International Meeting on
PULMONARY RARE DISEASES
AND ORPHAN DRUGS

Sarcoidosis-associated pulmonary hypertension (SAPH)

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Conflicts of interest

I have the following real or perceived conflicts of interest that relate to this presentation:

Affiliation / Financial interest	Commercial company
Grants/research support:	Bayer, GSK, Janssen, Pfizer, MSD
Honoraria or consultation fees:	Acceleron, Bayer, Boerhinger, Chiesi, GSK, Janssen, MSD, Pfizer
Participation in a company sponsored bureau:	None
Stock shareholder:	None
Spouse / partner:	None
Other support / potential conflict of interest:	None

WASOG statement on sarcoidosis associated PH (SAPH)

EUROPEAN RESPIRATORY REVIEW
REVIEW
L. SAVALE ET AL.

WASOG statement on the diagnosis and management of sarcoidosis-associated pulmonary hypertension

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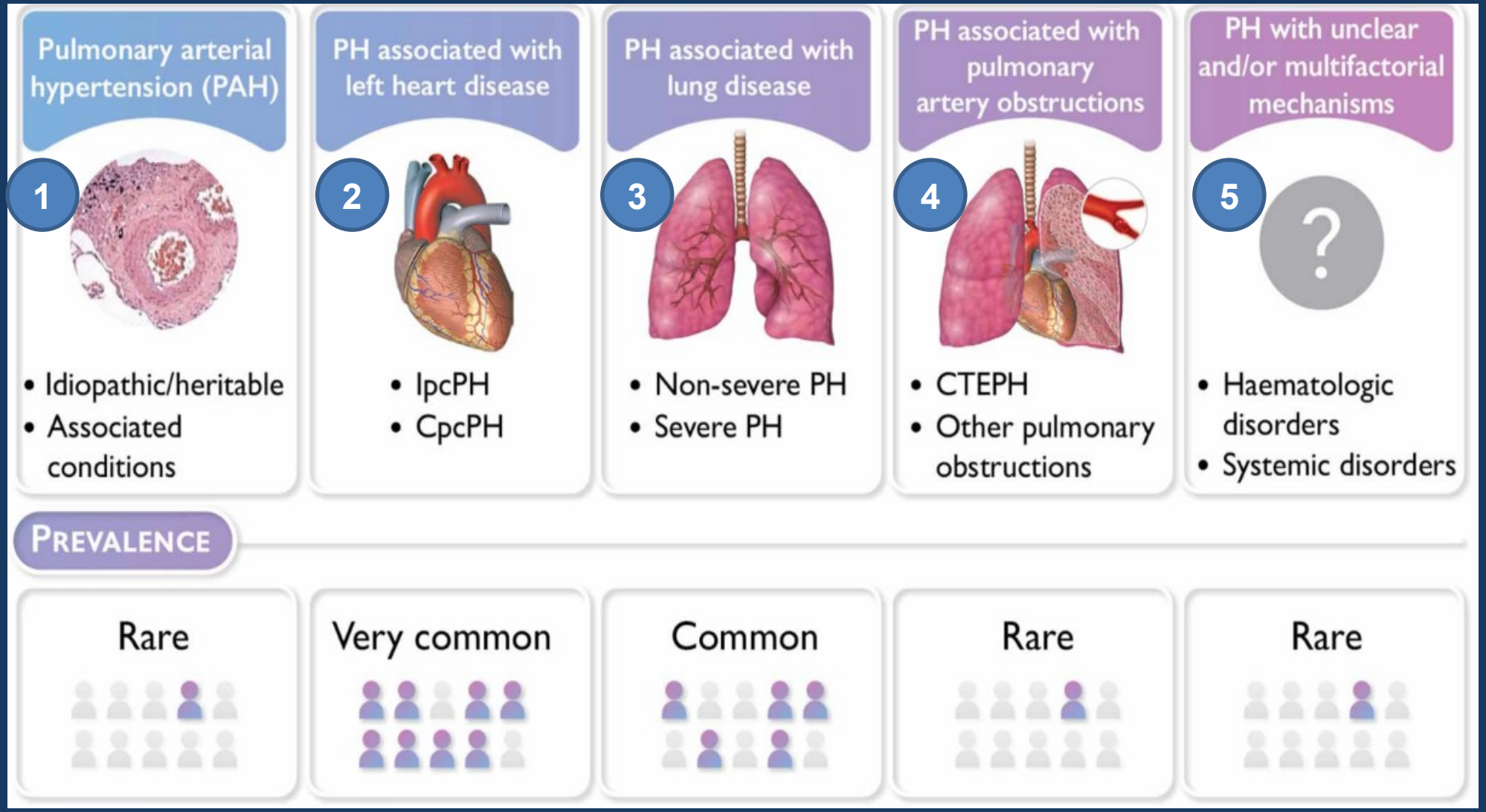
CLASSIFICATION – ESC/ERS Guidelines 2022

ESC/ERS GUIDELINES 2022



Classification – Group 5 PH

PH with unclear and/or multifactorial mechanisms

5

?

- Haematologic disorders
- Systemic disorders

PREVALENCE

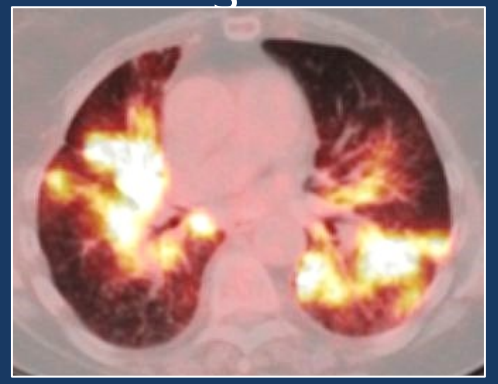
Rare

2022 ESC/ERS GUIDELINES

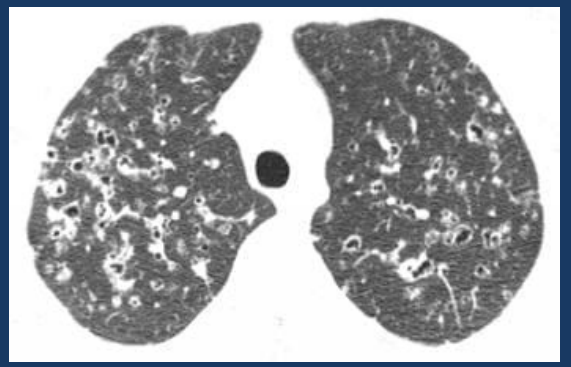
GROUP 5 PH with unclear and/or multifactorial mechanisms

- 5.1 Haematological disorders[d]
- 5.2 Systemic disorders[e]
- 5.3 Metabolic disorders[f]
- 5.4 Chronic renal failure with or without haemodialysis
- 5.5 Pulmonary tumour thrombotic microangiopathy
- 5.6 Fibrosing mediastinitis

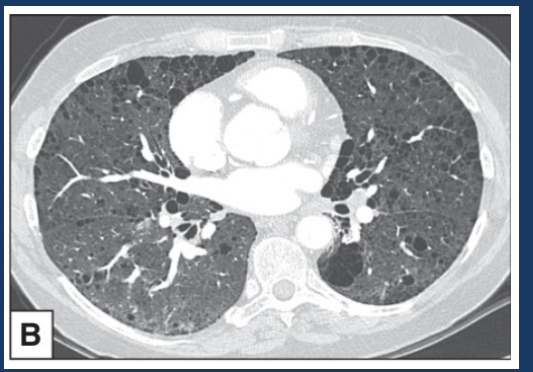
Sarcoidosis



Pulmonary Langerhans's cell histiocytosis

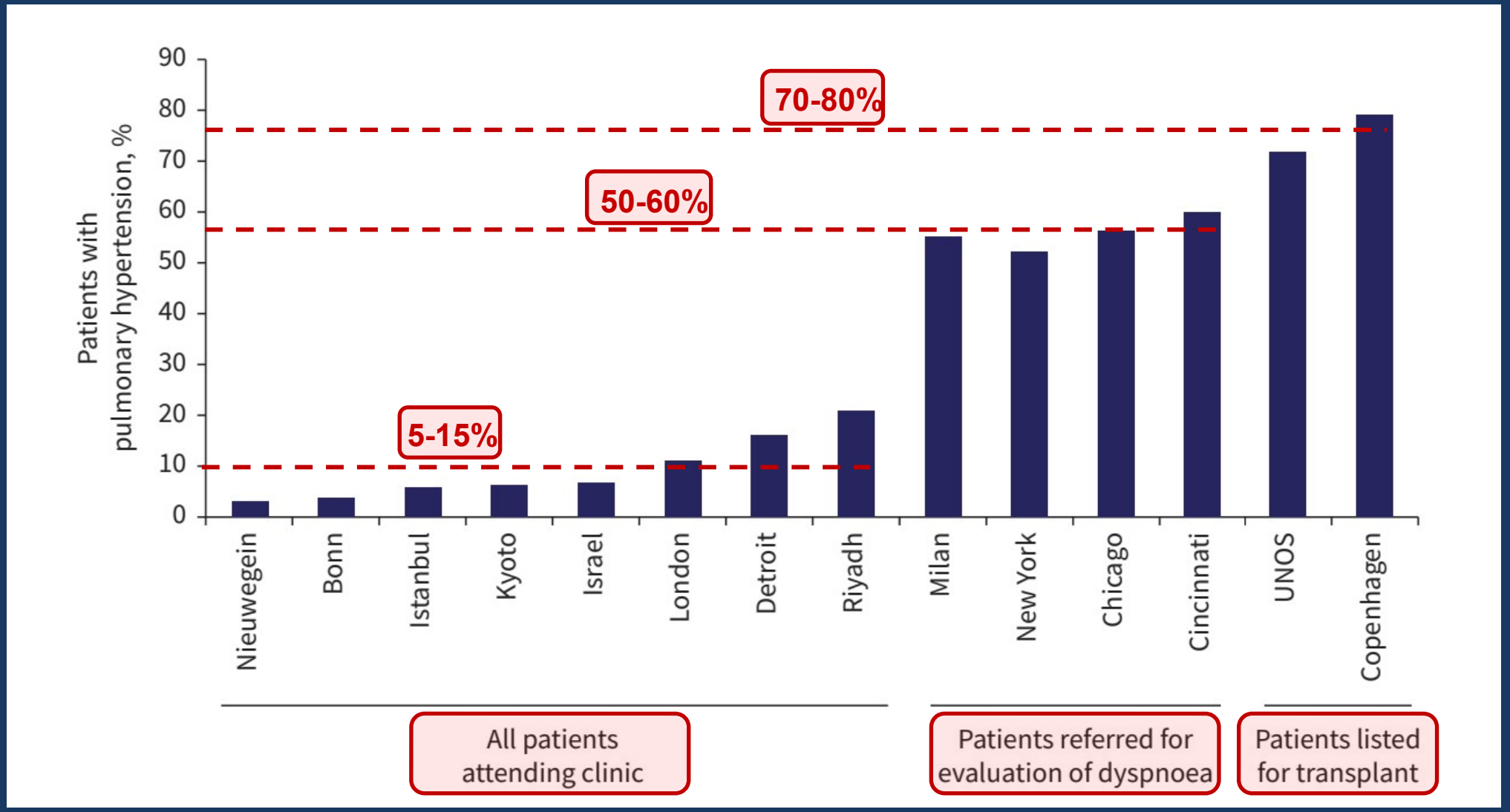


Neurofibromatosis type 1



Epidemiology of PH in sarcoidosis

Epidemiology of SAPH



Savale, *Eur Respir Rev* 2022

HEMODYNAMIC DEFINITION – ESC/ERS Guidelines 2022

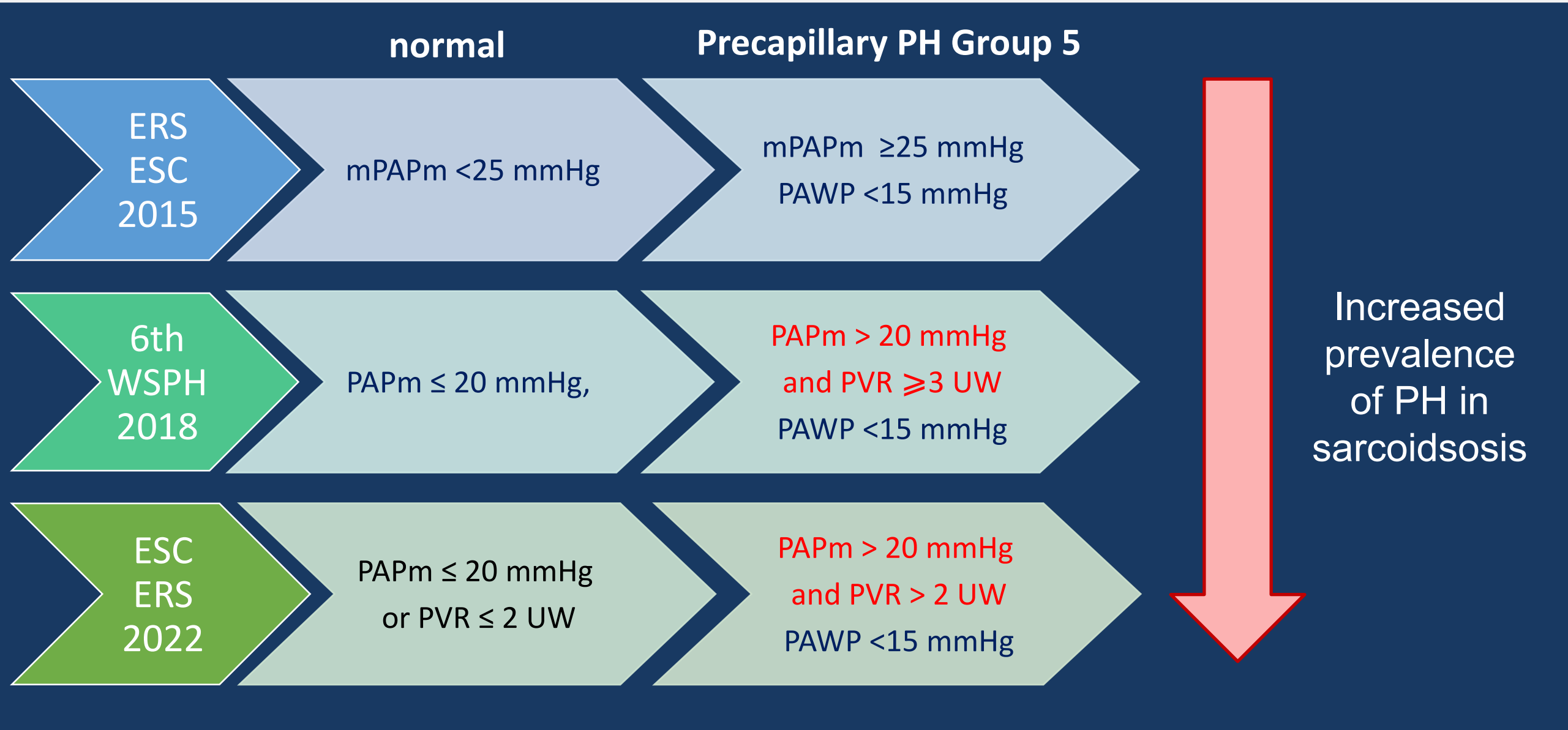
ESC/ERS GUIDELINES 2022

TABLE 5 Haemodynamic definitions of pulmonary hypertension

Definition	Haemodynamic characteristics
PH	**PAPm > 20 mmHg**
Pre-capillary PH	mPAP >20 mmHg PAWP ⩽15 mmHg **PVR > 2 WU**
IpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR ⩽2 WU
CpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU
Exercise PH	mPAP/CO slope between rest and exercise >3 mmHg/L/min

Group 5 PH
SAPH

Changes in hemodynamic definition of GROUP 5 PH

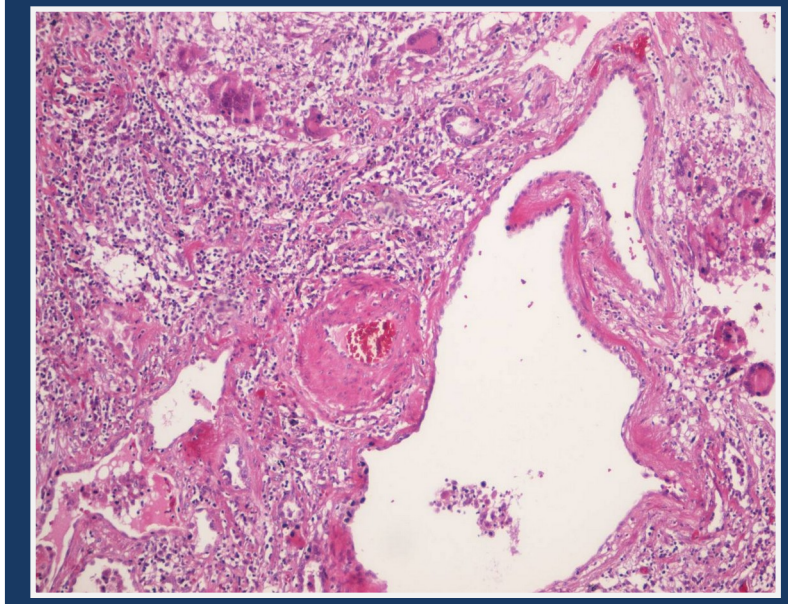


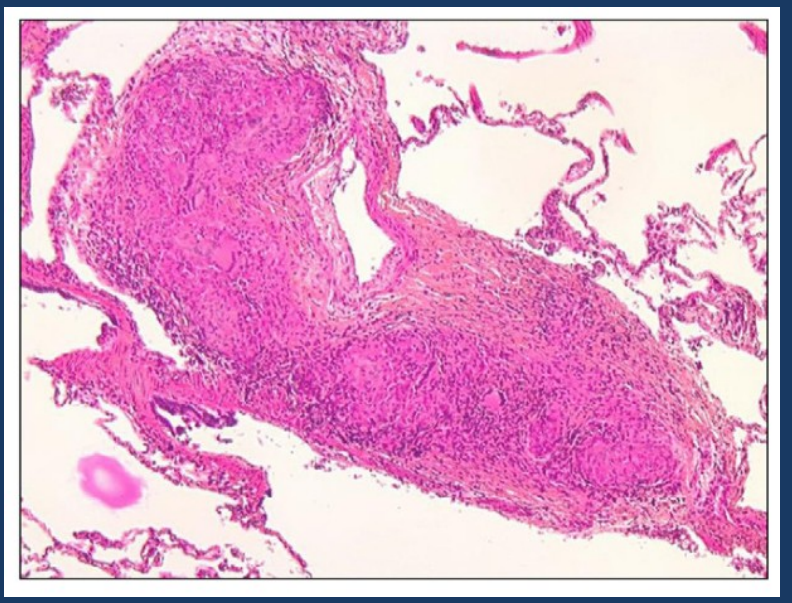
Mechanisms of sarcoidosis associated PH

Causes of sarcoidosis associated PH

Vascular disease
Vasculitis
Granulomatous vascular involvement
Veno-occlusive disease
Pulmonary embolism (CTEPH)
Interstitial lung disease
Parenchymal lung disease due to granulomas
Parenchymal lung disease due to fibrosis
Hilar and mediastinal distortion
Pulmonary artery/vein extrinsic compression
Fibrosing mediastinitis
Extrapulmonary disease
Left ventricular systolic dysfunction
Left ventricular diastolic dysfunction
Sleep apnoea
Liver disease

Sarcoidosic pulmonary vasculopathy
= granulomatous arterial involvement





Nunes et al, *Presse Med* 2012
Nunes et al, *Thorax* 2006

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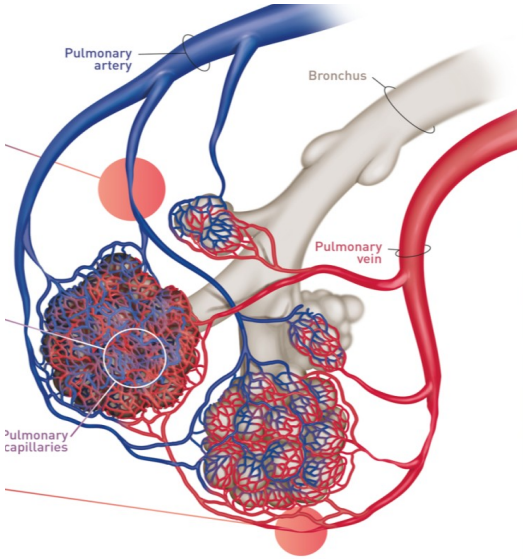
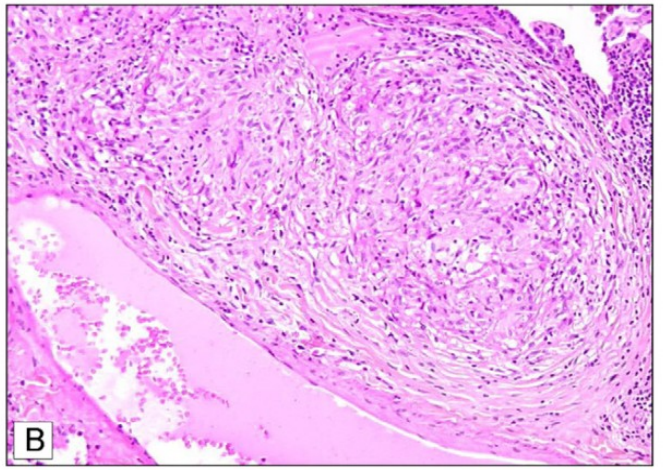
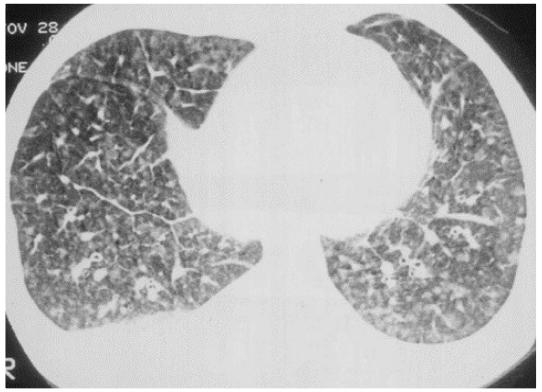
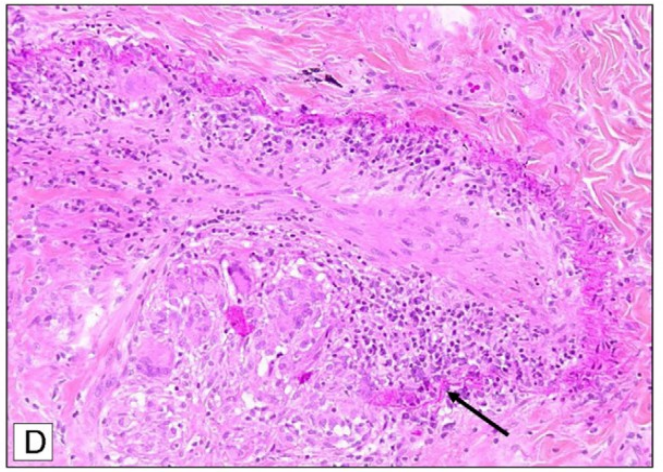
Sleep apnoea
Liver disease

Sarcoidosic pulmonary vasculopathy = venous involvement +++









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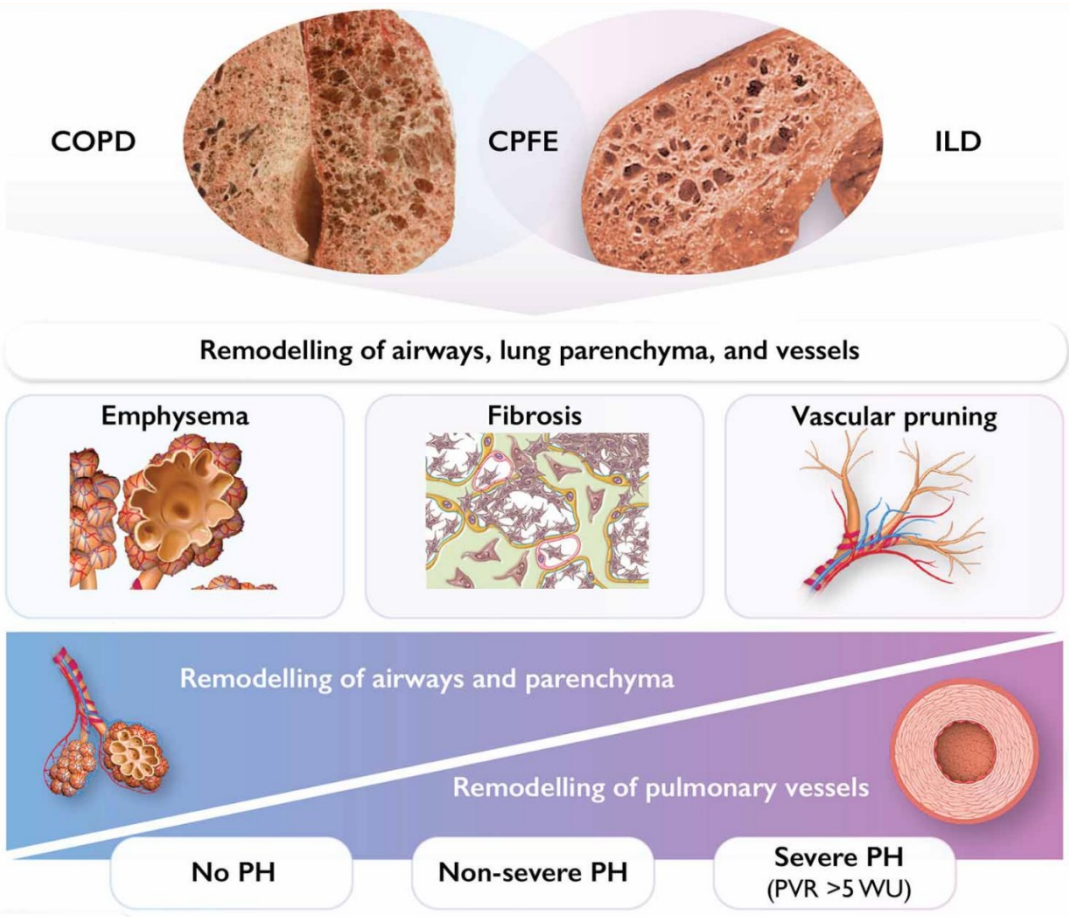
Sleep apnoea
Liver disease

PH group 3 « like »



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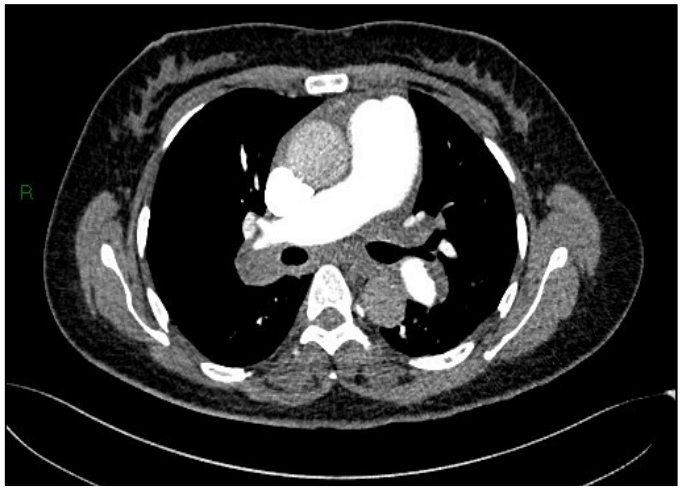
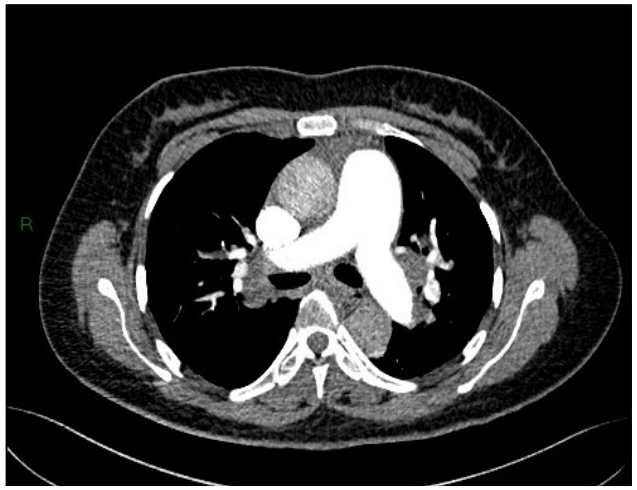
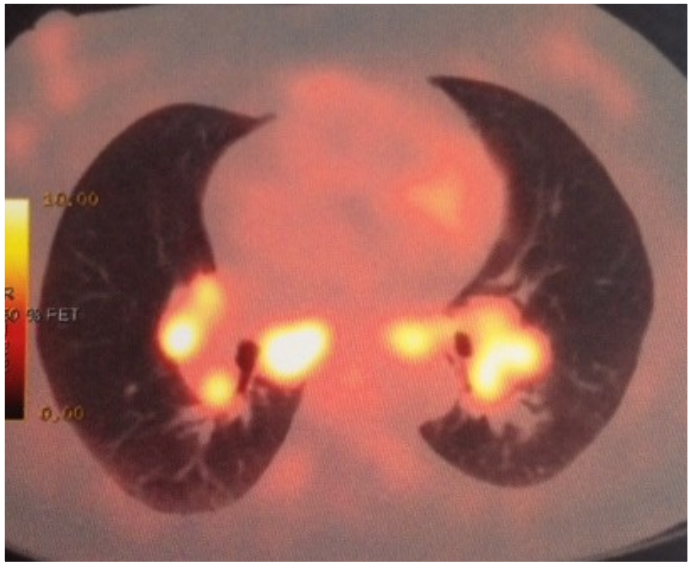
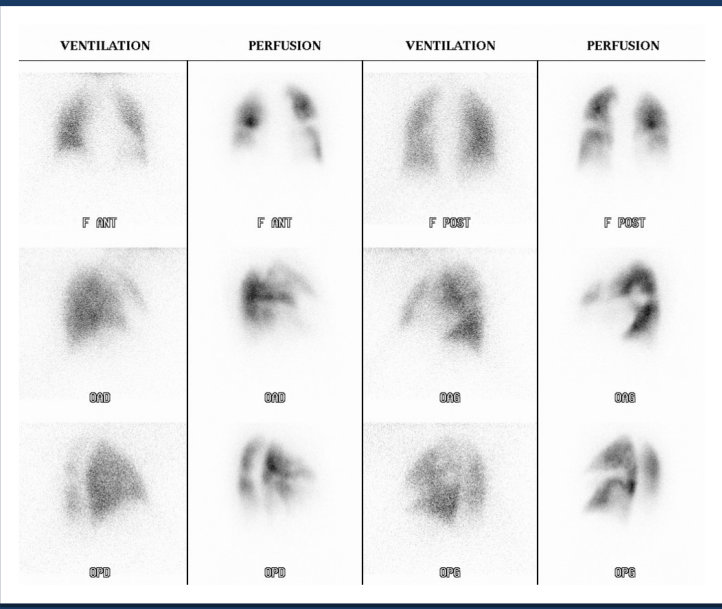
Liver disease









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Left ventricular diastolic dysfunction
Sleep apnoea
Liver disease

Proliferation of fibrous tissue in the mediastinum leading to extrinsic compression of mediastinal bronchovascular structures including pulmonary arteries and veins

TABLE 1. Etiologies of Fibrosing Mediastinitis

	PH Associated with Fibrosing Mediastinitis, n = 27
Sarcoidosis (stage 4)	13 (7)
Tuberculosis	9
–confirmed	3
–possible	6
Mediastinal irradiation	2
Idiopathic	3

50%

Seferian et al, *Medicine* 2015

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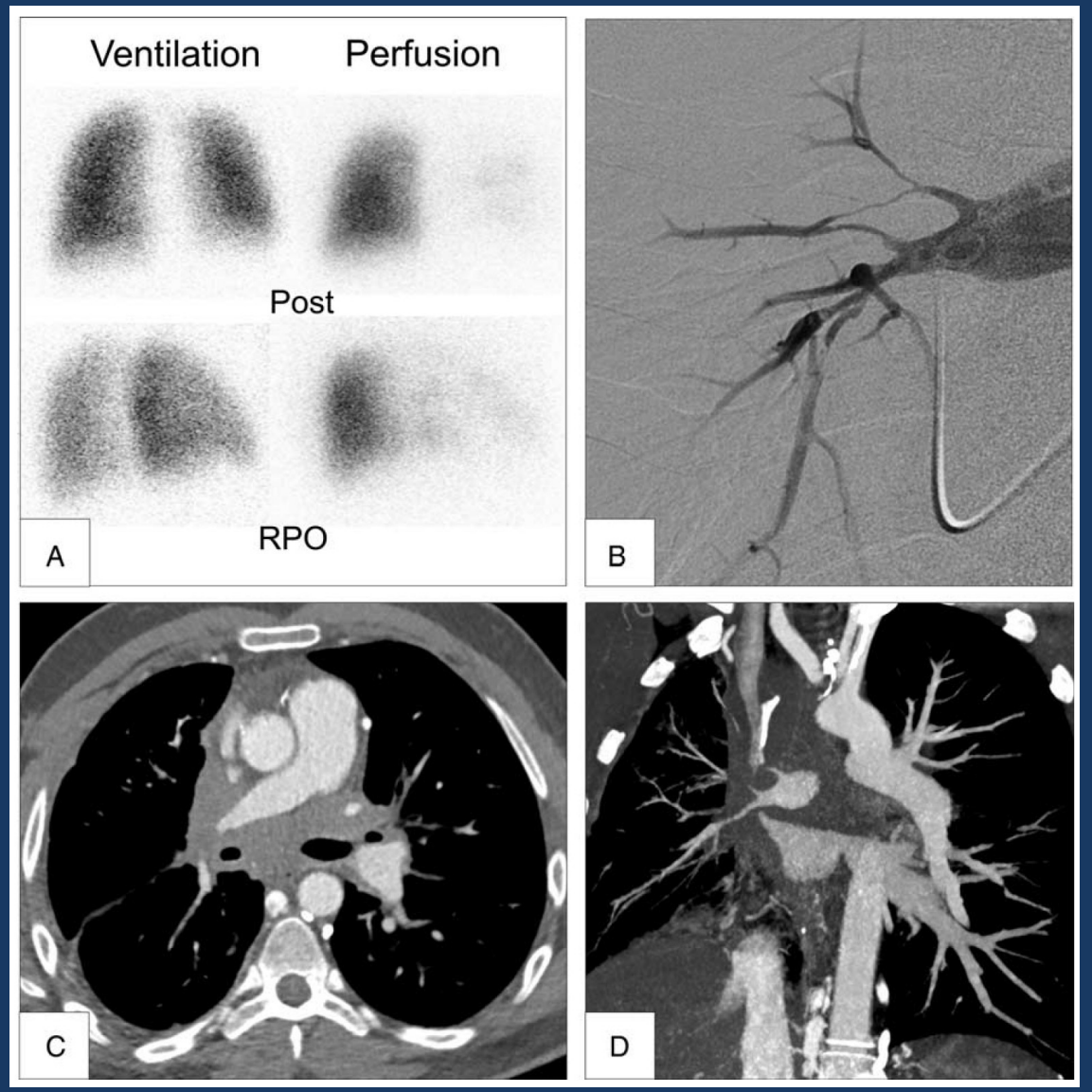
Sleep apnoea
Liver disease



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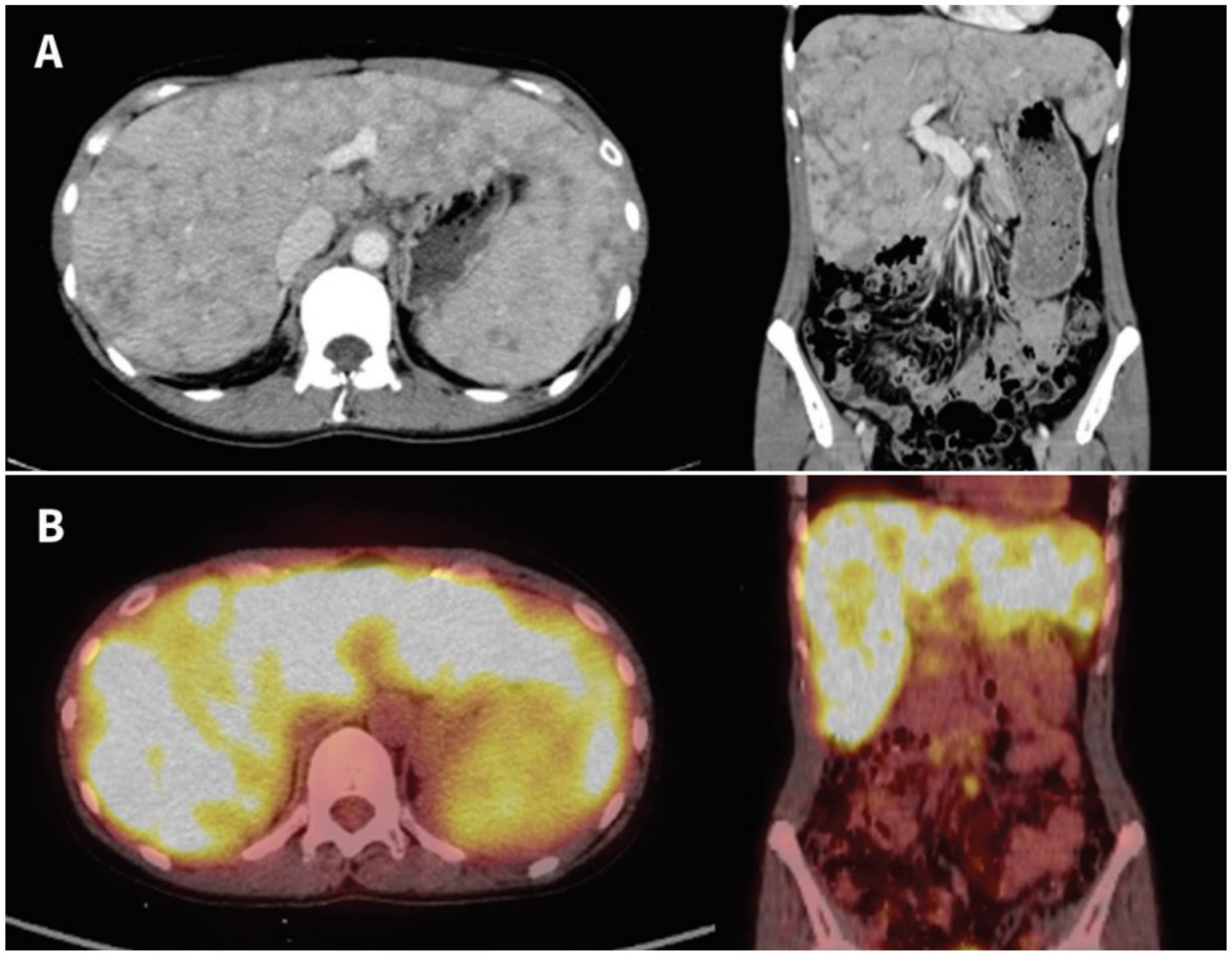
Portopulmonary hypertension



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Association of Sarcoidosis With Increased Risk of VTE

A Population-Based Study, 1976 to 2013

Patompong Ungprasert, MD; Cynthia S. Crowson, MS; and Eric L. Matteson, MD, MPH

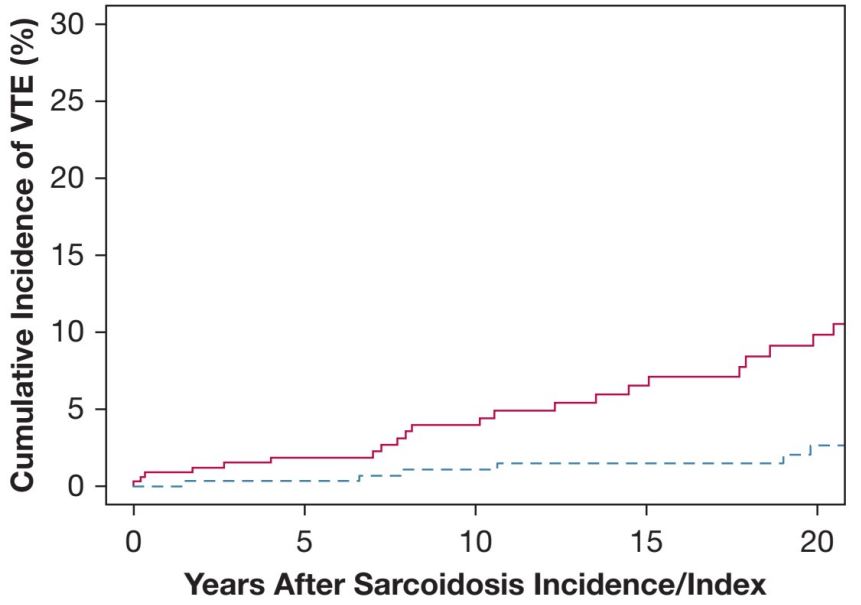

Figure 1 – *Cumulative incidence of VTE among patients with sarcoidosis (solid line) and comparators without sarcoidosis (dashed line).*

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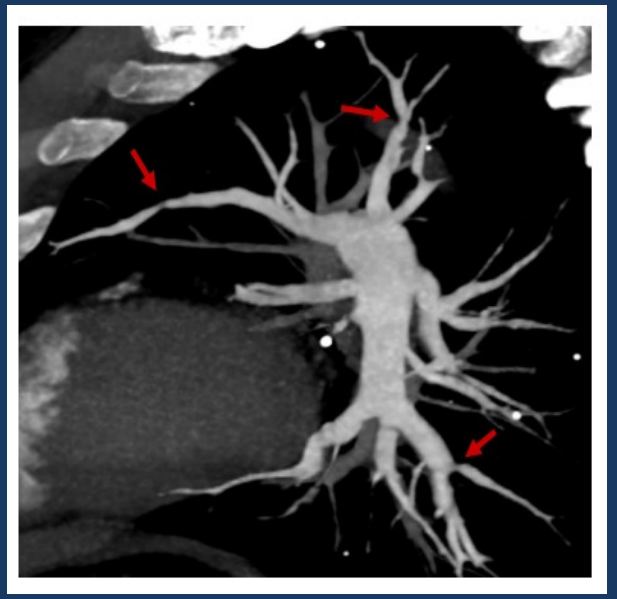

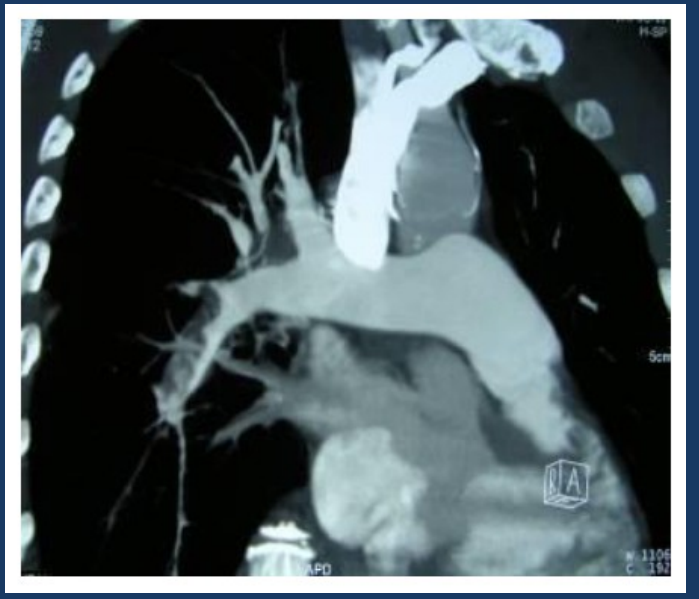

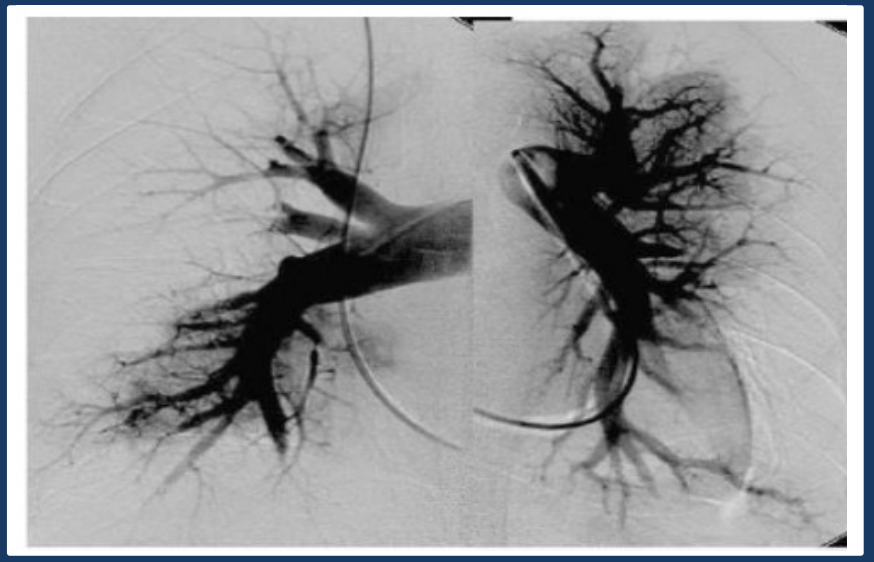

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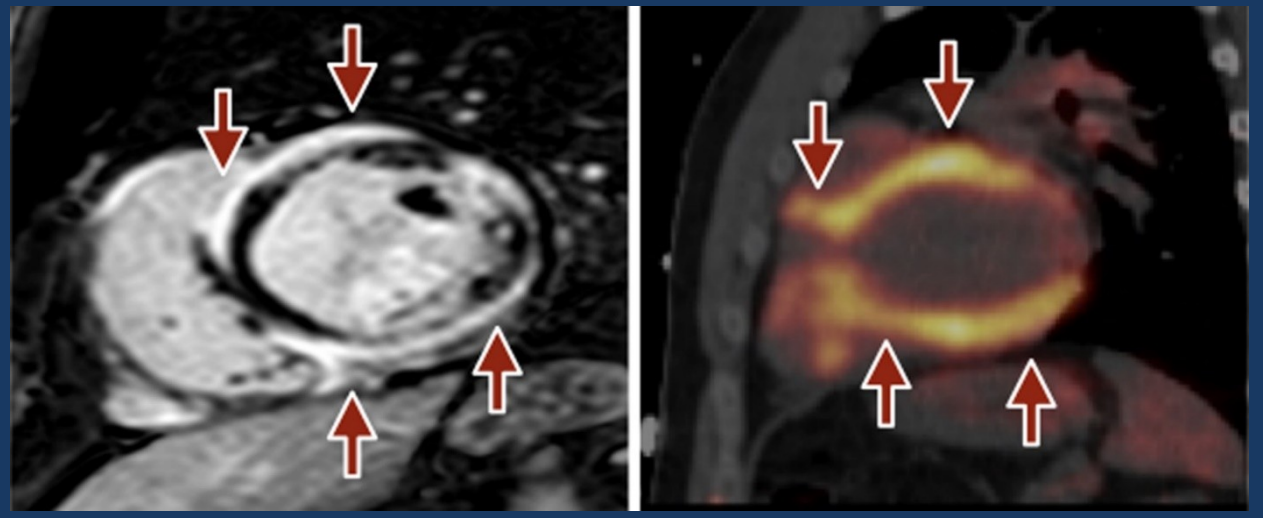
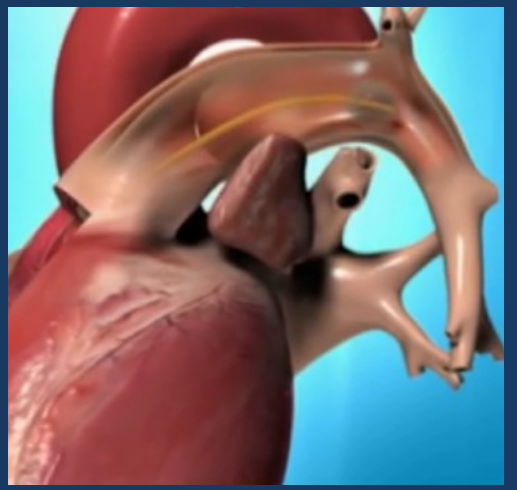
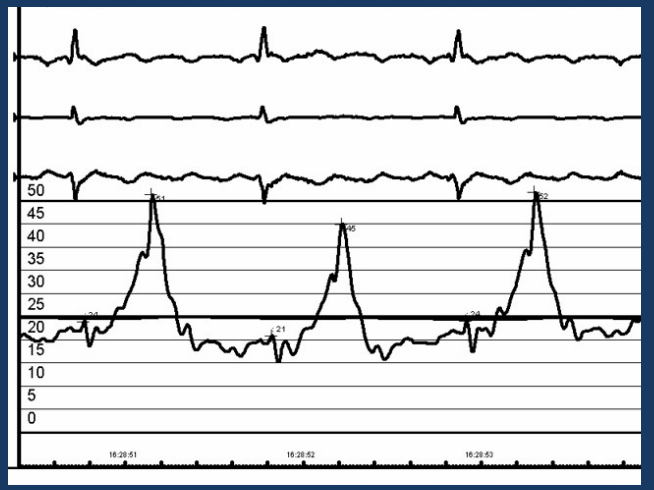
Post-capillary PH

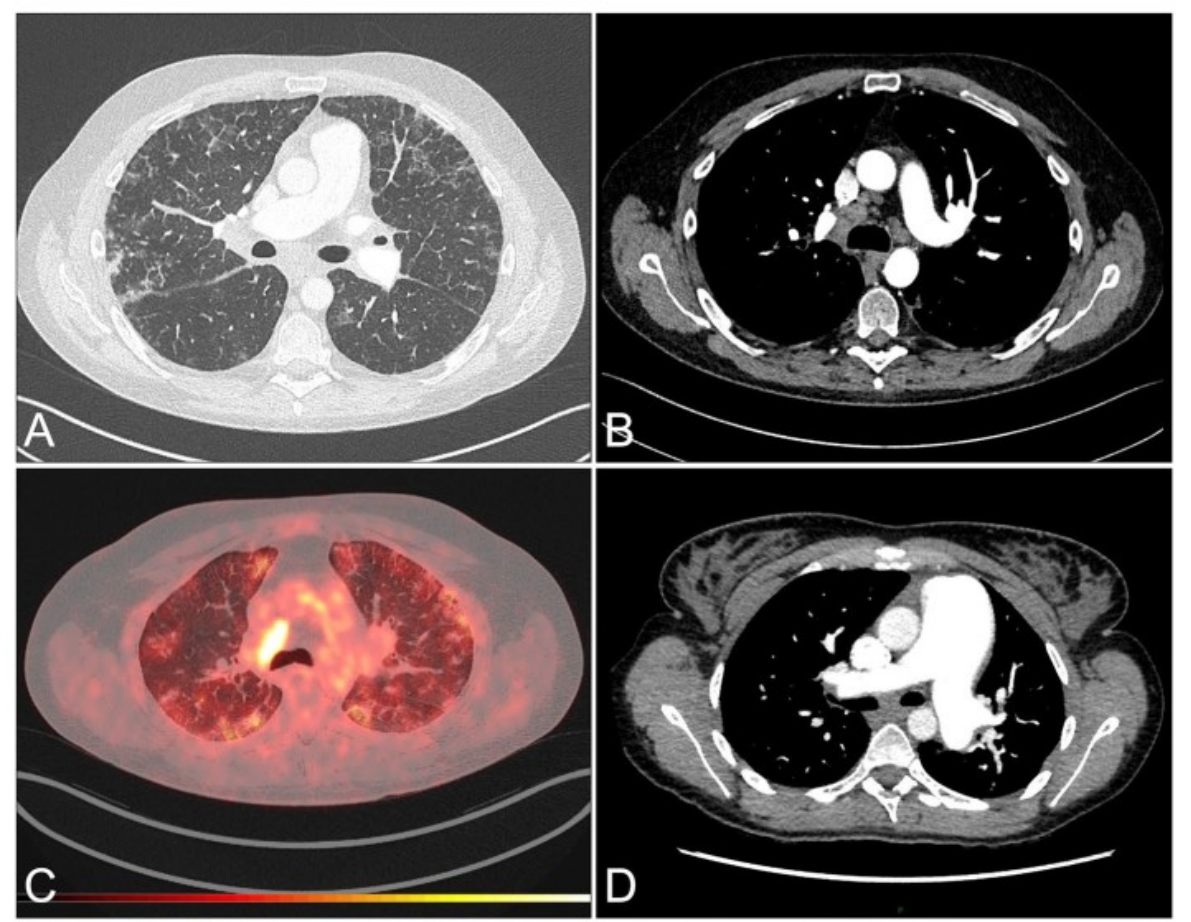


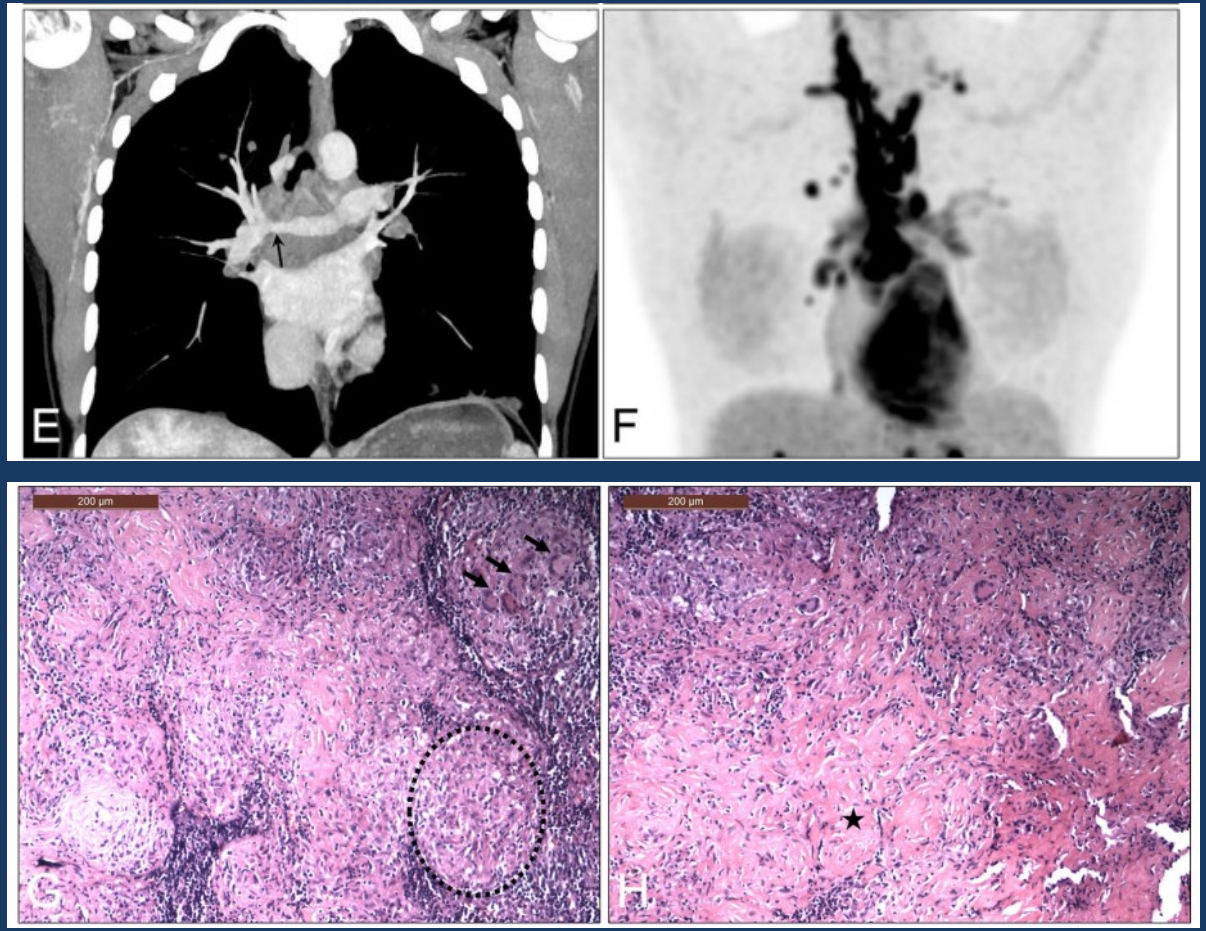




A pitfall…..

PH associated with common variable immunodeficiency (CVID)

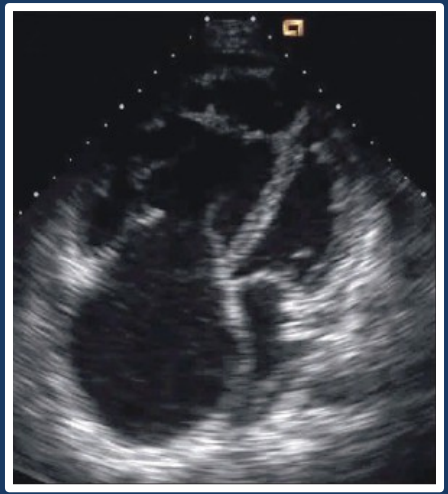




Thoré et al, *J Clin Immunol* 2021

Diagnosis of SAPH

Screening for PH in sarcoidosis = Echocardiography



All sarcoidosis patients candidates for lung transplantation

Clinical signs, circulating biomarkers, imaging and/or ECG features suggestive of PH (≥1 criteria)

- Persistent dyspnoea despite aggressive anti-inflammatory therapy
- Clinical signs of right ventricular failure

- 6MWD of <300 m and/or desaturation >5%
- >20% decrease in 6MWD without modification of PFTs

- High level of BNP or NT-proBNP[#]

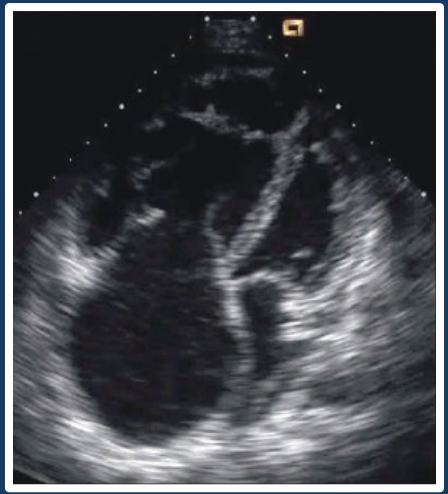
- Pulmonary fibrosis >20% of lung parenchyma
- Increased pulmonary artery to aorta ratio[¶]
- Suspicion of PH and/or RV dysfunction on cardiac MRI
- Signs of PH on contrast CT scan

- Worsening of NYHA-FC without modification of FVC
- >15% decrease in D_{LCO} without modification of FVC, especially if other signs of PH are present

Transthoracic doppler echocardiography to estimate PH probability

Savale et al, *Eur Respir Rev* 2022

Screening for PH in sarcoidosis = Echocardiography



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Savale et al, *Eur Respir Rev* 2022

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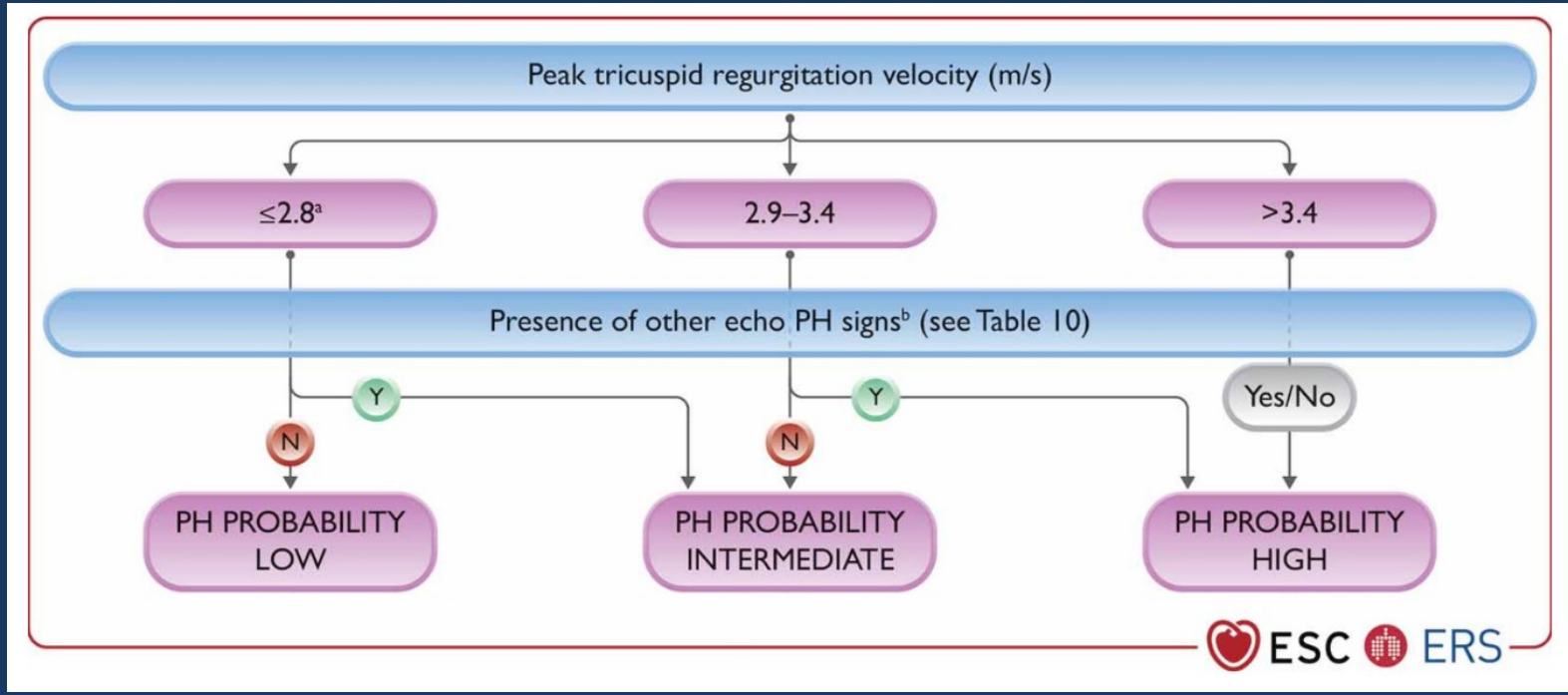
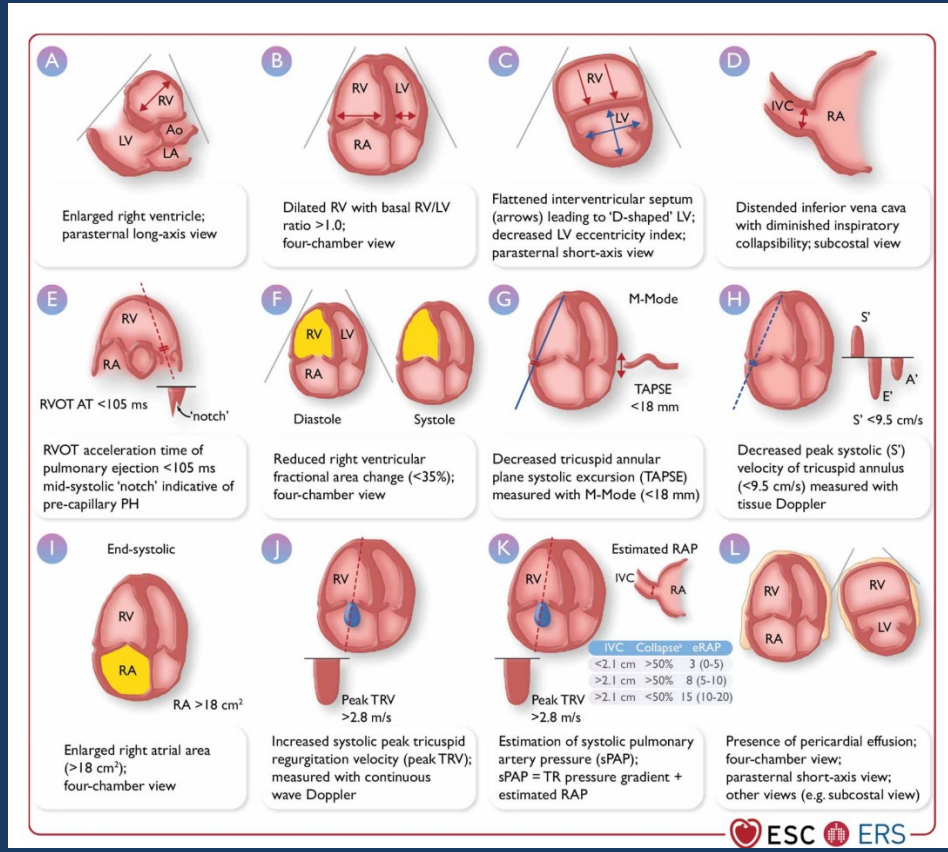
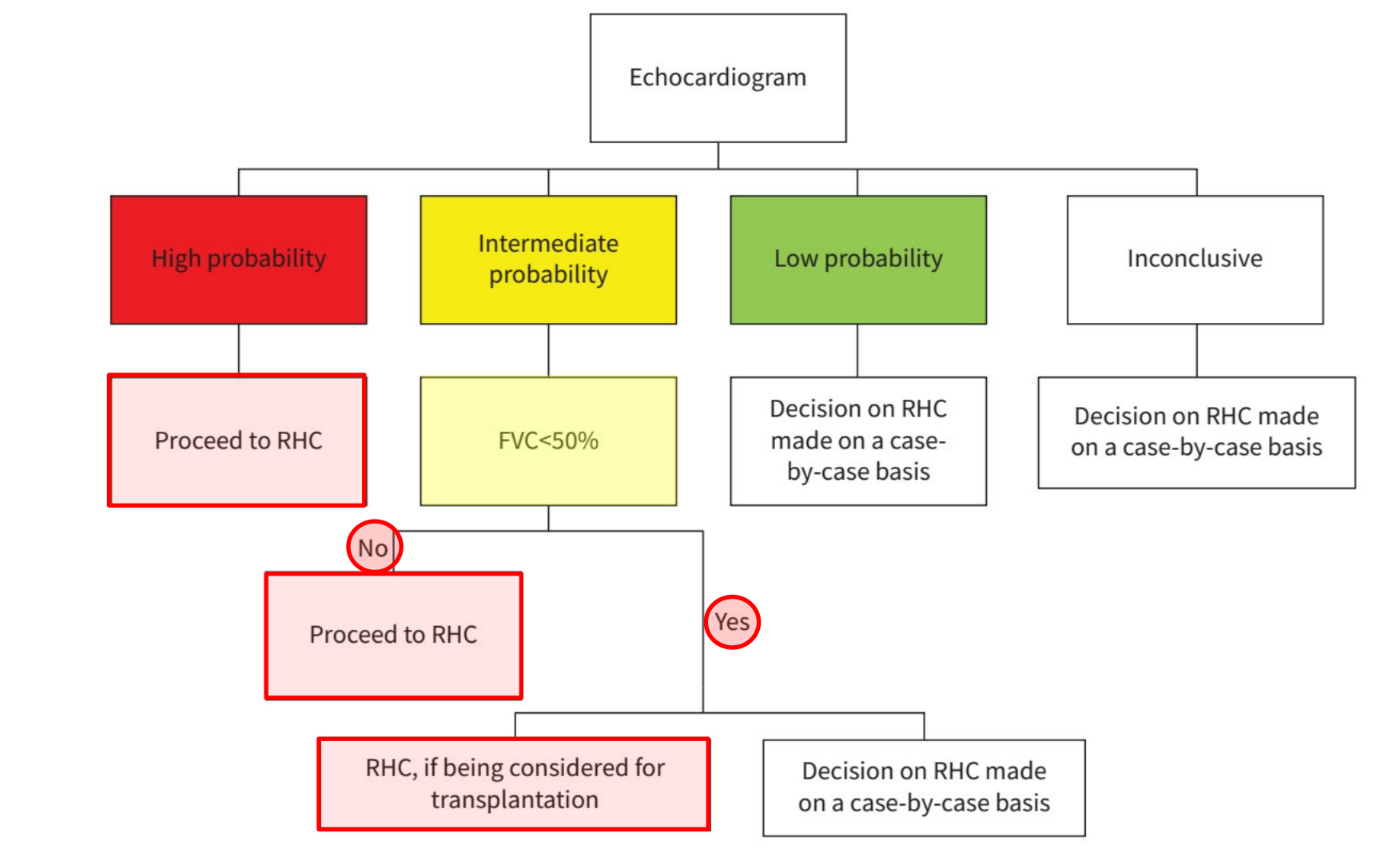




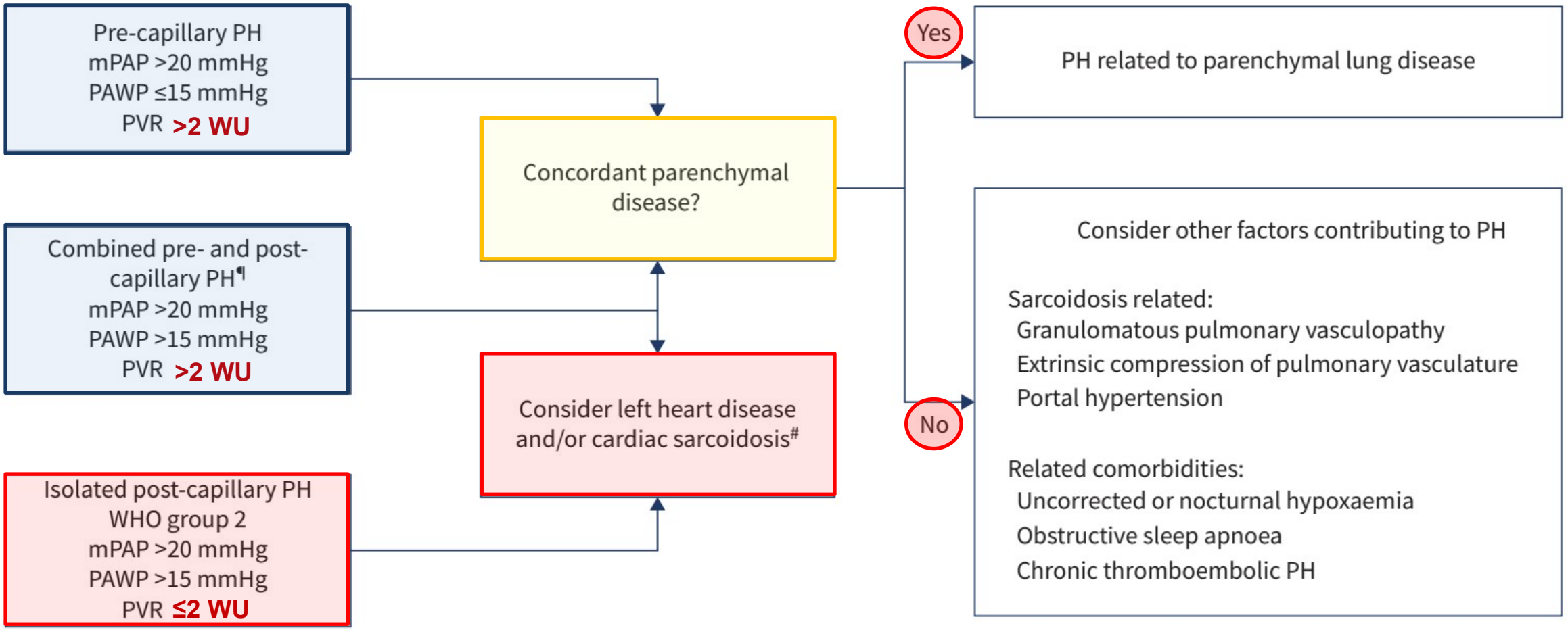
Humbert et al, *Eur Respir J* 2021

When should we perform a RHC ?



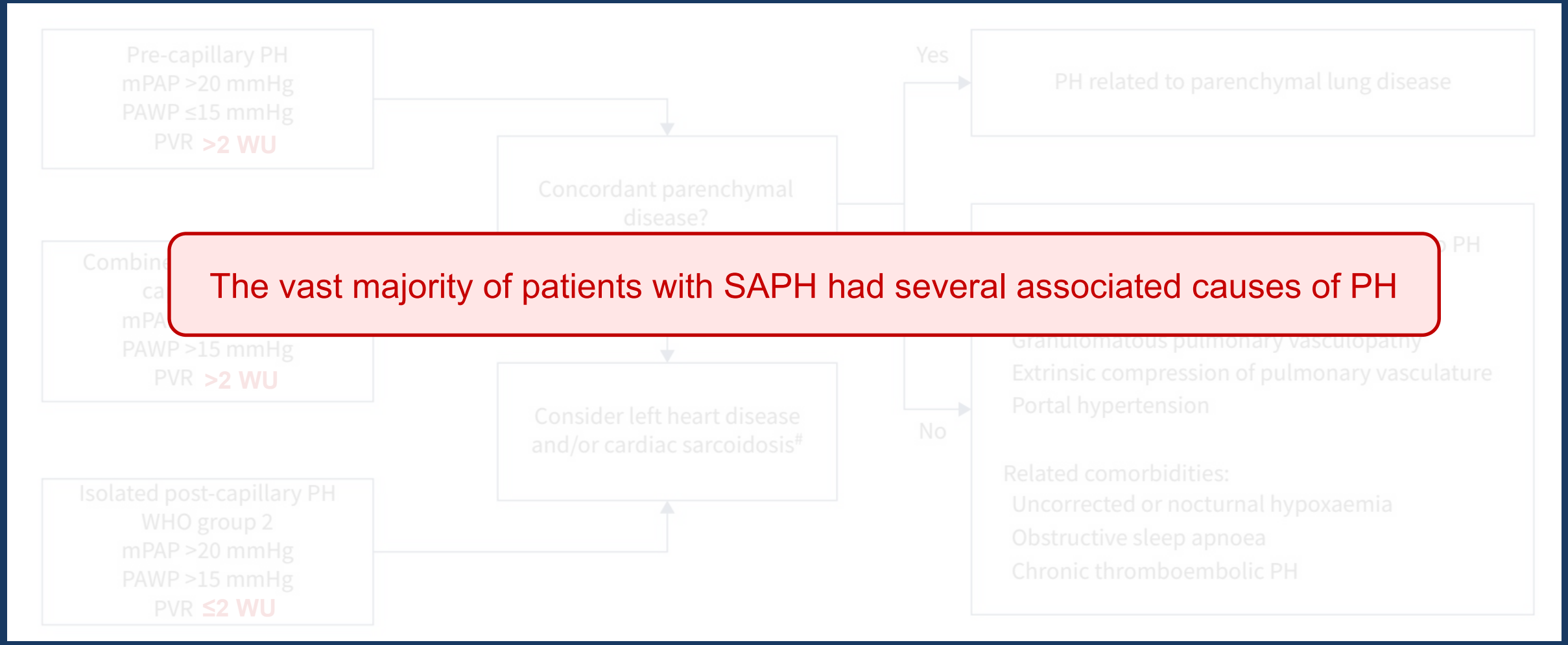
Savale et al, *Eur Respir Rev* 2022

Diagnostic algorithm based on RHC



Adapted from Savale et al, *Eur Respir Rev* 2022

Diagnostic algorithm based on RHC



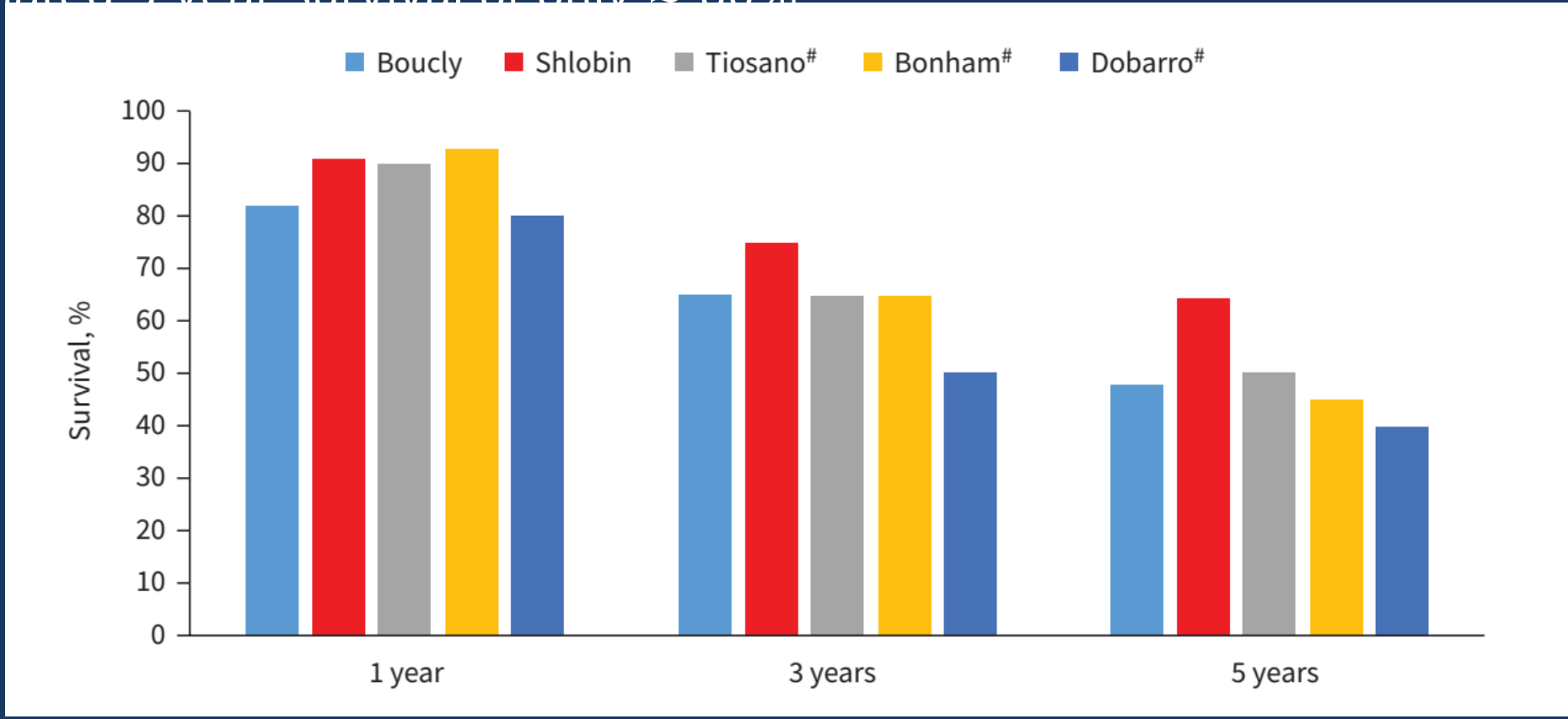
The vast majority of patients with SAPH had several associated causes of PH

Adapted from Savale et al, *Eur Respir Rev* 2022

Prognosis of SAPH

PH is an independent predictor of mortality

The mortality implications of any PH, both pre- and post-capillary, in the context of sarcoidosis are also profound, with a 10-fold increase in mortality and an estimated 5-year survival of only ≈ 60%

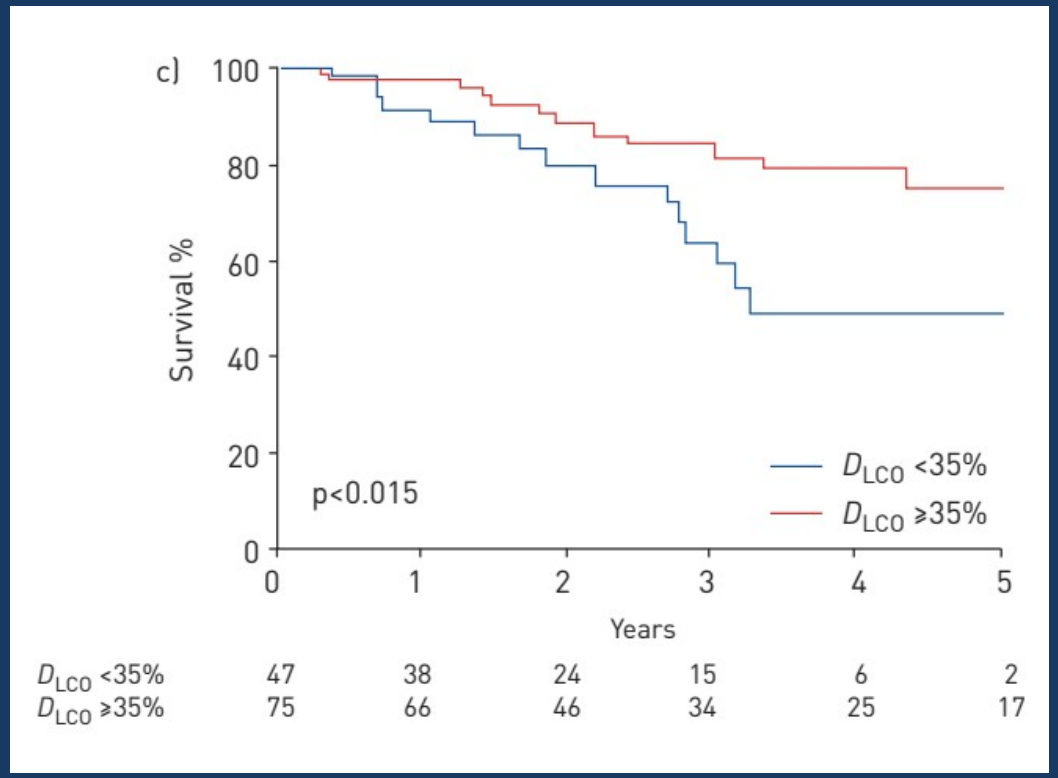


Savale et al, *Eur Respir Rev* 2022

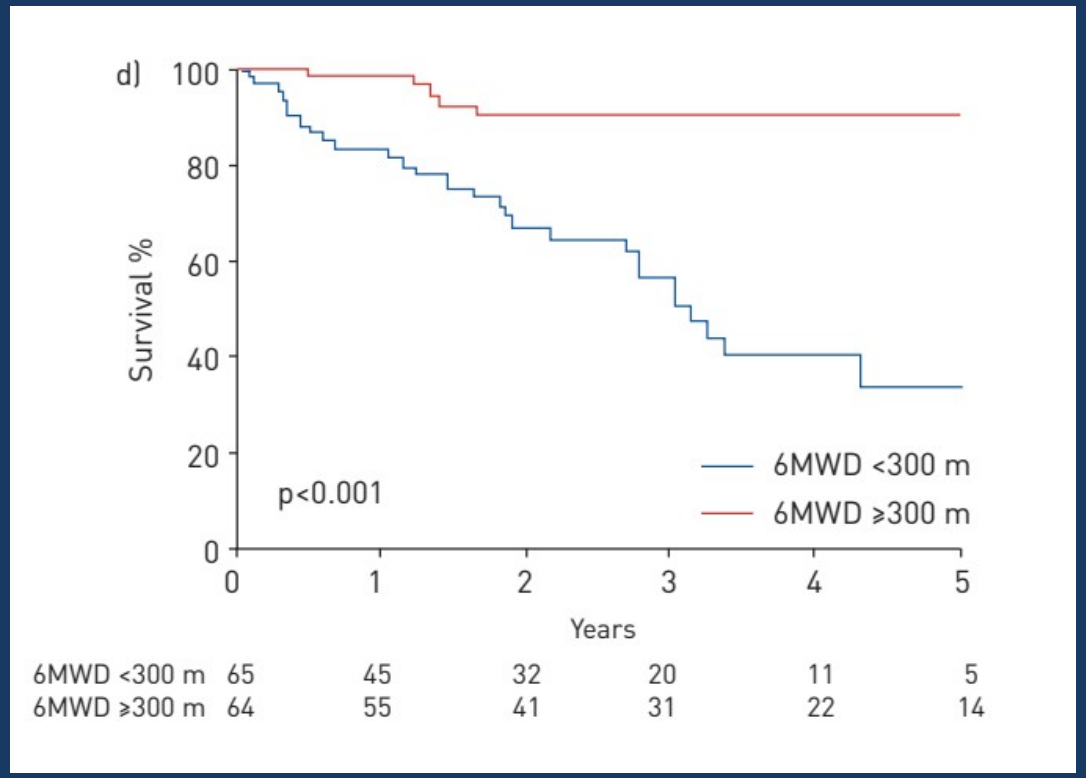
Prognostic factors in precapillary SAPH

International Registry for SAPH (ReSAPH)
159 precapillary PH

DLco < 35%



6-MWD < 300 m



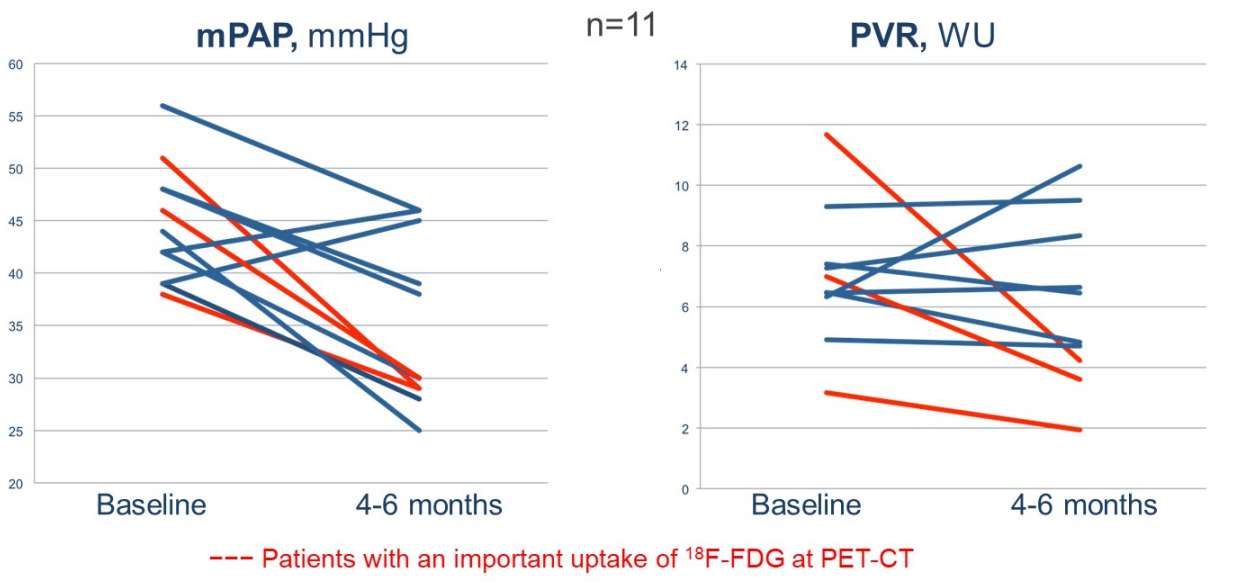
Shoblin et al, *Eur Respir J* 2020

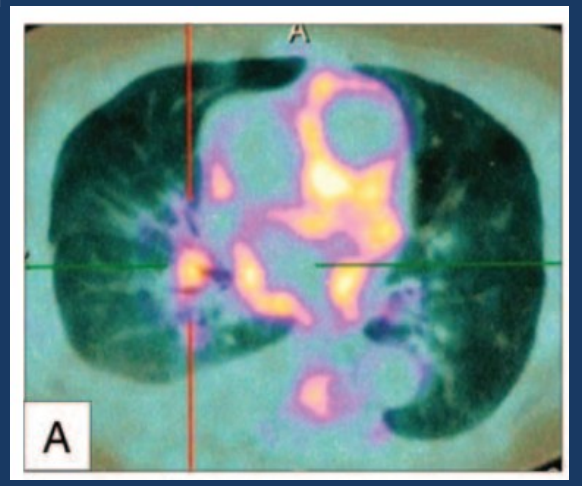
Management of SAPH

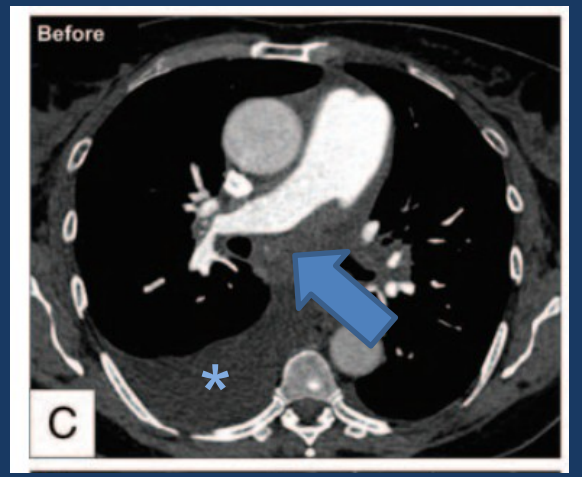
1st step : Optimize treatment of sarcoidosis

French PH registry: 126 patients with severe precapillary SAPH

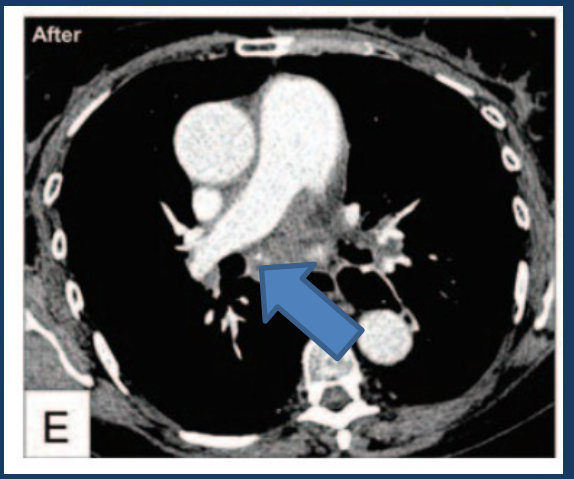
Immunosuppresive treatment only







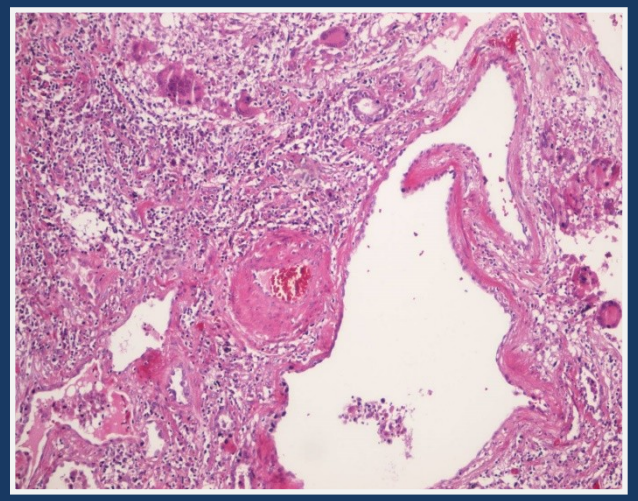
corticosteroids

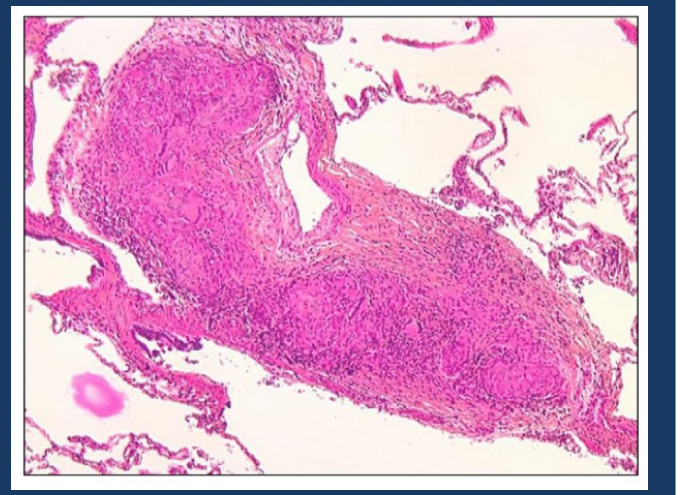


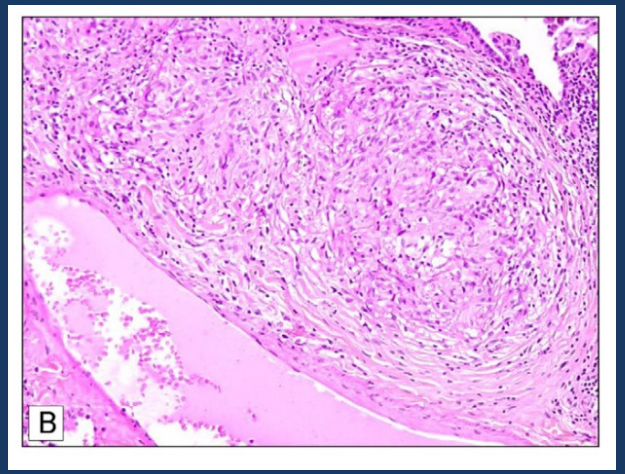
Boucly et al, *Eur Respir J* 2017
Seferian et al, *Medicine* 2015

PAH-approved drugs in precapillary SAPH

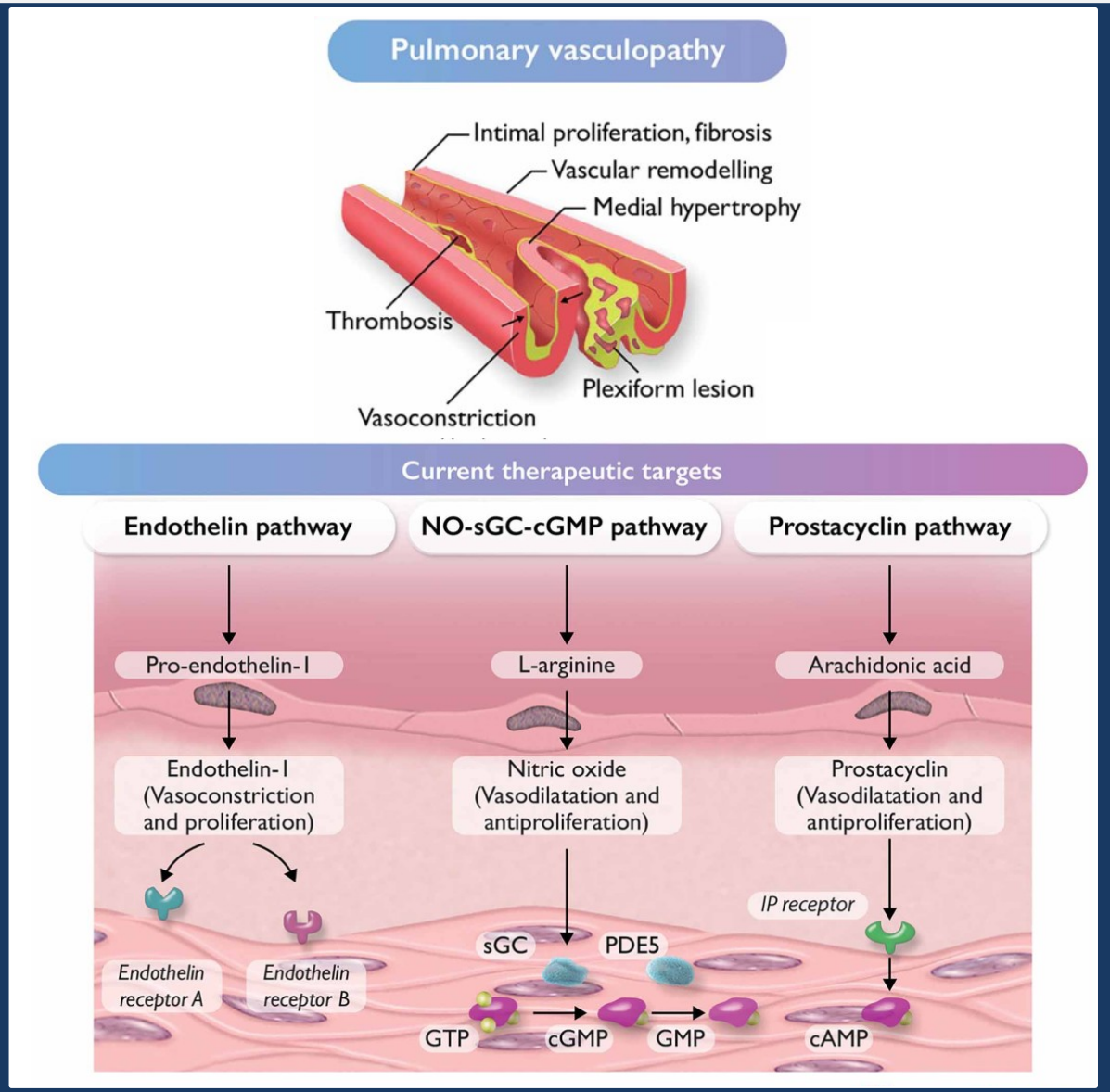
Sarcoidosic pulmonary vasculopathy







Arterial but also frequent venous involvement

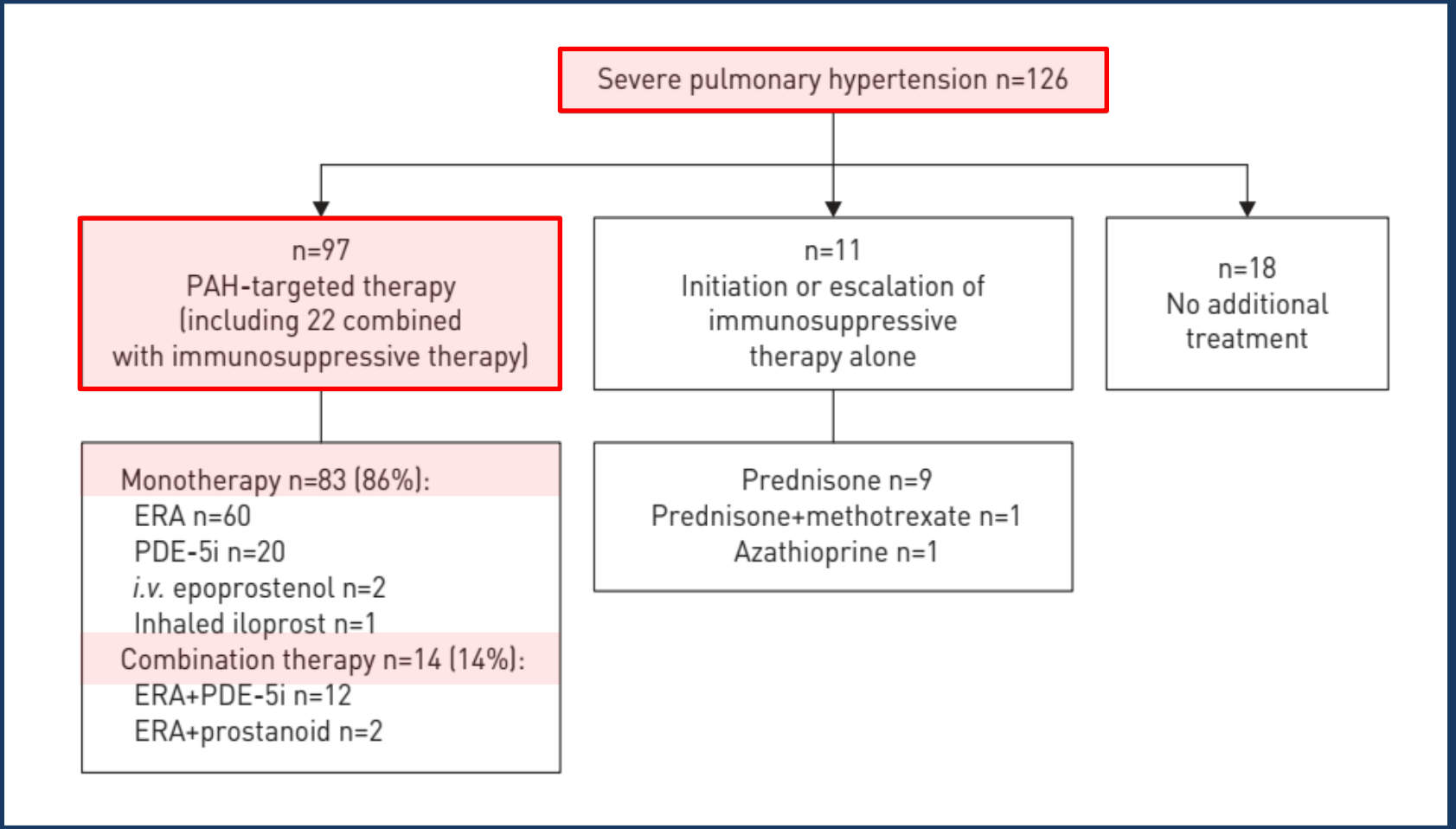


PAH-approved drugs in precapillary SAPH

	Highest level of evidence study in patients with SAPH	Total number of patients with SAPH treated	Results in sarcoidosis
Prostenoids			
Epoprostenol	Retrospective OL positive [78, 79]	12	Haemodynamics improved [78, 79]
Iloprost	Prospective, OL [72]	15 of 22 enrolled completed 16 weeks' therapy	In sarcoidosis, haemodynamics and QoL improved [72]
Endothelin receptor antagonists			
Bosentan	DBPC [71]	23	Haemodynamics improved, no change in 6MWD [71]
Ambrisentan	Prospective OL [73]	21	Nonsignificant improved QoL, no change 6MWD [73]
Macitentan	Retrospective OL [82]	6	WHO FC improved in 4/6 treated patients [82]
Phosphodiesterase 5 inhibitors			
Sildenafil	Retrospective OL [16]	12	Haemodynamics improved, 6MWD no changes
Tadalafil	Prospective OL [74]	12	No significant changes in 6MWD and QoL
Others			
Riociguat	DBPC [70]	16	TCW and 6MWD significantly better compared with placebo
Combination therapy	Retrospective OL positive [8, 21, 77]	29	Haemodynamics and 6MWD improved in some

PAH-approved drugs in severe precapillary SAPH

French PH registry



Boucly et al, *Eur Respir J* 2017

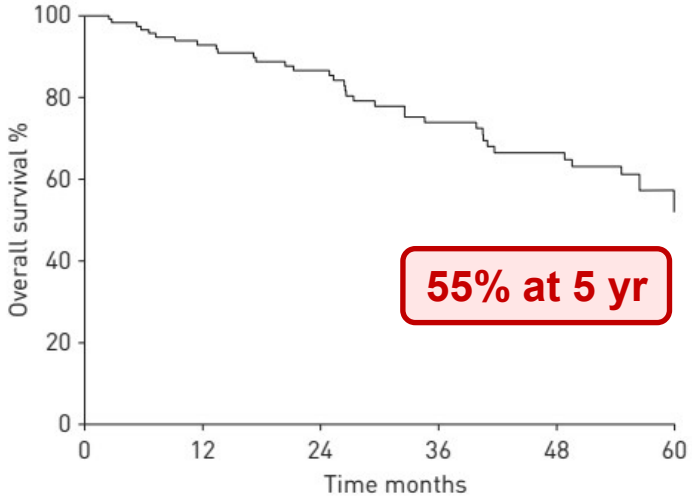
PAH-approved drugs in severe precapillary SAPH

French PH registry

126 severe SAPH - 97 receiving specific PAH therapy

	Baseline	First follow-up visit[¶]	Difference	p-value
WHO/NYHA functional class I–II/III/IV	11/52/18	26/45/10		0.01
6MWD m	311±127	324±138	+13 m	0.33
RAP mmHg	7±4	6±4	−14%	0.007
mPAP mmHg	48±9	42±11	−13%	<0.00001
Cardiac index L·min^{-1}·m^{-1}	2.6±0.8	2.9±0.8	+12%	<0.00001
PVR Wood units	9.7±4.4	6.9±3.0	−29%	<0.00001

Data are expressed as n or mean±SD, unless otherwise stated. 6MWD: 6-min walk distance; RAP: right atrial pressure; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance. [#]: n=81; [¶]: median (interquartile range) 4.5 (4.0–6.7) months.

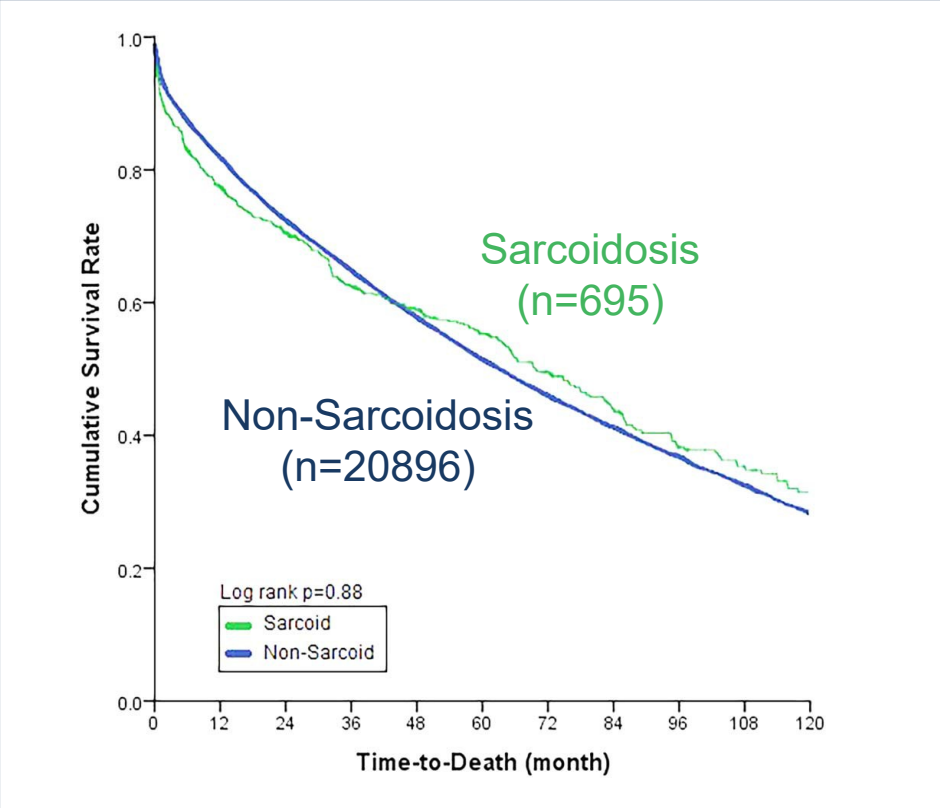


Boucly et al, *Eur Respir J* 2017

Lung transplantation in sarcoidosis

US Experience

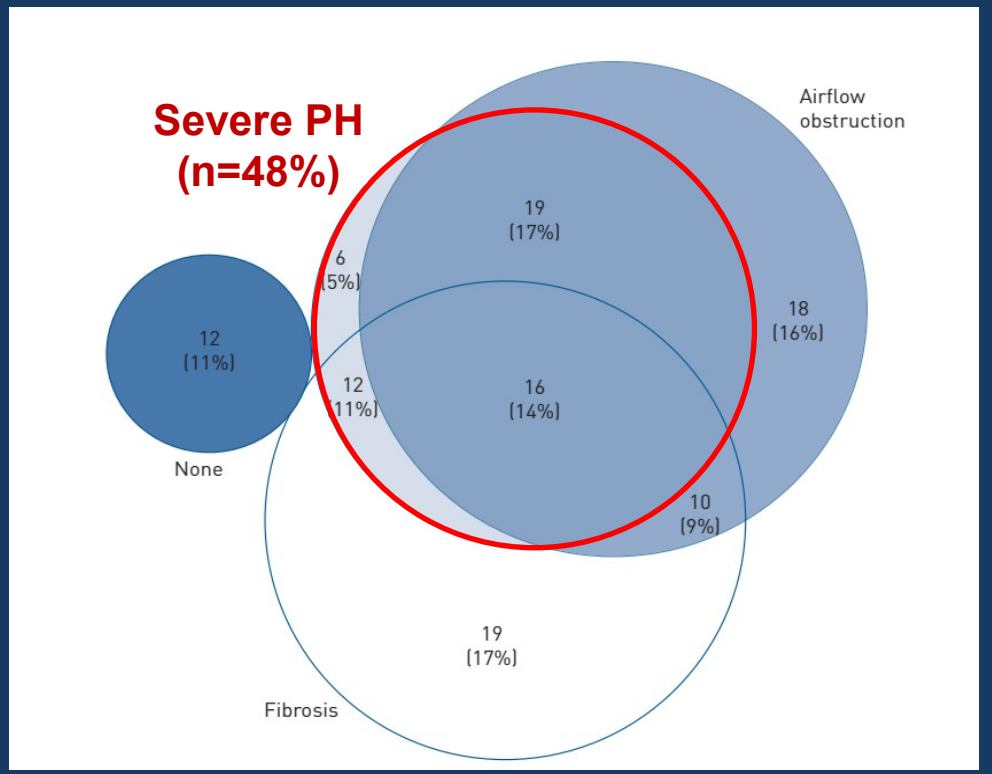
Similar long-term outcomes compared with nonsarcoid lung recipients



Taimeh et al, *Thorax* 2016

European experience

Hemodynamic parameters were not associated with impaired post-transplant survival

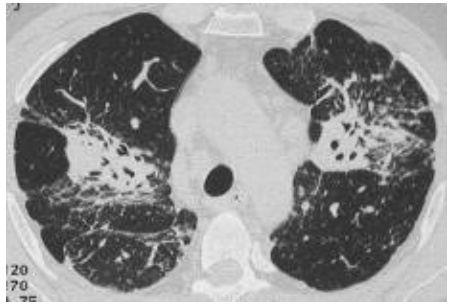


Le Pavec et al, *Eur Respir J* 2021

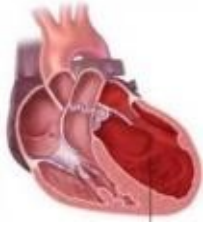
Conclusions

Sarcoidosis associated PH = MULTIFACTORIAL PH

Hypoxic vasoconstriction
Destruction of pulmonary vascular bed



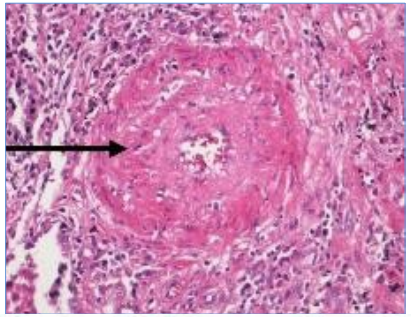
Left heart disease



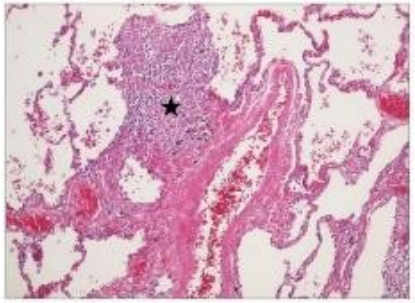
Portal Hypertension

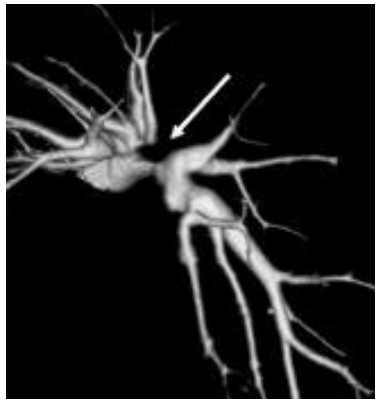
Pulmonary Hypertension

Pulmonary arterial remodeling



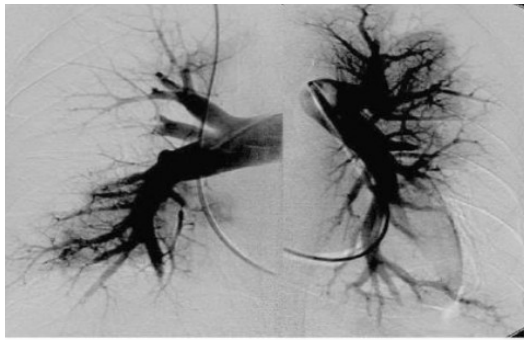
« Pulmonary veno-occlusive disease »



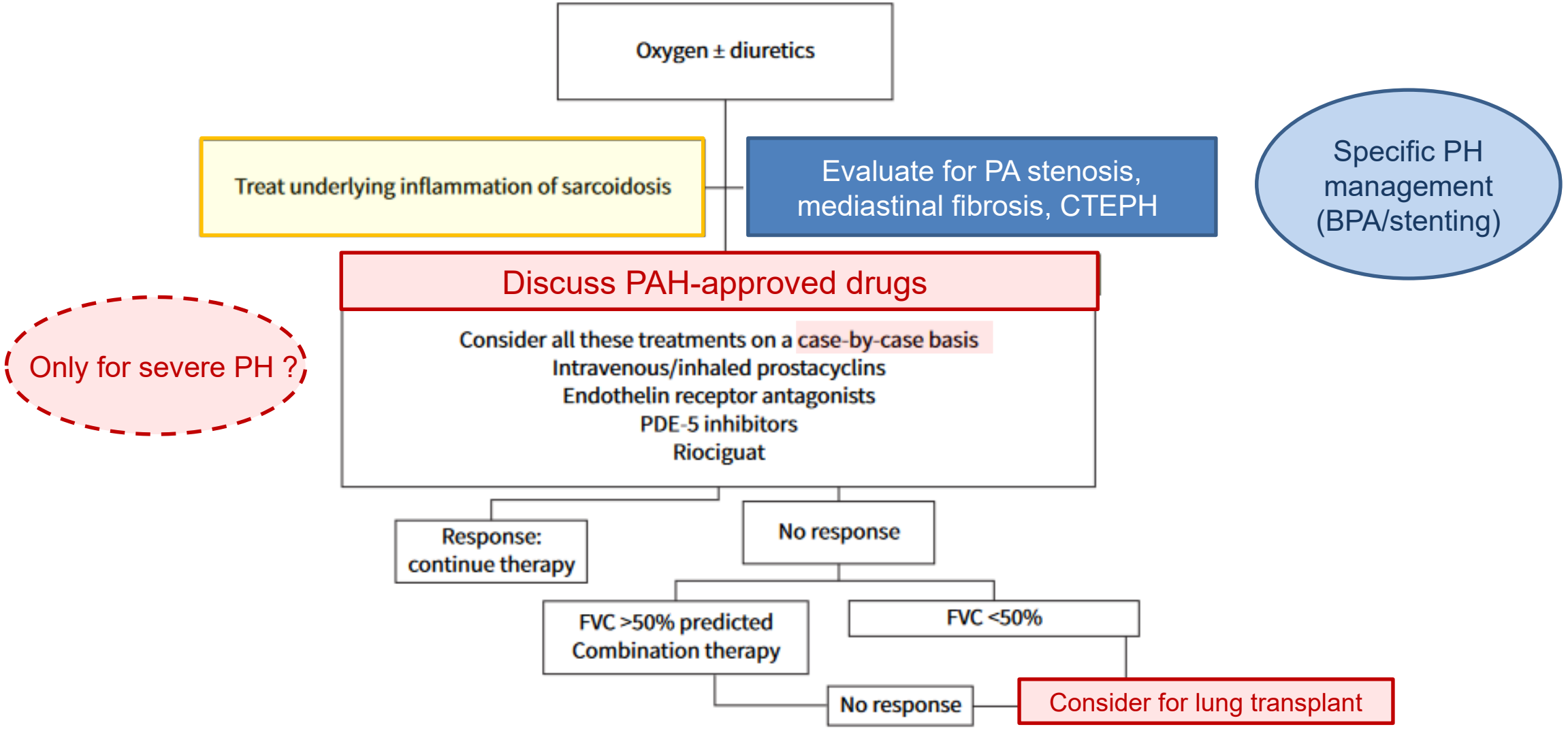


Mediastinal fibrosis
Compression of
pulmonary arteries or veins

CTEPH



Management of Precapillary SAPH



Adapted from Savale et al, *Eur Respir Rev* 2022

International Meeting on
PULMONARY RARE DISEASES
AND ORPHAN DRUGS

Sarcoidosis-associated pulmonary hypertension

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