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Quality of life in sarcoidosis

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ABSTRACT

Having sarcoidosis often has a major impact on quality of life of patients and their families. Improving quality of life is prioritized as most important treatment aim by many patients with sarcoidosis, but current evidence and treatment options are limited. In this narrative review, we describe the impact of sarcoidosis on various aspects of daily life, evaluate determinants of health-related quality of life (HRQoL), and provide an overview of the different patient-reported outcome measures to assess HRQoL in sarcoidosis. Moreover, we review the current evidence for pharmacological and non-pharmacological interventions to improve quality of life for people with sarcoidosis.

1. Introduction

Sarcoidosis is a rare, inflammatory driven, multisystem disease with an unpredictable disease course. Having sarcoidosis often has a major impact on a person's quality of life (QoL) [1,2]. Due to the heterogeneity of the disease, sarcoidosis-related QoL is a complex, multi-faceted concept, with various interrelated factors that may impair QoL. Quality of life is a broad term defined as an individual's wellbeing in relation to their goals and expectations, in the context of the cultural and value systems they live in (WHO) [3]. Health-related quality of life refers to the impact of physical and mental health on an individual's QoL (HRQoL). The term 'health status' concerns the perceived health of an individual; it is often used interchangeably with HRQoL.

The two main aims of care for sarcoidosis are to prevent organ damage and death, and to improve or maintain QoL [2,4]. Unfortunately, evidence-based treatments that improve QoL in sarcoidosis are scarce [4]. To develop effective pharmacological and non-pharmacological interventions focusing on HRQoL, structured measurement of (HR)QoL and health status are essential. Moreover, better understanding of the impact of sarcoidosis on various aspects of daily life and relevant determinants of (HR)QoL is needed.

In this review, we describe the impact of sarcoidosis on patients and their families, we evaluate determinants of HRQoL, and provide an overview of the different methods to assess HRQoL in sarcoidosis. In the last part, we review the current evidence for pharmacological and non-pharmacological interventions to improve quality of life for people with sarcoidosis.

2. Patients' needs and priorities

A large European survey in 2018 evaluated patient priorities in treatment for sarcoidosis. The most important outcome for patients was QoL, followed by functionality. Objective measures such as pulmonary function tests, laboratory results, imaging, and adverse events were deemed less important [5]. In other studies, patients highlighted the

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need for alternative medication with better efficacy and fewer side-effects, and improved prognostic tests [6–8]. HRQoL and symptoms were considered the most important aspects of new treatment [7]. In 2011, a group of sarcoidosis experts developed recommendations for clinical trial endpoints. One of their main recommendations was to include HRQoL as endpoint in all clinical trials [9]. This was also emphasized in a recent Delphi survey study organized by the Foundation for Sarcoidosis Research (FSR) [7]. HRQoL was included in the core outcome set for future sarcoidosis research after an online consensus meeting. Other important needs identified by patients during their disease trajectory include early referral and easy access to disease specialists, better multidisciplinary collaboration, accurate disease information, practical, emotional and psychological support, and contact with peers [6–8].

2.1. Impact of sarcoidosis on daily lives of patients and their families

It is well recognized that sarcoidosis can significantly reduce (HR) QoL of patients [1]. Notably, several studies also found a major impact of sarcoidosis on the lives of their families [6,7,10]. One study found that 75 % of patients and partners reported (very) much influence of sarcoidosis on their daily lives. Both patients and their partners experienced anxiety and misunderstanding related to sarcoidosis [6]. Interestingly, a large study that used validated generic questionnaires found that QoL of partners was significantly reduced compared to healthy controls, albeit better than for patients with sarcoidosis [10]. Patients can suffer from relationship problems, role changes (e.g., in family life), fear of stigma, and social isolation [11].

Sarcoidosis can impact numerous aspects of daily living, including work participation as it often affects people in the midst of their working lives. Work ability is often reduced due to non-organ specific symptoms, such as fatigue and depression [8,12]. In a Dutch survey, almost half of patients with paid work answered that they have undergone work disability assessments; 17 % were on sick leave, 28 % were fully unfit for work, and 13 % partially unfit for work. Of all patients that were employed at the time of the survey, 69 % reported sarcoidosis-related absence of varying duration [12]. Importantly, more than one third of patients responded that they felt not taken seriously and many patients disagreed with the disability assessment outcome. Reduced work ability often leads to significant loss of income in the years after diagnosis of sarcoidosis [13,14]. A United States (US) claims database study found that sarcoidosis was associated with more work loss days, and higher healthcare costs compared to matched controls [13]. Another US study found that low income was significantly associated with poor outcomes and worse HRQoL [15]. Job loss following a diagnosis of sarcoidosis was more common in patients with low income. Moreover, low income was the strongest predictor of developing new sarcoidosis-related morbidity, such as depression, fatigue, and chronic pain [15]. It is important to realize that economic burden of sarcoidosis and impact on patients may vary across the world, due to major differences in health care systems.

3. Relation between HRQoL and disease-related factors

Reduced HRQoL in sarcoidosis has been associated with the direct and indirect effects of disease, organ and non-organ related manifestations, the potential toxicities of the medications used to treat disease, the lack or perceived lack of benefit of some of the medications (or other interventions) deployed in disease management, and the uncertainty and perceived psychosocial implications of having a rare disease with an unpredictable nature [16–18]. Besides, specific patient characteristics (e.g., gender), environmental, and societal factors may influence HRQoL.

3.1. Organ involvement and HRQoL

Organ manifestations can negatively impact HRQoL in sarcoidosis (e.g., impaired vision, skin lesions, neurological involvement, or severe shortness of breath) [15]. One study found that patients with both pulmonary and extrapulmonary involvement had worse HRQoL than patients with isolated pulmonary involvement [19]. The impact of different organ manifestations on HRQoL can be evaluated with PROMs. The King's Sarcoidosis Questionnaire (KSQ) for example has specific domains for lung, eye, and skin involvement that can be combined with the general health domain (see below for more details). In this way it becomes possible to objectively measure the impact of common organ manifestations on health status. With the caveat that some relevant organ manifestations, such as cardiac sarcoidosis, pulmonary hypertension, and neurosarcoidosis, are not directly targeted in any of the sarcoidosis specific questionnaires, whilst their impact on patient's functioning and quality of life is often large.

The association between cardiac sarcoidosis and HRQoL is not completely unraveled. Although it could be hypothesized that cardiac sarcoidosis further impairs quality of life as it is a severe disease manifestation, a systematic review found no studies that specifically assessed the impact of cardiac sarcoidosis on overall HRQoL [20]. Pulmonary hypertension is an important disease manifestation of sarcoidosis, and is associated with increased symptomatology, significant morbidity, excess mortality, and overall reduced HRQoL [21–26].

3.2. Disease severity and HRQoL

In general, disease severity is one of the main factors thought to be related with HRQoL in chronic diseases. However, in sarcoidosis, this relation is less clear. In a retrospective study evaluating over 600 patients from a single tertiary center in the US, Judson and colleagues observed that sarcoidosis patients with symptoms at presentation had more organ involvement and worse HRQoL than patients with incidentally detected disease [27]. Interestingly, there was no difference between groups in lung function and Scadding stage. Several other studies also found that there was no relation between lung function and HRQoL [1,28,29]. Conversely, diffusion capacity of the lung for carbon monoxide significantly predicted HRQoL in one large cross-sectional study [30]. Not FVC or DLCO, but forced expiratory volume in 1 s (FEV1) was correlated with a reduced general health status and a lower cough-related quality of life in a German study [31,32]. Besides, a lower 6 min walking distance may be associated with a lower HRQoL [30,33,34].

3.3. Specific patient characteristics

It has been suggested that female patients with sarcoidosis experience lower HRQoL than male patients, corrected for potential confounding factors [30,35–37]. Being female and having a lower age was associated with lower HRQoL in a US study [15]. In contrast, Cox et al. found that gender, age, ethnicity, and smoking status were not related to HRQoL [1]. Finally, obesity may have a negative impact on HRQoL in patients with sarcoidosis [31,32,38].

Table 1
Overview of patient-reported outcome measures in sarcoidosis.

PROM	Description	Validation studies, Internal consistency (Cronbach's α coefficient) and MCID	Advantages	Disadvantages	Ref.
Generic PROMs					
Short Form-36 (SF-36)	Generic 36-item eight-domain HRQoL instrument	Good correlation with sarcoidosis-specific PROMs; no MCID for sarcoidosis	Division in physical and mental aspects; includes all aspects of disease and comorbidities	No MCID for sarcoidosis	[76]
EQ-5D-5L	Generic questionnaire with two parts (descriptive system and Visual Analogue Scale), each with a five-point Likert-Scale	Similar HRQoL trends in ILD and sarcoidosis compared to K-BILD	Short and easy to complete; comparison with other diseases possible	Very general questions, not specific enough to capture all aspects of disease	[77]
World Health Organization – Quality of Life 100 (WHOQOL-100)	Generic multidimensional measure of QoL with 100-items in six domains (Physical health, Psychological independence, Level of independence, Social relationships, Environment, Spirituality/religion/ personal beliefs)	Tested in a sarcoidosis population with good validity; no MCID for sarcoidosis	Validated in sarcoidosis	Takes long to complete; no MCID for sarcoidosis	[78]
WHOQOL-BREF	Abbreviation of the WHOQOL-100 with four domains and two questions on overall QoL and general health	Evaluated in a sarcoidosis population; no MCID for sarcoidosis	Shorter than WHOQOL-100	Relevant questions for sarcoidosis are missing	[3]
Disease-specific PROMs					
Sarcoidosis Health Questionnaire (SHQ)	Sarcoidosis specific 29-item health status questionnaire with 3 domains: daily, physical, and emotional functioning	Developed and validated in sarcoidosis; internal consistency 0.75–0.84; no MCID	Different languages; used in many studies; takes 10 min to complete	No validity testing regarding certain organ systems. No MCID available	[79]
King's Sarcoidosis Questionnaire (KSQ)	29-item, multidomain instrument with five modules: General health status, Lung, Skin, Eye, Medications. Different domains: General health (KSQ GH) and pulmonary specific (KSQ lung health status)	Developed and validated in sarcoidosis; Internal consistency 0.70–0.93; better validity for pulmonary sarcoidosis than SHQ; MCID: KSQ GH 8 points, KSQ lung 4 points	Recommended as standard for QoL in pulmonary sarcoidosis; 14 languages; 10 min; available online	No questions on all important organ systems involved in sarcoidosis	[80]
Sarcoidosis Assessment Tool (SAT)	PRO to assess health status in sarcoidosis with eight domains: Physical Function, Satisfaction with Roles and Activities, Fatigue, Pain Interference, Sleep, Skin concerns, Skin stigma, Lung concerns, Eye concerns); Modification of PROMIS	Validated in chronic lung and skin sarcoidosis; Internal consistency 0.87–0.97; good construct validity; MCID for each SAT module: 2–5 points	Focus on health status; organ specific subscales; 10–15 min	Not widely available (in many languages)	[81]
SAT fatigue module (PROMIS PFI)	Specific SAT module on fatigue	Validated in Sarcoidosis; excellent consistency; MCID: 3 points	1–3 min	Not widely available (in many languages)	[82]
Fatigue Assessment Scale (FAS)	Sarcoidosis-specific Fatigue questionnaire with ten items, five questions for physical and five for mental fatigue	Developed and validated in sarcoidosis; high internal consistency and validity; MCID: 4 points	Most used in sarcoidosis; recommended as standard; 1–2 min; different languages	–	[83]
Small Fibre Neuropathy Screening List (SFNSL)	21-item questionnaire to measure symptomatology related to SFN	Validated in sarcoidosis; good reliability and validity; no MCID	Useful for screening of SFN	Not specifically evaluating impact on HRQoL	[84]
St. George's Respiratory Questionnaire (SGRQ)	Fifty-item questionnaire with three domains assessing HRQOL in chronic respiratory diseases	Validated in sarcoidosis; no MCID for sarcoidosis	Used in many clinical trials; sensitive to extrapulmonary manifestations	Originally developed for obstructive lung disease; difficult questionnaire; duration up to 20 min	[85, 86]

Adapted from [56,72,74].
FAS, Fatigue Assessment Scale; KSQ, King's Sarcoidosis Questionnaire; MCID, minimum clinically relevant difference; PROM, patient-reported outcome measure; PROMIS, patient-reported outcomes measurement information system; SAT, Sarcoidosis Assessment Tool; SF-36, Short Form-36; SFNSL, Small Fibre Neuropathy Screening List; SGRQ, St. George's Respiratory Questionnaire; SHQ, Sarcoidosis Health Questionnaire; WHOQOL-100, World Health Organization – Quality of Life 100.

3.4. Symptoms

Symptoms causing reduced HRQoL may be organ- or non-organ specific and can be due to reversible active (inflammatory) disease, irreversible (eg, fibrotic) damage, or even be present in the absence of any clear disease activity or organ damage [18]. Fatigue has consistently been identified as the most frequent and burdensome symptom of sarcoidosis, being present in up to 90 % of patients [6,8,39,40]. Fatigue is one of the strongest drivers of QoL [34,37,41]. Interestingly, sarcoidosis-associated fatigue seems not related to disease severity or physical parameters [28,37]. Fatigue often persists, even in patients with no other signs of active sarcoidosis. Fatigue is interrelated with many other symptoms that can impair HRQoL, such as dyspnea, cough, anxiety, depressive symptoms, cognitive dysfunction, pain, and small fiber neuropathy [37,41,42]. Fatigue may also be associated with sleep disorders in sarcoidosis. Sleep disturbance and obstructive sleep apnea (OSA) are more common in patients with sarcoidosis that in the general population. In one study, sleep disturbance was not related to disease severity or activity; however, it strongly correlated with quality of life and symptoms as fatigue, anxiety, depression, and cognitive dysfunction [43]. Roeder et al. found that having OSA did not lead to increased fatigue, but significantly impacted QoL [44].

Dyspnea is one of the most common symptoms of sarcoidosis, especially in patients with pulmonary involvement. Nevertheless, it can be

present when lung function and radiology is completely normal, as dyspnea may for example also occur due to cardiac involvement, or reduced muscle strength and physical condition [45]. It has been suggested that hyperventilation may also play a role in the onset and persistence of dyspnea in sarcoidosis, and may be associated with HRQoL [46]. A recent registry study showed that dyspnea had a moderate to strong correlation with fatigue and HRQoL [45].

Chronic cough occurs in over 50 % of patients with sarcoidosis and is associated with decreased HRQoL [47–49]. Cough is not always associated with radiographic pulmonary disease; however, patients with pulmonary sarcoidosis are more likely to report worse cough especially in the presence of endobronchial or submucosal granulomas causing increased airway hyper-responsiveness [49–54]. Presence of airway distortion and bronchiectasis in fibrotic sarcoidosis is also associated with worse cough [49–52,55]. Patients with higher cough counts, worse cough severity and more cough triggers report worse HRQoL [48,56]. Cough-related quality of life is a significant predictor of generic QoL [42].

It is well known that sarcoidosis affects the psychological/emotional state of patients, leading to high prevalence of stress, anxiety, depressive symptoms, and cognitive dysfunction. Cognitive dysfunction leads to reduced self-management and negatively impact treatment [57]. These symptoms are strongly correlated with generic and disease-specific HRQoL [41], [1,58–61]. The causes of depression in sarcoidosis are complex and include the direct effects of disease on the central nervous system, the psychosocial effects of living with a chronic disease, and the toxic side effects of medications on functional status and QoL [62]. One study found that patients with perceived poor access to health care and lower socioeconomic status had more depressive symptoms [61]. Patients with worse dyspnea and more organ involvement are also more likely to report depression [57,61,63]. The relation between anxiety, depressive symptoms and sarcoidosis can be bidirectional: poor HRQoL can lead to depressive symptoms, but depression can also lead to lower HRQoL. The cross-sectional design of most published studies makes it difficult to determine the direction of the relation.

Finally, other highly prevalent non-organ related manifestations of sarcoidosis, such as chronic pain and small fiber neuropathy (SFN) are also associated with significant impairment in HRQoL [10,40,64]. Chronic pain may occur in up to 70 % of patients with sarcoidosis. Hoitsma et al. evaluated over 800 members of the Dutch Sarcoidosis Society and noted that the most frequently reported pain was arthralgia (54 %), followed by muscle pain (40 %), headaches (28 %) and chest pain (27 %). Patients with more types of pain had lower HRQoL [65]. SFN occurs in 40–60 % of patients and is a disabling non-granulomatous, non-organ manifestation of sarcoidosis that is associated with significant impairment in HRQoL [40,66–68]. It occurs as a result of loss of thinly myelinated and unmyelinated nerve fibers and is characterized by dysautonomia and severe neuropathic symptoms such as paresthesia's, allodynia, numbness, gastrointestinal dysmotility, diaphoresis, orthostasis and palpitations [67,69].

Clinicians involved in care for patients with sarcoidosis should structurally assess these organ and non-organ related symptoms during outpatient clinic visits, in order to provide adequate symptom palliation.

3.5. How to measure quality of life in sarcoidosis?

3.5.1. Outcome measures

Since (HR)QoL of patients with sarcoidosis is influenced by various factors, measuring QoL can be challenging. Nevertheless, structured measurements of QoL can improve shared-decision making, and may result in higher patient satisfaction [70].

Quality of life can be quantified using patient-reported outcome measures (PROMs). PROs are defined as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else" [71]. PROMS can measure symptom burden, health status, and (HR) QoL. A distinction can be made between "generic" and "disease-specific" PROMs. Generic PROMs relate to the entire population, while disease-specific PROMs refer to a specific disease [70].

In sarcoidosis, PROMs are mainly used in the context of clinical trials [9], but regular use of PROMs in our daily clinical practice can also be of added value for patient care. It may result in an earlier detection of disease progression, improvement of education, and a better communication between patients and healthcare providers [72]. Nevertheless, PROMs can be time consuming to complete in clinical practice; 1-item visual analogue scales have been proposed as reliable and quick alternative for use in daily practice [73]. In order to detect changes in PROM scores over time, the minimum clinically important difference (MCID) can be used. The MCID is the smallest difference in scores that reflects a meaningful change for a patient [56]. In clinical trials, the MCID is needed to assess whether an intervention leads to a clinically meaningful improvement in (HR)QoL for patients.

3.5.2. Generic PROMs used in sarcoidosis

Different generic PROMs are commonly used in sarcoidosis (Table 1). An advantage of generic PROMs is that outcomes in patients with sarcoidosis can be compared to patients with other chronic diseases, but also related to the overall population. As sarcoidosis is a complex disease, various symptoms relating to the different organ manifestations may be present. Thus, many other domain- or symptom-specific PROMs can be of added value, e.g. for dyspnea (modified Medical Research Council Dyspnea scale, Borg Dyspnea Score), depression (Hospital Anxiety and Depression Scale, Center for Epidemiologic Studies-Depression measure, Beck Depression Inventory), sleep apnoea (Epworth Sleepiness Scale), and eye (National Eye Institute Visual Function Questionnaire) or skin involvement (Skindex-29) [56,74]. For the evaluation of cough-related QoL, the Leicester cough questionnaire, consisting of a physical, psychological, and social domain, is commonly used in sarcoidosis [75]

One of the generic measures for HRQoL is the Medical Outcome Study 36-Item Short Form Health Survey (SF-36). This instrument contains 36 items in eight domains and results in two scores for physical (SF-36_PCS) and mental status (SF-36_MCS) [76]. Good correlation has been shown with sarcoidosis-specific PROMs [79]. Another generic tool is the EuroQol-5-5 L (EQ-5D-5L), which includes a visual analogue scale and 5 questions on a 5-point Likert scale. The EQ-5D-5L has been used in several studies in interstitial lung disease and sarcoidosis. A study that compared the EQ-5D-5L with the ILD-specific King's brief interstitial lung disease questionnaire, found a strong correlation between both PROMs [77].

The World Health Organization – Quality of Life 100 (WHOQOL-100) and the short form WHOQOL-BREF are both generic instruments to assess QoL [74,98,99]. The WHOQOL-100 is well established and validated in sarcoidosis, however, with 100 items in six domains completion of the questionnaire takes the longest [56]. The WHOQOL-BREF is validated in sarcoidosis as well, nevertheless, fatigue is not included in this questionnaire which makes it less relevant in sarcoidosis [99].

3.5.3. Disease-specific PROMs in sarcoidosis

Several PROMs have been developed to assess sarcoidosis-related symptom burden and HRQoL. Three PROMs have been specifically developed and validated to measure overall health status and/or HRQoL in sarcoidosis: the King's Sarcoidosis Questionnaire (KSQ), Sarcoidosis Health Questionnaire (SHQ), and Sarcoidosis Assessment Tool (SAT) [79,80,81]. Symptom-specific PROMs as Fatigue Assessment Scale (FAS) and Small Fibre Neuropathy Screening List (SFNSL) have also been developed for a sarcoidosis population [83,84] *(Table 1)*. The FAS is a 10-item questionnaire that evaluates both mental and physical fatigue in sarcoidosis. The MCID is a 4-point difference or 10 % change in score [100]. The SFNSL is a validated 21 item self-administered instrument that is useful to screen for the presence of SFN associated symptoms in sarcoidosis patients [84,101].

Fig. 1. Global overview of interventions to improve quality of life in sarcoidosis. For some interventions evidence is still lacking or scarce.

The SHQ was developed in 2002 [79]. Patients reflect on three domains: daily, physical and emotional functioning. The SHQ takes 10 min, is validated in different languages and has been used in many studies, but no MCID is available [56]. Additionally, the SHQ does not include certain organ systems as skin involvement and fatigue [81,102].

The KSQ takes some of the limitations of the SHQ into account and has a better validity for pulmonary sarcoidosis. Therefore, it has been recommended as standard PROM to assess HRQoL in patients with pulmonary sarcoidosis [56]. The KSQ consists of 29 items in different domains: general health, pulmonary, eye and skin involvement, and medication [80].

The SAT is based on selected measures from the Patient Reported Outcomes Measurement Information System (PROMIS), together with several newly developed sarcoidosis-specific measures. Organ specific subscales are available and can be used separately [81].

Many clinical trials in sarcoidosis use the St. George's Respiratory Questionnaire (SGRQ) [74,85]. Originally, the questionnaire was developed for chronic airway diseases. Thus, it is not specific for sarcoidosis and contains irrelevant questions.

4. Interventions to improve HRQoL in sarcoidosis

The interventions required to improve symptoms and HRQoL are multi-modal and include pharmacological and non-pharmacological interventions (Fig. 1) [103].

4.1. Pharmacological interventions to improve HRQoL

Pharmacological interventions directed to the active inflammatory component of disease may be regarded as disease modifying therapy [4], while pharmacological therapy directed to symptom palliation may be considered "non-disease modifying".

As mentioned before, the recently published clinical practice guidelines on the treatment of sarcoidosis emphasize that the decision of who and when to treat depends on two major factors: risk of death or organ failure and impact of disease on HRQoL [4]. A summary of immunomodulatory therapies and their role in improving HRQoL in sarcoidosis is provided in Table 2.

Table 2
Summary of immunomodulatory therapies and their role in improving HRQoL in sarcoidosis.

Drug Intervention	Study Design/ number of patients enrolled (n)	Intervention	Effect on HRQoL	HRQoL Instrument used
Dexamethasone *Vis* et al. [87]	RCT/n = 16	1 mg/day	Improved	SF-36
Prednisone *Judson* et al. [88]	Retrospective/ n = 114	Cumulative prednisone >500 mg/ year	Reduced	SHQ SAT
Methotrexate *Fang* et al. [89]	Retrospective/ n = 60	10–15mg/ weekly	Improved	SGRQ
Infliximab (Pulmonary sarcoidosis) *Baughman* et al. [90]	RCT/n = 138	3 mgKg or 5 mg/kg IV on weeks 0, 2 and every 6 weeks	No effect	SGRQ
Infliximab (Cutaneous sarcoidosis) *Baughman* et al. [91]	RCT/n = 26	3 mgKg or 5 mg/kg IV on weeks 0, 2 and every 6 weeks	No effect	SGRQ
Infliximab *Vorselaars* et al. [92]	Prospective/n = 56	5 mg/kg IV weeks 0, 2 and every 4 weeks	Improved	PGA SF-36
Adalimumab (Pulmonary sarcoidosis) *Sweiss* et al. [93]	Prospective/n = 11	40 mg SQ weekly	Improved	PGA
Adalimumab (Cutaneous Sarcoidosis) *Pariser* et al. [94]	RCT/n = 16	80 mg loading, followed by 40 mg weekly	Improved	DLQI
Golimumab *Judson* et al. [95]	RCT/n = 173	200 mg week 0, 100 mg weeks 4, 8, 12, 16, 20 and 24	No effect	SGRQ
RCI *Chopra* et al. [96]	Retrospective/ n = 300	Varying doses	Improved	Not stated
RCI *Baughman* et al. [97]	RCT/n = 16	40-units or 80-units of RCI twice a week	Improved	KSQ

DLQI = dermatology Life Quality Index, SF-36 = Short Form-36, PGA = Patient global assessment, SQRG = Saint George's Respiratory Questionnaire, KSQ = Kings Sarcoidosis Questionnaire, SHQ = Sarcoidosis Health Questionnaire, SAT = Sarcoidosis assessment tool, RCT = randomized controlled trial, RCI = Repository Corticotropin.

4.1.1. Disease modifying immunomodulatory therapy

Reduced HRQoL in sarcoidosis has been associated with active, untreated, or incompletely treated disease [18]. At all times, sarcoidosis disease modifying pharmacological therapy should be directed to those symptoms or aspects of disease resulting from active ongoing granulomatous inflammation, thereby always balancing the risks versus the expected benefits of treatment. When the decision is made to start disease modifying immunomodulatory treatments, the sarcoidosis clinical practice guidelines and a recently published Delphi consensus statement reiterate the stepwise approach to treatment beginning with systemic corticosteroids (CS) and stepping up to steroid sparing anti-inflammatory (non-biologic) agents followed by biologic agents for those who have severe or persistent disease [4,104].

4.1.1.1. Corticosteroids and HRQoL. Corticosteroids (CS) are the prototypical first-line therapy for sarcoidosis [4,104]. Prednisone and

prednisolone are the two most used corticosteroids; however, hydrocortisone and dexamethasone have also been used [4,87,105,106]. For patients with symptomatic sarcoidosis believed to be at risk for future mortality (or permanent disability) or who have a resultant impairment in HRQoL (due to active disease), the guidelines recommend that CS be initiated to improve or preserve organ function and restore HRQoL [4]. These recommendations are applicable to all organ manifestations of disease and include those with troubling pulmonary and extra-pulmonary manifestations [4].

A small, randomized study that enrolled 16 patients with pulmonary sarcoidosis found that low dose dexamethasone (given 1 mg/day or 6.5 mg/day prednisone equivalent for six months) was associated with improvement in HRQoL [107]. Patients who received dexamethasone had significant improvement in the SF-36 bodily pain and vitality domains and this was present as early as 3-months after initiation of therapy [107]. Conversely, a larger single-center retrospective study found that patients who received a cumulative prednisone dose of 500 mg or more in the preceding year ($\sim<$ 2 mg/day) had worse fatigue and worse HRQoL than those who received 500 mg or less [17]. Several other studies also found that glucocorticosteroids can negatively affect QoL [1,37]. There are no established initial doses of CS [88]; however, several observational studies have shown that treatment strategies associated with higher initial doses ($\geq$ 30 mg/day) are associated with significant toxicities and worse side-effects without concomitant therapeutic benefit [108–110]. Furthermore, as prolonged use of CS has also been associated with significant dose and duration dependent toxicities [111–114], the goal of therapy is to achieve a rapid taper to a minimum effective goal dose of <10 mg/day within 3–6 months [4,115]. In the dexamethasone study noted above, subjects who received dexamethasone had more significant weight gain (mean increase in body mass index of 3.3) compared to those who received placebo and this was evident as early as 3-months after initiation of therapy [107].

The most recent guidelines [4] recommend a prednisone/prednisone-equivalent starting dose of 20 mg/day with a rapid taper to a minimum effective goal dose of <10 mg/day within 3–6 months [4,115]. A strategy that combined a starting prednisone dose of 20 mg with rapid taper to 10 mg/day within 3.5 months was found to have lower cumulative prednisone doses and less toxicity compared to 40 mg/day without loss of therapeutic benefit [116].

4.1.1.2. Non-biologic immunosuppressive therapy and HRQoL. For patients whose disease remains uncontrolled or for whom symptoms (resulting in reduced HRQoL) persist while on minimal prednisone doses (goal dose <10 mg/day), the guidelines recommend addition of steroid-sparing non-biologic therapy with a goal of maintaining minimal prednisone doses [4]. For patients unable to taper prednisone (to goal <10 mg/day), or who develop significant steroid-related side effects, early initiation of second line steroid-sparing therapy paired with ongoing efforts to taper prednisone is recommended [4]. Second-line therapeutic agents may also be initiated concomitantly with corticosteroids for patients who have high risk life- or organ-threatening disease (such as cardiac sarcoidosis) or where prolonged steroid use is anticipated [4,115].

Methotrexate is the preferred second-line steroid-sparing agent with the most data supporting its use in sarcoidosis [4,115,117–120]. Methotrexate has shown benefit in improving HRQoL in sarcoidosis [89]. Fang and colleagues evaluated 60 patients with pulmonary sarcoidosis and observed that 80 % of patients who received methotrexate for at least 3-months responded favorably (had radiographic improvement) and there was a significant improvement in the HRQoL of responders [89]. Responders also had a significant decrease in corticosteroid doses [89]. Methotrexate is generally better tolerated than prednisone [119,89,121]. The most common adverse effects are gastrointestinal (nausea, vomiting) and infectious complications [119,89,121,122]. Kahlmann and colleagues found that 80 % of patients on prednisone reported side-effects versus 50 % of patients on methotrexate; and patients on prednisone were more likely to report multiple and more bothersome side-effects [121]. The treatment guidelines recommend a dose of 5 mg–15 mg given weekly [4] however, there is some suggestion that treatment with 15 mg/week (as compared to lower dose) is associated with more rapid regression of disease without concomitant increase in rate of serious adverse effects [123]. Multinational evidence-based guidelines regarding the use of methotrexate in sarcoidosis have been published [118]. There is some evidence that initial monotherapy with methotrexate may be as efficacious as initial therapy with prednisone fewer side effects [118,124,125] and a large randomized multinational study evaluating this treatment approach is ongoing [126].

Other second-line agents used in the treatment of sarcoidosis include Azathioprine, Leflunomide and Mycophenolate [4]. The data supporting the use of these latter second-line agents in sarcoidosis is weak and the decision on which agent to use is largely based on tolerance and side effect profile [4]. There are no studies evaluating their role in improving HRQoL in sarcoidosis.

4.1.2. Biologic immunosuppressive therapy and HRQoL

Anti-TNF-α Therapy and HRQoL

For patients who remain symptomatic and/or have progressive disease despite optimal doses or who develop significant toxicity or intolerance to second-line therapy, the guidelines recommend addition of infliximab or adalimumab to preserve organ function and to improve HRQoL [4]. Infliximab and adalimumab are inhibitors of tumor necrosis factor alpha (TNF-α) and are considered third-line therapy for sarcoidosis [4].

Infliximab is the preferred third-line agent and has the most data supporting its use in sarcoidosis [4,115,127]. Infliximab has been shown to be effective in patients with pulmonary and extra-pulmonary sarcoidosis [90,91,128,129]. In a large, multi-national randomized trial that included over 130 patients with chronic symptomatic pulmonary sarcoidosis randomized to receive intravenous infusions of infliximab (versus placebo), Baughman and colleagues observed a significant improvement in lung function; however, there was no associated improvement in HRQoL or dyspnea scores [90]. There was also no change in HRQoL scores in the subset of patients with chronic cutaneous sarcoidosis despite improvement in skin lesions [91]. Contrary to these findings, a prospective observational study by Vorselaars and colleagues found that patients with severe pulmonary sarcoidosis refractory to first- and second-line therapy treated with infliximab had a significant improvement in HRQoL; and this was in addition to improvement in pulmonary function, cutaneous lesions, and resolution of 18-FDG uptake on PET-CT imaging [92]. HRQoL was assessed by the patient global assessment (PGA) and the physical functioning score on the SF-36 questionnaire; scores on both questionnaires improved after 26-weeks of Infliximab given as 5 mg/kg at weeks 0, 2 and every 4 weeks [92]. The reasons for the divergent results from the two studies are unclear – but may be related to the population of patients studied and the dose of medication used [90,92]. Lower mean trough levels were achieved in the study of Baughman et al., and a subsequent posthoc analysis revealed that patients with more chronic disease and those with worse baseline dyspnea and HRQoL scores derived more benefit from infliximab [90]. Infliximab is generally well tolerated; however, there is a significant risk of allergic reactions and infectious complications – most commonly pneumonia [90,92,130]. A recently published systematic review found that the mean weighted rate of adverse events in sarcoidosis patients treated with infliximab was 39.9 per 100 patient-years [131].

Adalimumab is a non-chimeric human monoclonal antibody to TNF-α. Unlike Infliximab, it is given subcutaneously and can be self-administered [132]. There is some suggestion that it is associated with less toxicity and may be better tolerated than infliximab [130]; however, data in support of its efficacy and experience in sarcoidosis is less robust

[4].

Several studies have shown an improved HRQoL in patients with sarcoidosis treated with adalimumab [93,94]. An open label prospective study of adalimumab in 11 patients with refractory pulmonary sarcoidosis found that all patients reported an improved HRQoL after 24-weeks of adalimumab given as a 40 mg weekly subcutaneous injection [93]. Seven patients reported symptomatic improvement (in dyspnea) and pulmonary function improved or stabilized in all patients. A similar size prospective study in patients with cutaneous sarcoidosis also found that patients who received an 80 mg loading dose of adalimumab followed by a 40 mg weekly maintenance dose also had improvement in skin lesions and HRQoL as assessed by the dermatology life quality index [94]. Other studies have also shown that adalimumab improved fatigue scores in patients with refractory uveitis [133].

Other TNF-α inhibitors have been evaluated in patients with sarcoidosis however they have not been found to be effective. A study that evaluated Etanercept (a TNF receptor antagonist) in patients with chronic progressive pulmonary sarcoidosis was terminated early because an excessive number of patients experienced disease progression while taking etanercept [134]. A large retrospective study that compared outcomes in over 120 patients treated with various TNF inhibitors showed that only 23 % of patients who received etanercept improved and 39 % had disease progression while on therapy [135]. Golimumab was also found to lack efficacy in a large phase II randomized placebo-controlled study that enrolled over 170 patients with chronic pulmonary and cutaneous sarcoidosis [95]. Although treatment was well tolerated, golimumab did not improve pulmonary function, 6-min walk distance or HRQoL [95]. Neither etanercept nor golimumab is recommended in patients with sarcoidosis [4].

4.1.3. Other biologic immunomodulatory therapy and HRQoL

Other immunomodulatory agents have been used in sarcoidosis patients who are refractory to, or intolerant of TNF inhibitors [4]. Rituximab, Repository corticotropin (RCI), Tofacitinib and Apremilast have been advocated as fourth-line investigational therapy in patients who have severe, persistent, or progressive disease despite use of third line therapy nonetheless, data in support of their use in sarcoidosis is very weak [4]. Several small studies suggest that Rituximab may be useful in patients with advanced pulmonary, ocular, neurologic and cardiac sarcoidosis [136–139]; however, its efficacy on sarcoidosis associated HRQoL has not been evaluated.

RCI is a naturally sourced complex mixture of adrenocorticotropic hormone analogs and other pituitary peptides that was initially approved for treatment of sarcoidosis in the 1950s [140]. RCI is only available in the US. Several studies suggest that RCI is steroid-sparing and associated with overall benefit in patients with advanced pulmonary and extra pulmonary sarcoidosis [96,97,141]. In a large retrospective study that included over 300 patients with symptomatic pulmonary and extra pulmonary sarcoidosis who received at least 6-months of RCI, treating physicians assessed that over 95 % of patients felt improved and this included 32 % of patient who reported improved HRQoL [96]. Baughman and colleagues also evaluated the efficacy of RCI in 16 patients with chronic pulmonary sarcoidosis refractory to other therapy and found that it was steroid sparing and associated with improvement in pulmonary function and HRQoL [97]. Patients received either 40-units or 80-units of RCI twice a week and there was significant improvement in several domains of the KSQ after seven weeks of therapy and this was sustained at the end of 24 weeks [97]. There was also a significant improvement in fatigue that was sustained after 24 weeks [97]. RCI has an adverse effect profile that is similar to that of corticosteroids and may not be efficacious in all patients [141,142]. Older patients with multi-organ involvement and higher symptom burden (worse dyspnea, fatigue and HRQoL) are more likely to respond favorably to RCI [143]. Guidelines for the use of RCI in sarcoidosis have been published [144].

Tofacitinib is a Janus Kinase and signal transducer and activator of transcription (JAK-STAT) inhibitor that has been shown in some case reports and case series to be beneficial in patients with refractory pulmonary and cutaneous sarcoidosis [145–152]. The reports suggest improvement in pulmonary symptoms and cutaneous lesions, however none of the studies reported on the effect of tofacitinib on HRQoL.

4.1.3.1. PAH therapy and HRQoL.

The World Symposium on Pulmonary Hypertension concluded in 2019 that there was insufficient data to make routine recommendations for therapy in sarcoidosis-associated pulmonary hypertension (SAPH) [153]. More recent guidance by the World Association of Sarcoidosis and Granulomatous Diseases (WASOG) suggests that treatment decisions in patients with SAPH be made on a case-by-case basis by a multidisciplinary team in conjunction with a sarcoidosis and PH expert [25].

There are no randomized studies evaluating the role of PAH therapies in HRQoL of patients with SAPH. Available studies are small and largely retrospective; however, three prospective studies that evaluated the role of PAH therapy in SAPH did not find a consistent effect of therapy on HRQoL [154–156]. Baughman and colleagues evaluated 22 patients with pre-capillary SAPH and found that inhaled prostacyclin (Iloprost) given as a 5 mcg inhalation every 2–3 h for 4 months was associated with significantly improved pulmonary hemodynamics and HRQoL as assessed by the SGRQ activity score [154]. On the contrary, Judson and colleagues evaluated the role of ambrisentan in patients with SAPH and observed that over 50 % of patients dropped out of the study and although there was some improvement in the WHO Functional class and HRQoL of subjects who completed the study (10/21), this did not achieve statistical significance [155]. Of note, the high dropout rate was attributable to poor medication tolerance [155]. Finally, Ford and colleagues performed an open label trial of tadalafil in SAPH at two academic medical centers and found that there was no improvement in symptom burden (dyspnea), exercise tolerance or HRQoL (as assessed by both the SGRQ and SF-36) in those who completed the study [156]. 12-patients were enrolled however 5 patients (42 %) dropped out of the study largely as a result of poor medication tolerance [156].

These are all small observational studies and larger well-designed studies are needed to better elucidate the role of PAH therapies on the prognosis, symptomatology and HRQoL of patients with SAPH.

4.1.3.2. Anti-fibrotic therapy and HRQoL.

10–30 % of patients with pulmonary sarcoidosis develop fibrotic lung disease and this is often complicated by respiratory failure and significantly increased mortality [157–160]. These patients also have reduced HRQoL [2,161]. The mechanisms underlying the transition from chronic granulomatous inflammation to progressive fibrosis in sarcoidosis are not fully understood – however recently published work suggests that in addition to unbridled inflammation, patients who develop fibrosis also share gene and protein expressions that are similar to patients with idiopathic pulmonary fibrosis [161–165].

The INBUILD trial evaluating the role of the anti-fibrotic agent nintedanib (an oral tyrosine kinase inhibitor) in patients with progressive pulmonary fibrosis (PPF) found that patients with pulmonary fibrosis (regardless of radiographic pattern or etiology of fibrosis) experienced a deceleration in the rate of lung function decline; however, there was no meaningful change in HRQoL as assessed by the King's interstitial Lung Disease (K-BILD) questionnaire [166,167]. In the same study, the novel PROM Living with Pulmonary Fibrosis (L-PF) was used, which suggested that nintedanib reduced worsening of cough, dyspnea and HRQoL [168].

Although the INBUILD study included patients with PPF regardless of etiology, <2 % of the study population had sarcoidosis [166,167], and a subsequent systematic review did not find a clear benefit of nintedanib in the subgroup of patients with fibrotic pulmonary sarcoidosis [169]. There are no studies that have specifically evaluated the role of nintedanib in patients with fibrotic pulmonary sarcoidosis. A small feasibility

study that evaluated the role of pirfenidone (another anti-fibrotic agent) in fibrotic pulmonary sarcoidosis did not find any effect of pirfenidone on HRQoL in sarcoidosis patients with >20 % fibrosis on high resolution CT scan [170]. This study enrolled only 16 patients and was terminated early due to the COVID-19 pandemic [170]. The role of anti-fibrotic therapy in fibrotic pulmonary sarcoidosis is largely unknown and large well designed randomized studies are needed to better elucidate this.

4.2. Symptomatic pharmacological treatment

4.2.1. Role of neurostimulants in sarcoidosis associated fatigue and reduced HRQoL

The sarcoidosis treatment guidelines recommend that patients with persistent troublesome fatigue after optimization of sarcoidosis therapy and pulmonary rehabilitation/inspiratory muscle training be considered for treatment with Dexmethylphenidate and Armodafinil [4]. These therapies have been evaluated in two randomized control trials and one observational study [171–173].

Dexmethylphenidate hydrochloride (d-MPH) is a central nervous system (CNS) stimulant that is FDA approved for the treatment of Attention-deficit/hyperactivity disorder and shown to be effective in other chronic diseases [174–176]. A small randomized controlled cross-over trial that evaluated the role of d-MPH in patients with pulmonary sarcoidosis and troublesome fatigue despite adequate systemic therapy found that d-MPH was well tolerated and associated with significant and clinically relevant improvement in fatigue and HRQoL [171]. There was no difference in toxicity between drug and placebo, and 36 % of patients had improvement in fatigue which is similar to reported rates in patients with cancer chemotherapy related fatigue [171]. A more recently published double blind placebo-controlled study reinforced that methylphenidate was safe and well tolerated in sarcoidosis patients [177]. 98 % of patients randomized to the methylphenidate arm remained compliant with their medications, and although there was no between-group difference in fatigue and HRQoL scores at the end of 24-weeks, a greater percentage of patients in the methylphenidate arm accurately predicted their allocated treatment than those receiving placebo [177]. The study authors concluded that a large multi-center trial is both necessary and feasible to establish the role of methylphenidate in sarcoidosis associated fatigue [177,178].

Armodafinil has also been shown to be effective in sarcoidosis associated fatigue [172]. 15 patients with persistent fatigue despite adequate sarcoidosis therapy were randomized to receive armodafinil (versus placebo) 150 mg daily for four weeks followed by 250 mg daily for another four weeks [172]. Patients randomized to armodafinil had a significant improvement in both the FAS and FACIT-F scales and this effect was seen even in patients who did not have excessive daytime somnolence [172]. Armodafinil also significantly improved fatigue on the SF-36 vitality score but it did not have any effect on other HRQoL measures; nonetheless, the study was not powered to detect changes in HRQoL [172].

Both Armodafinil and methylphenidate are generally well tolerated, but contraindicated in people with a history of psychiatric disorders, cardiovascular or cerebrovascular disease. Known side effects include addiction, insomnia, headaches, anxiety, and tachycardia [4,173,179].

4.2.2. Sarcoidosis associated small fiber neuropathy and reduced HRQoL in sarcoidosis

There are no large randomized or prospective studies of medications or therapeutic interventions to guide the treatment of SFN and the recently published guidelines declined to make any management recommendations due to insufficient data. Several studies have evaluated the role of IVIG [180,181], anti-TNF therapy [180–184] and Cibinetide [185–188] in sarcoidosis patients with SFN.

Cibinetide (ARA-290) a nonerythropoietic peptide is an innate repair receptor agonist with anti-inflammatory and neuroprotective effects [188–190]. Three randomized placebo-controlled trials of cibinetide in SSFN suggest that it is effective, safe, and well tolerated [186,187,191]. Heij and colleagues evaluated the role of cibinetide in sarcoidosis patients with SFN and found that at the end of four weeks, patients who received cibinetide (given as a 2 mg infusion three times per week) versus placebo had a significant improvement in the severity and frequency of symptoms and in HRQoL as assessed by improvement in the pain and physical functioning dimensions of the SF-36 [187]. Other studies found that in addition to improvement in symptoms, cibinetide is disease modifying [186,191]. Patients randomized to cibinetide had a significant increase in the abundance of small nerve fibers in the cornea and skin [186,191] and the effects of cibinetide on symptom burden, HRQoL and small fiber density persisted for up to 12 weeks after the medication was stopped [191]. Cibinetide is currently not approved by the US Food and Drug Administration Agency for use and is currently not commercially available for clinical use.

Other studies have found that intravenous immunoglobulin (IVIG) given alone or in conjunction with anti-TNF agents also improved symptoms in patients with SSFN; however, the mechanism of action and the magnitude of effect are unclear [4,180,181].

4.2.3. Cough suppressants, anesthetics, and other palliative therapy to improved HRQoL

Attention to palliation of cough as a symptom in sarcoidosis is necessary to improve HRQoL. While immunosuppressive therapy may be indicated in those for whom cough has caused reduced HRQoL, such therapy may not always be desirable or necessary if overall disease burden is minimal.

An open label non-controlled study that evaluated the role of azithromycin in sarcoidosis patients with chronic cough found that it improved cough count, cough severity, and overall HRQoL [192]. At the end of 3-months, patients receiving 250 mg azithromycin daily had a significant reduction in cough frequency (50 %), cough severity and urge to cough and this was independent of baseline steroid therapy [192]. There was also a significant improvement in the LCQ, KSQ-general health status and Lung subdomain scores [192]. Absolute changes in cough counts correlated with changes in the LCS and KSQ-general health status scores suggesting that an improvement in cough directly correlated with improvement in HRQoL [192].

Additional studies evaluating the role of cough suppressants are necessary to better understand the role of these medications in sarcoidosis. Non-sarcoid causes of cough in sarcoidosis patients such as gastroesophageal disease should also be identified and addressed.

Attention to identifying and addressing psychological symptoms (anxiety and depression) and chronic pain in sarcoidosis is important to improve HRQoL in patients [61]. To treat these debilitating symptoms collaborating with other medical specialists in a multidisciplinary approach is needed.

4.3. Non pharmacological intervention to improve HRQoL

Several physical and psychological based treatments have been investigated to improve patient-relevant outcomes in sarcoidosis. Many studies included fatigue as their primary endpoint; (HR)QoL was often reported as a secondary endpoint. Table 3 gives an overview of all studies that investigated the effect of non-pharmacologic treatment options on QoL (as primary or secondary outcome) in patients with sarcoidosis.

4.3.1. Physical activity training and pulmonary rehabilitation

Physical training and pulmonary rehabilitation (PR) are considered to be an important element of comprehensive care in patient with chronic pulmonary diseases and recommended by international guidelines [202]. PR consists of exercise training, combined with education sessions to improve behavioral change and self-management [202]. PR is most commonly conducted in an outpatient setting, but can also be

Table 3
Studies evaluating efficacy of non-pharmacological interventions to improve QoL in sarcoidosis.

Author	Design	Number of patients	Duration	Program	Results
Physical-activity based modalities					
Hupmann et al, 2012 [193,194]	Retrospective cohort study	−402 patient with ILD −50 patients with sarcoidosis	−30 days inpatient program −5.5 h a day - four to five days a week	- Exercise and breathing training - Group education	- Improved exercise capacity (+34 m on 6 MWT) - Improved QoL (SF-36 questionnaire score: physical sum score + 6, SD + 1; mental sum score + 10, SD + 1)
Marcellis et al, 2015 [195]	Prospective study	−24 patients with sarcoidosis −18 completed program (75 %) and were included in analysis	−13 weeks outpatients physical training program −1 h training three times a week	- Endurance training - Peripheral muscle training	Primary endpoint: Improvement in fatigue (mean difference in FAS score −2.7, 95 % CI -4.4 to −1.1) Secondary endpoints: - Improved health status (Mean difference psychological health domain WHO QOL-BREF -0.9, 95 % CI 0.2 to 1.7 - Improvement in dyspnea (MRC dyspnea score −0.4, 95 % CI -0.8 to −0.1) - Improved exercise capacity (Mean change in 6 MWD +34.6 m; 95 % CI 20.3 to 49.0) - Improvement in quadriceps muscle strength
Lingner et al, 2018 [196]	Prospective cohort study	−296 patients	−3 weeks in patients PR		Primary endpoints: - Improved exercise capacity (6 MWD +39.8 m) - Improved QoL, SGRQ showed significant improvements in all 3 domains (symptom score -8.28, activity -7.76, impact -5.79) Secondary endpoints: - Improved QoL, SF-36 (physical health + 2.0, mental health + 5.3) - Improved fatigue (FAS -4.09) - Improved anxiety and depression (HADS anxiety −1.88, HADS depression −1.24)
Naz et al, 2018 [197]	Randomized controlled trial	18 patients with stage 3 and 4 sarcoidosis −9 patients received supervised exercise training −9 patients received usual care	12 weeks of supervised exercise training	-Breathing exercises -Endurance training -Strength training	Primary endpoint (within group difference in intervention group) -Improved exercise capacity median 40 (IQR 31–62) m in the intervention group Secondary endpoints (within group difference in intervention group) -Improved QoL (SGRQ symptoms median + 8 (IQR -20 to 5), activity -23 (-36 to 6), impact -14 (-24 to 0), total -19 (-25 to 1) - Improved anxiety (HADS median −2 (IQR-4 to 1) - Improved fatigue (FSS median −7 (IQR -10 to 2) -Improved dyspnea (mMRC median −1 (−1.5 to 0) - Improved leg fatigue, modified Borg Scale (median −2 (IQR -2 to 0)
Guber, respiration, 2021 [198]	Prospective cohort study	−52 recruited for trainings program −38 patient returned for follow-up visit after 6 months	−12-week training program of a twice-weekly 90 min work-out	-Balance, weight, flexibility, and range of motion exercises -Aerobic exercises -Strength exercises	- Improved exercise capacity (VO2max (1.8 ± 2.3 mL/kg/min, $p = 0.002$) - Improved dyspnea (mMRC −0.3 ± 0.8, $p = 0.03$) - Improved QoL (SGRQ scores −3.87 ± 10.4, $p = 0.03$) Long-term follow: beneficial effects on exercise capacity and QoL maintained during 6 months follow-up.
Kullberg, 2020 [199]	Prospective study	−12 patients −11 completed the program and were included in analysis	−12 week training progam	- High-intensity resistance training twice a week - Daily inspiratory muscle training	- SGRQ and mMRC pointed in direction of improvement at first follow-up training, but did not reach significance - FSS improved significantly. - No absolute numbers were provided in this study Changes in scores at second follow up were small and non-significant
Psychological-based modalities					
Saketkoo et al 2018 [200]	Prospective study	26 participants (23 patients with sarcoidosis and three family members)	Single 45-min workshop in mindfulness techniques	Exercises of 3–15 min focusing on body sensation and breath -exposure to emotion and thought concepts	- Improvement in all physical and psychological symptoms - Statistically significant difference in pre-/post-mindfulness well-being ($p = 0.003$) and motivation ($p = 0.005$)
Kahlmann and Moor et al, 2023 [201]	Randomized controlled trial	93 participants - Intervention group 46 - Control group 47	12-weeks of eMBCT	-Psycho-education - Mindfulness exercises 30 min, 6 days/week - Fatigue diary	Primary endpoint: -Mean change in FAS score after eMBCT was −4·53 (SD 5·77; $p < 0·0001$) in the eMBCT group and −1·28 (3·80; $p = 0·026$) in the control group -Between-group difference was 3·26 (95 % CI 1·18 to 5·33; $p = 0·0025$). Secondary endpoints: -Significant improvement in KSQ- General Health Status (mean between-group difference 6.28 points, 2.51–10.06, $p = 0.002$)

(*continued on next page*)

Table 3 (*continued*)

Author	Design	Number of patients	Duration	Program	Results
					- Significant improvement in anxiety (between-group difference 1.69 points, 0.22–3.16, p = 0.025) and depressive symptoms (1.52, 0.08–2.59, p = 0.039) measured with HADS. - Effects persisted after 3 months

Effects of the intervention on HRQoL are provided in bold. 36-item short-form health survey (SF-36) questionnaire score, 6-min walk distance (6 MWT), fatigue assessment scale (FAS), World Health Organization Quality of Life-BREF assessment instrument (WHOQOL-BREF), Saint George's Respiratory Questionnaire (SGRQ), hospital anxiety and depression questionnaire (HADS), fatigue severity scale (FSS), modified Medical Research Council Dyspnea Scale (mMRC), King's sarcoidosis questionnaire (KSQ), Hospital Anxiety and Depression Scale (HADS).

conducted in an inpatient or telerehabilitation setting. Most evidence of the beneficial effects of physical activity training and PR is derived from studies in chronic obstructive lung disease (COPD), but studies in sarcoidosis also found generally positive effects. Nevertheless, studies are difficult to compare due to heterogeneity in study population, duration and content of the program and varying endpoints.

The first large trial that investigated the effect of PR in patients with interstitial lung disease was conducted by Huppmann and colleagues in 2012 [193]. This retrospective cohort study included 402 patients with interstitial lung disease, including 50 patients with sarcoidosis. All patients underwent a standardized inpatient PR program, which consisted of supervised exercise training, breathing exercises, and groups education session, four to five times a week. In the subgroup of patients with sarcoidosis, a significant improvement in HRQoL measured with the SF-36 was reported [194].

Marcellis and colleagues prospectively investigated the effect of a 13-week physical training program on fatigue in 24 patients with sarcoidosis [195]. The authors found a significant improvement of FAS scores after completion of the program. Furthermore, they found an improvement in WHOQOL-BREF psychological health domain. In 2019, a large prospective trial assessed the effect of a 3-week pulmonary rehabilitation program on QoL and clinical outcomes in 296 patients with sarcoidosis [196]. SGRQ and SF-36 scores showed improvement in all domains. Other observed benefits were improvement in exercise capacity, fatigue, anxiety and depression. One small RCT investigated the effect of a 12-week supervised exercise training in patients with Scadding stage III and IV sarcoidosis [197]. The exercise training consisted of breathing exercises, endurance training, and strength training. Both physical parameters (6-min walking distance) and HRQoL significantly improved.

Data on long-term effects of PR and physical training in sarcoidosis are scarce and larger well-designed trials are needed. Guber and colleagues showed that improvement in QoL and exercise capacity persisted at 6 months, after a 12-week training program in 38 patients with sarcoidosis [198]. In contrary, Kullberg and colleagues did not find long-term benefits of a 12-week training program in 11 patients with sarcoidosis, which might be related to the small sample size [199].

Recently, a Cochrane review evaluated the effect of tele-rehabilitation in chronic lung diseases [203]. The authors found that tele-rehabilitation had similar beneficial effect on HRQoL and other clinical outcomes, as center-based PR. Whether this also account for patients with sarcoidosis remains to be elucidated. Recently, a pilot RCT investigated the effect of telerehabilitation in patients with sarcoidosis. Although this online program did not improve exercise capacity or HRQoL, there was a high patient satisfaction and acceptable adherence [204]. Larger randomized controls are needed to assess the effect of tele rehabilitation in patients with sarcoidosis.

4.3.2. Psychological-based treatment modalities

As discussed before, patients with sarcoidosis often experience burdensome symptoms of fatigue, anxiety and depression, which negatively impact QoL. Although it may seem logical that patients could benefit from psychological treatment, this has not been extensively investigated in sarcoidosis. A small pilot study showed that a single 45-min mindfulness workshop improved fatigue and psychological symptoms in 26 patients with sarcoidosis [200].

Recently, a multicenter RCT investigated the effect of online mindfulness-based cognitive therapy (eMBCT) on fatigue in 93 patients with sarcoidosis. The eMBCT program consisted of 8 sessions during approximately 12 weeks. Patients received online written education about a specific theme each week via an online platform, performed mindfulness exercises, and communicated asynchronously about their experiences with their treating psychologist. A significant and clinically relevant improvement in fatigue was reported directly after 12 weeks of eMBCT, which persisted after 3 months follow-up. eMBCT significantly improved HRQoL measured with the general health domain of the KSQ, and anxiety and depression measured with the HADS after the program and 3 months later [201].

A feasibility randomized clinical trial assessing the effect of a Health app for sarcoidosis-associated fatigue is currently ongoing [205]. The health care app encourages patients to conduct breathing awareness meditation and contains education to improve self-efficacy. Secondary end-points of this trial are fatigue, stress, and HRQoL.

The choice of program (e.g. physical training or psychological based) should be tailored to the patient's needs and discussed with the patients to ensure the highest buy in. It seems intuitive that people with more physical impairment might benefit more of physical training and PR, whereas people with more psychological symptoms might benefit more from psychological interventions, but this remains to be elucidated.

4.3.3. Patient education and support groups

Better disease education, peer support and practical support has been mentioned by patient as important needs to improve quality of care [6]. Evidence whether this improves HRQoL is lacking. Nonetheless, it seems likely that improving education, general awareness of sarcoidosis in society, and support programs for patients and partners could have a positive effect on QoL. Patient associations, such as the FSR and Sarcoidosis UK provide disease education and organize peer support groups, which can be of added value for patients and their families. Referral to local or national patient associations should therefore be integrated in daily clinical practice.

4.3.4. Other non-pharmacological interventions to improve quality of life

In patients with fibrotic sarcoidosis with hypoxemia, supplemental oxygen can be considered. One RCT showed that ambulatory oxygen improves quality of life in patients with fibrotic lung disease with an oxygen saturation of 88 % or less on the 6 min walking test [103]. This study included a few patients with fibrotic sarcoidosis. Although the potential benefit of a healthy diet and certain nutritional components have been proposed in sarcoidosis, studies investigating efficacy are lacking [206].

5. Conclusion

Quality of life is impaired for many patients with sarcoidosis. Both patients and healthcare providers struggle to find optimal ways to improve (HR)QoL. Improving quality of life is prioritized as most important treatment aim by many patients. Determinants of HRQoL are

diverse in sarcoidosis and mirror the heterogeneous nature of the disease. Whilst treating the underlying inflammation that drives the disease may improve HRQoL for some patients, there is no strong relation between inflammation, organ impairment and HRQoL in many other patients. Structural use of PROMs in clinical care and research is needed to better identify needs and gain more insights into the effects of treatments on patient's wellbeing. Besides optimizing disease modifying and symptomatic pharmacological treatment, with a clear assessment of risks and benefits for each patient, physical training, PR programs and cognitive behavioral therapy have shown to have a positive impact on quality of life, fatigue, anxiety, and depression in patients with sarcoidosis. A multidisciplinary approach that takes into account individual patients' needs and preferences is probably the best way to identify the optimal interventions to improve quality of life for each individual with sarcoidosis.

Declaration of competing interest

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