five-year deterioration in patients with lung involvement at baseline (n = 68). D. Five-year deterioration in patients without cardiac involvement at baseline (n = 65).

LVEF was not predictive for 5-year deterioration in this study.

The PF domain is composed of six questions, four of which deal with respiratory and/or cardiac symptoms (easy breathing; shortness of breath; cough; wheezing), and two with pain (headache; arthralgia) [5]. Of these six questions, the scores on the two questions for pain were associated with the long-term outcome (unadjusted OR of 0.79 [95%CI, 0.58–0.89]), whereas those on the four questions for respiratory and/or cardiac symptoms were not (unadjusted OR of 0.90 [95%CI, 0.80–1.03]). The SF-36 bodily pain subscale was also marginally associated with five-year deterioration. On the other hand, the SF-36 PF subscale addresses the restriction of several daily activities, but not painful symptoms. The SGRQ also includes no question about pain. Thus, painful symptoms, rather than respiratory and/or cardiac ones and general physical activity, may be predictive of long-term deterioration of patients with sarcoidosis.

It should be also noted that, in this study cohort, most events of 5-year deterioration were cardiac (9/20), or non-pulmonary, non-cardiac (9/20). The predictive properties of these PRO instruments may be altered in other sarcoidosis populations with different outcomes (e.g. more frequent pulmonary deteriorations). In addition, the SF-36 PF subscale shows the ceiling effect in this study (Figure e1), which may affect its association with long-term outcome.

Reported indicators for poor prognosis in sarcoidosis include disease onset > 40 years old, involvement of the central nervous system (beyond an isolated central nerve palsy), heart, bone, or sino-nasal organ involvement, radiographic stage IV, bronchial stenosis, and pulmonary hypertension [20]. Composite physiological index and high-resolution computed tomography parameters were recently reported to predict mortality in patients with pulmonary sarcoidosis [30]. Our data suggest that some PRO measures, including SHQ scores, should also be considered as potential predictors of outcomes. Different results on organ involvement and physiological impairment may be associated with different study populations and definitions of outcomes.

Decreased LVEF and cardiac involvement at baseline are significant and marginal risks for 5-year deterioration after adjustment for total SHQ scores, respectively. Japanese sarcoidosis patients have a higher prevalence of cardiac involvement than do Western patients, with cardiac involvement being a major cause of mortality [31–33]. In fact, 45% of the cases of 5-year deterioration in this study were cardiac. Another significant predictor of deterioration is the usage of systemic CS/IS at baseline. It is reasonable because the usage of systemic CS/IS can be a surrogate marker for active disease at baseline, whatever organ systems are predominantly affected. Usage of systemic CS is also associated with health status of sarcoidosis patients [21].

There are several limitations of our study to consider. There were only 20 events of deterioration at the 5-year follow-up. We were too underpowered to construct multivariate models that included all potential covariates. Analysis in larger multi-center cohorts and enrichment of more severe cases would be more definitive. None of the questionnaires used in this study specifically addresses fatigue,

Table 3
Univariate logistic regression analyses for long-term deterioration.

	Odds	95% CI	*P*
Age, years	1.00	(0.96, 1.03)	0.81
Male	1.01	(0.37, 2.80)	0.98
Duration of disease	1.00	(1.00, 1.01)	0.46
Number of organ systems involved	0.96	(0.50, 1.83)	0.91
Pulmonary involvement	0.85	(0.27, 2.72)	0.78
Cardiac involvement	3.16	(1.09, 9.10)	0.03
Ocular involvement	0.67	(0.24, 1.84)	0.43
Skin involvement	0.64	(0.19, 2.18)	0.48
Radiographic stage	1.14	(0.75, 1.72)	0.54
Serum biomarkers			
ACE	0.90	(0.81, 1.00)	0.06
sIL-2R	1.00	(1.00, 1.00)	0.26
Pulmonary function tests			
% FVC	1.00	(0.97, 1.03)	0.98
% FEV_1	1.00	(0.97, 1.03)	0.88
% DLCO	0.99	(0.96, 1.02)	0.52
Echocardiogram			
LVEF	0.91	(0.86, 0.98)	0.01
PASP	1.02	(0.94, 1.11)	0.68
Systemic CS or IS	4.24	(1.42, 12.6)	0.01
SHQ			
Daily Functioning	0.56	(0.33, 0.96)	0.04
Physical Functioning	0.48	(0.27, 0.85)	0.01
Emotional Functioning	0.69	(0.41, 1.14)	0.15
Total	0.52	(0.28, 0.94)	0.03
SF-36			
Physical functioning	0.99	(0.97, 1.01)	0.30
Role-physical	0.98	(0.96, 1.00)	0.04
Bodily pain	0.98	(0.96, 1.00)	0.05
General health perceptions	0.97	(0.94, 0.99)	0.02
Vitality	0.97	(0.94, 0.99)	0.01
Social functioning	0.99	(0.97, 1.01)	0.34
Role-emotional	0.98	(0.96, 1.00)	0.06
Mental health	0.98	(0.96, 1.01)	0.19
SGRQ			
Symptoms	1.00	(0.97, 1.02)	0.79
Activity	1.01	(0.99, 1.03)	0.33
Impact	1.01	(0.98, 1.05)	0.40
Total	1.01	(0.98, 1.05)	0.42
MRC	1.53	(0.84, 2.78)	0.16
CES-D	1.06	(1.00, 1.12)	0.06

Abbreviations: Odds, odds ratio; CI, confidential interval.

although fatigue impairs the health status of sarcoidosis patients [34–36]. In fact, the SF-36 vitality subscale score was predictive for 5-year deterioration in this study. Assessment of fatigue, vitality, and energy by the SF-36 and other PRO instruments may provide additional predictive information to the SHQ.

Baseline evaluation does not include ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET). ^{18}F-FDG PET at diagnosis is reported to be a predictor of pulmonary deterioration within one year [37], although ^{18}F-FDG PET has not been widely used at regular follow-ups.

In conclusion, we demonstrate that worse health status, as assessed by the SHQ, is a risk for deterioration during the following 5 years, although the usage of systemic CS/IS and LVEF at baseline are stronger risks. If validated in other cohorts and with other questionnaires such as the KSQ and the SAT, this suggests that health status should be evaluated to address both subjective disease burdens for sarcoidosis patients and patients' risks for future deterioration, in addition to common objective measures.

Table 4
Multivariate logistic regression analyses with SHQ total score for long-term deterioration.

Model 1	Odds ratio	95% CI	P value
SHQ total	0.54	(0.29, 0.99)	0.047
Cardiac involvement	2.95	(0.99, 8.81)	0.053
Model 2			
SHQ total	0.61	(0.32, 1.16)	0.13
LVEF	0.92	(0.86, 0.99)	0.02
Model 3			
SHQ total	0.58	(0.31, 1.10)	0.09
Systemic CS or IS	3.46	(1.12, 10.7)	0.03
Model 4 (forward stepwise)			
SHQ total	0.63	(0.33, 1.21)	0.17
Cardiac involvement	1.37	(0.35, 5.42)	0.65
LVEF	0.95	(0.87, 1.02)	0.16
Systemic CS or IS	2.03	(0.53, 7.69)	0.30

Table 5
Multivariate logistic regression analyses with the SHQ Physical Functioning domain for long-term deterioration.

Model 1	Odds ratio	95% CI	*P* value
SHQ Physical Functioning	0.48	(0.27, 0.87)	0.02
Cardiac involvement	3.10	(1.03, 9.37)	0.045
Model 2			
SHQ Physical Functioning	0.51	(0.28, 0.93)	0.03
LVEF	0.92	(0.86, 0.98)	0.01
Model 3			
SHQ Physical Functioning	0.45	(0.25, 0.83)	0.01
Systemic CS or IS	4.66	(1.46, 14.8)	0.01
Model 4 (forward stepwise)			
SHQ Physical Functioning	0.48	(0.26, 0.90)	0.02
Cardiac involvement	1.23	(0.30, 5.13)	0.78
LVEF	0.95	(0.87, 1.02)	0.17
Systemic CS or IS	2.73	(0.68, 10.9)	0.16

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Table 6
Univariate logistic regression analyses for the five-year deterioration.

Number	With lung involvement			Without cardiac involvement		
	68			65		
Long-term deteriorations	Odds	15 (22)	*P*	Odds	11 (17)	*P*
		95% CI			95% CI	
Age, years	1.01	(0.96, 1.05)	0.81	0.99	(0.95, 1.04)	0.70
Male	1.10	(0.34, 3.55)	0.87	0.51	(0.12, 2.12)	0.35
Duration of disease	1.00	(1.00, 1.01)	0.32	1.01	(1.00, 1.01)	0.09
Number of organ systems involved	0.89	(0.42, 1.89)	0.77	0.67	(0.27, 1.67)	0.39
Pulmonary involvement	–	–	–	1.15	(0.22, 6.11)	0.87
Cardiac involvement	2.87	(0.83, 9.92)	0.10	–	–	–
Ocular involvement	0.45	(0.13, 1.48)	0.19	0.42	(0.11, 1.62)	0.21
Skin involvement	0.63	(0.16, 2.57)	0.52	0.69	(0.16, 2.91)	0.62
Radiographic stage	1.23	(0.74, 2.07)	0.42	0.84	(0.48, 1.47)	0.54
Blood laboratory tests						
ACE	0.91	(0.81, 1.01)	0.08	0.90	(0.78, 1.04)	0.14
sIL-2R	1.00	(1.00, 1.00)	0.41	1.00	(1.00, 1.00)	0.49
Pulmonary function tests						
%FVC	1.01	(0.97, 1.04)	0.66	1.01	(0.97, 1.05)	0.54
$\%FEV_1$	1.00	(0.97, 1.03)	0.93	1.01	(0.97, 1.04)	0.70
%DLCO	0.99	(0.96, 1.03)	0.73	0.98	(0.94, 1.02)	0.24
Echocardiogram						
LVEF	0.91	(0.84, 0.98)	0.01	0.95	(0.84, 1.07)	0.38
PASP	0.99	(0.90, 1.10)	0.91	1.08	(0.95, 1.22)	0.26
Systemic CS or IS	5.75	(1.58, 20.9)	0.01	7.14	(1.45, 35.2)	0.02
SHQ						
Daily Functioning	0.57	(0.31, 1.06)	0.08	0.34	(0.14, 0.79)	0.01
Physical Functioning	0.45	(0.24, 0.86)	0.02	0.49	(0.24, 0.98)	0.04
Emotional Functioning	0.68	(0.38, 1.21)	0.19	0.70	(0.35, 1.38)	0.30
Total	0.51	(0.26, 1.02)	0.057	0.40	(0.18, 0.93)	0.03
SF-36						
Physical functioning	0.99	(0.97, 1.02)	0.44	0.97	(0.94, 1.00)	0.09
Role-physical	0.98	(0.96, 1.00)	0.04	0.96	(0.94, 0.99)	0.01
Bodily pain	0.98	(0.95, 1.00)	0.03	0.96	(0.94, 0.99)	0.02
General health perceptions	0.95	(0.92, 0.99)	0.01	0.95	(0.91, 0.99)	0.01
Vitality	0.97	(0.94, 1.00)	0.02	0.95	(0.92, 0.99)	0.01
Social functioning	0.99	(0.96, 1.01)	0.23	0.98	(0.95, 1.01)	0.17
Role-emotional	0.98	(0.96, 1.00)	0.048	0.97	(0.94, 0.99)	0.01
Mental health	0.99	(0.96, 1.01)	0.28	0.97	(0.94, 1.00)	0.06
SGRQ						
Symptoms	1.00	(0.97, 1.03)	0.91	1.00	(0.97, 1.04)	0.86
Activity	1.01	(0.99, 1.04)	0.28	1.00	(0.99, 1.03)	0.87
Impact	1.02	(0.98, 1.06)	0.32	1.02	(0.97, 1.07)	0.41
Total	1.02	(0.98, 1.05)	0.31	1.01	(0.97, 1.06)	0.60
MRC	1.80	(0.94, 3.43)	0.08	2.17	(1.00, 4.73)	0.05
CES-D	1.06	(0.99, 1.13)	0.08	1.09	(1.00, 1.19)	0.06

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Appendix ASupplementary data

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