

# Pulmonary Fibrosis in Sarcoidosis

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Sarcoidosis Clinic

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# Pharmaceutical Support for Dr. Baughman

- Centocor: Research Grants, Consultant
- Celgene: Research Grants
- Actelion: Research Grants
- Cephalon: Research Grants
- Intermune: Research Grants
- Genetech: Research Grants
- Gilead: Research Grants
- Glaxo Smith Kline: Consultant

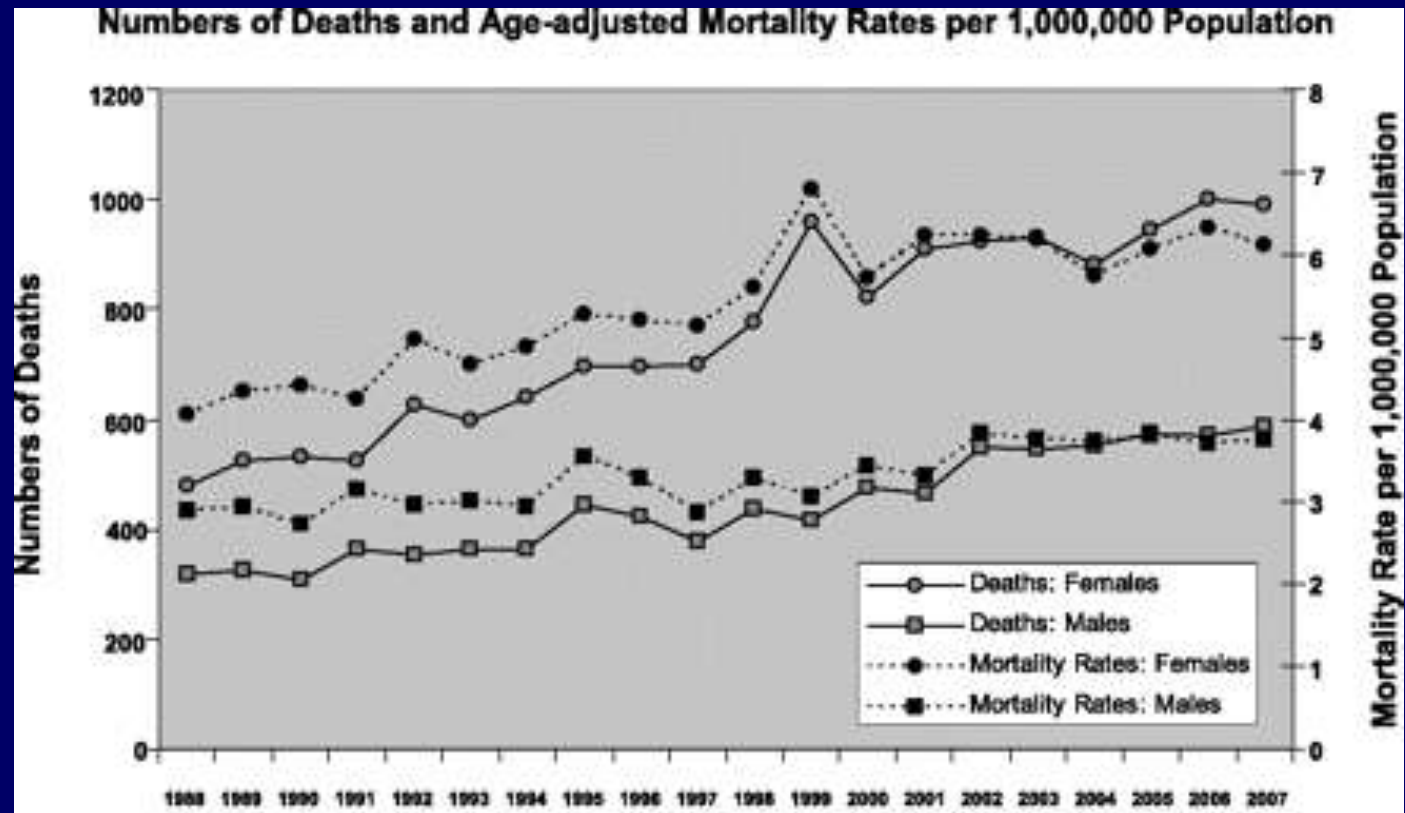
# Off Label Use of Therapy

- Prednisone and ACTHAR are the only drugs approved for use in pulmonary sarcoidosis
- All other drugs discussed here are off label use for treatment of sarcoidosis

# Introduction

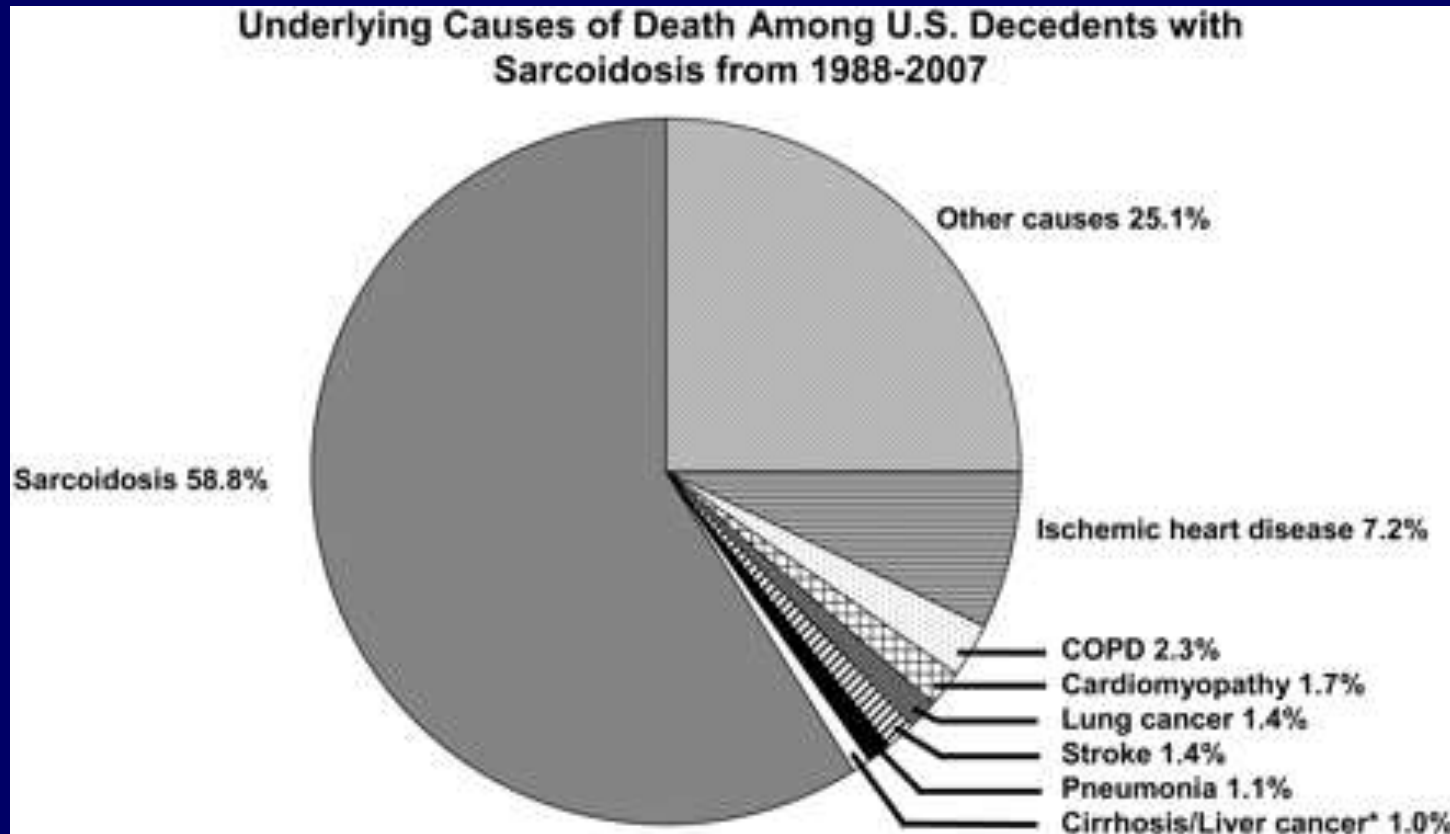
- Pulmonary fibrosis occurs a significant proportion of pulmonary sarcoidosis patients
- It is associated with morbidity and some mortality
- However not all patients with fibrosis are impaired by their disease
- Treatment options are unclear

# Increasing mortality from sarcoidosis



Swigris JJ, et al. Am J Respir Crit Care Med 2011; 183(11):1524-1530.

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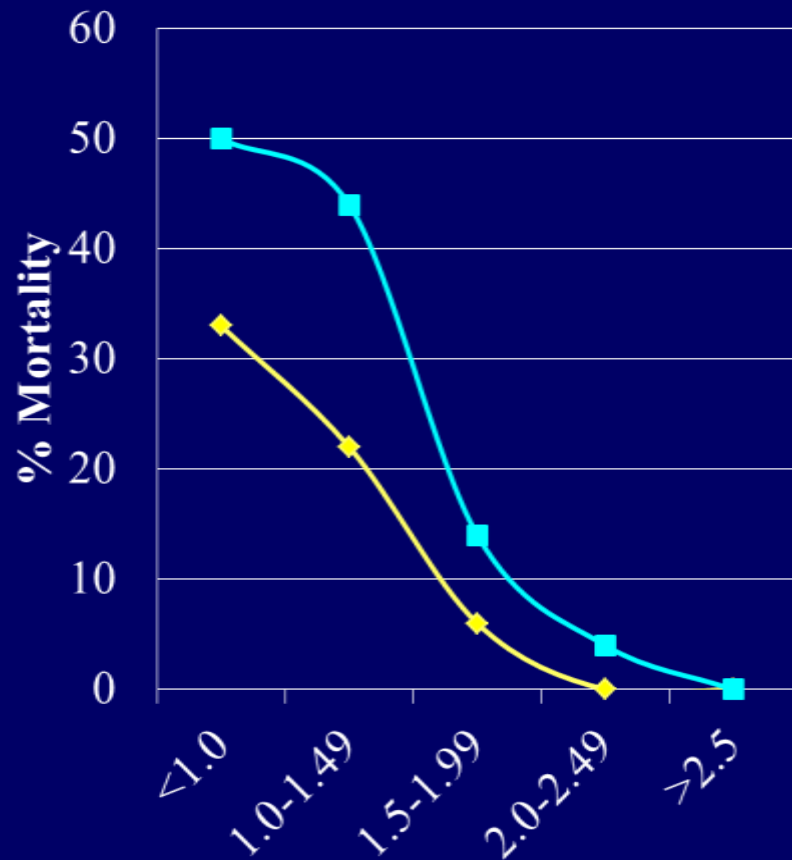
# Respiratory Failure in Sarcoidosis

- Seven year study at one institution
- 479 patients followed for at least 1 year
  - 22 (4.6%) died
  - 13 died of respiratory failure
  - 2 died from causes unrelated to sarcoidosis

Chest X-ray Stage	All Patients	Died of Respiratory Failure
0	27	0
1	101	0
2	92	0
3	41	0
4	62	13 (21%)

# Respiratory Failure in Sarcoidosis

■ Highest VC after therapy  
◆ Lowest VC



Vital Capacity, l	Lowest VC	Highest VC after Therapy
<1.0	9	4
1-1.49	32	9
1.5-1.99	52	22
2.0-2.5	34	63
>2.5	352	381



# IPF versus Sarcoidosis Pulmonary Fibrosis

## **Idiopathic Pulmonary Fibrosis**

- Most patients die from progressive fibrosis
- Honeycombing in basilar and subpleural regions
- Anti-inflammatory therapy has very limited role
- Acute exacerbations have a high morbidity and mortality
- Pulmonary hypertension is seen in some patients

## **Sarcoidosis Pulmonary Fibrosis**

- Only a small percentage have progressive fibrosis
- Traction bronchiectasis in upper lobes
- Anti-inflammatory therapy is useful in most patients
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- Pulmonary hypertension is a common complication

# IPF versus Sarcoidosis Pulmonary Fibrosis

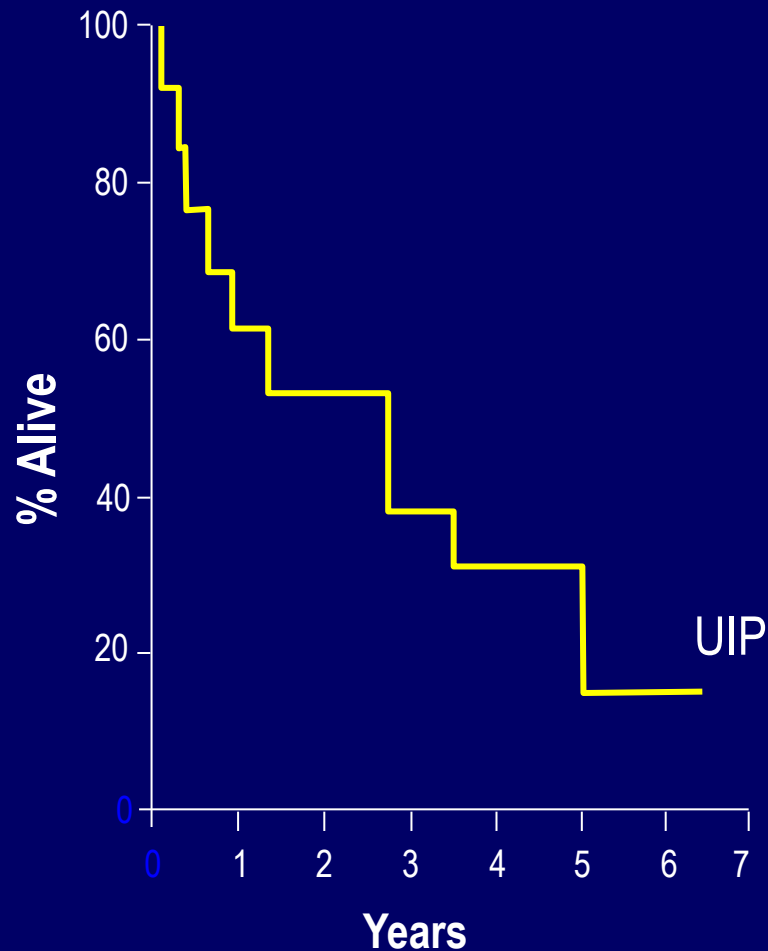
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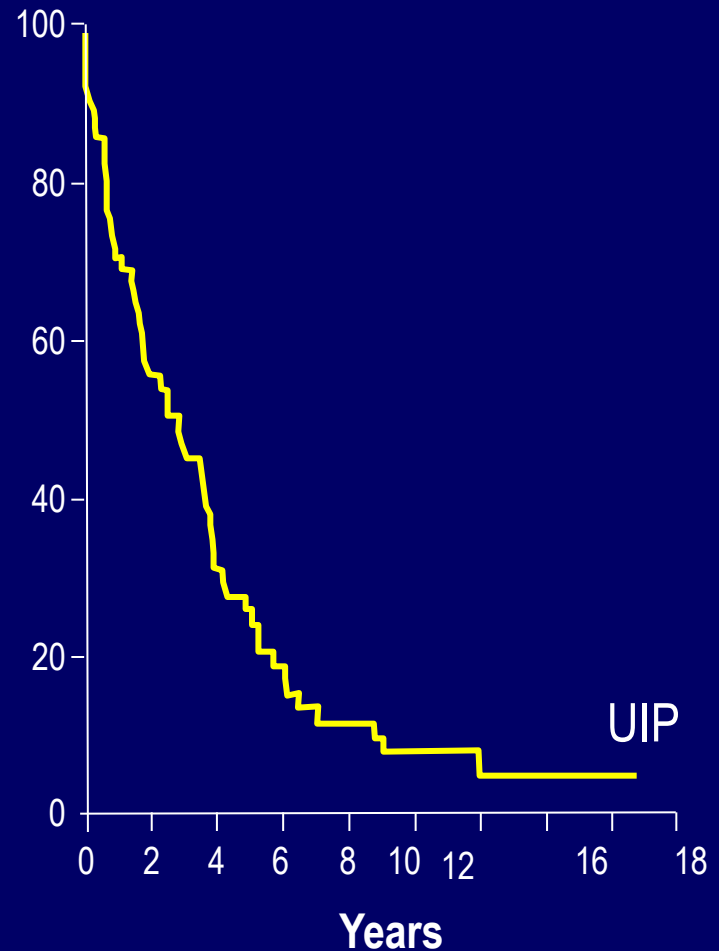
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# SURVIVAL FOR UIP VS NSIP

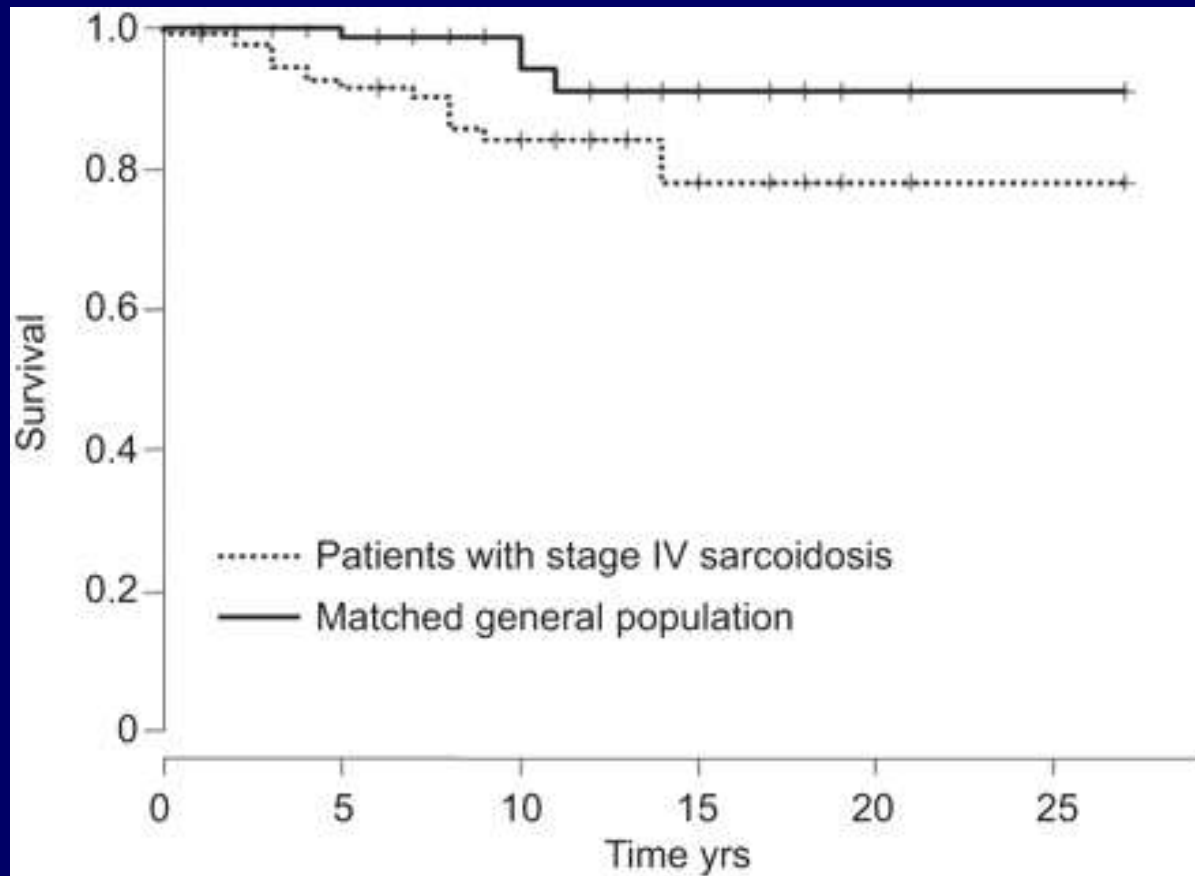


Daniil ZD et al. *Am J Respir Crit Care Med.* 1999;160:899.

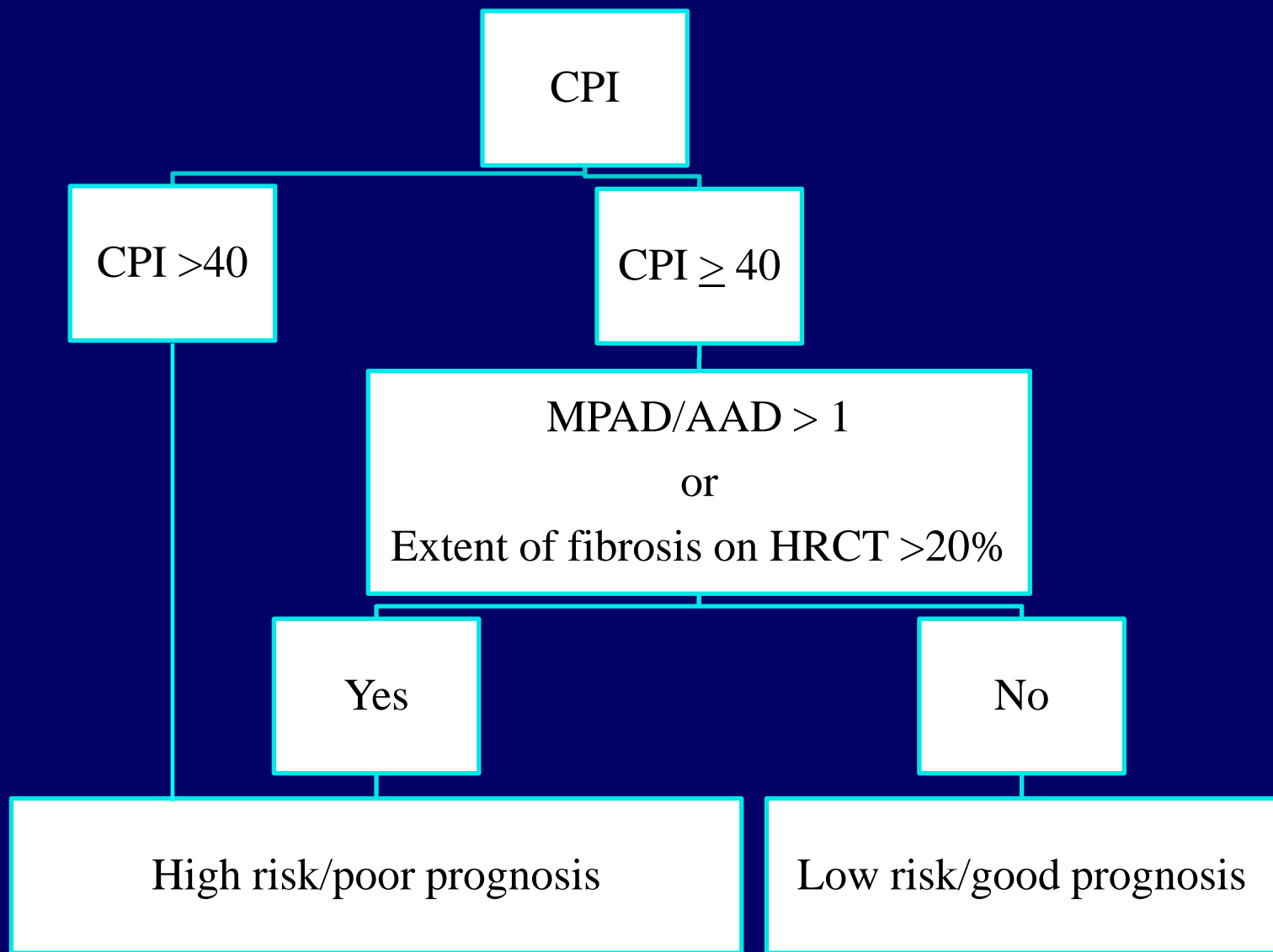


Bjoraker JA et al. *Am J Respir Crit Care Med.* 1998;157:199.

# Survival of Stage 4 sarcoidosis

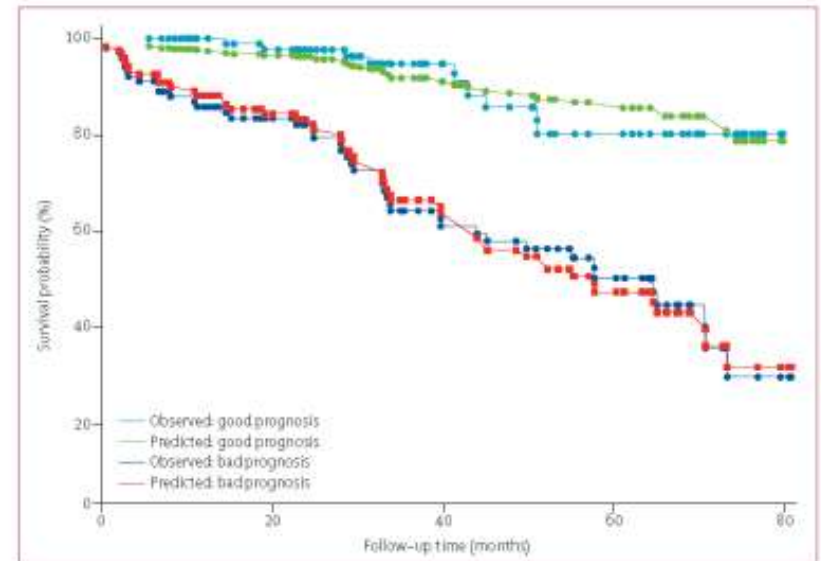
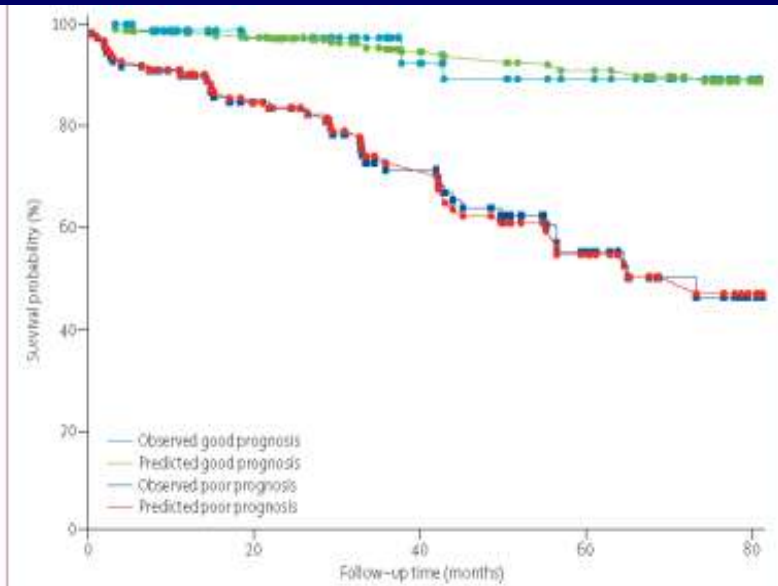


Nardi A, et al. Eur Respir J 2011; 38(6):1368-1373.



$$\text{CPI} = 91.0 - (0.65 * \text{percent predicted DLCO}) - (0.53 * \text{percent predicted FVC}) + (0.34 * \text{percent predicted FEV-1})$$

# Survival of Fibrotic Sarcoidosis Brompton Experience



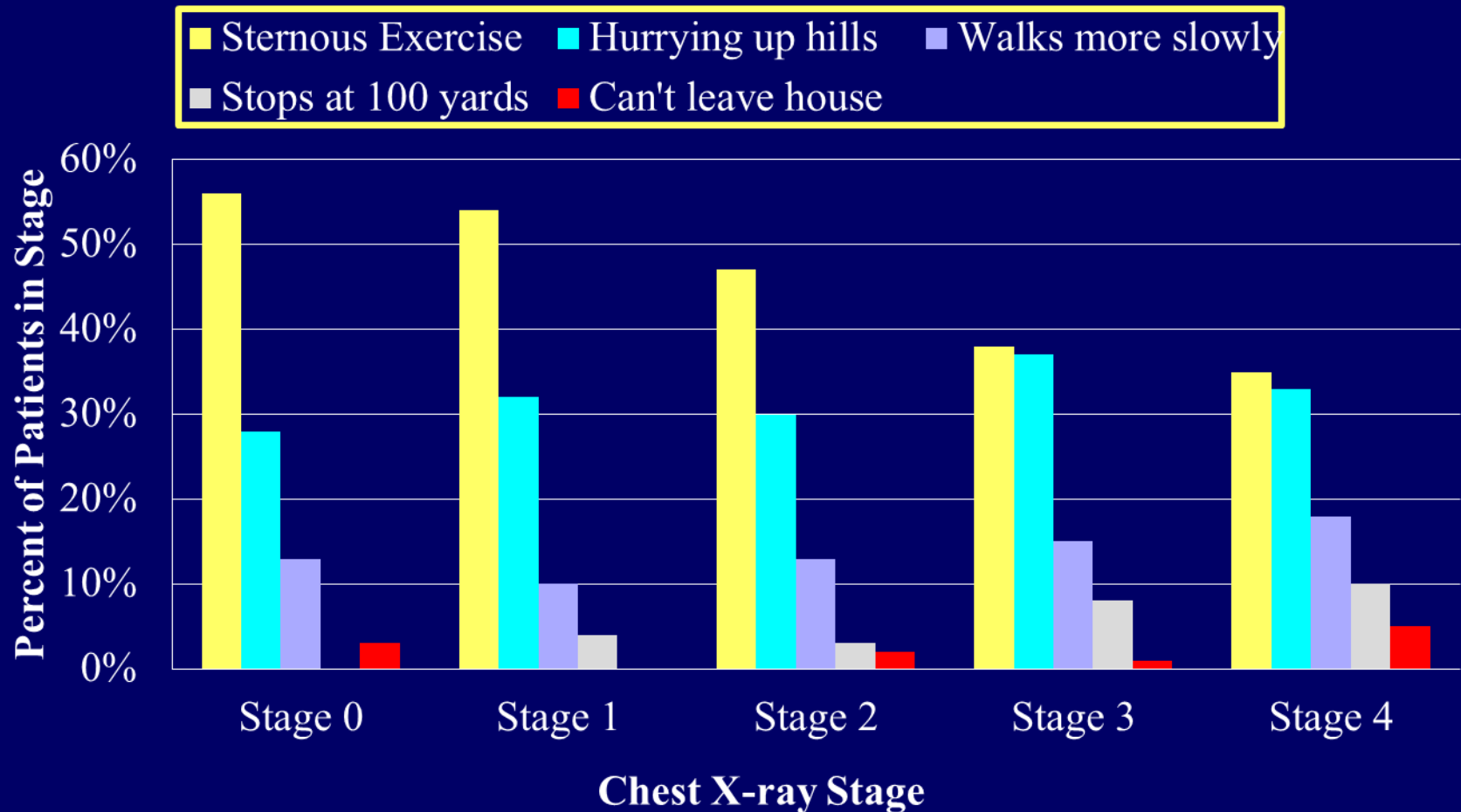
Original

Confirmation

# PFT changes in Fibrotic Sarcoidosis

	<b>Nardi</b>	<b>Baughman</b>	<b>Walsh (Group A)</b>
Number	142	129	251
FVC % predicted	71.6 $\pm$ 22.4 *	78.4 $\pm$ 20.4	82.4 $\pm$ 24.2
FEV-1% predicted	63.9 $\pm$ 20.7	57.2 $\pm$ 18.0	72.9 $\pm$ 25.7
FEV1/FVC %	73.4 $\pm$ 14.0	72.4 $\pm$ 13.4	N.R.
DLCO % predicted	56.2 $\pm$ 17.8	75.2 $\pm$ 23.8	58.5 $\pm$ 21.4

# Not all stage 4 patients are dyspneic





# IPF versus Sarcoidosis Pulmonary Fibrosis

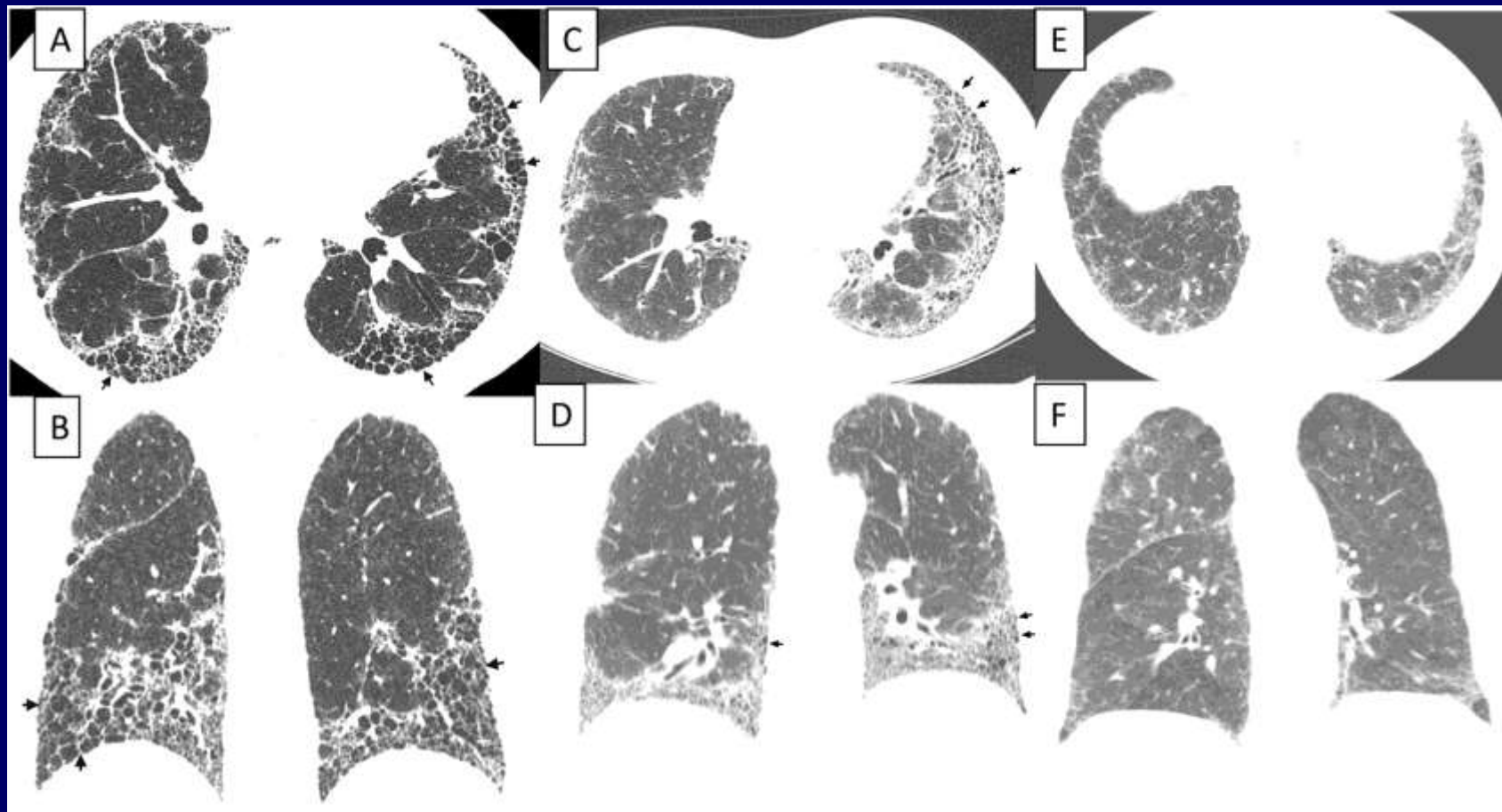
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## Sarcoidosis Pulmonary Fibrosis

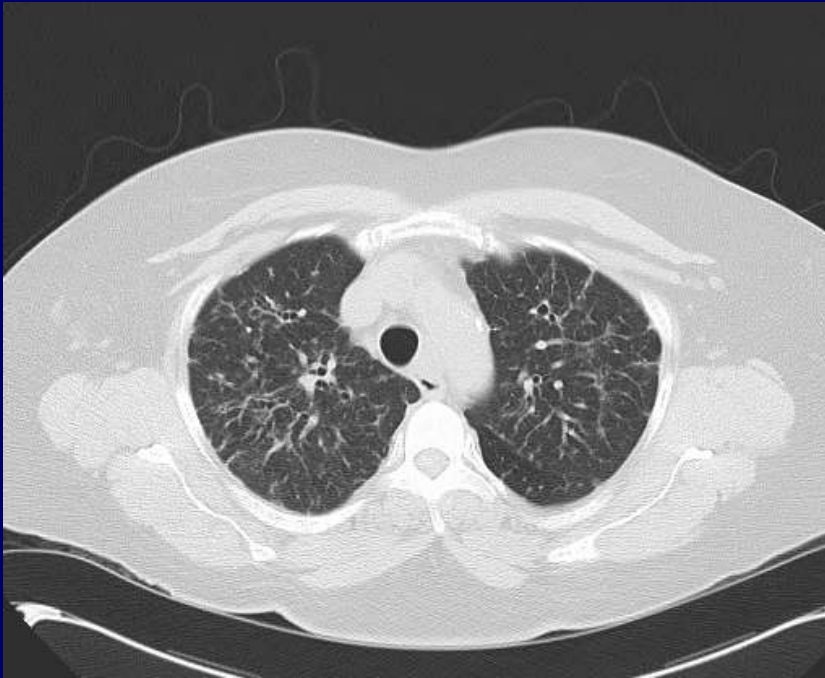
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# HRCT Pattern of Usual Interstitial Pneumonia

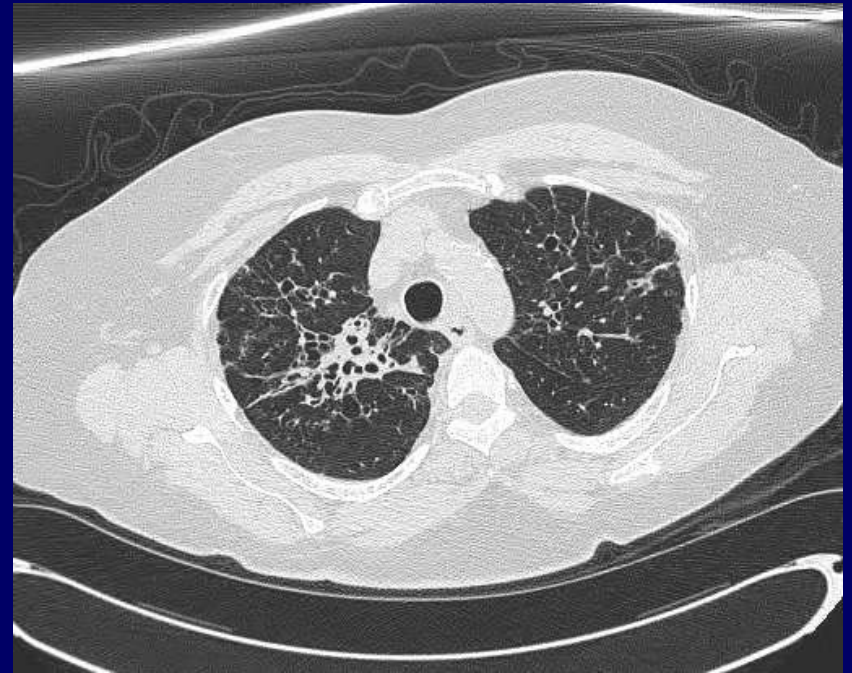


# Progressive fibrosis in sarcoidosis patient on prednisone

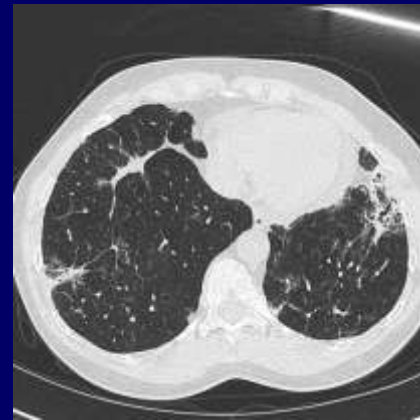
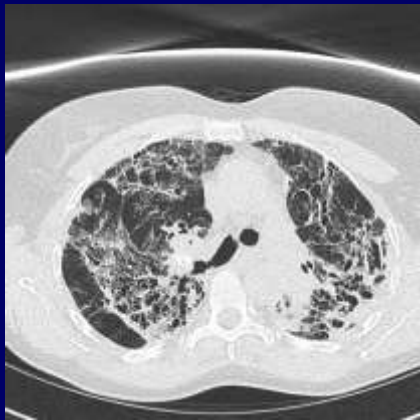
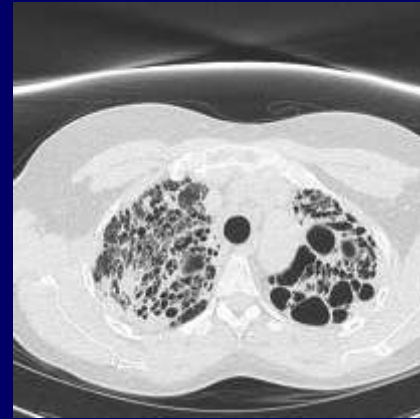
2008



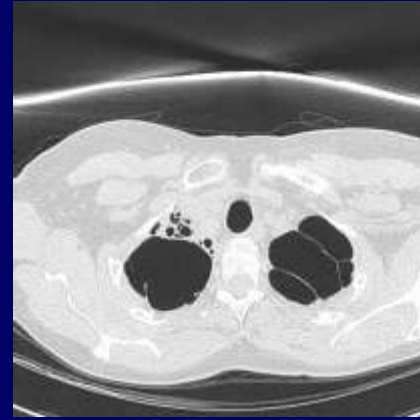
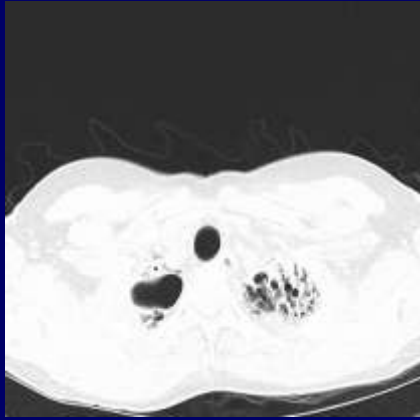
2014



# Asymptomatic Patient with Sarcoidosis Associated Pulmonary Fibrosis 2009



# Asymptomatic Patient with Sarcoidosis Associated Pulmonary Fibrosis 2012



# Fibrosis patient with no symptoms

	2009	2012
FVC	2.47	2.42
FVC % predicted	99%	100%
FEV-1	1.80	1.63
FEV1/FVC	73%	68%
DLCO	9.39	10.46
DLCO % predicted	52%	59%

# HRCT in sarcoidosis: Major Features

- Three main CT patterns
  - Bronchial distortion,
  - Honeycombing
  - Linear opacities.
- Other patterns
  - Endobronchial granulomatous lesions
  - Aspergilloma colonization
  - Bronchiectasis
  - Air trapping

Naccache JM, et al *J Comput Assist Tomogr* 2008;32:905-912.

Hennebicque AS, et al *Eur Radiol* 2005;15:23-30.



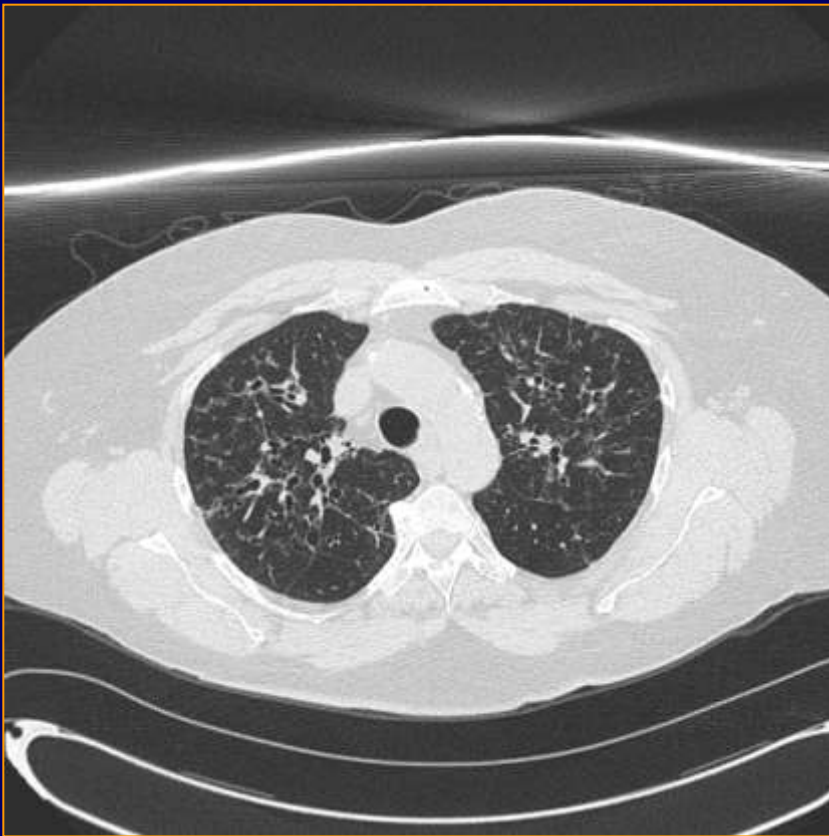
# HRCT Pattern versus PFT findings

Main Pattern	VC	FEV <sub>1</sub>	FEV <sub>1</sub> /VC	TCO
Linear	84	77	90	65
Bronchial distortion	76	64	82	58
Honeycombing	58	56	92	44
p	0.001	0.02	0.15	0.002

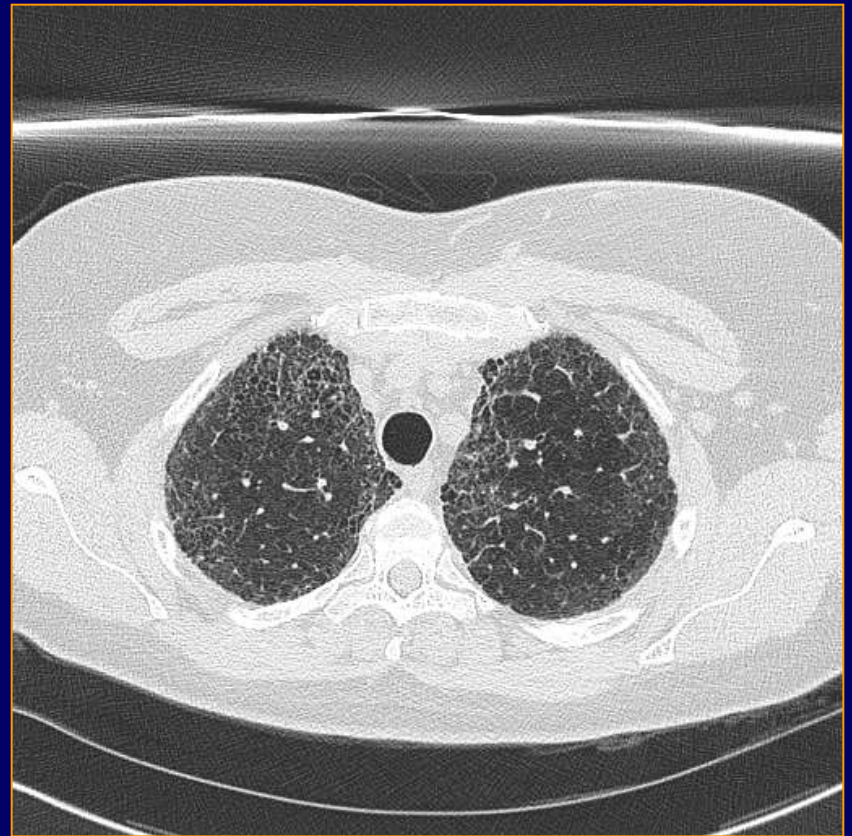


# Not all fibrosis is the same

**Traction  
Bronchiectasis**



**Subpleural  
Honeycombing**



# Pathology of fibrotic sarcoidosis

- Prospectively evaluated histologic sections from 9 lung explants with end-stage sarcoid lung disease
  - 7 women and 2 men.
- Four lungs showed active granulomatous disease, with nonfibrotic nodular granulomas in the interstitium;
- Five were predominantly fibrotic, of which 3 had areas of honeycombing (cysts lined by respiratory epithelium with surrounding scar).
  - Patients in the fibrotic phase were significantly older ( $P=0.016$ ).

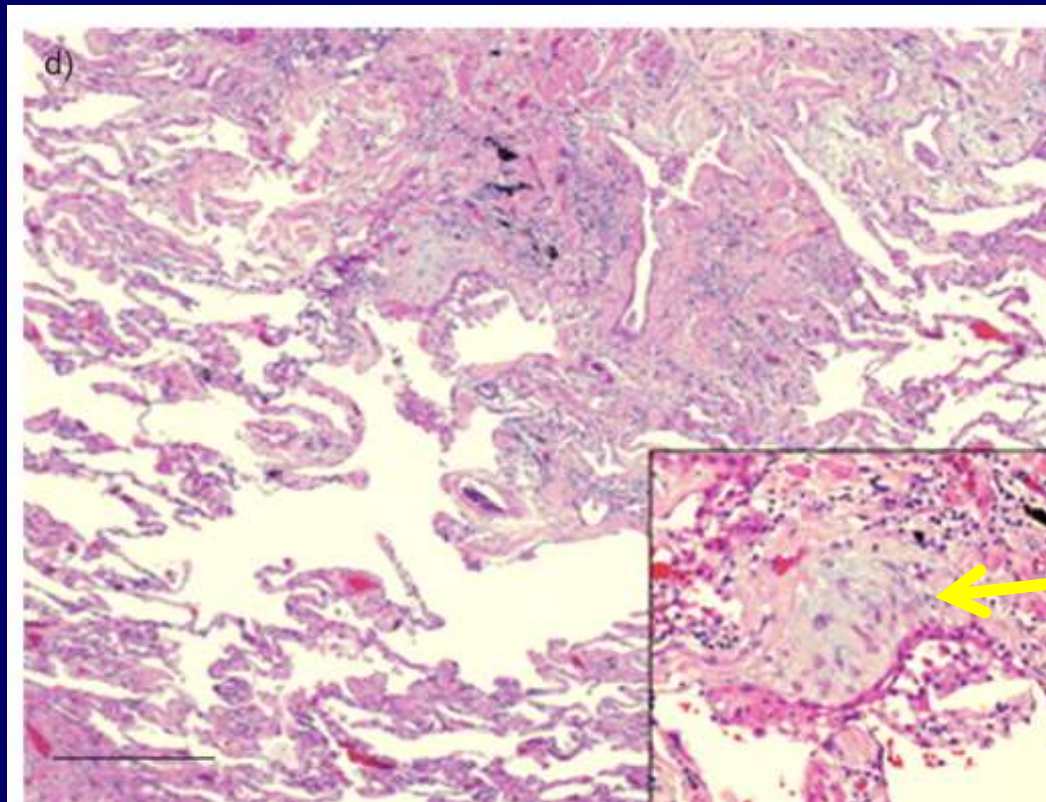
# Pathology of fibrotic sarcoidosis

- Granulomas were present in a lymphatic distribution (along bronchi, the lobular septa, and the pleura)
- Granulomas were not identified in 2 lungs in the fibrotic phase.
- In contrast to the honeycombing of UIP, the honeycombing was predominantly central, with prominent bronchiectasis.
- These end-stage sarcoid lungs were characterized by a fibrotic and active granulomatous pattern, both of which are very distinct from that seen in UIP.

# End stage pulmonary sarcoidosis: Features of explanted lung of 7 pts

Radiographic findings	Interstitial fibrosis	Other findings
Upper lobe bullous emphysema with hilar adenopathy	Mild	None
Fibronodular changes, focal emphysematous blebs with hilar and mediastinal adenopathy	Moderate	None
BHL with fibronodular disease	Severe	None
Hilar adenopathy with hilar retraction	Severe	Severe IP with occasional fibroblastic foci
Upper lobe honeycombing with mediastinal adenopathy and sparing of lung bases	Mild	Severe IP with superimposed DAD
Upper lobe disease with mediastinal and hilar adenopathy	Severe	Honeycomb with UIP pattern
Upper lobe disease with ground-glass opacities in the left lower lobe	Severe	Honeycomb with UIP pattern

# End stage sarcoidosis with usual interstitial pneumonitis pattern



Fibroblastic  
foci

# IPF versus Sarcoidosis Pulmonary Fibrosis

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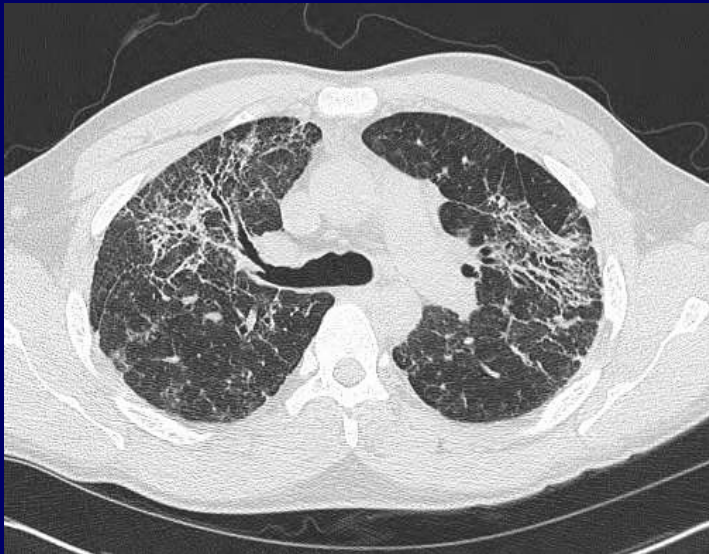
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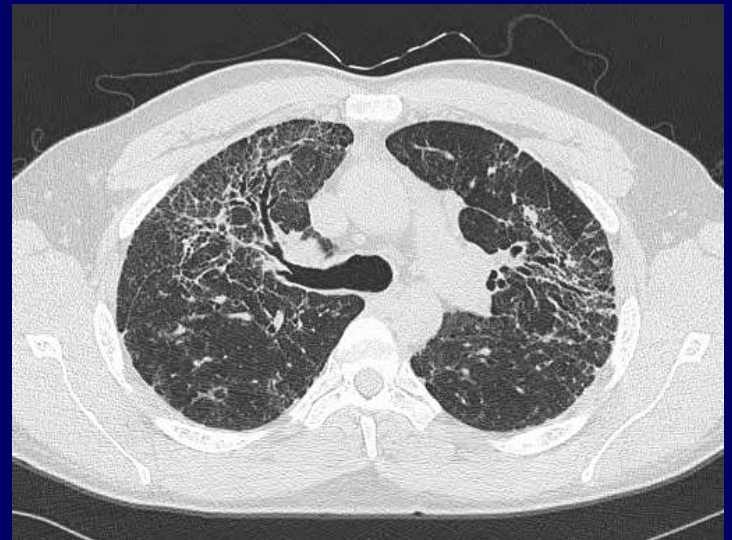


# Treat the Inflammation

## Three months of Infliximab

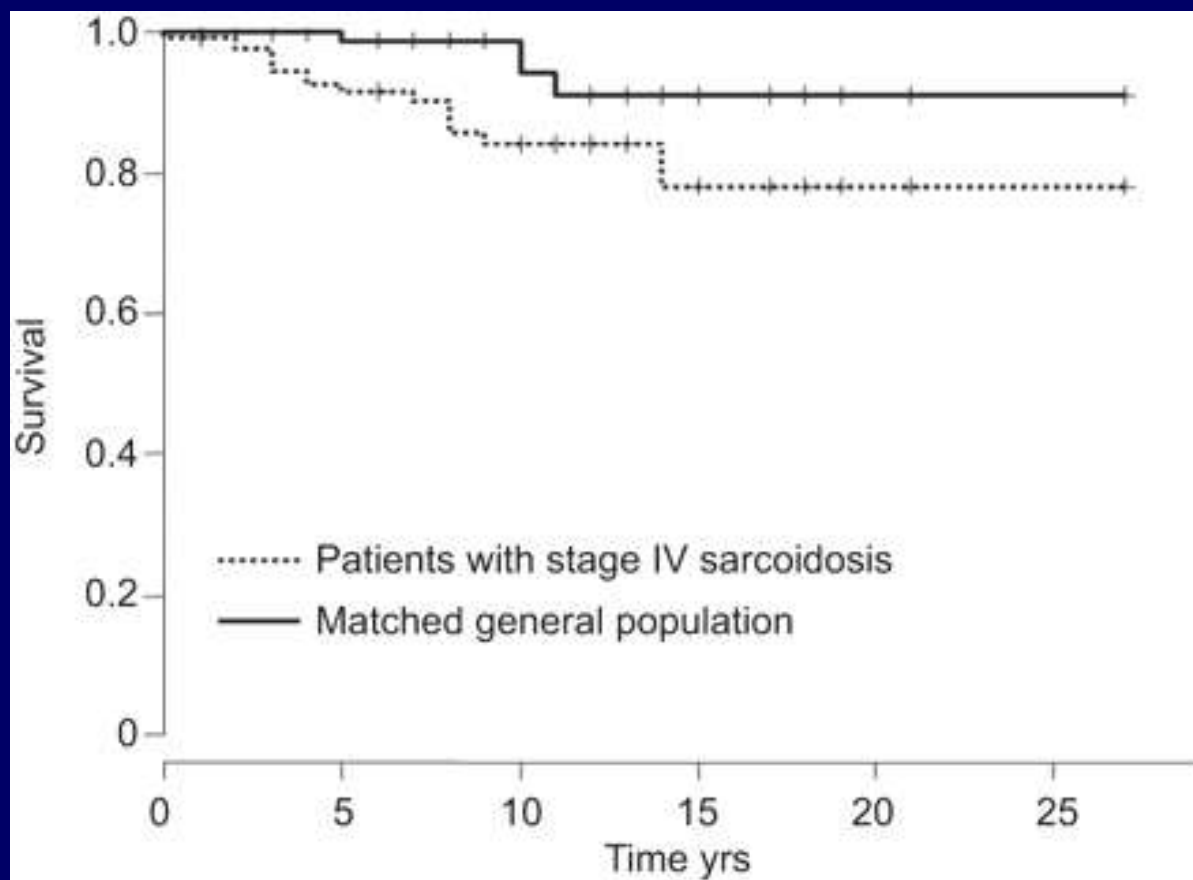


PRE



POST

# Survival of Stage 4 sarcoidosis



Nardi A, et al. Eur Respir J 2011; 38(6):1368-1373.



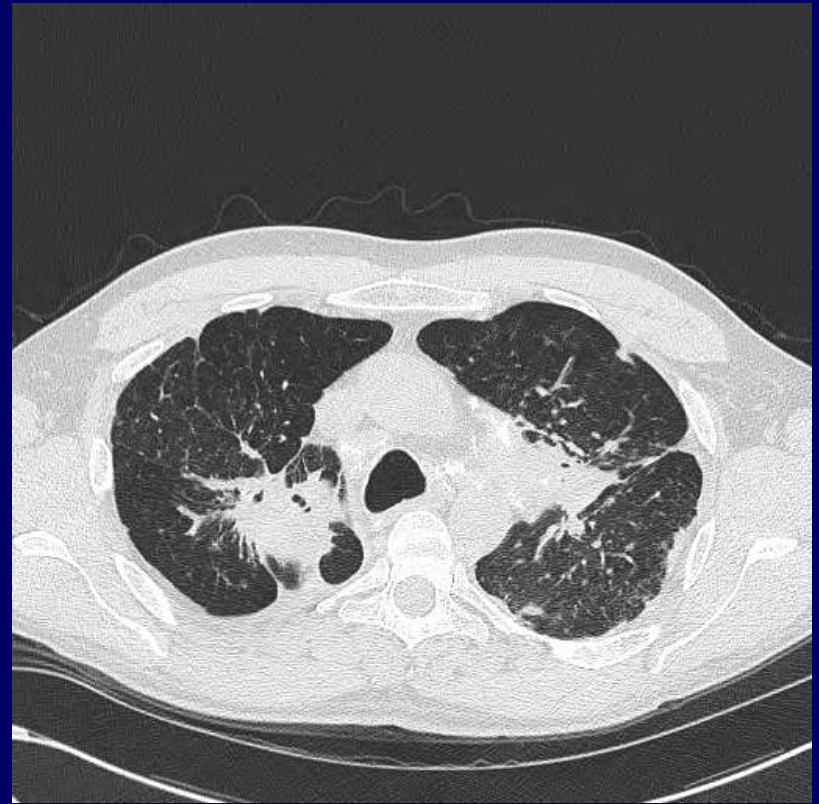
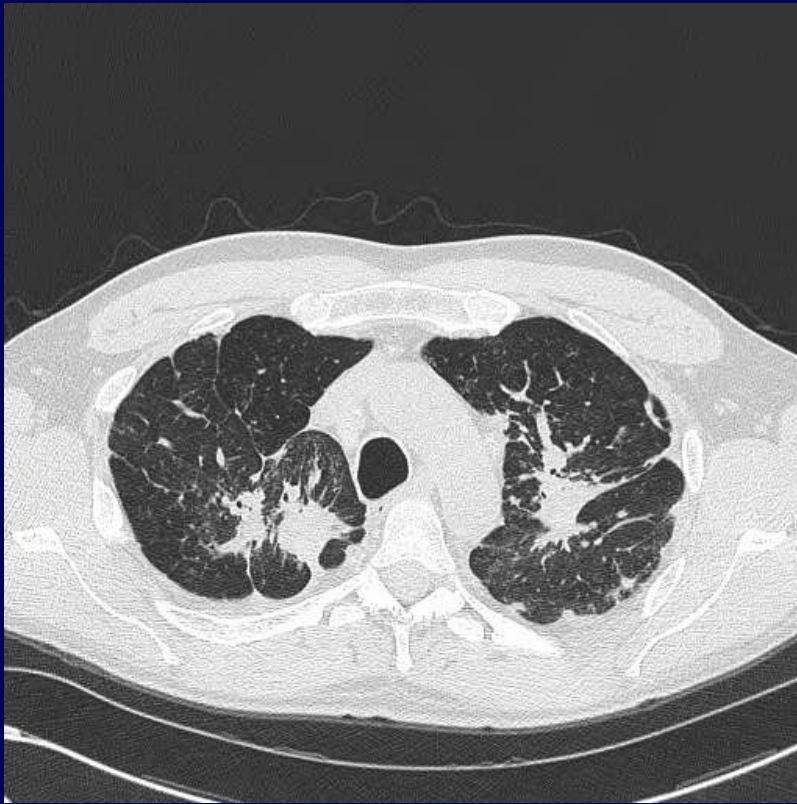
# Treatment of Stage 4 sarcoidosis

- 95 (67.4%) patients had their sarcoidosis therapy significantly intensified after inclusion.
  - Corticosteroids
    - Initiation or reintroduction in 39 cases
    - Increase dosage in 19 cases
  - Other drugs
    - Methotrexate in 19 cases
    - Hydroxychloroquine in 11 cases
    - Azathioprine in 5 cases
    - Thalidomide in 1 case
    - Mycophenolate in 1 case

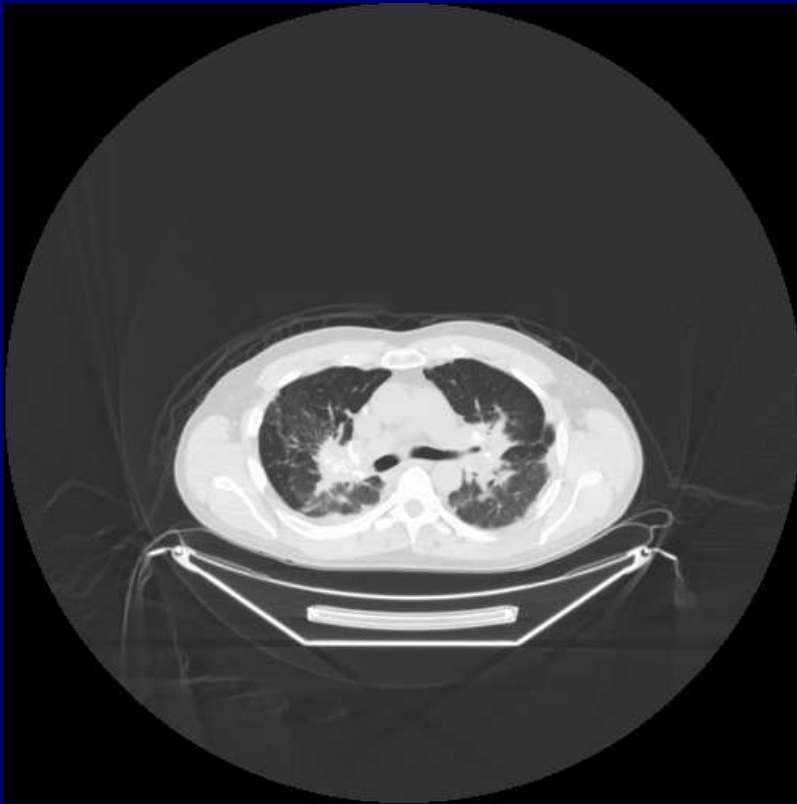
# Treatment of Stage 4 sarcoidosis

- Evaluation of PFTs within 3–12 months of therapy was available in 57 patients. HRCT (51 patients), SACE (52 patients) and BAL (25 patients) were performed before the initiation of therapy.
- The recorded outcomes were:
  - Improvement (36.8%),
  - Stability (50.9%)
  - Worsening (12.3%).

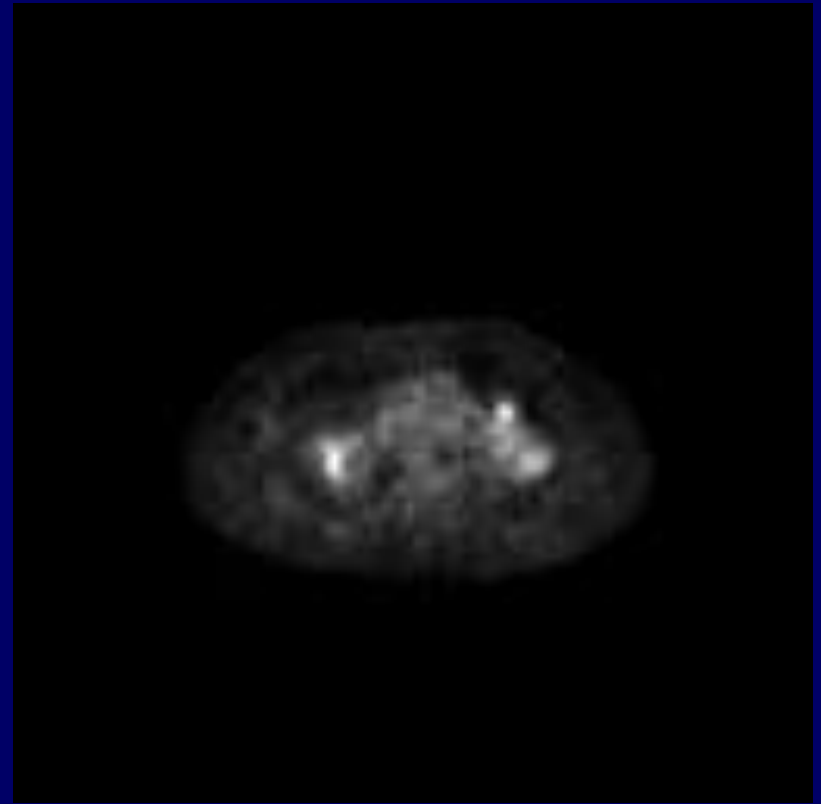
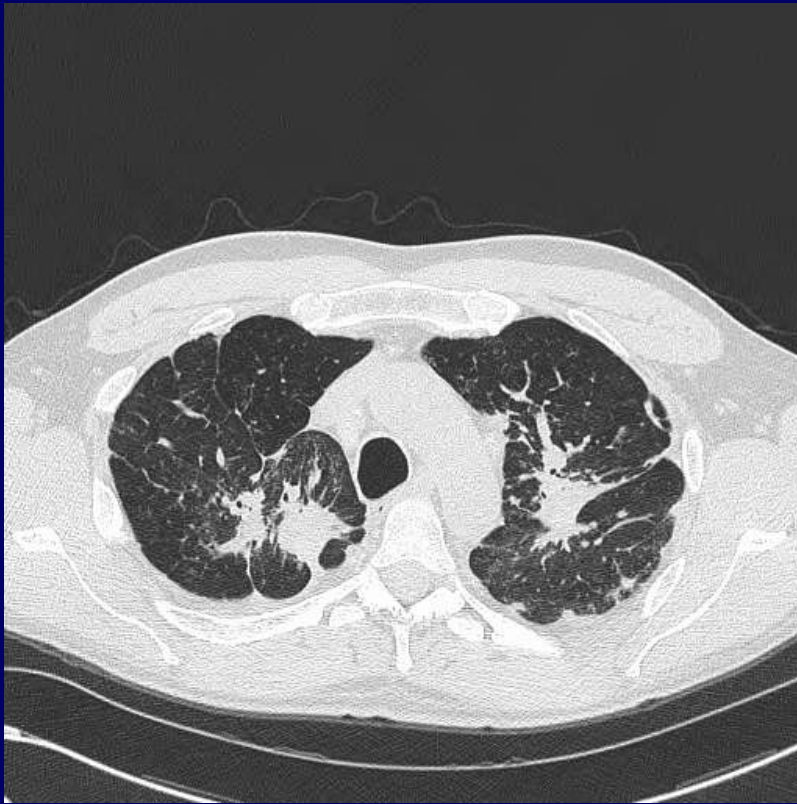
# Fibrotic Sarcoidosis: HRCT



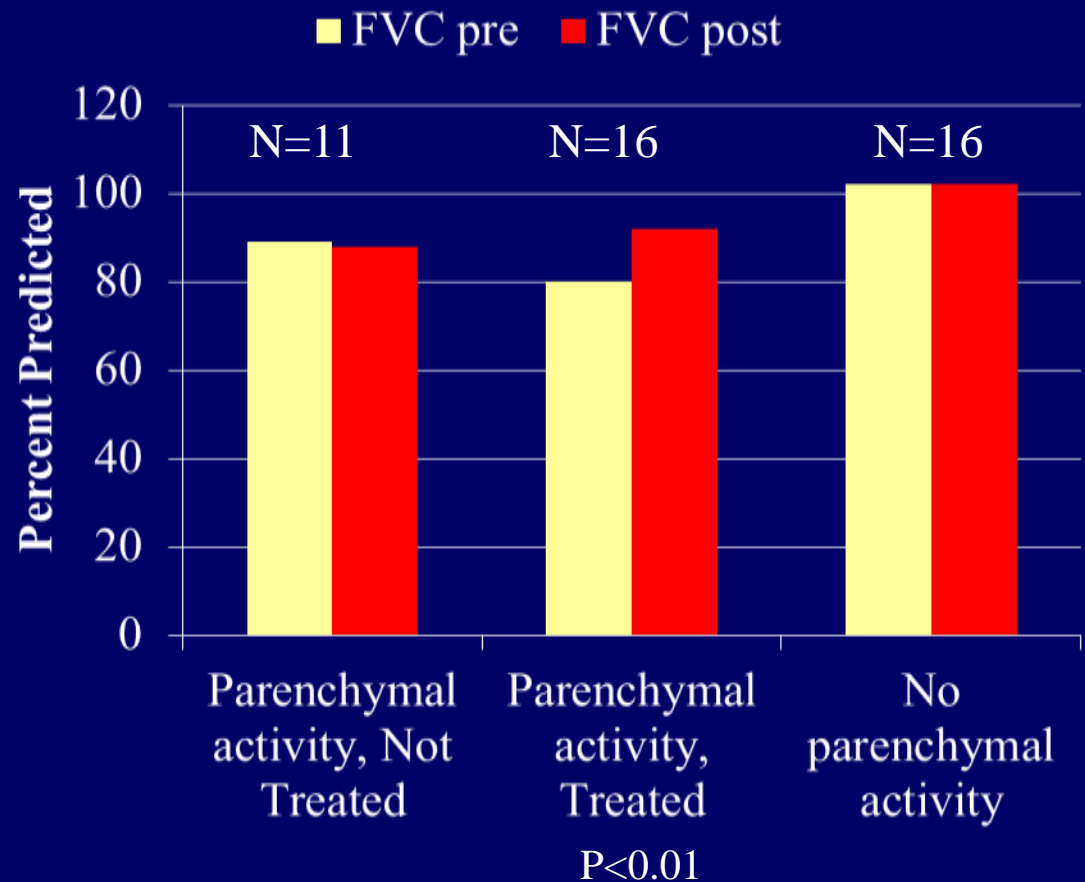
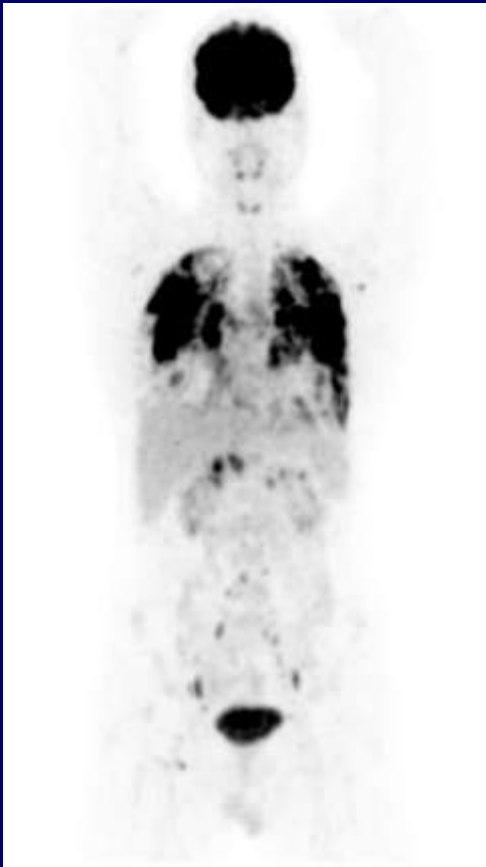
# Fibrotic Sarcoidosis with positive parenchymal PET activity



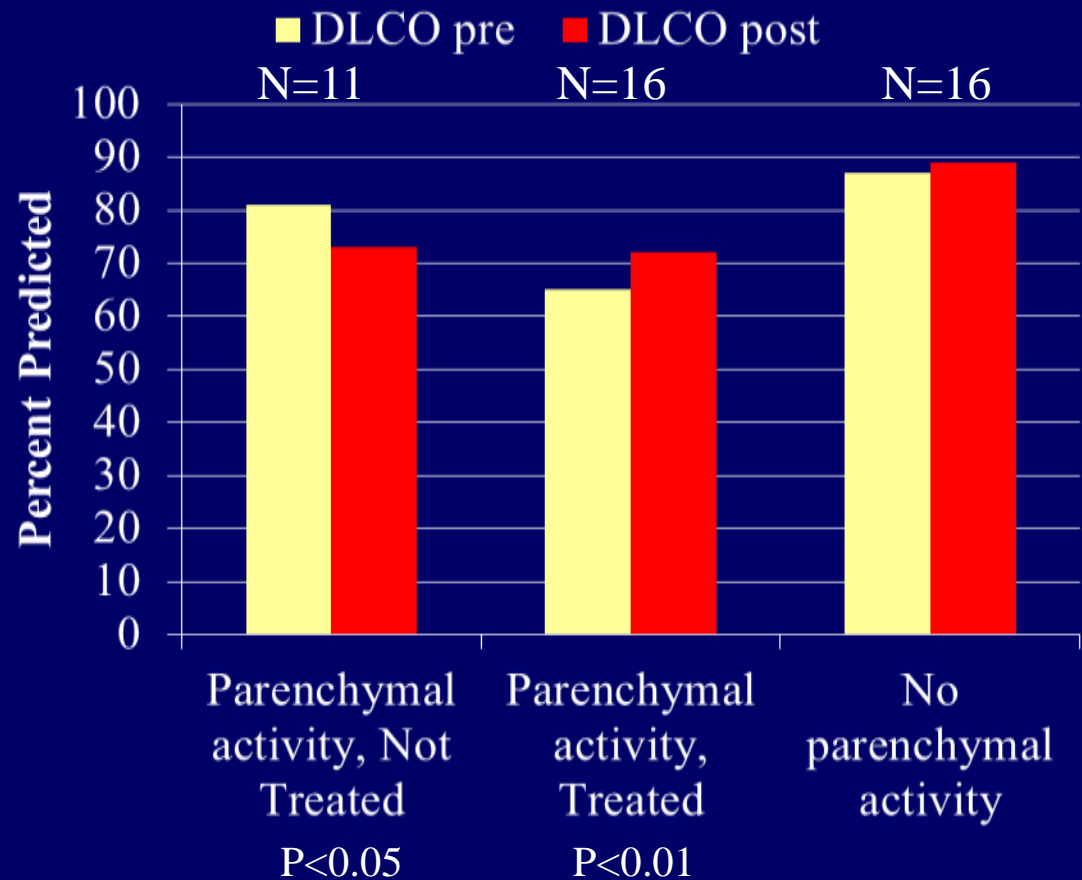
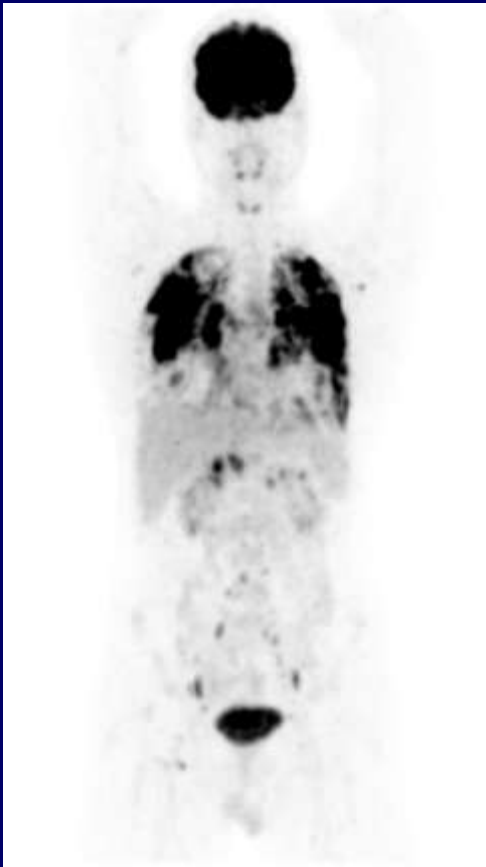
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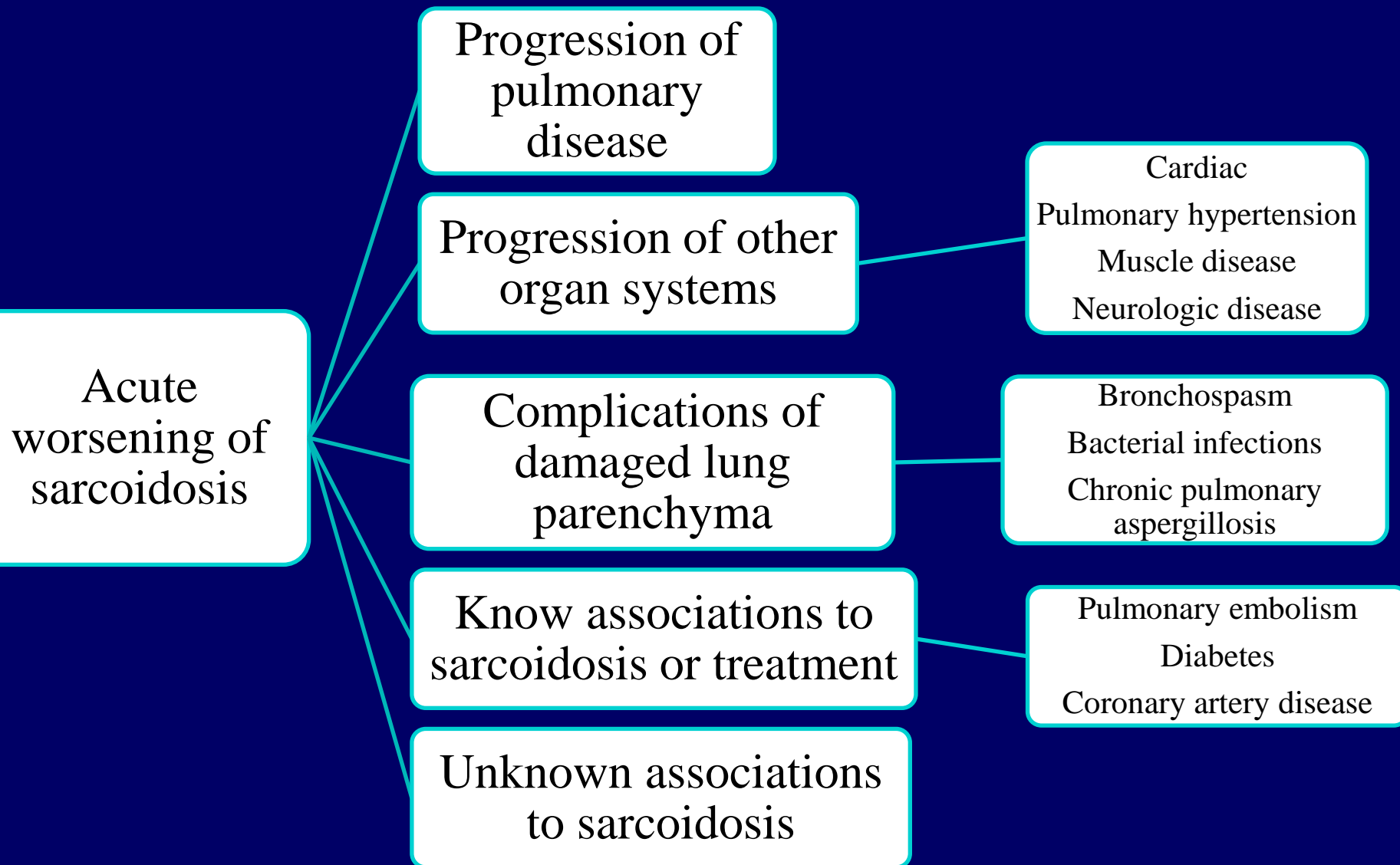


# PET scan predicting response to therapy in sarcoidosis: FVC change

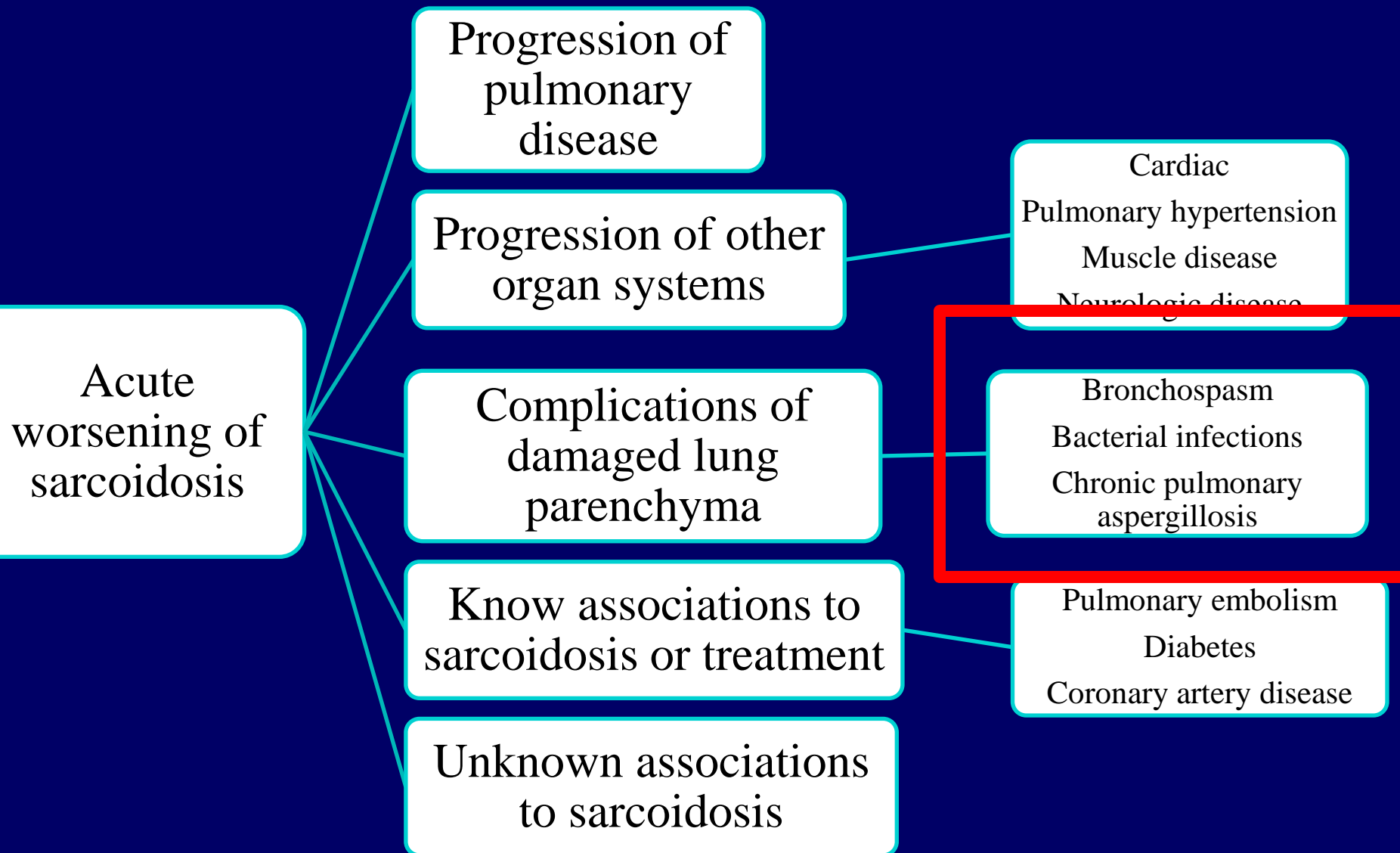


# PET scan predicting response to therapy in sarcoidosis: DLCO change

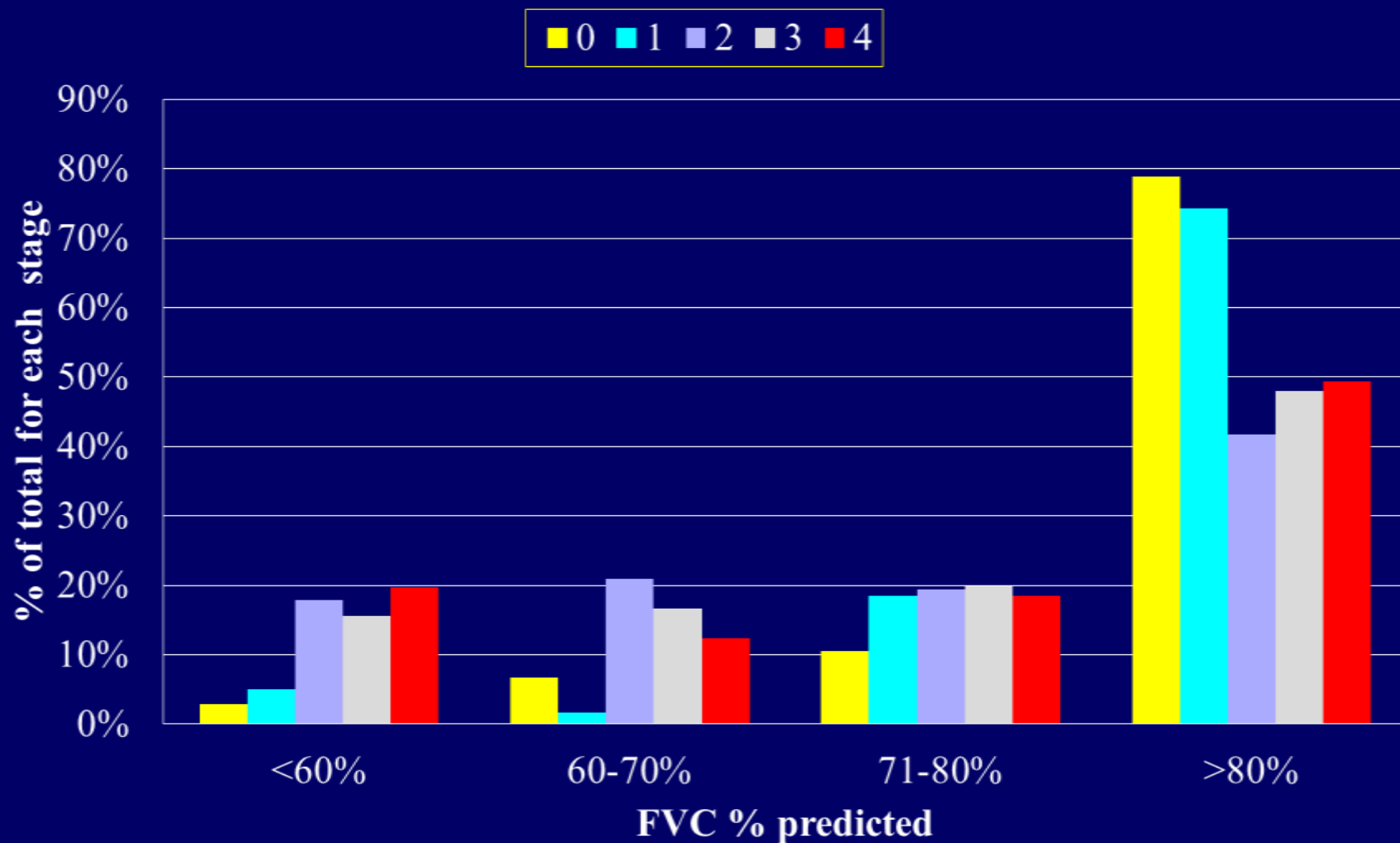






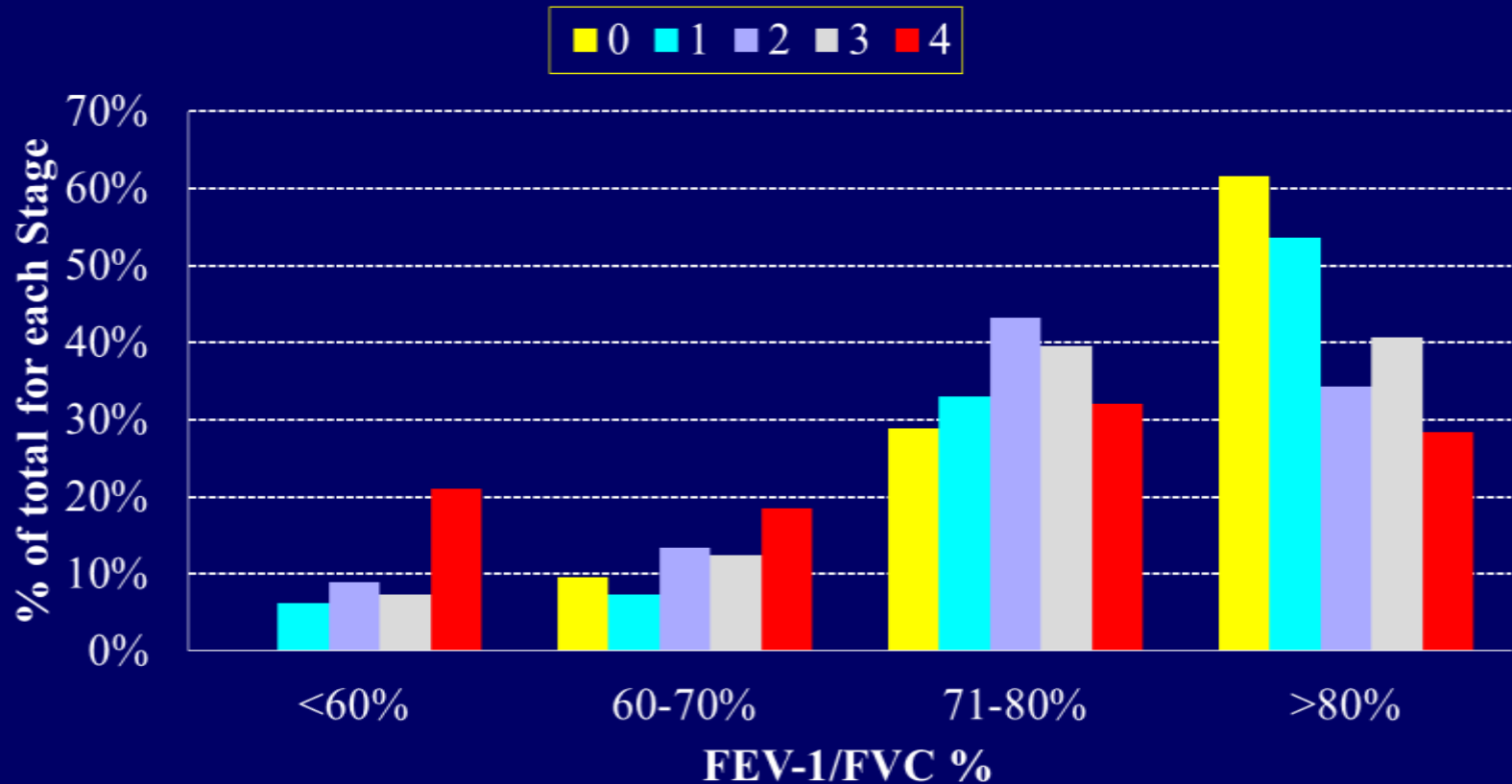


# FVC % predicted versus Chest X-ray stage



Significant difference between groups Chi square=72.9,  $P < 0.0001$

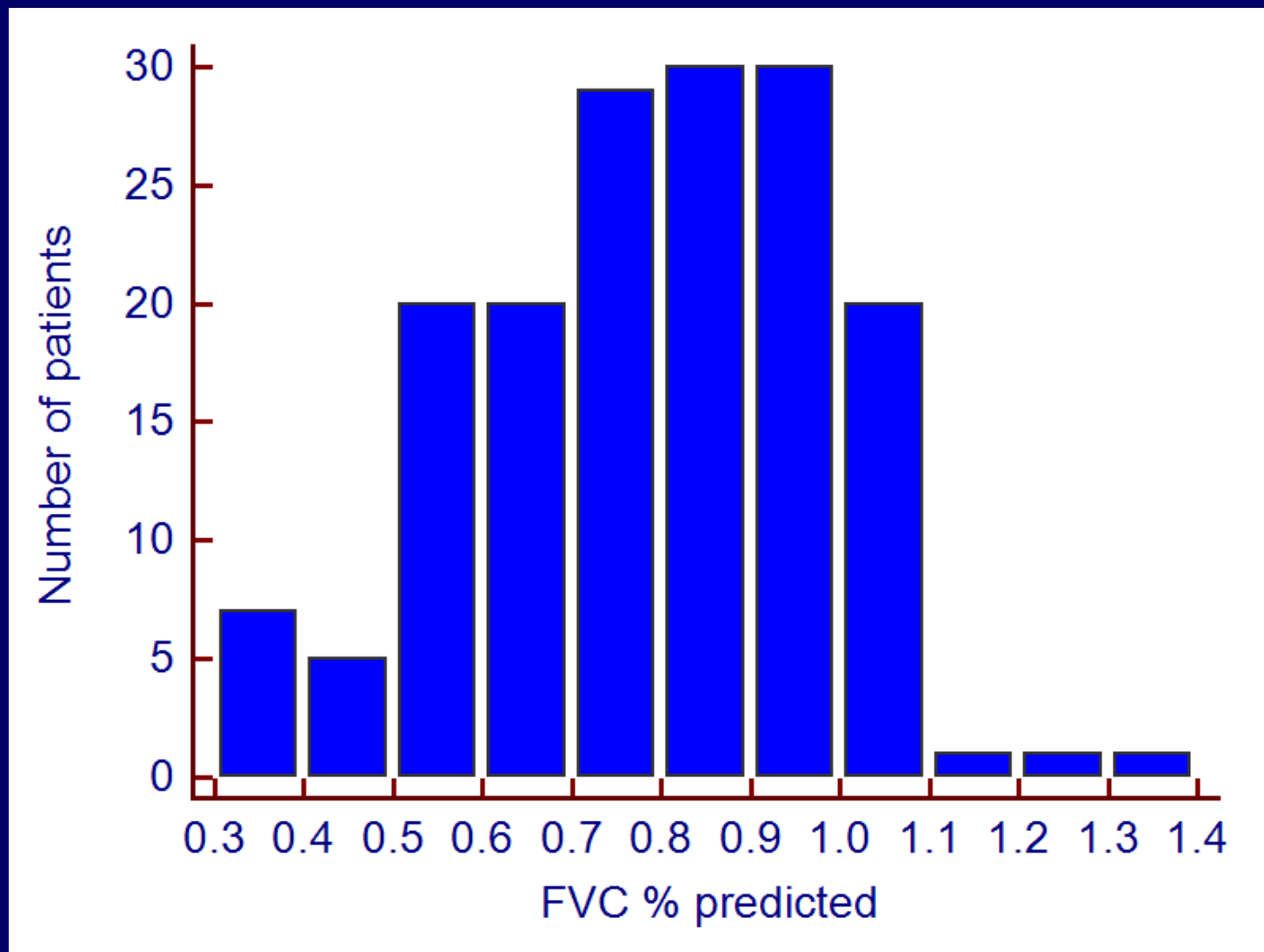
# FEV-1/FVC versus Chest X-ray stage



Significant difference between groups Chi square=53.3,  $P < 0.0001$

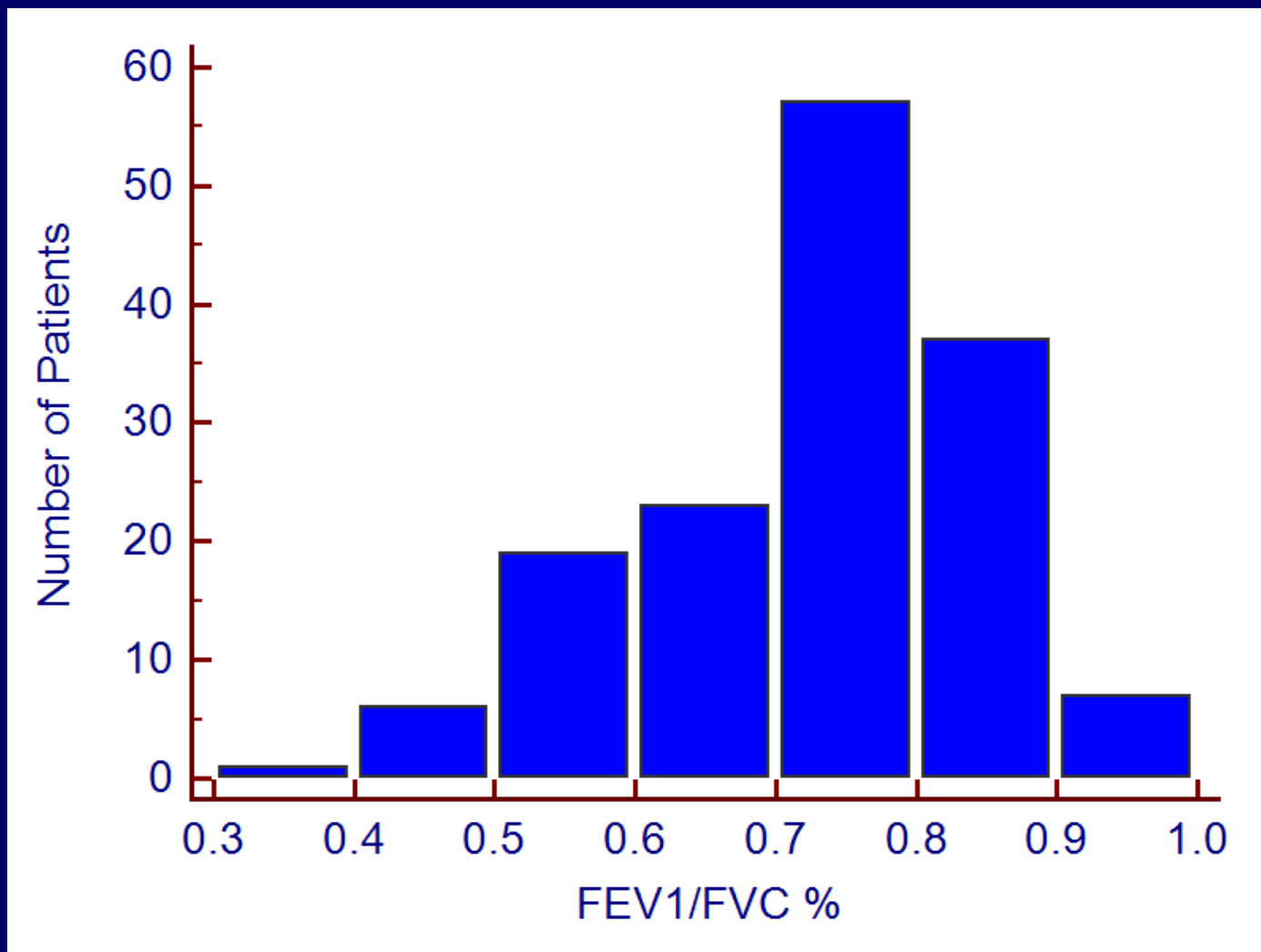
# Stage 4 sarcoidosis at University of Cincinnati

N=164



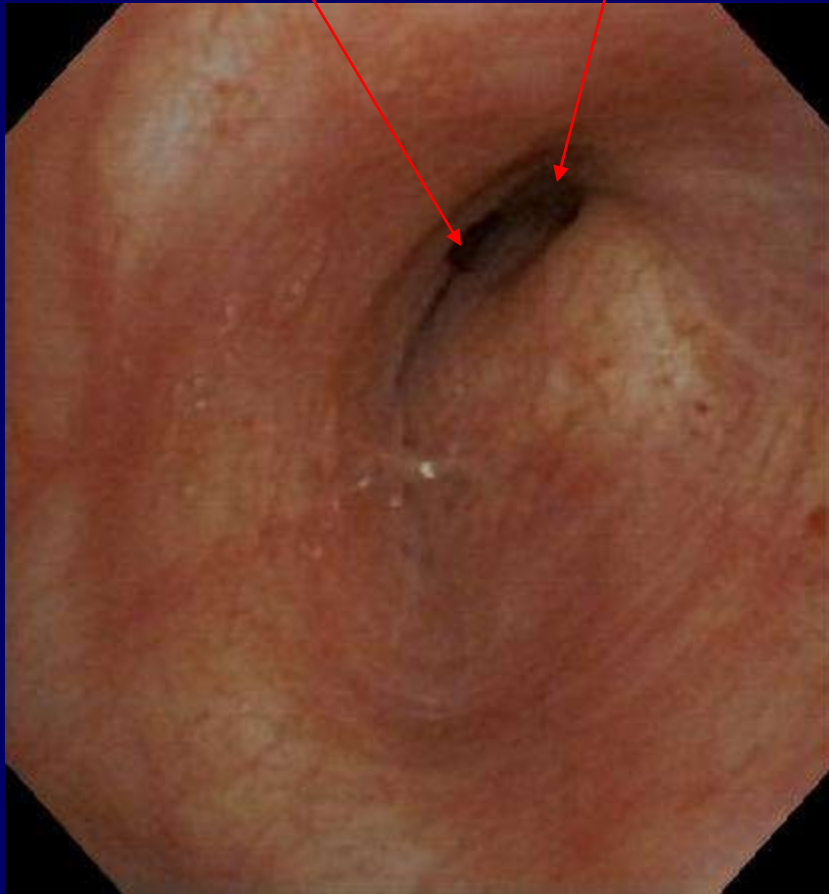
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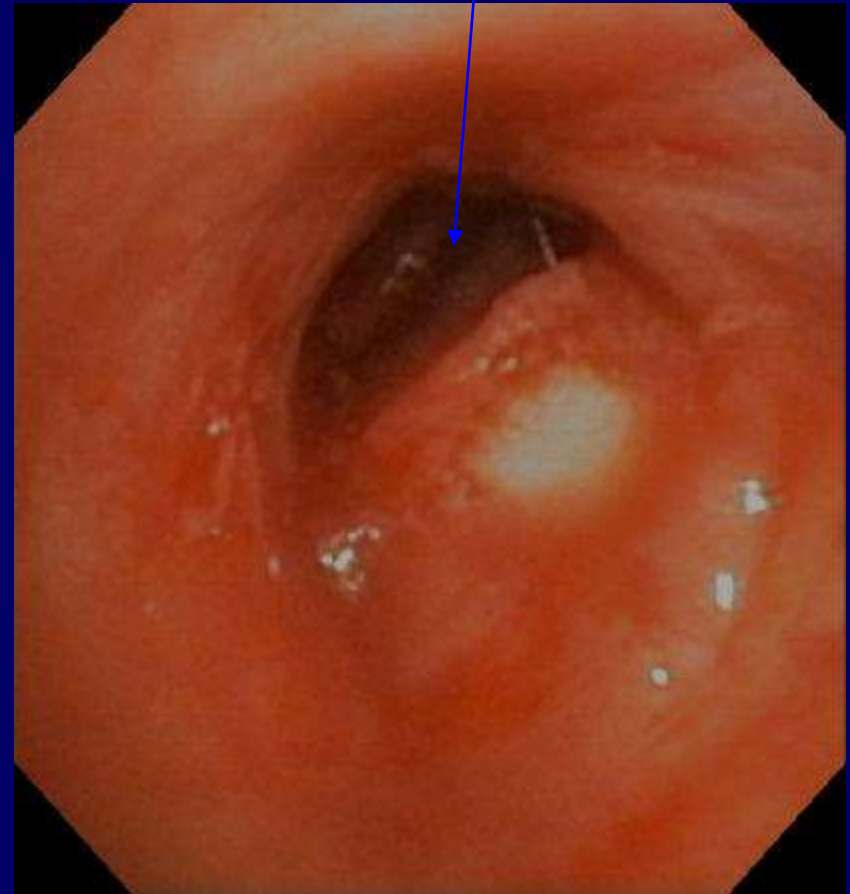


Lateral segment occluded

Medial segment



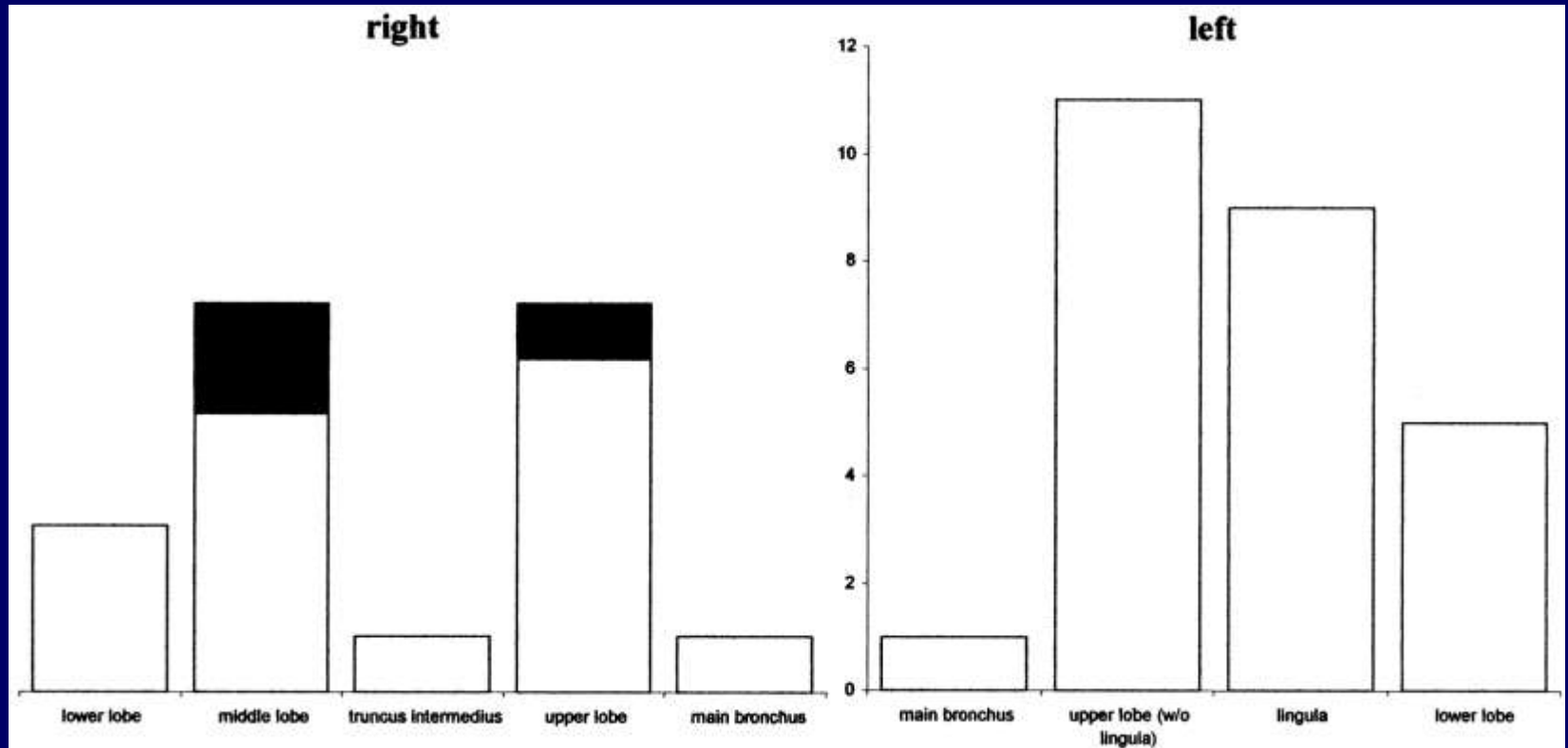
Lateral segment patent



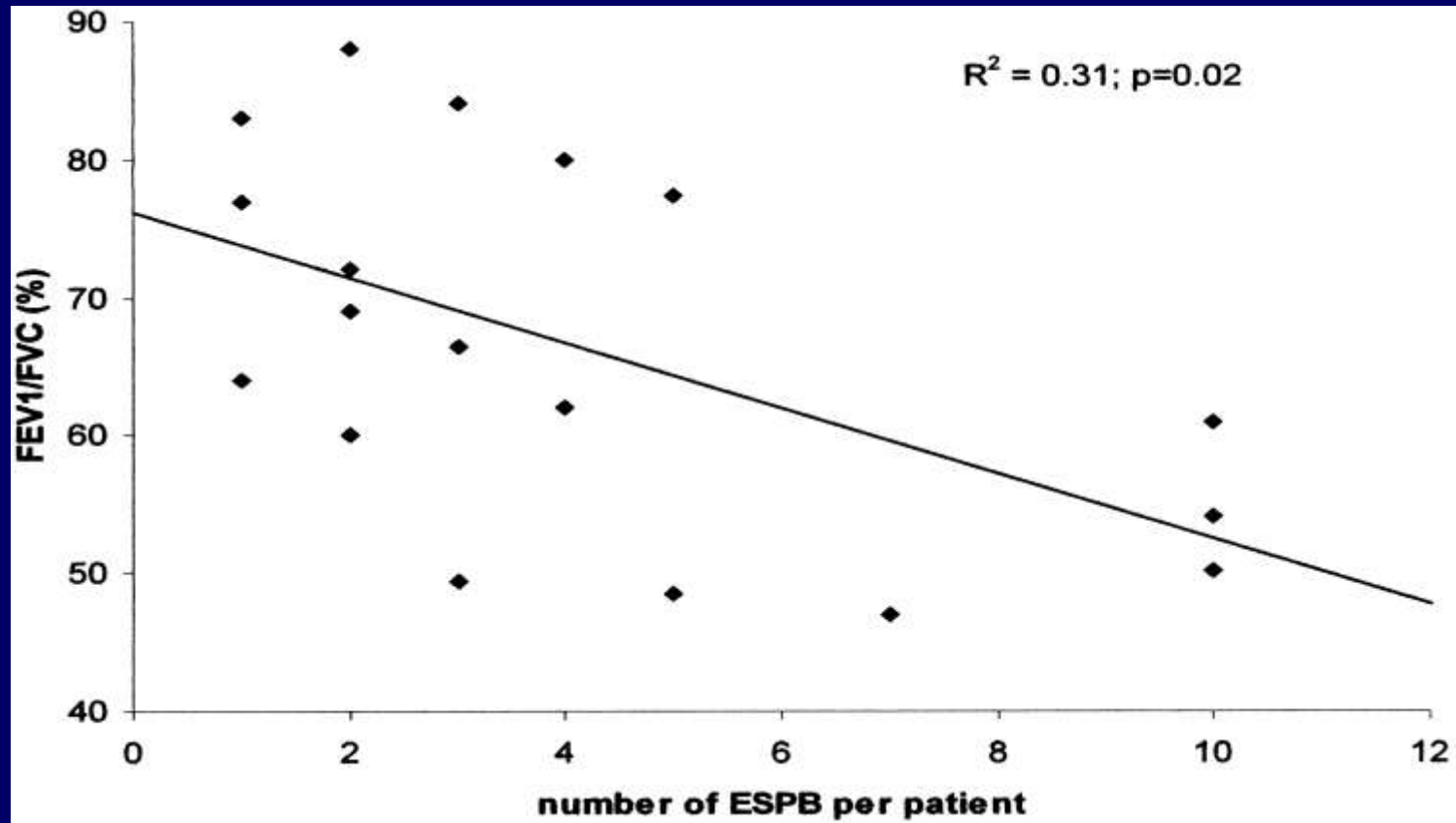
RML view from its orifice

RML view post dilation

# Bronchoscopic localization of the Endoluminal Stenotic Proximal Bronchi (ESPB) in 15 patients presenting a single (■) or multiple stenosis (□).



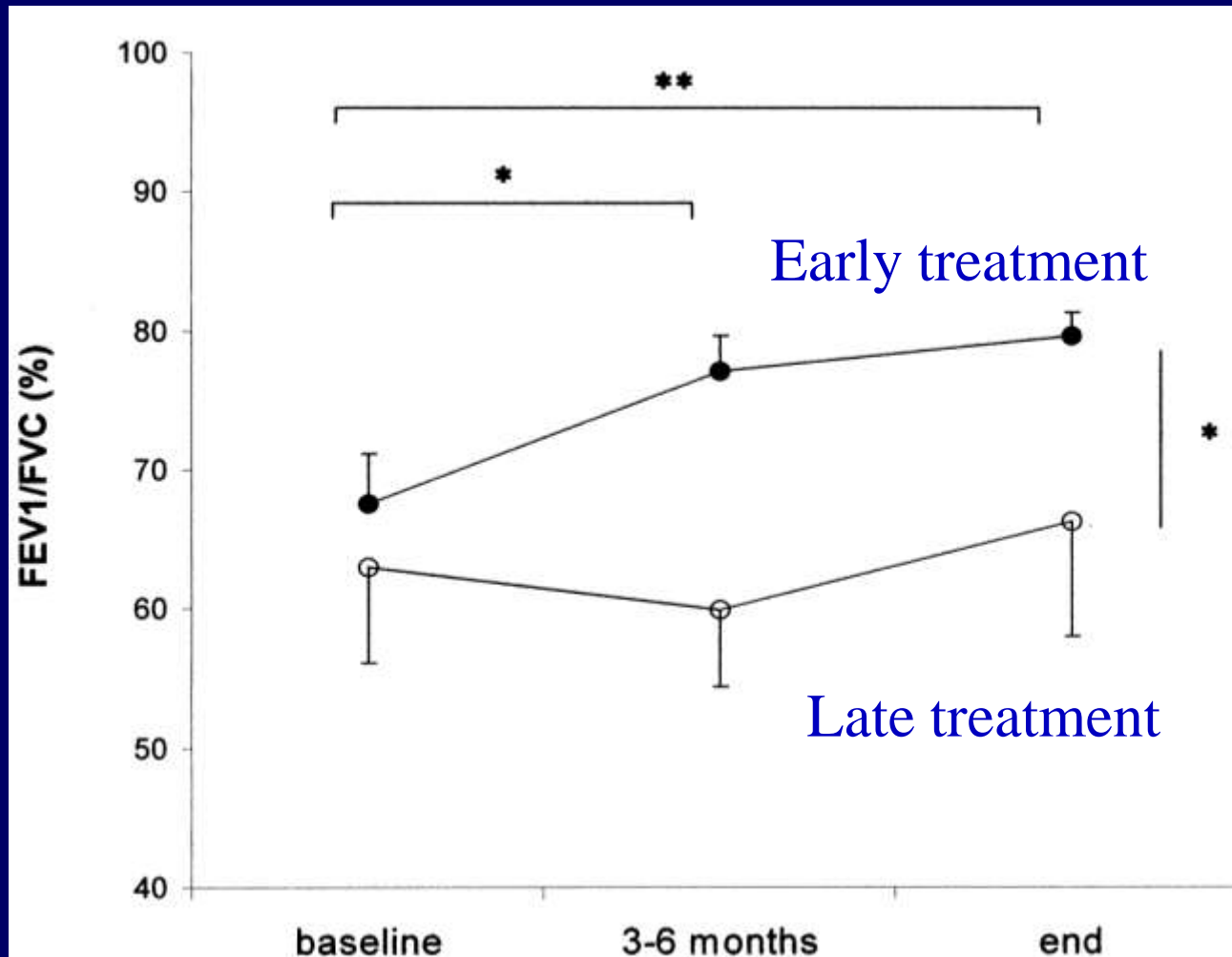
# Relationship between FEV1/FVC and the number of Endoluminal Stenotic Proximal Bronchi (ESPB) at baseline.



Chambellan A et al. Chest 2005;127:472-481



# Outcome of FEV-1/FVC with Corticosteroid Therapy



Chambellan A et al. Chest 2005;127:472-481

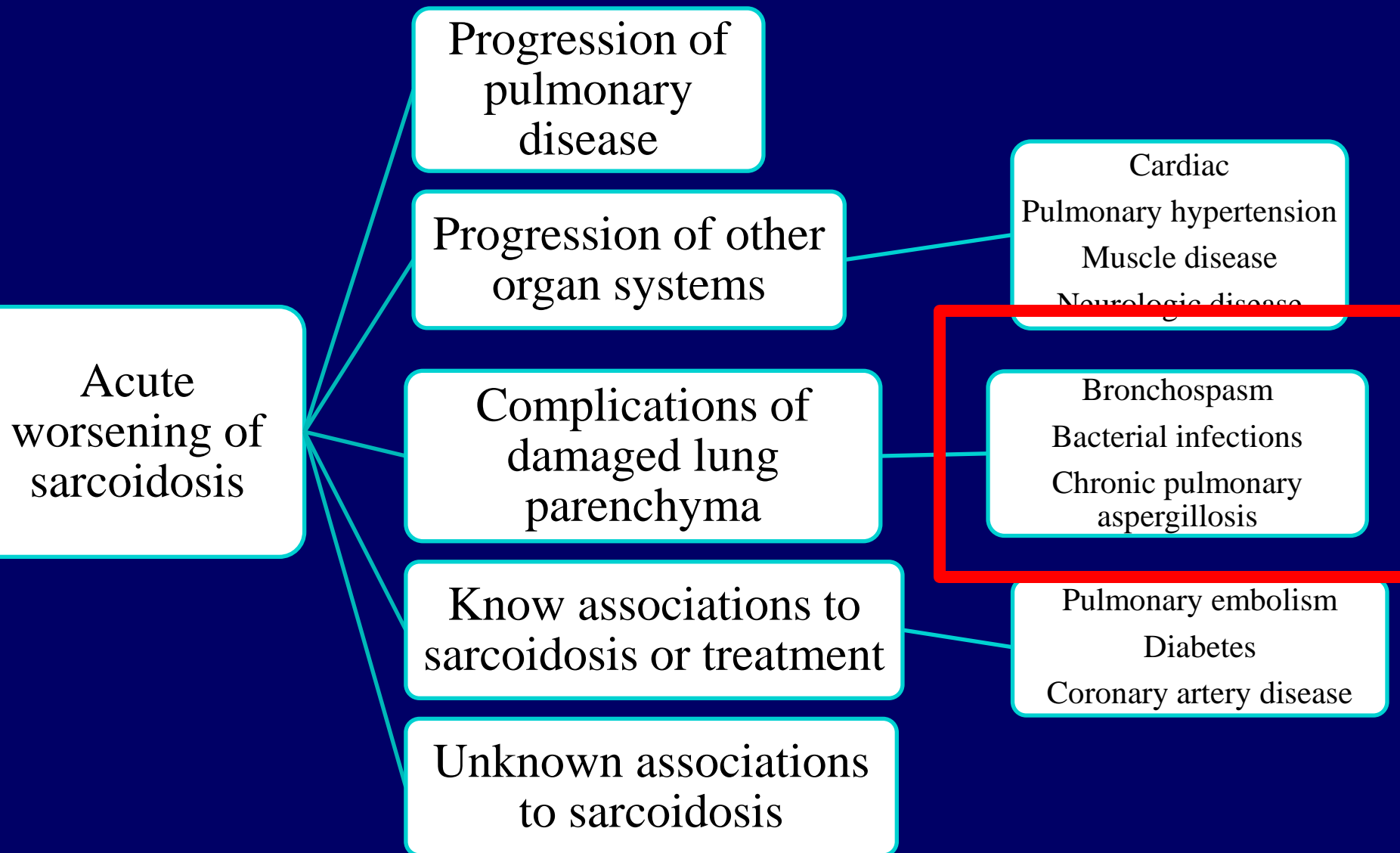
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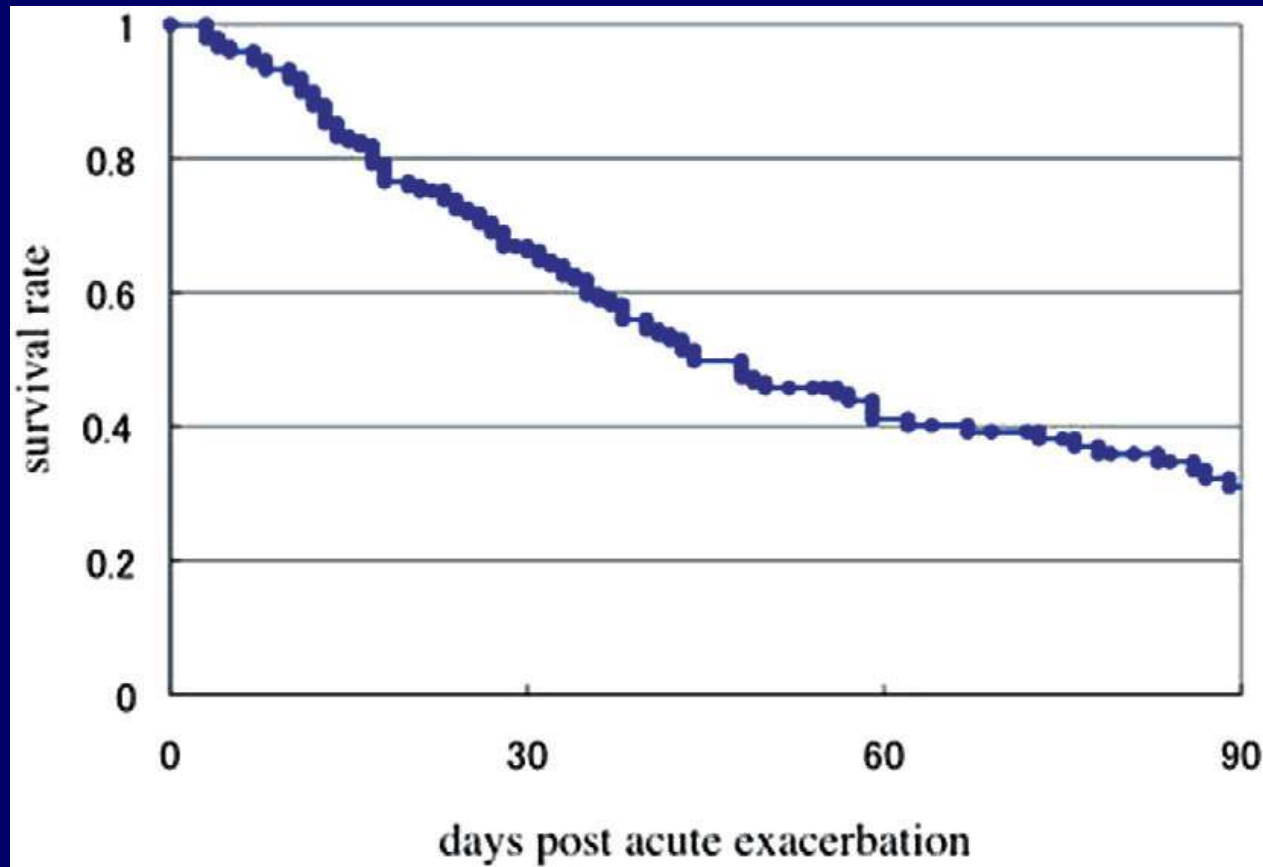
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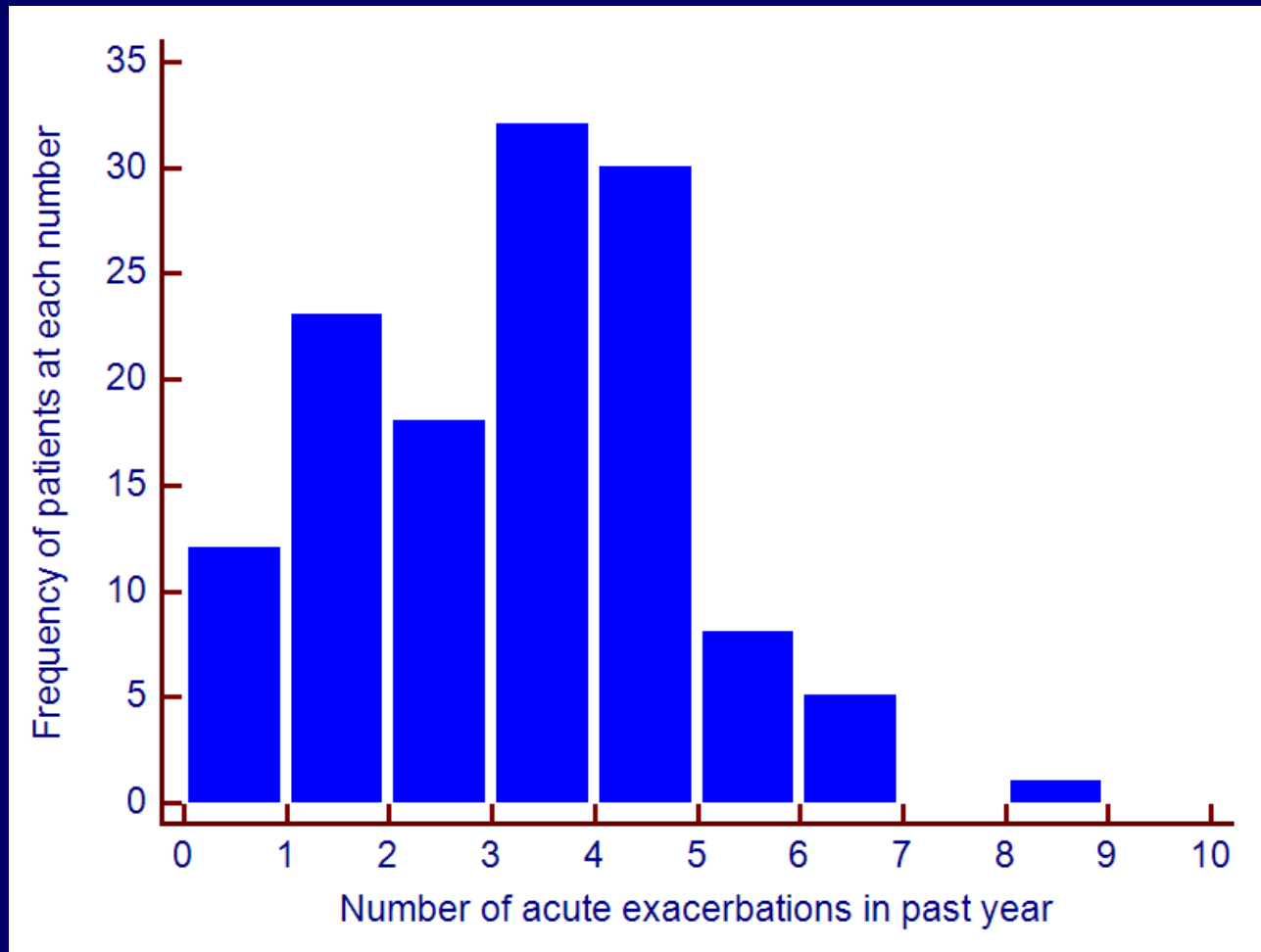
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# Acute exacerbations in IPF are associated with significant short term mortality

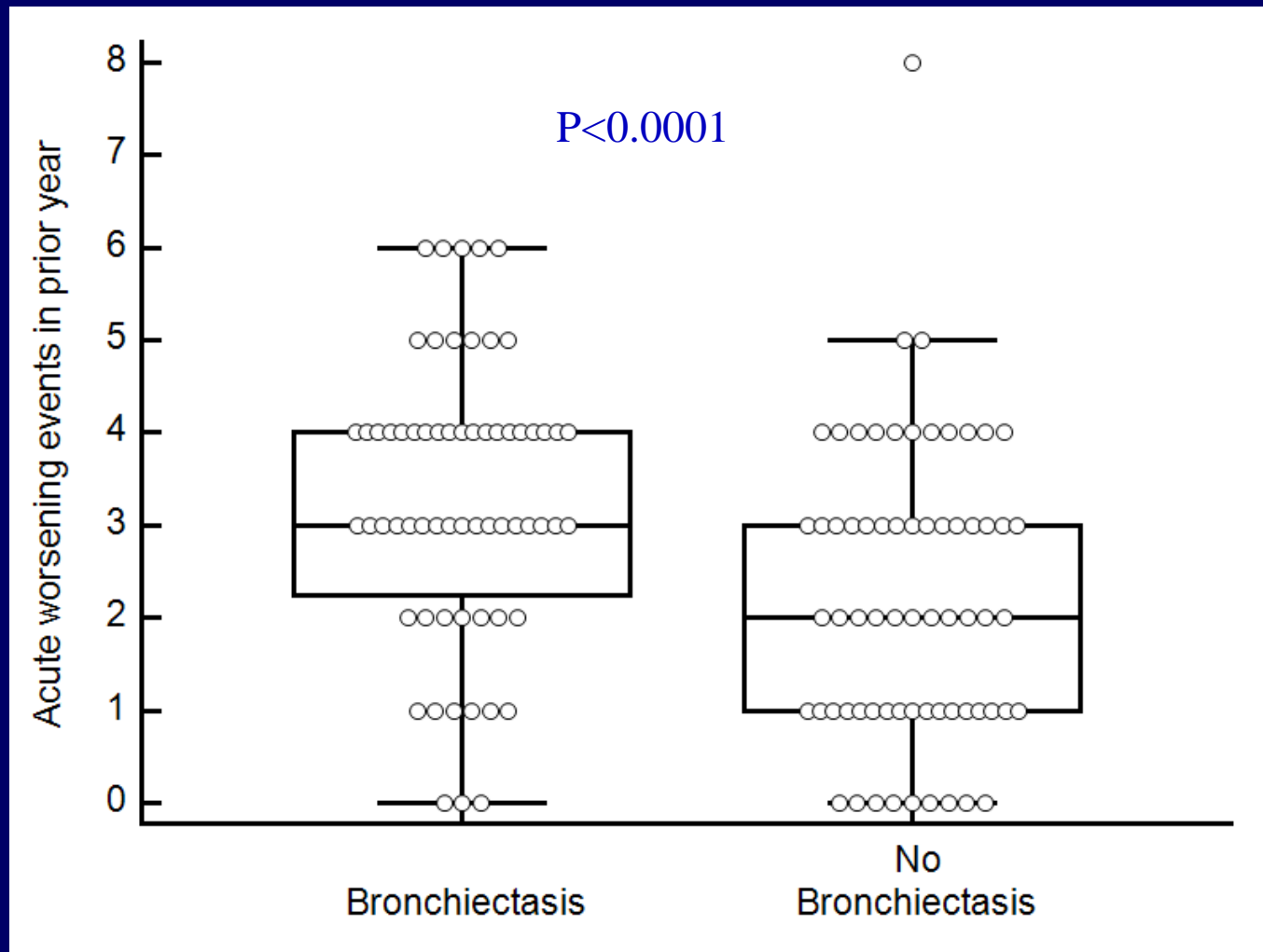


# Number of acute worsening events in past year reported in 129 Stage 4 sarcoidosis patients University of Cincinnati



Baughman RP, Lower EE. Respir Med 2013; 107(12):2009-2013.

# Number of events were higher in Bronchiectasis patients (n=63) versus those without Bronchiectasis (n=66)



# IPF versus Sarcoidosis Pulmonary Fibrosis

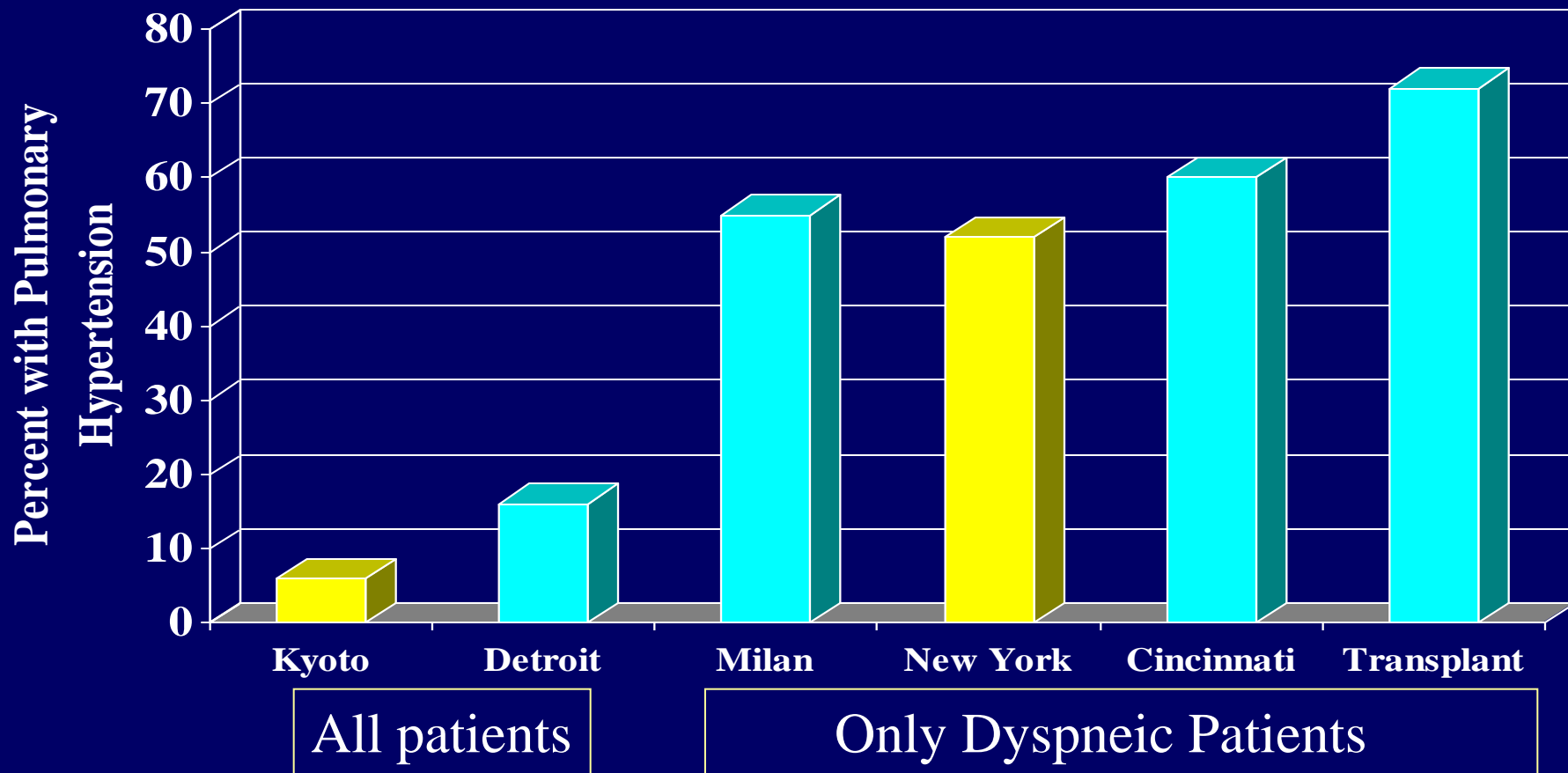
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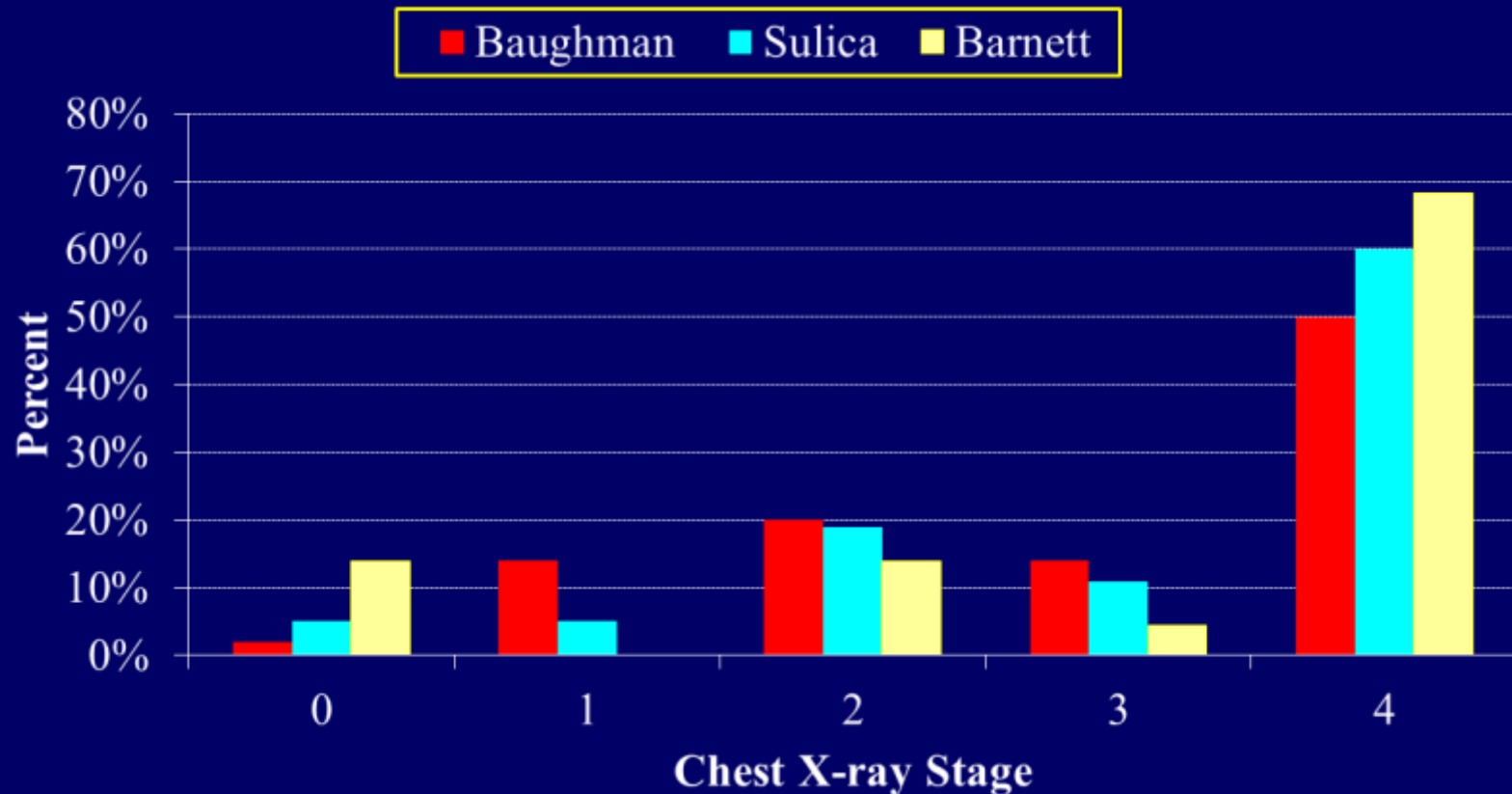
# Pulmonary Hypertension in Sarcoidosis



Blue bars indicate those centers who confirmed pulmonary hypertension by right heart cath



# Pulmonary Hypertension associated with Stage 4 disease



Baughman RP, et al. *Chest* 2010;138:1078-1085.

Sulica R, et al. *Chest* 2005;128:1483-1489.

Barnett CF, et al. *Chest* 2009;135:1455-1461.

# Bosentan for sarcoidosis associated pulmonary arterial hypertension (BoSAPAH): a double-blind, placebo controlled study

Robert P. Baughman, University Cincinnati

Dan A Culver, Cleveland Clinic Foundation

Francis Cordova, Temple University

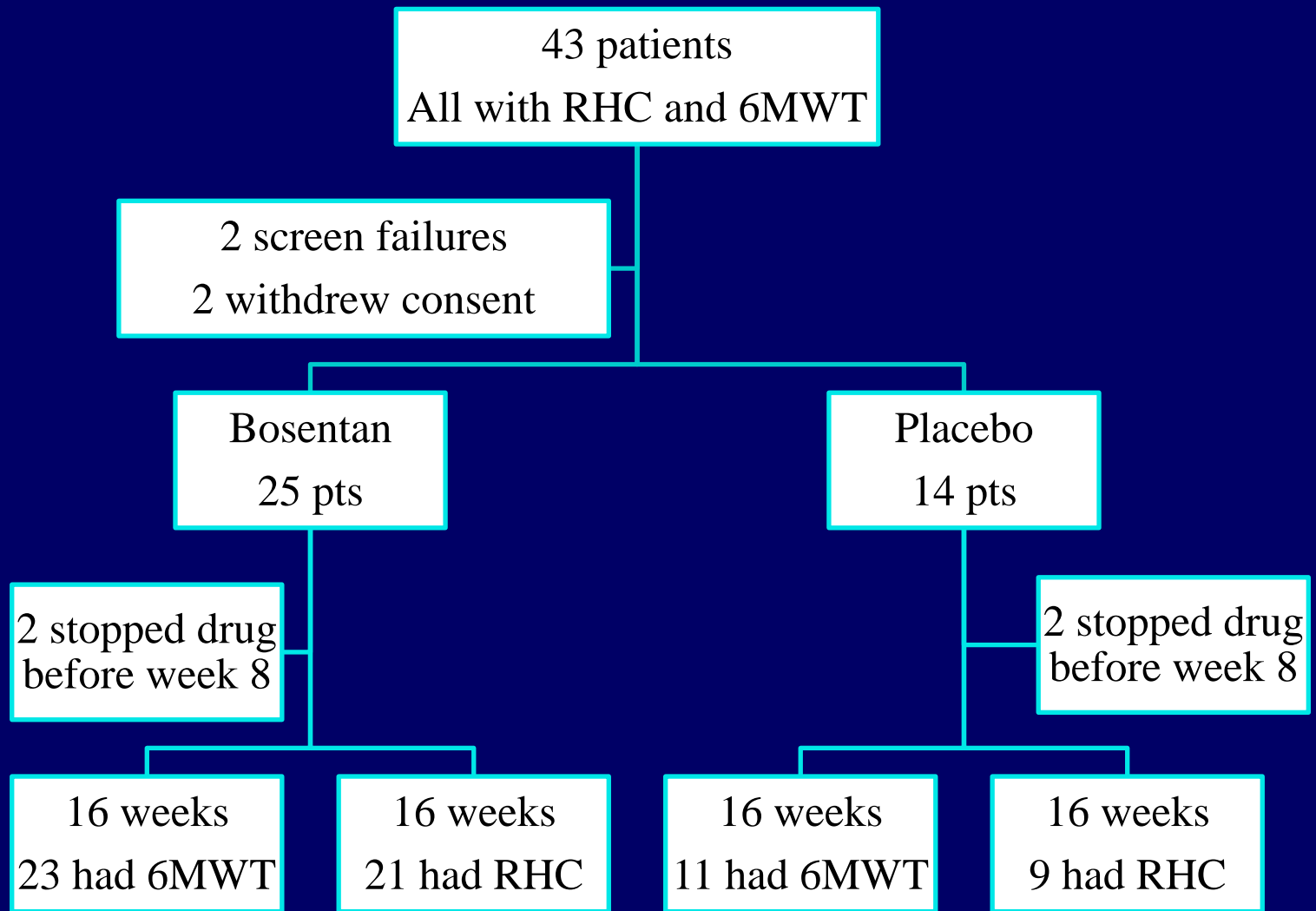
Maria Padilla, Mount Sinai New York

Kevin Gibson, University of Pittsburgh

Elyse E Lower, University of Cincinnati

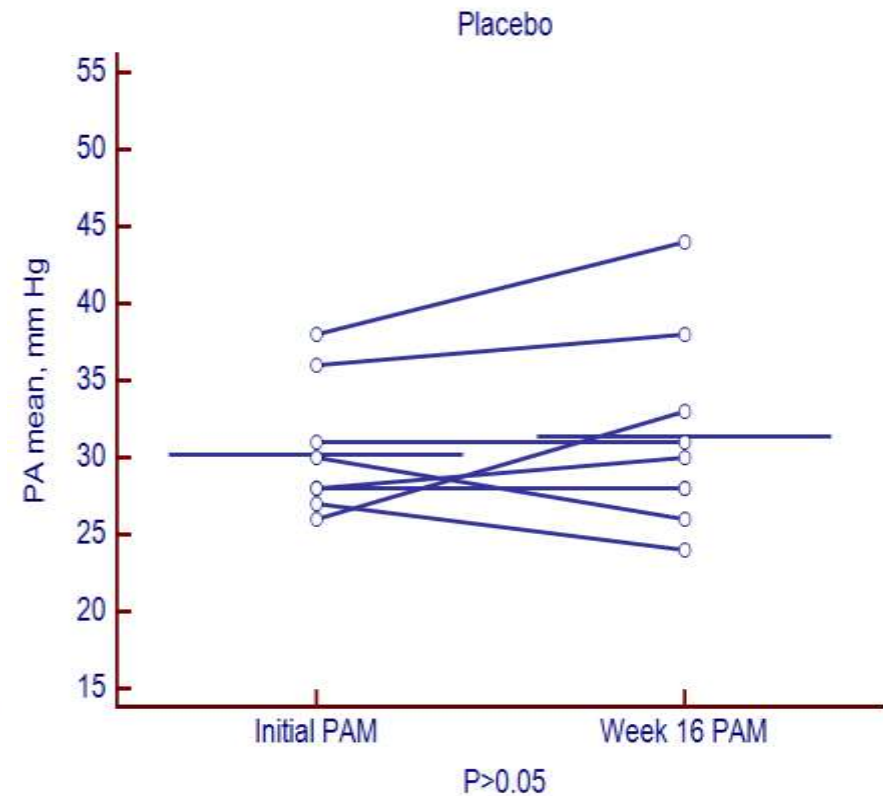
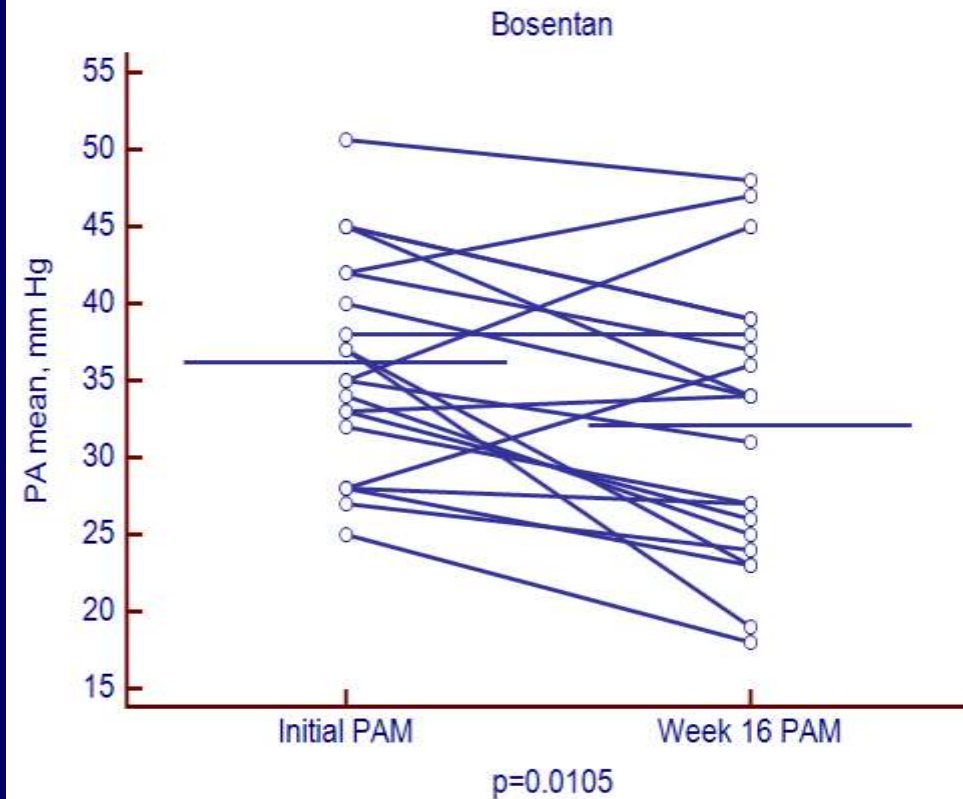
Peter J Engel, Ohio Heart and Cardiovascular

# Study Outcome at 16 weeks



RHC: right heart catheterization; 6MWT: 6 minute walk test

# PA Mean pressure before and after 16 weeks of therapy



# Conclusion

- Pulmonary fibrosis is a significant problem in pulmonary sarcoidosis
- Not all patients with pulmonary fibrosis are dyspneic
- For the dyspneic patient, there is significant mortality
- Treatment may helpful in the dyspneic patient

# Acknowledgements

- Dr. Elyse Lower
  - Co-director of ILD/Sarcoidosis Clinic
- Dr. Peter Engel
  - Co-Director of PH Clinic
- Research coordinators
  - Felicia Thompson
  - Joyce Zeigler
- Our patients



[www.wasog.com](http://www.wasog.com)

[www.sarcoidosis.it](http://www.sarcoidosis.it)