BEYOND IPF

Chairs: *Marco Confalonieri (Trieste, Italy), Paola Faverio (Monza, Italy)*

15.10 New therapies for LAM *Sergio Harari (Milan, Italy)*
15.30 Non-CF bronchiectasis *James Chalmers (Dundee, UK)*
15.50 Sarcoidosis treatment practice guidelines *Katerina Antoniou (Heraklion, Greece)*

Katerina Antoniou, FERS
Head ERS Assembly for ILDs
Professor of Respiratory Medicine
School of Medicine, UOC

Introduction & background

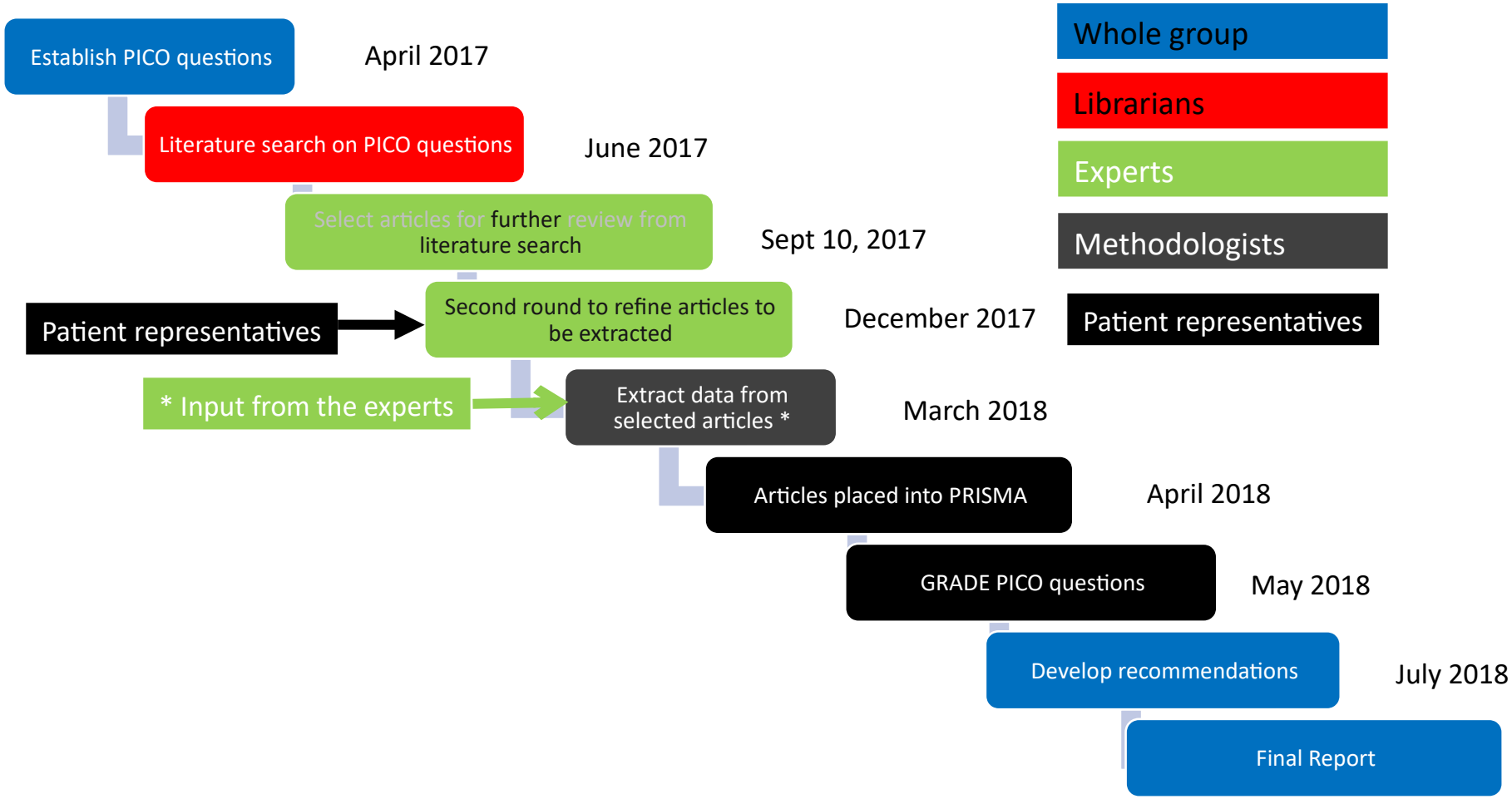
- The ERS task force for treatment of sarcoidosis began in April 2017
- Final approval of the task force recommendations was made April 2021
- The task force developed GRADE recommendations and comments regarding various aspects of sarcoidosis.

ERS Task Force Clinicians

Valeyre	Dominique	Paris	France
Baughman	Robert	Cincinnati	USA
Israel-Biet	Dominique	Paris	France
Wells	Athol	London	UK
Rottoli	Paola	Siena	Italy
Culver	Dan	Cleveland	USA
Wuyts	Wim	Leuven	Belgium
Drent	Marjolein	Bennekom	Netherland
Antoniou	Katerina	Heraklion	Greece
Grütters	Jan	Utrecht	Netherland
Lower	Elyse	Cincinnati	USA
Nunes	Hilario	Bobigny	France
Judson	Marc	Albany	USA
Bonella	Francesco	Essen	Germany

ERS Task Force

Methodologist			
Korsten	Peter	Gottingen	Germany
Ouellette	Dan	Detroit	USA
Mathioudakis	Alexander	Manchester	UK
Tonia	Thomy	ERS	
David	Rigau	ERS	
Nagavci	Blin	ERS	
Patient Representatives			
Martone	Filippo		Italy
Quadder	Bernd		Germany
Spitzer	Ginger	Chicago	USA


Establish PICO questions
April 2017
Literature search on PICO questions
June 2017
Select articles for further review from literature search
Sept 10, 2017
Patient representatives
Second round to refine articles to be extracted
December 2017
* Input from the experts
Extract data from selected articles *
March 2018
Articles placed into PRISMA
April 2018
GRADE PICO questions
May 2018
Develop recommendations
July 2018
Final Report
Whole group
Librarians
Experts
Methodologists
Patient representatives

Eur Respir J. 2021 Jun 17;2004079. doi: 10.1183/13993003.04079-2020. Online ahead of print.

ERS clinical practice guidelines on treatment of sarcoidosis

Robert P Baughman [1], Dominique Valeyre [2], Peter Korsten [3], Alexander G Mathioudakis [4], Wim A Wuyts [5], Athol Wells [6], Paola Rottoli [7], Hiliaro Nunes [8], Elyse E Lower [9], Marc A Judson [10], Dominique Israel-Biet [11], Jan C Grutters [12 13], Marjolein Drent [12 14 15], Daniel A Culver [16], Francesco Bonella [17], Katerina Antoniou [18], Filippo Martone [19], Bernd Quadder [20], Ginger Spitzer [21], Blin Nagavci [22], Thomy Tonia [23], David Rigau [24], Daniel R Ouellette [9]

Affiliations + expand

PMID: 34140301 DOI: 10.1183/13993003.04079-2020

PICO

- Population
- Intervention
- Control
- Outcome

N	Section	Population	Intervention (s)	Clinicans	Methoidologists	Patients
1	Pulmonary sarcoidosis	Patients with pulmonary sarcoidosis	Corticosteroid treatment	Athol Wells, Paola Rottoli	Alexander Mathiou	Fillipo Martone
2	Pulmonary sarcoidosis	Patients with pulmonary sarcoidosis	Switch to immunosupressive treatment	Dominique Valeyre, Elyse Lower	Alexander Mathioudakis	Bernd Quadder
3	Extra-pulmonary sarcoidosis	Patients with extra-pulmonary sarcoidosis	Corticosteroid treatment	Marjolein Drent, Francesco Bonella	Peter Korsten	Ginger Spitzer
4	Extra-pulmonary sarcoidosis	Patients with extra-pulmonary sarcoidosis	Switch to immunosupressive treatment	Robert Baughman, Katerina Antoniou	Dan Oullette	Bernd Quadder
5	Cardiac sarcoidosis	Patients with cardiac sarcoidosis	Systemic immunosuppressive treatment	Dan Culver, Hilario Nunes	Peter Korsten	Fillipo Martone
6	Neuro sarcoidosis	Patients with neurologic sarcoidosis	Systemic immunosuppressive treatment	Dominique Israel-Biet, Marc Judson	Peter Korsten	Ginger Spitzer
7	Fatigue	Patients with sarcoidosis associated fatigue	Anti-inflammatory, neurostimulants, exercise, other	Wim Wuyts, Jan Grütters	Dan Oullette	Bernd Quadder
8	Small fiber neuropathy	Patients with small fiber neuropathy	Anti-inflammatory, IV Ig, GABA analogues, ARA-290	Dan Culver, Marjolein Drent	Alexander Mathioudakis	Ginger Spitzer

Individual PICOs

In patients with pulmonary sarcoidosis, should glucocorticoid treatment be used versus no immunosuppressive treatment?
In patients with pulmonary sarcoidosis, should one add immunosuppressive treatment or remain on glucocorticoid treatment alone?
In patients with cutaneous sarcoidosis, should glucocorticoid treatment be used versus no immunosuppressive treatment?
In patients with cutaneous sarcoidosis, should one add other immunosuppressive treatment when treatment with glucocorticoids has not been effective?

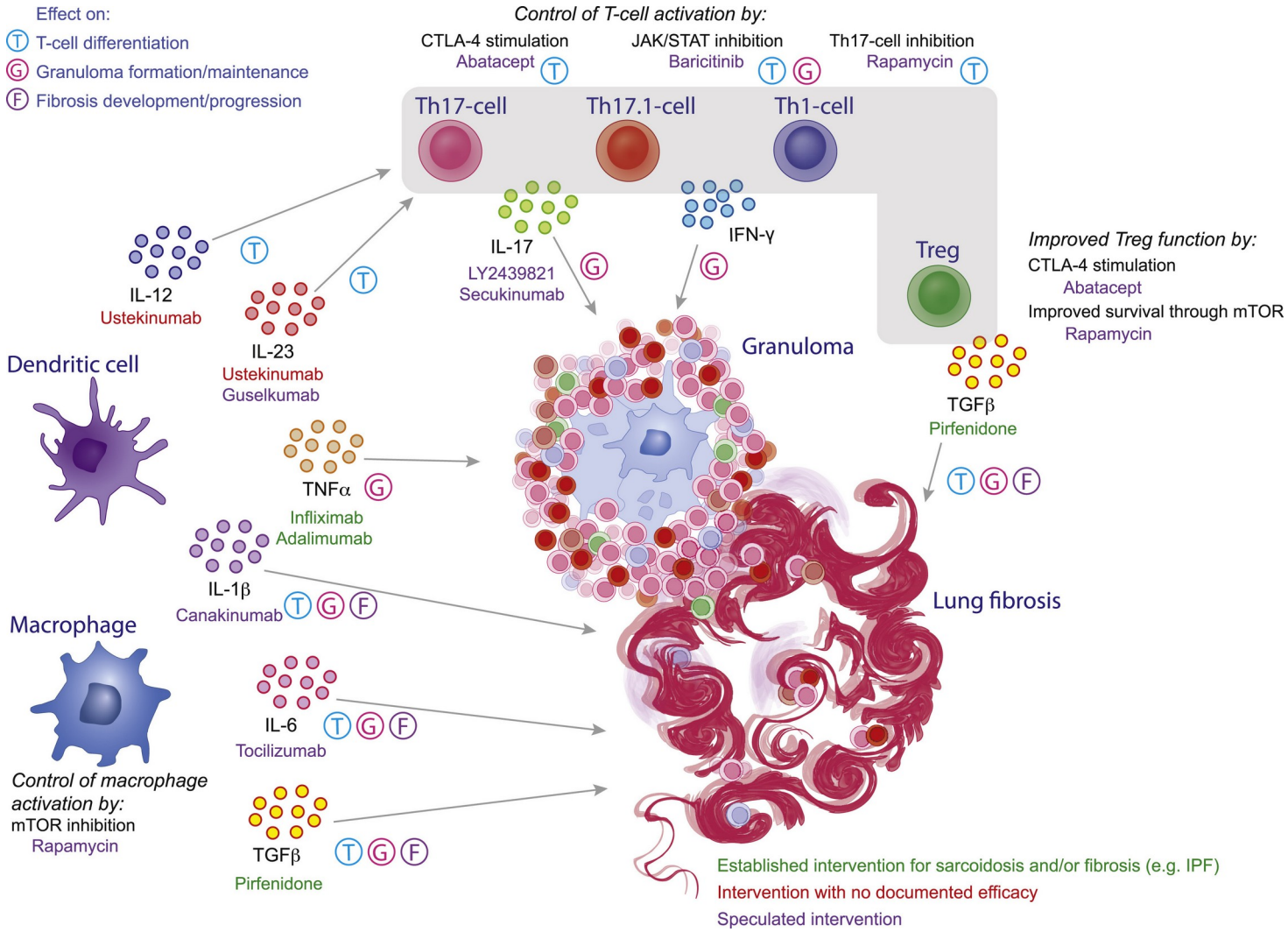
Individual PICOs

In patients with clinically relevant cardiac sarcoidosis, should glucocorticoids with or without other immunosuppressives versus no immunosuppression be used?
In patients with neurosarcoidosis, should immunosuppressive treatment be used versus no immunosuppressive treatment?
In patients with sarcoidosis associated fatigue, should immunosuppressants , neurostimulants, exercise, or other treatments be used versus no treatment for fatigue?
In sarcoidosis patients with small fiber neuropathy, should immunosuppressants or intravenous immunoglobulin be prescribed versus no treatment?

GRADE Recommendations for sarcoidosis beyond the lung

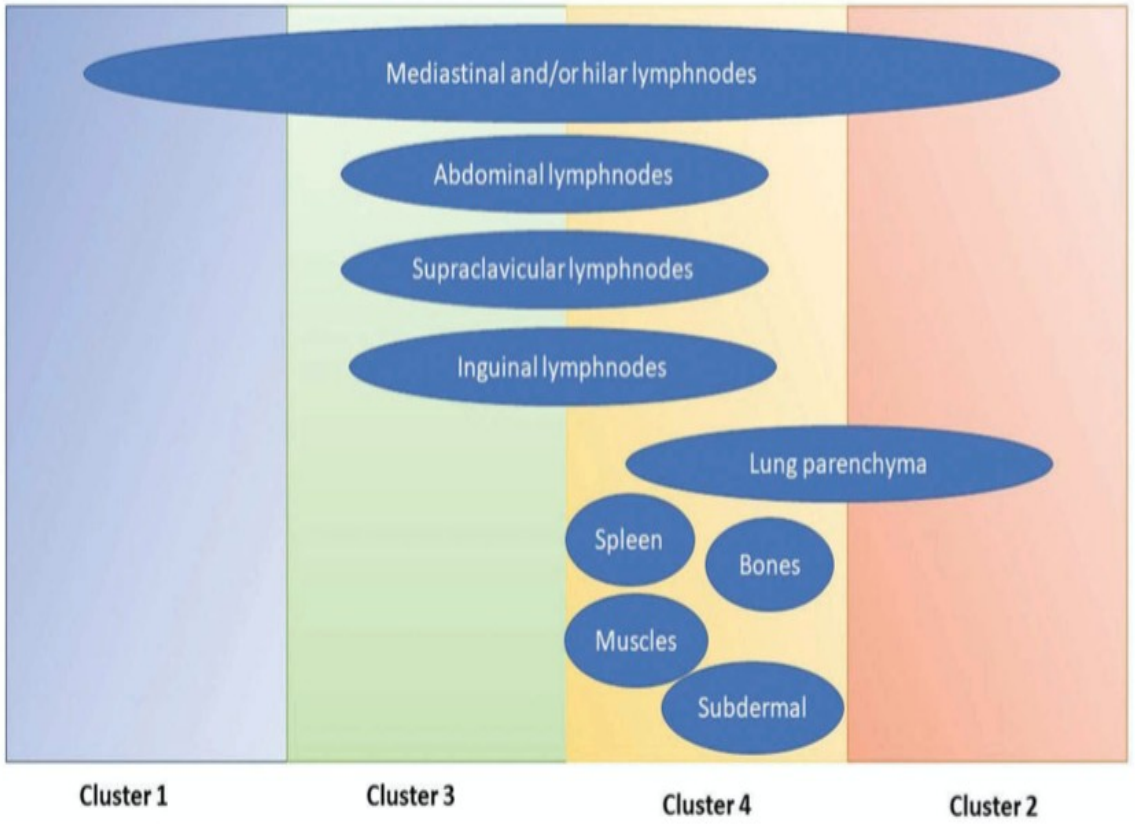
- Six additional PICOs were investigated
  - Extra pulmonary sarcoidosis
    - Corticosteroids
    - Non steroidal therapy
  - Cardiac sarcoidosis
  - Neurologic sarcoidosis
  - Fatigue
  - Small fiber neuropathy
- Recommendations and comments were made on all these PICOs

Multiple pathways play a role in sarcoidosis; many unexplored…

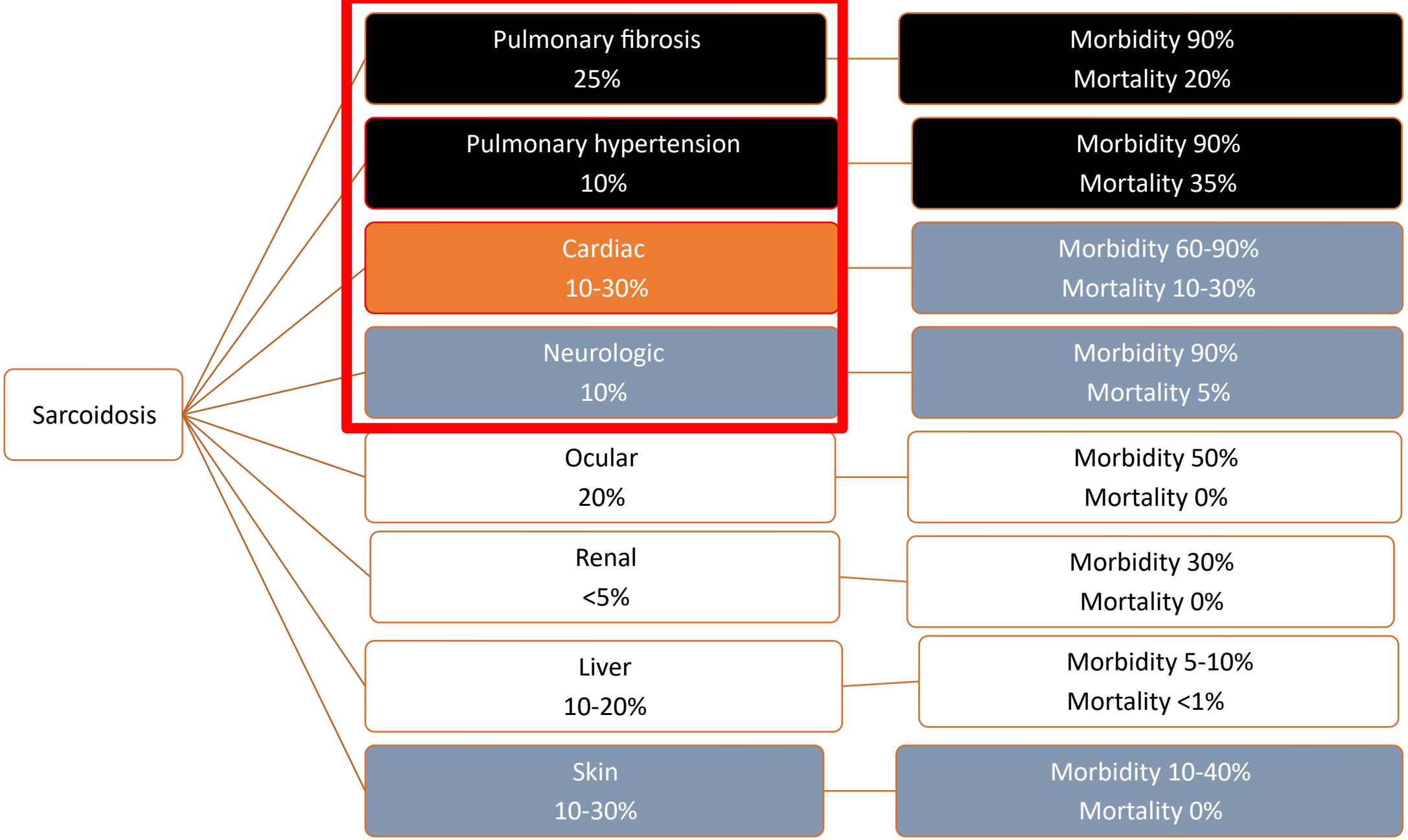


Miedema JR et al. J Autoimmun 2018;87:82-96.

Identification of sarcoidosis phenotypes according to organ involvement using two step cluster analysis.



Schupp JC, Freitag-Wolf S, Bargagli E, et al. Phenotypes of organ involvement in sarcoidosis. Eur Respir J. 2018;
Mostard RL, Verschakelen JA, van Kroonenburgh MJ, et al. Severity of pulmonary involvement and (18)F-FDG PET activity in sarcoidosis. Respir Med. 2013



Baughman RP, Wells AU. Advanced sarcoidosis. Curr Opin Pulm Med 2019

Hazards ratio for mortality from pulmonary sarcoidosis

	Great Britain	France	United States
HRCT >20% fibrosis	3.43 *	2.80 *	2.80 *
CPI >40	4.24 *	3.78 *	1.48 †
MPAD/AAD	2.27	1.49 †	NR
MPAD/BSA	NR	2.61	NR
Pulmonary hypertension	NR	3.42 §	8.96 ¶
Walsh high risk	4.91 *	5.54 *	3.71

Great Britain: Walsh SL, et al. Lancet Respir Med 2014; 2(2):123-130; France: Jeny F et al. Respir Med 2020; 169:105997; United States: Kirkil G et al. Chest 2018; 153(1):105-113.

*Independent factor in multi-regression model; †Not significant; §Determined by echocardiogram; ¶Confirmed by right heart catheterization

HRCT: high resolution computer tomography; CPI: composite physiologic index; MPAD: mean pulmonary artery diameter; AAD: ascending aorta diameter; BSA: body surface area.

18F-FDG PET/CT in Pulmonary Sarcoidosis:Quantifying Inflammation by the TLG index

Spyros A Papiris[a*], Effrosyni D Manali[a*], Nikoletta K Pianou[b], Maria Kallergi[b,c], Andriana I Papaioannou[a], Alexandros Georgakopoulos[b], Katerina Malagari[d], Nikolaos L Kelekis[d], Helias Gialafos[e] and Sofia Chatziioannou[b,f]

[a]2nd Pulmonary Medicine Department, General University Hospital "Attikon", Medical School, National and Kapodistrian University of Athens, Athens, Greece; [b]Nuclear Medicine Division, Biomedical Research Foundation of the Academy of Athens, Athens, Greece; [c]Department of Biomedical Engineering, University of West Attika, Athens, Greece; [d]2nd Department of Radiology, General University Hospital "Attikon", Medical School, National and Kapodistrian University of Athens, Athens, Greece; [e]Aiginitio Hospital, Medical School, National and Kapodistrian University of Athens, Greece; [f]2nd Department of Radiology, Division of Nuclear Medicine, General University Hospital "Attikon", Medical School, National and Kapodistrian University of Athens, Athens, Greece

ABSTRACT

Objectives: In sarcoidosis progressive pulmonary disease affects prognosis. Pulmonary disease activity estimated by classic means poorly predicts severity and progressiveness. ^{18}F-fluoro-2-deoxyglucose-positron-emission-tomography computed-tomography (^{18}F-FDG-PET/CT) estimates pulmonary activity by inflammatory-cells metabolism. We aimed to investigate pulmonary sarcoidosis by ^{18}F-FDG-PET/CT and evaluate the role of total-lesion-glycolysis (TLG) value, as an index quantifying the whole burden of lung inflammation.

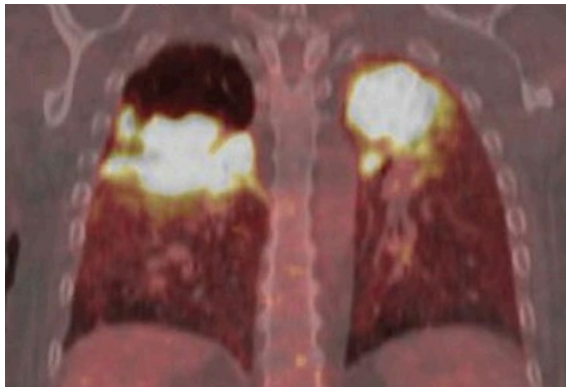
Methods: This is a retrospective study of sequentially gathered data. From a Greek cohort of 195 sarcoidosis-patients, 87 were identified with lung increased ^{18}F-FDG uptake and further studied.

Results: Visualizing lung by ^{18}F-FDG-PET/CT identified new imaging patterns and revealed activity in all Scadding stages. Ever-smokers presented significantly higher TLG and lower DLCO compared to never-smokers. However, TLG value did not correlate with functional indices and did not differ between symptomatic and non-symptomatic patients. Among treatment-naïve patients, TLG did not differ significantly in those requiring therapy compared to those remained off.

Conclusion: ^{18}F-FDG PET/CT improved imaging and detection of pulmonary involvement and through TLG value revealed the deleterious smoking effect. The fact that TLG neither detected patients with clinical symptoms and functional impairment nor identified those requiring treatment once again confirms that in pulmonary sarcoidosis the link between activity, severity and decision to treat still eludes us.

ARTICLE HISTORY
Received 10 July 2019
Accepted 17 October 2019

KEYWORDS
^{18}F-FDG-PET/CT; total lesion glycolysis value; sarcoidosis pulmonary activity; smoking; SUV



TLG: total lesion glycolysis value;
Quantification the whole burden of Lung inflammation

Emerging phenotypes of sarcoidosis based on 18F-FDG PET/CT: a hierarchical cluster analysis

Spyros A Papiris[a*], Alexandros Georgakopoulos[b*], Andriana I Papaioannou[a], Nikoletta Pianou[b], Maria Kallergi[b], Nikolaos L. Kelekis[c], Helias Gialafos[d], Effrosyni D Manali[a*] and Sofia Chatziioannou[b,c*]

- 18F-FDG PET/CT succeeded to identify despite the random distribution of the disease, an ordered stratification into 4 phenotypes:
- I) thoracic nodal hilar-mediastinal
- II) thoracic nodal hilarmediastinal and lungs
- III) an extended thoracic and extra-thoracic only nodal phenotype including inguinal-abdominal-supraclavicular stations, and
- IV) all the above plus systemic organs and tissues such as muscles-bones-spleen and skin.

EXPERT REVIEW OF RESPIRATORY MEDICINE

PICOs 1 and 2
Pulmonary sarcoidosis

1	Pulmonary sarcoidosis	Patients with pulmonary sarcoidosis	Corticosteroid treatment	Athol Wells, Paola Rottoli	Alexander Mathiou	Fillipo Martone
2	Pulmonary sarcoidosis	Patients with pulmonary sarcoidosis	Switch to immunosupressive treatment	Dominique Valeyre, Elyse Lower	Alexander Mathioudakis	Bernd Quadder

Anti-inflammatory therapies for sarcoidosis

- First line: Corticosteroids
  - Prednisone/Prednisolone
- Second line: Non biologics
  - Methotrexate
  - Azathioprine
  - Leflunomide
  - Mycophenolate
  - Hydroxychloroquine

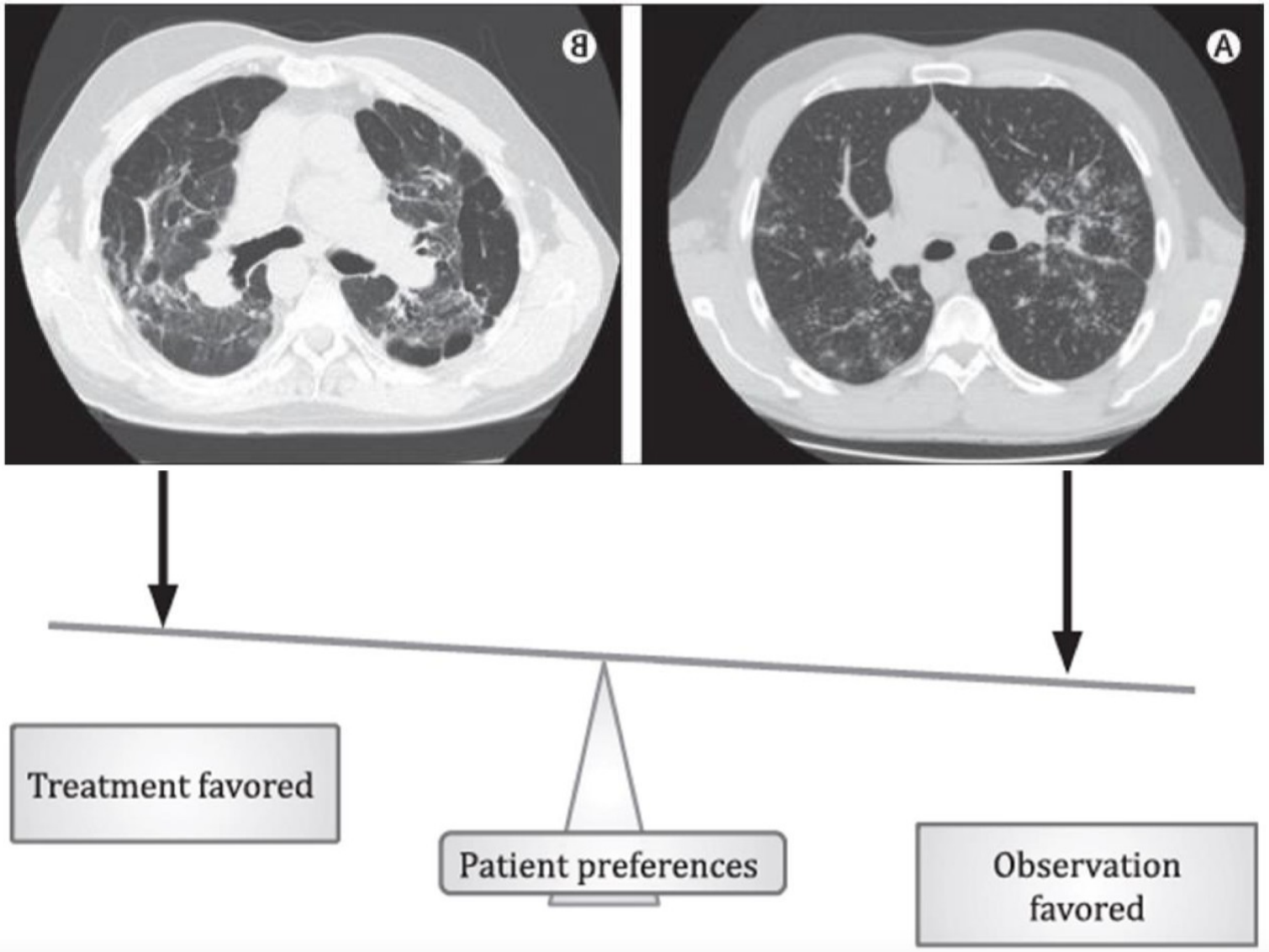
Anti-inflammatory therapies for sarcoidosis

- Third line: Biologics
  - Anti-TNF monoclonal antibodies
    - Infliximab
    - Adalimumab
  - Rituximab
  - Repository corticotropin injection

PICO 1

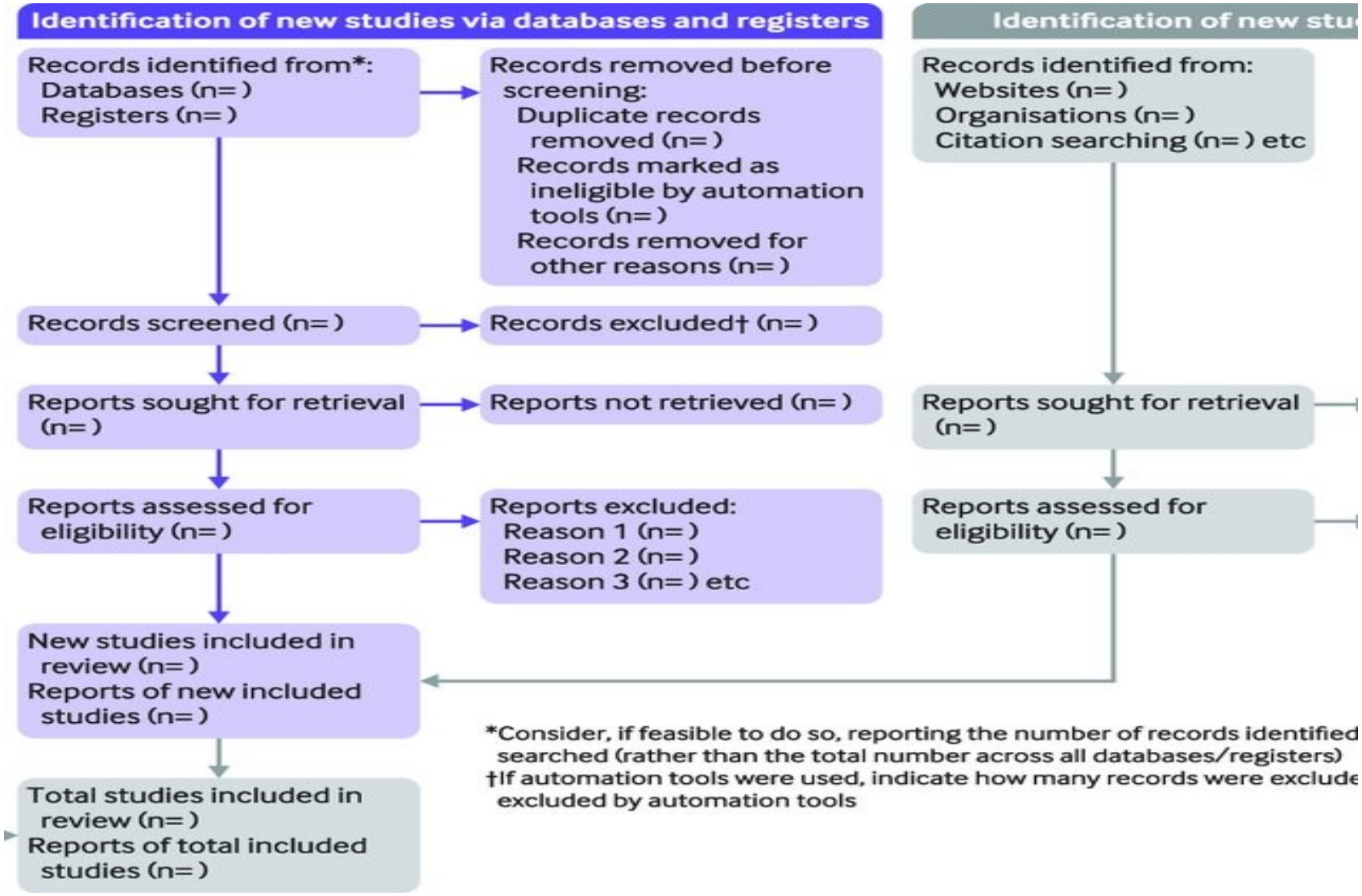
In patients with pulmonary sarcoidosis, should glucocorticoid treatment be used versus no immunosuppressive treatment?

TREATMENT AIMED AT PREVENTING ORGAN DAMAGE AND IMPROVING QUALITY OF LIFE

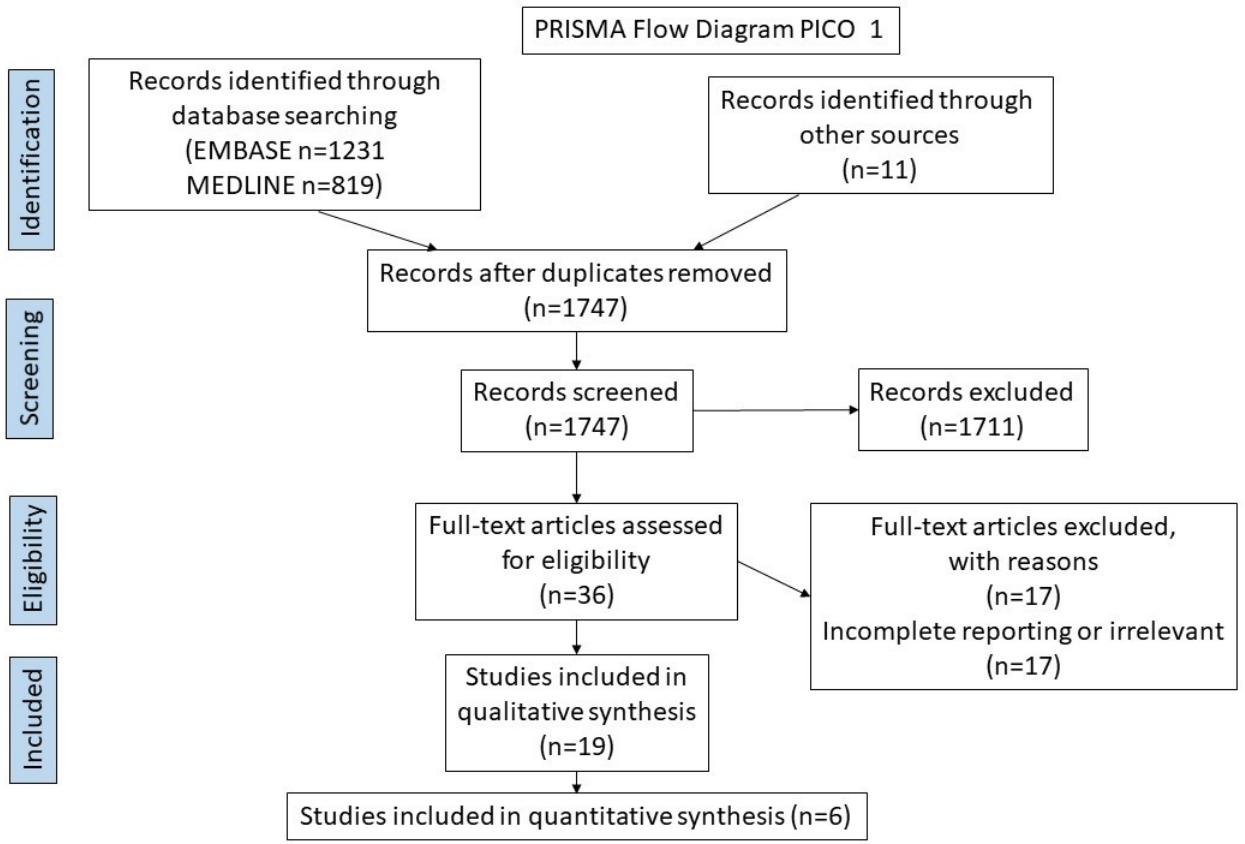


Wijsenbeek, Clin Chest Med, 2015

Preferred Reporting Items for Systematic Reviews and Meta-Analyses: PRISMA



PICO 1
In patients with pulmonary sarcoidosis, should glucocorticoid treatment be used versus no immunosuppressive treatment?



PICO 1

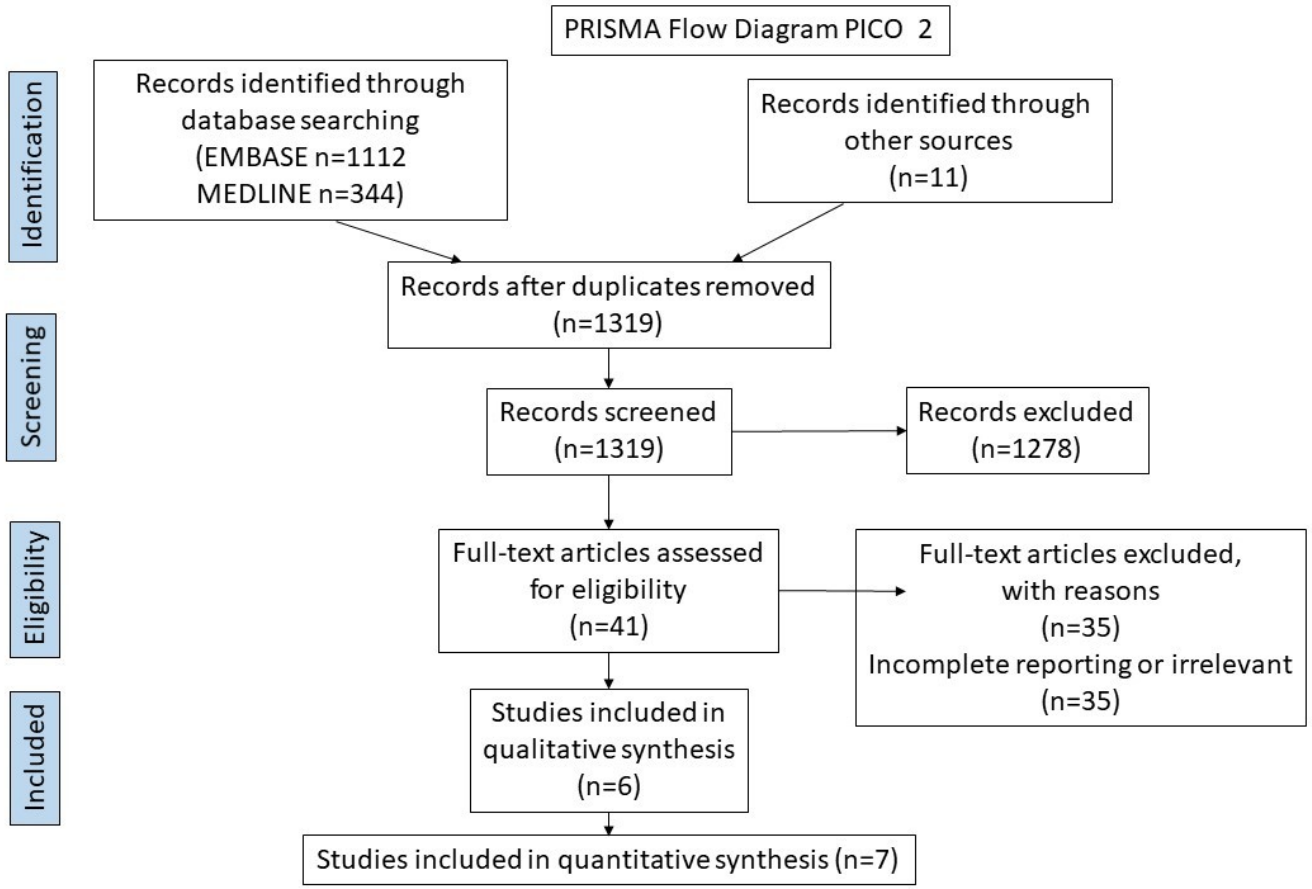
In patients with pulmonary sarcoidosis, should glucocorticoid treatment be used versus no immunosuppressive treatment?

For untreated patients with major involvement from pulmonary sarcoidosis believed to be at higher risk of future mortality or permanent disability from sarcoidosis, we recommend the introduction of glucocorticoid treatment, to improve and/or preserve FVC and QoL. (Strong recommendation, low quality of evidence).

PICO 2

In patients with pulmonary sarcoidosis, should one add immunosuppressive treatment or remain on glucocorticoid treatment alone?

PICO 2
In patients with pulmonary sarcoidosis, should one add immunosuppressive treatment or remain on glucocorticoid treatment alone?



PICO 2
In patients with pulmonary sarcoidosis, should one add immunosuppressive treatment or remain on glucocorticoid treatment alone?

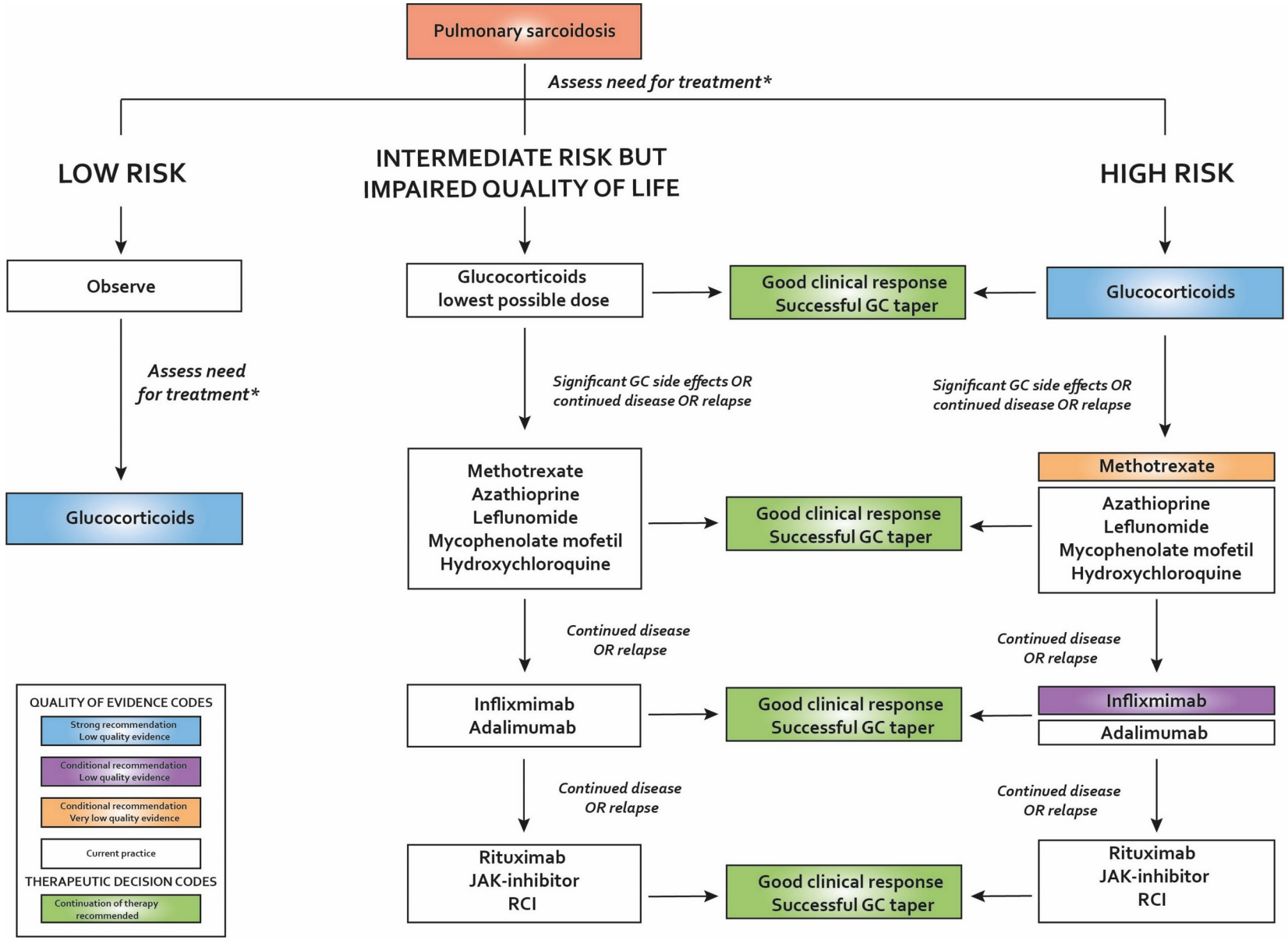
For patients with symptomatic pulmonary sarcoidosis believed to be at higher risk of future mortality or permanent disability from sarcoidosis who have been treated with glucocorticoids and have continued disease or unacceptable side effects from glucocorticoids, we suggest the addition of **methotrexate** to improve and/or preserve FVC and QoL. (Conditional recommendation, very low quality of evidence).

PICO 2
In patients with pulmonary sarcoidosis, should one add immunosuppressive treatment or remain on glucocorticoid treatment alone?

For patients with symptomatic pulmonary sarcoidosis believed to be at higher risk of future mortality or permanent disability from sarcoidosis who have been treated with glucocorticoids or other immunosuppressive agents and have continued disease, we suggest the addition of **infliximab** to improve and/or preserve FVC and QoL. (Conditional recommendation, low quality of evidence).

Recommendation versus comments by the committee

- Specific GRADE recommendations were made by the committee
- Comments regarding additional treatments
  - General treatment options
  - Case by case treatments
- Recommendations and comments were endorsed by all members of the committee


Pulmonary sarcoidosis
Assess need for treatment*
LOW RISK
INTERMEDIATE RISK BUT IMPAIRED QUALITY OF LIFE
HIGH RISK
Observe
Assess need for treatment*
Glucocorticoids
Glucocorticoids lowest possible dose
Good clinical response Successful GC taper
Glucocorticoids
Significant GC side effects OR continued disease OR relapse
Significant GC side effects OR continued disease OR relapse
Methotrexate Azathioprine Leflunomide Mycophenolate mofetil Hydroxychloroquine
Good clinical response Successful GC taper
Methotrexate
Azathioprine Leflunomide Mycophenolate mofetil Hydroxychloroquine
Continued disease OR relapse
Continued disease OR relapse
Inflixmimab Adalimumab
Good clinical response Successful GC taper
Inflixmimab
Adalimumab
Continued disease OR relapse
Continued disease OR relapse
Rituximab JAK-inhibitor RCI
Good clinical response Successful GC taper
Rituximab JAK-inhibitor RCI
QUALITY OF EVIDENCE CODES
Strong recommendation Low quality evidence
Conditional recommendation Low quality evidence
Conditional recommendation Very low quality evidence
Current practice
THERAPEUTIC DECISION CODES
Continuation of therapy recommended

Extra pulmonary disease

- Sarcoidosis is a multi-organ disease
- Significant morbidity associated with some organ involvement
  - Cardiac
  - Neurologic
- Other organ involvement can lead to some morbidity
  - Skin, eye, liver, renal

@ERSpublications
Severe pulmonary hypertension remains a life-threatening complication of sarcoidosis in the modern management era http://ow.ly/fIln30etYkE

Cite this article as: Boucly A, Cottin V, Nunes H, *et al.* Management and long-term outcomes of sarcoidosis-associated pulmonary hypertension. *Eur Respir J* 2017; 50: 1700465 [https://doi.org/10.1183/13993003.00465-2017].

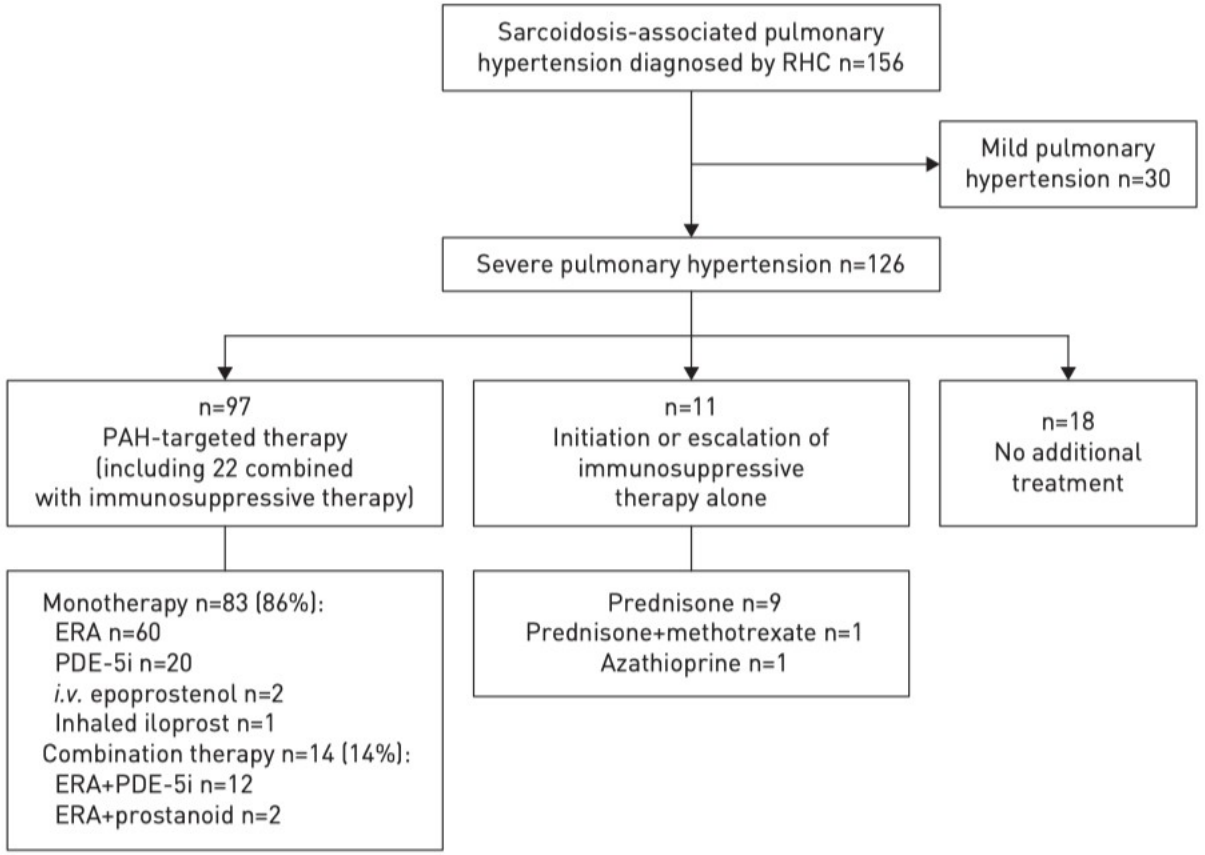


FIGURE 1 Patient disposition and initial therapy. RHC: right heart catheterisation; PAH: pulmonary arterial hypertension; ERA: endothelin receptor antagonist; PDE-5i: phosphodiesterase type 5 inhibitor.

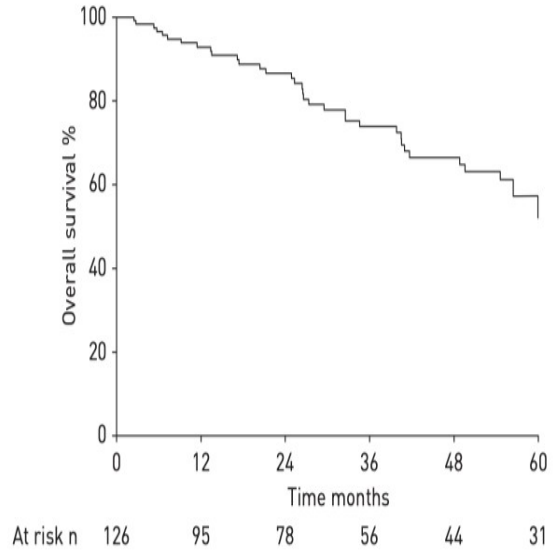


FIGURE 3 Kaplan-Meier analysis of the overall survival in patients with severe sarcoidosis-associated pulmonary hypertension. Survival at 1, 3 and 5 years was 93%, 74% and 55%, respectively.

Arrhythmias and sudden death
Original research

Heart 2023

Diagnosis of cardiac sarcoidosis in patients presenting with cardiac arrest or life-threatening arrhythmias

Suzan Hatipoglu [1, 2], Syed K M Gardezi [1], Alessia Azzu [1], John Baksi [1, 3, 4], Francisco Alpendurada [1, 4], Cemil Izgi [1, 4], Raj Khattar [3], Vasileios Kouranos [5], Athol Umfrey Wells [5], Rakesh Sharma [3], Kshama Wechalekar [6], Dudley J Pennell [1, 4], Raad Mohiaddin [1, 4]

Methods An imaging database of a CS referral centre (Royal Brompton Hospital, London) was screened for patients presenting with cardiac arrest or life-threatening arrhythmias and having imaging features of suspected CS. Patients diagnosed with definite or probable/possible CS were included.

Results Study population included 60 patients (median age 49 years) with male predominance (76.7%). The left ventricle was usually non-dilated with mildly reduced ejection fraction (53.4±14.8%). CMR studies showed extensive late gadolinium enhancement (LGE) with 5 (4–8) myocardial segments per patient affected; the right ventricular (RV) side of the septum (28/45) and basal anteroseptum (28/45) were most frequently involved. Myocardial inflammation by FDG-PET was detected in 45 out of 58 patients vs 11 out of 33 patients with oedema imaging available on CMR. When PET was treated as reference to detect myocardial inflammation, CMR oedema imaging was 33.3% sensitive and 77% specific.

Conclusions In patients with CS presenting with cardiac arrest or life-threatening arrhythmias, LGE was located in areas where the cardiac conduction system travels (basal anteroseptal wall and RV side of the septum). While CMR was the imaging technique that raised possibility of cardiac scarring, oedema imaging had low sensitivity to detect myocardial inflammation compared with FDG-PET.

Regional extracellular volume within late gadolinium enhancement-positive myocardium to differentiate cardiac sarcoidosis from myocarditis of other etiology: a cardiovascular magnetic resonance study

Julia Treiber[1,3], Dijana Novak[1], Ulrich Fischer-Rasokat[1,3], Jan Sebastian Wolter[1,3], Steffen Kriechbaum[1,3], Maren Weferling[1,3], Beatrice von Jeinsen[1,3], Andreas Hain[1], Andreas J. Rieth[1,3], Tamo Siemons[1], Till Keller[1,2,3], Christian W. Hamm[1,2,3] and Andreas Rolf[1,2,3*]

Caforio AL, Pankuweit S, Arbustini E, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European society of cardiology working group on myocardial and pericardial diseases. Eur Heart J. 2013.

- Myocarditis-typical tissue characterization by CMR: subepicardial or intramural LGE and elevated native T1 and T2 values

and at least two of the following features:

- Typical clinical presentation
- Recent-onset arrhythmias in 12-lead electrocardiogram (ECG)
- Elevation of troponin above the 99th percentile [15].

- PET/CT confirmed CS patients and myocarditis patients (both acute and chronic) from a prospective registry were compared with respect to regional native T1, T2, and ECV.
- Acute and chronic myocarditis were defined based on the 2013 European Society of Cardiology position paper on myocarditis.
- All parametric measures and ECV were acquired in standard fashion on three short-axis slices according to the ConSept study for global values and within PET-CT positive regions of LGE.

This study was designed to investigate whether parametric measurements and ECV within regions of LGE can differentiate CS from acute and chronic myocarditis. The main findings of our study are:

1) Regional ECV within LGE regions can differentiate CS from active acute or chronic myocarditis. ROC analysis found 0.57 to be the best cut off to differentiate CS and myocarditis.
2) Global native T1, T2, and ECV values in CS patients were elevated compared with healthy controls but not compared with myocarditis patients, regardless of the degree of acuteness. In fact global native T1 was even lower in CS patients.

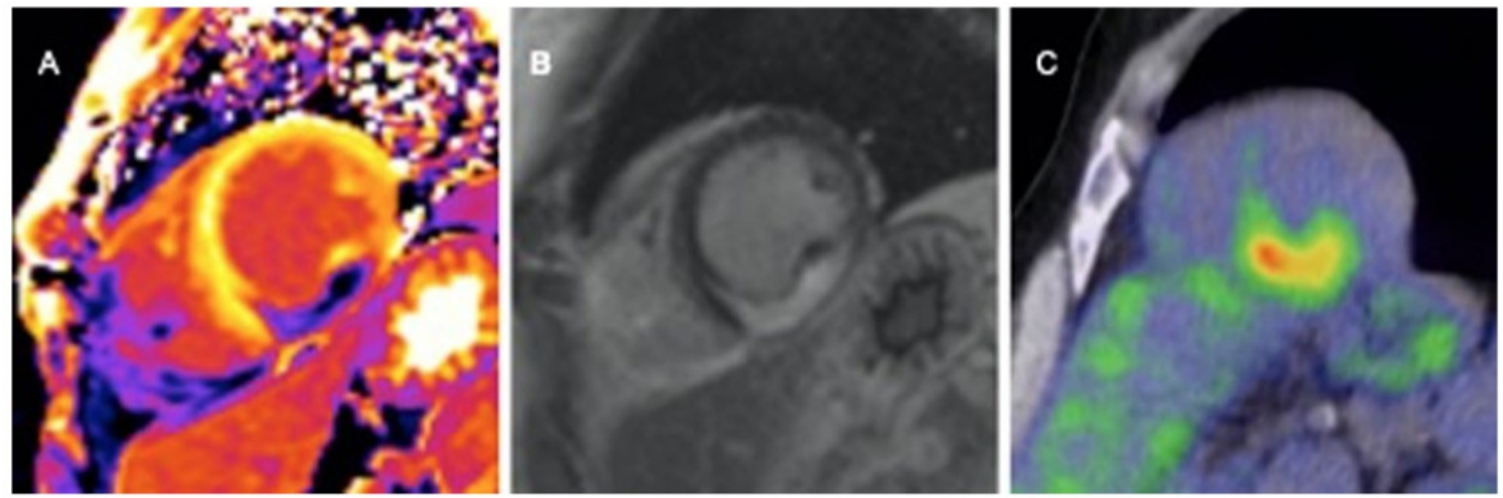


Fig. 1 Example for determination of active cardiac sarcoidosis. Imaging findings in one patient with cardiac sarcoidosis (CS) in cardiovascular magnetic resonance (CMR) and 18-fluorodeoxyglucose positron-emission tomography-computed tomography (PET-CT). **A** Shows post contrast T1-map, **B** typical intense intramural Late gadolinium enhancement (LGE) and **C** pathological 18-fluorodeoxyglucose-uptake in PET-CT

RESEARCH ARTICLE

Cardiac sarcoidosis: A long term follow up study

Patrice Cacoub[1,2,3,4]*, Catherine Chapelon-Abric[1,4], Matthieu Resche-Rigon[5,6,7], David Saadoun[1,2,3,4], Anne Claire Desbois[1,4], Lucie Biard[5,6,7]

The 10-year survival rate was 90% (95% CI, 84–96). Baseline factors associated with mortality were the presence of high degree atrioventricular block (HR, 5.56, 95% CI 1.7–18.2, $p = 0.005$), left ventricular ejection fraction below 40% (HR, 4.88, 95% CI 1.26–18.9, $p = 0.022$), hypertension (HR, 4.79, 95% CI 1.06–21.7, $p = 0.042$), abnormal pulmonary function test (HR, 3.27, 95% CI 1.07–10.0, $p = 0.038$), areas of late gadolinium enhancement on cardiac magnetic resonance (HR, 2.26, 95% CI 0.25–20.4, $p = 0.003$), and older age (HR per 10 years 1.69, 95% CI 1.13–2.52, $p = 0.01$). The 10-year relapse-free survival rate for cardiac relapses was 53% (95% CI, 44–63). Baseline factors that were independently associated with cardiac relapse were kidney involvement (HR, 3.35, 95% CI 1.39–8.07, $p = 0.007$), wall motion abnormalities (HR, 2.30, 95% CI 1.22–4.32, $p = 0.010$), and left heart failure (HR 2.23, 95% CI 1.12–4.45, $p = 0.023$). After adjustment for cardiac involvement severity, treatment with intravenous cyclophosphamide was associated with a lower risk of cardiac relapse (HR 0.16, 95% CI 0.033–0.78, $p = 0.024$).

Plos one 2020

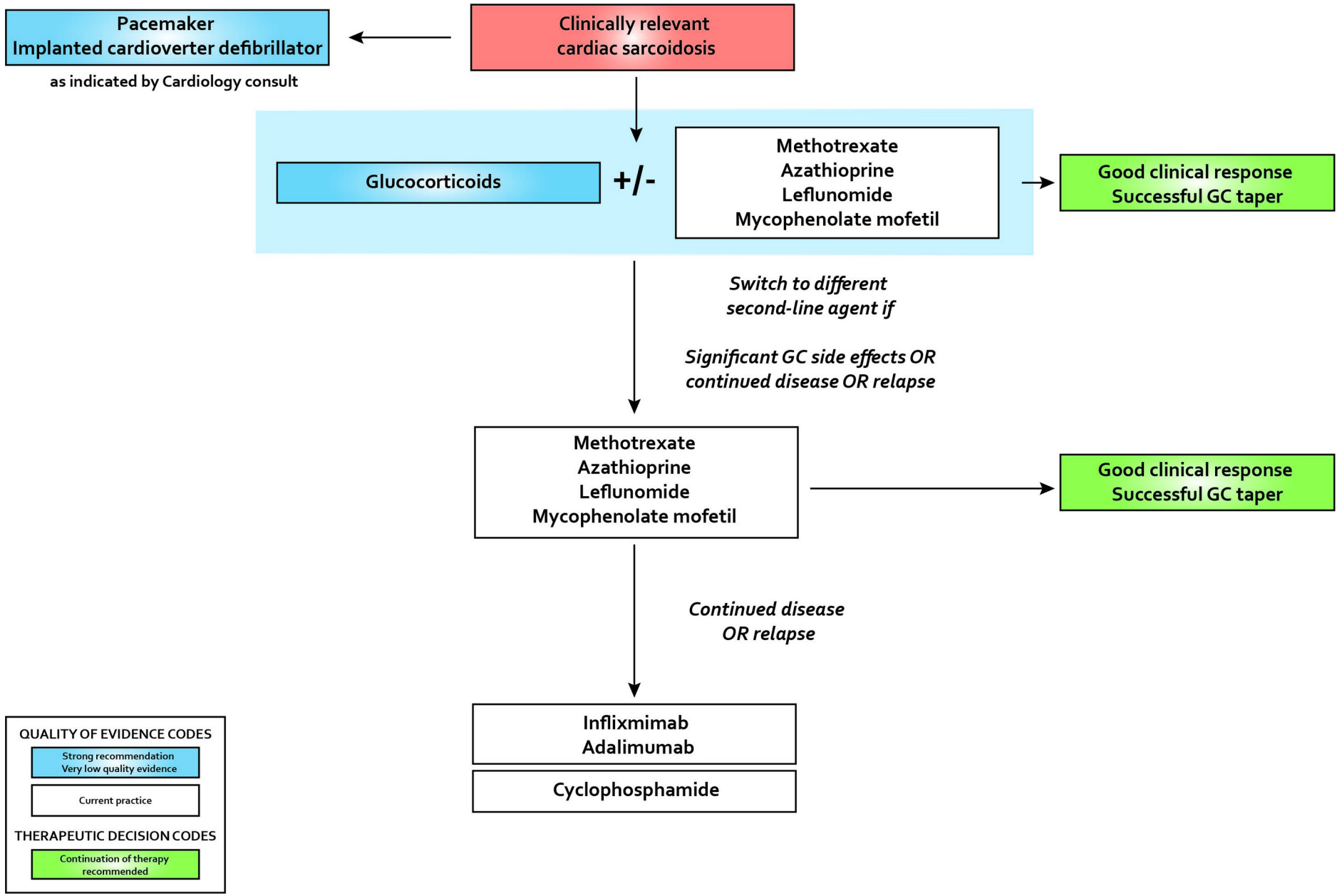
Comparative Study > Int J Cardiol. 2019 Feb 1;276:208-211. doi: 10.1016/j.ijcard.2018.11.131. Epub 2018 Nov 30.

Treatment of cardiac sarcoidosis: A comparative study of steroids and steroids plus immunosuppressive drugs

Thomas Ballul [1], Raphael Borie [2], Bruno Crestani [2], Eric Daugas [3], Vincent Descamps [4], Philippe Dieude [5], Antoine Dossier [1], Fabrice Extramiana [6], Damien van Gysel [7], Thomas Papo [8], Karim Sacre [9]

Results: 326 consecutive patients with histologically proven sarcoidosis were screened. Among them, 36 (11%) had symptomatic CS (20 (55.5%) men, median age at diagnosis 48.5 [22.8-76]). Twenty-four patients received steroids and 12 received steroids + IS (azathioprine n = 5, methotrexate n = 5, cyclophosphamide n = 2) at CS diagnosis. Over a median follow up of 3.6 [1-15.2] years, 13 (36.1%) patients suffered a cardiac relapse including reduced left ventricular ejection fraction (LVEF, n = 4), third degree heart block (n = 2), atrio-ventricular (n = 1) or ventricular (n = 1) tachycardia and sudden cardiac death (n = 1). Except for a higher frequency of black patients in patients receiving IS, CS features at diagnosis and median time to relapse did not significantly differ between patients who did or did not receive IS. Relapse rate was 45.8% in the steroids group versus 16.7% in the steroids + IS group (p = 0.048).

Conclusions: In cardiac sarcoidosis, the combination of steroids with immunosuppressive drugs might reduce the risk of cardiac relapse, as compared to steroids alone.


Pacemaker
Implanted cardioverter defibrillator
as indicated by Cardiology consult
Clinically relevant
cardiac sarcoidosis
Glucocorticoids
+/-
Methotrexate
Azathioprine
Leflunomide
Mycophenolate mofetil
Good clinical response
Successful GC taper
Switch to different
second-line agent if
Significant GC side effects OR
continued disease OR relapse
Methotrexate
Azathioprine
Leflunomide
Mycophenolate mofetil
Good clinical response
Successful GC taper
Continued disease
OR relapse
Inflixmimab
Adalimumab
Cyclophosphamide
QUALITY OF EVIDENCE CODES
Strong recommendation
Very low quality evidence
Current practice
THERAPEUTIC DECISION CODES
Continuation of therapy
recommended

JAMA Neurology | Original Investigation

Association of Prognostic Factors and Immunosuppressive Treatment With Long-term Outcomes in Neurosarcoidosis

RESULTS The 234 patients undergoing assessment included 117 women (50.0%) and 117 men (50.0%); median age was 42 years (interquartile range, 32-53 years). The probable 10-year survival rate was 89% (95% CI, 84%-94%). Older age (hazard ratio [HR] per 10 years, 1.64; 95% CI, 1.19-2.27; $P = .003$), peripheral nervous system involvement (HR, 6.75; 95% CI, 2.31-19.7; $P < .001$), and higher baseline EDSS score (HR per point, 1.21; 95% CI, 1.06-1.39; $P = .005$) were associated with mortality. The estimated 10-year RFS rate was 14% (95% CI, 9%-22%) for all relapses and 28% (95% CI, 20%-38%) for neurologic relapses. Encephalic involvement was associated with shorter neurologic RFS (HR, 2.35; 95% CI, 1.44-3.83; $P < .001$). A lower risk for relapse was associated with cyclophosphamide (HR, 0.26; 95% CI, 0.11-0.59; $P = .001$), methotrexate sodium (HR, 0.47; 95% CI, 0.25-0.87; $P = .02$), and infliximab (HR, 0.16; 95% CI, 0.02-1.24; $P = .08$) treatments. Follow-up was greater than 60 months in 160 patients (68.4%). An elevated baseline EDSS score (odds ratio [OR] per point, 1.92; 95% CI, 1.55-2.37; $P < .001$), tobacco use (OR, 3.64; 95% CI, 1.36-9.73; $P = .01$), encephalic symptoms (OR, 3.04; 95% CI, 1.11-8.38; $P = .03$), and less than 4 extraneurologic sarcoidosis localizations (OR, 3.06; 95% CI, 1.04-8.98; $P = .04$) were associated with an EDSS value of at least 2.5 at 60 months. Encephalic involvement (16 of 17 patients [94.1%]; $P = .008$) and peripheral nervous system involvement (5 of 17 patients [29.4%]; $P = .03$) were associated with worsening of the EDSS score at 60 months.

CONCLUSIONS AND RELEVANCE This study identifies putative factors affecting morbidity and mortality in patients with NS. Immunosuppressive therapies (ie, intravenous cyclophosphamide, methotrexate, and infliximab) in these patients may be associated with lower relapse rates.

Key Points

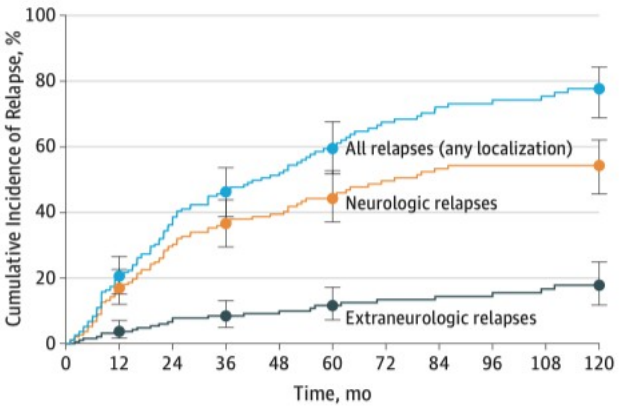
Question What are the prognostic factors in neurosarcoidosis, and what is the association of immunosuppressive treatment with relapse of the disease?

Findings In this cohort study of 234 patients with neurosarcoidosis, encephalic and peripheral nervous system involvement were associated with worsening of the functional score. Immunosuppressive therapies, (ie, intravenous cyclophosphamide, methotrexate sodium, and infliximab) in these patients are associated with lower relapse rates.

Meaning The presence of encephalic or peripheral nervous system involvement in neurosarcoidosis should affect the decision to use immunosuppressive therapies to help lower relapse rates.

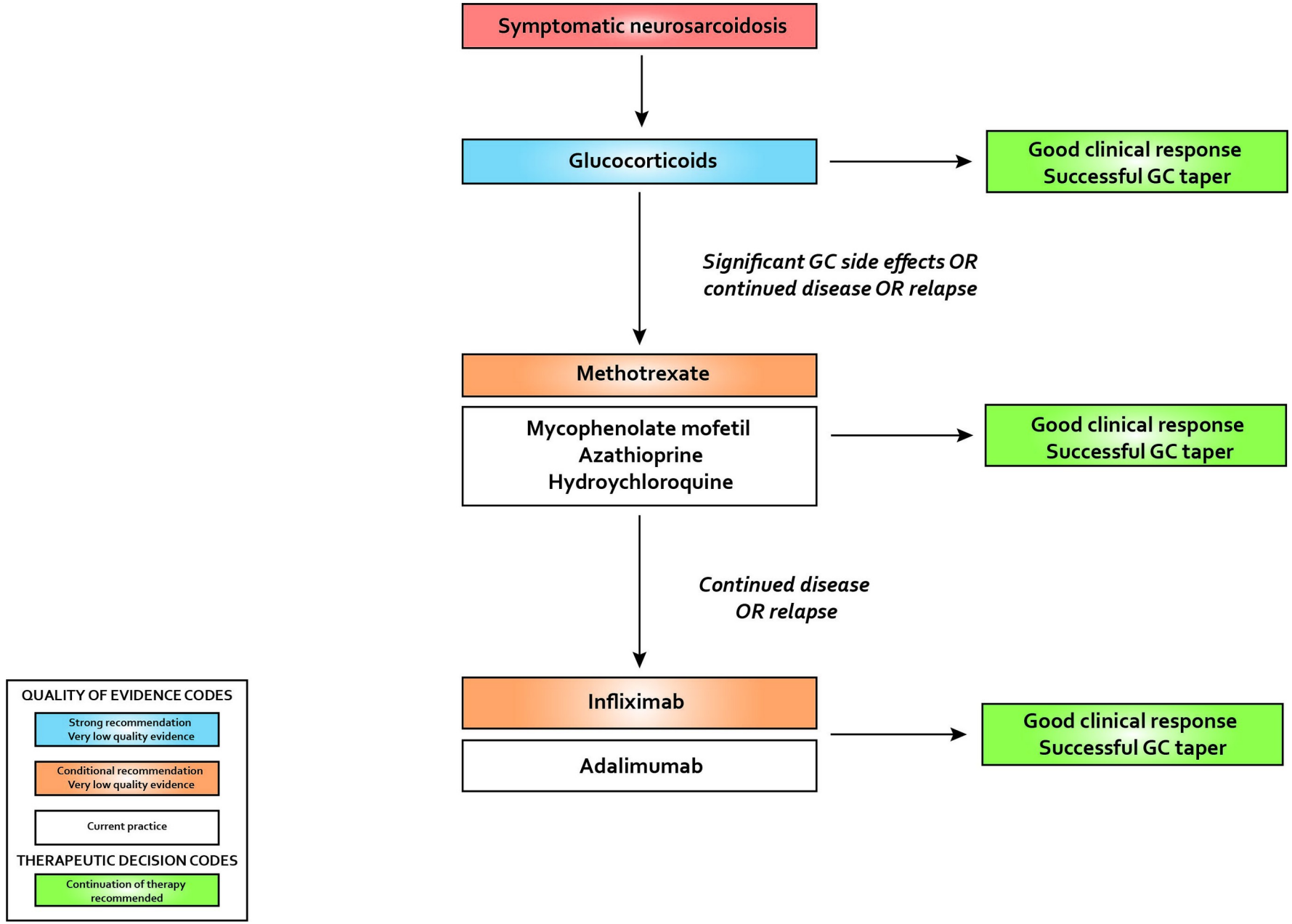
JAMA Neurol. 2017

C Cumulative incidence of relapse



No. at risk

All	194	143	103	76	58	40	28	22	15	14	9
Neurologic	0	32	54	65	69	76	81	85	86	86	86
Extraneurologic	0	7	12	15	17	19	21	22	23	24	25


Symptomatic neurosarcoidosis
Glucocorticoids
Good clinical response
Successful GC taper
Significant GC side effects OR
continued disease OR relapse
Methotrexate
Mycophenolate mofetil
Azathioprine
Hydroychloroquine
Good clinical response
Successful GC taper
Continued disease
OR relapse
Infliximab
Adalimumab
Good clinical response
Successful GC taper
QUALITY OF EVIDENCE CODES
Strong recommendation
Very low quality evidence
Conditional recommendation
Very low quality evidence
Current practice
THERAPEUTIC DECISION CODES
Continuation of therapy
recommended

Prevalence, distribution and clinical significance of joints, muscles and bones in sarcoidosis: an ^{18}F-FDG-PET/CT study

Spyros A. Papiris[a,*], Effrosyni D. Manali[a,*], Andriana I. Papaioannou[a], Alexandros Georgakopoulos[b,c], Lykourgos Kolilekas[d], Nikoletta K. Pianou[c,e], Maria Kallergi[c,f], Anastasia Papaporfyriou[a], Maria Kallieri[a], Vasiliki Apollonatou[a], Georgia Papadaki[a], Katerina Malagari[g], Nikolaos L. Kelekis[g], Spyros G. Pneumatikos[h,*] and Sofia Chatziioannou[b,c,*]

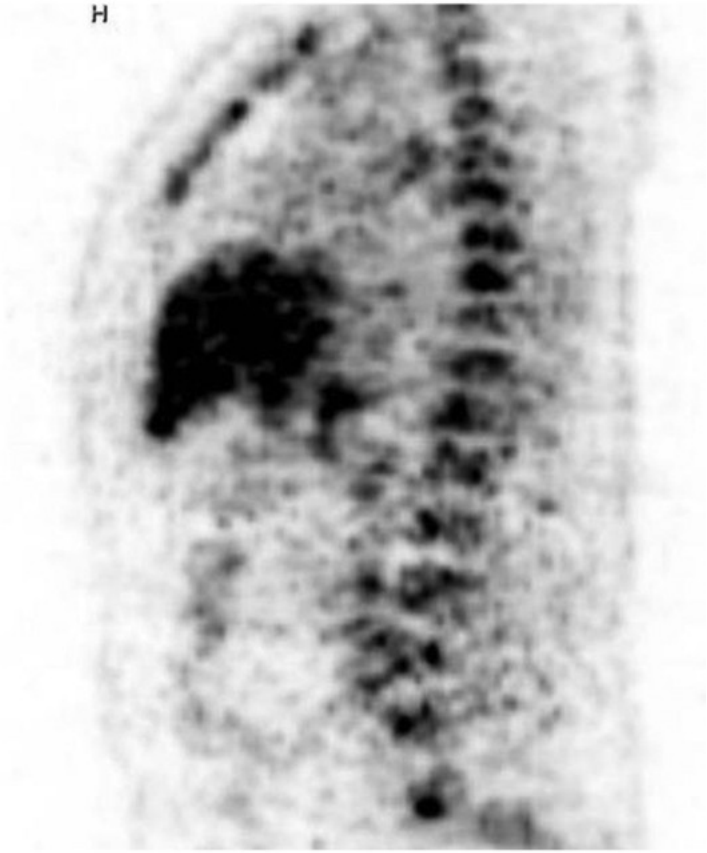


Figure 1. It regards a 63-year-old ex-smoker male with a history of long-lasting sarcoidosis documented by skin and lung biopsy 8 years ago in another hospital and initially treated with corticosteroids for 4 years and then remained off-treatment because asymptomatic. He presented in our clinic with severe anorexia and fatigue. Upon admission calcium of 17.6 mg/dl and creatinine levels of 2.8 mg/dl were measured. Sagittal ^{18}F-FDG PET image showed multiple foci of increased ^{18}F-FDG uptake in the spine and sternum. Bone marrow biopsy and aspiration both revealed multiple non-necrotizing, epithelioid granulomas compatible with sarcoidosis.^{18}F-FDG: fluorodeoxyglucose; PET: positron emission tomography.

Article highlights

- Joints-muscles-bones (JMBs) localizations of sarcoidosis are considered rare.
- ^{18}F-FDG-PET/CT revolutionized detection of JMBs involvement by adding metabolic information and allowing a comprehensive, whole-body map of the disease.
- ^{18}F-FDG-PET/CT whole body imaging revealed muscle and bone localizations of sarcoidosis and confirmed the multi-organ involvement supporting the concept that sarcoidosis is a systemic disease.
- The presence of muscle and bone localizations in sarcoidosis did not appear to increase the clinical burden of the disease and required mostly therapeutic interventions regarding the calcium homeostasis.
- Osseous localization always raises the fear of primary or metastatic malignancy while muscle localization is often difficult to interpret. In that case, ^{18}F-FDG-PET/CT proved useful allowing an integrative interpretation of multi-organ involvement in the context of a pattern highly suggestive of sarcoidosis, strongly keeping off the diagnosis of malignancy.

Only treat sarcoidosis to avoid danger or improve quality of life

Non-organ-specific manifestations

- Fatigue
- Anxiety
- Depression
- pain
- cognitive dysfunction and
- small-fibre neuropathy
- These symptoms do not usually require immunosuppressive therapy and often persist, even while there are no signs of organ-specific sarcoidosis activity.
- ***These invisible manifestations of sarcoidosis often have significant impact on health-related quality of life***

Frequent invisible burden of sarcoidosis

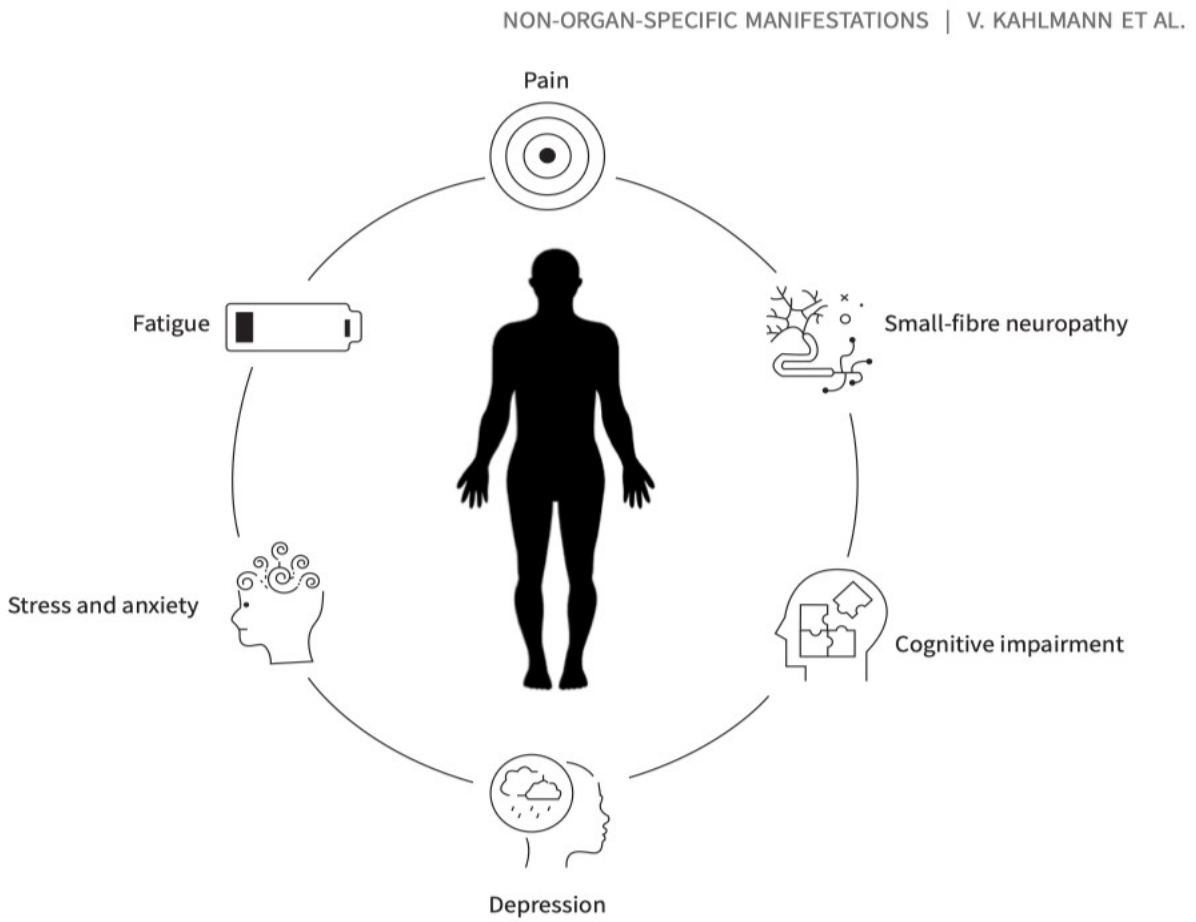
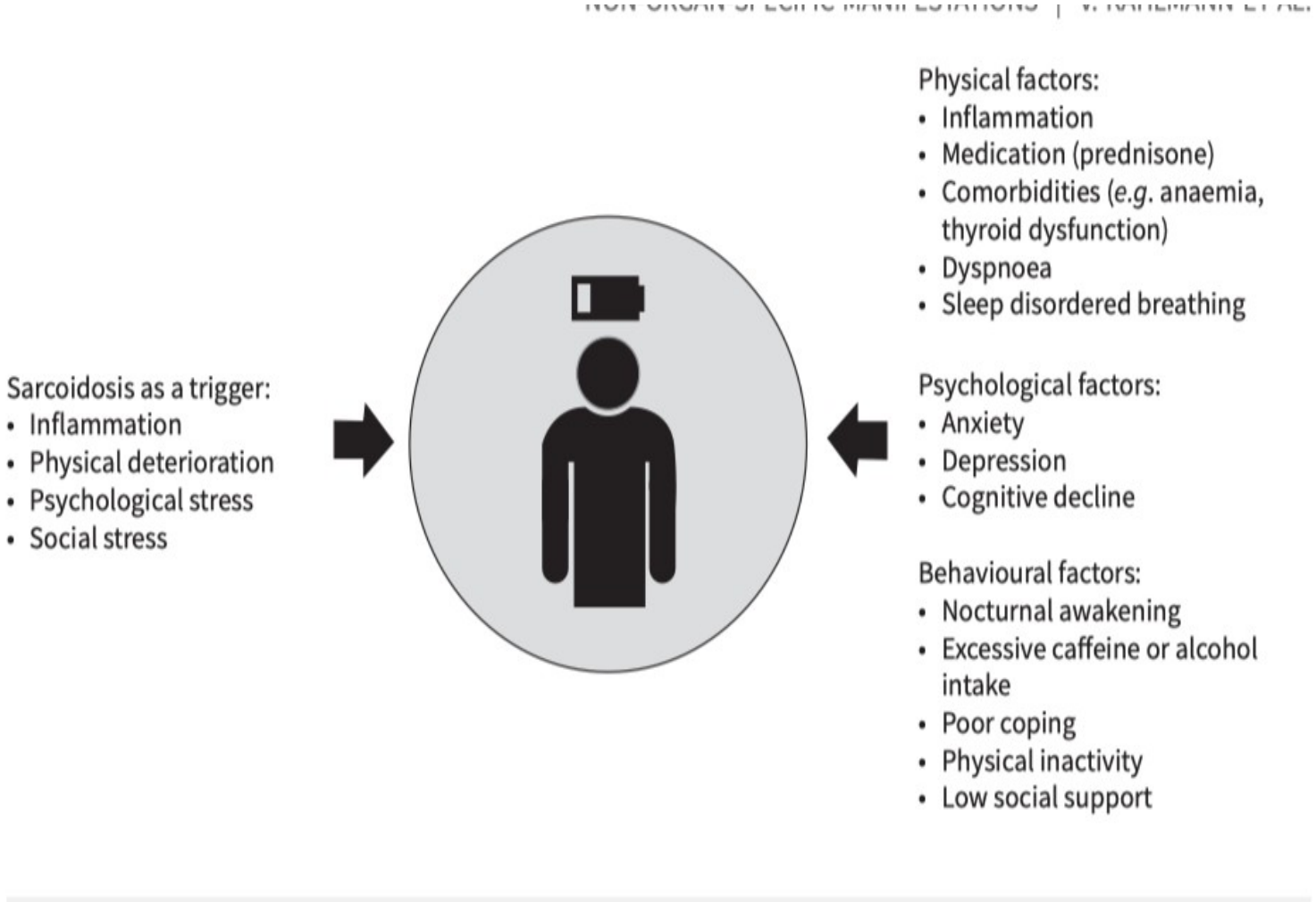
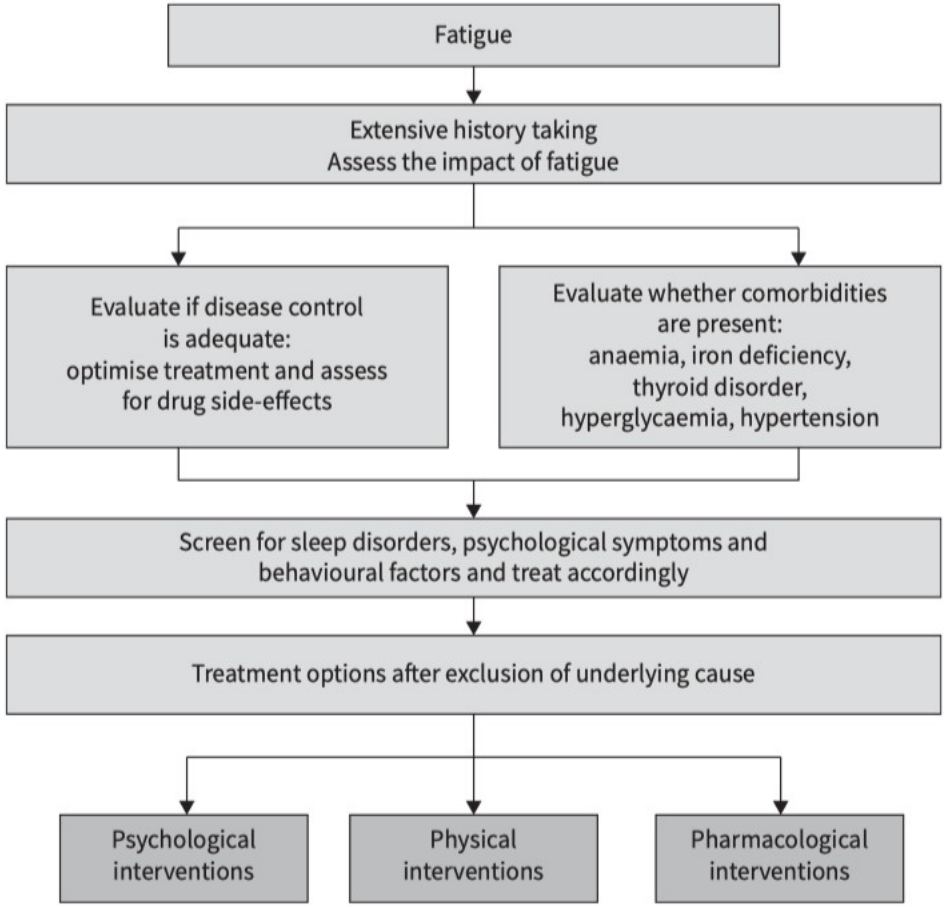


FIGURE 1 Non-organ manifestations of sarcoidosis include fatigue, pain, anxiety, depression, cognitive impairment and small-fibre neuropathy.

The various factors that play a role in the onset and persistence of fatigue in sarcoidosis including physical, psychological and behavioural factors



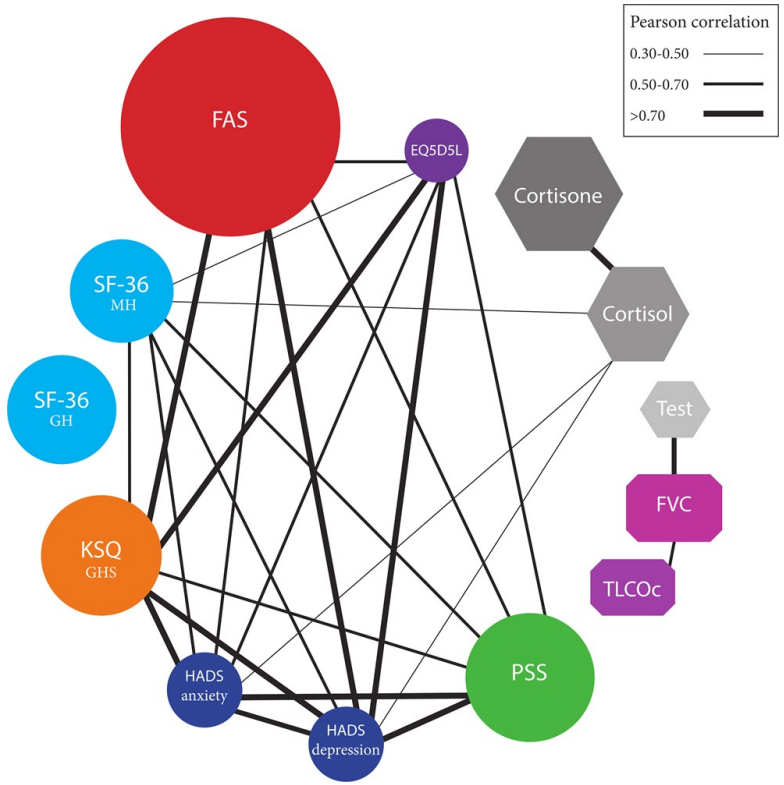
Algorithm for the assessment and management of fatigue in sarcoidosis patients



Fatigue and psychological symptoms

- Psychological factors play an important role in fatigue

- Online mindfulness-based cognitive therapy (eMBCT) is an effective intervention to improve fatigue after cancer



Van Manen et al. PloS One 2019

Online mindfulness-based cognitive therapy for fatigue in patients with sarcoidosis (TIRED): a randomised controlled trial

Vivienne Kahlmann, MD * • Catharina C Moor, MD * • Sanne J van Helmondt, MSc • Rémy L M Mostard, MD • Prof Marije L van der Lee, PhD • Prof Jan C Grutters, MD • et al. Show all authors • Show footnotes

Published: November 22, 2022 • DOI: https://doi.org/10.1016/S2213-2600(22)00387-3 •

- Multicenter randomized controlled trial
  - eMBCT vs. regular care
- Inclusion criteria:
  - Adult patients with stable sarcoidosis
  - Score of >21 points on the Fatigue Assessment Scale (FAS)
- Primary endpoint: between-group difference in change in FAS score at 3 months

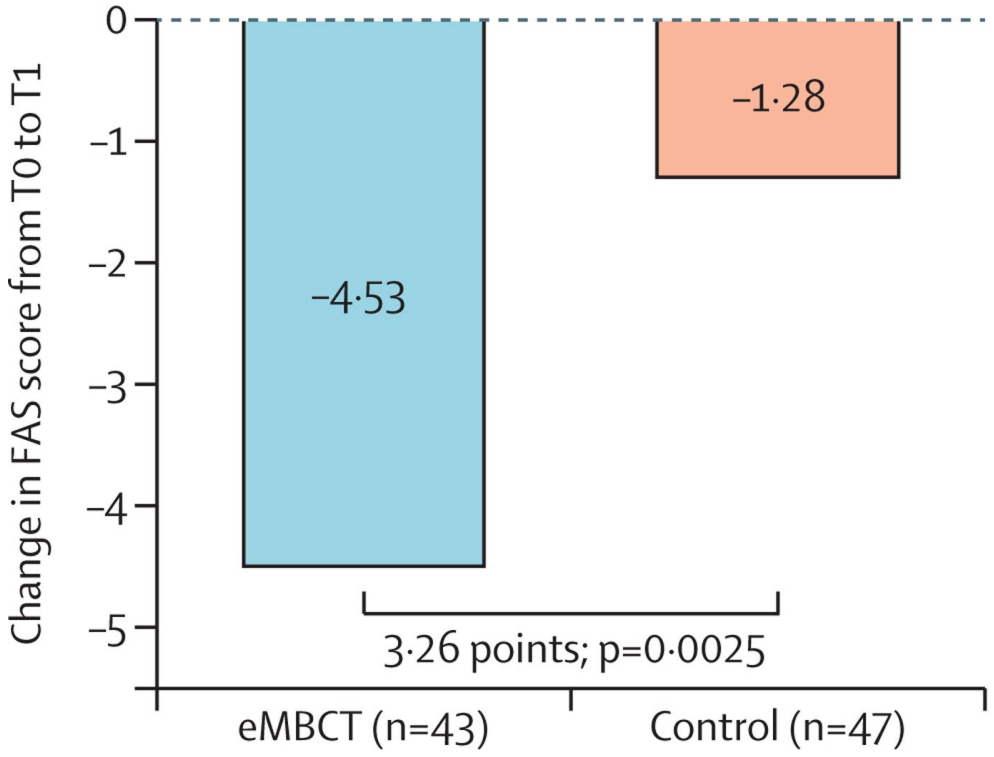
Kahlmann and Moor et al, Lancet Respiratory Medicine, 2022

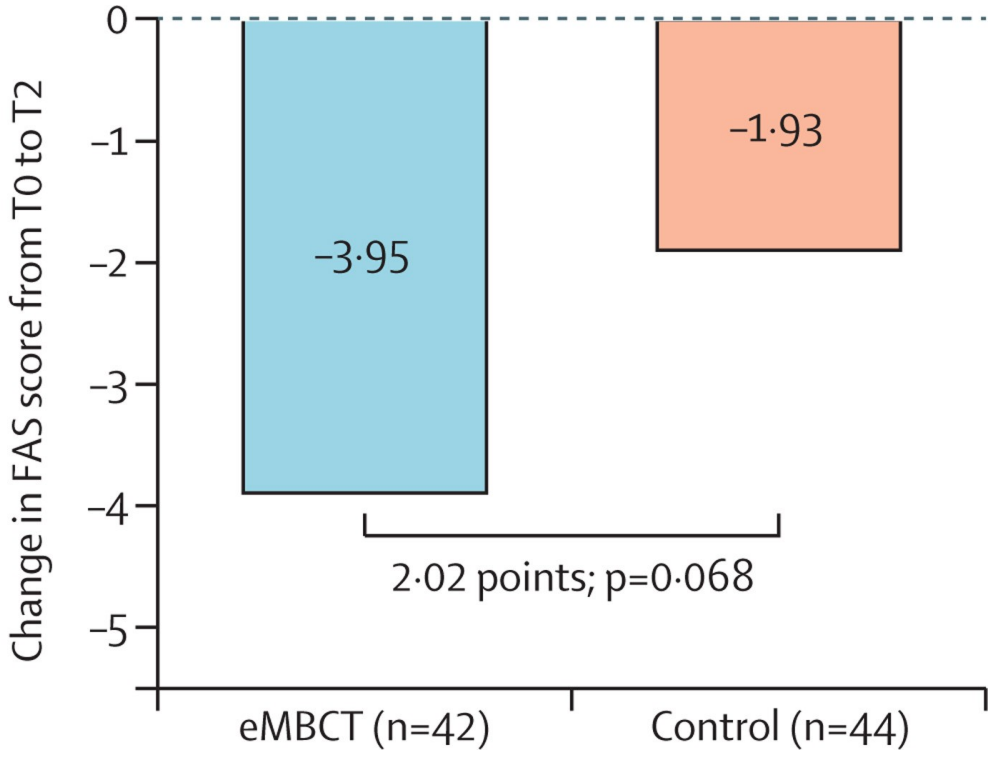
Fatigue assesment scale

- Range 10-50
- Higher scores indicate worse fatigue
- Minimal important difference 4.0 points or 10% change

	Never	Sometimes	Regularly	Often	Always
1. I am bothered by fatigue	○	○	○	○	○
2. I get tired very quickly	○	○	○	○	○
3. I don't do much during the day	○	○	○	○	○
4. I have enough energy for everyday life	○	○	○	○	○
5. Physically, I feel exhausted	○	○	○	○	○
6. I have problems to start things	○	○	○	○	○
7. I have problems to think clearly	○	○	○	○	○
8. I feel no desire to do anything	○	○	○	○	○
9. Mentally, I feel exhausted	○	○	○	○	○
10. When I am doing something, I can concentrate quite well	○	○	○	○	○

Fatigue improved after 3 months





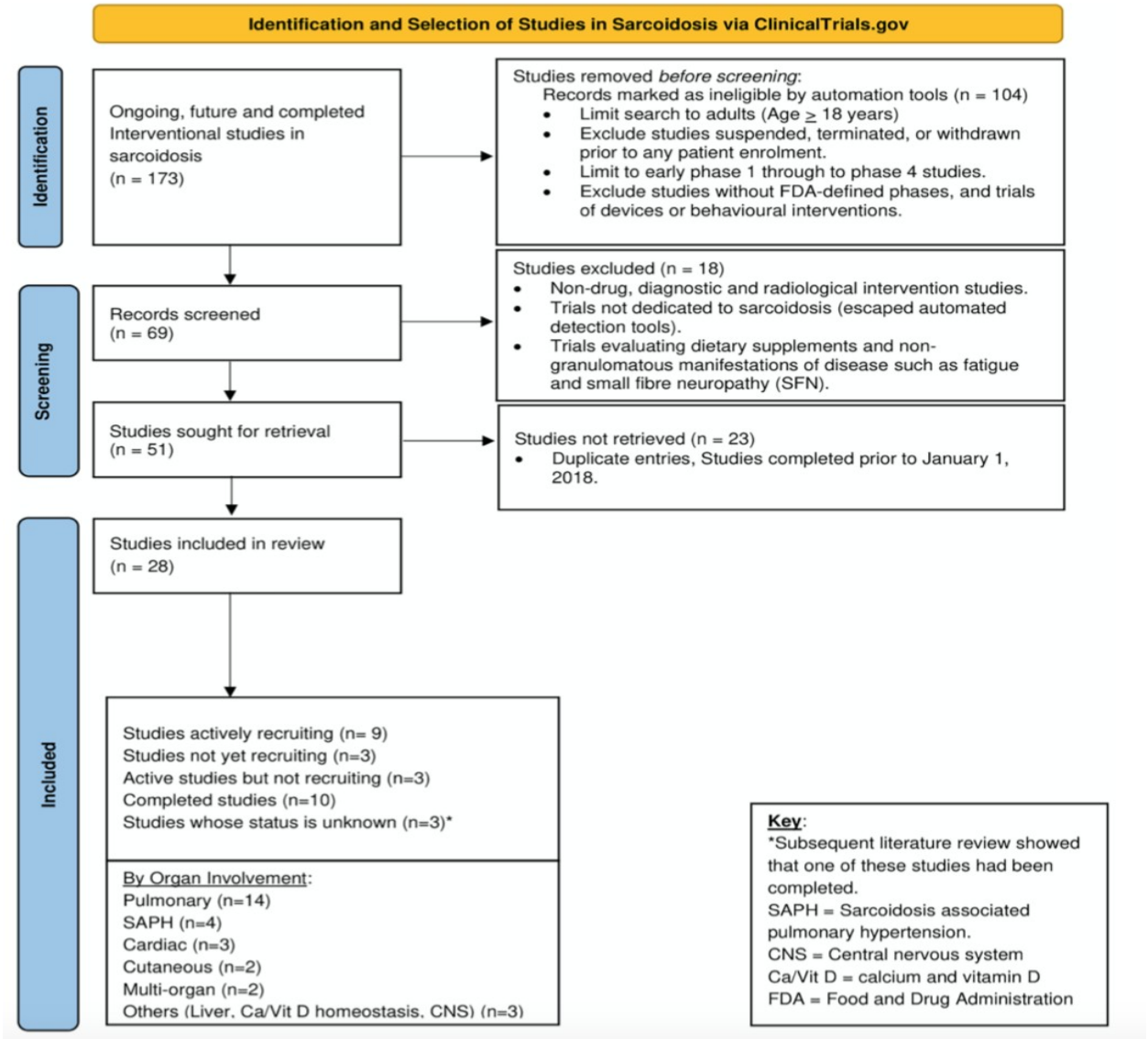
Changes persisted after 6 months

Kahlmann and Moor et al, Lancet Respiratory Medicine, 2022

Conclusions

- eMBCT is an effective treatment for fatigue in patients with sarcoidosis
- It can be easily integrated in daily practice as it is online

Active, future, and recently concluded clinical trials in sarcoidosis in the past 5-years (2018–2022).



Current widely accepted stepwise medications for the treatment of Sarcoidosis

Historic designation	Drug name	Usual dosage	Major toxicity	Drug monitoring	Comments
"First-Line"	Prednisone/ Prednisolone	20 mg/day initial dose, tapered to 5–10 mg QD to QoD	Weight gain, Diabetes Mellitus, Hypertension, Osteoporosis, Cataracts, Glaucoma, Sleep disturbance, Depression	Blood pressure and serum glucose monitoring, Bone density, Eye exams Body mass index	Causes cumulative toxicity that is dose and duration dependent.
"Second-Line" (Anti-metabolites)	Methotrexate	10–15 mg once a week PO Maybe given SQ if severe GI intolerance	GI Intolerance, Hepatotoxicity, Leukopenia, Fatigue, Pneumonitis.	CBC, LFT, renal function Folate supplementation is recommended.	Preferred anti-metabolite Teratogenic; avoid in pregnancy in both males and females of child-bearing age. Cleared by kidney, avoid in significant renal failure. Doses < 15 mg/week associated with inefficacy.
	Azathioprine	50–250 mg QD	Nausea, Leukopenia, Hepatotoxicity, Risk of Infections, Cutaneous and Lymphoproliferative Cancers.	CBC, LFT	Consider check TPMT level at initiation
	Leflunomide	10–20 mg QD	Nausea, Leukopenia, Hepatotoxicity, Peripheral Neuropathy, Pneumonitis	CBC, LFT, renal function	Due to long half-life, cholestyramine may be necessary to clear drug and its metabolites in toxicity. Teratogenic, avoid in pregnancy and breastfeeding. Cleared by kidney, avoid in significant renal failure
	Mycophenolate Mofetil	500–1,500 mg BID	Diarrhea, Leukopenia, risk of infections, Lymphoproliferative, and Cutaneous cancers	CBC, LFT Negative hepatitis B/C screening and negative IGRA are required prior to initiation	Less experience in sarcoidosis than other agents. Non-nephrotoxic
"Third-Line" Reserved for patients who have failed prior treatment with steroids and/or anti-metabolites	Infliximab or Biosimilars	3–5 mg/Kg IV at weeks 0, 2 and every 4–6weeks	Infections, allergic reactions. Contraindicated in demyelinating neurologic disease, active tuberculosis, deep fungal infections, prior malignancy, and severe CHF	Monitor for allergic reactions Screen for prior tuberculosis (negative IGRA testing) prior to initiation. Negative hepatitis B/C screening also advised.	Allergic reactions can be life threatening. Consider co-administration with Methotrexate to minimize formation of anti-drug antibodies.
	Adalimumab	40 mg SQ every 1–2 weeks	Infections, Allergic reactions Contraindicated in demyelinating neurologic disease, active tuberculosis, deep fungal infections, prior malignancy, and severe CHF	Monitor for allergic reactions Screen for prior tuberculosis (negative IGRA testing) prior to initiation. Negative hepatitis B/C screening also advised.	Less toxic than infliximab. Has been successfully used in patient's intolerant to infliximab.
	Rituximab	500–1,000 mg IV every 1–6 months	Infections	Screen for viral hepatitis. Check IgG level with chronic therapy	High risk for viral reactivation. Can lead to IgG deficiency.
	Repository corticotropin Injection (RCI)	40–80 Units SQ twice a week	Diabetes Mellitus, Hypertension, Anxiety, Edema, Weight gain, Cataracts, Glaucoma, Sleep Disturbance.	Blood pressure and serum glucose monitoring, Bone density, Eye Exams Body Mass Index	Need to wean prednisone quickly to avoid cumulative toxicity.
Others	Hydroxychloroquine	200–400 mg QD	Loss of vision GI side effects,—abdominal pain, anorexia.	Regular eye exams depending on age and renal function	Beneficial for cutaneous disease. Minimal impact in cardiac and neurologic disease.

Global approach to treatment of Sarcoidosis

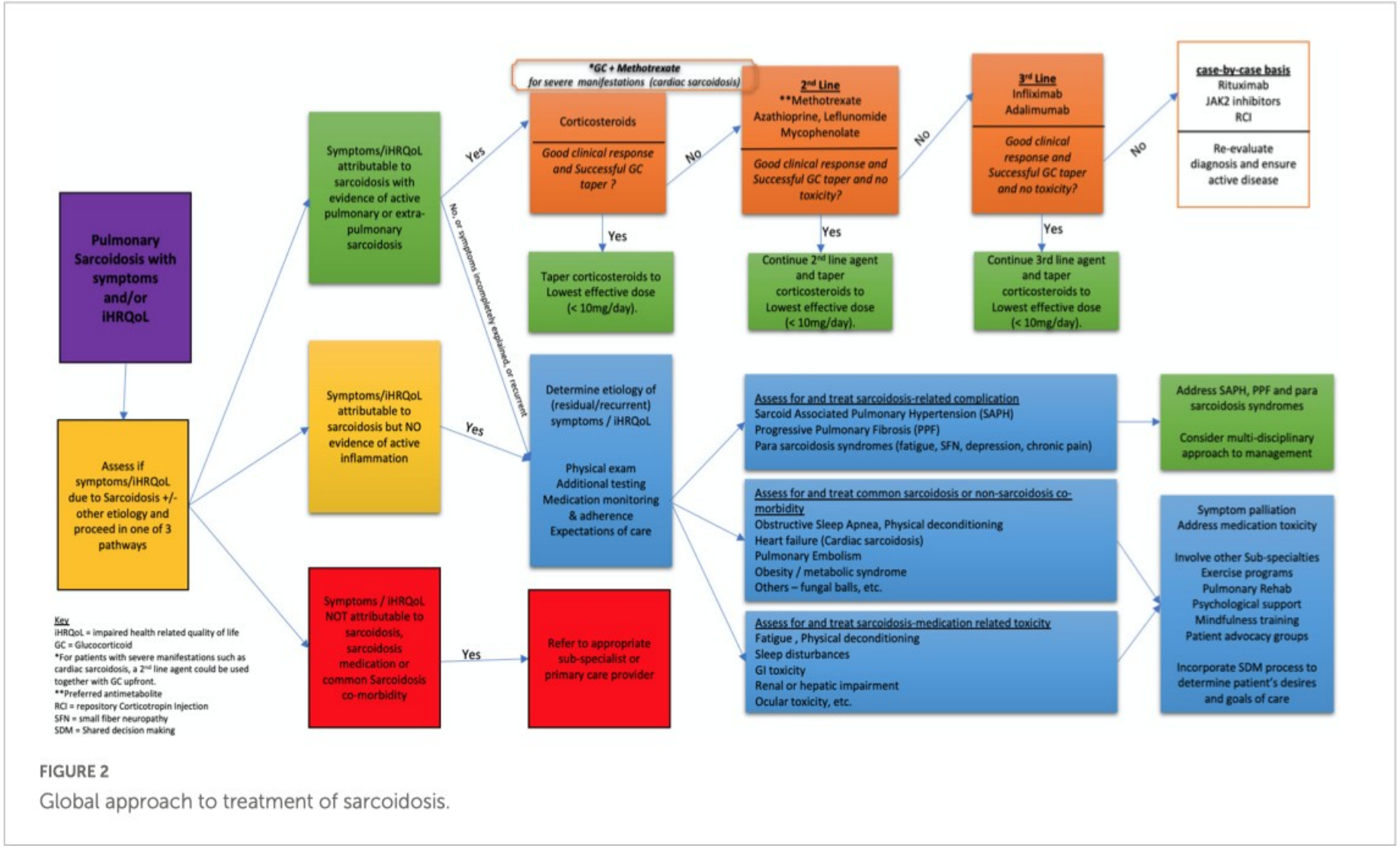


FIGURE 2
Global approach to treatment of sarcoidosis.

Proposed endpoints for clinical trials in sarcoidosis

Organ involvement	Domain	Measure	Comments
Pulmonary sarcoidosis	**Symptoms	Dyspnea—mMRC, BDI/TDI Cough—Leicester scale Fatigue—FAS	This should be customized to capture multi-organ and/or extra pulmonary involvement.
	*Physician judgment	Clinical judgment of improvement, worsening or progression.	This is applicable to systemic and all organ-specific forms of sarcoidosis.
	*Steroid sparing	% Reduction in steroid dose, Cumulative steroid dose, Duration of time at minimal steroid doses, % Of participants able to achieve steroid taper to < 10 mg/day.	Consider analyzing drop-out from placebo arm as a secondary outcome. Confounding results may occur from withdrawal from steroid or flare-ups in non-target organs. Measures of steroid toxicity and ways of addressing them need to be put in place.
	Radiology/evidence of activity	Changes in PET/CT chest imaging	Changes in PET scans will need to be defined in terms of SUVmean or SUVmax. There is a need to determine what constitutes a meaningful difference in SUV levels.
	*Medication toxicity/tolerance	Serious AEs, Life threatening AEs, AEs leading to discontinuation of therapy Other AEs	This should be captured in all clinical trials and tailored to investigational drugs and organ system targeted.
	Pulmonary function	FEV1, FVC, DLCo, CPI	There is a need to determine what is clinically meaningful disease specific change in FVC, FEV1 and DLCo for patients with pulmonary sarcoidosis. The CPI has also been validated as a prognostic severity marker in pulmonary sarcoidosis.
	Exercise capacity	6MWD	There is a need to determine what constitutes meaningful change in 6MWD for patients with pulmonary sarcoidosis.
	*HRQoL	SGRQ, SF-36, SAT-Lung FAS KSQ General Health; KSQ Lung	Various PROMs have been used to capture HRQoL. There is a need to create core sets of outcome measures for organ specific and systemic sarcoidosis.
	Mortality	Mortality often not feasible Consider composite outcome—TTCW	TTCW is a predefined composite endpoint that can be customized to capture such events as disease-related hospitalization, all-cause hospitalization, death, transplantation, worsening of 6MWD, PFT or symptom burden.
is	Cutaneous sarcoidosis disease activity HRQoL	PGA, SASI, CSAMI, Photographs SAT skin, KSQ Dermatology Questionnaire, SAT Fatigue	
	Symptoms Radiology/Evidence of Disease Activity Exercise Capacity Mortality	Arrythmias/arrythmia burden cPET Scan, cMRI, Echocardiogram (LVEF) 6MWD Mortality is often not feasible. Consider composite outcomes assessing all-cause hospitalization, cardiac hospitalization,	Note that mortality will likely never be feasible in view of rarity of disease and much improved prognosis. Though composite outcomes are more achievable, sample size is likely to be prohibitive in view of rarity of disease and much improved prognosis.
	Imaging/evidence of disease activity HRQoL	MRI Measures assessing cognitive functioning, Functional independence, strength measures of limbs, General Health status questionnaires.	
	HRQoL measures	General and organ specific HRQoL measures	This can be customized for each organ involved.

WHAT do patients aim for in treatment?

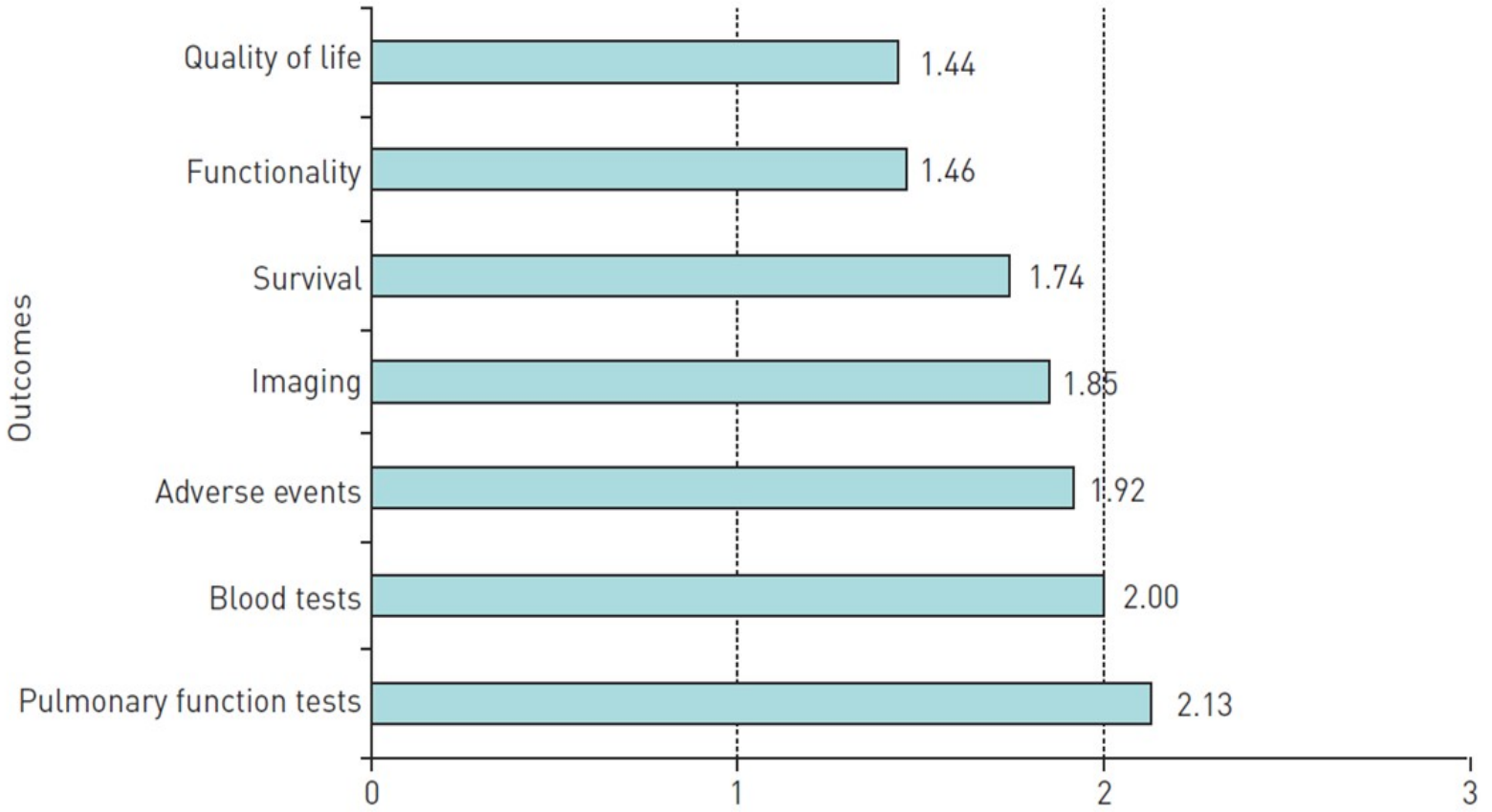


FIGURE 1 Summary of the ranking for the outcome of the seven survey questions. The mean scores were between 1 (extremely important) and 3 (moderately important).

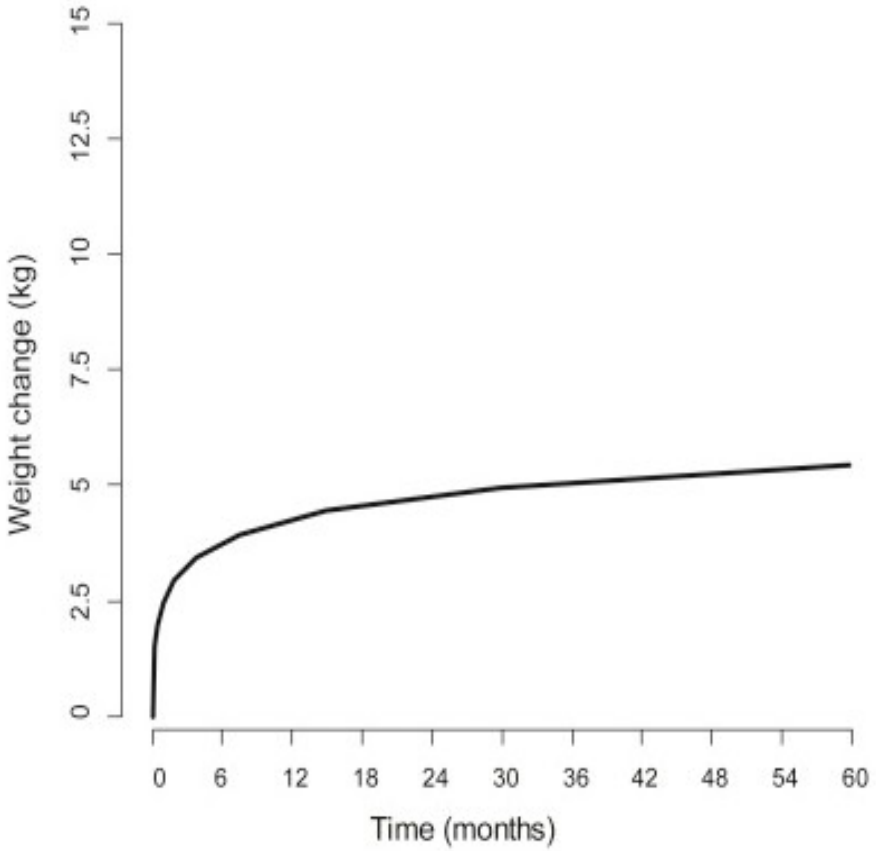
Baughman et al, ERJ Open Res 2018

POOR CORRELATION between granulomatous inflammAtion and quality of Life

- “Para-sarcoidosis syndroms”
  - Small fiber neuropathy
  - Fatigue syndromes
  - pain syndromes
  - Cognitive decline

- *Adverse effect of corticosteroids*

on quality of life



CAREFUL AND TAILORED STEROID USE ?

DRB1*03 + > resolve
DRB1*03 - > chronicity
DRB1* 03 – and steroids > chronicity

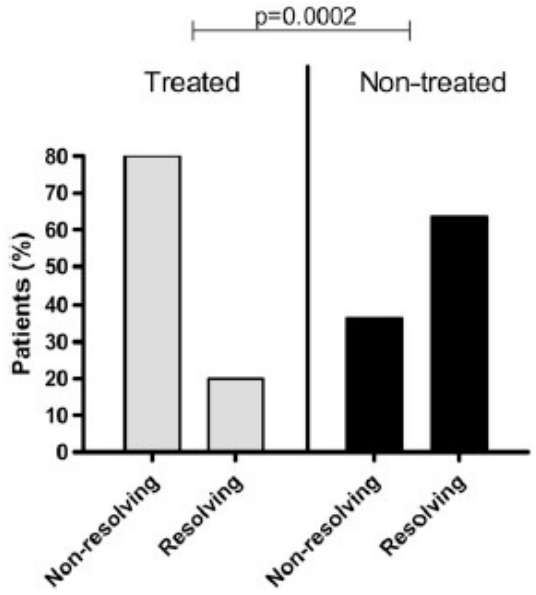
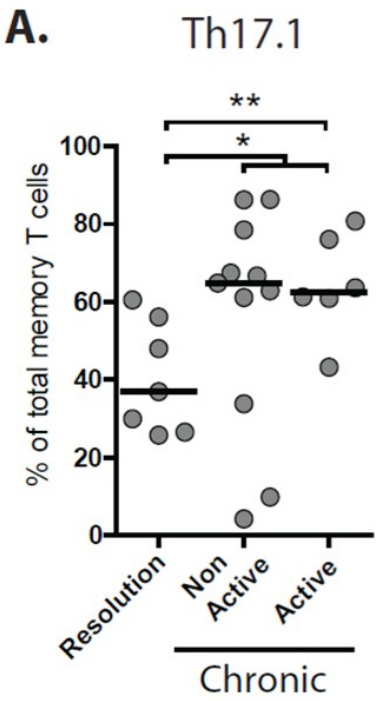


Figure 5. Disease course in HLA-DRB1*03-negative patients treated (n = 25) or nontreated (n = 63) with oral steroids ($P = 0.0002$).

High Th 17.1 porportions in BAL at diagnosis associated with chronicity



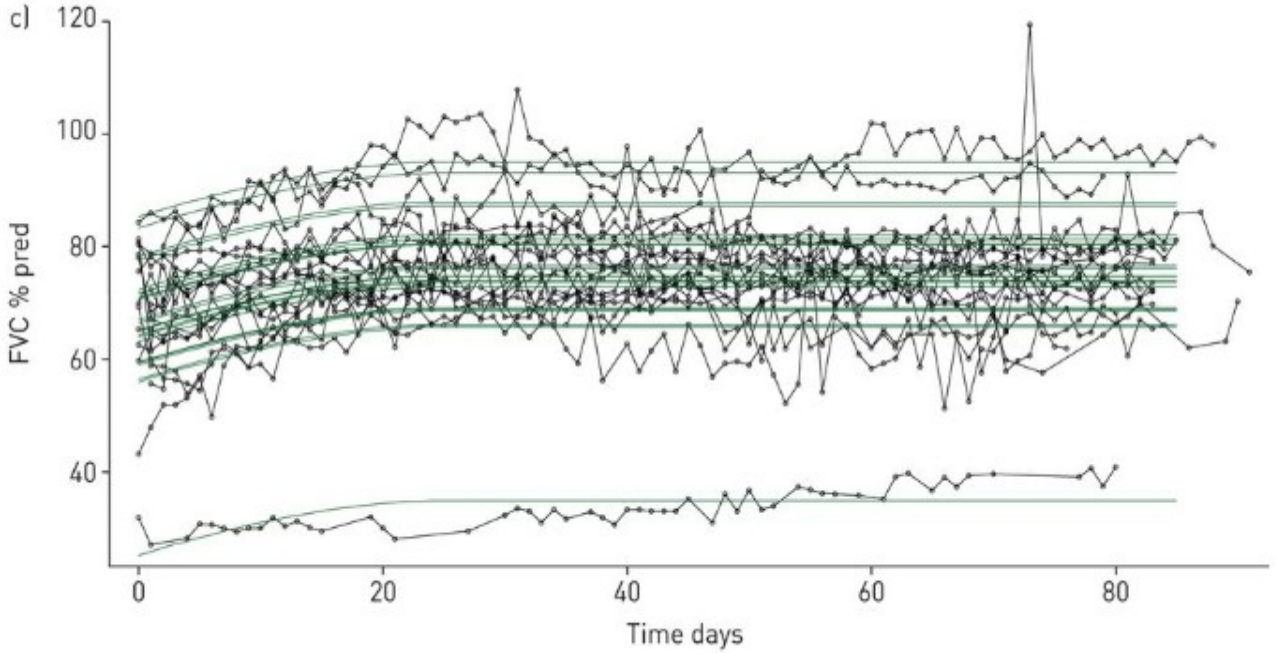
Grunewald Am J Respir Crit Care Med 2009, Broos Eur Respir J 2018, Ramesh J Exp Med 2014

Home monitoring in interstitial lung diseases

Marlies S Wijsenbeek, MD PhD • Catharina C Moor, PhD • Kerri A Johannson, MD • Peter D Jackson, MD • Yet H Khor, MD PhD • Yasuhiro Kondoh, MD PhD • et al. Show all authors

Published: October 04, 2022 • DOI: https://doi.org/10.1016/S2213-2600(22)00228-4 • Check for updates

PERSONALISED STEROID USE?



Broos et al, Eur Respir J, 2018 18;51(1).

Identifying a core outcome set for pulmonary sarcoidosis research – the Foundation for Sarcoidosis Research – Sarcoidosis Clinical OUtcomes Taskforce (SCOUT)

Nicola L. Harman[1], Sarah L. Gorst[1], Paula R. Williamson[1], Elliot S. Barnathan[2], Robert P. Baughman[3], Marc A. Judson[4], Heidi Junk[5], Nynke A. Kampstra[6,11], Eugene J. Sullivan[7], David E. Victorson[8], Marc K. Walton[9], Tamara AL-Hakim[10], Hana Nabulsi[10], Noopur Singh[10], Jan C. Grutters[11,12], Daniel A. Culver[13]*

Table 1. Definition of consensus

Consensus Classification	Description	Definition
Consensus in	Consensus that outcome should be included in the core outcome set	70% or more participants in EACH stakeholder group scoring as 7-9 AND <15% participants in each stakeholder group scoring as 1-3
Consensus out	Consensus that outcome should not be included in the core outcomes set	50% or fewer participants scoring 7-9 in EACH stakeholder group.
No consensus	Uncertainty about importance of outcome	Anything else

SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2022;

Table 2 . Outcomes included in the Core Outcome Set

Domain	Outcome	Outcome description
Physiological/Clinical	Disease activity	A measure of current, active, inflammation indicating active sarcoidosis.
Physiological/Clinical	Extra pulmonary organ involvement	Having sarcoidosis in other organs as well as the lungs
Physiological/Clinical	Extra pulmonary organ impairment	When sarcoidosis causes problems in other organs meaning that they don't function properly and/or may worsen over time.
Physiological/Clinical	Dyspnoea	Shortness of breath/being unable to catch breath
Physiological/Clinical	Pulmonary function	How well someone's lungs are working
Physiological/Clinical	Oxygenation	How well oxygen is being sent to parts of the body
Physiological/Clinical	Functional exercise capacity	Includes what day to day activities someone is able to do including the ability to do physical activity and exercise. This includes the ability to walk (including, for example, walking up an incline, walking a long distance and walking whilst talking)
Quality of Life	Health related quality of life	An overall measure of how a person's health affects their general wellbeing; perceived physical, mental and social health over time
Treatment	Adherence to treatment	The degree to which someone follows medical advice or guidance from their doctor, for example, taking their prescribed medications.
Treatment	Tolerability of treatment	How tolerable the treatment is, for example, burden of treatment, side effects etc.
Treatment	Treatment failure	When the current treatment is no longer working to control pulmonary sarcoidosis symptoms
Treatment	Side effects of treatment	When the treatment given causes unwanted/unintended effects
Resource Use	Need for hospitalisation because of pulmonary sarcoidosis	How often someone is admitted to hospital because of pulmonary sarcoidosis
Death	Death - any cause	Death from any cause
Death	Death - pulmonary sarcoidosis	Death as a result of having pulmonary sarcoidosis

Take home messages

- Treatment goals in sarcoidosis are preventing permanent end-organ dysfunction and preserving quality of life.
- Corticosteroids remain the first-line treatment, although with significant cumulative side effects.
- Second- and third-line agents may be used in refractory or relapsing disease or when corticosteroids cause unacceptable toxicity;
- Advanced sarcoidosis refers to high mortality disease manifestations (pulmonary fibrosis, pulmonary hypertension, cardiac sarcoidosis, and neurosarcoidosis) and necessitates treatment.
- Cardiac sarcoidosis requires immunosuppressive treatment and recognition of patients at risk for sustained arrythmias, which have to be managed thoroughly.
- Long-term maintenance therapy remains controversial.

MORE RESEACH NEEDED

- Evidence based therapies
- Better insights in pathogenisis and potential therapeutic targets
- Better outcome measures
- Predicting disease behavior
- More research into non pharmacological treatments
- Measuring and improving what matters to patients
- New guidelines

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Sarcoidosis Patient Charter

As the Sarcoidosis Patient Advisory Group (SPAG) of the ELF (European Lung Foundation), we believe it is essential to raise awareness and understanding of the impact of sarcoidosis among patients, caregivers, healthcare professionals, policy makers, and the general public.

~ ELF Sarcoidosis PAG | April 2022

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World Sarcoidosis Day means the day that we, as sarcoidosis patients in every corner of this wide world, are one voice, it means awareness, it means visibility, it means not being alone.

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