Essences From ERS Congress 2021

COBEL DAROU

ERS/WASOG 2021 sarcoidosis guideline

A departure from the past, clinical evaluation with a view to treatment

Athol Wells
Royal Brompton Hospital, London, UK

• Clinical approach and changes from previous guidelines

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• Department of Medicine, University of Cincinnati Medical Center, Cincinnati, OH USA

• SEVERE SARCOIDOSIS: CLINICAL FEATURES AND MANAGEMENT

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17/JUN/2022

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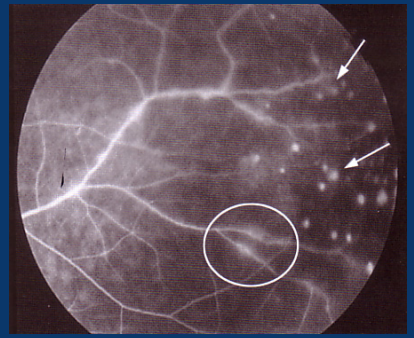
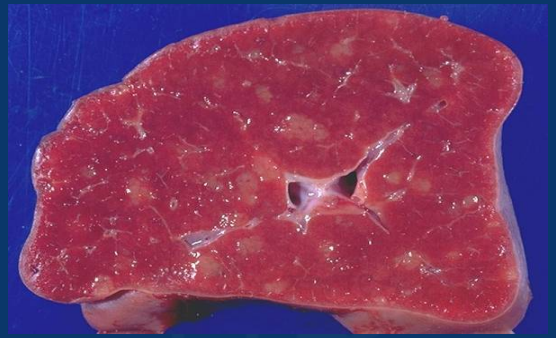
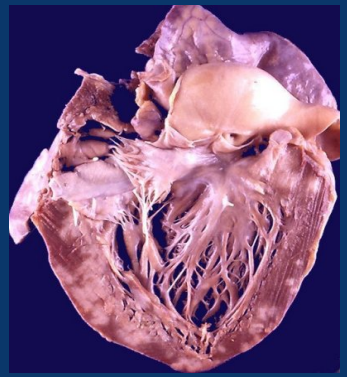
DISEASE DEFINITION

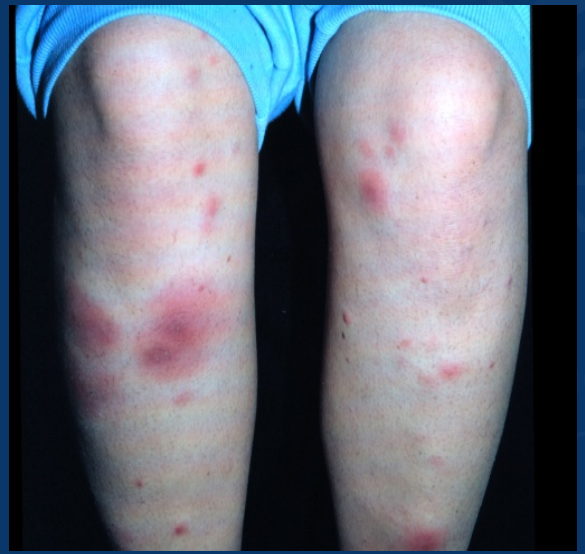
Sarcoidosis is a chronic systemic disease of unknown etiology that affects individuals worldwide and is characterized pathologically by the presence of nonnecrotizing granulomas in involved organs

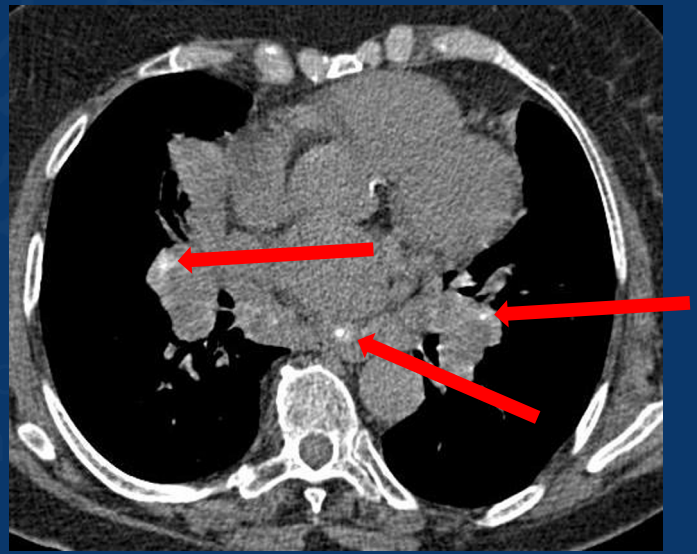
Am J Respir Crit Care Med 1999;160:736-55











When should sarcoidosis be treated?

Many patients with sarcoidosis should not receive treatment

- However, there has until now been no distillation of the “big picture” reasons to treat
- In published treatment data, reasons for treatment and satisfaction of treatment goals have not been defined explicitly although some data can be evaluated against logical treatment goals
- Long lists of reasons to treat, based on individual variables, have been put forward in various tomes

The 2021 guideline is different because…

Reasons to treat are stated as a simple dichotomy & treatment recommendations are geared to this dichotomy.

Fabulous methodologist support in accepting the limitations of the literature and distilling a pragmatic approach, generally based on low quality evidence

Reasons to treat matched to key patient wishes from a treatment:

- ***To live longer***
- ***To feel better***

The two indications for treatment

1. **DANGER (of death or permanent disability)**

2. **UNACCEPTABLE LOSS OF QUALITY OF LIFE**

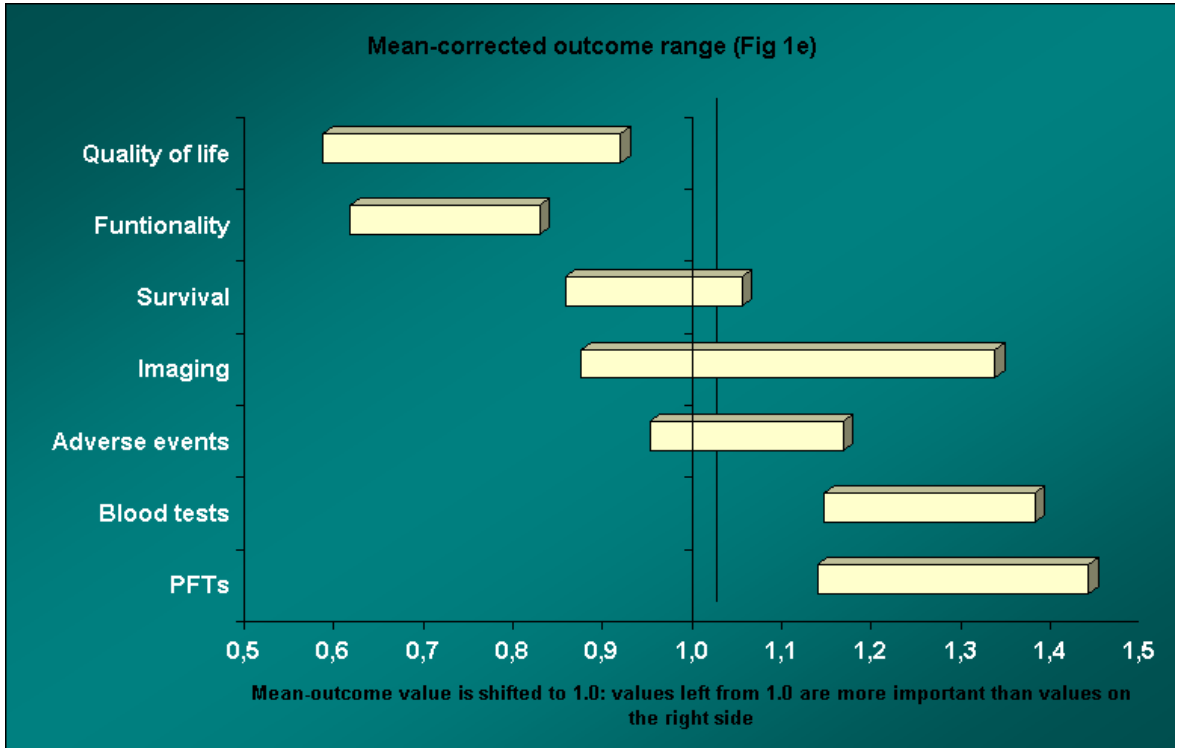
➢ **Therefore, clinical evaluation with regard to treatment indications is a two-step process:**

a) Risk stratification (pulmonary disease covered in this talk)

b) Candid discussion of loss of quality of life

Only treat sarcoidosis to avoid danger or improve quality of life

What factors are important to patients? Survey of 1842 sarcoidosis patients



Baughman, R. P. et al. Sarcoidosis: patient treatment priorities. ERJ.Open.Res., 2018; 4: 00141-02018.

Unacceptable loss of quality of life

In the end, the patient is the only expert in the room on the impact of sarcoidosis on his/her quality of life

Important to establish that loss of quality of life is truly due to sarcoidosis

The quality of life “package” extends beyond pulmonary symptoms but also includes fatigue, arthralgia, major skin involvement and many other complaints

Unacceptable loss of quality of life (2)

Treatment for loss of quality of life is not always straightforward

Sometimes, treatment is worse than the disease

Essential to form a close doctor/patient partnership, negotiating the choice and dose of therapy, often determined by patient views. Low dose therapy with adjustments titrated against a) ongoing symptoms and b) side-effects is appropriate

In essence, this often involves 20 different deals in 50 different patients

WHAT IS SEVERE SARCOIDOSIS?

Synonyms: serious, grave, dire, dangerous, distressing, high-risk

Severe = at risk of poor outcomes: fibrotic lung disease, cardiac, neurologic, and multiorgan disease

DISEASE COURSE

Bothersome disease

50-65%

Persistent disease

30-50%

Significant organ impairment/comorbidities/ death

5-10%

Progressive disease

20-30%

Lung fibrosis

10-30%

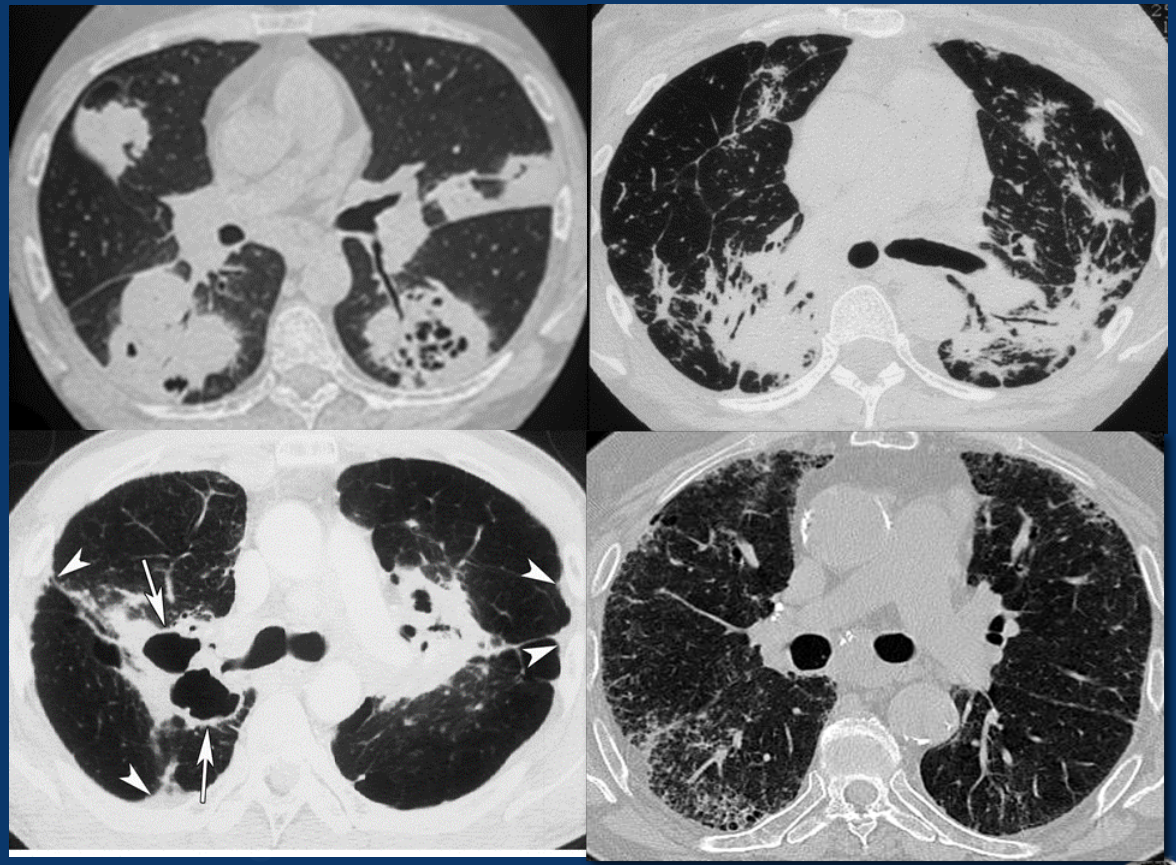
Baughman RP. QJM 2006; Mana J. Respiration 1994; Viskum K. Eur Respir J 1993; Nagai S. Curr Opin Pulm Med 1999; Judson MA. SVDLD 1993; Neville E. QJM 1983; Israel HL. Ann NY Acad Sci 1986

RISK FACTORS FOR DEVELOPMENT OF ADVANCED DISEASE

PERSISTENT DISEASE	CLINICALLY BOTHERSOME DISEASE
Black race	Black race
Older age	More dyspnea at time of diagnosis
Female gender	Need for Tx during first 6 months after diagnosis
Multiple organ involvement	Multiple organ involvement
Ascending Scadding radiograph stage	Ascending Scadding radiograph stage
Scadding stage at presentation	Lower socioeconomic status
Architectural distortion of the airways or cystic changes	
Absence of lymphadenopathy	
Need for systemic therapy	
Splenomegaly	

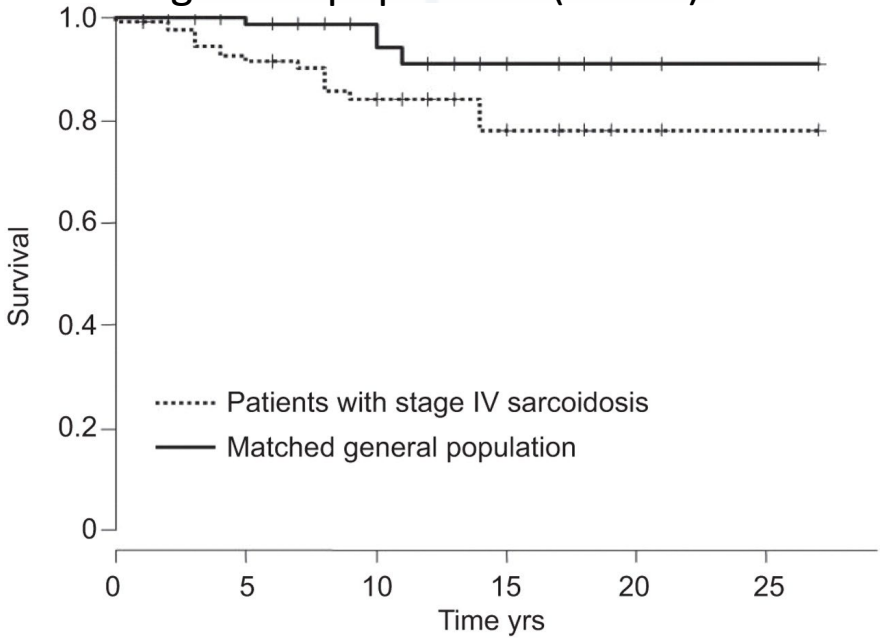
COMPLICATIONS OF FIBROTIC PULMONARY SARCOIDOSIS

- Fibrocystic disease
- Mycetoma
- (Traction) bronchiectasis
- Pulmonary hypertension



FIBROTIC SARCOIDOSIS IMPACT ON SURVIVAL

Comparison of survival between patients with radiographic stage IV disease and a matched French general population (n=142)



Nardi A et al. Eur Respir J 2011;38:1368-73

Predictors of mortality in Pulmonary Sarcoidosis

Study of 452 sarcoid patients with PFT and chest imaging, with evidence of pulmonary sarcoidosis

PH confirmed by right heart study in 28 (6.4%)

42 died during the study, including 38 (8%) with sarcoidosis-associated respiratory failure

Outcome = mortality

[1]Kirkil G, Lower EE, Baughman RP. Predictors of Mortality in Pulmonary Sarcoidosis. Chest 2018;153:105–13.

No cohort bias towards severe disease

TABLE 2] Comparison of Patients With Sarcoidosis Dying of Respiratory Failure Compared With Control Group Subjects

Characteristic	Control Subjects (n = 414)	Died of Sarcoidosis (n = 38)
Age, y	50 ± 9.9	54 ± 9.9[a]
Race[b]		
White	292	19
Black	117	19
Asian	5	0
Sex		
Female	289	24
Male	125	14
FEV_1, % predicted	81.0 ± 20.84	79.6 ± 20.17
FVC, % predicted	83.1 ± 18.29	83.6 ± 16.95
DLCO, % predicted	75.3 ± 24.01	82.1 ± 21.76
CPI	26 ± 18.0	21 ± 15.9

Data are presented as mean ± SD unless otherwise indicated. CPI = composite physiologic index; DLCO = diffusion lung carbon monoxide.
[a]Differs from control subjects, $P = .0139$.
[b]Differs from control subjects, $\chi^2 = 8.058$, $P = .0178$.

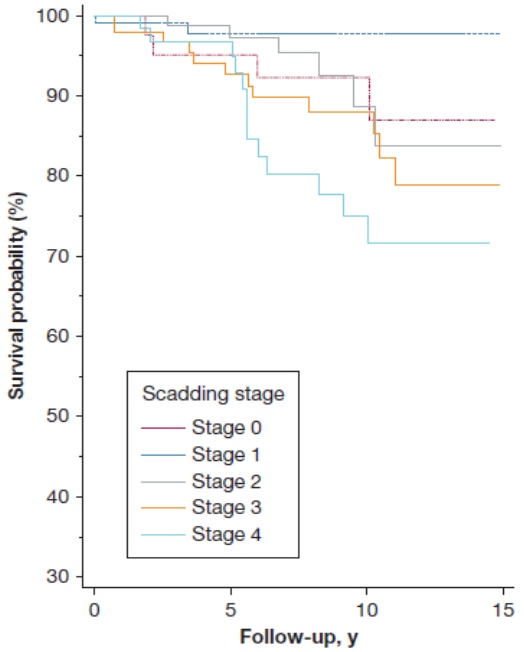
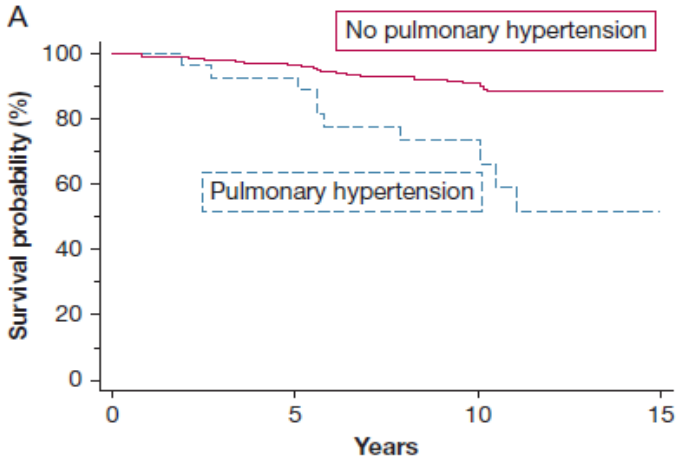
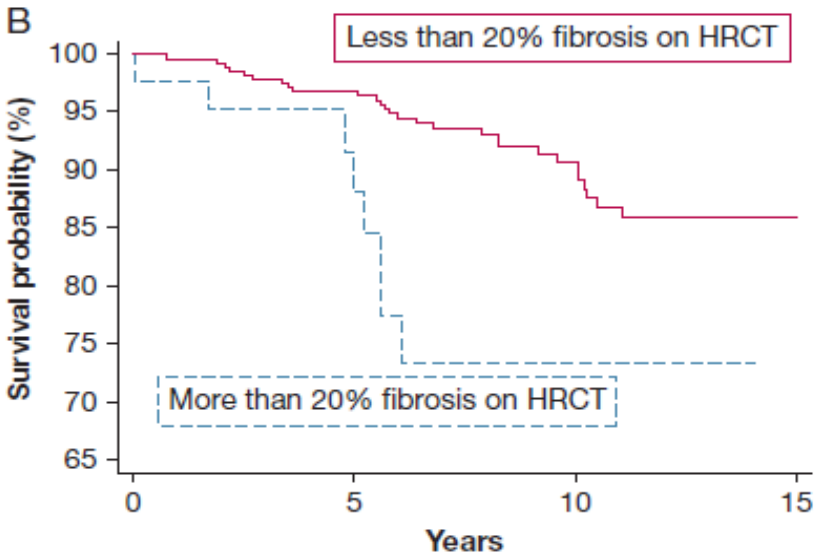


Figure 1 – *Survival vs Scadding chest radiograph stage.*[25] *Significant difference between groups,* P = .0043.

[1]Kirkil G, Lower EE, Baughman RP. Predictors of Mortality in Pulmonary Sarcoidosis. Chest 2018;153:105–13.

What can be concluded…





[1]Kirkil G, Lower EE, Baughman RP. Predictors of Mortality in Pulmonary Sarcoidosis. Chest 2018;153:105–13.

An integrated clinicoradiological staging system for pulmonary sarcoidosis: a case-cohort study

Simon LF Walsh, Athol U Wells, Nicola Sverzellati, Gregory J Keir, Lucio Calandriello, Katerina M Antoniou, Susan J Copley, Anand Devaraj, Toby M Maher, Elizabetta Renzoni, Andrew G Nicholson, David M Hansell

Lancet Respir Med 2014;
2: 123–30

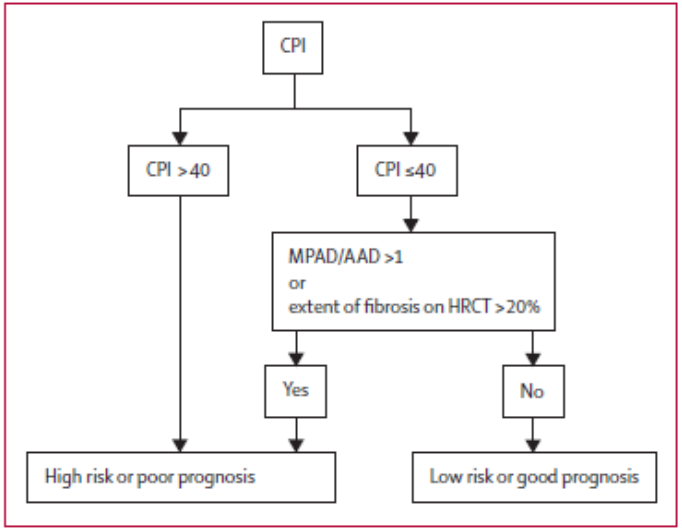


Figure 1: **Clinical staging algorithm for stratification of clinical risk in pulmonary sarcoidosis**
CPI=composite physiological index. HRCT=high-resolution computed tomography. MPAD/AAD=main pulmonary artery diameter to ascending aorta diameter ratio.

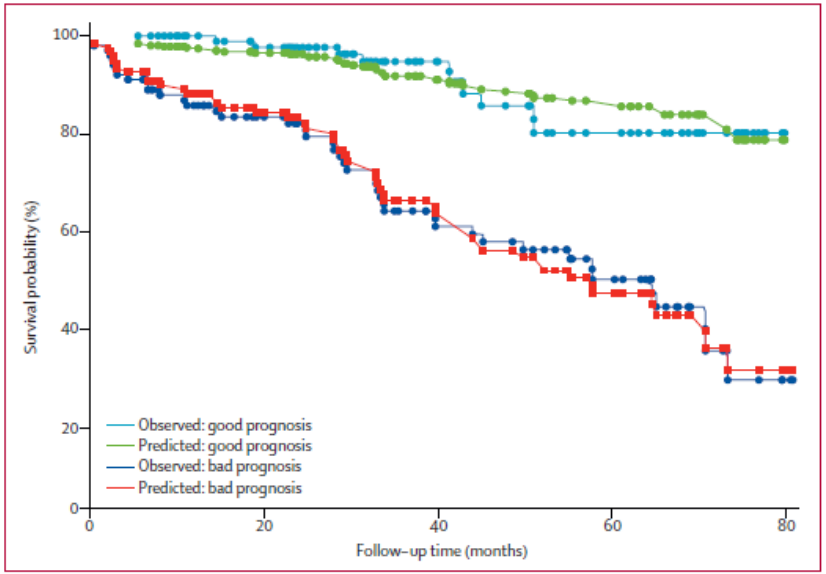
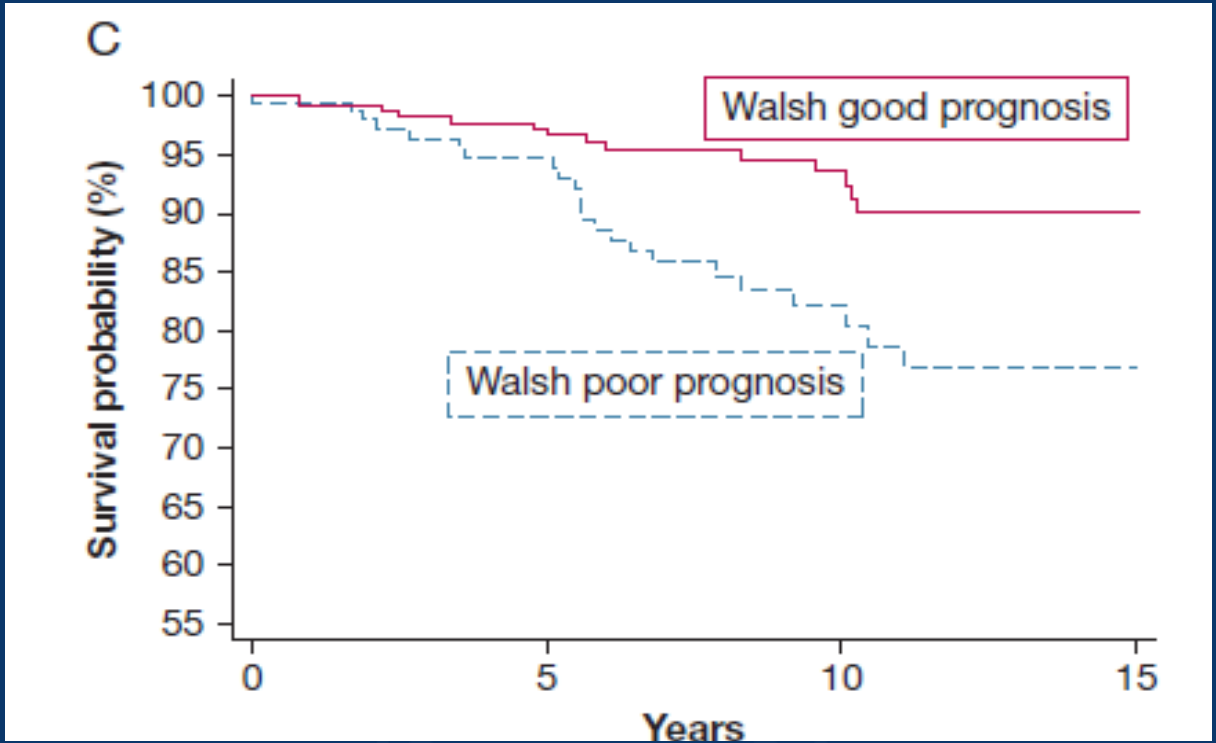
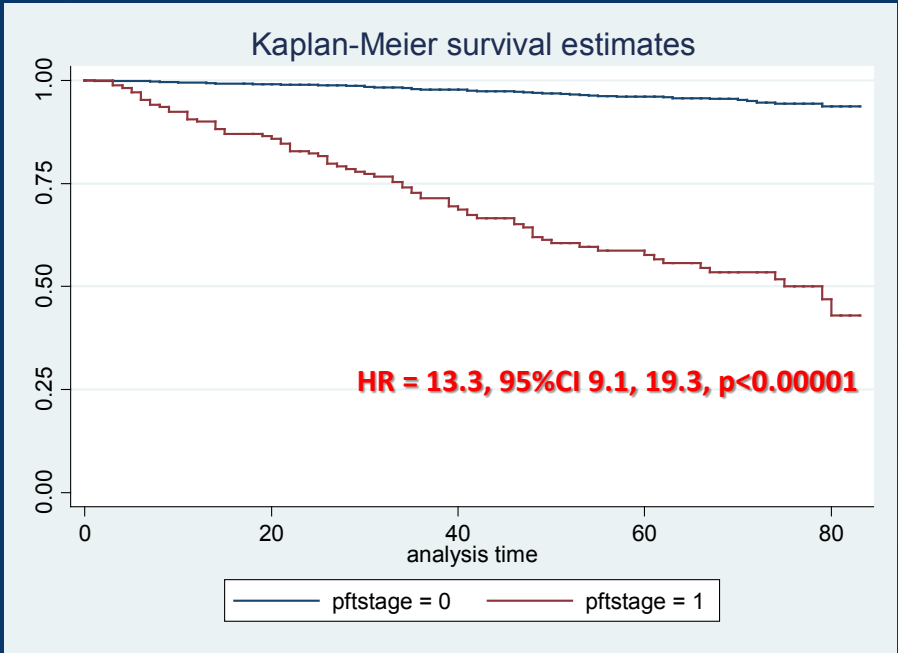


Figure 3: **Comparison of survival predicted by the sarcoidosis staging model with observed Kaplan-Meier estimates in the test cohort (group B, n=252).**

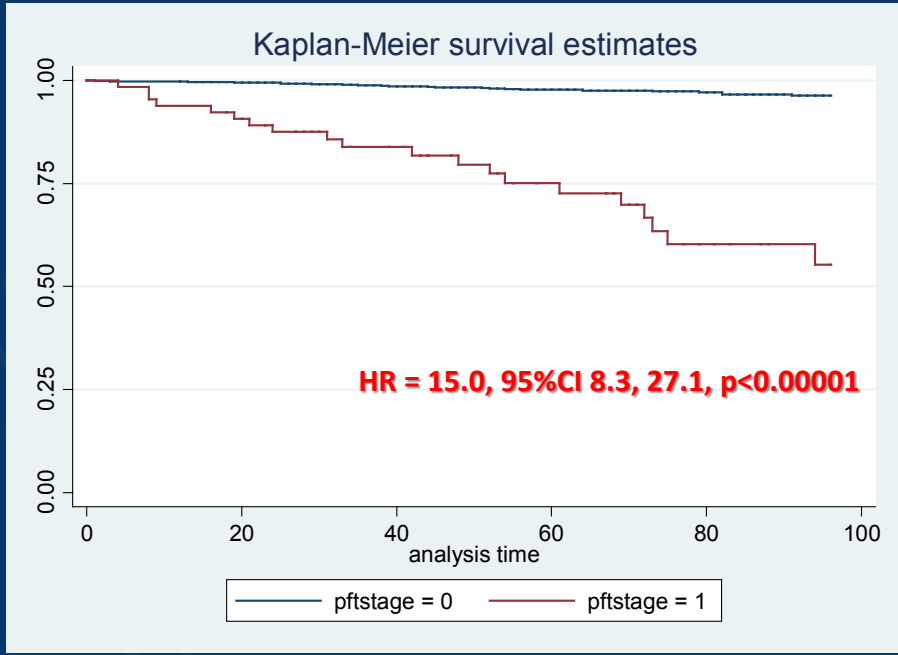


[1]Kirkil G, Lower EE, Baughman RP. Predictors of Mortality in Pulmonary Sarcoidosis. Chest 2018;153:105–13.

RBH derivation cohort (n=1245)



Utrecht validation cohort (n=1139)



Simple PFT staging (CXR provides no added value) mostly driven by Dlco<40%

[1]Kouranos V, Jacob J, Nicholson A, Renzoni E. Fibrotic Hypersensitivity Pneumonitis: Key Issues in Diagnosis and Management. JCM 2017;6:62

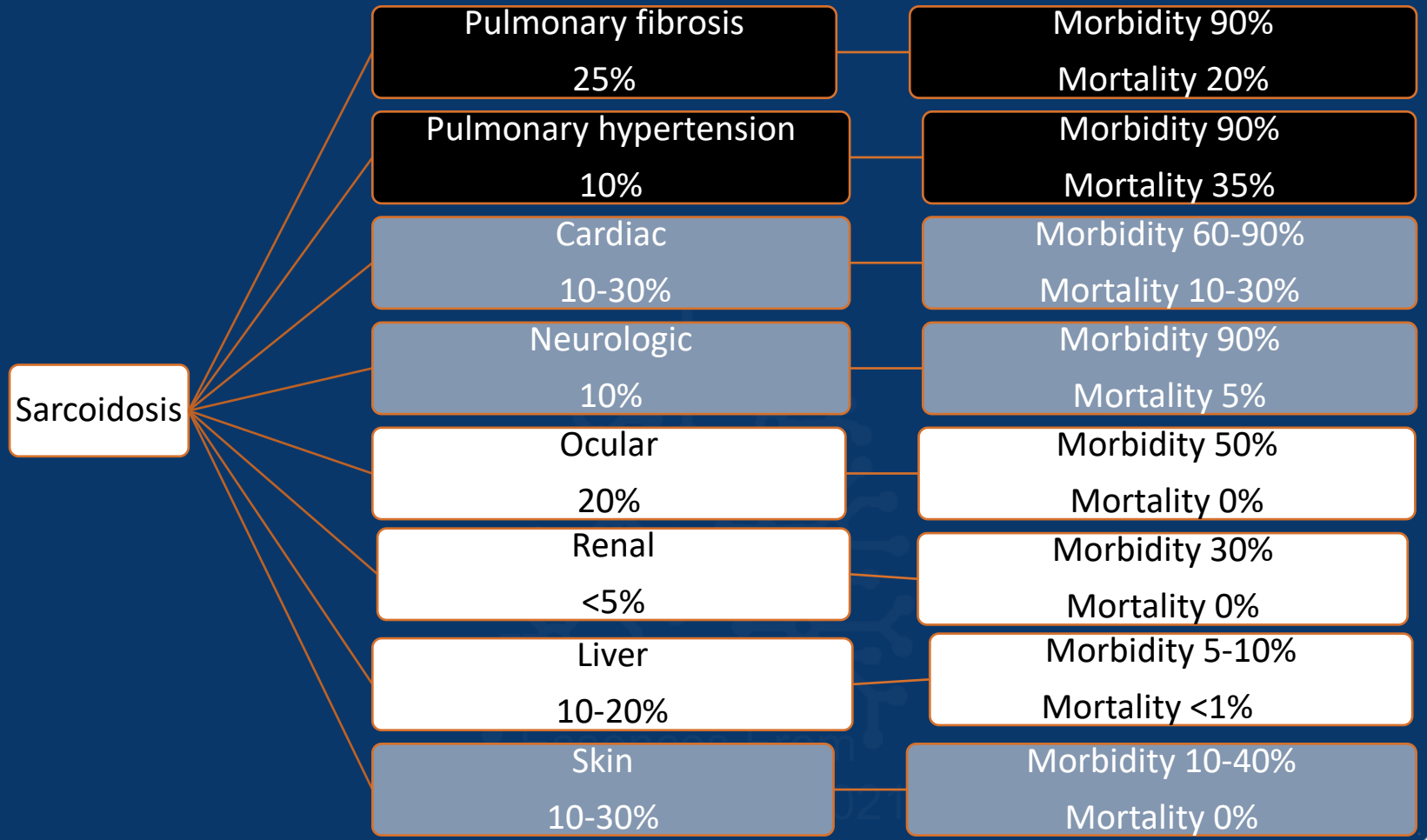
Hazards ratio for mortality from pulmonary sarcoidosis

	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.



Baughman RP, Wells AU. Advanced sarcoidosis. Curr Opin Pulm Med 2019; 25:497-504.

Sarcoidosis mortality in Sweden: a population-based cohort study

IR/OTH/2022/0005

Aim :

We aimed to investigate sarcoidosis mortality in a large, population-based cohort, taking into account disease heterogeneity.

Population :

Individuals with incident sarcoidosis (n=8207) were identified from the Swedish National Patient Register using International Classification of Disease codes (2003–2013).

Methods:

In a subset, cases receiving treatment ±3 months from diagnosis were identified from the Prescribed Drug Register. Nonsarcoidosis comparators from the general population were matched to cases 10:1 on birth year, sex and county. Individuals were followed for all-cause death in the Cause of Death Register. Adjusted mortality rates, rate differences and hazard ratios (HRs) were estimated, stratifying by age, sex and treatment status.

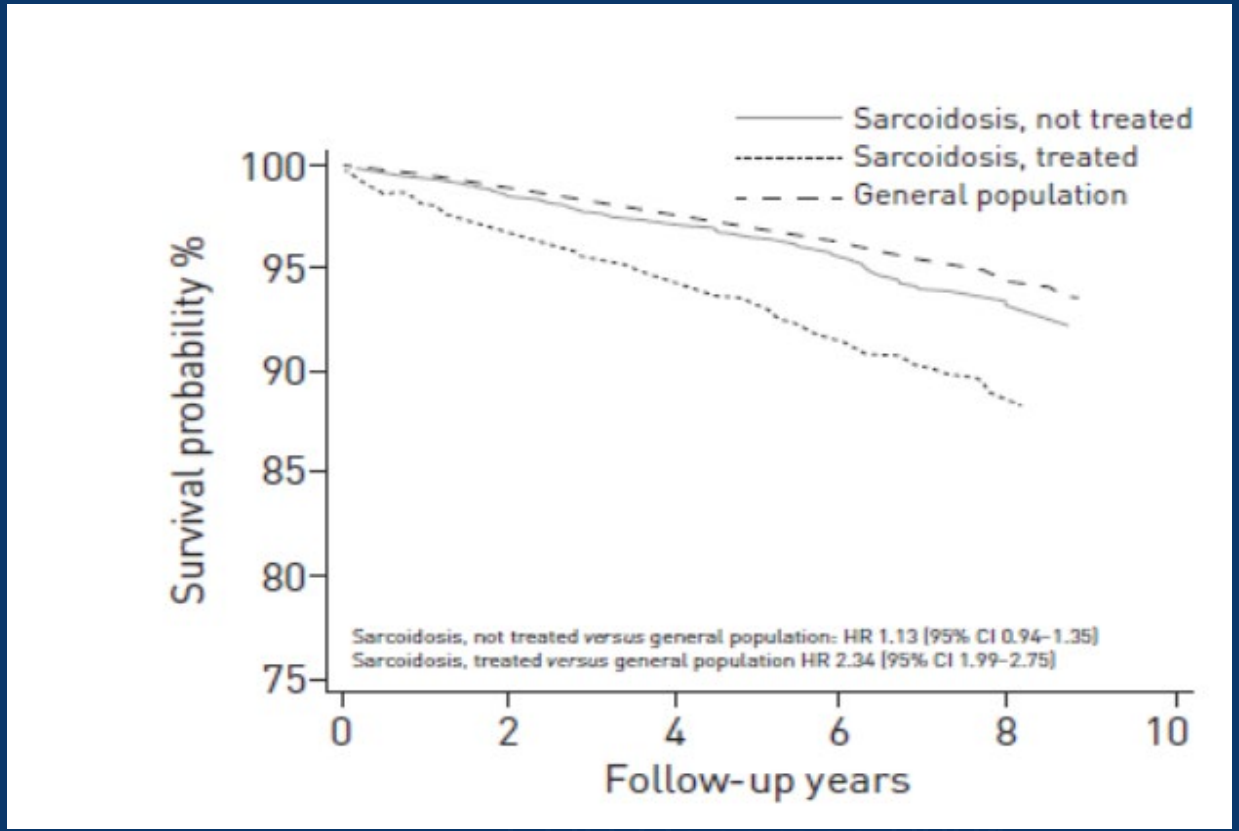
Results:

The mortality rate was 11.0 per 1000 person-years in sarcoidosis *versus* 6.7 in comparators (rate difference 2.7 per 1000 person-years). The HR for death was 1.61 (95% CI 1.47–1.76), with no large variation by age or sex. For cases not receiving treatment within the first 3 months, the HR was 1.13 (95% CI 0.94–1.35). The HR was 2.34 (95% CI 1.99–2.75) for those receiving treatment.Individuals with sarcoidosis are at a higher risk of death compared to the general population. For the majority, the increased risk is small. However, patients whose

.

[1]Rossides M, Kullberg S, Askling J, Eklund A, Grunewald J, Arkema EV. Sarcoidosis mortality in Sweden: a population-based cohort study. Eur Respir J 2018;51:1701815

Excess mortality: disease severity or treatment-related?



[1]Rossides M, Kullberg S, Askling J, Eklund A, Grunewald J, Arkema EV. Sarcoidosis mortality in Sweden: a population-based cohort study. Eur Respir J 2018;51:1701815

Under-treatment vs over-treatment

- Treatment should be introduced **ONLY** if there is:
  - "danger" (moderate progressive disease or severe disease)
  - or unacceptable loss of quality of life

- Risk stratification in fibrotic disease based on severity as judged by CT/PFT/exercise intolerance and evidence of pulmonary vasculopathy

The 2021 international guideline…….>>>>>>>>

ERS clinical practice guidelines on treatment of sarcoidosis

The major reasons to treat sarcoidosis are:

1. To lower the morbidity and mortality risk or
2. To improve quality of life (QoL).

The indication for treatment varies depending on which manifestation is the cause of symptoms: lungs, heart, brain, skin or other manifestations.

While glucocorticoids remain the first choice for initial treatment of symptomatic disease, prolonged use is associated with significant toxicity.

Glucocorticoid-sparing alternatives are available.

The presented treatment guidelines aim to provide guidance to physicians treating the very heterogenous sarcoidosis manifestations. Given the diverse nature of the disease, treatment decisions require an assessment of organ involvement, risk for significant morbidity, and impact on QoL of the disease and treatment.

Baughman RP, Valeyre D, Korsten P, et al. ERS clinical practice guidelines on treatment of sarcoidosis. Eur Respir J 2021; 58: 2004079.

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

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Pulmonary sarcoidosis:
General considerations

At presentation, patients usually undergo:

- PFT (FVC), (FEV1) and DLCO,
- CXR,
- HRCT (in those with clinically significant pulmonary sarcoidosis).
- 6MWD (may be reduced in some cases because of pulmonary or cardiac disease, muscle involvement, or fatigue).
- Transthoracic echocardiography may be indicated in patients with chronic exercise intolerance or suspected pulmonary hypertension.

General treatment goals are:

1. to achieve either disease regression or short-term disease stabilization (when irreversible) with higher dose GC treatment,
2. to identify the minimum longer term GC dose required for stabilization of sarcoidosis.

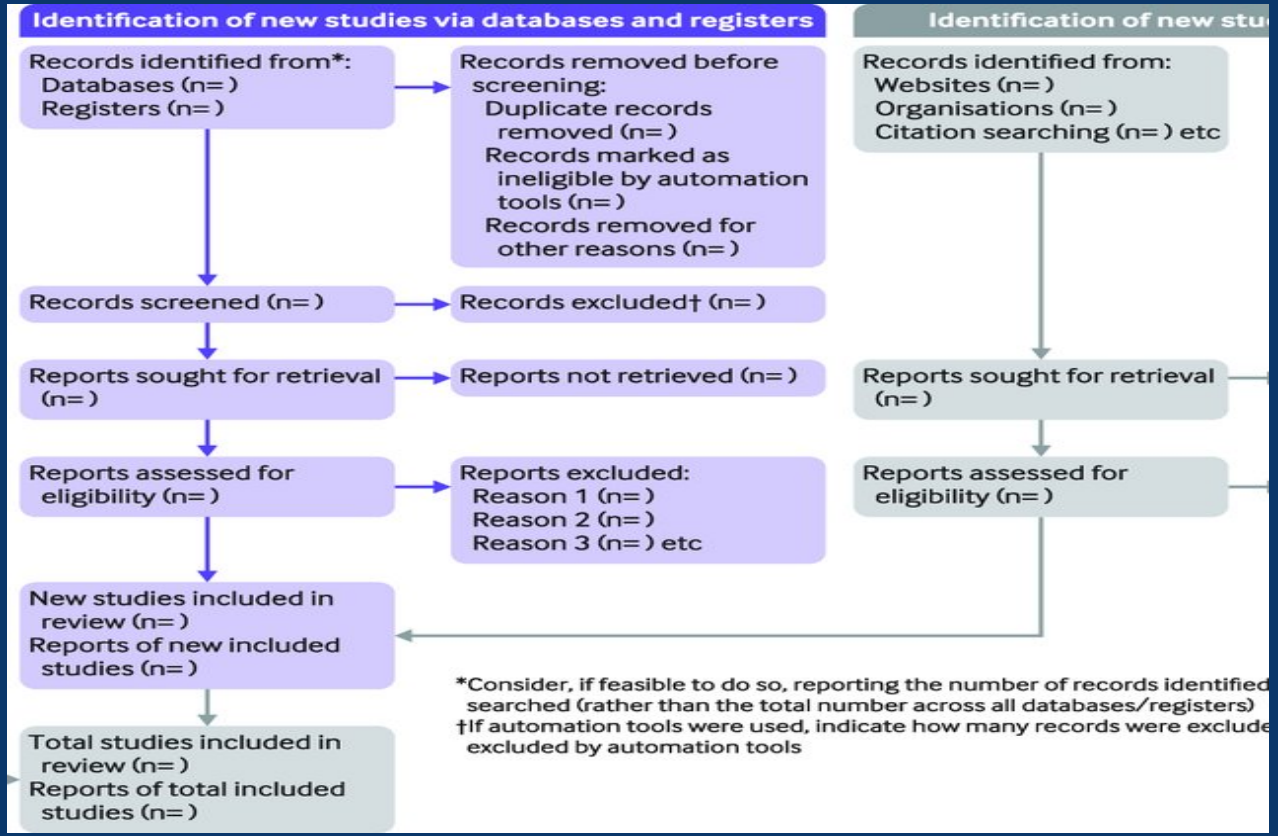
PICO 1

In patients with pulmonary sarcoidosis, should glucocorticoid treatment be used

versus

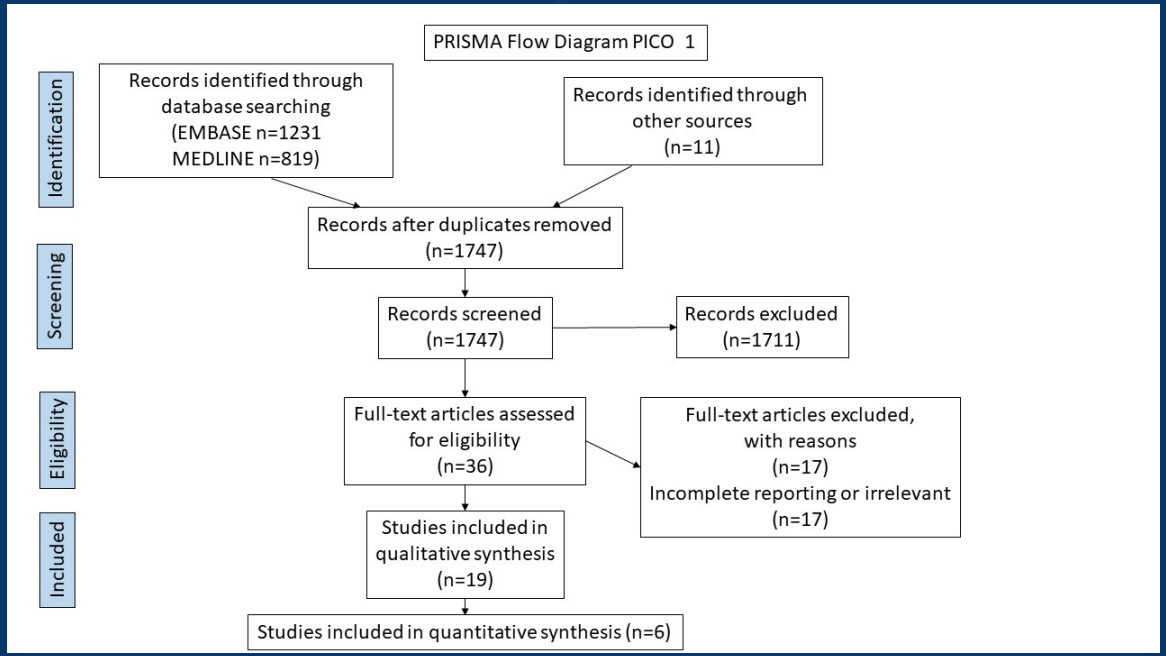
no immunosuppressive treatment?

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



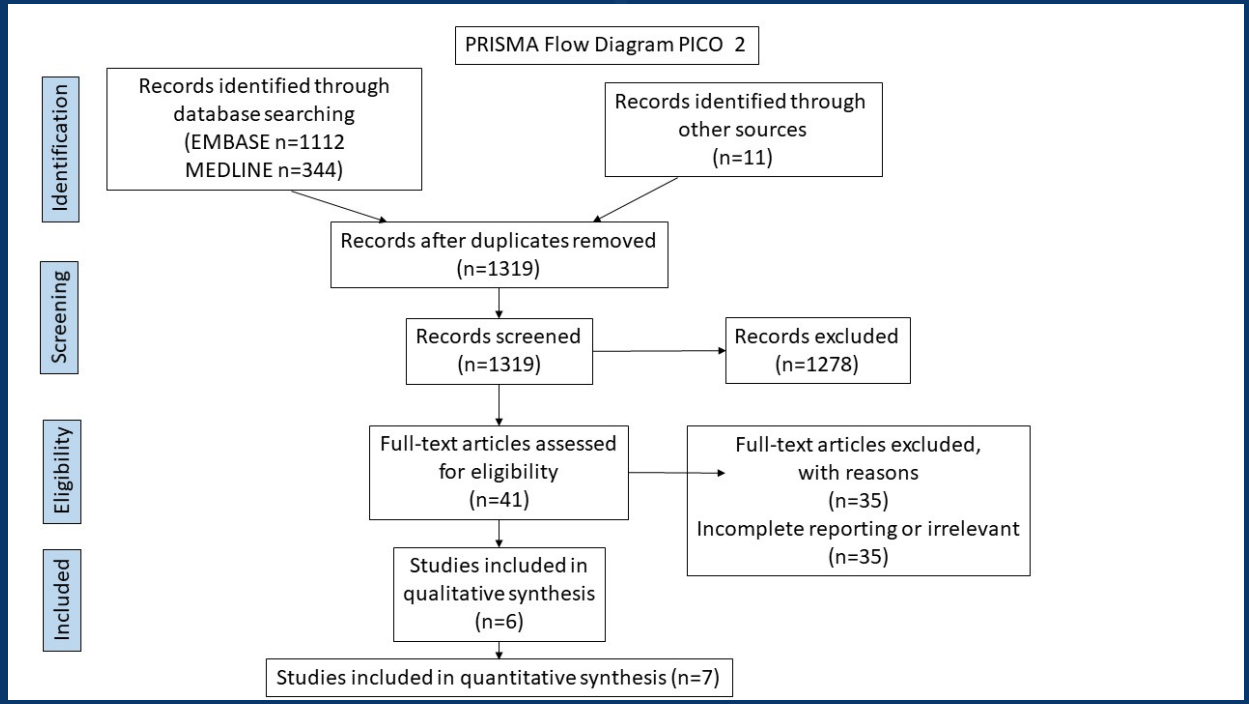
PICO 1

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



PICO 2

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



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

Treatment algorithms

Grade recommendations

Strong recommendation
Conditional recommendation

Current practice

Most committee members used this interventions

Intervention on a case by case basis

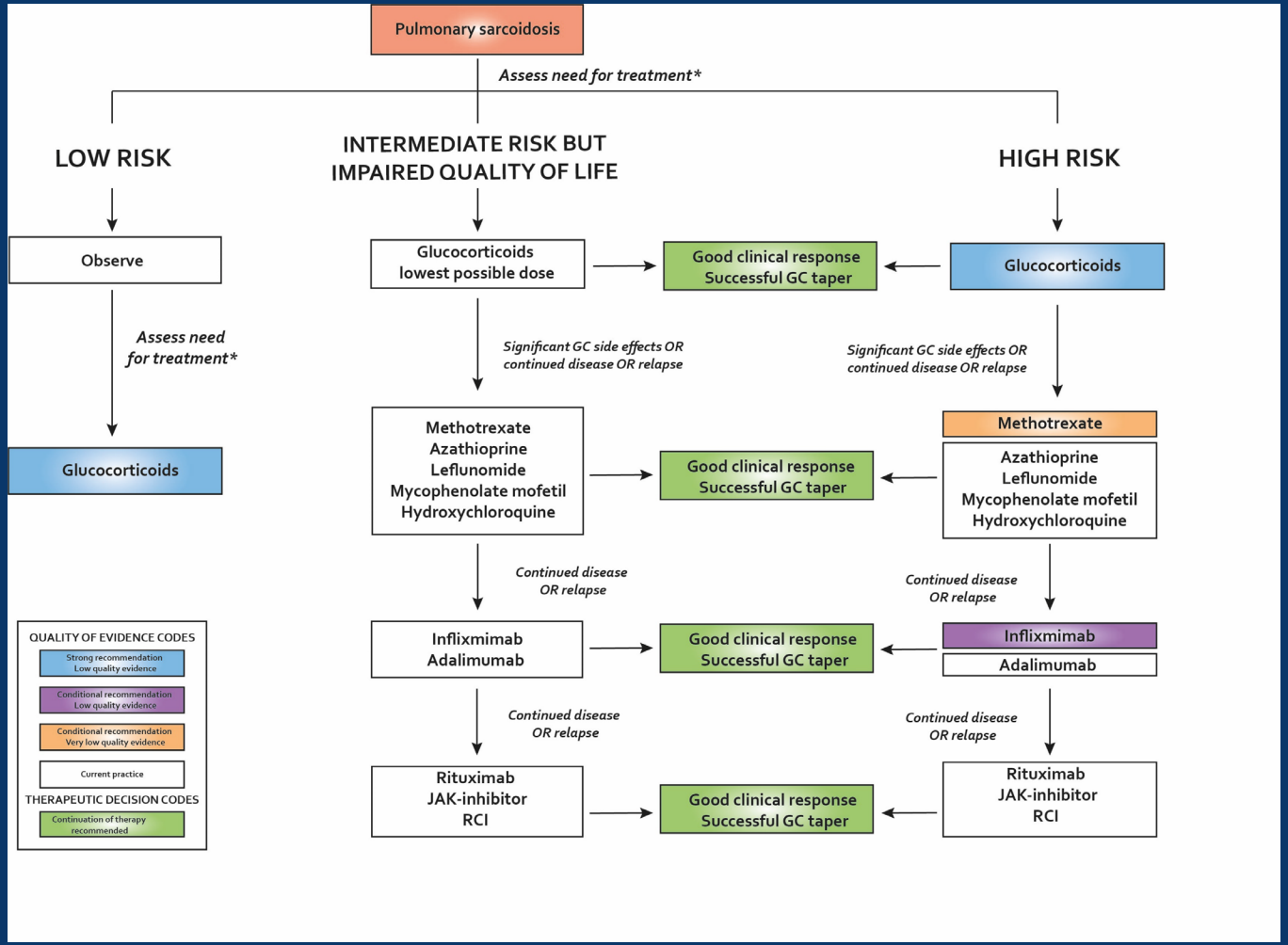
Committee members felt this intervention could be considered in some situations

Implications of a *strong/category A* recommendation

- Patients: Most people in this situation would want the recommended course of action and only a small proportion would not
- Clinicians: Most patients should receive the recommended course of action
- Policy makers: The recommendation can be adapted as a policy in most situations

Implications of a *conditional/weak/category B* recommendation

- Patients: The majority of people in this situation would want the recommended course of action, but many would not
- Clinicians: Be more prepared to help patients to make a decision that is consistent with their own values/decision aids and shared decision making
- Policy makers: There is a need for substantial debate and involvement of stakeholders



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).

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PICO 2

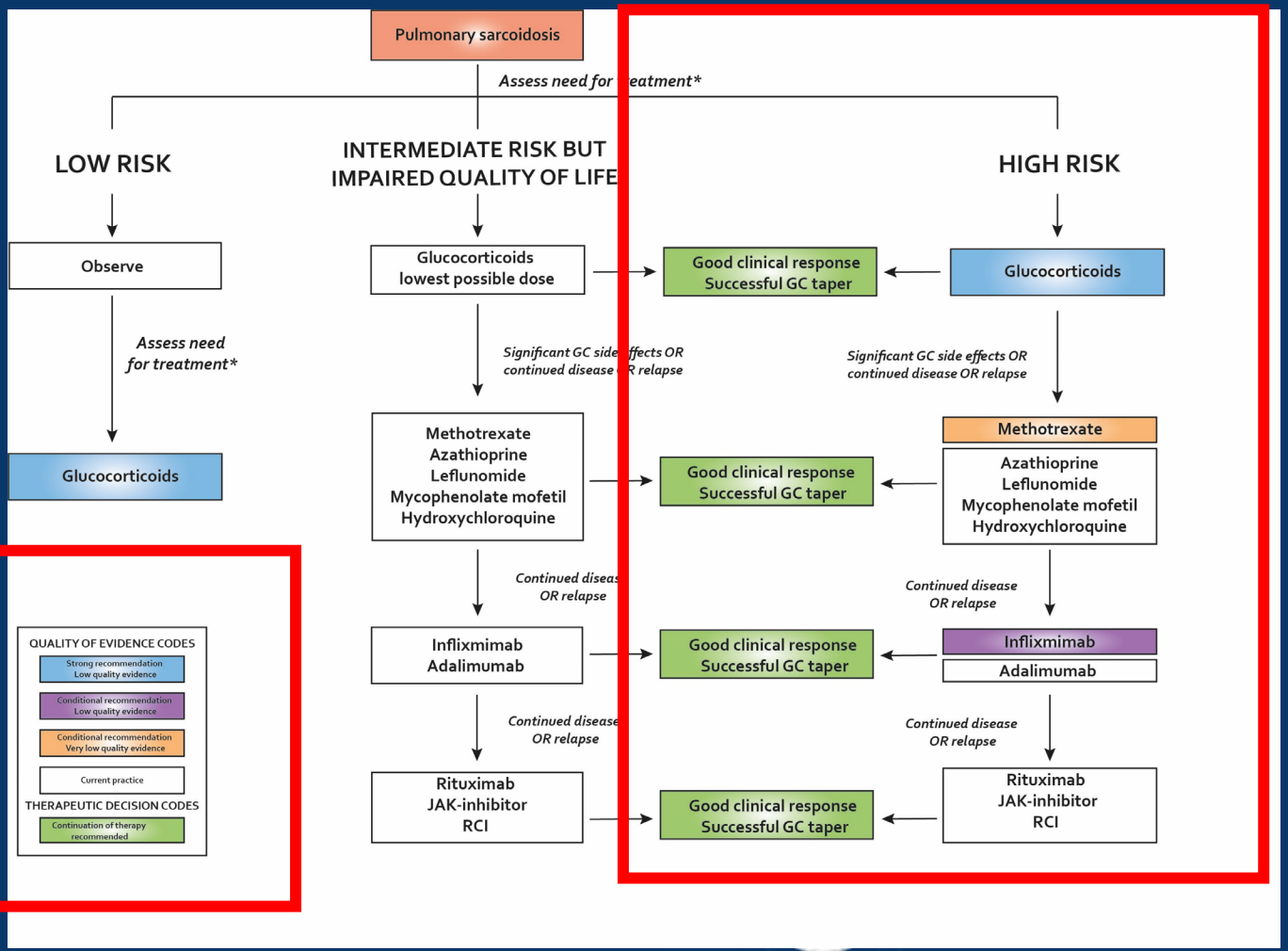
In patients with pulmonary sarcoidosis, should one add immunosuppressive treatment or remain on glucocorticoid treatment alone?

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).



Only treat sarcoidosis to avoid danger or improve quality of life

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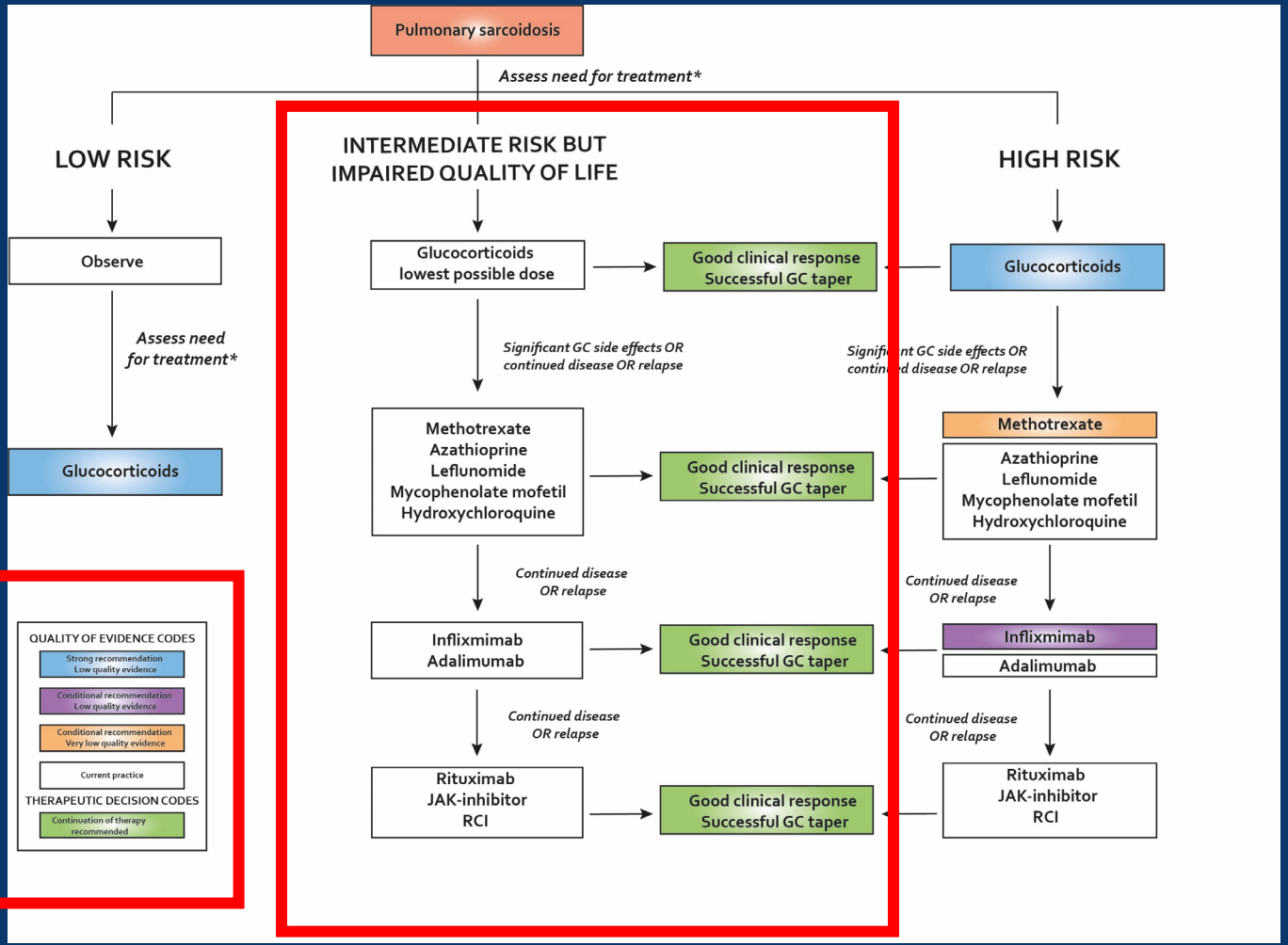

Future research

There is an urgent need for accurate risk stratification in pulmonary sarcoidosis.

Unmet needs include:

1. *Optimal pulmonary function thresholds, integrated with disease duration.*
2. *Risk assessment for progression in higher risk disease.*
3. *When higher risk disease is best managed with GC monotherapy as opposed to combination therapy with second- or third-line agents.*
4. *The role of PET in rationalising long-term treatment following initial stabilisation of irreversible disease (requires exploration in large cohorts).*
5. *A database is needed to quantify the therapeutic efficacy of GC in patients with unacceptable loss of QoL, to explore the efficacy and adverse effects with the use of low-dose GC treatment, and to evaluate the optimal dose and duration driven by patient choice.*
6. *How high the initial GC dosage should be, how long to stay on that dose and how to taper.*
7. *The efficacy, safety and cost efficiency of rituximab, repository corticotropin injection, anti TNF biosimilars and other immunosuppressive agents.*
8. *The role of antifibrotic agents such as nintedanib and pirfenidone.*
9. *Valdation the newer end-points, including change in PET and QoL.*

Conclusion

An ERS Task Force has developed specific guidelines regarding treatment of sarcoidosis

Baughman RP, Valeyre D, Korsten P, Mathioudakis AG, Wuyts WA, Wells A et al. ERS clinical practice guidelines on treatment of sarcoidosis. Eur Respir J 2021;2004079-2020.

For pulmonary disease, GRADE recommendations have been based on available evidence

In addition, comments regarding other specific therapies were made by the committee

The role of these guidelines in treatment of sarcoidosis will be discussed in the following case(s)

Thank You

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