DIAGNOSIS AND DETECTION OF SARCOIDOSIS

An Official American Thoracic Society Clinical Practice Guideline

ONLINE SUPPLEMENT

Elliott D. Crouser MD[*‡,1], Lisa A. Maier MD[*‡,2], Kevin C. Wilson MD[‡,3], Catherine A. Bonham MD[4], Adam S. Morgenthau MD[5], Karen C. Patterson MD[6,7], Eric Abston MD[3], Richard C. Bernstein MD[8], Ron Blankstein MD[9], Edward S. Chen MD[10], Daniel A. Culver DO[11], Wonder Drake MD[12], Marjolein Drent MD[13], Alicia K. Gerke MD[14], Michael Ghobrial MD[11], Praveen Govender MD[3], Nabeel Hamzeh MD[14], W. Ennis James MD[15], Marc A. Judson MD[16], Liz Kellermeyer MSLS[17], Shandra Knight MSLS[17], Laura L. Koth MD[18], Venerino Poletti MD[19], Subha V. Raman MD[20], Melissa H. Tukey MD[21], Gloria E. Westney MD[22], and Robert P. Baughman MD[‡,23] on behalf of the ATS Assembly on Clinical Problems.

[*] Co-first authors, [‡]Co-chairs of the Clinical Practice Guidelines Panel

Affiliations:

[1] Division of Pulmonary, Critical Care, & Sleep Medicine, The Ohio State University, Columbus, OH
[2] Division of Environmental & Occupational Health, National Jewish Health, Denver, CO
[3] Division of Pulmonary, Allergy, Sleep, & Critical Care Medicine, Boston University School of Medicine, Boston, MA
[4] Division of Pulmonary & Critical Care Medicine, University of Virginia, Charlottesville, VA,
[5] Division of Pulmonary, Critical Care, & Sleep Medicine, Icahn School of Medicine at Mount Sinai, New York, NY
[6] Division of Pulmonary, Allergy, & Critical Care Medicine, University of Pennsylvania, Philadelphia, PA
[7] Brighton and Sussex Medical School, Brighton, England
[8] Division of Pulmonary, Allergy, & Critical Care Medicine, Penn State University, Hershey, PA
[9] Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA
[10] Division of Pulmonary & Critical Care Medicine, Johns Hopkins Medical School, Baltimore, MD
[11] Department of Medicine, Respiratory Institute, Cleveland Clinic, Cleveland, OH
[12] Division of Infectious Diseases, Vanderbilt University, Nashville, TN
[13] ILD Center of Excellence, Department of Pulmonology, St. Antonius Hospital, Nieuwegein, the Netherlands & Department of Toxicology and Pharmacology, FHML, University Maastricht, the Netherlands
[14] Division of Pulmonary, Critical Care, & Occupational Medicine, University of Iowa, Iowa City, IA
[15] Division of Pulmonary, Critical Care, Allergy, & Sleep Medicine, Medical University of South Carolina, Charleston, SC
[16] Division of Pulmonary Medicine, Albany Medical College, Albany, NY
[17] Library and Knowledge Services, National Jewish Health, Denver, CO

[18] Division of Pulmonary & Critical Care Medicine, University of California, San Francisco, CA
[19] Department of Diseases of the Thorax, Morgagni Hospital. Forlì, Italy and Department of Respiratory Diseases & Allergy, Aarhus University Hospital, Aarhus, Denmark

[20] Division of Cardiovascular Medicine, The Ohio State University, Columbus OH
[21] Kaiser Permanente Northern California, Oakland, CA
[22] Division of Pulmonary & Critical Care Medicine, Morehouse School of Medicine, Atlanta, GA
[23] Department of Medicine, University of Cincinnati Medical Center, Cincinnati, OH

TABLE OF CONTENTS

Markov model
Evidence profile

Question 4: Screening renal function testing

Search strategy
Approach
Selected studies with outcomes
Meta-analysis Forest plots
Markov model
Evidence profile

Question 5: Screening liver function testing

Search strategy
Approach
Selected studies with outcomes
Meta-analysis Forest plots
Markov model
Evidence profile

Question 6: Screening calcium and vitamin D testing

Search strategy
Approach
Selected studies with outcomes
Meta-analysis Forest plots
Markov model
Evidence profile

Question 7: Screening complete cell counts

Search strategy
Approach
Selected studies with outcomes
Meta-analysis Forest plots
Markov model
Evidence profile

Question 8: Screening for cardiac sarcoidosis (electrocardiography, transthoracic echocardiography, and 24-hour electrocardiography [Holter] monitoring)

Search strategy
Approach
Selected studies with outcomes
Meta-analysis Forest plots
Markov model
Evidence profiles

Question 9: Diagnostic evaluation of suspected cardiac sarcoidosis (cardiac MRI, PET scanning, and transthoracic echocardiography)

Search strategy
Approach
Selected studies with outcomes
Meta-analysis Forest plots
Markov model
Evidence profiles

Question 10: Echocardiography for suspected pulmonary hypertension

Search strategy
Approach
Selected studies with outcomes
Meta-analysis Forest plots
Markov model
Evidence profiles

METHODS

Panel Composition

The project was proposed by one of the co-chairs (EDC) through an application to the American Thoracic Society (ATS). The project formally commenced January 1, 2018. The co-chairs (EDC, RPB, LAM) identified potential panelists based on their expertise in the investigation and clinical management of sarcoidosis. The committee was diverse with respect to gender, specialties and disciplines, level of seniority, and geographical locations; in addition, a patient representative provided perspective on patient values and preferences. All potential panelists disclosed their conflicts of interest, which were vetted and managed according to the policies and procedures of the ATS. The final panel was approved by the ATS.

Questions

The co-chairs and lead methodologist (KCW) drafted key clinical questions in a PICO (Population, Intervention, Comparator, and Outcome) format. The questions were revised, and additional questions were proposed via a series of electronic surveys. Further discussion,

modification, and approval was performed by the full guideline panel at a face-to-face meeting held at the 2018 ATS International Conference in San Diego, California in May 2018.

Literature search

The published literature was searched by the librarian (SK) in the following databases: Medline, Excerpta Medica Database (EMBASE), and Cochrane Database of Systematic Reviews. Searching was conducted in June 2018 by the librarian and then a targeted updated was performed in April 2019 by the lead methodologist (KCW). The methodology team (KCW, MG, PG, MHT) reviewed all publications retrieved from the literature searches, initially screening based on title and/or abstract and then reviewing the full text of potentially relevant publications. Bibliographies of selected studies and relevant systematic reviews were also reviewed.

Evidence synthesis

Findings from relevant publications were extracted into data tables. When data were amenable to weighted pooling (i.e., meta-analysis), a random effects model was implemented in the Cochrane Collaboration Review Manager, version 5.3. For controlled studies, relative risk (RR) was used to report dichotomous outcomes and the mean difference (MD) was used to report continuous outcomes. For uncontrolled studies, proportion was estimated using generic inverse; in cases when generic inverse variance could not be used, data was pooled without weighting. Regardless of the approach used to pool individual studies, the accompanying 95% confidence interval (CI) was determined. Statistical heterogeneity was measured using the I^2 test; an $I^2 \geq 75\%$, 50-75%, and 25-50% was considered severe, moderate, and mild heterogeneity,

respectively. When heterogeneity was encountered, sensitivity analyses were initially performed to identify contributors and, if indicated, subgroup analyses and meta-regression was performed. No cause was usually found, so we eliminated outliers and the resulting estimates were presented to the committee to inform their discussion and judgements. Results are provided in the evidence tables.

The Grading, Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used to assess certainty in the estimated effects (i.e., the quality of evidence) for each intervention on each outcome of interest (1). The methodologist created evidence profiles using the Guideline Development Tool (2), which categorized the overall certainty in the evidence into one of four levels: high, moderate, low, or very low. Each level represents the certainty in the accuracy of the estimated effects for a specific intervention. The full guideline panel reviewed the evidence profiles and provided input and feedback.

Recommendations

The methodology team presented the completed evidence syntheses to subcommittees via webinars, during which the evidence was discussed. Following each webinar, the subcommittees made conclusions and formulated and rated recommendations by email and teleconferences. The panelists made decisions about whether to recommend for or against an intervention based on: the balance of desirable consequences (benefits) and undesirable consequences (burdens, adverse effects, and costs), quality of evidence, feasibility, and acceptability to patients (i.e., patient values and preferences). Using the GRADE approach, each recommendation was rated as either “strong” or “conditional”. Best practice statements were made when it was concluded that there was no appropriate alternative course of action. The full guideline panel met at the 2019 ATS

Conference in Dallas, Texas in May 2019. Evidences syntheses and subcommittee conclusions and recommendations were presented to the full guideline panel, which was followed by discussion, revisions, and approvals.

Manuscript preparation

The initial draft of the manuscript was written by the co-chairs (EDC, RPB, LAM) and lead methodologist (KCW). All members of the guideline panel reviewed the manuscript; comments were addressed by the co-chairs and then incorporated into the revised manuscript. The manuscript was redistributed to the full panel for further review. The final product was the result of collective work from all co-chairs, panelists, and methodologists. Once the manuscript was approved by the full panel, it was submitted for external peer review.

Peer review

Peer review was overseen by the ATS Documents Editor. The guideline was peer reviewed by four content experts and a guideline methodologist. Following several cycles of review and revisions, the manuscript was deemed satisfactory and sent to the AT Board of Directors for further review and final approval.

Updating

The guideline will be reviewed by the ATS' Clinical Problems Assembly within five years. If one or more questions is deemed in need of an update, or related new questions need answered, a new task force will be approved to develop an updated guideline. Otherwise, the

resources will be redirected toward developing a guideline on an alternative interstitial lung disease-related topic.

Methods references:

1. Schunemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A, Fahy BF, Gould MK, Horan KL, Krishnan JA, et al. An Official ATS Statement: Grading the Quality of Evidence and Strength of Recommendations in ATS Guidelines and Recommendations. Am J Respir Crit Care Med 2006; 174:605-614.
2. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from gradepro.org.

IMPLICATIONS OF THE STRENGTH OF A RECOMMENDATION

The strength of a recommendation can be conceptualized in several ways. First, a **strong** recommendation conveys that the recommended course of action is the appropriate in >95% of patients, whereas a **conditional** recommendation conveys that the recommended course of action is appropriate in >50% of patients but may not be appropriate in a sizeable minority. Second, a **strong** recommendation conveys "just do it", whereas a **conditional** recommendation conveys "slow down, think about it, discuss it". Third, **strong** recommendation also conveys that criticism may be warranted if the recommended course of action is not followed, whereas a **conditional** recommendation conveys that a decision to not follow the recommended course of action may be a matter of style or equipoise. Finally, a **strong** recommendation is often the basis of a performance measure, whereas **conditional** recommendations seldom make reasonable performance measures.

TABLE: Implications of strong and conditional recommendations

	Strong Recommendation ("We recommend . . .")	Conditional Recommendation ("We suggest . . .")
For patients	The overwhelming majority of individuals in this situation would want the recommended course of action and only a small minority would not.	The majority individuals in this situation would want the suggested course of action, but a sizeable minority would not.
For clinicians	The overwhelming majority of individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices will be appropriate for different patients and you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may be useful to help individuals make decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
For policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policy-making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

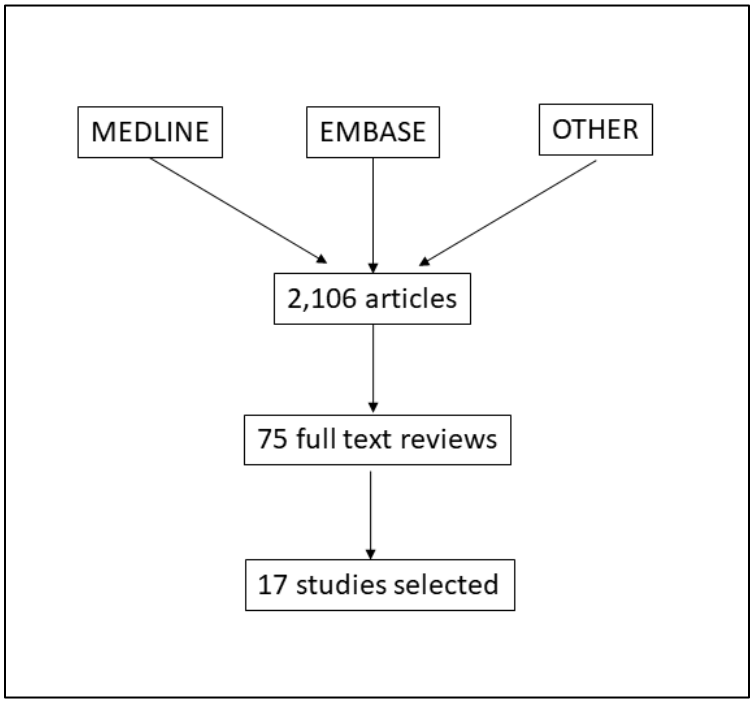
QUESTION #1: *Should a lymph node biopsy be performed in a patient presenting with asymptomatic bilateral hilar lymphadenopathy?*

Search strategy

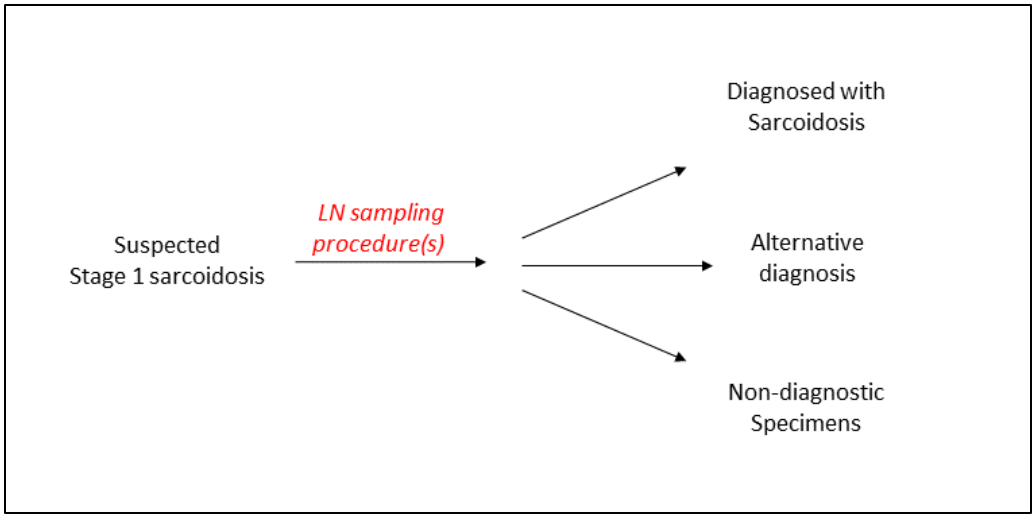
#	Searches
1	lymphadenopathy/
2	((enlarg$ or swollen) adj2 lymph node$).mp.
3	(Hilar adj3 (lymph$ or adenopath$)).mp.
4	(Bilateral adj3 (hilar or lymph$ or adenopath$)).mp.
5	or/1-4 [lymphadenopathy]
6	lymph node biopsy/
7	(lymph$ adj2 (tissue$ or node$ or gland$) adj2 (biops$ or puncture$ or aspirat$)).mp.
8	6 or 7 [biopsy]
9	5 and 8
10	exp sarcoidosis/
11	sarcoidosis/
12	sarcoid$.mp.
13	(besnier adj boeck$).tw.

14	(boeck$ adj (disease or sarcoid)).tw.
15	(schaumann$ adj (disease or syndrome)).tw.
16	uveoparoti$.tw.
17	(benign$ adj lymphogranuloma$).tw.
18	((junging or heerfordt or lofgren) adj syndrome).tw.
19	neurosarcoidosis.tw.
20	(lupus adj pernio).tw.
21	(idiopathic adj3 inflammat$ adj3 granulomat$).tw.
22	or/13-24 [sarcoidosis]
23	9 and 22

Flow of information



Approach



Note: In contrast to the approach taken for PICO 2, we assumed that the all procedures alone or in combination yielded adequate samples

Selected studies with outcomes

Diagnostic findings

Study	Size, N	Procedure	Sarcoidosis confirmed	Alternative diagnosis	Alternative diagnoses	Non-diagnostic evaluation
Boujaoude 2012*	78	EBUS-TBNA	56/78 (72%)	14/78 (18%)	Lymphoma 8 cases, malignant other 1 case, non-malignant other 5 cases	NR
Fritscher-Ravens 2000	12	EUS-FNA	11/12 (92%)	1/12 (8%)	Tuberculosis (1)	0/12 (0%)
Garwood 2007	32	EBUS-TBNA	30/32 (94%)	0/32 (0%)	N/A	2/32 (6%)
Hong 2013	11	EBUS-TBNA, TBBX, EBBX, BAL	9/11 (82%)	NR	NR	NR
Iwashita 2008	41	EUS-FNA	35/41 (85%)	1/41 (2%)	Lymphoma (1)	5/41 (12%)
Koerner 1975	10	TBBX	7/10 (70%)	2/10 (20%)	Tuberculosis (1), Pulmonary embolism (1)	1/10 (10%)
Koonitz 1976	20	TBBX	18/20 (90%)	0/20 (0%)	N/A	2/20 (10%)
Leonard 1997	5	TBBX, TBNA, BAL	3/5 (60%)	1/5 (20%)	Lymphoma (1)	1/5 (20%)
Oki 2007	11	EBUS-TBNA	11/11 (100%)	0/11 (0%)	N/A	0/11 (0%)
Oki 2012	44	EBUS-TBNA, TBBX	37/44 (84%)	NR	NR	NR
Oki 2013	18	EUS-FNA	17/18 (94%)	NR	NR	NR
Oki 2018	58	EBUS-TBNA	47/58 (81%)	NR	NR	NR
Pakhale 2006	55	Mediastinoscopy	49/55 (89%)	1/55 (1.8%)		1/55 (2%)
Pauli 1984	152	TBNA	121/152 (80%)	0/152 (0%)	N/A	31/152 (20%)
Ribeiro 2014	27	EBUS-TBNA	21/27 (28%)	2/27 (7.4%)	Tuberculosis (1), Non-tuberculous mycobacterium (1)	1/27 (4%)
Trisolini 2004	17	TBNA, TBBX	17/17 (100%)	0/17 (0%)	N/A	0/17 (0%)
Yanardag 2006**	43	Mediastinoscopy	42/43 (98%)	0/43 (0%)	N/A	1/43 (2.3%)
Pooled (weighted)	***N/A***	***N/A***	***Not estimable***	***Not estimable***	***N/A***	***Not estimable***

Pooled (unweighted)	***556***	***N/A***	***475/556 (85.4%) (95% CI 82.2- 88.3%)***	***8/425 (1.9%) (95% CI 1.0- 3.7%)***	***N/A***	***45/425 (10.6%) (95% CI 7.8- 13.9%)***
Median (range)	***N/A***	***N/A***	***87.2% (60.0-100%)***	***0.9% (0- 20.0%)***	***N/A***	***5.0% (0- 20.4%)***

NR= not reported, N/A= not applicable
* Study was selected because it met selection criteria but was excluded from the analysis as an outlier.
**Assumed 1 patient in the entire cohort who had a non-diagnostic mediastinoscopy was stage 1.

Complications

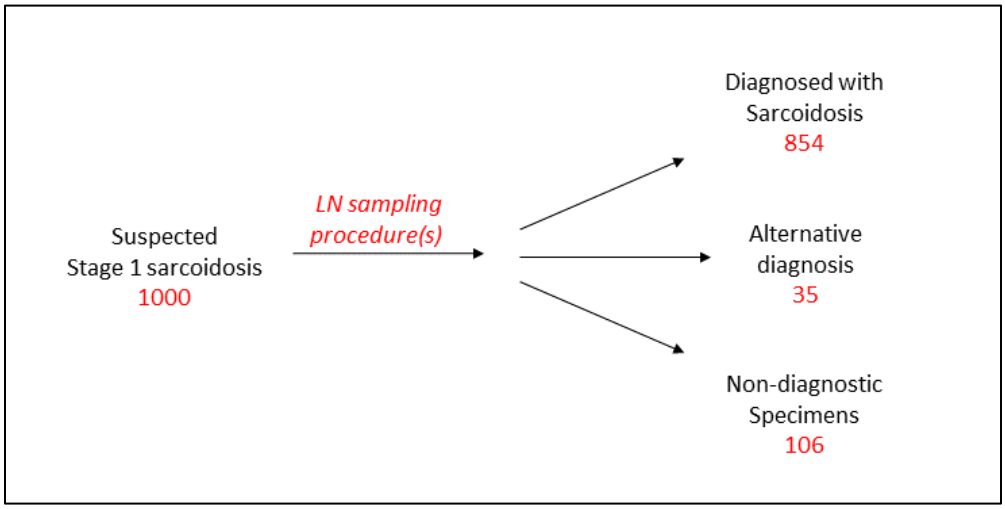
Study	Mortality	Major bleeding	Pneumo-thorax	Other
Boujaoude 2012*	0/60 (0%)	0/60 (0%)	0/60 (0%)	0/60 (0%)
Fritscher-Ravens 2000	0/12 (0%)	0/12 (0%)	0/12 (0%)	0/12 (0%)
Garwood 2007	0/32 (0%)	0/32 (0%)	0/32 (0%)	0/32 (0%)
Hong 2013	0/11 (0%)	0/11 (0%)	NR	0/11 (0%)
Iwashita 2008	0/41 (0%)	0/41 (0%)	0/41 (0%)	1/41 (2%) - mediastinitis
Koerner 1975	0/10 (0%)	0/10 (0%)	NR	0/10 (0%)
Koonitz 1976	0/20 (0%)	0/20 (0%)	NR	0/20 (0%)
Leonard 1997	0/5 (0%)	0/5 (0%)	0/5 (0%)	0/5 (0%)
Oki 2007	0/11 (0%)	0/11 (0%)	0/11 (0%)	0/11 (0%)
Oki 2012	0/44 (0%)	0/44 (0%)	NR	0/44 (0%)
Oki 2013	0/18 (0%)	0/18 (0%)	0/18 (0%)	0/18 (0%)
Oki 2018	0/58 (0%)	0/58 (0%)	0/58 (0%)	0/58 (0%)
Pakhale 2006	NR	NR	NR	NR
Pauli 1984	0/152 (0%)	0/152 (0%)	0/152 (0%)	0/152 (0%)
Ribeiro 2014	0/27 (0%)	0/27 (0%)	0/27 (0%)	0/27 (0%)
Trisolini 2004	0/17 (0%)	0/17 (0%)	0/17 (0%)	0/17 (0%)
Yanardag 2006*	0/43 (0%)	0/43 (0%)	0/43 (0%)	0/43 (0%)
Pooled (weighted)	***Not estimable***	***Not estimable***	***Not estimable***	***Not estimable***
Pooled (unweighted)	***0/501 (0%) (95% CI 0- 0.01%)***	***0/501 (0%) (95% CI 0- 0.01%)***	***0/232 (0%) (95% CI 0- 0.02%)***	***1/501 (0.001%) (95% CI 0- 0.01%)***
Median (range)	***0% (0- 0%)***	***0% (0- 0%)***	***0% (0- 0%)***	***0% (0- 2.4%)***

NR= not reported
* Study was selected because it met selection criteria but was excluded from the analysis as an outlier.

Meta-analysis Forest plots

None. Studies without control groups require Generic Inverse Variance for meta-analysis, which cannot be used if individual studies yield 0% or 100%. Thus, studies underwent only unweighted pooling instead.

Markov model



Evidence profile

Comparison: Lymph node sampling versus no lymph node sampling

Bibliography:

1. Boujaoude Z, et al. Endobronchial ultrasound with transbronchial needle aspiration in the diagnosis of bilateral hilar and mediastinal lymphadenopathy. J Bronchology and Interv Pulmonology 2012; 19(1):19-23.[1]
2. Fritscher-Ravens, A., et al. (2000). "Diagnosing sarcoidosis using endosonography-guided fine-needle aspiration." Chest 118(4): 928-935.
3. Garwood S, et al. Endobronchial ultrasound for the diagnosis of pulmonary sarcoidosis. CHEST 2007; 132(4):1298-1304.
4. Hong G. et al. Usefulness of Endobronchial Ultrasound guided transbronchial needle aspiration for diagnosis of sarcoidosis. Yonsei Med J 2013;5(4)6):1416-1421
5. Iwashita, T., et al. (2008). "The yield of endoscopic ultrasound-guided fine needle aspiration for histological diagnosis in patients suspected of stage I sarcoidosis." Endoscopy 40(5): 400-405.
6. Koerner, S. K., et al. (1975). "Transbronchinal lung biopsy for the diagnosis of sarcoidosis." N Engl J Med 293(6): 268-270.
7. Koonitz, C. H., et al. (1976). "Transbronchial lung biopsy via the fiberoptic bronchoscope in sarcoidosis." Ann Intern Med 85(1): 64-66
8. Leonard, C., et al. (1997). "Bronchoscopic diagnosis of sarcoidosis." European Respiratory Journal 10(12): 2722-2724.
9. Oki, M., et al. (2007). "Real-time endobronchial ultrasound-guided transbronchial needle aspiration is useful for diagnosing sarcoidosis." Respirology 12(6): 863-868.
10. Pakhale SS et al. Has mediastinoscopy still a role in suspected stage I sarcoidosis? Sarcoidosis Vasculitis & Diffuse Lung Diseases. 2006;23(1)66-69.
11. Pauli, G., et al. (1984). "Transbronchial needle aspiration in the diagnosis of sarcoidosis." Chest 85(4): 482-484.
12. Ribeiro, C., et al. (2014). "Diagnosis of sarcoidosis in the endobronchial ultrasound-guided transbronchial needle aspiration era." Revista Portuguesa de Pneumologia 20(5): 237-241.
13. Trisolini, R., et al. (2004). "Transbronchial needle aspiration improves the diagnostic yield of bronchoscopy in sarcoidosis." Sarcoidosis Vasculitis & Diffuse Lung Diseases 21(2): 147-151.
14. Oki, M., et al. (2012). "Prospective study of endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes versus transbronchial lung biopsy of lung tissue for diagnosis of sarcoidosis." Journal of Thoracic & Cardiovascular Surgery 143(6): 1324-1329.
15. Oki, M., et al. (2013). "Transesophageal bronchoscopic ultrasound-guided fine needle aspiration for diagnosis of sarcoidosis." Respiration 85(2): 137-143.
16. Oki, M., et al. (2018). "How Many Passes Are Needed for Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration for Sarcoidosis? A Prospective Multicenter Study." Respiration 95(4): 251-257.Yanardag, H., et al. (2006). "Clinical value of mediastinoscopy in the diagnosis of sarcoidosis: an analysis of 68 cases." Thoracic & Cardiovascular Surgeon 54(3): 198-201.
17. Yanardag, H., et al. (2006). "Clinical value of mediastinoscopy in the diagnosis of sarcoidosis: an analysis of 68 cases." Thoracic & Cardiovascular Surgeon 54(3): 198-201.

Quality assessment	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Confirmed sarcoidosis (%)									
16[2]	Case series	Serious[3]	Serious[4]	None	None[5]	None	475/556 (85.4%) (95% CI 82.2- 88.3%)	VERY LOW	TBD
Alternative diagnoses (%)									
12[6]	Case series	Serious[3]	Serious[4]	None	None[5]	None	15/425 (3.5%) (95% CI 2.0- 5.8%)	VERY LOW	TBD
Non-diagnostic sampling (%)									
12[6]	Case series	Serious[3]	Serious[4]	None	None[5]	None	45/425 (10.6%) (95% CI 7.8- 13.9%)	VERY LOW	TBD
Mortality, procedural (%)									
15[7]	Case series	Serious[3]	None	None	None[5]	None	***0/501 (0%) (95% CI 0- 0.01%)***	VERY LOW	TBD
Major bleeding (%)									
15[7]	Case series	Serious[3]	None	None	None[5]	None	***0/501 (0%) (95% CI 0- 0.01%)***	VERY LOW	TBD
Pneumothorax (%)									
10[8]	Case series	Serious[3]	None	None	None[5]	None	***0/232 (0%) (95% CI 0- 0.02%)***	VERY LOW	TBD

Footnotes:
[1] Bonjaoude, et al. was excluded from the analysis and evidence profile as an outlier, likely due to enrollment of a slightly different population.
[2] Included all studies in the bibliography except Bonjaoude (2012).
[3] Most studies were retrospective analyses, rather than prospective studies that enrolled consecutive patients with legitimate uncertainty.
[4] Could not do a meta-analysis using Generic Inverse Variance and, therefore, could not calculate the I^2. However, the wide range suggests inconsistency across studies.
[5] The ends of the confidence interval would likely lead to the same clinical decision.
[6] Included all studies in the bibliography except Bonjaoude (2012), Hong (2013), Oki (2012, 2013, and 2018).
[7] Included all studies in the bibliography except Bonjaoude (2012) and Pakhale (2006).
[8] Included all studies in the bibliography except Bonjaoude (2012), Hong (2013), Koerner (1975), Koonitz (1976), Oki (2012), and Pakhale (2006).

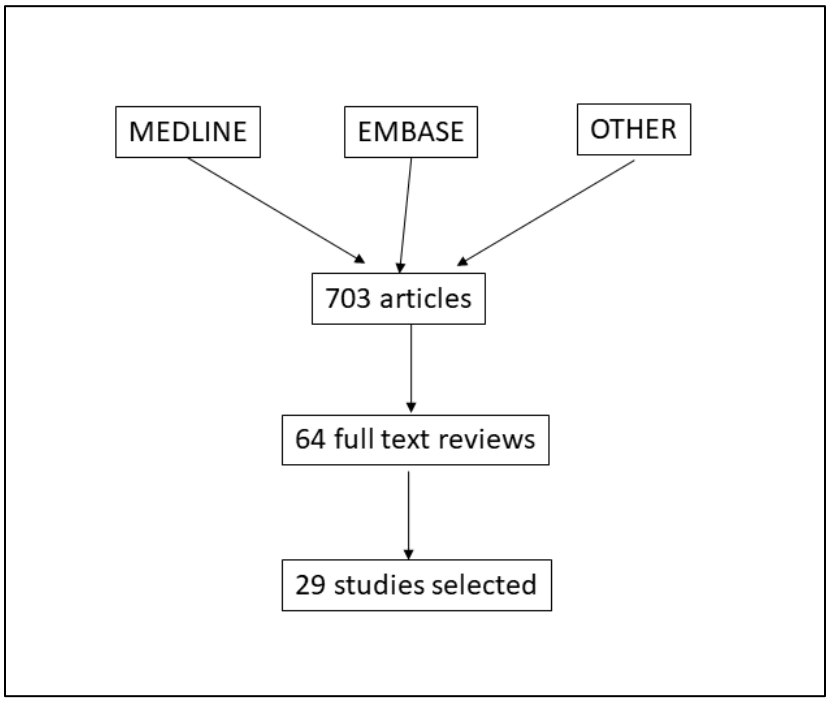
QUESTION #2: *Should patients with suspected sarcoidosis and mediastinal and/or hilar lymphadenopathy for whom it has been determined that tissue sampling is necessary undergo EBUS-guided lymph node sampling or mediastinoscopy as the initial mediastinal and/or hilar lymph node sampling procedure?*

Search strategy

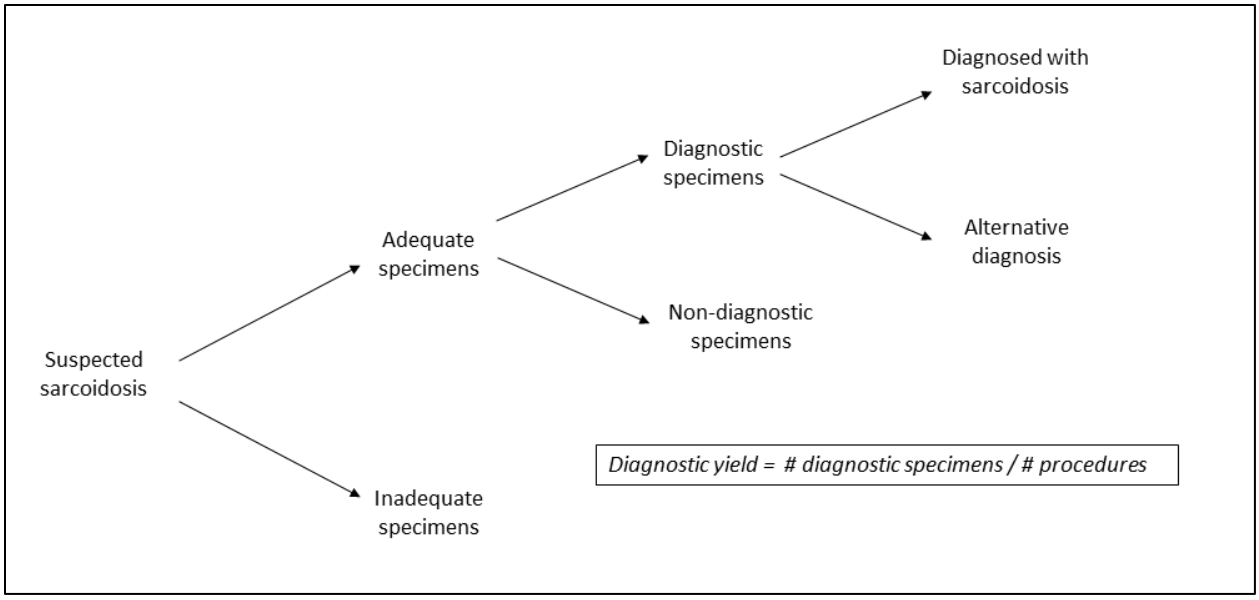
#	Searches
1	Endoscopic Ultrasound-Guided Fine Needle Aspiration/
2	EBUS$.mp.
3	(endoscop$ adj3 (ultrasound or ultrasonograph$)).mp.
4	endosonograph$.mp.
5	"Ultrasonography, Interventional"/
6	or/1-5 [all EBUS]
7	Mediastinoscopy/
8	Mediastinoscopes/
9	mediastinoscop$.mp.
10	(endoscop$ adj3 (mediastin$ or lymph$)).mp.

11	or/7-10 [mediastinoscopy]
12	6 or 11
13	exp sarcoidosis/
14	sarcoidosis/
15	sarcoid$.mp.
16	(besnier adj boeck$).tw.
17	(boeck$ adj (disease or sarcoid)).tw.
18	(schaumann$ adj (disease or syndrome)).tw.
19	uveoparoti$.tw.
20	(benign$ adj lymphogranuloma$).tw.
21	((junging or heerfordt or lofgren) adj syndrome).tw.
22	neurosarcoidosis.tw.
23	(lupus adj pernio).tw.
24	(idiopathic adj3 inflammat$ adj3 granulomat$).tw.
25	or/13-24 [sarcoidosis]
26	12 and 25 [EBUS or mediastinoscopy and sarcoidosis]

Flow of information



Definitions



1. % Adequate samples = adequate samples / procedures
2. % Inadequate samples = inadequate samples / procedures
3. % Diagnostic samples = specific diagnoses / adequate specimens
4. % Non-diagnostic samples = non-diagnostic samples / adequate specimens
5. % Sarcoidosis diagnoses = sarcoidosis diagnoses / specific diagnoses
6. % Other diagnoses = other diagnoses / specific diagnoses
7. Diagnostic yield = specific diagnoses / procedures
8. Note that when all procedures yield adequate specimens, then % diagnostic samples = diagnostic yield

Selected studies with outcomes

EBUS-guided lymph node sampling								
Study	**Adequate samples**	**Inadequate samples**	**Diagnostic samples among adequate samples**	**Non-diagnostic samples among adequate samples**	**Sarcoidosis among diagnostic samples**	**Other diagnoses among diagnostic samples**	**Diagnoses other than sarcoidosis**	**Diagnostic yield (diagnoses among all procedures)**
~~**Adolfo Aragaki-Nakahodo 2017**~~	~~NR~~	~~NR~~	~~NR~~	~~NR~~	~~12/14 (86%)~~	~~2/14 (14%)~~	~~1 tuberculosis, 1 mantle cell lymphoma~~	~~14/36 (39%)~~
Balwan 2018	15/15 (100%)	0/15 (0%)	14/15 (93%)	1/15 (7%)	14/14 (100%)	0/14 (0%)	None	14/15 (93%)
Boujaoude 2012	NR	NR	NR	NR	53/64 (83%)	11/64 (17%)	4 NHL, 2 HL, 2 silicosis, 2 fibrosis, 1 cancer	64/78 (82%)
Garwood 2007	NR	NR	NR	NR	41/41 (100%)	0/41 (0%)	N/A	41/49 (84%)
Hong 2013	NR	NR	NR172 our	NR	29/30 (97%)	1/30 (3%)	1 cancer	30/33 (91%)
Li 2014	NR	NR	NR	NR	29/30 (97%)	1/30 (3%)	1 tuberculosis	30/31 (97%)
Low 2014	13/15 (87%)	2/15 (13%)	9/13 (69%)	4/13(31%)	9/9 (100%)	0/10 (0%)	N/A	9/15 (60%)

Navasakulpong 2016	44/45 (98%)	1/45(2%)	36/44 (82%)	8/44 (18%)	36/36 (100%)	0/36 (0%)	N/A	36/45 (80%)
Oki 2012	NR	NR	NR	NR	51/53 (96%)	2/53 (4%)	2 tuberculosis	53/62 (85%)
Raddaoui 2014	NR	NR	NR	NR	16/16 (100%)	0/16 (0%)	N/A	16/19 (84%)
Ribeiro 2014	38/39 (97%)	1/39 (3%)	31/38 (82%)	7/38 (18%)	31/31 (100%)	0/31 (0%)	N/A	31/39 (79%)
Tremblay 2009	NR	NR	NR	NR	23/23 (100%)	0/23 (0%)	N/A	23/24 (96%)
Wong 2007	62/65 (95%)	3/65 (5%)	56/62 (90%)	6/62 (10%)	56/56 (100%)	0/56 (0%)	N/A	56/65 (86%)
Oki 2007	NR	NR	NR	NR	13/13 (100%)	0/13 (0%)	N/A	13/15 (87%)
Yanardag 2006	NR	NR	NR	NR	66/66 (100%)	0/66 (0%)	N/A	66/68 (97%)
Dziedzic 2017	NR	NR	NR	NR	549/549 (100%)	0/549 (0%)	N/A	549/653 (84%)
Oki 2018	NR	NR	NR	NR	81/90 (90%)	9/90 (10)	5 lung cancers, 3 other cancers, 1 necrotizing granulomas	90/109 (83%)
Pooled (weighted)	***Not estimable***	***Not estimable***	***86% (95% CI 81-92%)***	***14% (95% CI 8-20%)***	***Not estimable***	***Not estimable***		***87% (95% CI 84-91%)***
Pooled (unweighted)	***172/179 (96.1%) (95% CI 92.2-98.1%)***	***7/179 (3.9%) (95% CI 1.9-7.9%)***	***146/172 (84.9%) (95% CI 78.8-89.5%)***	***26/172 (15.1%) (95% CI 10.5-21.2%)***	***1097/1121 (97.9%) (95% CI 96.8- 98.6%)***	***24/1121 (2.1%) (95% CI 1.4- 3.2%)***		***1121/1320 (84.9%) (95% CI 82.9-86.8%)***
Median (range)	***97.4% (86.7% to 100%)***	***2.6% (0% to 13.3%)***	***81.8% (69.2% to 93.3%)***	***13.9% (6.7% to 30.8%)***	***100% (82.8% to 100%)***	***0% (0% to 17.2%)***		***84.8% (60.0% to 97.1%)***

Mediastinoscopy

Study	Adequate samples	Inadequate samples	Diagnostic samples among adequate samples	Non-diagnostic samples among adequate samples	Sarcoidosis among diagnostic samples	Other diagnoses among diagnostic samples	Diagnoses other than sarcoidosis	Diagnostic yield (diagnoses among all procedures)
Pakhale 2006	55/55 (100%)	0/55 (0%)	54/55 (98%)	1/55 (2%)	49/54 (91%)	5/54 (9%)	Reactive LAN x5	54/55 (98%)

Study	Sarcoidosis among all procedures	Other diagnosis or non-diagnostic samples among all procedures
Pakhale 2006	49/55 (89%)	6/55 (11%)
Tucker 1970	48/50 (96%)	2/50 (4%)
Carlens 1959	118/123 (96%)	5/123 (4%)
Nielsen 1966	115/121 (95%)	6/121 (5%)
Maassen 1967	115/115 (100%)	0/115 (0%)
Jepsen 1966	41/43 (95%)	2/43 (5%)
Lofgren 1964	32/35 (91%)	3/35 (9%)
Palva 1964	27/28 (96%)	1/28 (4%)
Patilia 1964	25/25 (100%)	0/25 (0%)
Mikhail 1971	121/130 (93%)	9/130 (7%)

Berge 1964	33/33 (100%)	0/33 (0%)
Friedel 1964	30/30 (100%)	0/30 (0%)
Pooled (weighted)	***Not estimable***	***Not estimable***
Pooled (unweighted)	***754/787 (95.8%) (95% CI 94.2% to 97.0%)***	***33/787 (4.2%) (95% CI 3.0 to 5.8%)***
Median (range)	***96.0% (90.7% to 100%)***	***4.0% (0% to 9.3%)***

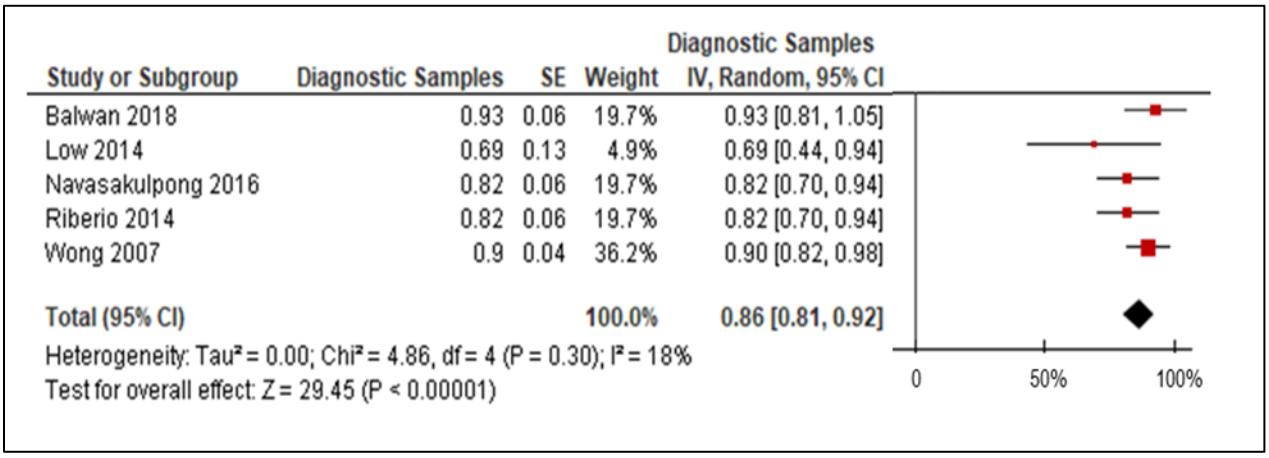
Apples to apples, and oranges to oranges			
	Sarcoidosis among all procedures		
	Pooled (weighted)	**Pooled (unweighted)**	**Median (range)**
EBUS	85% (95% CI 80% to 89%)	83.1% (95% CI 81.0-85.0%)	84.1% (60.0 – 97.1%)
Mediastinoscopy	Not estimable	95.8% (95% CI 94.2 – 97%)	96% (90.7 – 100%)
	Diagnostic yield		
	Pooled (weighted)	**Pooled (unweighted)**	**Median (range)**
EBUS	87% (95% CI 84-91%)	84.9% (95% CI 82.9- 86.8%)	84.8% (60% to 97.1%)
Mediastinoscopy	98% (95% CI 90-99.9%) Single study		

Mediastinoscopy						***EBUS-guided sampling***				
Study	**Mortality**	**Major bleeding**	**Minor bleeding**	**Pneumo-thorax**	**Other**	**Study**	**Mortality**	**Major bleeding**	**Pneumo-thorax**	**Other**
Pakhale 2006	NR	NR	NR	NR	NR	**Adolfo Aragaki-Nakahodo 2017**	0/36 (0%)	0/36 (0%)	NR	0/36 (0%)
Tucker 1970	NR	NR	NR	NR	NR	**Balwan 2018**	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/15 (0%)
Carlens 1959	NR	NR	NR	NR	NR	**Boujaoude 2012**	0/78 (0%)	0/78 (0%)	0/78 (0%	0/78 (0%)
Nielsen 1966	NR	NR	NR	NR	NR	**Garwood 2007**	0/50 (0%)	0/50 (0%)	0/50 (0%)	1/50 (2%) stridor
Maassen 1967	NR	NR	NR	NR	NR	**Hong 2013**	0/33 (0%)	0/33 (0%)	NR	0/33 (0%)
Jepsen 1966	NR	NR	NR	NR	NR	**Li 2014**	0/31 (0%)	0/31 (0%)	0/31 (0%)	0/31 (0%)
Lofgren 1964	NR	NR	NR	NR	NR	**Low 2014**	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/15 (0%)
Palva 1964	NR	NR	NR	NR	NR	**Navasakulpong 2016**	NR	NR	NR	NR

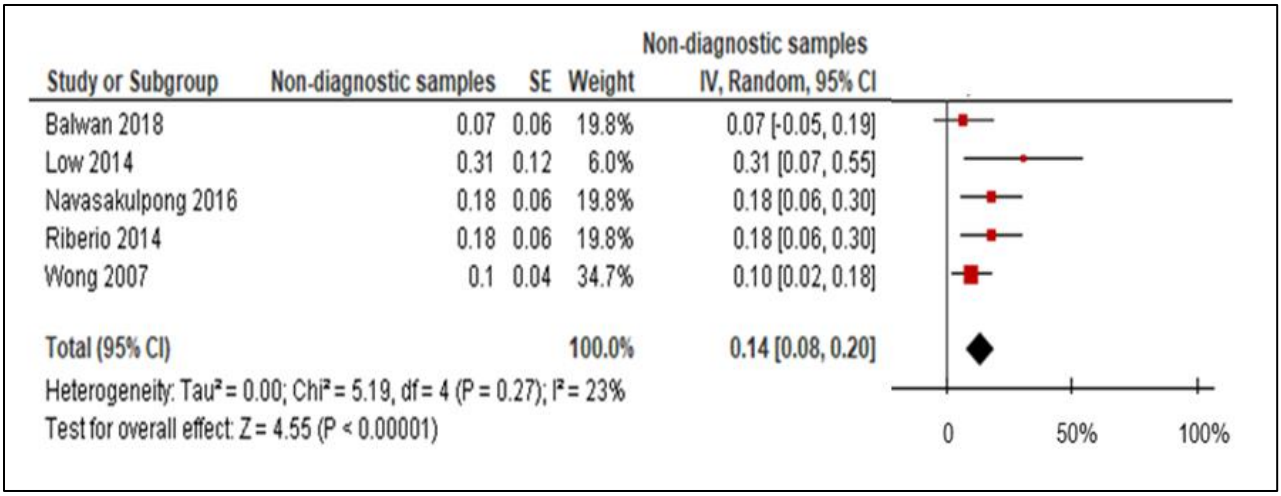
Patilia 1964	NR	NR	NR	NR	NR	**Oki 2012**	0/62 (0%)	0/62 (0%)	0/62 (0%)	0/62 (0%)
Mikhail 1971	NR	NR	NR	NR	NR	**Raddaoui 2014**	NR	NR	NR	NR
Berge 1964	NR	NR	NR	NR	NR	**Ribeiro 2014**	0/39 (0%)	0/39 (0%)	0/39 (0%)	0/39 (0%)
Friedel 1964	NR	NR	NR	NR	NR	**Tremblay 2009**	0/24 (0%)	0/24 (0%)	0/24 (0%)	0/24 (0%)
						Wong 2007	0/65 (0%)	0/65 (0%)	0/65 (0%)	0/65 (0%)
						Oki 2007	0/15 (0%)	0/15 (0%)	0/15 (0%)	0/15 (0%)
						Yanardag 2006	0/68 (0%)	0/68 (0%)	0/68 (0%)	0/68 (0%)
						Dziedzic 2017	0/653 (0%)	0/653 (0%)	0/653 (0%)	NR
						Oki 2018	0/109 (0%)	0/109 (0%)	0/109 (0%)	0/109 (0%)
Pooled (weighted)	***Not estimable***	***Not estimable***	***Not estimable***	***Not estimable***	***Not estimable***	***Pooled (weighted)***	***Not estimable***	***Not estimable***	***Not estimable***	***Not estimable***
Pooled (unweighted)	***Not estimable***	***Not estimable***	***Not estimable***	***Not estimable***	***Not estimable***	***Pooled (unweighted)***	***0/1293 (0%) (95% CI 0- 0.3%)***	***0/1293 (0%) (95% CI 0- 0.3%)***	***0/1224 (0%) (95% CI 0-0.3%)***	***1/1293 (0.01%) (95% CI 0- 0.4%)***
Median (range)	***Not estimable***	***Not estimable***	***Not estimable***	***Not estimable***	***Not estimable***	***Median (range)***	***0% (0% to 0%)***	***0% (0% to 0%)***	***0% (0% to 0%)***	***0% (0% to 2%)***

Forest plots

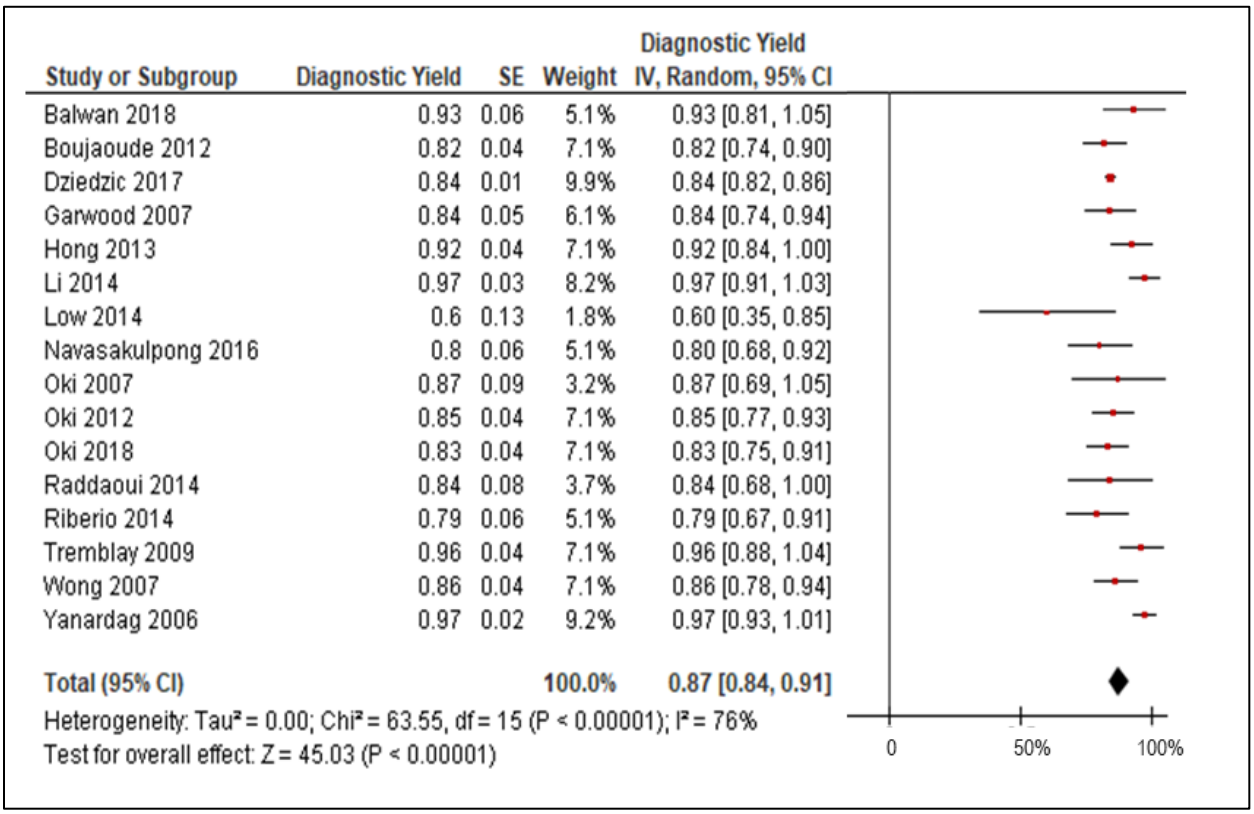
EBUS diagnostic samples among adequate specimens



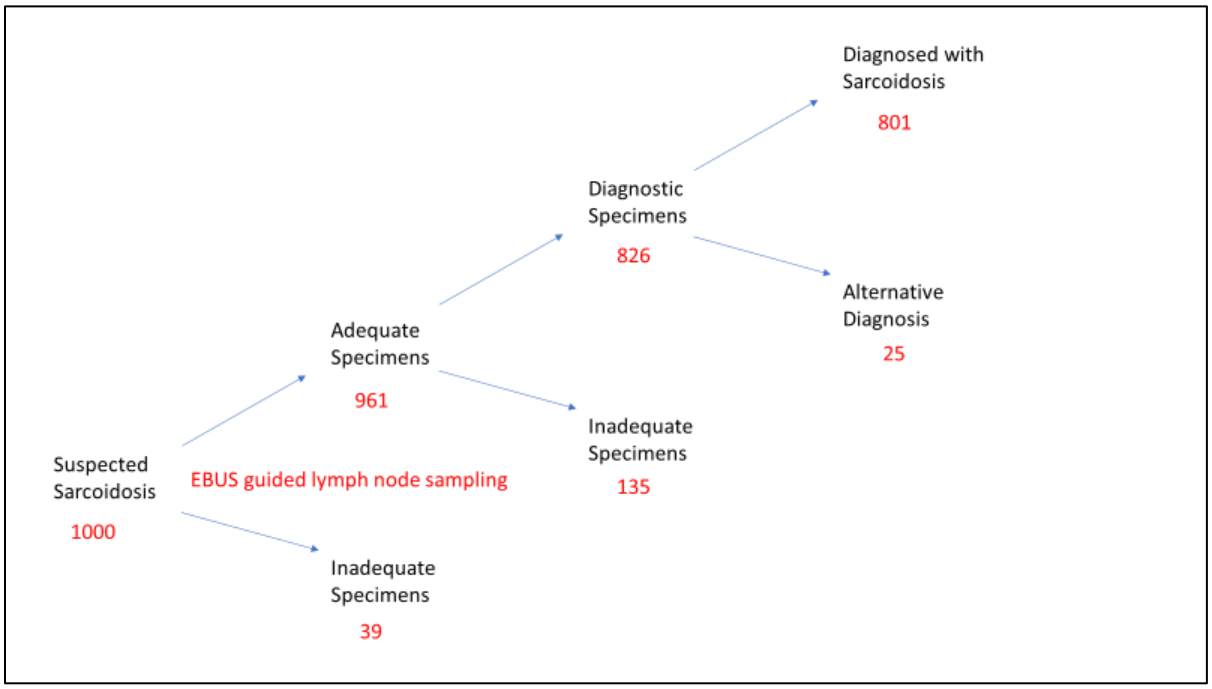
EBUS non-diagnostic samples among adequate specimens

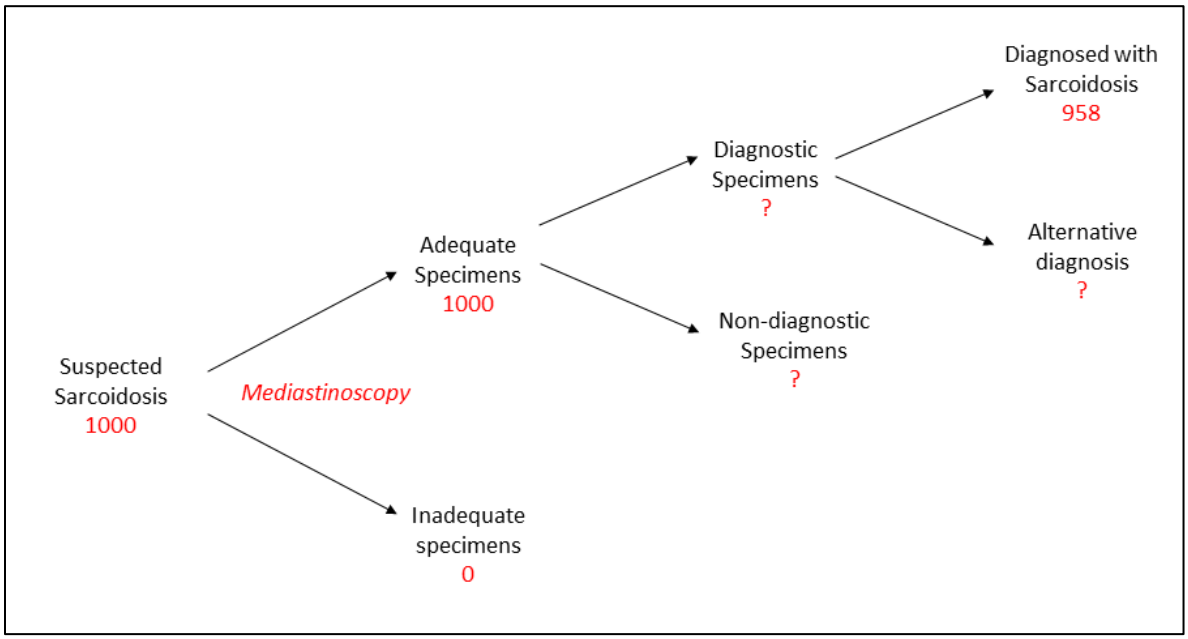


EBUS diagnostic yield



Markov model





Evidence profile

Comparison: EBUS-guided lymph node sampling versus mediastinoscopy

Bibliography:

1. Pakhale SS et al. Has mediastinoscopy still a role in suspected stage I sarcoidosis? Sarcoidosis Vasculitis & Diffuse Lung Diseases. 2006;23(1)66-69.
2. Tucker JA et al. Mediastinoscopy with special reference to the diagnosis of sarcoid. Annals of Otology, Rhinology & Laryngoscopy. 1970;79(5):937-943.
3. Carlens E. Mediastinoscopy; a method of inspection and tissue biopsy in the superior mediastinum. Dis Chest 1959; 36:343-352.
4. Nielsen EG and Olsen H. Mediastinoscopy. Danish Med Bull. 1966; 13:193
5. Maassen W. Ergebnisse und Bedutung der Mediastinoskopie . 1967.
6. Jepsen O. Mediastinoscopy. Einar Munkegaard Forlag. 1966.
7. Lofgren S and Snellman B. Principles and procedures for obtaining biopsies in sarcoidosis. Acta Med Scand Suppl. 1964-1965; 425-431:225-227.
8. Palva T. Mediastinal Sarcioidosis. Acta oto-laryngologica, Supplement. 1964;188:258.
9. Patilia Jr. Observations on the significance of mediastinoscopy in the diagnosis of sarcoidosis. Acta Med Scand Suppl. 1964-1965;425-431:239-240
10. Mikhail JR et al. Mediastinoscopy: a diagnostic procedure in hilar and paratracheal adenopathy. Postgraduate Medical Journal. 1971;47:698-704.
11. Bergh et al. Mediastinal exploration by the technique of Carlens. Diseases of the Chest. 1964;64:399.
12. Friedel H et al. The significance of bronchoscopy and mediastinoscopy for the diagnosis of sarcoidosis. Zeitschrift fur Tuberkulose und Erkrankungen der Thoraxorgane. 1964;121:152.
13. Adolfo Aragaki-Nakahodo, et al. The complimentary role of transbronchial lung cryobiopsy and endobronchial ultrasound fine needle aspiration in the diagnosis of sarcoidosis. Respiratory Medicine 2017;131:65-69.
14. Balwan A. Endobronchial ultrasound-guided transbronchial needle aspiration using 19-G needle for sarcoidosis. J Bronchol Intervent Pulmonol 2018; epub ahead of print.
15. Boujaoude Z, et al. Endobronchial ultrasound with transbronchial needle aspiration in the diagnosis of bilateral hilar and mediastinal lymphadenopathy. J Bronchology and Interv Pulmonology 2012; 19(1):19-23.
16. Garwood S, et al. Endobronchial ultrasound for the diagnosis of pulmonary sarcoidosis. CHEST 2007; 132(4):1298-1304.
17. Hong G. et al. Usefulness of Endobronchial Ultrasound guided transbronchial needle aspiration for diagnosis of sarcoidosis. Yonsei Med J 2013;5(4)6):1416-1421.
18. Li K et al. A randomized controlled study of conventional TBNA versus EBUS-TBNA for diagnosis of suspected stage I and II sarcoidosis. Sarcoidosis, vasculitis, and diffuse lung diseases : official journal of WASOG. 2014;31(3):211-218.
19. Low et al. Use of endobronchial ultrasound guided transbronchial needle aspiration in the diagnosis of granulomatous mediastinal lymphadenopathy. Ann Acad Med Singapore 2014;43:250-4.
20. Navasakulpong A et al. Yield of EBUS-TBNA for the diagnosis of sarcoidosis: impact of operator and cytopathologist experience. BMJ open respiratory research. 2016;3(1).
21. Oki M et al. Prospective study of endobronchial ultrasound-guided transbronchial needle aspiration of lymph nodes versus transbronchial lung biopsy of lung tissue for diagnosis of sarcoidosis. Journal of Thoracic & Cardiovascular Surgery. 2012;143(6):1324-1329.
22. Raddaoui et al. Utility of endoscopic ultrasound guided transbronchial fine-needle cytology in the dianosis of sarcoidosis: A Saudi experience. Cytojournal. 2014;11
23. Ribeiro C et al. Diagnosis of sarcoidosis in the endobronchial ultrasound-guided transbronchial needle aspiration era. Revista Portuguesa de Pneumologia. 2014;20(5):237-241.
24. Tremblay A et al. A randomized controlled trial of standard vs endobronchial ultrasonography-guided transbronchial needle aspiration in patients with suspected sarcoidosis. Chest. 2009;136(2):340-346.
25. Wong M et al. Endobronchial ultrasound: new insight for the diagnosis of sarcoidosis. European Respiratory Journal. 2007;29(6):1182-1886.
26. Oki M. et al. Real-time endobronchial ultrasound guided transbronchial needle aspiration is useful for diagnosing sarcoidosis. Respirology. 2007;12(6):863-868.
27. Yanardag H et al. Clinical valuve of mediastinoscopy in the diagnosis of sarcoidosis: an analysis of 68 cases. Thoracic & Cardiovascular Surgeon. 2006;54(3):198-201.
28. Dziedzic DA et al. The role of EBUS-TBNA and standard bronchoscopic modalities in the diagnosis of sarcoidosis. The clinical respiratory journal. 2017;11(1):58-63.
29. Oki M et al. How many needle passes are needed for endobronchial ultrasound guided transbronchial needle aspiration for sarcoidosis? A prospective multicenter study. Respiration. 2018;95(4):251-257.

Quality assessment							Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Diagnostic yield (%)									
18[1]	Case series	Serious[2]	Serious[3]	None	None	None	EBUS: 87% (95% CI 84-91%) MED: 98% (95% CI 90-99.9%)	VERY LOW	TBD
Mortality, procedural (%)									
15[4]	Case series	Serious[2]	None	None	None	None	EBUS: 0% (95% CI 0 – 0.3%) MED: Not reported	VERY LOW	TBD

Major bleeding (%)									
15[4]	Case series	Serious[2]	None	None	None	None	EBUS: 0% (95% CI 0 – 0.3%) MED: Not reported	VERY LOW	TBD
Pneumothorax (%)									
13[5]	Case series	Serious[2]	None	None	None	None	EBUS: 0% (95% CI 0 – 0.3%) MED: Not reported	VERY LOW	TBD

Footnotes:
[1] Of the 18 studies that measured diagnostic yield, 17 were for EBUS and only 1 was for mediastinoscopy.
[2] The retrospective design creates a risk of selection bias.
[3] There was serious heterogeneity of the EBUS estimates per the I^2 statistic.
[4] Of the 15 studies that measured procedural mortality, all were for EBUS.
[5] Of the 13 studies that measured procedural mortality, all were for EBUS.

QUESTION 3: *Should patients with sarcoidosis who do not have ocular symptoms undergo screening for ocular sarcoidosis with routine ophthalmological exams?*

Search strategy

#	Searches
1	exp sarcoidosis/
2	sarcoidosis/
3	sarcoidosis/ or sarcoidosis, pulmonary/ or uveoparotid fever/
4	sarcoid$.mp.
5	(besnier adj boeck$).tw.
6	(boeck$ adj (disease or sarcoid)).tw.
7	(schaumann$ adj (disease or syndrome)).tw.
8	uveoparoti$.tw.
9	(benign$ adj lymphogranuloma$).tw.
10	((junging or heerfordt or lofgren) adj syndrome).tw.
11	neurosarcoidosis.tw.
12	(lupus adj pernio).tw.
13	(idiopathic adj3 inflammat$ adj3 granulomat$).tw.
14	or/1-13 [all sarcoidosis]
15	exp Diagnostic Techniques, Ophthalmological/ [medline]
16	exp ophthalmological diagnostic device/ [embase]
17	eye examination/ [embase]
18	((eye$ or vision or retina$ or ocular or ophthalm$) adj3 (technique$ or exam$ or test$)).mp.
19	15 or 16 or 17 or 18
20	14 and 19

Selected studies with outcomes

Study	Frequency abnormal eye exams c/w ocular sarcoidosis	Symptomatic patients among those with abnormal eye exams	Frequency of anterior uveitis as the abnormality
Ungprasert 2017	23/151 (15%)	21/23 (91%)	7/23 (30%)
Birnbaum 2015	1256/3364 (37%)	NR	1013/1256 (81%)
Sungur 2013	26/48 (53%)	NR	4/26 (15%)
Judson 2012	363/1582 (23%)	NR	NR
Baughman 2012	465/1587 (29%)	NR	NR
Sheu 2010	19/55 (35%)	13/19 (68%)	NR
Atmaca 2009	18/139 (13%)	NR	12/18 (67%)
Lee 2009	22/104 (21%)	14/22 (64%)	10/22 (45%)
Morimoto 2008	309/1001 (31%)	NR	404/994 (41%)
Khanna 2007	14/48 (29%)	12/14 (86%)	5/15 (33%)
Evans 2007	65/81 (80%)	NR	NR
Baughman 2001	87/736 (12%)	NR	NR
Drobecka 1999	6/33 (18%)	NR	NR
Jabs 1986	47/183 (26%)	NR	33/47 (70%)
Obenauf 1978	202/532 (38%)	NR	106/202 (52%)
Siltzbach 1974	354/1609 (22%)	NR	NR
Jackson 1970	12/82 (15%)	NR	NR
James 1964	123/442 (28%)	NR	89/123 (72%)
Pooled (weighted)	***26% (95% CI 23-29%)***	***78% (95% CI 64- 91%)***	***53% (95% CI 41-64%)***
Pooled (unweighted)	***29% (95% CI 28-30%)***	***77% (95% CI 66-85%)***	***62% (95% CI 60-64%)***
Median (range)	***27% (12% to 80%)***	***77% (64% to 91%)***	***49% (15% to 81%)***

NR= not reported.

Study	No therapy	Topical steroid therapy	Systemic steroid therapy [1]	Both therapies	Visual acuity
Ungprasert 2017	2/23 (9%)	5/23 (22%)	6/23 (26%)	10/23 (43%)	With Rx: Improved= 3/20 (15%) [2] Stabilized= 8/20 (40%) Worse= 9/20 (45%)
					Without Rx: Improved= 1/1 (100%)

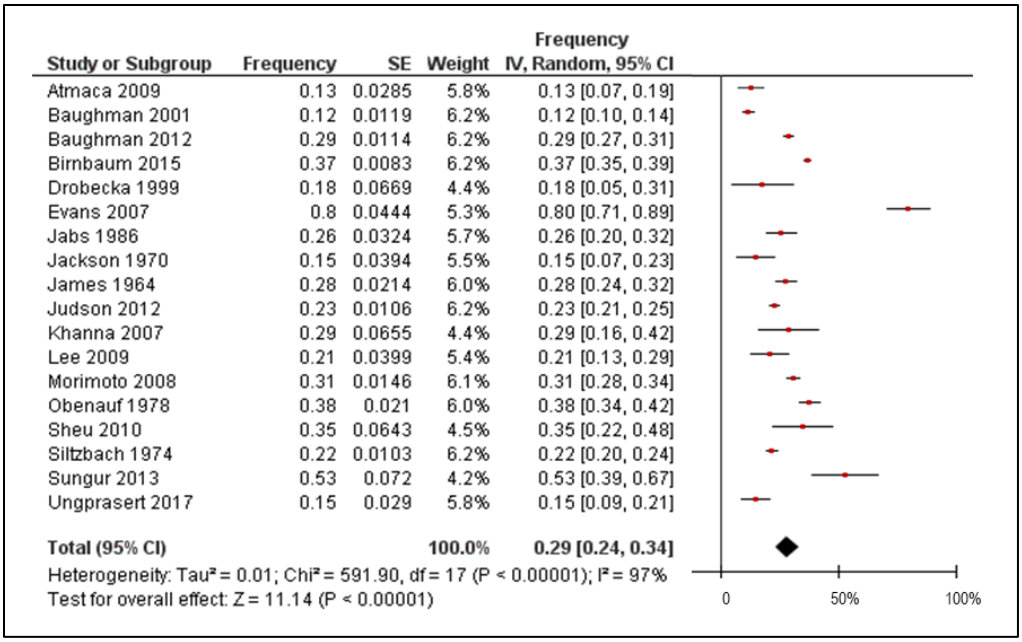
					Stabilized= none Worse= none
Judson [3] 2012	188/287 (66%)	99/287 (34%)			NR
Baughman [3] 2012	108/465 (23%)	357/465 (77%)			NR
Lee 2009	3/22 (14%)	4/22 (18%)	2/22 (9%)	13/22 (59%)	With Rx: Improved= 9/18 (50%) Stabilized= 4/18 (22%) Mixed= 4/18 (22%) Worse= 1/18 (6%)
					Without Rx: Improved= ½ (50%) Stabilized= ½ (50%)
Pooled (weighted)	***17% [4] (95% CI 7-26%)***	***83% [4] (95% CI 74-93%)***			***Improvement or stabilization w/ treatment 64% (95% CI 47-81%)***
Pooled (unweighted)	***22% [4] (95% CI 19-26%)***	***78% [4] (95 CI 74-81%)***			***Improvement or stabilization w/ treatment 63% (95% CI 47-77%)***
Median (range)	***14% [4] (9-23%)***	***86% [4] (77-91%)***			***Improvement or stabilization w/ treatment 63% (55-72%)***

NR= not reported.
[1] Systemic therapy was often initiated to treat concomitant non-ocular disease.
[2] Reported treatment and no treatment; didn't specify the type of treatment.
[3] 7/8 (88%) of those stable with treatment had normal eyesight at baseline, suggesting early detection = preservation of eyesight.
[4] Removed Judson, et al. as an outlier. As a result, I^2 for heterogeneity went from 98% to 67%. The reason for the outlying results are unknown.

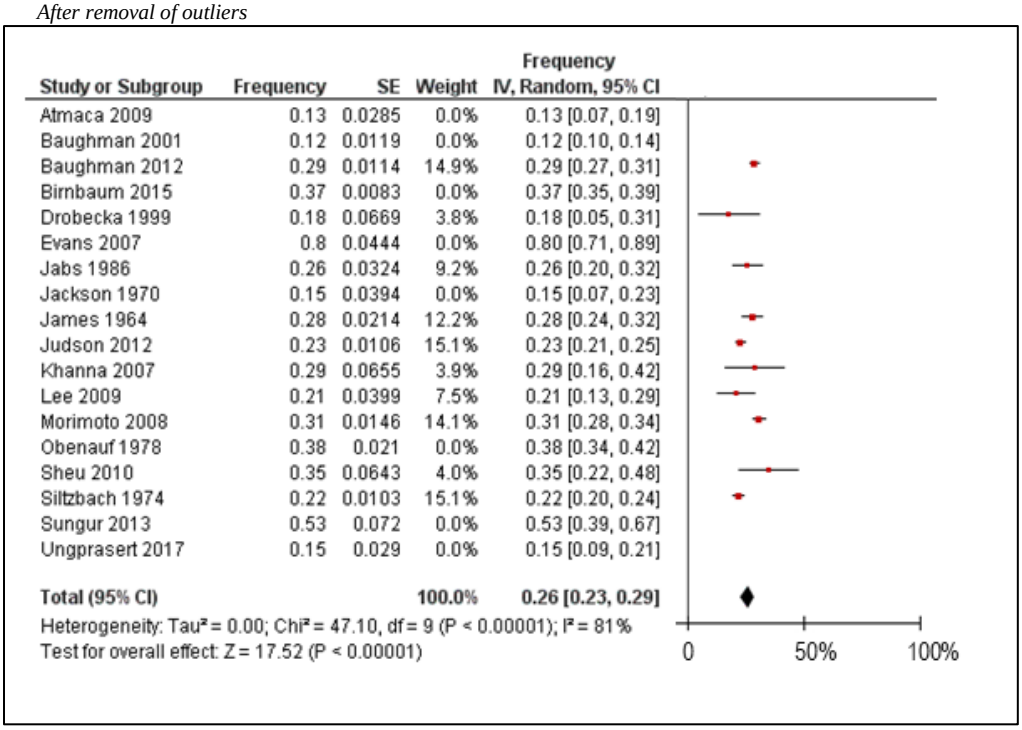
Forest plots

Frequency of abnormal eye exams

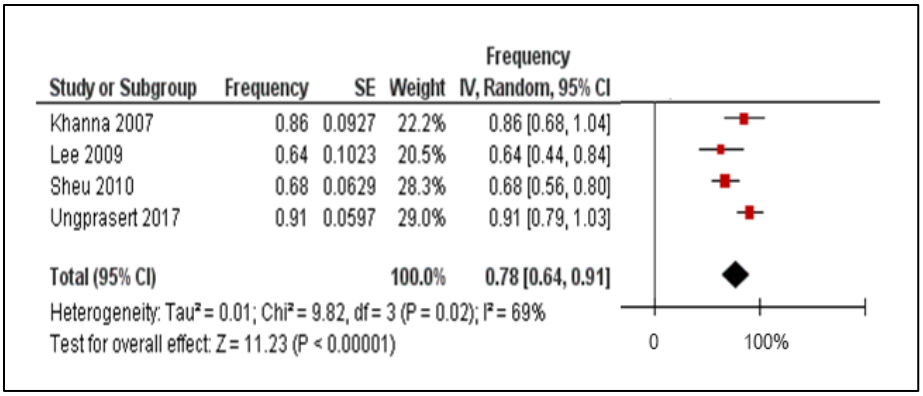
Initial



After removal of outliers

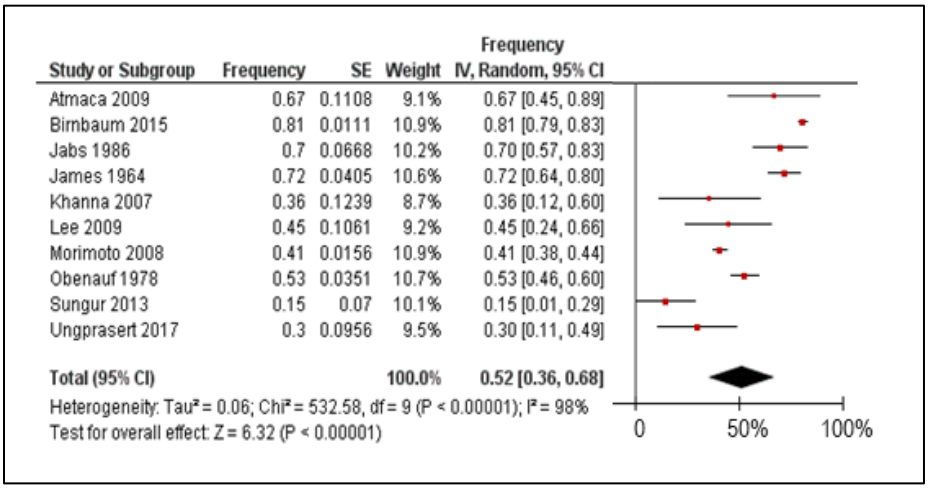


Frequency of symptoms among those with abnormal eye exams

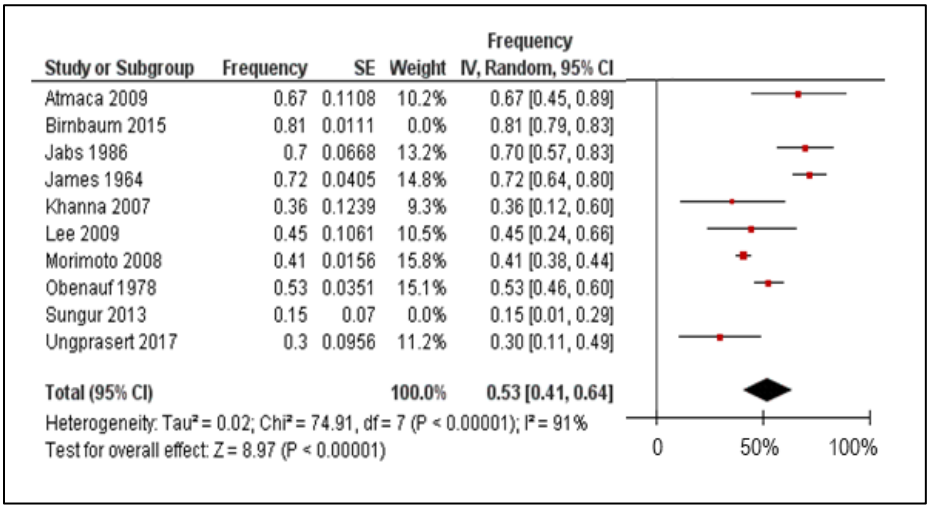


Frequency of anterior uveitis among abnormal eye exams

Initial

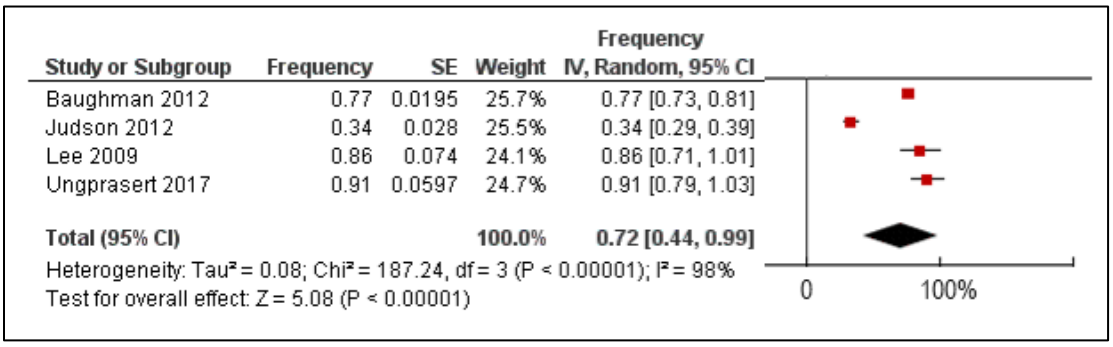


After removal of outliers

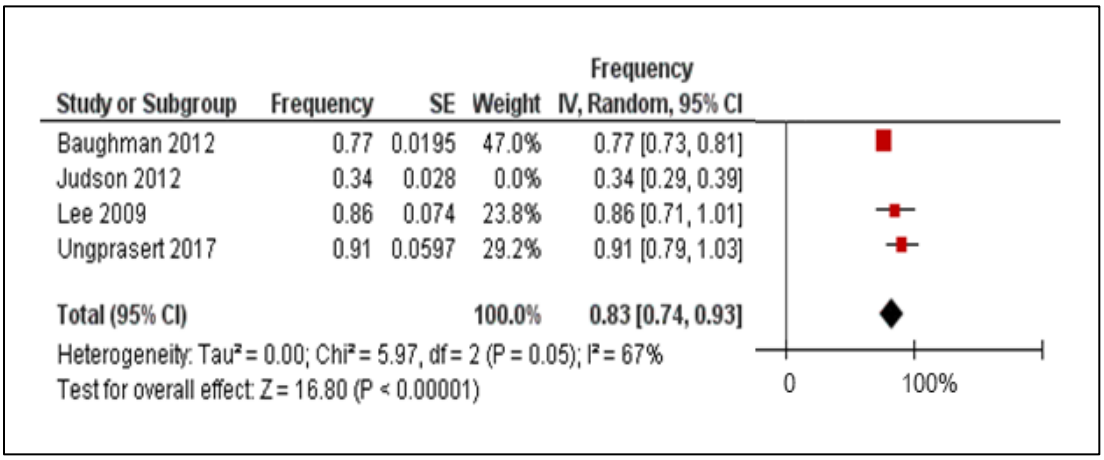


Frequency of treatment

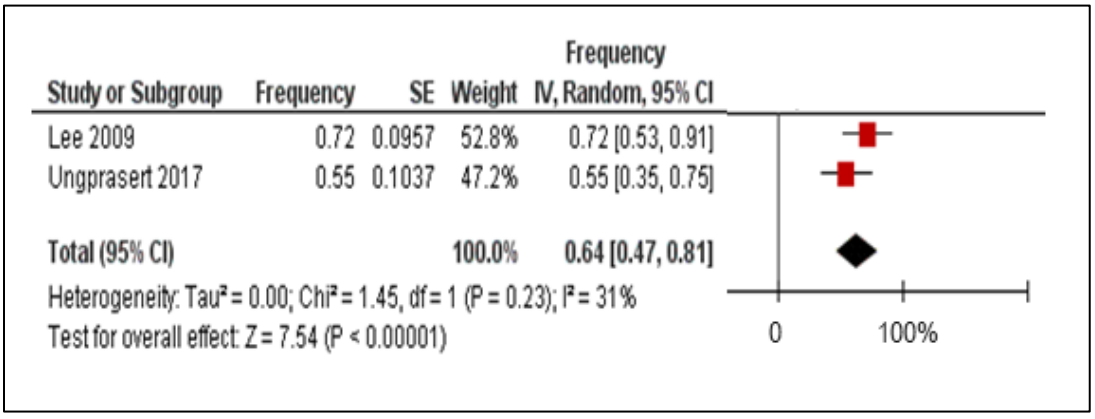
Initial



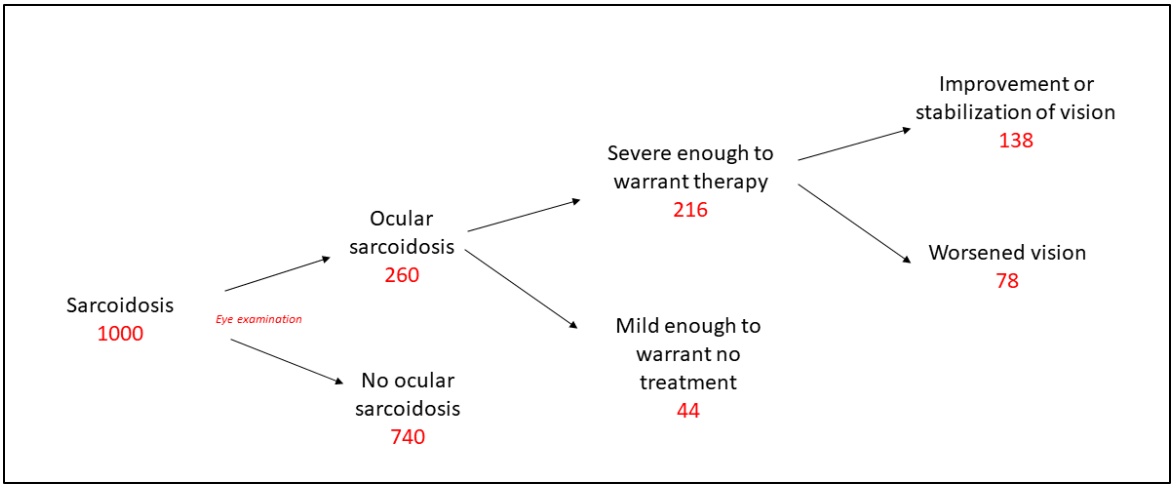
After removal of outliers



Frequency of improvement or stabilization of vision



Markov model



For every 1000 sarcoidosis patients who undergo routine eye exam, abnormalities consistent will ocular sarcoidosis will be found in roughly 260 patients, approximately 216 of whom will have ocular involvement severe enough to warrant treatment with topical or systemic corticosteroids and 138 will have their vision improved or remain stable.

Evidence profile

Comparison: Eye examination versus none

Bibliography:

1) Birnbaum AD, et al. Sarcoidosis in the National Veteran Population: Association of Ocular Inflammation and Mortality. Ophthalmology 2015; 122(5):934-938.
2) Ungprasert P, et al. Clinical Characteristics of Ocular Sarcoidosis: A Population-based study 1976-2013. Ocul Immunol Inflamm 2017; Oct 12:1-7.
3) Lee SY, et al. Ocular Sarcoidosis in a Korean Population. J Korean Med Sci 2009; 24:413-419.
4) Evans M. Differences in Clinical Findings between Caucasians and African-Americans with Biopsy-Proven Sarcoidosis. Ophthalmology 2007; 114(2):325-333.
5) Drobecka E, et al. Ocular Manifestations in Sarcoidosis. Klin Oczna 1999; 101(3):201-204.
6) Atmaca LS, et al. Ocular Involvement in Sarcoidosis. Ocul Immunol Inflamm 2009; 17(2):91-94.
7) Baughman RP, et al. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med 2001; 164:1885-1889.
8) Judson MA, et al. The clinical course of sarcoidosis: presentation, diagnosis, and treatment in a large white and black cohort in the United States. Sarc Vasc Diffuse Lung Dis 2012; 29:119-127.
9) Jabs DA. Ocular sarcoidosis and chronic sarcoidosis. Am J Ophthamol 1986; 102(3):297-301.
10) James DG, et al. Ocular sarcoidosis. Br J Ophthalmol 1964; 48:461-470.
11) Siltzbach LE, et al. Course and prognosis of sarcoidosis around the world. Am J Med 1974; 57:847-852.
12) Jackson H. Ocular sarcoidosis. Postgrad Med J 1970; 46:501-504.
13) Obenauf CD. Sarcoidosis and its ophthalmic manifestations. Am J Ophthalmol 1978; 86:648.
14) Khanna A, et al. Pattern of ocular sarcoidosis in patients with sarcoidosis in developing countries. Acta Ophthalmologica Scandinavia 2007; 85(6):609-612.
15) Sungar G, et al. Pattern of ocular findings in patients with biopsy-proven sarcoidosis in Turkey. Ocular Immunology and Inflammation 2013; 21(6):455-461.
16) Sheu SJ, et al. Ocular sarcoidosis in southern Taiwan. Ocular Immunol Inflamm 2010; 18(3):152-157.
17) Baughman, et al. Management of ocular sarcoidosis. Sarc Vasc Diff Lung Dis 2012; 29:26-33.
18) Morimoto T, et al. Epidemiology of sarcoidosis in Japan. Eur Respir J 2008; 31:371-379.

Quality assessment						Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Detection of ocular sarcoidosis (frequency of abnormal eye examinations, %)									

18[1]	Case series	serious[2]	serious[3]	serious[4]	serious[5]	none	26% (95% CI 23-29%)	⊕OOO VERY LOW	TBD
Initiation of treatment (%)									
4[6]	Case series	serious[2]	none	serious[4]	serious[5]	none	83%[7] (95% CI 74-93%)	⊕OOO VERY LOW	TBD
Frequency of improvement or stabilization treatment (%)									
2[8]	Case series	serious[2]	none	serious[4]	serious[5]	none	64% (95% CI 47-81%)	⊕OOO VERY LOW	TBD

Footnotes:
[1]All studies.
[2]Many were retrospective chart reviews; therefore, there was a risk of selection bias.
[3]When pooled by meta-analysis, the I^2 >90%; thus, the median (range) are the primary outcomes for these outcomes rather than the pooled analyses. Also, the range is wide.
[4]The PICO question asks about patients without ocular symptoms; however, all of the studies enrolled both symptomatic and asymptomatic patients.
[5]A large proportion of the studies are small, with <100 patients.
[6]Baughman, Judson, Lee, and Ungprasert.
[7]Judson was eliminated as an outlier, bringing the I^2 from 98% to 0%.
[8] Lee and Ungprasert.

QUESTION #4: ***Should patients with sarcoidosis who do not have renal symptoms undergo screening for renal sarcoidosis by routine serum creatinine testing?***

Search strategy

#	Searches
1	exp sarcoidosis/
2	sarcoidosis/
3	sarcoidosis/ or sarcoidosis, pulmonary/ or uveoparotid fever/
4	sarcoid$.mp.
5	(besnier adj boeck$).tw.
6	(boeck$ adj (disease or sarcoid)).tw.
7	(schaumann$ adj (disease or syndrome)).tw.
8	uveoparoti$.tw.
9	(benign$ adj lymphogranuloma$).tw.
10	((junging or heerfordt or lofgren) adj syndrome).tw.
11	neurosarcoidosis.tw.
12	(lupus adj pernio).tw.
13	(idiopathic adj3 inflammat$ adj3 granulomat$).tw.
14	or/1-13 [all sarcoidosis]
15	exp Kidney Function Tests/
16	Creatinine/
17	Urea/

18	(creatinine adj2 (test$ or excret$)).mp.
19	(((kidney$ or renal or uremi$ or urea or urin$) adj2 (test$ or function$)) or azotemi$).mp.
20	(blood adj2 urea adj2 nitrogen).mp.
21	or/15-20
22	14 and 21

Selected studies with outcomes

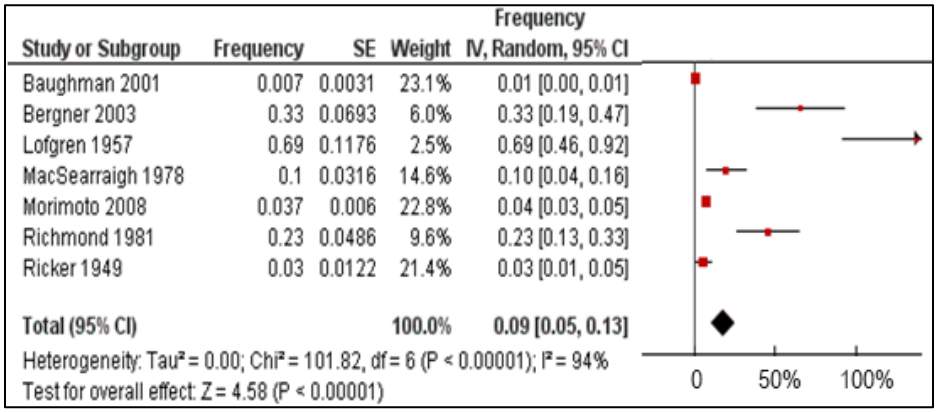
Study	Test	Definition of abnormal test	Frequency of abnormal renal function	Biopsy results	Renal function outcomes
More recent studies					
Baughman 2001	Serum Cr	Improvement of serum Cr post-immunosuppressant therapy	5/736 (0.7%)	NR	Cannot be determined because improvement is part of definition
Bergner 2003	Serum Cr + 24-hr urine	Serum Cr >1.2 mg/dL or urine protein >150 mg/24 hours	15/46 (33%)	10 performed - 5/10 (50%) nephrocalcinosis, 4/10 (40%) granulomatous interstitial nephritis, 1/10 (10%) non-granulomatous interstitial nephritis, and 2/10 (20%) IgA GN.	15 treated- 13/15 (87%) serum Cr improved [7 of which normalized] and 2/15 (13%) lost to follow-up; 8/15 (53%) proteinuria improved and 7/15 (47%) lost to follow-up.
Morimoto 2008	Urine calcium	Elevated urine calcium; threshold not defined	36/974 (3.7%)	NR	NR
Older studies					
Lebacq 1970	24-hr urine + urine sediment	Proteinuria, urine calcium >200mg/24 hours, abnormal sediment, CrCl <100 mL/min	N/R	25 performed- 10/25 (40%) granulomas, 9/25 (36%) hyaline deposits, 8/25 (32%) interstitial inflammation, 4/25 (16%) glomerular hypercellularity, 2/25 (8%) interstitial fibrosis, 2/25 (8%) pericapsular fibrosis and adhesions, 1/25 (4%) amyloid.	2/2 (100%) improved
Lofgren 1957	24-hr urine + urine sediment	Proteinuria, sediment with granular casts, CrCl <100 mL/min	11/16 (69%)	16 performed- 1/16 (16%) granular casts, 0/16/ (0%) nephrocalcinosis	NR
MacSearraigh 1978	24-hr urine	Proteinuria, urine calcium >5mmol/24 hours, CrCl <100 mL/min	9/90 (10%)	8 performed- 8/8 (100%) biopsies abnormal; 8/8 (100%) with more than one abnormality; 5/8 (63%) granulomas, 4/8 (50%) nephrocalcinosis; other	8/9 (89%) improved

Richmond 1981	Urine sediment + renal biopsy	Any abnormality of sediment or histopathology	17/75 (23%)	17 performed- 8/17 (47%) abnormal sediment, 7/17 (41%) nephrocalcinosis, 1/17 (6%) membranous GN, 1/17 (1%) granulomatous interstitial nephritis	NR
Ricker 1949	Not specified	Not specified ("kidneys effected")	5/195 (3%)	Not confined to those with renal abnormalities	NR
Pooled (weighted)	***N/A***	***N/A***	***7% [1] (95% CI 3-11%)***	***N/A***	***Not estimable***
Pooled (unweighted)			***5% [1] (95 4-6.3%)***		***88% (95% CI 71-96%)***
Median (range)			***10% (0.7-69%)***		***89% (87%-100%)***

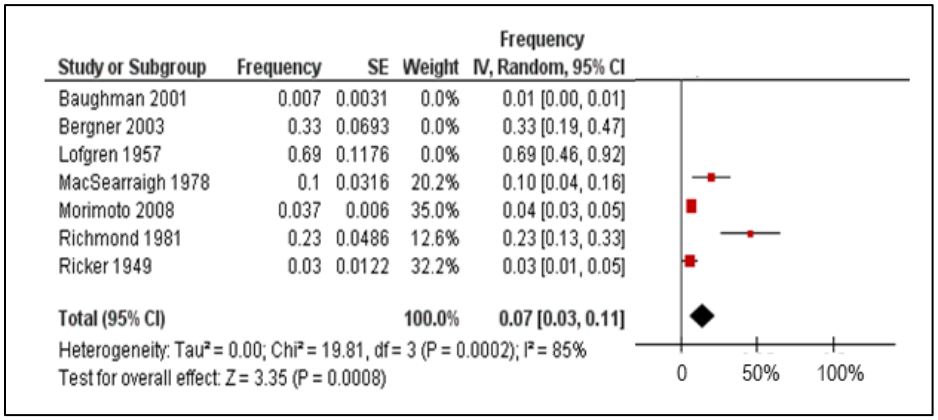
NR= not reported, Cr= creatinine, CrCl= creatinine clearance, GN= glomerulonephritis.
[1] After outliers removed

Forest plots

Initial



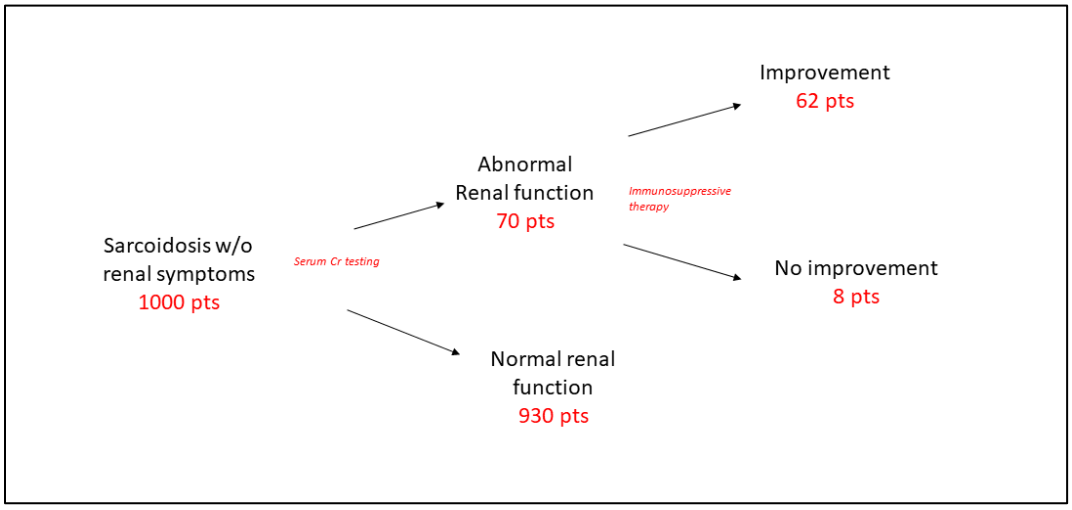
After removal of outliers



Treatment effect

Meta-analysis not possible

Markov Model



Evidence profile

Bibliography:

1) Baughman RP, et al. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med 2001; 164:1885-1889.
2) Morimoto T, et al. Epidemiology of sarcoidosis in Japan. Eur Respir J 2008; 31:371-379.
3) Bergner R, et al. Frequency of kidney disease in chronic sarcoidosis. Sarc Vasc Diffuse Lung Dis 2003; 20(2):126.
4) Richmond JM, et al. Renal disease and sarcoidosis. Med J Aust 1981; 2(1):36-37.
5) Ricker W, et al. Sarcoidosis: A clinicopathologic review of 300 cases, including 22 autopsies. Am J Clin Pathol 1949; 19:725-749.
6) MacSearraigh ET, et al. Sarcoidosis with renal involvement. Postgrad Med J 1978; 56(634):528.
7) Lebacq E, et al. Renal involvement in sarcoidosis. Postgrad Med J 1970; 46(538):526.
8) Lofgren S, et al. Renal complications in sarcoidosis; functional and biopsy studies. Acta Med Scand 1957; 159(4):295.

Quality assessment							Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Detection of renal dysfunction (frequency of abnormal renal function testing, %)									
7[1]	Case series	serious[2]	serious[3]	none	serious[4]	none	7% [5] (95% CI 3-11%)	⊕OOO VERY LOW	TBD
Improvement in renal dysfunction with treatment (frequency of improvement in renal function tests, %)									
3[6]	Case series	serious[2]	serious[3]	none	serious[4]	none	88% (95% CI 71-96%)	⊕OOO VERY LOW	TBD

Footnotes:
[1] All of the studies in the bibliography except Lebacq.
[2] Many were retrospective chart reviews; therefore, there was a risk of selection bias.
[3] The studies were judged too different in the test used and the definition of an abnormal test to pool.
[4] Likely, since 6/8 studies had <100 patients.
[5] After removal of outliers.

[6] Bergner, Lebacq, and MacSerraigh

QUESTION #5: *Should patients with sarcoidosis who do not have hepatic symptoms undergo screening for hepatic sarcoidosis by routine transaminase and alkaline phosphatase testing?*

Search strategy

#	Searches
1	exp sarcoidosis/
2	sarcoidosis/
3	sarcoidosis/ or sarcoidosis, pulmonary/ or uveoparotid fever/
4	sarcoid$.mp.
5	(besnier adj boeck$).tw.
6	(boeck$ adj (disease or sarcoid)).tw.
7	(schaumann$ adj (disease or syndrome)).tw.
8	uveoparoti$.tw.
9	(benign$ adj lymphogranuloma$).tw.
10	((junging or heerfordt or lofgren) adj syndrome).tw.
11	neurosarcoidosis.tw.
12	(lupus adj pernio).tw.
13	(idiopathic adj3 inflammat$ adj3 granulomat$).tw.
14	or/1-13 [all sarcoidosis]
15	Liver Function Tests/
16	alkaline phosphatase/
17	exp Transaminases/
18	((hepati$ or liver$) adj (test$ or function)).mp.
19	(transmininase$ or alkaline phosphatase or SGOP or SGPT).mp.
20	or/15-19
21	14 and 20

Selected studies with outcomes

Study	Freq. abnormal LFTs	Biopsy granulomas	Initiation of therapy	LFT response to treatment	Progression to liver failure
Cremers 2012	127/837 (15%)	21/22 (95%)	NR	NR	NR
Kahi 2006	340/1436 (24%)	34/34 (100%)	NR	NR	NR
Cowdell 1954	10/22 (45%)[1]	NR	NR	NR	NR
Morimoto 2008	56/995 (5.6%)	NR	NR	NR	NR
Baughman 2001	85/736 (11.5%)	NR	NR	NR	NR

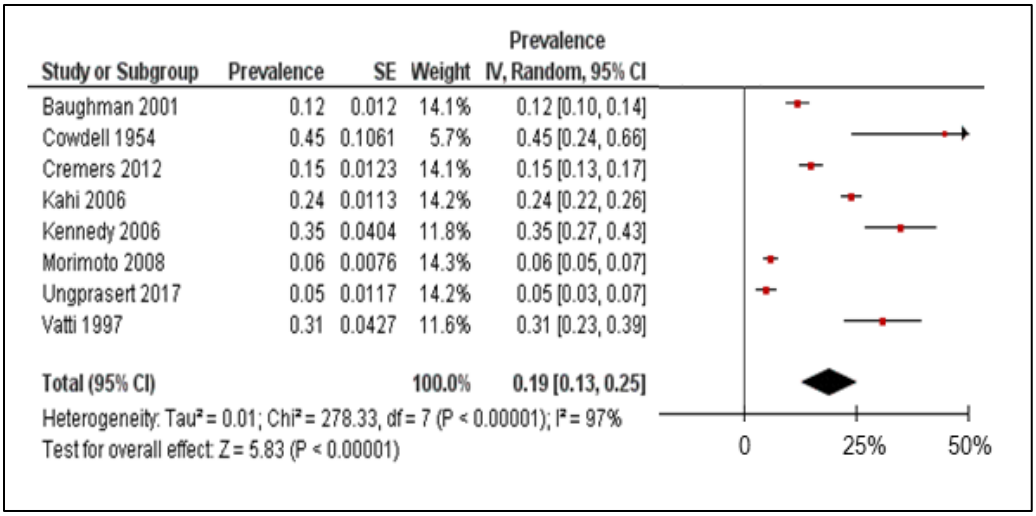
Vatti 1997	44/125 (35%)	NR	25/44 (57%)[2]	w/ therapy 12/25 (48%) improved, 13/25 (52%) unchanged 0/25 (0%) worsened	NR
				w/o therapy 10/19 (53%) improved 9/19 – unreported course	
Ungprasert 2017	16/345 (5%)[3]	11/13 (85%)	4/16 (25%)[2]	w/ therapy 6/10 (60%) improved, 4/10 (40%) mixed response[4] 0/10 (0%) worsened	w/therapy[5] 0/4 (0%) progressed to cirrhosis
				w/o therapy 4/6 (67%) improved, 1/6 (16%) worsened 1/6 lost to follow-up.	w/o therapy[5] 1/4 (25%) had cirrhosis at diagnosis
Kennedy 2006	41/131 (31%)	NR	39/41 (95%)[2]	w/therapy[6] 15/24 (62%) resolution, 5/24 (21%) improved, 3/24 (13%) no response, 1/24 (5%) did not tolerate treatment	w/therapy[6] 5/24 (21%) progressed to cirrhosis
				w/o therapy[6] 3/3 (100%) resolution (12 not treated because cirrhotic) (10 not treated because diagnosis uncertain)	w/o therapy[6] 9/25 (36%) had cirrhosis at diagnosis
Pooled (weighted)	***12% (95% CI 6-19%)***	***Not estimable***	***Did not assess***	***38/59 (64%) versus 17/28 (61%) RR 1.09 (95% CI 0.76 to 1.57)***	***5/28 (18%) vs. 10/29 (34%) RR 0.54 (95% CI 0.22 to 1.33)***
Pooled (unweighted)	***16% (95% CI 15-17%)***	***96% (95% CI 88- 99%)***	***Did not assess***	***38/59 (64%) versus 17/28 (61%) RR 1.06 (95% CI 0.75 to 1.51)***	***5/28 (18%) vs. 10/29 (34%) RR 0.52 (95% CI 0.20 to 1.33)***
Median (range)	***20% (5% to 45%)***	***95% (85% to 100%)***	***Did not assess***	***60% (48% to 83%) vs. 83% (53% to 100%)***	***10% (0% to 21%) vs. 31% (25% to 36%)***

NR= not reported.
[1]In Cowdell, et al., only alkaline phosphatase was measured.
[2] In Vatti, et al., it is implied that therapy was initiated for liver disease. In Ungprasert, et al., 4/16 (25%) had therapy initiated due to abnormal liver disease, while an additional 6/16 (38%) had therapy initiated for other organ systems; therefore, overall 10/16 (63%) received therapy. In Kennedy et al., 39/41 (95%) had therapy initiated, but the article is unclear if initiated due to liver disease, co-existing lung disease, or both.
[3] Assumes that all patients enrolled had LFTs performed.
[4] Mixed responses = some LFTs improved while others stayed the same or worsened.
[5] Among treated for presumed hepatic sarcoidosis.
[6] Kennedy et al., included two cohorts. The first was 131 patients with sarcoidosis but mostly no symptoms, undergoing screening; this cohort was used to determine frequency of LFT abnormalities, frequency of positive biopsies, and frequency of new treatment. The second was 49 patients with presumed hepatic sarcoidosis; this cohort was used to determine effects of treatment on LFT abnormalities and progression to cirrhosis.

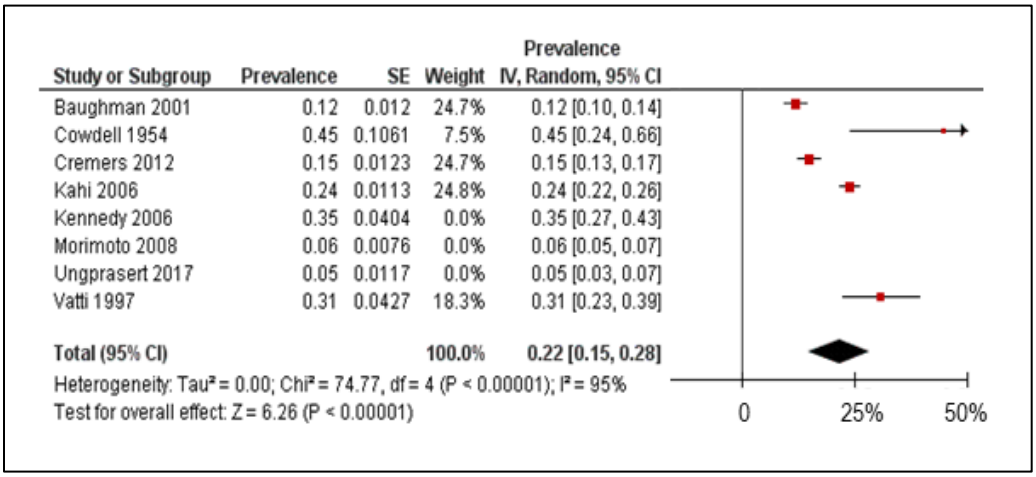
Forest plots

Frequency of abnormal LFTs

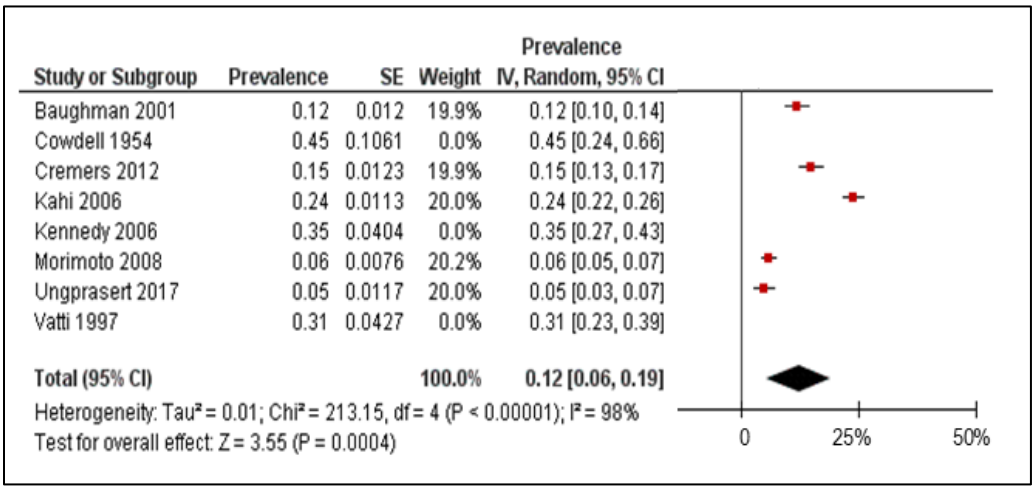
Initial



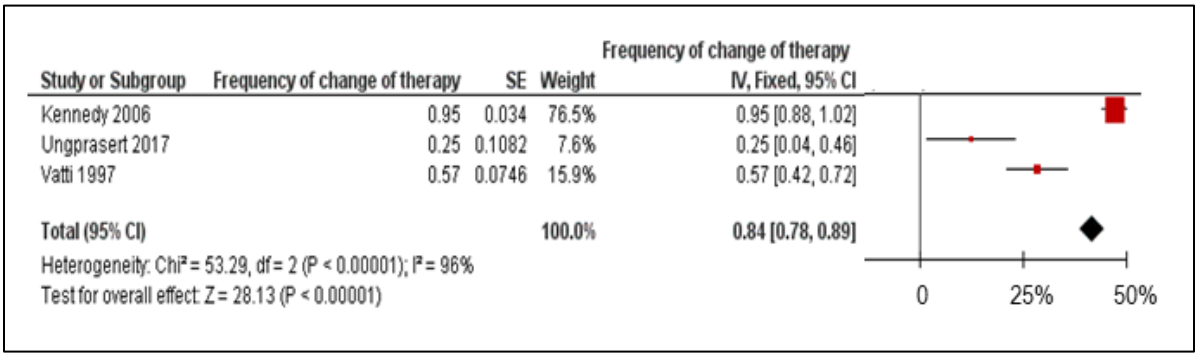
After removal of outliers



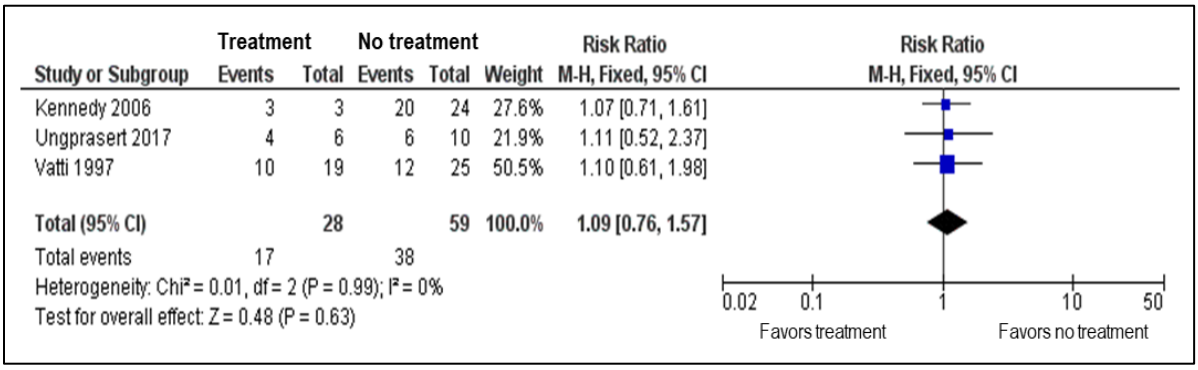
After removal of studies with N<300



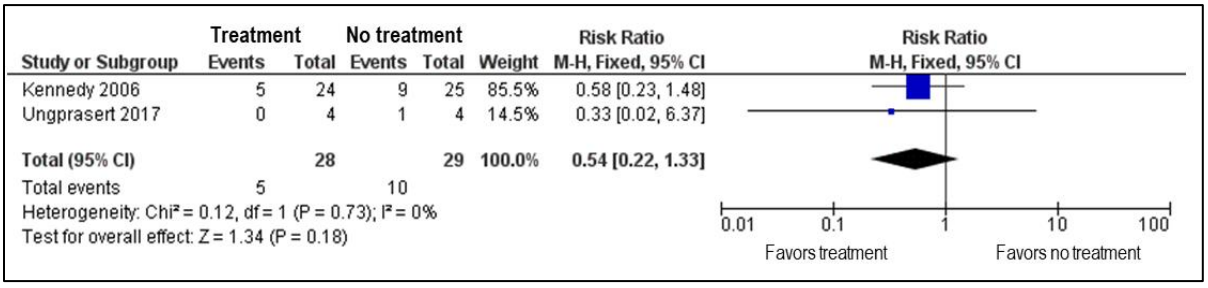
Frequency of initiation of therapy



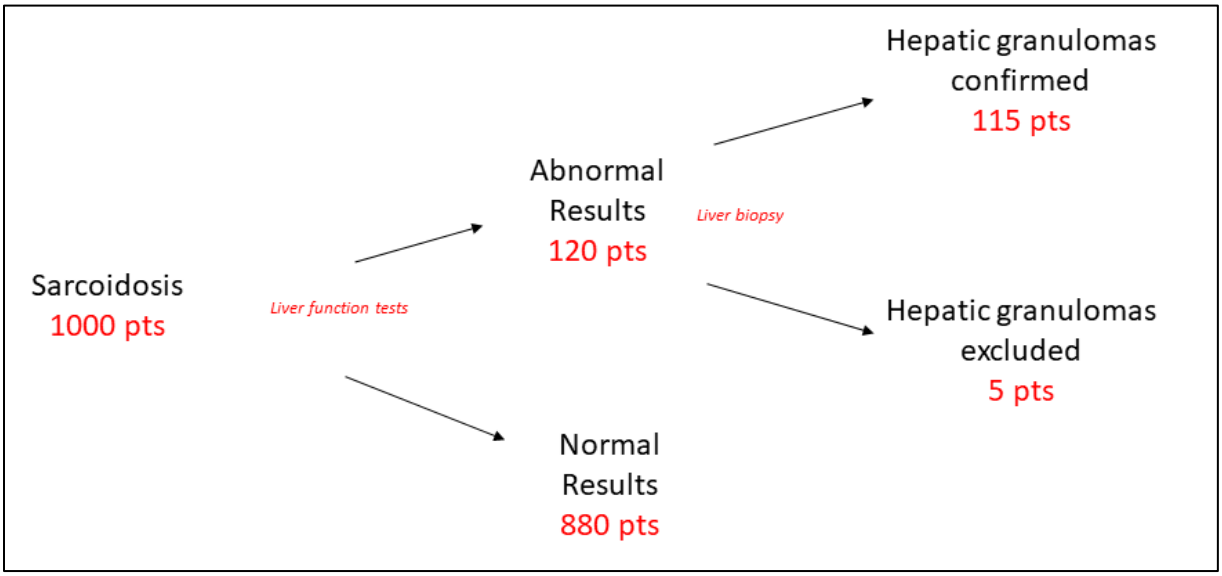
Effect of treatment on resolution or improvement of LFTs



Effect of treatment on progression to cirrhosis



Markov model



For every 1000 sarcoidosis patients without hepatic symptoms who undergo routine LFT testing, abnormalities will be found in roughly 120, 115 of whom will be confirmed to have hepatic granulomas and 5 of whom will not. Among treated patients, there is no difference in the rate of improvement of LFTs (64% vs. 61%, RR 1.09, 95% CI 0.76 – 1.57), but a trend toward less development of cirrhosis (18% vs. 34%, RR 0.54, 95% CI 0.22 – 1.33).

Evidence profile

Bibliography:

1) Cremers J, Drent M, Driessen A, Nieman F, Wijnen P, Baughman R, Koek G.Liver-test abnormalities in sarcoidosis. Eur J Gastroenterol Hepatol. 2012; 24(1):17-24.
2) Kahi CJ, Saxena R, Temkit M, Canlas K, Roberts S, Knox K, Wilkes D, Kwo PY.Hepatobiliary disease in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2006; 23(2):117-23.
3) Vatti R, Sharma OP. Course of asymptomatic liver involvement in sarcoidosis: role of therapy in selected cases. Sarcoidosis Vasc Diffuse Lung Dis. 1997;14(1):73-6.
4) Ungprasert P et al. Clinical characteristics and outcome of hepatic sarcoidosis: A population-based study 1976-2013. Am J Gastroenterol 2017; 112(10):1556-1563.
5) Kennedy PT, et al. Natural history of hepatic sarcoidosis and its response to treatment. Eur J Gastroenterol Hepatol 2006; 18(7):721-726.
6) Baughman RP, et al. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med 2001; 164:1885-1889.
7) Morimoto T, et al. Epidemiology of sarcoidosis in Japan. Eur Respir J 2008; 31:371-379.
8) Cowdell RH. Sarcoidosis: a special reference to diagnosis and prognosis. Quart J Med 1954; 23:29.

Quality assessment							Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Detection of liver dysfunction (frequency of abnormal liver function tests, %)									
8[1]	Case series	serious[2]	serious[3]	serious[4]	serious[5]	none	12% (95% CI 6-19%)	⊕OOO VERY LOW	TBD
Initiation of treatment (%)									

3[6]	Case series	serious[2]	serious[3]	serious[4]	serious[5]	none	Did not assess[6]	⊕OOO VERY LOW	TBD
Improvement in liver dysfunction (frequency of improvement in liver function tests, %)									
3[7]	Case series	serious[2]	none	serious[4]	serious[8]	none	RR 1.09 (95% CI 0.76 to 1.57)	⊕OOO VERY LOW	TBD
Progression to liver failure (frequency of development of cirrhosis, %)									
2[9]	Case series	serious[2]	none	serious[4]	serious[8]	none	RR 0.52 (95% CI 0.20 to 1.33)	⊕OOO VERY LOW	TBD
Liver transplantation (%)									
0	-	-	-	-	-	-	-	-	TBD
Mortality (%)									
0	-	-	-	-	-	-	-	-	TBD

Footnotes:
[1] Cremers, Kahi, Vatti, Ungprasert, Kennedy, Baughman, Morimoto, and Cowdell.
[2] Many were retrospective chart reviews; therefore, there was a risk of selection bias.
[3] When pooled by meta-analysis, the I^2 >90%; thus, eliminated outliers and small studies before reporting summary statistic.
[4] The PICO question asks about patients without hepatic symptoms; however, only one statement explicitly stated that the patients had no hepatic symptoms.
[5] The 95% CI for prevalence is >10%.
[6] The results of the study were so disparate, that a summary statistic is not reported.
[7] Vatti, Ungprasert, and Kennedy.
[8] The conference intervals are wide; the ends will lead to opposite clinical decisions.
[9] Unprasert and Kennedy.

QUESTION #6: *Should patients with sarcoidosis who do not have symptoms or signs of hypercalcemia undergo screening for abnormal calcium metabolism by routine serum calcium and vitamin D testing?*

Search strategy

#	Searches
1	exp sarcoidosis/
2	sarcoidosis/
3	sarcoidosis/ or sarcoidosis, pulmonary/ or uveoparotid fever/
4	sarcoid$.mp.
5	(besnier adj boeck$).tw.
6	(boeck$ adj (disease or sarcoid)).tw.
7	(schaumann$ adj (disease or syndrome)).tw.
8	uveoparoti$.tw.
9	(benign$ adj lymphogranuloma$).tw.
10	((junging or heerfordt or lofgren) adj syndrome).tw.
11	neurosarcoidosis.tw.
12	(lupus adj pernio).tw.
13	(idiopathic adj3 inflammat$ adj3 granulomat$).tw.

14	or/1-13 [all sarcoidosis]
15	calcium/
16	exp vitamin D/
17	(hypercalcem$ or calcium or vitamin D).mp.
18	15 or 16 or 17
19	14 and 18

Selected studies with outcomes

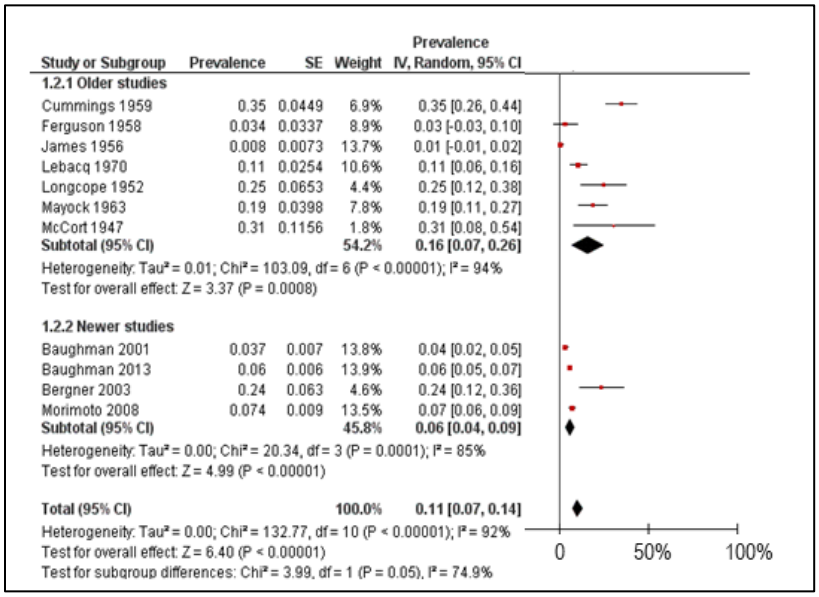
Study	Frequency of hypercalcemia	Definition of hypercalcemia	Initiation of therapy	Course of calcium outcomes	Course of clinical outcomes
Baughman 2001	27/736 (3.7%)	Increased serum Ca w/o alternative cause	NR	NR	NR
Baughman 2013	97/1606 (6%)	Ca > 10.2 mg/dL	Implied 97/97 (100%)	81/86 (94%) improved 78/86 (91%) resolved 11/97 (6%) lost to f/u	41/97 (42%) developed renal failure 20/37 (54%) normalized renal failure with treatment
Morimoto 2008	62/842 (7.4%)	Not specified	NR	NR	NR
Bergner 2003	11/46 (24%)	Not specified	NR	"Decreased to normal range rapidly"	NR
Lebacq 1970	17/152 (11%)	Ca > 11 mg/dL	NR	NR	NR
Mayock 1963	18/97 (19%)	Ca > 11 mg/dL	NR	NR	NR
McCort 1947	5/16 (31%)	Ca > 11 mg/dL	NR	NR	NR
Longcope 1952	11/44 (25%)	Ca > 11 mg/dL	NR	NR	NR
James 1956	1/150 (0.8%)	Not specified	NR	NR	NR
Ferguson 1958	1/29 (3.4%)	Not specified	NR	NR	NR
Cummings 1959	40/113 (35%)	Ca > 11 mg/dL	NR	NR	NR
Pooled (weighted)	***6% (95% CI 4-8%) Newer study subgroup***	***Not estimable***	***Did not assess***	***>90% resolution Single study***	***>40% renal failure >50% resolution Single study***
Pooled (unweighted)	***6.1% (95% CI 5.3-7%) Newer study subgroup***	***Not estimable***	***Did not assess***	***>90% resolution Single study***	***>40% renal failure >50% resolution Single study***

Median (range)	***6.7% (3.7% - 24%) Newer study subgroup***	***Not estimable***	***Did not assess***	***>90% resolution Single study***	***>40% renal failure >50% resolution Single study***

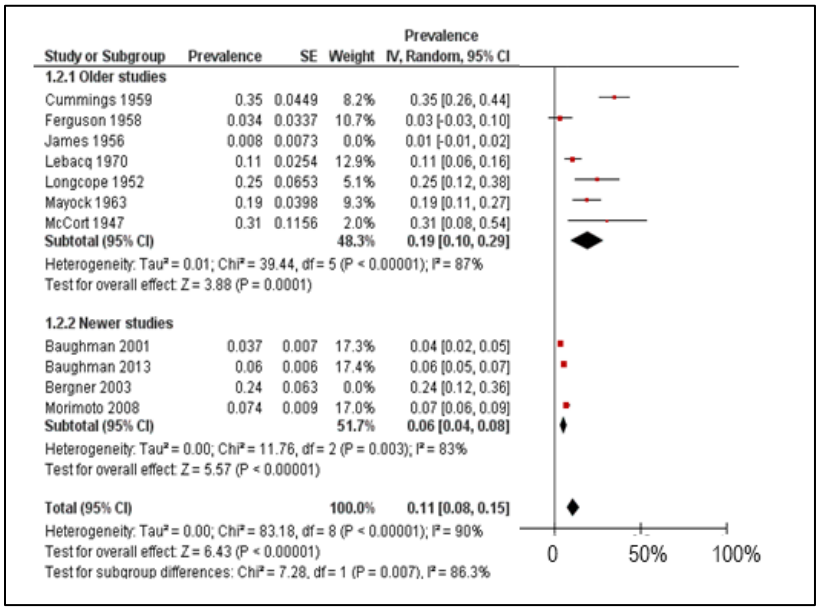
Forest plots

Prevalence of hypercalcemia

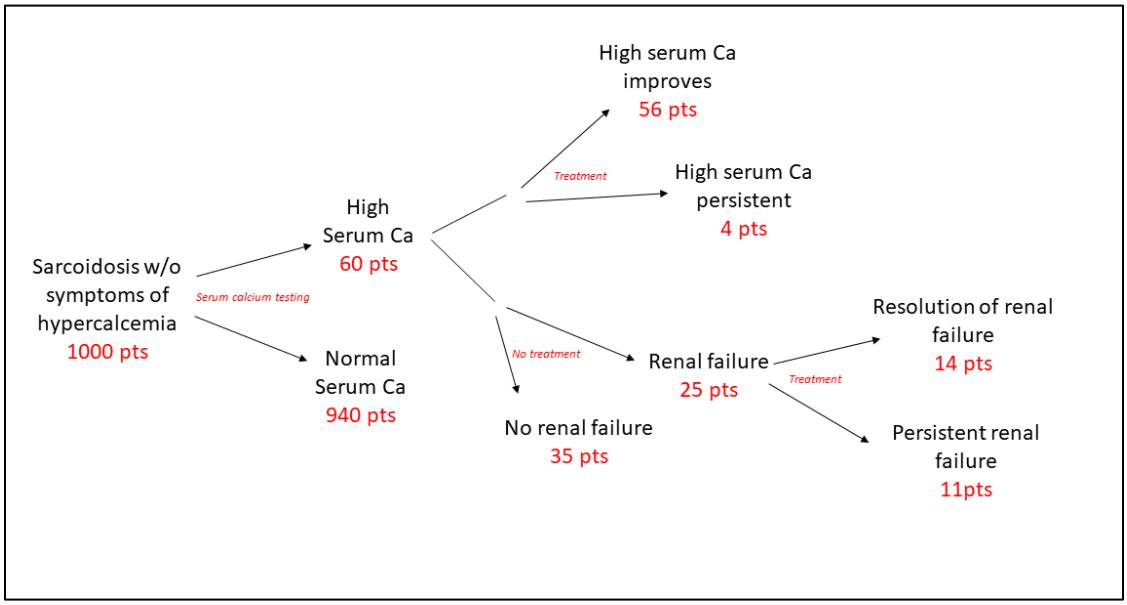
Initial



After removal of outliers



Markov model



Evidence profile

Bibliography:

1) Baughman RP, et al. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med 2001; 164:1885-1889.
2) Baughman RP, et al. Calcium and Vitamin D metabolism in sarcoidosis. Sarc Vasc Diffuse Lung Dis 2013; 30:113-120.
3) Morimoto T, et al. Epidemiology of sarcoidosis in Japan. Eur Respir J 2008; 31:371-379.
4) Bergner R, et al. Frequency of kidney disease in chronic sarcoidosis. Sarc Vasc Diffuse Lung Dis 2003; 20(2):126.
5) Lebacq E, et al. Renal involvement in sarcoidosis. Postgrad Med J 1970; 46(538):526.
6) Mayock, et al. Manifestations of sarcoidosis: Analysis of 145 patients with a review of nine series selected from the literature. Am J Med 1963; 35:67-89.
7) McCort JJ, et al. A clinical and roentgenologic study of twenty-eight proved cases. Arch Intern Med 1947; 80:293.
8) Longcope WT, et al. A study of sarcoidosis. Based on a combined investigation of one hundred sixty cases including thirty autopsies from JHH and MGH. Medicine 1952; 31:1.
9) James D. Diagnosis and treatment of sarcoidosis. BMJ 1956; 2:900.
10) Ferguson RH, et al. Sarcoidosis study of twenty-nine cases, with a review of splenic, hepatic, mucus membrane, retinal, and joint manifestations. Arch Int Med 1958; 101:1065.
11) Cummings MM. Epidemiologic and clinical observations in sarcoidosis. Ann Int Med 1959; 50:879.

Quality assessment							Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of hypercalcemia (frequency of abnormal serum calcium tests, %)									
11[1]	Case series	serious[2]	serious[3]	none	none	none	6% (95% CI 4-8%)	⊕OOO VERY LOW	TBD
Incidence of renal failure (frequency of patients who develop renal failure, %)									
1[4]	Case series	serious[2]	serious[3]	none	none	none	41/97 (42%) (95% CI 33-52%)	⊕OOO VERY LOW	TBD
Response to treatment (% patients whose serum calcium improved)									

1[4]	Case series	serious[2]	serious[3]	none	none	none	81/86 (94%) (95% CI 87-97%)	⊕OOO VERY LOW	TBD
Response to treatment (% patients whose renal failure resolved)									
1[4]	Case series	serious[2]	serious[3]	none	none	none	20/37 (54%) (95% CI 38-69%)	⊕OOO VERY LOW	TBD

Footnotes:
[1] All studies listed in the bibliography.
[2] Many were retrospective chart reviews; therefore, there was a risk of selection bias.
[3] When pooled by meta-analysis, the I^2 >90%; thus, looked at subgroups and eliminated outliers before reporting summary statistic.
[4] Baughman 2013.

QUESTION #7: *Should patients with sarcoidosis who do not have hematological symptoms undergo screening for bone marrow involvement by routine complete blood cell count testing?*

Search strategy

#	Searches
1	exp bone marrow cells/
2	exp blood cells/
3	bone marrow.mp.
4	((Progenitor or Precursor or Hematopoietic) adj2 Cell$).mp.
5	(Megakaryocyt$ or Monocyt or Reticulocyt$).mp.
6	(Blood Platelet$ or Erythrocyt$ or Hemocyt$).mp.
7	(Granulocyt$ or Basophil$ or Eosinophil$ or Neutrophil$).mp.
8	(Lymphocyt$ or Monocyt$).mp.
9	(Leukocyt$ or (Killer adj cell$)).mp.
10	or/1-9
11	exp sarcoidosis/
12	sarcoidosis/
13	sarcoidosis/ or sarcoidosis, pulmonary/ or uveoparotid fever/
14	sarcoid$.mp.
15	(besnier adj boeck$).tw.
16	(boeck$ adj (disease or sarcoid)).tw.
17	(schaumann$ adj (disease or syndrome)).tw.
18	uveoparoti$.tw.
19	(benign$ adj lymphogranuloma$).tw.
20	((junging or heerfordt or lofgren) adj syndrome).tw.
21	neurosarcoidosis.tw.
22	(lupus adj pernio).tw.
23	(idiopathic adj3 inflammat$ adj3 granulomat$).tw.
24	or/11-23 [all sarcoidosis]
25	mass screening/

```
26  "Risk Assessment"/
27  (screen$ or surveil$ or follow-up$).mp.
28  exp screening/
29  or/25-28
30  10 and 24 [Sarcoidosis and blood cells]
31  10 and 24 and 29 [Sarcoidosis and blood cells and screening]
32  30 not 31
```

Selected studies with outcomes

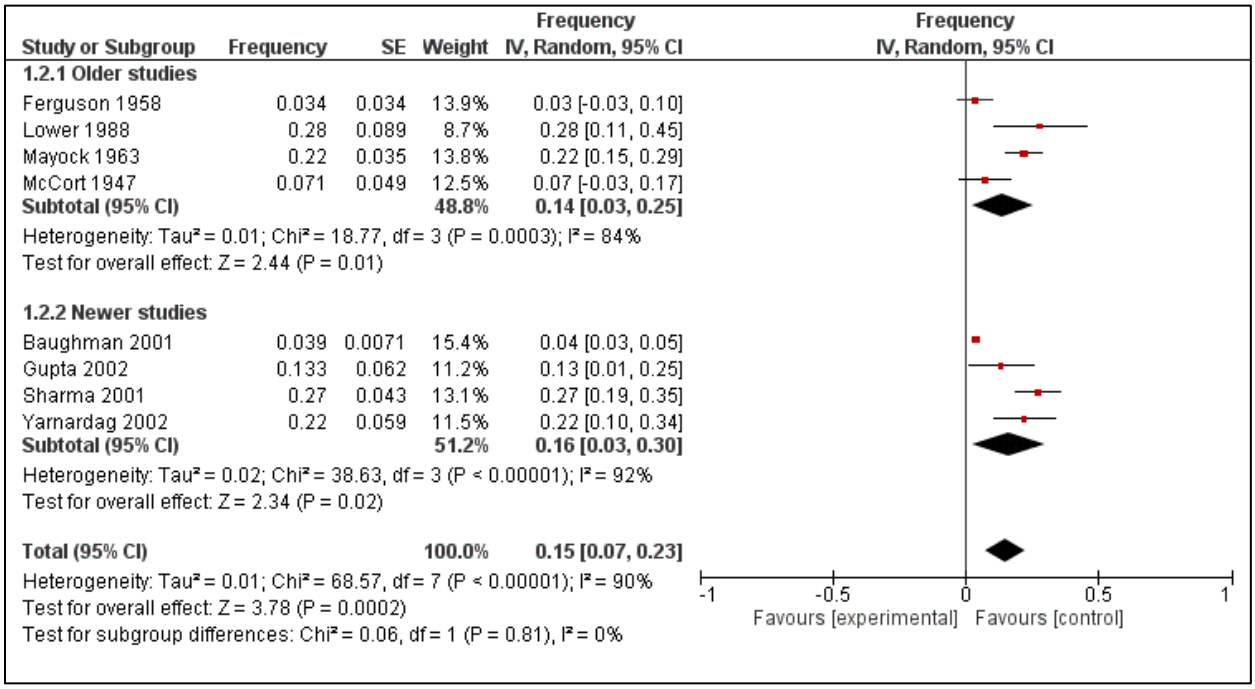
Study	Definition of anemia	Frequency of anemia	Definition of leukopenia	Frequency of leukopenia	Definition of lymphopenia	Frequency of lymphopenia
Yarnardag, et al. 2002	NR	11/50 (22%)	NR	NR	NR	NR
Gupta, et al. 2002	Hgb <11.5 g/dL	4/30 (13.3%)	<4000 /mm^3	1/30 (3.3%)	<1500 /mm^3	8/30 (27%)
Sharma, et al. 2001	Hgb <11.5 g/dL	29/106 (27%)	<4000 /mm^3	4/106 (4%)	<1500 /mm^3	NR
Baughman, et al. 2001	NR	29/736 (3.9%)	NR	NR	NR	NR
Lower, et al. 1988	NR	21/75 (28%)	NR	NR	NR	41/75 (55%)
Mayock, et al. 1963	Hgb <11.0 g %	31/144 (22%)	<5000 /mm^3	43/144 (30%)	NR	NR
Cummings, et al. 1959	NR	NR	<5000 /mm^3	51/175 (29%)	NR	NR
Ferguson, et al. 1958	Hgb <11.0 g/dL	1/29 (3.4%)	<5000 /mm^3	7/29 (24%)	NR	NR
Israel, et al. 1958	NR	NR	<5000 /mm^3	60/160 (38%)	NR	NR
McCort, et al. 1947	RBC < $4x10^6$	2/28 (7.1%)	<4500 /mm^3	7/28 (25%)	NR	NR
Pooled result (weighted)	***NR***	***15% 95% CI 7%-23%***	***NR***	***4% 95% CI 1-7% 4000 mm^3 subgroup***	***NR***	***42% (95% CI 14-69%)***
Pooled result (unweighted)	***NR***	***26% 95% CI 22%-30%***	***NR***	***4% 95% CI 3%-8% 4000 mm^3 subgroup***	***NR***	***47% (95% CI 37-56%)***
Median (range)	***NR***	***17% (3% to 28%)***	***NR***	***3.5% (3% to 4%) 4000 mm^3 subgroup***	***NR***	***41% (27% to 55%)***

Study	Frequency of granulomas on bone marrow biopsy	Frequency of treatment being changed	Notes
Yarnardag, et al. 2002	3/11 (27%) of pts. with anemia had granulomas in bone marrow; 7/11 (65%) had iron deficiency anemia	NR	NR
Gupta, et al. 2002	NR	NR	4/30 (13.3%) sarcoid patients had anemia; 3/30 (13.3%) healthy patients had anemia
Sharma, et al. 2001	NR	NR	NR

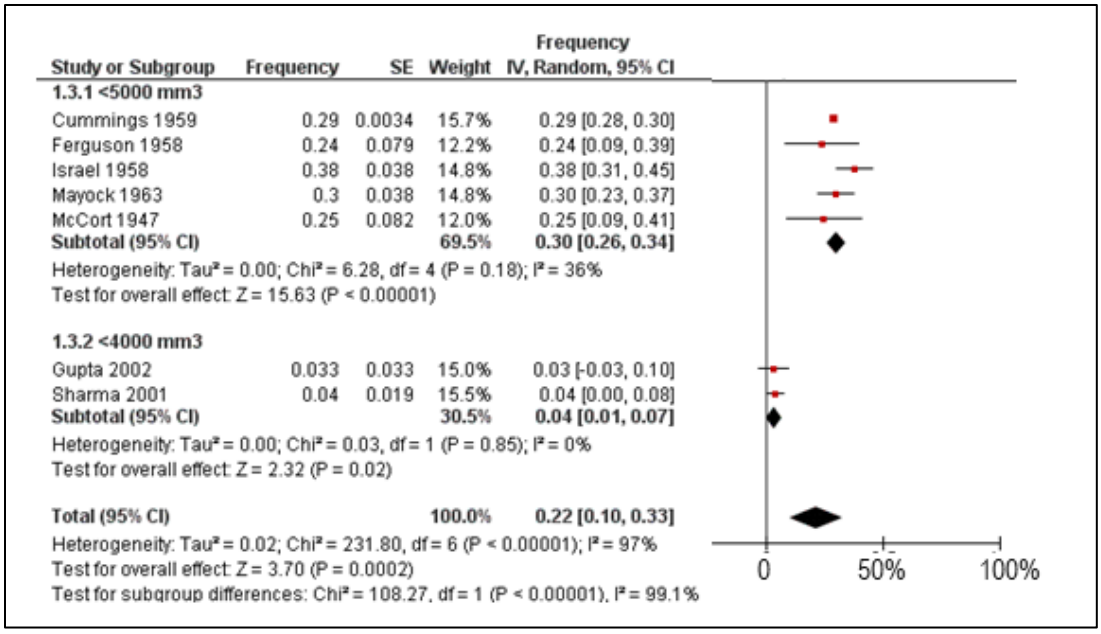
Baughman, et al. 2001	NR	NR	NR
Lower, et al. 1988	9/17 (53%) of pts. with anemia had granulomas in bone marrow; no alternative anemias	NR	NR
Mayock, et al. 1963	NR	NR	NR
Cummings, et al. 1959	NR	NR	NR
Ferguson, et al. 1958	NR	NR	Abnormalities occurred "on occasion"
Israel, et al. 1958	NR	NR	NR
McCort, et al. 1947	NR	NR	For most pts. the abnormality was seen on one measurement and didn't persist
Pooled result (weighted)	***38% (95% CI 13-64%)***	***N/A***	***N/A***
Pooled result (unweighted)	***43% (95% CI 27-61)***	***N/A***	***N/A***
Median (range)	***40% (27% to 53%)***	***N/A***	***N/A***

Forest plots

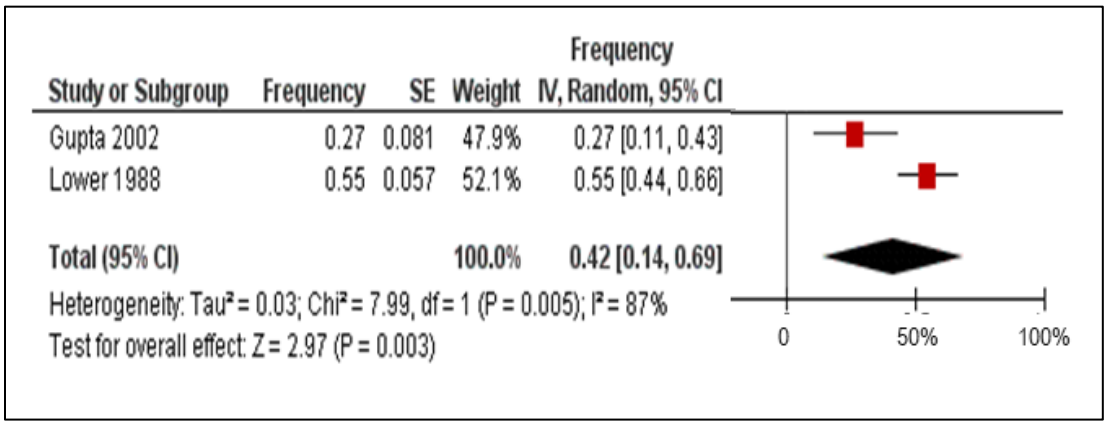
Frequency of anemia



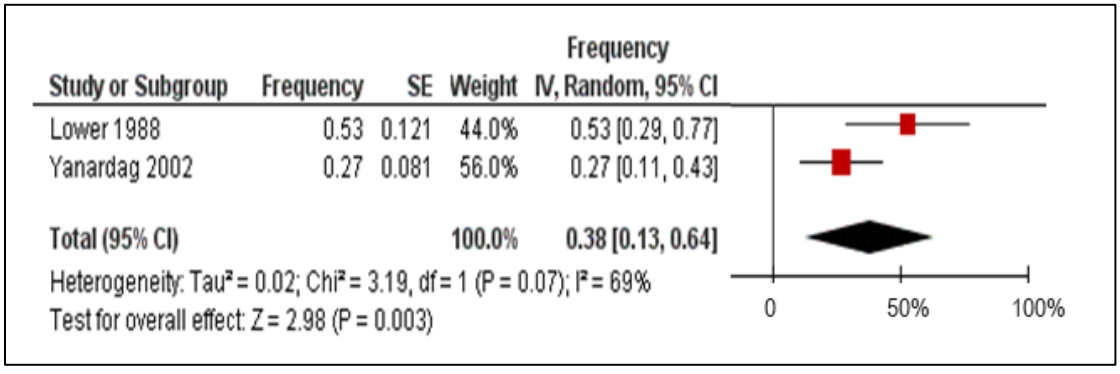
Frequency of leukopenia



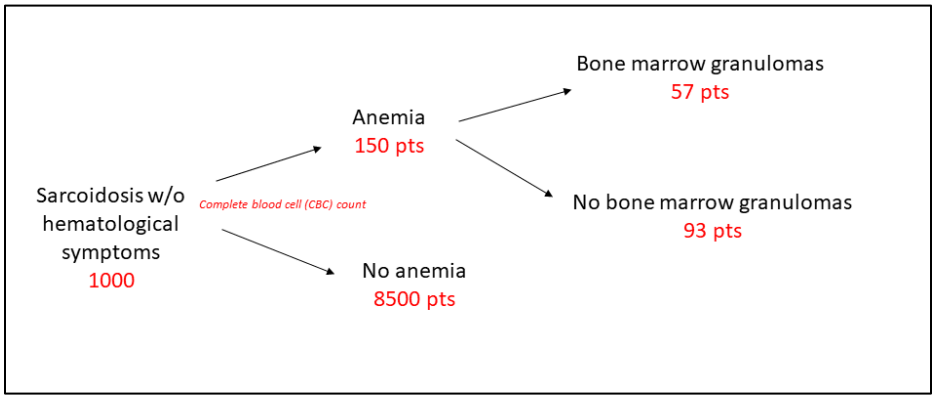
Frequency of lymphopenia

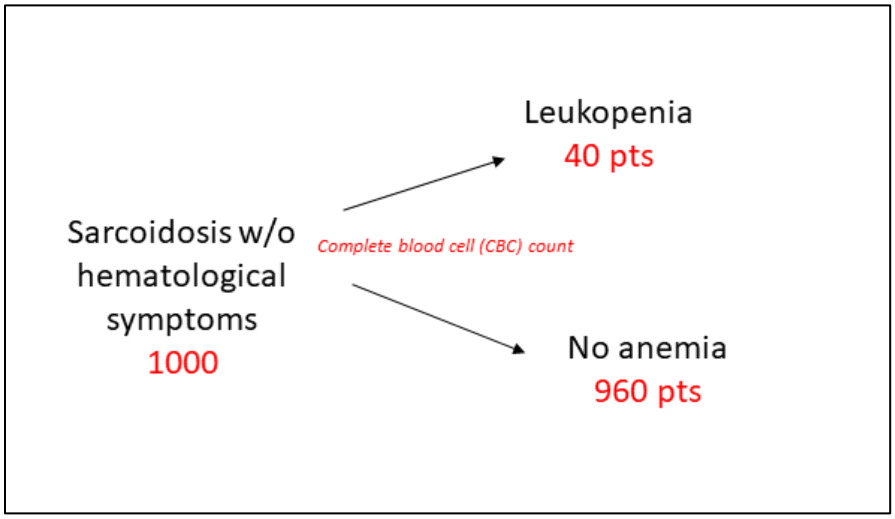


Frequency of bone marrow granulomas among those with anemia



Markov model





Evidence profile

Comparison: Complete blood cell count versus none

Bibliography:

1) Lower EE, et al. The anemia of sarcoidosis. Sarcoidosis 1988; 5(1):51-55.
2) Yanardag H, et al. Bone marrow involvement in sarcoidosis: an analysis of 50 bone marrow samples. Haematologia (Budap) 2002; 32(4):419-425.
3) Gupta D, et al. Haematological abnormalities in patients of sarcoidosis. Indian J Chest Dis All Sci 2002; 44(4):233-236.
4) Mayock, et al. Manifestations of Sarcoidosis: Analysis of 145 Patients with a Review of Nine Series Selected from the Literature. Am J Med 1963; 35:67-89.
5) Sharma SK, et al. Clinical characteristics, pulmonary function abnormalities, and outcome of prednisolone treatment in 106 patients with sarcoidosis. J Assoc Physicians India 2001; 49:697-704.
6) McCort JJ, et al. Sarcoidosis-- A clinical and roentogenographic study of 28 proved cases. Arch Intern Med 1947; 80:293.
7) Ferguson RH, et al. Sarcoidosis. Study of 29 cases, with review of splenic, hepatic, mucous membrane, retinal, and joint manifestations. Arch Intern Med 1958; 101:1065.
8) Israel HL, et al. Sarcoidosis. Clinical observations on one hundren and sixty cases. Arch Intern Med 1958; 102:766.
9) Cummings MM, et al. Epidemiologic and clinical observations in sarcoidosis. Ann Intern Med 1959; 50:879.

Quality assessment							Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			

Detection of anemia (frequency of anemia among CBCs, %)									
7[1]	Case series	serious[2]	serious[3]	none	serious[4]	none	15% 95% CI 7%-23%	⊕OOO VERY LOW	TBD
Detection of leukopenia (frequency of leukopenia among CBCs, %)									
7[5]	Case series	serious[2]	serious[3]	none	serious[4]	none	4% 95% CI 1-7%	⊕OOO VERY LOW	TBD
Detection of lymphopenia (frequency of lymphopenia among CBCs, %)									
2[4]	Case series	serious[2]	serious[3]	none	serious[4]	none	42% (95% CI 14-69%)	⊕OOO VERY LOW	TBD
Detection of bone marrow granulomas (frequency of granulomas among bone marrow biopsies, %)									
2[6]	Case series	serious[2]	serious[3]	none	serious[4]	none	38% 95% CI 13-64%	⊕OOO VERY LOW	TBD
Treatment change (%)									
-	-	-	-	-	-	-	-	–	-

Footnotes:
[1]Ferguson, Gupta, Lower, Mayock, McCort, Sharma, and Yanardag.
[2]Many were retrospective chart reviews; therefore, there was a risk of selection bias.
[3] When pooled by meta-analysis, the I^2 >50%. Also, the range is wide.
[4] A large proportion of the studies are small with <100 patients.
[5] Cummings, Ferguson, Gupta, Israel, Mayock, McCourt, and Sharma.
[6] Gupta and Lower.
[7] Yanardag and Lower.

QUESTION #8: *Should sarcoidosis patients who do not have cardiac symptoms or signs be routinely screened for cardiac sarcoidosis using ECG, TTE, or Holter?*

Search strategy for ECG, TTE, and Holter combined

#	Searches
1	exp Echocardiography/
2	(echocardiogra$ or echo cardiogra$ or ((heart or cardi$) adj echogra$)).mp.
3	1 or 2
4	Electrocardiography/ or electrocardiograph/
5	(electromyocardiograph$ or electrocardiogra$ or electro cardiograph$ or polycardiograph$ or ECG or EKG).mp.
6	4 or 5
7	Electrocardiography, Ambulatory/ or ambulatory electrocardiography/
8	Holter monitoring/ or Holter monitor/
9	(((event or holter) adj2 (monitor$ or record$ or ecg or electrocardiogra$)) or (electrocardiogra$ adj (record$ or monitor$)) or (electrocardiogra$ adj (record$ or monitor$)) or ((ambulatory or dynamic) adj2 electrocardiogra$)).mp.

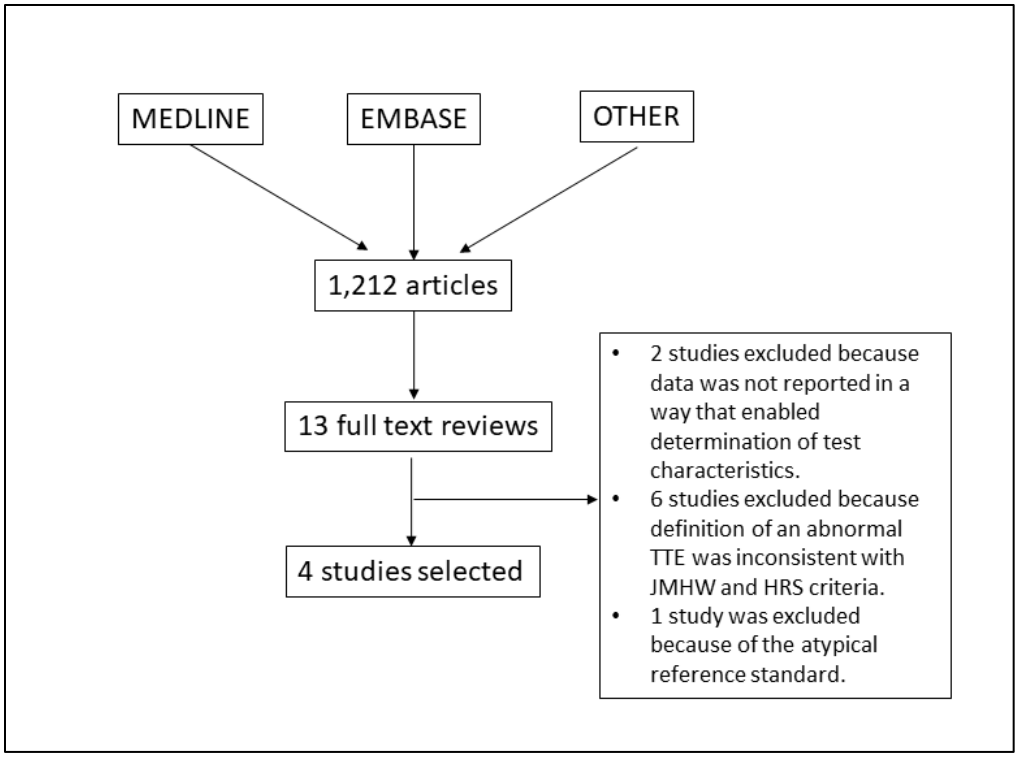
10	7 or 8 or 9
11	3 or 6 or 10
12	exp sarcoidosis/
13	sarcoidosis/
14	sarcoidosis/ or sarcoidosis, pulmonary/ or uveoparotid fever/
15	sarcoid$.mp.
16	(besnier adj boeck$).tw.
17	(boeck$ adj (disease or sarcoid)).tw.
18	(schaumann$ adj (disease or syndrome)).tw.
19	uveoparoti$.tw.
20	(benign$ adj lymphogranuloma$).tw.
21	((junging or heerfordt or lofgren) adj syndrome).tw.
22	neurosarcoidosis.tw.
23	(lupus adj pernio).tw.
24	(idiopathic adj3 inflammat$ adj3 granulomat$).tw.
25	or/12-24 [all sarcoidosis]
26	11 and 25
27	limit 26 to English language

Study selection criteria

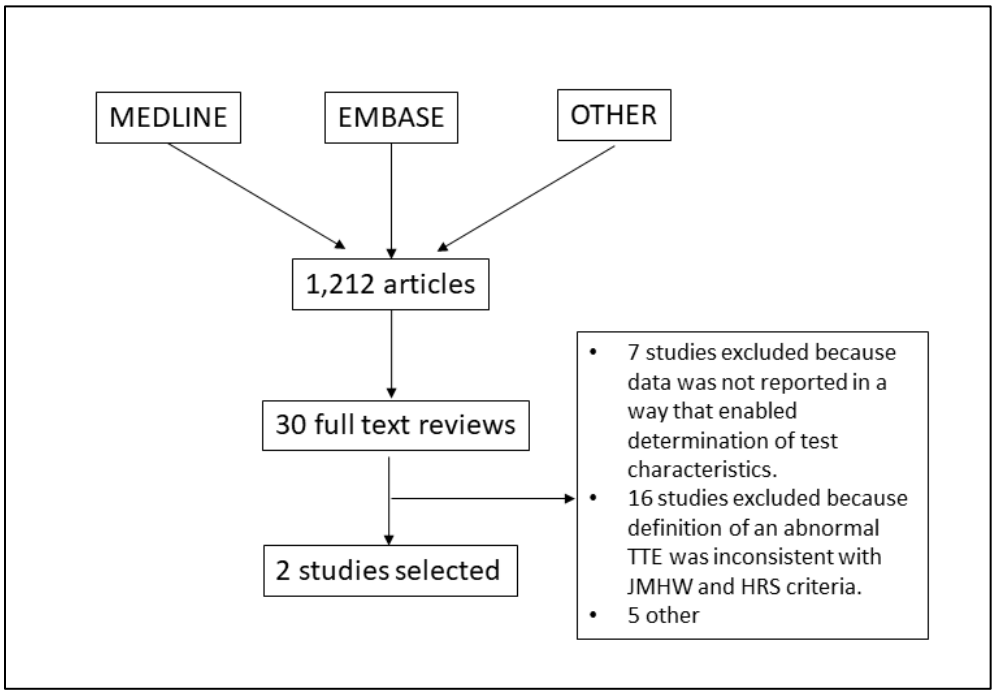
1	Randomized trials that enrolled patients with extracardiac sarcoidosis and no cardiac symptoms, compared performing the diagnostic test to not performing the diagnostic test, and measured patient-important outcomes. If none found, then next step.
2	Observational studies that enrolled patients with extracardiac sarcoidosis and no cardiac symptoms, compared performing the diagnostic test to not performing the diagnostic test, and measured patient-important outcomes. If none found, then next step.
3	Accuracy studies that enrolled patients with extracardiac sarcoidosis and no cardiac symptoms, and either reported test characteristics (true positive, false positive, true negative, false negative) or reported data that enabled the calculation of test characteristics. If none found, then “no recommendation”, “research recommendation”, or next step.
4	Case series that enrolled patients with extracardiac sarcoidosis and no cardiac symptoms and reported the frequency of abnormal diagnostic tests and related outcomes.

Flow of information diagrams

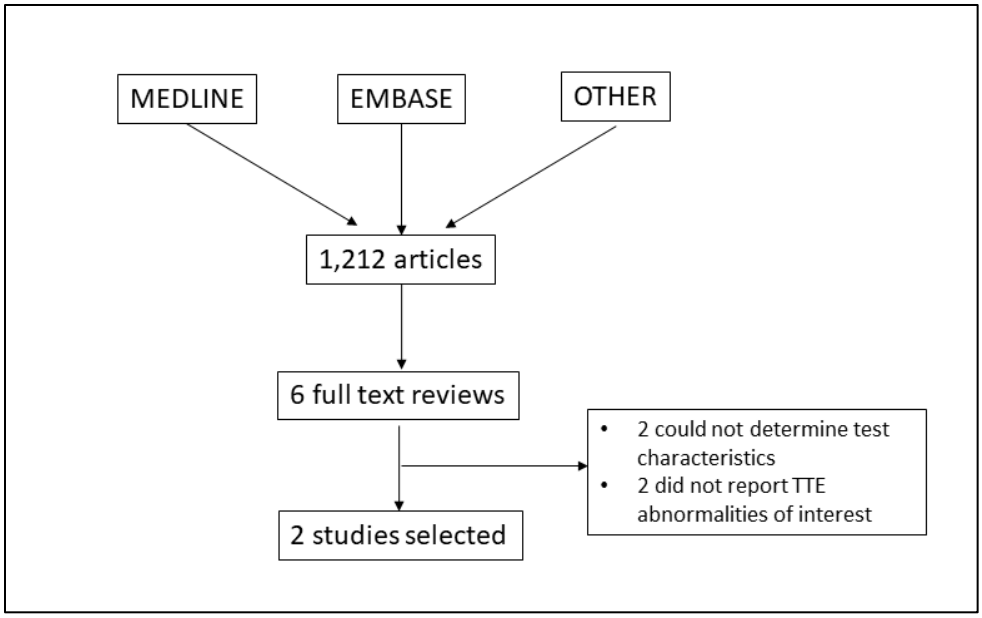
Flow of information for ECG



Flow of information for TTE



Flow of information for Holter



Selected studies with outcomes

Electrocardiograms (ECGs)					
Study	**N**	**Patients**	**Definition of abnormal ECG**	**Frequency of abnormal ECG Sarcoidosis (%)**	**Frequency of abnormal ECG Healthy (%)**
Mehta 2008	62	Non-cardiac sarcoidosis. 21% sx, 79% asx	RBBB, LBBB, Left Anterior Fascicular block, left posterior fascicular block, AV block	3/62 (5%)	N/A
Nagao 2015	227	Non-cardiac sarcoidosis. Sx and asx not reported	Prolonged PR int, RBBB, LAFB, and LBBB (the study included others too, but we extracted data only for these abnormalities for consistency with JMHW and HRS criteria).	23/227 (10%)	N/A
Langer 1995	244	Non-cardiac sarcoidosis. Sx and asx not reported	Incomplete RBBB, RBBB, AVB, ventricular extrasystole, ST depressions (the study included others too, but we extracted data only for these abnormalities for consistency with JMHW and HRS criteria).	18/244 (7%)	N/A
Suzuki 1994	99	38 w/ non-cardiac sarcoidosis, sx and asx not reported; 58 healthy controls.	Left axis deviation, RBBB, LBBB, AV block (the study included others too, but we extracted data only for these abnormalities for consistency with JMHW and HRS criteria).	18/38 (47%)	5/58 (9%)
Summary estimates			***Weighted (%, 95% CI)***	***7% * (95% CI 4-11%)***	***N/A***
			Unweighted (%, 95% CI)	***8% * (95% CI 6-11%)***	***9% (95% CI 4-19%)***
			Median (Range)	***7% * (5-10%)***	***N/A***

* Includes Langer, Mehta, and Nagao (patients presented to medical pulmonary clinic) but not Suzuki (patients presented to cardiology clinic) because results are heterogeneous and the former more closely reflect the patients of interest.

Study	**Diagnosis of cardiac sarcoid**							**Cardiac events (AV block, VT, and systolic dysfunction)**			**All-cause Mortality**		
	Diagnosis standard	**TP**	**FP**	**TN**	**FN**	**Se**	**Sp**	**Abn ECG**	**Norm ECG**	**Abnormal vs. normal**	**Abn ECG**	**Norm ECG**	**Abnormal vs. normal**
Mehta 2008	+cMRI or +PET scan	2	1	38	21	9% 95% CI 1-27%	97% 95% CI 86-100%	NR	NR	NR	NR	NR	NR
Nagao 2015	N/A	NR	NR	NR	NR	N/A	N/A	NR	NR	HR 11.27 (95% CI 3.29-38.64)	NR	NR	NR

Langer 1995	N/A	NR	NR	NR	NR	N/A	N/A	NR	NR	NR	8/18 * (44%)	21/59 * (36%)	RR 1.4 (95% CI 0.80-2.42)
Suzuki 1994	a) myocardial granulomas, b) +PET, c) +ECG, AND d) no alternative explanation for heart disease.	11	7	19	1	92% 95% CI 65-99%	73% 95% CI 54-86%	NR	NR	NR	NR	NR	NR
Summary Estimates		***Too different too pool, may reflect different diagnostic standards***						***HR 11.27 (95% CI 3.29-38.64)***			***44% vs. 36% RR 1.40 (95% CI 0.80-2.42)***		

* Determined over a median 27-years (range 0-36 years) of follow-up.

Echocardiograms (TTEs)					
Study	**N**	**Patients**	**Definition of abnormal TTE**	**Abnormal TTE sarcoidosis (%)**	**Abnormal TTE healthy (%)**
Mehta 2008	62	Non-cardiac sarcoidosis. 21% sx, 79% asx	LV EF <45%, SWMA, diastolic dysfunction, or RV systolic dysfunction without PH	5/62 (8%)	N/A
Burstow 1989	88	Non-cardiac sarcoidosis. Sx and asx not reported	EF <50% and/or SWMA not attributable to CAD	12/88 (14%)	N/A
Summary Estimates			***Weighted (%, 95% CI)***	***11% 95% CI 5-17%***	***N/A***
			Unweighted (%, 95% CI)	***11% 95% CI 7-17%***	***N/A***
			Median (Range)	***11% (8% - 14%)***	***N/A***

Study	**Diagnosis of cardiac sarcoid**							**Conduction system abnormalities**		
	Diagnosis standard	**TP**	**FP**	**TN**	**FN**	**Se**	**Sp**	**Abnormal TTE**	**Normal TTE**	**Abnormal vs. normal**
Mehta 2008	+cMRI or +PET	6	2	36	18	25% 95% CI 10-47%	97% 95% CI 86-99%	NR	NR	NR
Burstow 1989	+cMRI	NR	NR	NR	NR	N/A	N/A	7/12 (58%)	17/76 (22%)	RR 2.6 95% CI 1.38-4.92
Summary Estimates	***Sensitivity 25%, 95% CI 10-47% Specificity 95%, 95% CI 83-99%***							***58% vs. 22% RR 2.6 95% CI 1.38-4.92***		

Continuous ambulatory electrocardiography (Holter)												
Study	**N**	**Patients**	**Defn Abnl Holter**	**Abnl Holter sarcoid (%)**	**Abnl Holter Hlthy (%)**	**Diagnosis of cardiac sarcoid**						
						Diagnosis standard	**TP**	**FP**	**TN**	**FN**	**Se**	**Sp**
Mehta 2008	62	Non-cardiac sarcoidosis. 21% sx, 79% asx	RBBB, LBBB, AV block, PVC, VT, SVTs	3/62 (5%)	N/A	+cMRI or +PET	12	1	37	12	50% 95% CI 29-71%	97% 95% CI 86-100%
Suzuki 1994	99	38 w/ non-cardiac sarcoidosis; 58 healthy controls.	PVCs	15/38 (39%)	12/58 (21%)	a) myocardial granulomas, b) +PET, c) +ECG, AND d) no alternative explanation for heart disease.	8	2	24	4	67% 95% CI 39-86%	92% 95% CI 76-98%

Summary Estimates	***Weighted (%, 95% CI)***	***N/A***	***N/A***	***Sensitivity 56%, 95% CI 40-70% Specificity 95%, 95% CI 87-98%***
	Unweighted (%, 95% CI)	***5% * 95% CI 1-9%***	***N/A****	
	Median (Range)	***N/A***	***N/A***	

* Includes Mehta only (patients presented to medical pulmonary clinic) but not Suzuki (patients presented to cardiology clinic) because results are heterogeneous and the former more closely reflect the patients of interest.

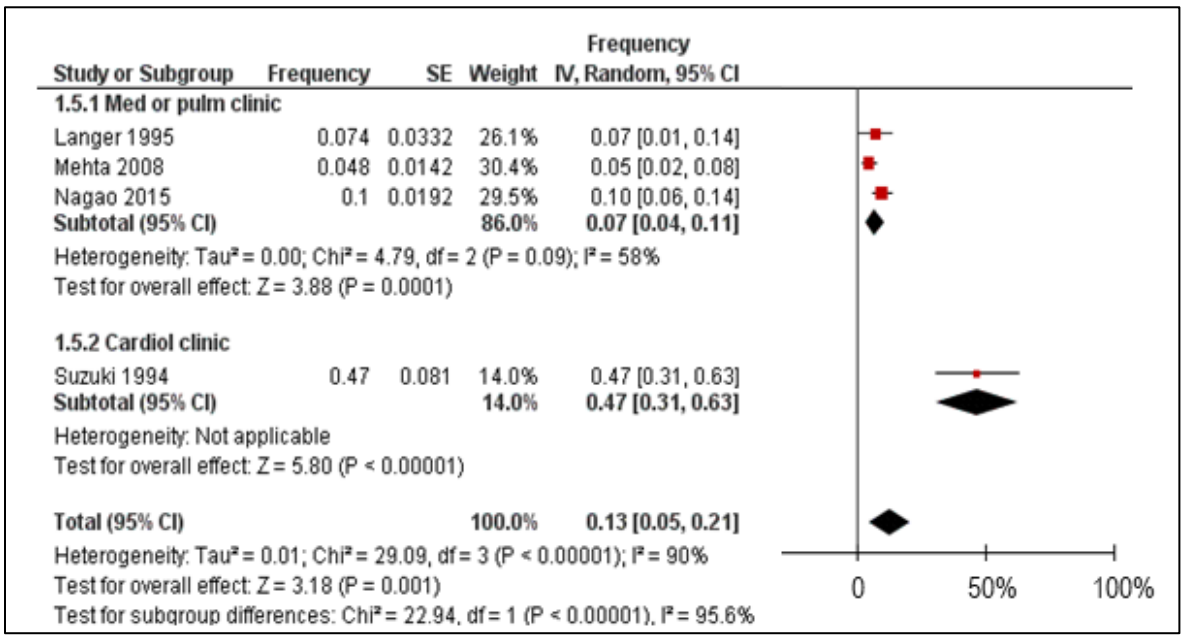
Side-by-side comparisons of diagnostic test characteristics

	ECG	TTE	Holter
Mehta study (only selected study that compared modalities in same population)	Sensitivity= 9%, 95% CI 1-27% Specificity= 97%, 95% CI 86-100%	Sensitivity= 25%, 95% CI 10-47% Specificity= 95%, 95% CI 83-99%	Sensitivity= 50%, 95% CI 29-71% Specificity= 97%, 95% CI 86-100%
Evidence base	2 studies that can't be pooled: Sensitivity= 9%, 95% CI 1-27% Specificity= 97%, 95% CI 86-100% Sensitivity= 92%, 95% CI 62-100% Specificity= 73%, 95% CI 52-88%	1 study Sensitivity= 25%, 95% CI 10-47% Specificity= 97%, 95% CI 86-99%	2 studies Sensitivity= 56%, 95% CI 40-70% Specificity= 95%, 95% CI 87-98%

*One additional study was encountered that evaluated all three modalities in the same population. The study was not selected for our systematic review because it defined an abnormal test based upon any abnormalities, not just those considered important by the JMHW and HRS. This will tend to overestimate the sensitivity and underestimate the specificity. It found the following: ECG- Se 39%, Sp 90%; TTE- Se 70%, Sp 58%; and, Holter- Se 39%, Sp 85%.

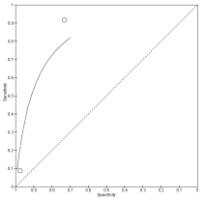
Forest plots

ECG- prevalence of abnormal electrocardiography

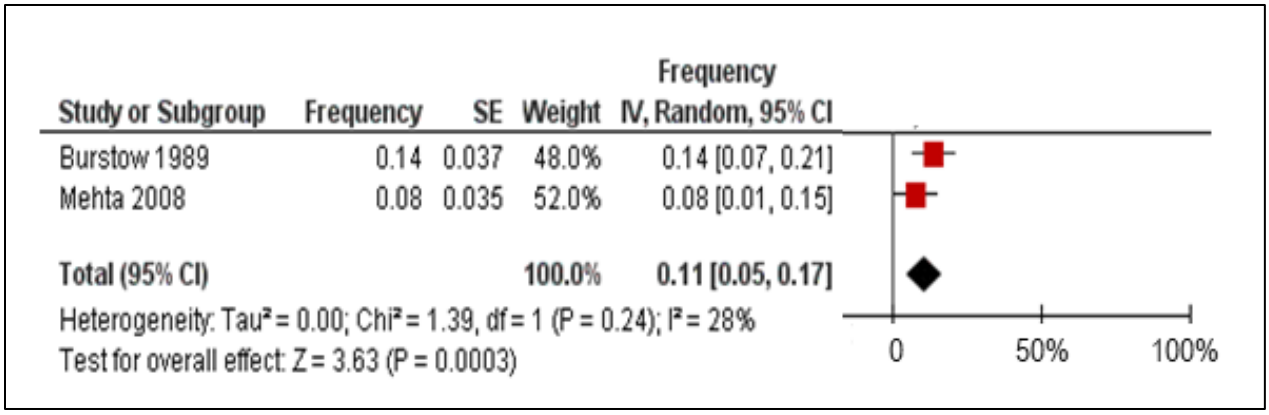


ECG- diagnostic accuracy

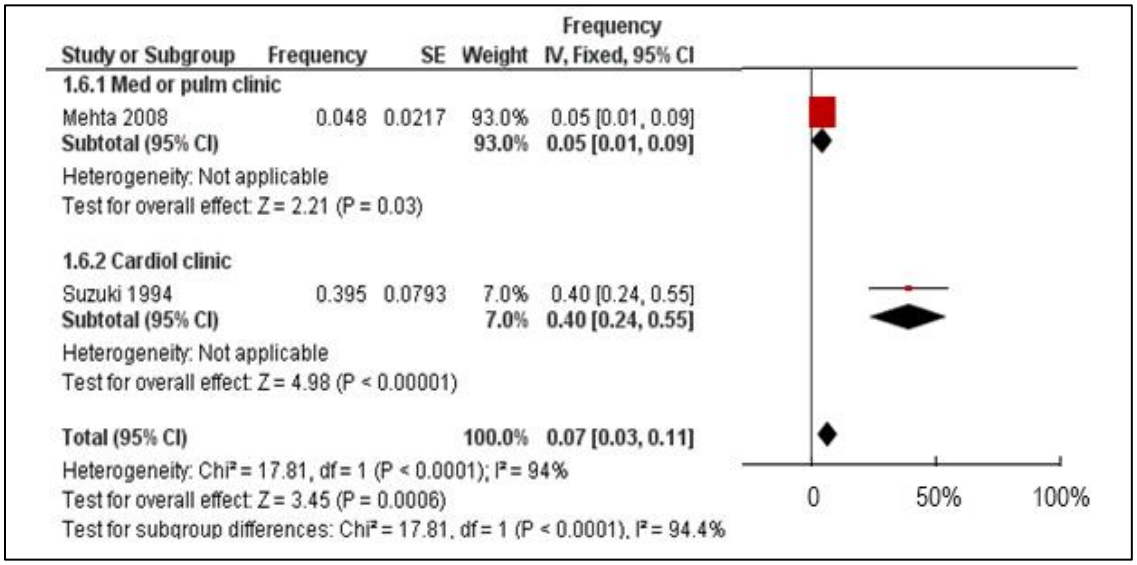
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Mehta 2008	2	1	21	38	0.09 [0.01, 0.28]	0.97 [0.87, 1.00]
Suzuki 1994	11	7	1	19	0.92 [0.62, 1.00]	0.73 [0.52, 0.88]



TTE- prevalence of abnormal TTE

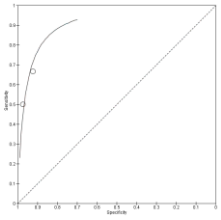


Holter- prevalence of abnormal Holter



Holter- diagnosis of cardiac sarcoid

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Mehta 2008	12	1	12	37	0.50 [0.29, 0.71]	0.97 [0.86, 1.00]		
Suzuki 1994	8	2	4	24	0.67 [0.35, 0.90]	0.92 [0.75, 0.99]		



Evidence profiles

ECG-related profile

Bibliography:
1. Nagao, et al. Electrocardiographic abnormalities and risk of developing cardiac events in extracardiac sarcoidosis. Int J Cardiol 2015; 189:1-5.
2. Mehta, et al. Cardiac involvement in patients with sarcoidosis: diagnostic and prognostic value of outpatient testing. Chest 2008; 133(6):1426-1435.
3. Langer, et al. Electrocardiographic changes in patients with intrathoracic sarcoidosis: influence on prognosis. Sarcoidosis 1995; 12(1):42-45.
4. Suzuki, et al. Holter Monitoring as a Noninvasive Indicator of Cardiac Involvement in Sarcoidosis. Chest 1994; 106:1021-24

Quality assessment							Summary of findings				Quality	Importance
							Patients		Effects			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Abnl. ECG	Nml. ECG	Relative	Absolute		
Frequency of abnormal ECG												
4[1]	case series	serious[2]	serious [3]	serious[4]	none	none	7% 95% CI 4-11%	-	-	-	⊕OOO VERY LOW	TBD
Diagnosis of cardiac sarcoidosis												
2[5]	accuracy study	serious[6]	serious[7]	serious[4]	serious[8]	none	Study 1 Sensitivity= 9%, 95% CI 1-27% Specificity= 97%, 95% CI 86-100% Study 2 Sensitivity= 92%, 95% CI 62-100% Specificity= 73%, 95% CI 52-88%				⊕OOO VERY LOW	TBD
Mortality												
1[8]	observational study	serious[10]	none	serious[4]	serious[8]	none	8/18 (44%)	21/59 (36%)	RR 1.4 (95% CI 0.80-2.42)	89 more per 1000 (from 148 less to 333 more)	⊕OOO VERY LOW	TBD
Cardiac events												
1[11]	observational study	serious[10]	none	serious[4]	none	none	-	-	HR 11.27 (95% CI 3.29-38.64)	N/A	⊕OOO VERY LOW	TBD

Footnotes:
[1] All studies.
[2] Two of four studies didn't enroll consecutive patients; therefore, there was a risk of selection bias. Can't exclude confounding bias.
[3] Studies were heterogenous but resolved with subgroups. Reporting results of the more relevant subgroup (med and pulm clinic).
[4] The question is about patients without cardiac symptoms, but the studies included patients with and without cardiac symptoms.
[5] Mehta and Suzuki.
[6] There is no universally accepted reference standard.
[7] The studies are too different to pool; need to be reported separately
[8] Low Optimal Information Size, OIS (studies with <200 patients).
[9] Langer.
[10] Study didn't enroll consecutive patients. Can't exclude confounding bias.
[11] Nagao.

Echocardiography profile

Bibliography:

1. Mehta D, Lubitz SA, Frankel Z, Wisnivesky JP, Einstein AJ, Goldman M, Machac J, Teirstein A, 2008. Cardiac involvement in patients with sarcoidosis: diagnostic and prognostic value of outpatient testing. Chest 133: 1426-1435.
2. Burstow, et al. Two-dimensional echocardiographic findings in systemic sarcoidosis. Am J Cardiol 1989; 63(7):478-482.

Quality assessment							Summary of findings				Quality	Importance
							Patients		Effects			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Abnl. TTE	Nml. TTE	Relative	Absolute		
Frequency of abnormal echocardiography (%)												
2[1]	case series	serious[2]	serious[3]	serious[4]	serious[5]	none	11% 95% CI 5-17%	-	-	-	⊕OOO VERY LOW	TBD
Diagnosis of cardiac sarcoidosis												
1[6]	accuracy study	none	none	serious[4]	serious[5]	none	Sensitivity= 25%, 95% CI 10-47% Specificity= 95%, 95% CI 83-99%				⊕OOO VERY LOW	TBD
Development of conduction abnormalities												
1[7]	observational study	serious[2]	none	serious[4]	serious[5]	none	7/12 (58%)	17/76 (22%)	RR 2.6 95% CI 1.38-4.92	360 more per 1000 (from 76 more to 597 more)	⊕OOO VERY LOW	TBD

Footnotes:
[1] All studies.
[2] Can't exclude confounding bias.
[3] High I^2 statistic.
[4] The question is about patients without cardiac symptoms, but the studies included patients with and without cardiac symptoms.
[5] Low optimum information size (<200 patients) and wide confidence intervals.
[6] Mehta.
[7] Burstow.

Holter-related profile

Bibliography:

1. Mehta, et al. Cardiac involvement in patients with sarcoidosis: diagnostic and prognostic value of outpatient testing. Chest 2008; 33(6):1426-1435.
2. Suzuki, et al. Holter Monitoring as a Noninvasive Indicator of Cardiac Involvement in Sarcoidosis. Chest 1994; 106:1021-24

Quality assessment							Summary of findings		Quality	Importance
	Design		Inconsistency	Indirectness	Imprecision	Other	Patients	Effects		

No of studies		Risk of bias					Abnl. Holter	Nml. Holter	Relative	Absolute		
Frequency of abnormal Holter (%)												
2	case series	serious[1]	serious[2]	serious[3]	serious[4]	none	5% 95% CI 1-9%	-	-	-	⊕OOO VERY LOW	TBD
Diagnosis of cardiac sarcoidosis												
2	accuracy study	serious[5]	none	serious[3]	serious[4]	none	Sensitivity= 56%, 95% CI 40-70% Specificity= 95%, 95% CI 87-98%				⊕OOO VERY LOW	TBD

Footnotes:
[1] Can't rule confounding bias.
[2] Studies were heterogenous, arguably too different to pool. Reporting results of only one study (med and pulm clinic).
[3] The question is about patients without cardiac symptoms, but the studies included patients with and without cardiac symptoms.
[4] Low optimum information size (<200 patients).
[5] There is no universally accepted reference standard.

QUESTION #9: *Should patients who are suspected of having cardiac sarcoidosis undergo cardiac MRI for diagnosis rather than TTE or PET?*

Search strategy for MRI, PET, and TTE combined

#	Searches
1	exp sarcoidosis/
2	sarcoidosis/
3	sarcoidosis/ or sarcoidosis, pulmonary/ or uveoparotid fever/
4	sarcoid$.mp.
5	(besnier adj boeck$).tw.
6	(boeck$ adj (disease or sarcoid)).tw.
7	(schaumann$ adj (disease or syndrome)).tw.
8	uveoparoti$.tw.
9	(benign$ adj lymphogranuloma$).tw.
10	((junging or heerfordt or lofgren) adj syndrome).tw.
11	neurosarcoidosis.tw.
12	(lupus adj pernio).tw.
13	(idiopathic adj3 inflammat$ adj3 granulomat$).tw.
14	or/1-13 [all sarcoidosis]
15	exp magnetic resonance imaging/
16	(MRI or MRIs or (magnetic adj2 resonance adj2 imag$)).mp.
17	(echo adj2 spin adj2 imag$).mp.
18	15 or 16 or 17 [MRI]
19	exp Positron-Emission Tomography/
20	((positron adj2 emission adj2 tomogra$) or (PET adj2 (scan$ or tomogra$))).mp.
21	19 or 20 [PET]
22	exp Echocardiography/

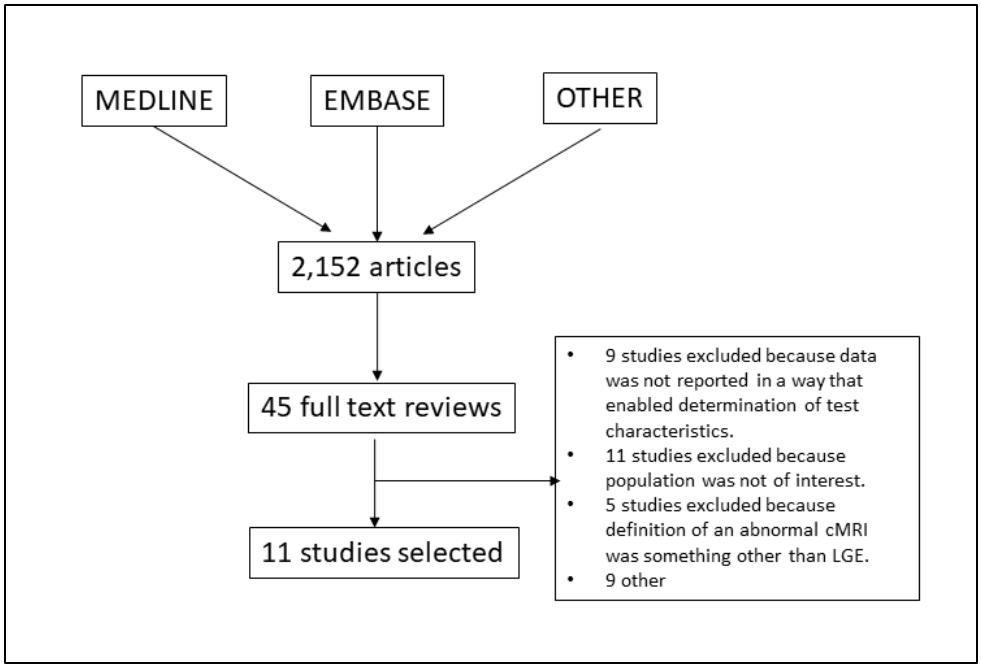
23	(echocardiogra$ or echo cardiogra$ or ((heart or cardi$) adj echogra$)).mp.
24	22 or 23 [TTE]
25	exp Cardiovascular System/ or exp Cardiovascular Diseases/ or Heart/
26	(cardi$ or myocardi$ or coronary or heart).mp.
27	25 or 26 [cardiac]
28	14 and 18
29	14 and 18 [Sarcoidosis and MRI]
30	14 and 21 [Sarcoidosis and PET]
31	14 and 24 [Sarcoidosis and TTE]
32	29 or 30 or 31 [Sarcoidosis and MRI or PET or TTE]
33	27 and 32 [with cardiac]
34	limit 33 to english language

Study selection criteria

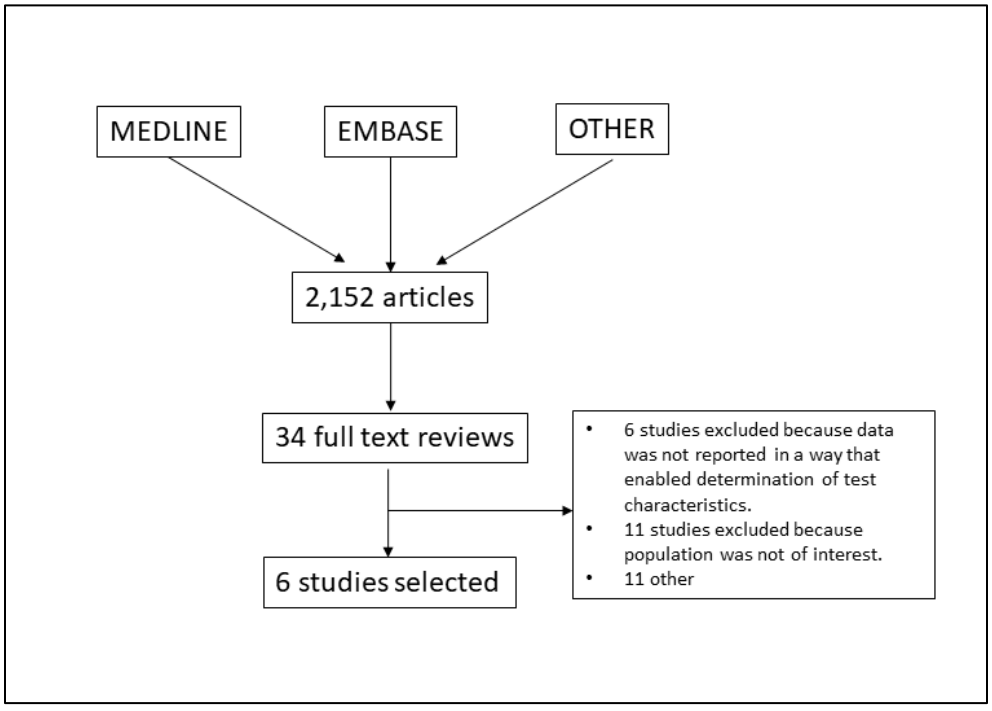
1	Randomized trials that enrolled patients with known extracardiac sarcoidosis and suspected cardiac involvement, compared performing the diagnostic test to not performing the diagnostic test, and measured patient-important outcomes. If none found, then next step.
2	Observational studies that enrolled patients with known extracardiac sarcoidosis and suspected cardiac involvement, compared performing the diagnostic test to not performing the diagnostic test, and measured patient-important outcomes. If none found, then next step.
3	Accuracy studies that enrolled patients with known extracardiac sarcoidosis and suspected cardiac involvement, and either reported test characteristics (true positive, false positive, true negative, false negative) or reported data that enabled the calculation of test characteristics. If none found, then "no recommendation", "research recommendation", or next step.
4	Case series that enrolled patients with known extracardiac sarcoidosis and suspected cardiac involvement, and reported the frequency of abnormal diagnostic tests and related outcomes.

Flow of information diagrams

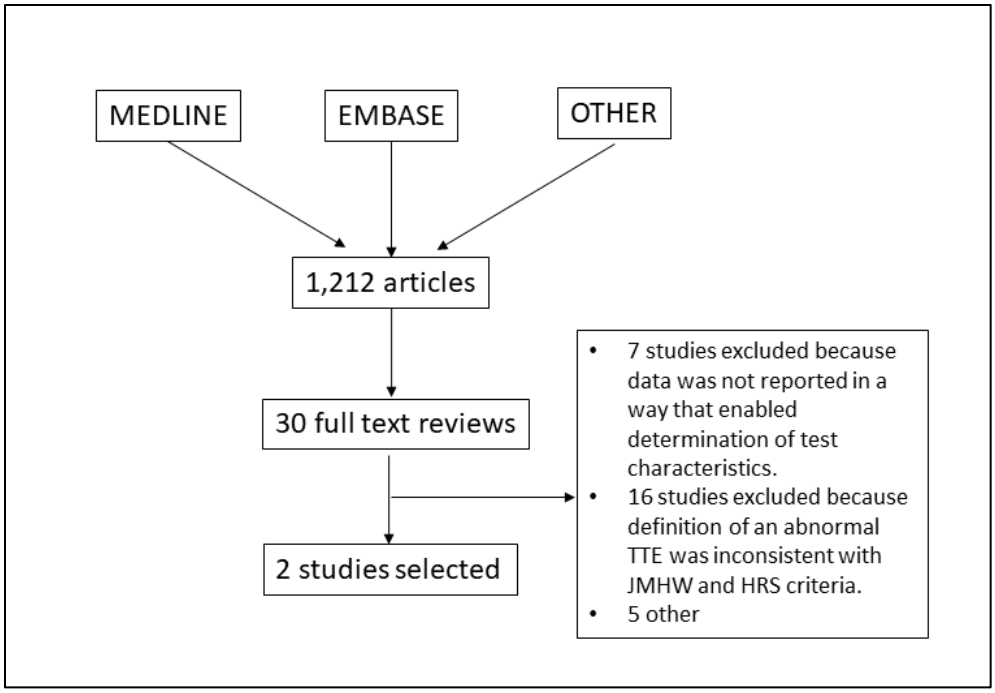
Flow of information for cMRI



Flow of information for PET



Flow of information for TTE



Selected studies with outcomes

Cardiac Magnetic Resonance Imaging (cMRI)					
Study	**N**	**Patients**	**Definition of abnormal**	**Abnormal cMRI sarcoidosis (%)**	**Abnormal cMRI healthy (%)**
Smedema 2005	101	Pulmonary sarcoidosis; 19 symptomatic 82 asymptomatic	Late gadolinium enhancement	10/14 (71%)	N/A
Ohira 2008	21	"Suspected cardiac sarcoidosis" (i.e., abnormal ECG or TTE); Did not specify sx versus asx	Late gadolinium enhancement	8/20 (40%)	N/A
Patel 2009	81	Non-cardiac sarcoidosis; 17 symptomatic 64 asymptomatic	Late gadolinium enhancement	21/81 (26%)	N/A
Patel 2011	152	Non-cardiac sarcoidosis; Did not specify sx versus asx	Late gadolinium enhancement	29/152 (19%)	N/A
Greulich 2013	155	"Suspected cardiac sarcoidosis" (abnormal sxs, ECG or TTE)	Late gadolinium enhancement	39/153 (25%)	N/A
Cain 2014	135	Non-cardiac sarcoidosis; Did not specify sx versus asx	Late gadolinium enhancement	44/135 (33%)	N/A
Kournas 2017	321	"Suspected cardiac sarcoidosis" (i.e., abnormal sx, ECG, or TTE); Mixture of sx versus asx	Late gadolinium enhancement	93/321 (29%)	N/A
Stanton 2017	46	Pulmonary sarcoidosis; At least 39% symptomatic	Late gadolinium enhancement	10/46 (22%)	N/A
Bravo 2017	56	"Suspected cardiac sarcoidosis"; Did not specify sx versus asx	Late gadolinium enhancement	31/56 (55%)	N/A
Nadel 2015	106	Non-cardiac sarcoidosis (n=74), non-cardiac and cardiac sarcoidosis (n=26), cardiac sarcoidosis only (n=6)	Late gadolinium enhancement	32/106 (30%)	N/A

Wicks 2018	51	"Suspected cardiac sarcoidosis" (n=44), known cardiac sarcoid (n=7)	Late gadolinium enhancement	32/51 (63%)	N/A
Summary estimates			***Weighted***	***27%, 95% CI 23-31% ****	
			Unweighted	***27%, 95% CI 25-30% ****	
			Median	***27%, range 19-40% ****	

*Bravo, Smedema, and Wick removed as outliers.

Study	**Diagnosis of cardiac sarcoid**							**Mortality**		
	Diagnosis standard for CS	**TP**	**FP**	**TN**	**FN**	**Se**	**Sp**	**Abnormal cMRI**	**Normal cMRI**	**Abnormal vs. normal**
Smedema 2005	+ modified JMHW criteria	9	1	2	2	82% 95% CI 48-98%	67% 95% CI 9-99%	NR	NR	NR
Ohira 2008	+ JMHW criteria	5	3	10	2	71% 95% CI 29-96%	77% 95% CI 46-95%	NR	NR	NR
Patel 2009	+ JMHW criteria	8	13	58	2	80% 95% CI 44-97%	82% 95% CI 71-90%	Cardiac 4/21 (19%)	Cardiac 1/60 (2%)	Cardiac RR 11.42 95% CI 1.35-96.57
Patel 2011	+ JMHW criteria	14	13	102	21	40% 95% CI 24-58%	89% 95% CI 81-94%	NR	NR	NR
Greulich 2013	NR	NR	NR	NR	NR	NR	NR	Overall 3/39 (7.7%)	Overall 1/114 (0.8%)	Overall RR 8.76 95% CI 0.94-81.86
Cain 2014	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kournas 2017	+ HRS criteria	93	0	225	3	97% 95% CI 91-99%	100% 95% CI 98-100%	NR	NR	NR
Stanton 2017	+ JMHW criteria	2	8	36	0	100% 95% CI 16-100%	82% 95% CI 67-92%	NR	NR	NR
Bravo 2017	+ HRS criteria	14	22	16	2	90% 95% CI 68-99%	100% 95% CI 98-100%	NR	NR	NR
	+ JMHW criteria	18	18	16	2	88% 95% CI 62-98%	42% 95% CI 26-59%			
Nadel 2015	NR	NR	NR	NR	NR	NR	NR	Overall 4/32 (12%)	Overall 8/74 (10%)	Overall RR 1.19 95% CI 0.38-3.66
								Cardiac 3/32 (9%)	Cardiac 1/74 (1.4%)	Cardiac RR 7.13 95% CI 0.77-65.94
Wicks 2018	+ JMHW criteria	26	6	13	7	79% 95% CI 61-91%	68% 95% CI 43-87%	NR	NR	NR
Summary Estimates	***JMHW **** ***Sensitivity- 82% (95 CI 72-89%)*** ***Specificity- 73% (95% CI 67-79%)*** ***PPV- 58% (95% CI 49-67%)*** ***NPV- 90% (95% CI 84-94%)*** ***HRS*** ***Sensitivity- 96% (95 CI 90-98%)*** ***Specificity- 93% (95% CI 89-96%)***							***Overall mortality*** ***9.9% versus 4.8%*** ***RR 2.51, 95% CI 0.36-17.47*** ***Cardiac mortality*** ***13.2% versus 1.5%*** ***RR 9.00, 95% CI 1.93-41.97***		

	PPV- 47% (95% CI 40-53%) ***NPV- 98% (95% CI 95-99%)***	

*Removed Patel 2011 as an outlier.

Study	Ventricular arrhythmias (VT and/or NSVT)			Other outcomes			
	Abnormal cMRI	Normal cMRI	Abnormal vs. normal	Outcome	Abnormal cMRI	Normal cMRI	Abnormal vs. normal
Smedema 2005	NR	NR	NR	N/A	NR	NR	NR
Ohira 2008	NR	NR	NR	N/A	NR	NR	NR
Patel 2009	NR	NR	NR	N/A	NR	NR	NR
Patel 2011	5/15 (33%)	4/67 (6%)	RR 5.58 95% CI 1.70-18.34	Diastolic heart failure	18/27 (67%)	41/123 (33%)	RR 2.0 95% CI 1.39-2.88
Greulich 2013	20/39 (51%)	0/114 (0%)	Not estimable	Aborted sudden cardiac death	11/39 (28%)	0/114 (0%)	Not estimable
Cain 2014	12/44 (27%)	3/91 (3.3%)	RR 8.27 95% CI 2.46-27.82	Atrial arrhythmias	16/44 (36%)	11/91 (12%)	RR 3.01 95% CI 1.53-5.93
Kournas 2017	NR	NR	NR	NR	NR	NR	NR
Stanton 2017	NR	NR	NR	Any arrhythmia (incl. heart block)	6/10 (60%)	5/36 (14%)	RR 4.32 95% CI 1.66-11.26
Bravo 2017	NR	NR	NR	Major adverse cardiac event (VT, VF, AICD shock, all-cause death)	15/36 (42%)	1/20 (5%)	RR 8.33 95% CI 1.18-58.51
Nadel 2015	NR	NR	NR	Complete heart block	4/32 (12%)	1/76 (1.4%)	RR 9.5 95% CI 1.10-81.76
				Heart failure	15/32 (47%)	3/76 (4%)	RR 11.88 95% CI 3.69-38.21
				Major adverse cardiac event (VT, VF, cardiac death)	NR	NR	RR 12.5 95% CI 1.35-116.18
				Pulmonary hypertension	8/32 (25%)	6/76 (8%)	RR 3.17 95% CI 11.19-8.39
Wicks 2018	NR	NR	NR	Major adverse cardiac event (PPM, VT, cardiac hospitalization, aborted sudden cardiac death, sudden cardiac death)	NR	NR	HR 10.63 95% CI 1.4-80.78
Summary Estimates	***Ventricular arrhythmias*** ***38% versus 3.6%*** ***RR 11.71, 95% CI 2.59-52.92***			***Aborted sudden cardiac death*** ***28% versus 0%*** ***RR not estimable*** ***Diastolic heart failure*** ***67% versus 33%*** ***RR 2.0, 95% CI 1.39-2.88*** ***Other heart failure*** ***47% versus 4%*** ***RR 11.88, 95% CI 3.69-38.21***			

		Atrial arrhythmias ***36% versus 12%*** ***RR 3.01, 95% CI 1.53-5.93*** ***Complete heart block*** ***12% versus 1.4%*** ***RR 9.5, 95% CI 1.10-81.72*** ***Any arrhythmia including heart block*** ***60% versus 14%*** ***RR 4.32, 95% CI 1.66-11.26*** ***Pulmonary hypertension*** ***25% versus 8%*** ***RR 3.17, 95% CI 1.19-8.39*** ***Major adverse cardiac events*** ***Unable to pool due to variation of reporting*** ***1. 42% versus 5%, RR 8.33, 95% CI 1.18-58.51*** ***2. RR 12.5, 95% CI 1.35-116.18*** ***3. HR 10.63, 95% CI 1.4-80.78***

Positron Emission Tomography (PET)					
Study	**N**	**Patients**	**Definition of abnormal**	**Abnormal PET sarcoidosis (%)**	**Abnormal PET healthy (%)**
Ohira 2008	21	"Suspected cardiac sarcoidosis" (abnormal ECG or TTE); Did not specify sx versus asx	Focal uptake alone or focal on diffuse uptake	15/21 (71%)	N/A
Yokoyama 2015	92	"Suspected cardiac sarcoidosis" (abnormal ECG or TTE); Did not specify sx versus asx	Focal uptake alone or focal on diffuse uptake	47/92 (51%)	N/A
Bravo 2017	56	"High clinical suspicious of cardiac sarcoidosis" 66% had known extra-cardiac sarcoidosis	Focal uptake alone	20/56 (36%)	N/A
Sperry 2018	203	"Suspected cardiac sarcoidosis" (VT, HB, HF, or other sx); 35% hx of immunosuppression	Focal uptake ± myocardial perfusion	109/203 (53%)	N/A
Sgard 2018	80	"Suspected cardiac sarcoidosis" (abnormal ECG, Holter, or TTE); Did not specify sx versus asx; 58% hx of immunosuppression	Focal or multifocal uptake	11/80 (14%)	N/A
Wicks 2018	51	All patients had extra-cardiac sarcoidosis; 14% had known cardiac involvement and 86% had suspected cardiac involvement	Focal uptake alone, or focal on diffuse uptake	28/51 (54%)	N/A
Summary estimates			***Weighted***	***52%, 95% CI 43-60%*** *	
			Unweighted	***54%, 95% CI 50-59%*** *	
			Median	***53%, range 36-71%*** *	

*Eliminated Sgard as an outlier.

Study	**Diagnosis of cardiac sarcoid**							**Other outcomes**			
	Definition of cardiac sarcoid	**TP**	**FP**	**TN**	**FN**	**Se**	**Sp**	**Outcome**	**Abnormal PET**	**Normal PET**	**Abnormal vs. normal**
Ohira 2008	+JMHW criteria	7	8	5	1	88% 95% CI 47-100%	38% 95% CI 14-68%	NR	NR	NR	NR
Yokoyama 2015	+JMHW criteria	37	10	45	0	100% 95% CI 91-100%	82% 95% CI 69-91%	NR	NR	NR	NR

Bravo 2017	N/A	NR	NR	NR	NR	NR	NR	Major adverse cardiac event (sVT, VF, AICD shock, all-cause death)	NR	NR	HR 3.3 95% CI, 1.1-10.0
Sperry 2018	N/A	NR	NR	NR	NR	NR	NR	Overall mortality	NR	NR	HR 1.33 95% CI, 0.68-2.62
								Major adverse cardiac events (VT or VF req defib, heart transplant, or all-cause death)	NR	NR	RR 2.0 95% CI, 1.26-3.17
Sgard 2018	+JMHW criteria	6	5	53	16	27% 95% CI 11-50%	91% 95% CI 81-97%	Major adverse cardiac event (sVT, VF, AICD shock, all-cause death)	0/11 (0%)	4/69 (6%)	Not estimable
	+HRS criteria	11	0	42	27	29% 95% CI 15-46%	100% 95% CI 92-100%				
Wicks 2018	+JMHW criteria	20	8	10	13	61% 95% CI 42-77%	43% 95% CI 18-71%	Major adverse cardiac event (sudden cardiac death, aborted sudden cardiac death, symptomatic VT, symptomatic bradycardia req. PPM, or cardiac hospitalization)	NR	NR	HR 2.29 95% CI, 0.72-7.33
Summary estimates	***JMHW **** ***Sensitivity- 70% (95 CI 60-78%)*** ***Specificity- 78% (95% CI 71-84%)*** ***PPV- 69% (95% CI 60-77%)*** ***NPV- 79% (95% CI 72-85%)***							***Overall mortality*** ***HR 1.33, 95% CI 0.68-2.62*** ***Major adverse cardiac events **** ***Unable to pool due to variation of reporting*** ***1. HR 3.30, 95% CI 1.1-10*** ***2. HR 2.29, 95% CI 0.72-7.33*** ***3. RR 2.0, 95% CI 1.26-3.17***			

*Eliminated Sgard as outlier.

Echocardiograms (TTEs)					
Study	**N**	**Patients**	**Definition of abnormal TTE**	**Abnormal TTE sarcoidosis (%)**	**Abnormal TTE healthy (%)**
Mehta 2008	62	Non-cardiac sarcoidosis. 21% sx, 79% asx	LV EF <45%, SWMA, diastolic dysfunction, or RV systolic dysfunction without PH	5/62 (8%)	N/A
Burstow 1989	88	Non-cardiac sarcoidosis. Sx and asx not reported	EF <50% and/or SWMA not attributable to CAD	12/88 (14%)	N/A
Summary Estimates			***Weighted (%, 95% CI)***	***11% 95% CI 5-17%***	***N/A***
			Unweighted (%, 95% CI)	***11% 95% CI 7-17%***	***N/A***
			Median (Range)	***11% (8% - 14%)***	***N/A***

Study	**Diagnosis of cardiac sarcoid**							**Conduction system abnormalities**		
	Diagnosis standard	**TP**	**FP**	**TN**	**FN**	**Se**	**Sp**	**Abnormal TTE**	**Normal TTE**	**Abnormal vs. normal**

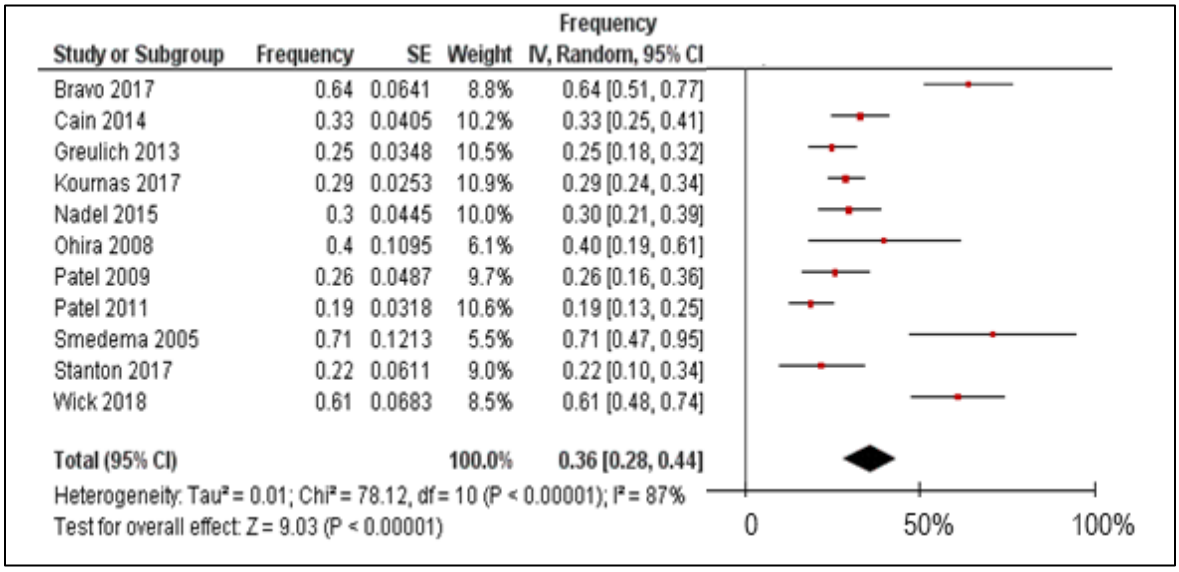
Mehta 2008	+cMRI or +PET	6	2	36	18	25% 95% CI 10-47%	97% 95% CI 86-99%	NR	NR	NR
Burstow 1989	+cMRI	NR	NR	NR	NR	N/A	N/A	7/12 (58%)	17/76 (22%)	RR 2.6 95% CI 1.38-4.92
Summary Estimates	***Sensitivity- 25%, 95% CI 10-47% Specificity- 97%, 95% CI 86-99% PPV – 75%, 95% CI 41-93% NPV- 67%, 95% CI 53-78%***							***58% vs. 22% RR 2.6 95% CI 1.38-4.92***		

Comparison

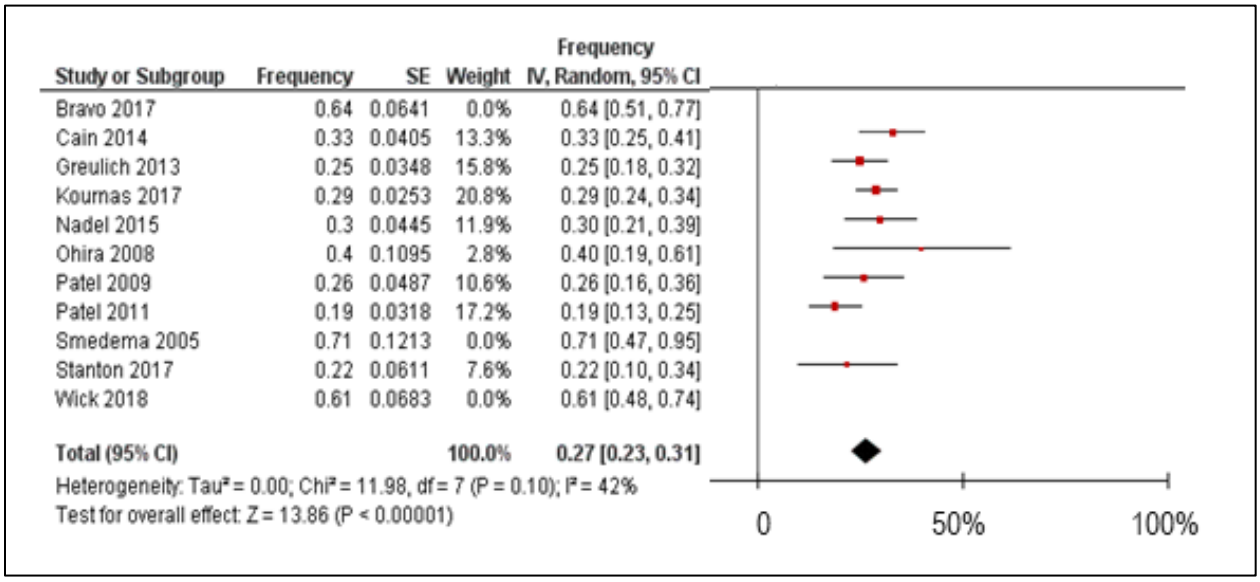
	PET	**cMRI**	**TTE**
Reference standard	JMHW criteria	JMHW criteria	+MRI or +PET
Diagnosis of cardiac sarcoidosis	Sensitivity 70% (95 CI 60-78%) Specificity 78% (95% CI 71-84%) PPV 69% (95% CI 60-77%) NPV 79% (95% CI 72-85%)	Sensitivity 82% (95 CI 72-89%) Specificity 73% (95% CI 67-79%) PPV 58% (95% CI 49-67%) NPV 90% (95% CI 84-94%)	Sensitivity 25%, 95% CI 10-47% Specificity 97%, 95% CI 86-99% PPV 75%, 95% CI 41-93% NPV 67%, 95% CI 53-78%

Forest plots

cMRI- prevalence of abnormal cMRI (outliers included)

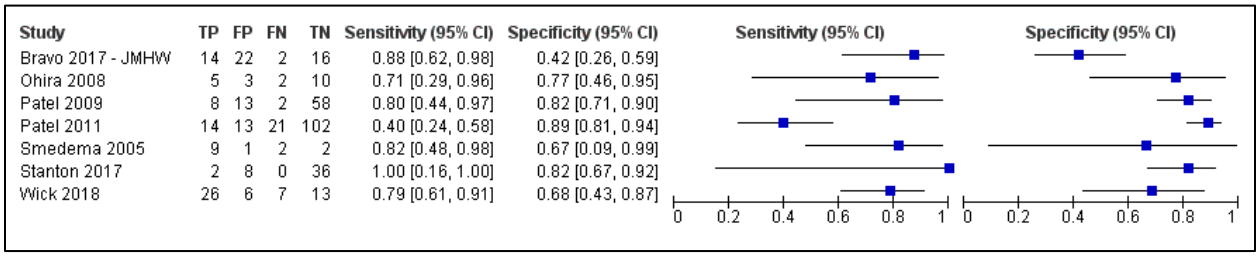


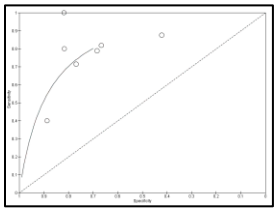
cMRI- prevalence of abnormal cMRI (outliers excluded)



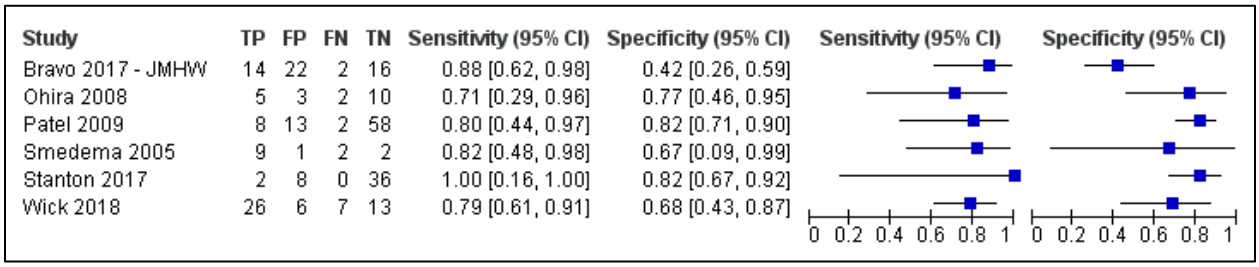
cMRI- Diagnosis of cardiac sarcoidosis

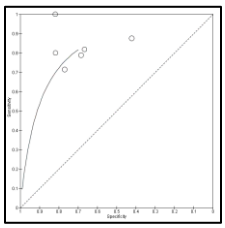
w/ outliers - JMHW



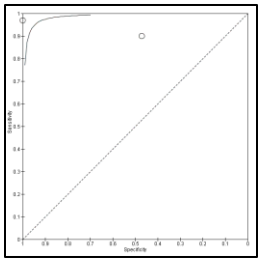


w/o outliers - JMHW

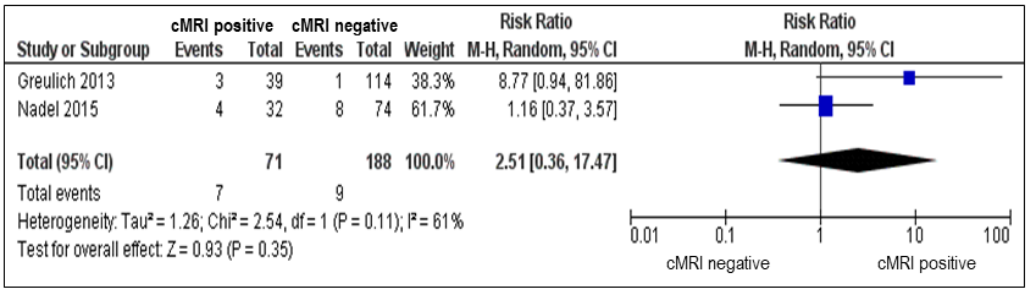




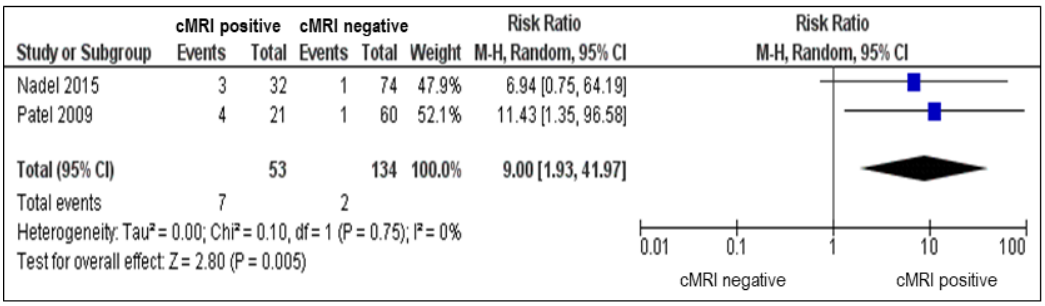
HRS



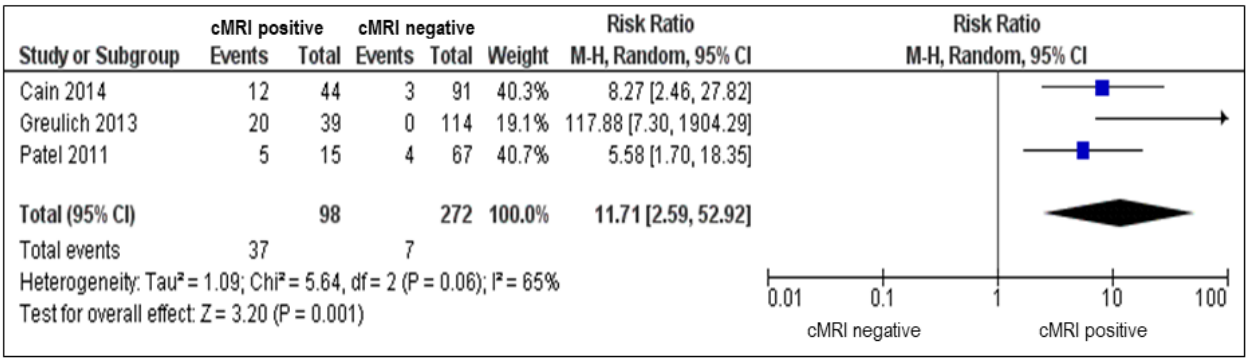
cMRI- Overall mortality



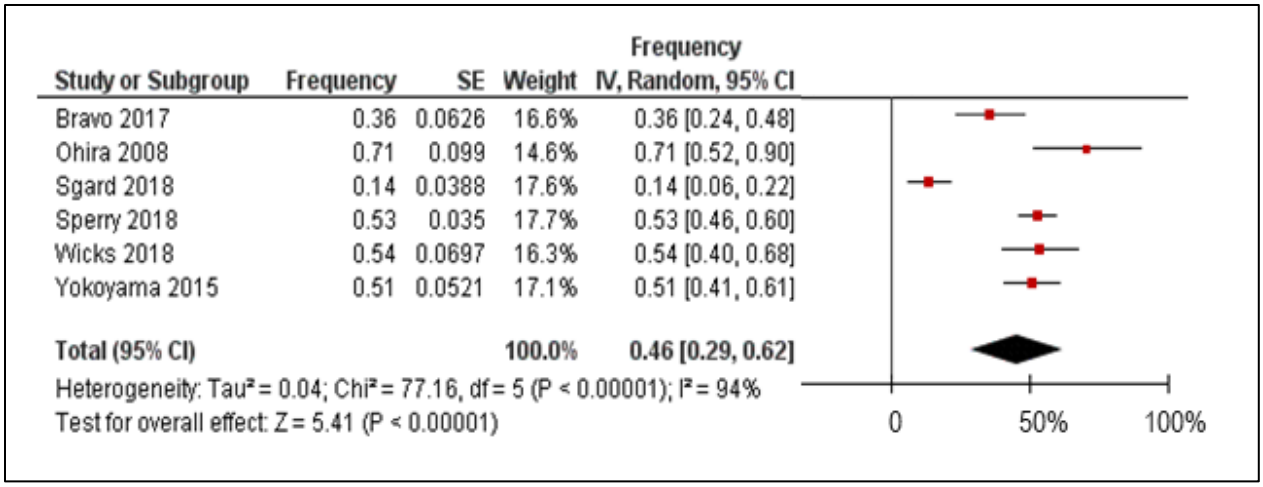
cMRI- Cardiac mortality



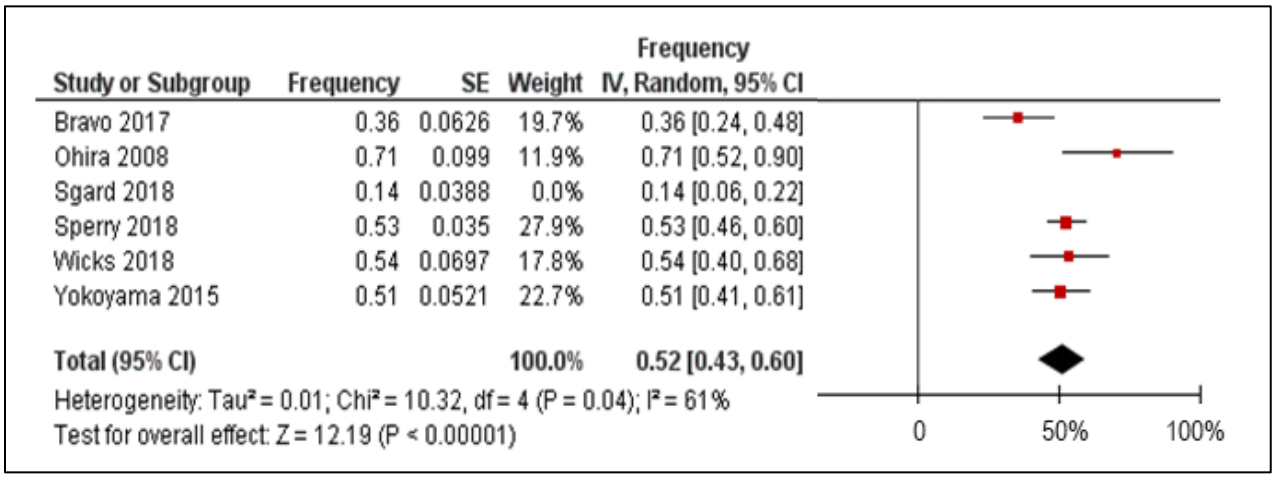
cMRI- Ventricular arrhythmias (outliers included)



PET- Prevalence of abnormal PET scans (outliers included)

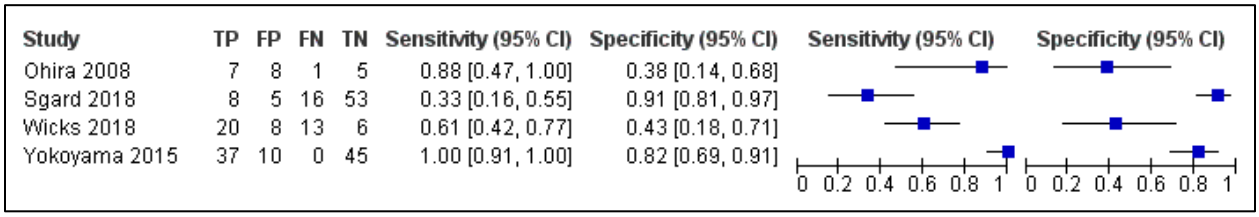


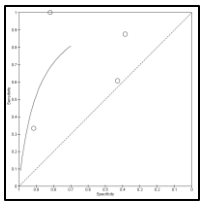
PET- Prevalence of abnormal PET scans (outliers excluded)



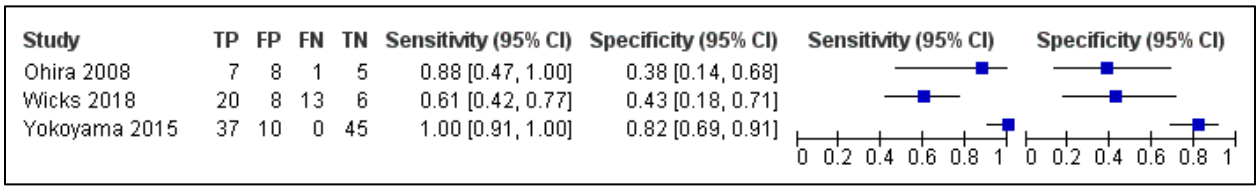
PET- Diagnosis of cardiac sarcoidosis

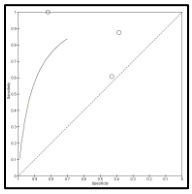
w/ outliers - JMHW



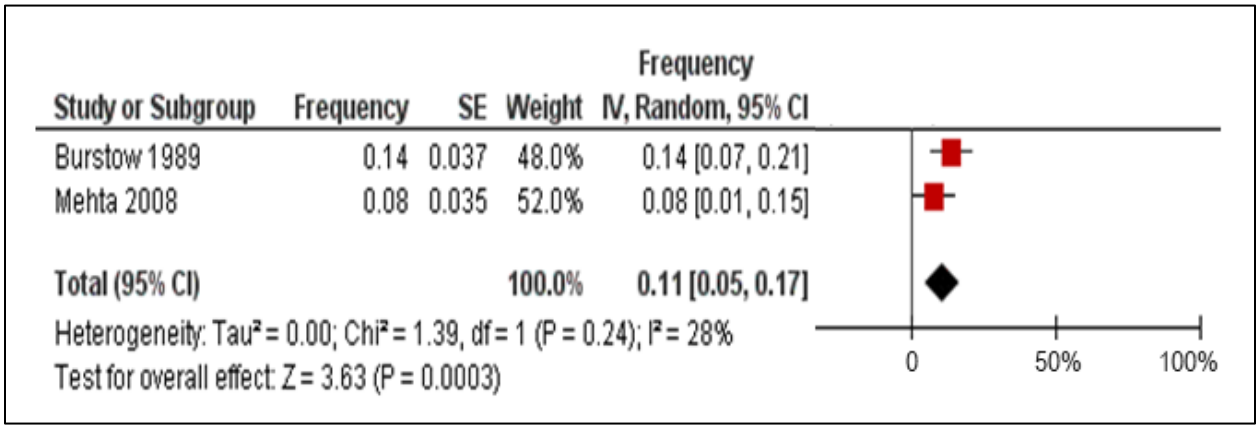


w/o outliers – JMHW





TTE- prevalence of abnormal TTE



Evidence profiles

cMRI evidence profile

Bibliography:

1. Smedema et al. Cardiac involvement in patients with pulmonary sarcoidosis assessed at two university medical centers in the Netherlands. Chest 2005; 128: 30-5.
2. Ohira et al. Myocardial imaging with 18F-fluoro-2-deoxyglucose positron emission tomography and magnetic resonance imaging in sarcoidosis. Eur J Nuc Med and Mol Imag 2008; 35: 933-41.
3. Patel et al. Detection of myocardial damage in patients with sarcoidosis. Circulation 2009. 120: 1969-77.
4. Patel et al. Myocardial damage in patients with sarcoidosis and preserved left ventricular systolic function: an observational study. Eur J Heart Fail 2011; 13: 1231-7.
5. Greulich et al. CMR imaging predicts death and other adverse events in suspected cardiac sarcoidosis. ACC Cardiovasc Imaging 2013; 6L 501-11.
6. Cain et al. Cardiac sarcoidosis detected by late gadolinium enhancement and prevalence of atrial arrhythmias. Am J Cardiol 2014; 113: 1556-60.
7. Kournas et al. Complementary Role of CMR to Conventional Screening in the Diagnosis and Prognosis of Cardiac Sarcoidosis. JACC Cardiovasc Imaging 2017; 10: 1437-1447.
8. Stanton et al. The Utility of Cardiac Magnetic Resonance Imaging in the Diagnosis of Cardiac Sarcoidosis. Heart Lung Circ 2017; 26: 1191-1199.
9. Bravo, P. E et al. Risk assessment of patients with clinical manifestations of cardiac sarcoidosis with positron emission tomography and magnetic resonance imaging. Int J Cardiol 2017; 241: 457–462.
10. Nadel et al. Late gadolinium enhancement identified with cardiac magnetic resonance imaging in sarcoidosis patients is associated with long-term ventricular arrhythmia and sudden cardiac death. Eur Heart J Cardiovasc Imaging 2015; 16: 634-41.
11. Wicks et al. Diagnostic accuracy and prognostic value of simultaneous hybrid 18F-fluorodeoxyglucose positron emission tomography/magnetic resonance imaging in cardiac sarcoidosis. Eur Heart J Cardiovasc Imaging 2018. 19: 757-767.

Quality assessment							Summary of findings				Quality	Importance
							Patients		Effects			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Abnl. cMRI	Nml. cMRI	Relative	Absolute		
Frequency of abnormal cMRI (%)												
11[1]	case series	serious[2]	serious[3]	serious[4]	serious[5]	none	27% [6], 95% CI 23-31%	N/A	N/A	N/A	⊕OOO VERY LOW	TBD
Diagnosis of cardiac sarcoidosis												
8[7]	accuracy studies	serious[8]	serious[3]	serious[4]	serious[5]	none	Sensitivity- 68% (95 CI 59-76%) [9] Specificity- 78% (95% CI 73-82%) [9]				⊕OOO VERY LOW	TBD
Overall mortality												
2[10]	observational studies	serious[2]	serious[3]	serious[4]	serious[5]	none	7/71 (9.9%)	9/190 (4.7%)	RR 2.54 95% CI 0.38-17.16	51 more per 1000 (from 13 fewer to 145 more)	⊕OOO VERY LOW	TBD
Cardiac mortality												
2[11]	observational studies	serious[2]	none	serious[4]	serious[5]	none	7/53 (13%)	2/136 (1.5%)	RR 9.00 95% CI 1.93-41.97	117 more per 1000 (from 41 more to 234 more)	⊕OOO VERY LOW	TBD
Aborted sudden cardiac death												
1[12]	observational studies	serious[8]	none	serious[4]	serious[5]	none	11/39 (28%)	0/114 (0%)	Not estimable	282 more per 1000 (from 161 more to 438 more)	⊕OOO VERY LOW	TBD

Ventricular arrhythmias												
3[13]	observational studies	serious[8]	none	serious[4]	serious[5]	none	37/98 (38%)	7/272 (3.6%)	RR 11.71 95% CI 2.59-52.9	352 more per 1000 (from 259 more to 452 more)	⊕OOO VERY LOW	TBD
Major adverse cardiac events (sustained VT, Ventricular Fibrillation, AICD shock, all-cause death)												
3[14]	observational studies	serious[8]	none	serious[4]	serious[5]	none	-	-	HR 10.63, 95% CI 1.4-80.78 RR 12.5 95% CI 1.35-116.18 RR 8.33 95% CI 1.18-58.51		⊕OOO VERY LOW	TBD
Diastolic heart failure												
1[15]	observational studies	serious[8]	none	serious[4]	serious[5]	none	18/27 (67%)	41/123 (33%)	RR 2.0 95% CI 1.39-2.88	499 more per 1000 (from 126 more to 499 more)	⊕OOO VERY LOW	TBD
All heart failure												
1[16]	observational studies	serious[8]	none	serious[4]	serious[5]	none	15/32 (47%)	3/76 (4%)	RR 11.88 95% CI 3.69-38.21	429 more per 1000 (from 254 more to 598 more)	⊕OOO VERY LOW	TBD
Supraventricular arrhythmias												
1[17]	observational studies	serious[8]	none	serious[4]	serious[5]	none	16/44 (36%)	11/91 (12%)	RR 3.01 95% CI 1.53-5.93	243 more per 1000 (from 92 more to 399 more)	⊕OOO VERY LOW	TBD
Complete heart block												
1[17]	observational studies	serious[8]	none	serious[4]	serious[5]	none	4/32 (12%)	1/76 (1.4%)	RR 9.5 95% CI 1.10-81.72	112 more per 1000 (from 17 more to 268 more)	⊕OOO VERY LOW	TBD
Pulmonary hypertension												
1[16]	observational studies	serious[8]	none	serious[4]	serious[5]	none	8/32 (25%)	6/76 (8%)	RR 3.17 95% CI 1.19-8.39	171 more per 1000 (from 27 more to 347 more)	⊕OOO VERY LOW	TBD

Footnotes:

[1] All studies.
[2] Many studies didn't enroll consecutive patients; therefore, there was a risk of selection bias. Can't eliminate confounding bias.
[3] High I^2 statistic.
[4] The question is about patients with suspected cardiac sarcoidosis, but many studies included patients with and without cardiac symptoms.
[5] Low optimum information size (most studies had <200 patients) and wide confidence intervals.
[6] After removal of Smedema, Bravo, and Wick as outliers
[7] Smedema, Ohira, Patel, Patel, Kouranos, Stanton, Bravo, and Wisk.
[8] Can't eliminate confounding bias.
[9] After removal of Patel as an outlier
[10] Greulich and Nadel.
[11] Patel and Nadel.
[12] Greulich.
[13] Patel, Greulich, and Cain.
[14] Bravo, Wicks, and Nadel.

[15] Patel.
[16] Nadel.
[17] Cain.

PET evidence profile

Bibliography:

1. Yokoyama, R et al Quantitative analysis of myocardial 18F-fluorodeoxyglucose uptake by PET/CT for detection of cardiac sarcoidosis. Intl J Cardiol 2015 195: 180–187.
2. Bravo, P. E et al. Risk assessment of patients with clinical manifestations of cardiac sarcoidosis with positron emission tomography and magnetic resonance imaging. Int J Cardiol 2017; 241: 457–462.
3. Sperry, BW et al. Prognostic Impact of Extent, Severity, and Heterogeneity of Abnormalities on 18F-FDG PET Scans for Suspected Cardiac Sarcoidosis. JACC. Cardiovascular Imaging, 2018 11: 336–345.
4. Sgard, B et al. Evaluation of FDG PET combined with cardiac MRI for the diagnosis and therapeutic monitoring of cardiac sarcoidosis. Clin Radiol 2018; 1–10.
5. Wicks et al. Diagnostic accuracy and prognostic value of simultaneous hybrid 18F-fluorodeoxyglucose positron emission tomography/magnetic resonance imaging in cardiac sarcoidosis. Eur Heart J Cardiovasc Imaging 2018. 19: 757-767.
6. Ohira et al. Myocardial imaging with 18F-fluoro-2-deoxyglucose positron emission tomography and magnetic resonance imaging in sarcoidosis. Eur J Nuc Med and Mol Imag 2008; 35: 933-41.

Quality assessment							Summary of findings				Quality	Importance
							Patients		Effects			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Abnl. cMRI	Nml. cMRI	Relative	Absolute		
Frequency of abnormal PET (%)												
6[1]	case series	serious[2]	serious[3]	serious[4]	serious[5]	none	53% [6] 95% CI 46-61%	-	-	-	⊕OOO VERY LOW	TBD
Diagnosis of cardiac sarcoidosis												
5[7]	accuracy studies	serious[8]	none	serious[4]	serious[5]	none	Sensitivity = 80%, 95% CI 73-86% [6] Specificity = 68%, 95% CI 59-75% [6]				⊕OOO VERY LOW	TBD
Overall mortality												
1[9]	observational studies	serious[8]	none	serious[4]	serious[5]	none	-	-	HR 1.33 95% CI 0.68-2.26		⊕OOO VERY LOW	TBD
Major adverse cardiac events (sustained VT, Ventricular Fibrillation, AICD shock, all-cause death)												
4[10]	observational studies	serious[2]	none	serious[4]	serious[5]	none	-	-	HR 3.30 [11] 95% CI 1.1-10.0 HR 2.29 [12] 95% CI 0.72-7.33 RR 2.0 [9] 95% CI 1.26-3.17		⊕OOO VERY LOW	TBD

Footnotes:

[1] All studies.
[2] One study didn't enroll consecutive patients; therefore, there was a risk of selection bias. Can't eliminate confounding bias.
[3] High I^2 statistic.
[4] The question is about patients with suspected cardiac sarcoidosis, but many studies included patients with and without cardiac symptoms.
[5] Low optimum information size (most studies had <200 patients) and wide confidence intervals.
[6] Eliminated Sgard as an outlier.
[7] Ohira, Yokoyama, Sperry, Sgard, and Wicks.
[8] Can't eliminate confounding bias.
[9] Sperry.
[10] Bravo, Sperry, Wicks, and Sgard.
[11] Bravo.
[12] Wicks.

Echocardiography profile

Bibliography:
3. Mehta D, Lubitz SA, Frankel Z, Wisnivesky JP, Einstein AJ, Goldman M, Machac J, Teirstein A, 2008. Cardiac involvement in patients with sarcoidosis: diagnostic and prognostic value of outpatient testing. Chest 133: 1426-1435.
4. Burstow, et al. Two-dimensional echocardiographic findings in systemic sarcoidosis. Am J Cardiol 1989; 63(7):478-482.

Quality assessment							Summary of findings				Quality	Importance
							Patients		Effects			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Abnl. TTE	Nml. TTE	Relative	Absolute		
Frequency of abnormal echocardiography (%)												
2[1]	case series	serious[2]	serious[3]	serious[4]	serious[5]	none	11% 95% CI 5-17%	-	-	-	⊕OOO VERY LOW	TBD
Diagnosis of cardiac sarcoidosis												
1[6]	accuracy study	none	none	serious[4]	serious[5]	none	Sensitivity= 25%, 95% CI 10-47% Specificity= 97%, 95% CI 86-99%				⊕OOO VERY LOW	TBD
Development of conduction abnormalities												
1[7]	observational study	serious[2]	none	serious[4]	serious[5]	none	7/12 (58%)	17/76 (22%)	RR 2.6 95% CI 1.38-4.92	360 more per 1000 (from 76 more to 597 more)	⊕OOO VERY LOW	TBD

Footnotes:
[1] All studies.
[2] Can't exclude confounding bias.
[3] High I^2 statistic.
[4] The question is about patients with suspected cardiac sarcoidosis, but many studies included patients with and without cardiac symptoms.
[5] Low optimum information size (<200 patients) and wide confidence intervals.
[6] Mehta.
[7] Burstow.

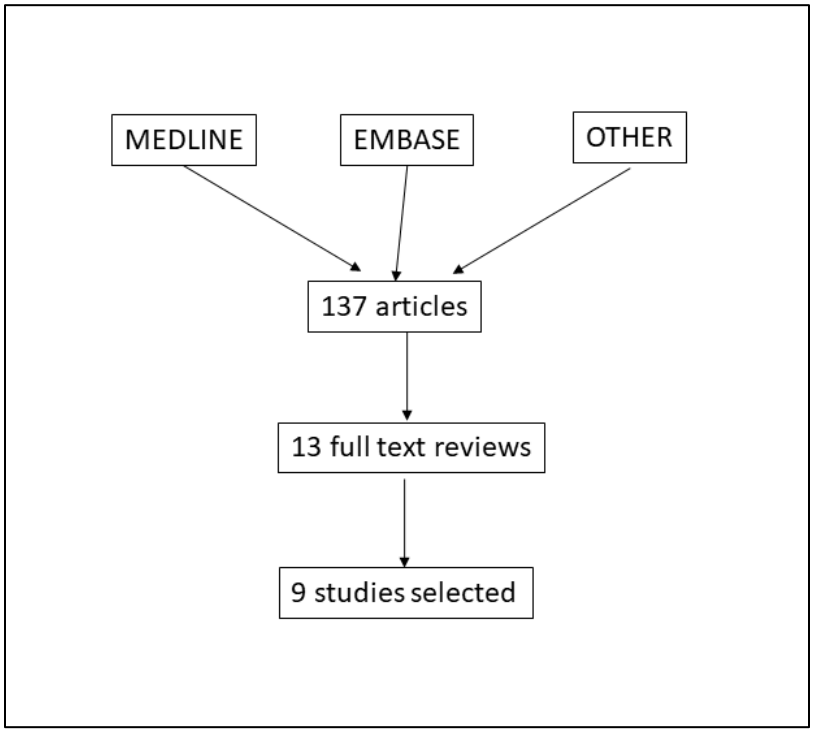
QUESTION #10: *Should patients with sarcoidosis who are suspected of having pulmonary hypertension undergo transthoracic echocardiography?*

Search strategy

#	Searches
1	exp sarcoidosis/
2	sarcoidosis/
3	sarcoidosis/ or sarcoidosis, pulmonary/ or uveoparotid fever/
4	sarcoid$.mp.
5	(besnier adj boeck$).tw.
6	(boeck$ adj (disease or sarcoid)).tw.
7	(schaumann$ adj (disease or syndrome)).tw.
8	uveoparoti$.tw.
9	(benign$ adj lymphogranuloma$).tw.
10	((junging or heerfordt or lofgren) adj syndrome).tw.

11	neurosarcoidosis.tw.
12	(lupus adj pernio).tw.
13	(idiopathic adj3 inflammat$ adj3 granulomat$).tw.
14	or/1-13 [all sarcoidosis]
15	pulmonary hypertension/
16	((pulmonary or lung) adj3 hypertensi$).mp.
17	(pulmonary adj2 (heart or vascular or arter$ or cardiac) adj2 disease$).mp.
18	(corpulmonale or cor pulmonale).mp.
19	15 or 16 or 17 or 18 [PH]
20	14 and 19 [sarcoid and PH]
21	exp Echocardiography/
22	(echocardiogra$ or echo cardiogra$).mp.
23	((heart or cardi$) adj echogra$).mp.
24	21 or 22 or 23 [echo]
25	19 and 24 [PH and echo]
26	20 and 24 [Sarcoidosis and PH and echo]
27	14 and 24 [sarcoid and echo]

Flow of information



Selected studies with outcomes

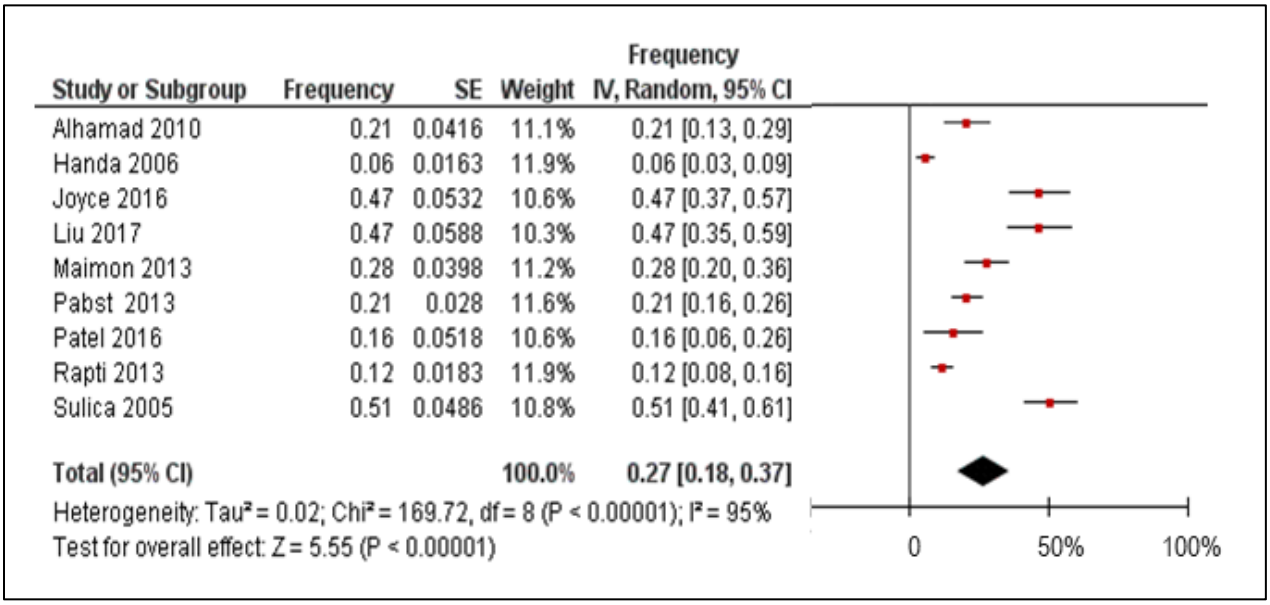
Study	Definition of PH	Frequency of echo suggestive of PH	Confirmation by right heart catheterization	Severity of lung disease (FVC % predicted) (means ± SDs)	
				PH	No PH
Alhamad 2010	estimated RVSP ≥ 40 mmHg	20/96 (21%)	5/5 (100%)	56.9 ± 21.3	79.5 ± 20.9
Handa 2006	estimated sPAP ≥40 mmHg	12/212 (6%)	NR	88 ± 24	106 ± 18
Joyce 2016	estimated RV global longitudinal peak systolic strain ≥ -19%	41/88 (47%)	NR	NR	NR
Liu 2017	estimated sPAP ≥40 mmHg	34/72 (47%)	34/34 (100%)	NR	NR
Maimon 2013	estimated RV SP ≥40 mmHg	36/127 (28%)	1/3 (33%)	90 ± 20	93±15
Pabst 2013	estimated SPAP > 50 mmHg	23/211 (21%)	5/10 (50%)	NR	NR
Patel 2016	estimated SPAP > 35 mmHg	8/50 (16%)	NR	NR	NR
Rapti 2013	estimated sPAP ≥ 40 mmHg	37/313 (12%)	9/12 (75%)	79.3 ± 26.8	96.2 ±16.8
Sulica 2005	estimated RVSP of at least 40 mm Hg,	54/106 (51%)	3/5 (60%)	54 ± 2.4	64 ± 2.8
Pooled (weighted)	***Not applicable***	***29% (95% CI 20% to 39%)***	***Not estimable***	***MD -16.5% (95% CI -22.4% to -10.6%)***	
Pooled (unweighted)		***21% (95% CI 19-23%)***	***78% (95% 67% to 86%)***	***Not estimable***	
Median (range)		***21% (6% to 51%)***	***68% (33% to 100%)***	***-16.9% (-3% to -22.6%)***	

NR= not reported.

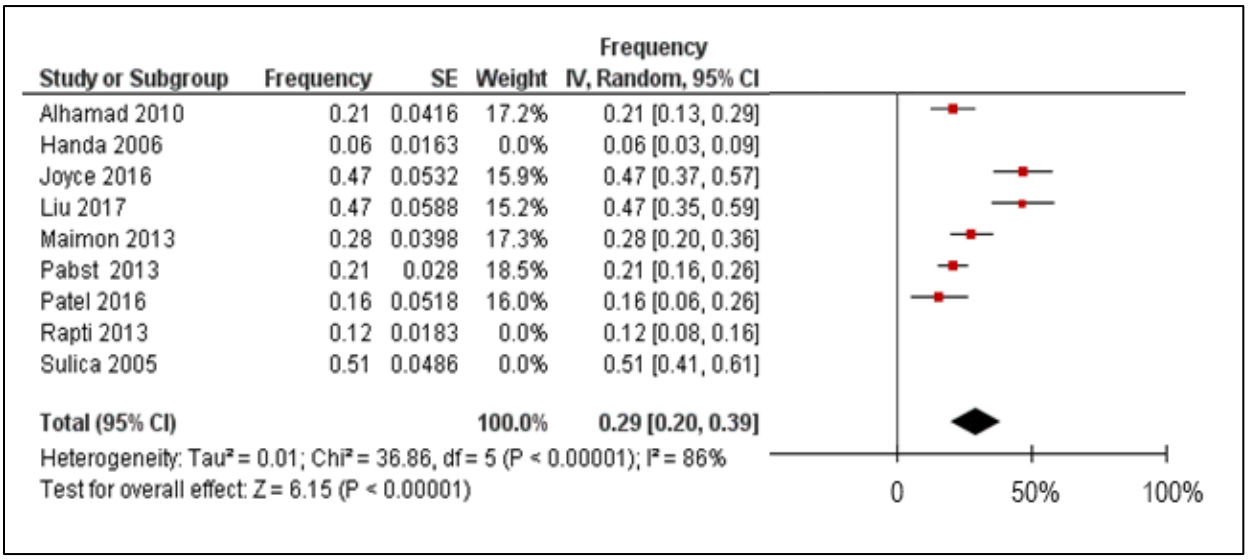
Forest plots

Frequency of echo suggestive of PH

Initial

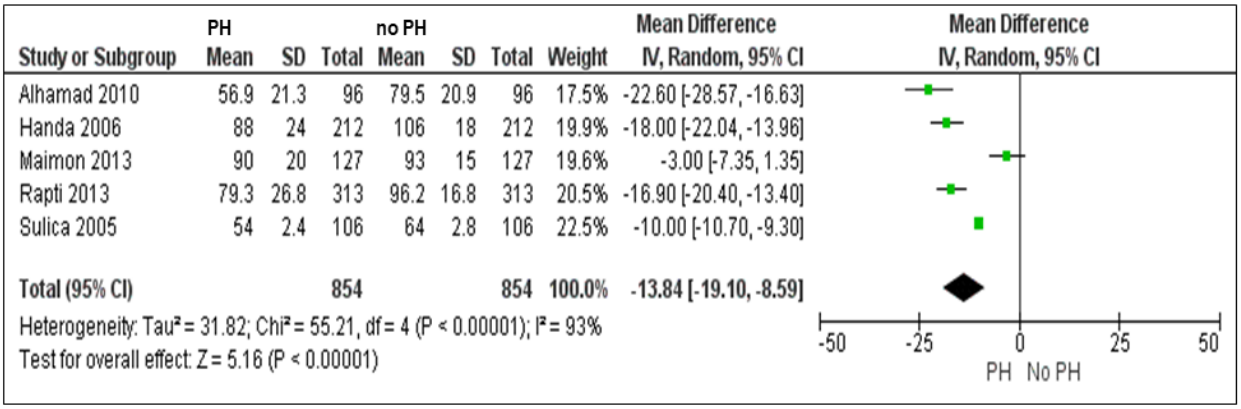


After removal of outliers

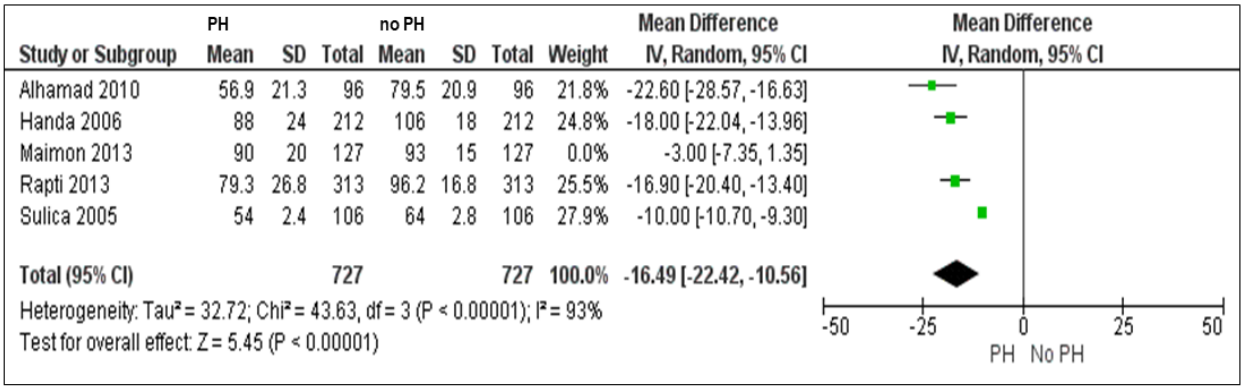


Severity of lung disease among PH verus no PH

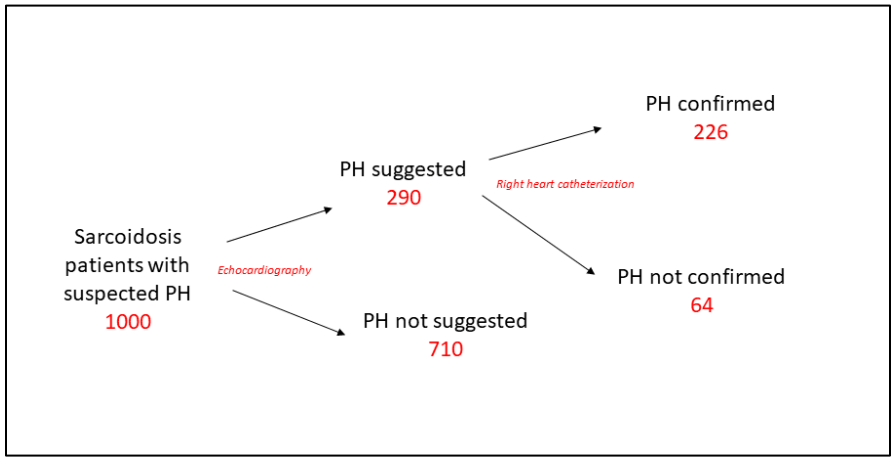
Initial



After removal of outliers



Markov model



For every 1000 sarcoidosis patients who are suspected of having PH and undergo echocardiography, abnormalities suggestive of PH will be found in roughly 290 patients, approximately 226 of whom will have PH confirmed by right heart catheterization.

Evidence profile

Bibliography:

1. Alhamad EH, et al. Sarcoidosis-associated pulmonary hypertension: Clinical features and outcomes in Arab patients. Ann Thorac Med 2010; 5(2):86-91.
2. Handa T, et al. Incidence of pulmonary hypertension and its clinical relevance in patients with sarcoidosis. CHEST 2006; 129(5):1246-1252.
3. Joyce E, et al. Prevalence and correlates of early right ventricular dysfunction in sarcoidosis and its association with outcome. J Am Soc Echo 2016; 29(9):871-878.
4. Liu L, et al. Interventional therapy in sarcoidosis-associated pulmonary arterial stenosis and pulmonary hypertension. Clin Respir J 2017; 11(6):906-914.
5. Maimon N, et al. Sarcoidosis-associated pulmonary hypertension in patients with near-normal lung function. Int J Tuberc Lung Dis 2013; 17(3):406-411.
6. Pabst S, et al. Pulmonary arterial hypertension in patients with sarcoidosis: the Pulsar single center experience. Adv Exp Med Biol 2013; 755:299-305.
7. Patel MB, et al. Right heart involvement in paitents with sarcoidosis. Echocardiogr 2016; 33(5):734-741.
8. Rapti A, et al. Elevated pulmonary arterial systolic pressure in patients with sarcoidosis: prevalence and risk factors. Lung 2013; 191(1):61-67.
9. Sulica R, et al. Distinctive clinical, radiographic, and functional characteristics of patients with sarcoidosis-related pulmonary hypertension. CHEST 2005; 128(3):1483-1489.

Quality assessment							Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Frequency of echocardiography suggestive of PH (%)									
9[1]	case series	serious[2]	serious[3]	none[4]	serious[5]	none	29% (95% CI 20% to 39%)	⊕OOO VERY LOW	TBD
Confirmation of PH by right heart catheterization (%)									
6[6]	case series	serious[2]	serious[3]	none[4]	serious[7]	none	78% (95% 67% to 86%)	⊕OOO VERY LOW	TBD
Initiation of anti-PH treatment (%)									

0	-	-	-	-	-	-	-	-	TBD
Mortality									
0	-	-	-	-	-	-	-	-	TBD
Exercise capacity									
0	-	-	-	-	-	-	-	-	TBD
Quality of life									
0	-	-	-	-	-	-	-	-	TBD

Footnotes:
[1] All studies.
[2] Many were retrospective chart reviews; therefore, there was a risk of selection bias.
[3] When pooled by meta-analysis, the I^2 >90%; thus, the median (range) are the primary outcomes for these outcomes rather than the pooled analyses. Also, the range is wide.
[4] The questions asks about sarcoidosis patients with suspected PH, but most studies did not state whether or not PH is suspected. Did not downgrade because difference minor.
[5] Four out of the nine studies are small, with <100 patients.
[6] Alhamad, Liu, Maimon, Pabst, Rapti, and Sulica.
[7] All of the studies are small, with <100 patients.