Pulmonary hypertension in scleroderma: different phenotypes

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Inserm

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Université de Lille 2 DROIT ET SANTÉ

Centre Hospitalier Régional Universitaire de Lille

Disclosures of interest

- Grants from Actelion, Pfizer, GSK

Pulmonary hypertension in systemic sclerosis

- Frequent (10 - 15 %)
- Severe
  - PH and ILD: first cause of morbimortality in SSc
  - Overall survival of SSc-PAH: 50% at 3 years
  - Overall survival of SSc-PH due to ILD : 35 % at 3 years
- Worse survival than idiopathic PAH ajusted for the severity
- PH in SSc : very heterogeneous disease with different phenotypes
  - Various pathophysiological mechanisms, sometimes associated, leading to PH in SSc
  - Heterogeneity of SSc with various subtypes and organ involvement

Lefèvre G et al. Arthritis Rheumatol 2013

Systemic sclerosis : an heterogneous disease➔ different PH

1. Pulmonary arterial hypertension

- 1.1 Idiopathic
- 1.2 Heritable
  - 1.2.1 BMPR2 mutation
  - 1.2.2 Other mutations
- 1.3 Drugs and toxins induced
- 1.4 Associated with:
  - 1.4.1 Connective tissue disease
  - 1.4.2 Human immunodeficiency virus (HIV) infection
  - 1.4.3 Portal hypertension
  - 1.4.4 Congenital heart disease (Table 6)
  - 1.4.5 Schistosomiasis

1'. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis

- 1'.1 Idiopathic
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1''. Persistent pulmonary hypertension of the newborn

2. Pulmonary hypertension due to left heart disease

- 2.1 Left ventricular systolic dysfunction
- 2.2 Left ventricular diastolic dysfunction
- 2.3 Valvular disease
- 2.4 Congenital / acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
- 2.5 Congenital /acquired pulmonary veins stenosis

3. Pulmonary hypertension due to lung diseases and/or hypoxia

- 3.1 Chronic obstructive pulmonary disease
- 3.2 Interstitial lung disease
- 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
- 3.4 Sleep-disordered breathing
- 3.5 Alveolar hypoventilation disorders
- 3.6 Chronic exposure to high altitude
- 3.7 Developmental lung diseases (Web Table III)

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

Galie N *et al.* Eur Respir J 2015; Galie N *et al.* Eur Heart J 2016.

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Precapillary PAH (group 1)

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CTEPH (group 4)

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Postcapillary PH (cardiac involvement=group2)

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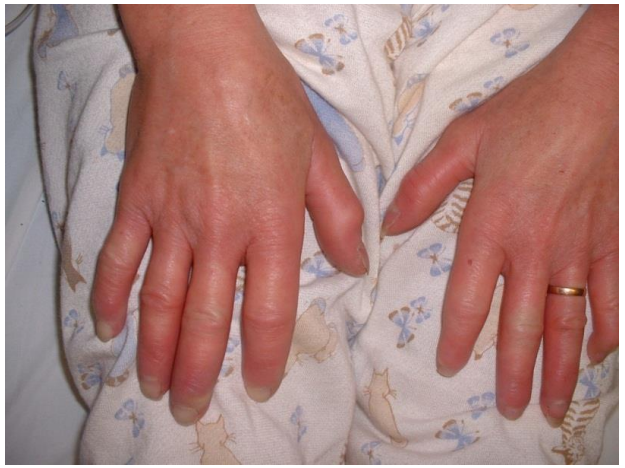
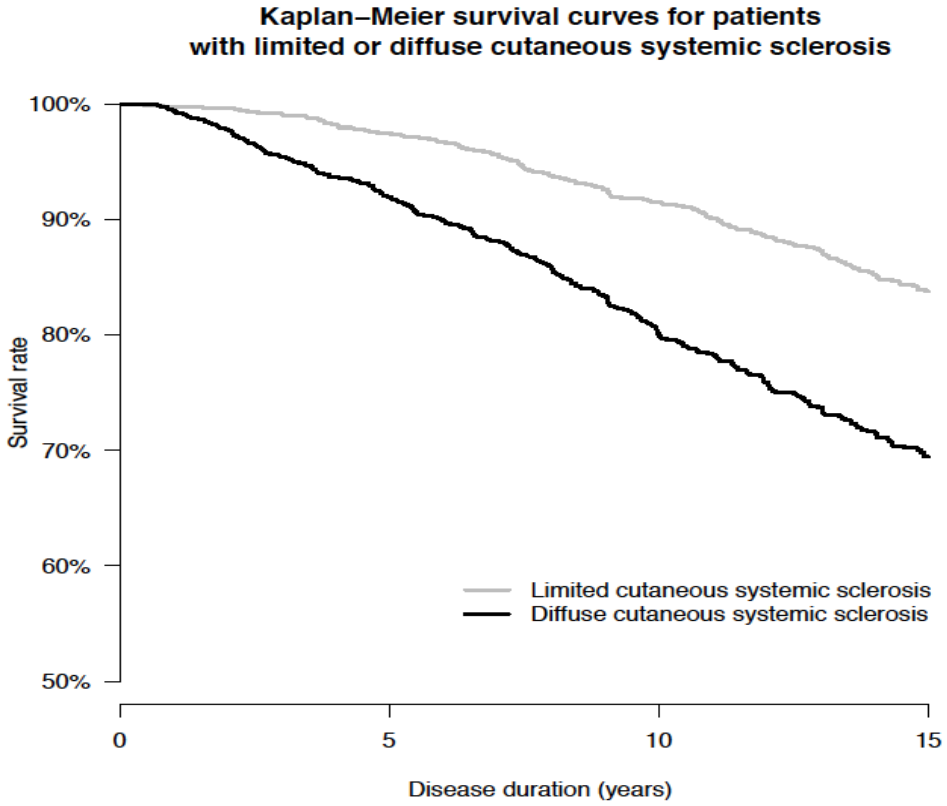
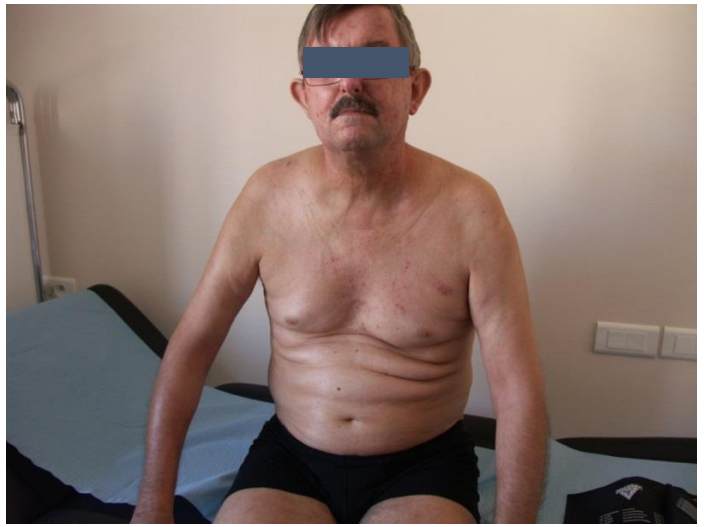
Systemic sclerosis : an heterogneous disease➔ cutaneous extension

- **Limited cutaneous(lcSSc) 70 %**
  - *Rare visceral involvement except PH*
  - *Anti-centromere Ab : 70 %*
- **Diffuse cutaneous(dcSSc) 30 %**
  - *Frequent and early visceral involvement*
  - *Anti-topo isomérase I : 30 %*



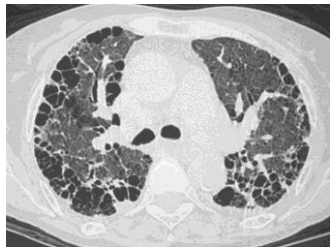




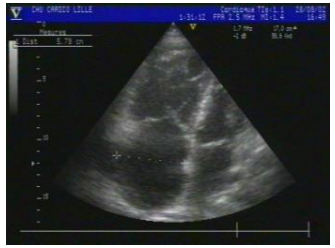
Sobanski V *et al.* JAMA. (submitted)

Systemic sclerosis : an heterogneous disease➔ organ involvement

ILD (50%)



Cardiac involvement

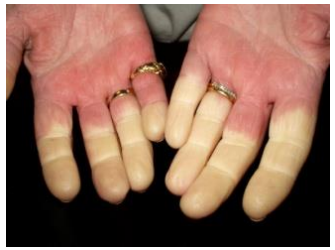


Cutanous involvement

GI

Kidney

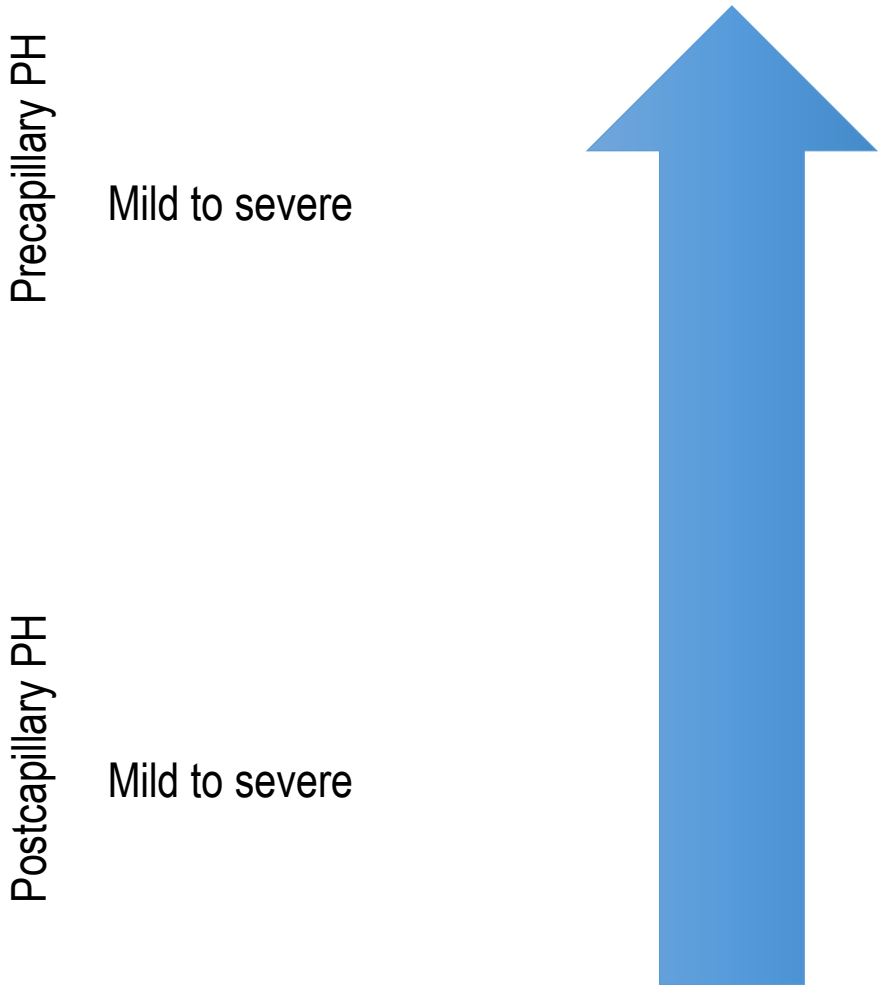
Raynaud



Articulations&muscles

Courtesy to Abraham D

PH in systemic sclerosis : major heterogeneity ≠ idiopathic PAH



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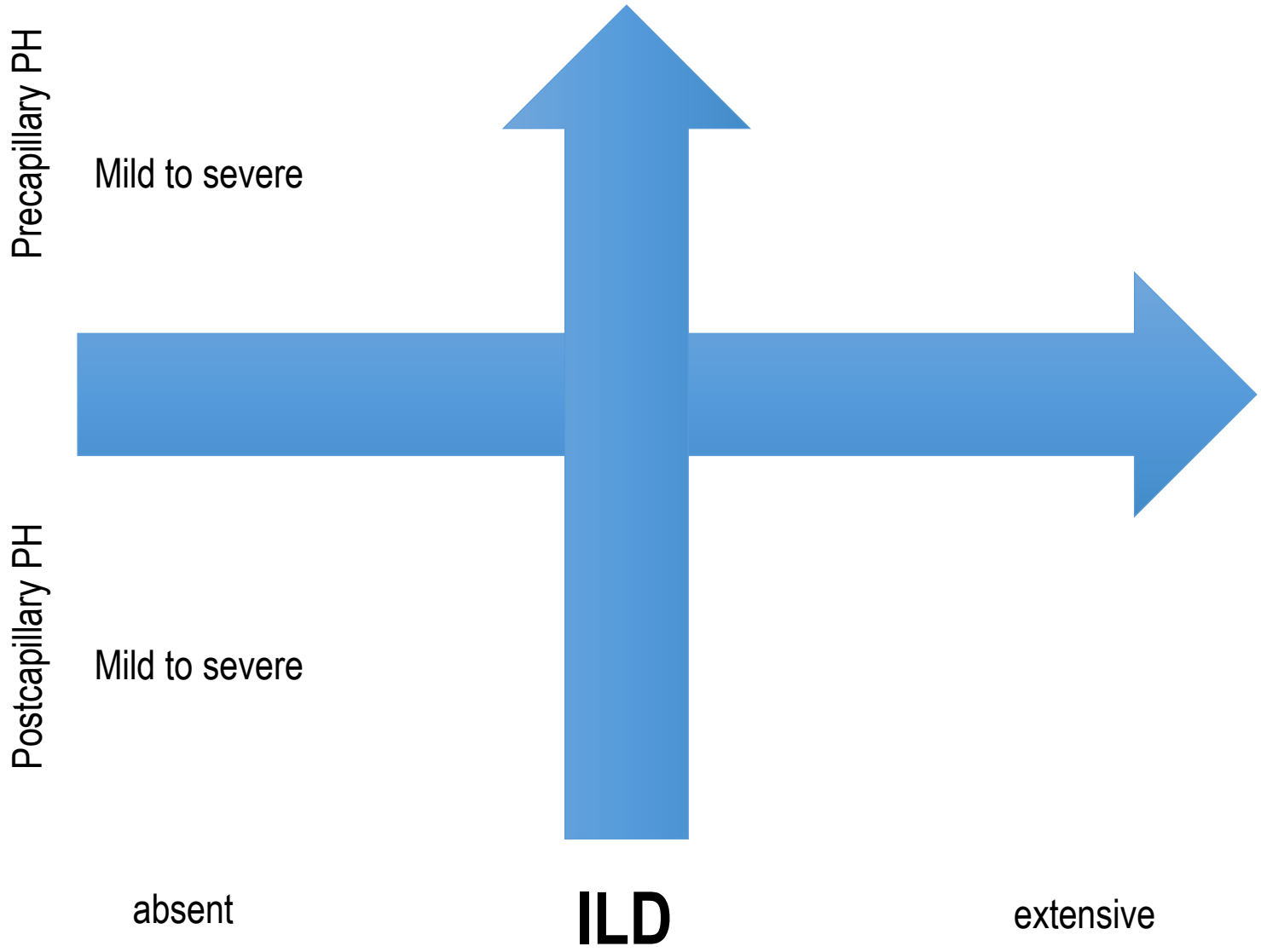

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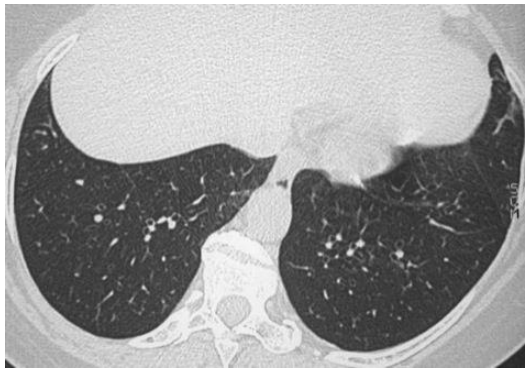

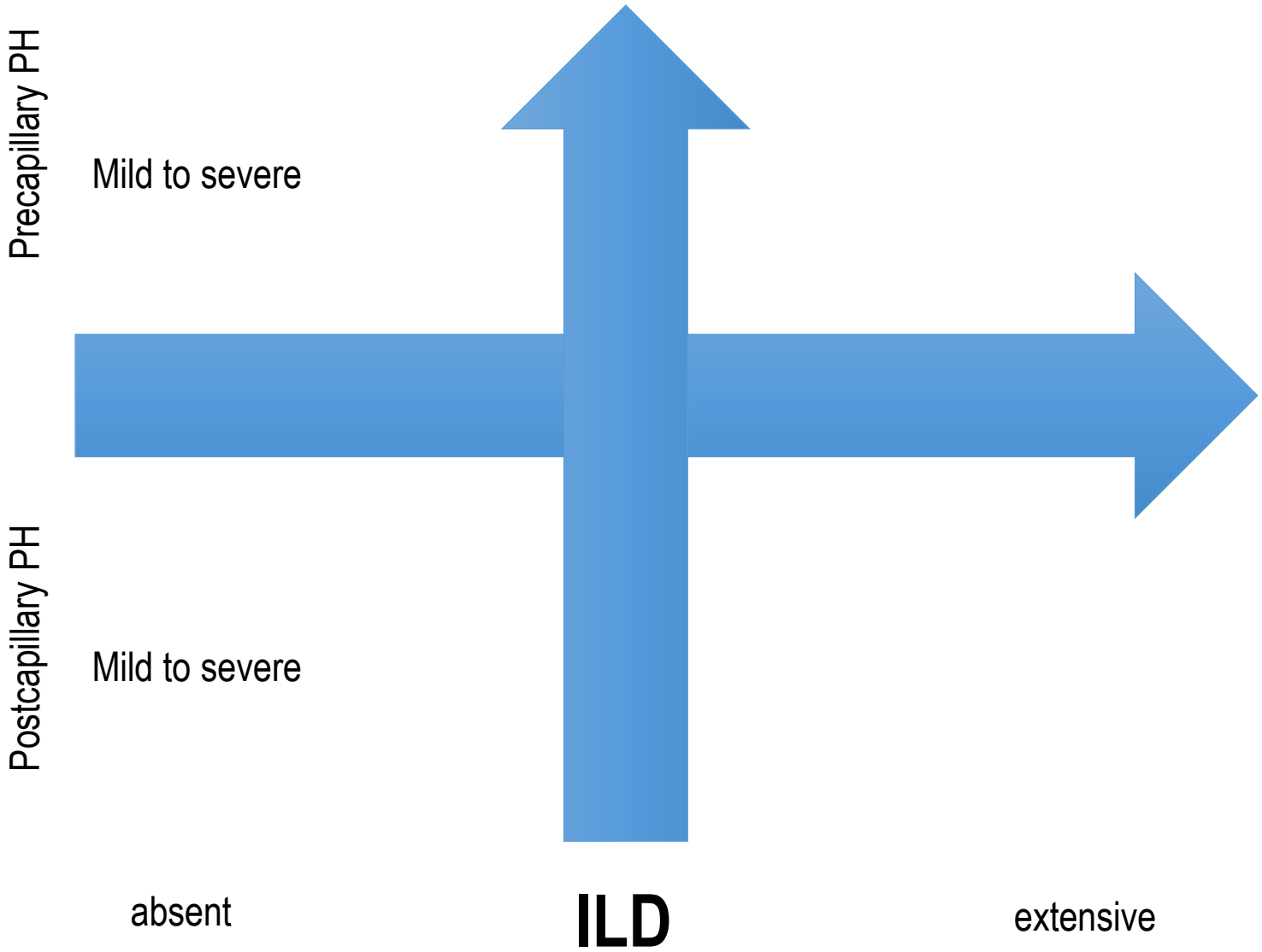

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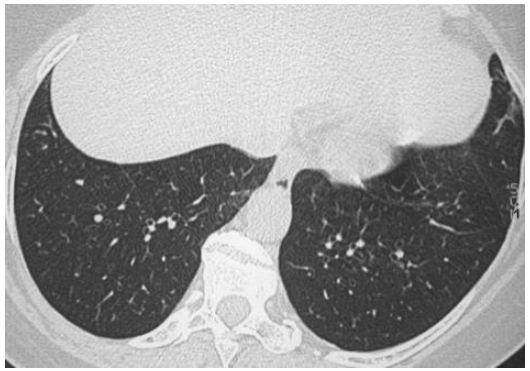
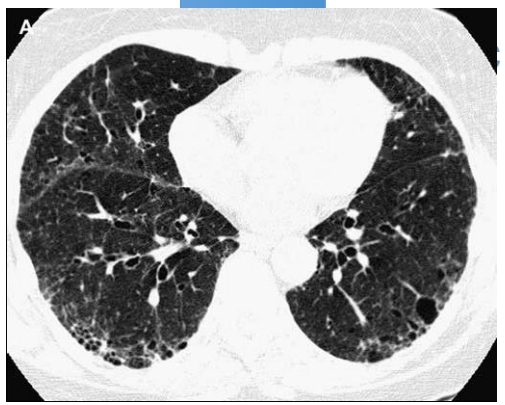


Precapillary PH

Mild to severe

Postcapillary PH

Mild to severe



absent

ILD

extensive

PH in systemic sclerosis : major heterogeneity ≠ idiopathic PAH

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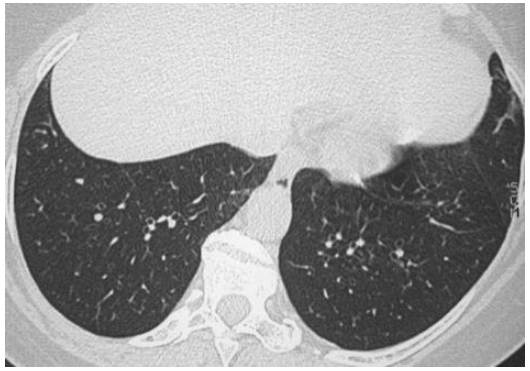

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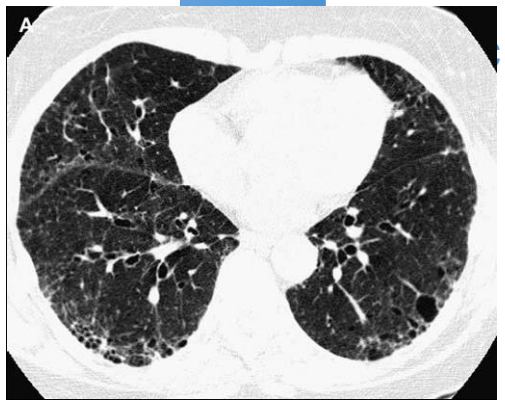

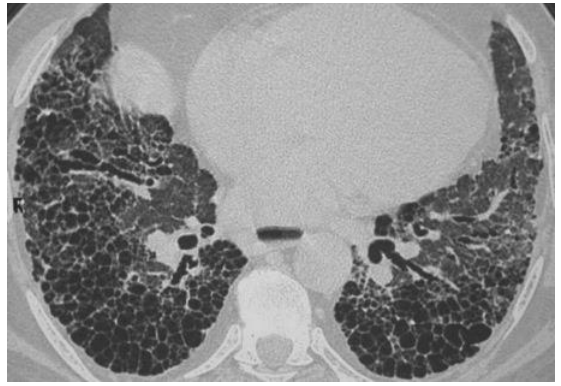

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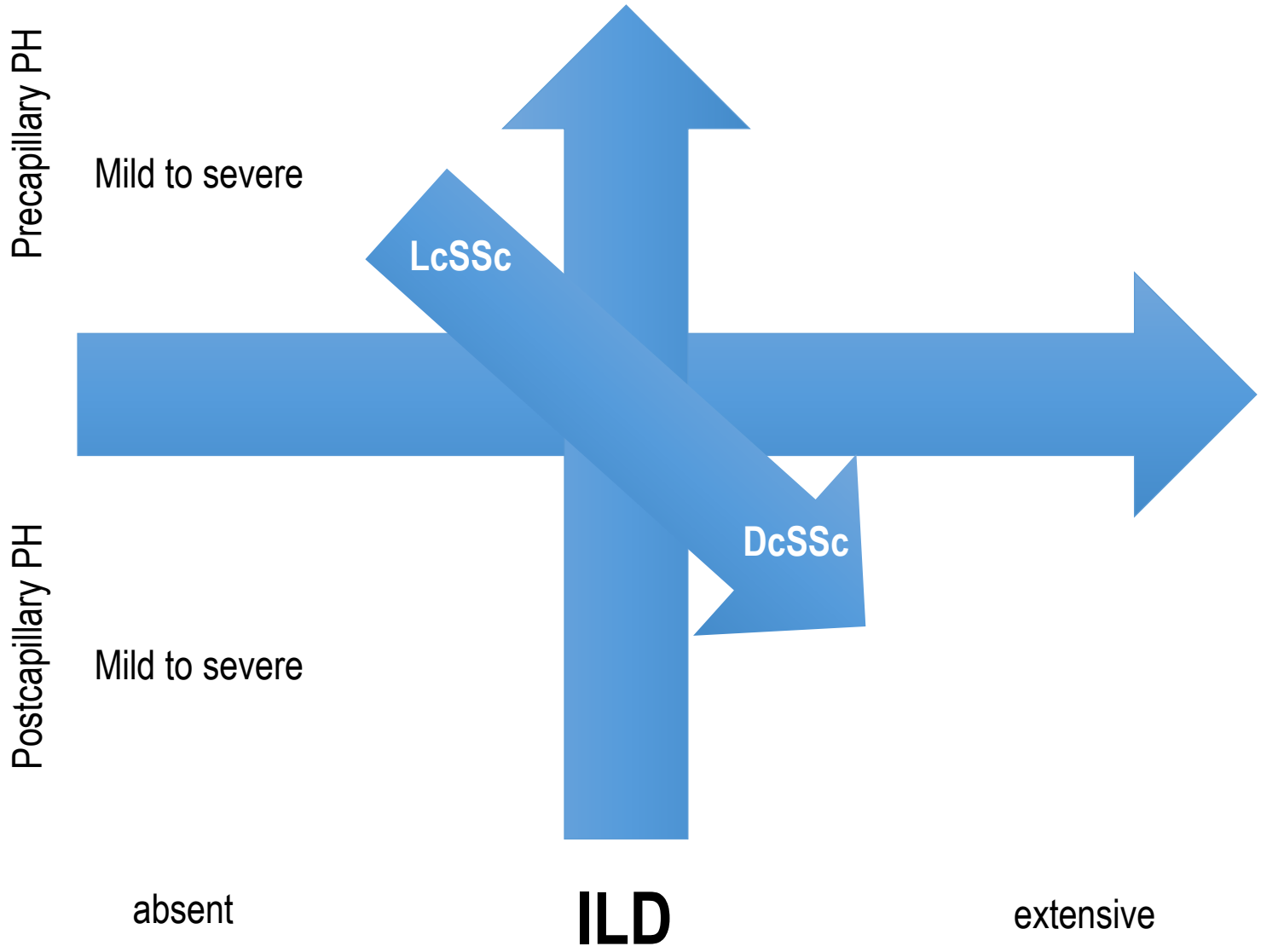
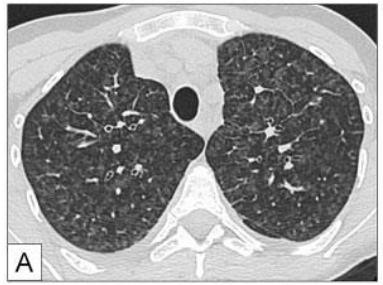
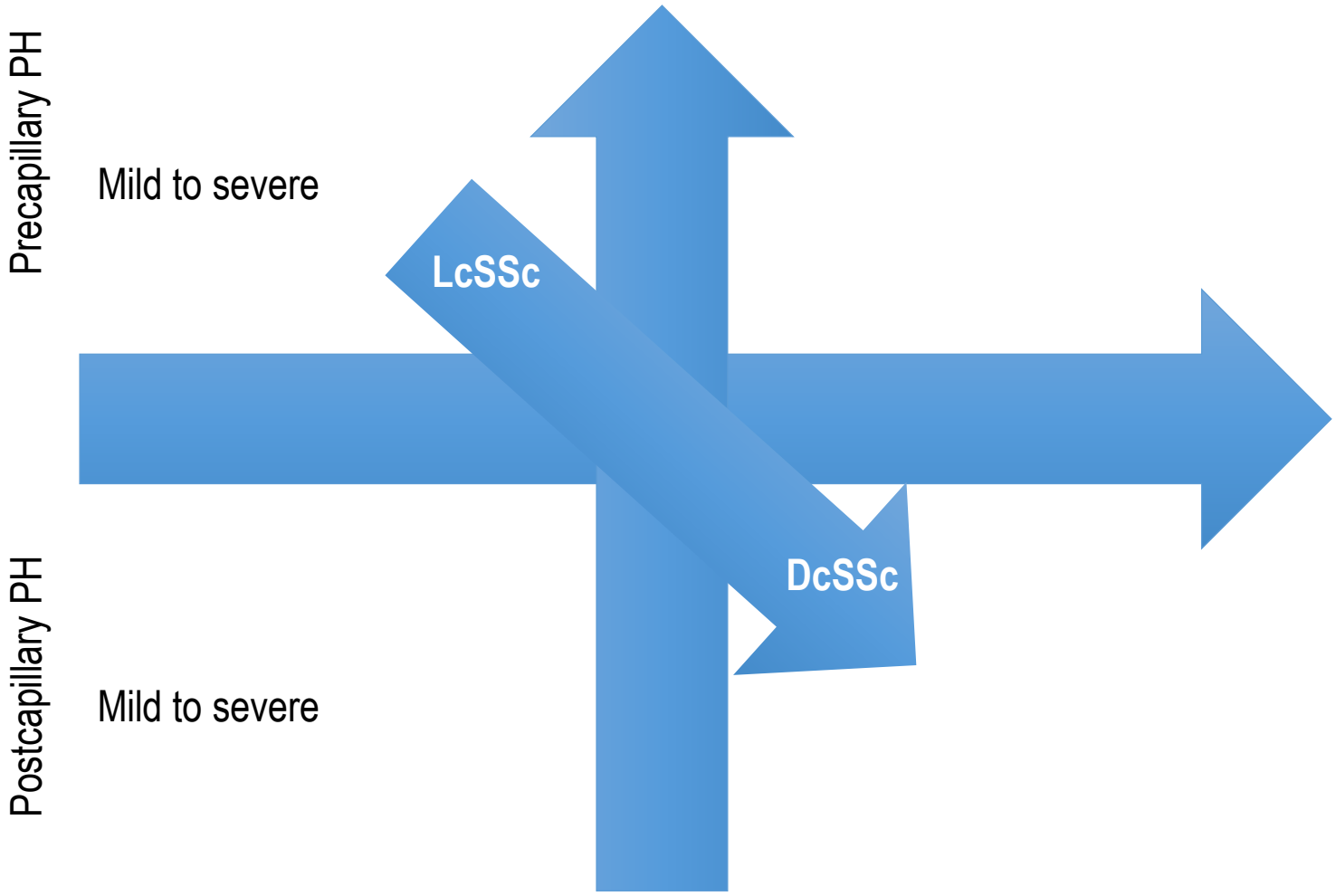


PH in systemic sclerosis : major heterogeneity ≠ idiopathic PAH

2/3 of patients

PVOD





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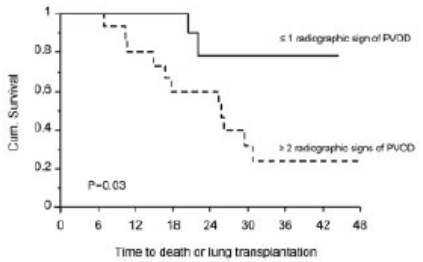

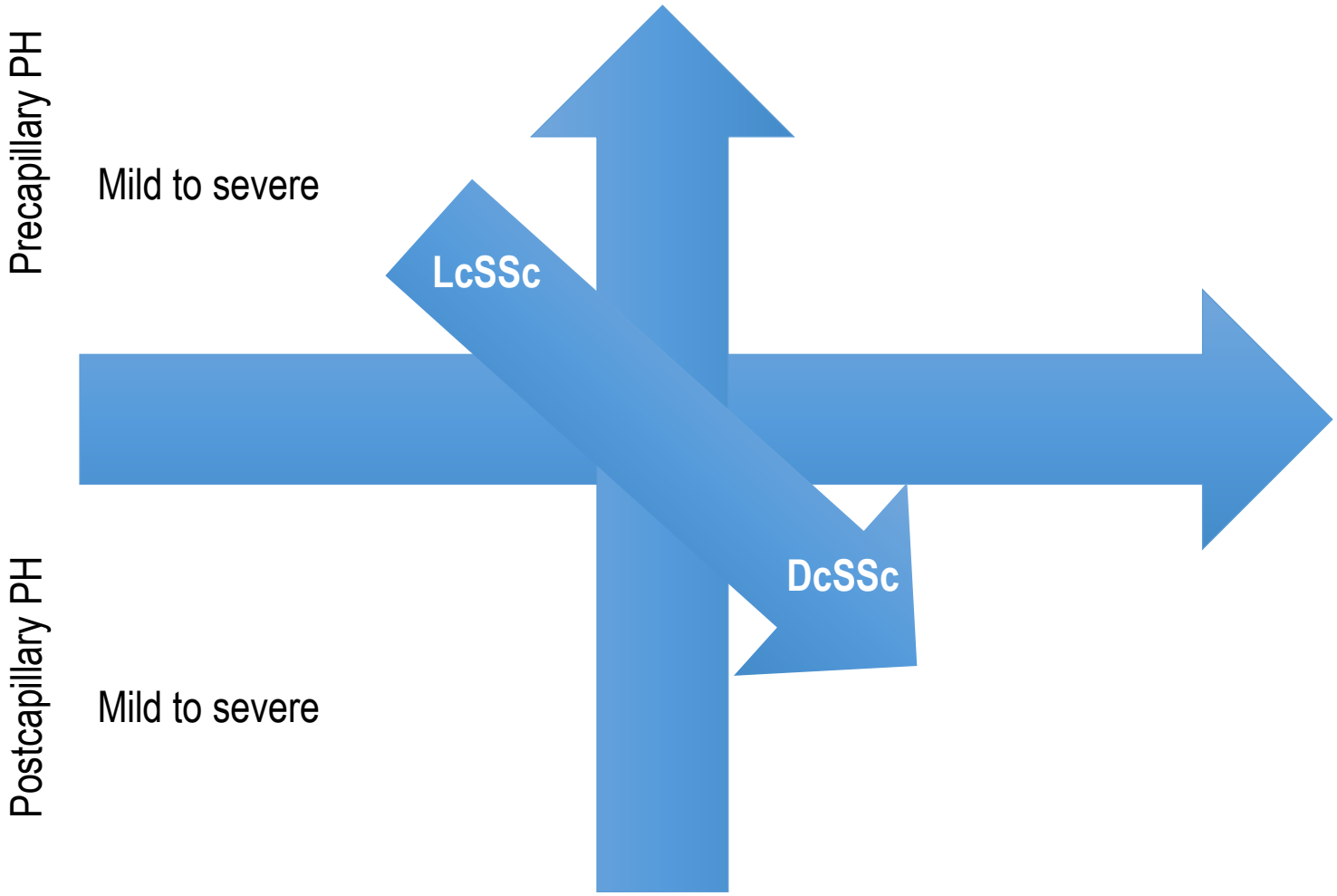

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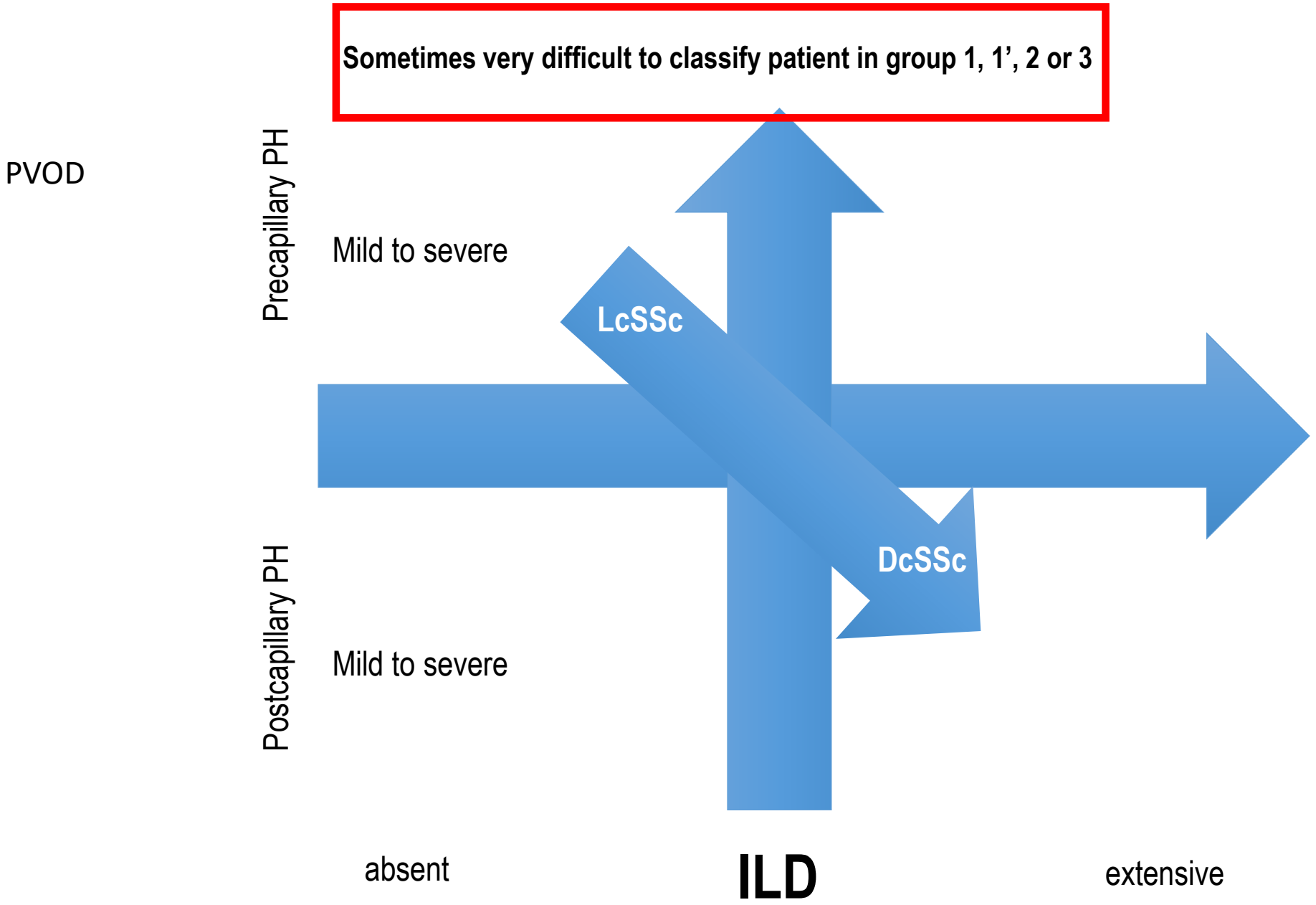

How to define homogeneous phenotypes in PH in scleroderma ?

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Cluster analysis : Principles

To find homogeneous groups in a heterogeneous population

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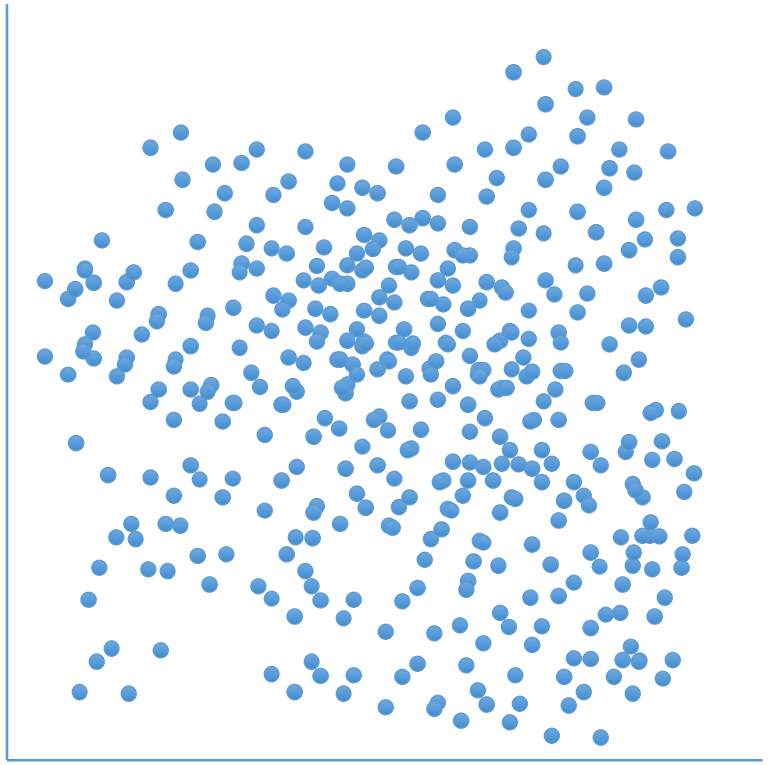
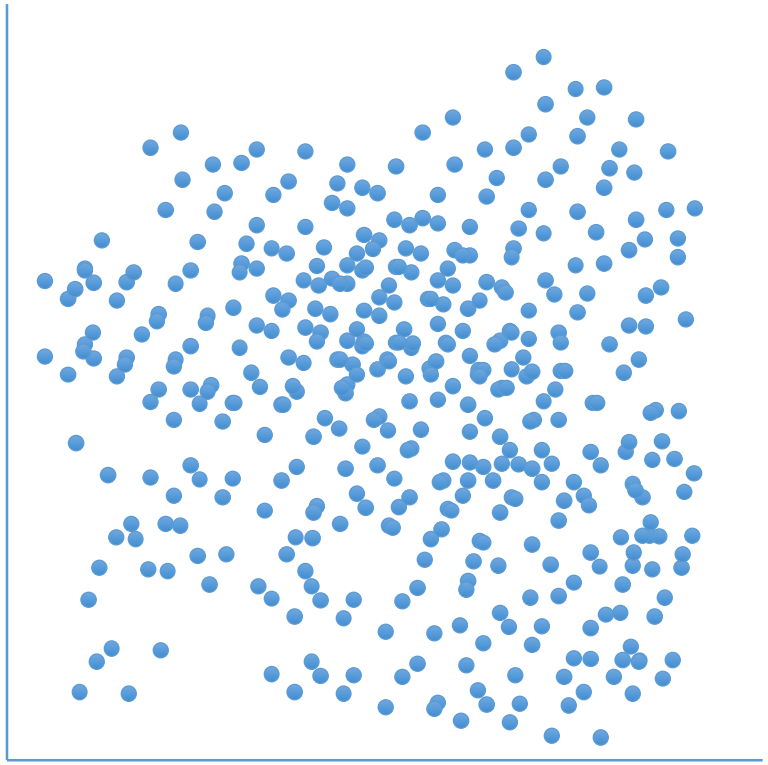


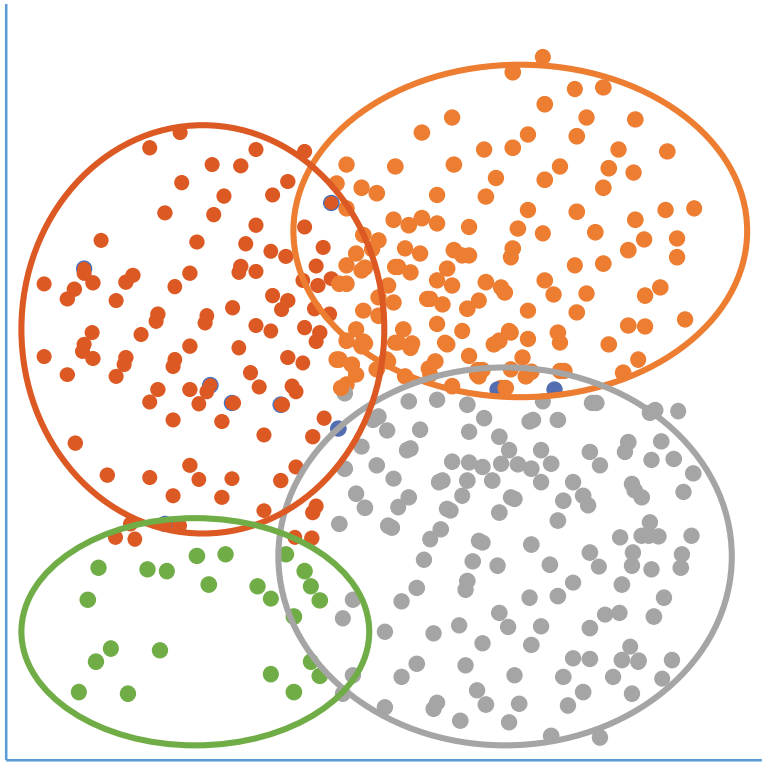
1. **Definition of clustering variables**
2. **The analysis finds homogeneous clusters according to these variables**
3. **Comparisons of the characteristics of the different clusters**

How to define homogeneous phenotypes in PH in scleroderma ?

Cluster analysis : Principles

To find homogeneous groups in a heterogeneous population





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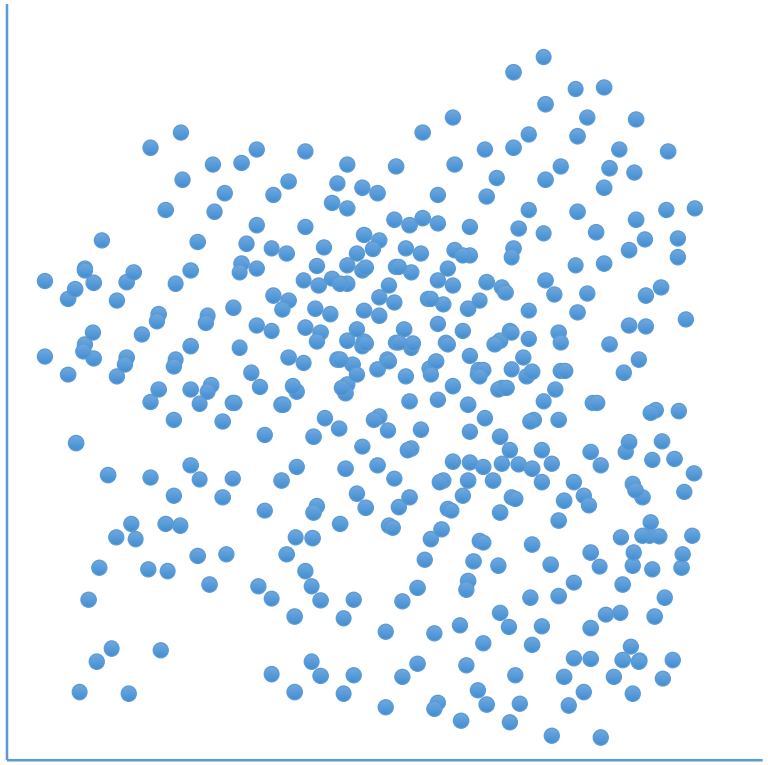
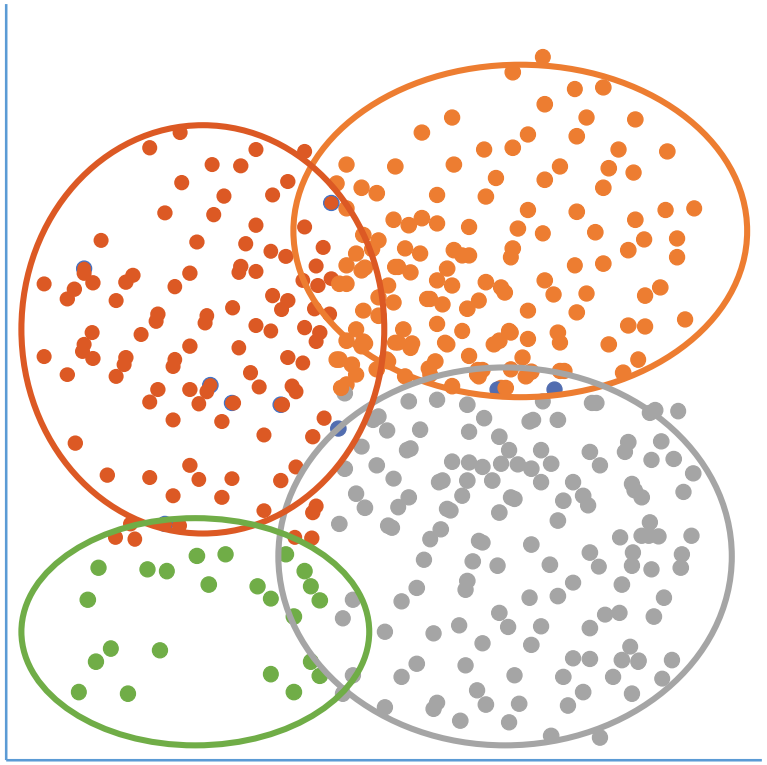
➔ **Personalized medicine and better understanding of the disease**





Cluster analysis in scleroderma patients with precapillary PH

- Collaborative study between Registry of the French National Pulmonary Hypertension Network and Johns Hopkins Hospital (Paul Hassoun, Fred Wigley, Baltimore)
- Primary objective : cluster analysis to define homogeneous groups of patients
- Secondary objective: survival analysis of clusters
- 200 patients
  - ACR-EULAR 2013 criteria for SSc
  - Precapillary PH at RHC
  - Baselien chest HRCT and LFT at baseline
  - No CTEPH
- ILD classified as absent/limited/extensive (Goh's staging system)
- Statistical method
  - Cluster analysis : K-means using 4 variables : FVC, DLCO, PVR et présence / extension ILD
  - Survival analysis

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- Collaborative study between Registry of the French National Pulmonary Hypertension Network and Johns Hopkins Hospital (Paul Hassoun, Fred Wigley, Baltimore)
- Primary objective : cluster analysis to define homogeneous groups of patients
- Secondary objective: survival analysis of clusters
- 200 patients
  - ACR-EULAR 2013 criteria for SSc
  - Precapillary PH at RHC
  - Baseline chest HRCT and LFT
  - No CTEPH
- ILD classified as absent/limited/extensive (Goh's staging system)
- Statistical method
  - Cluster analysis : K-means using 4 variables : FVC, DLCO, PVR et présence / extension ILD
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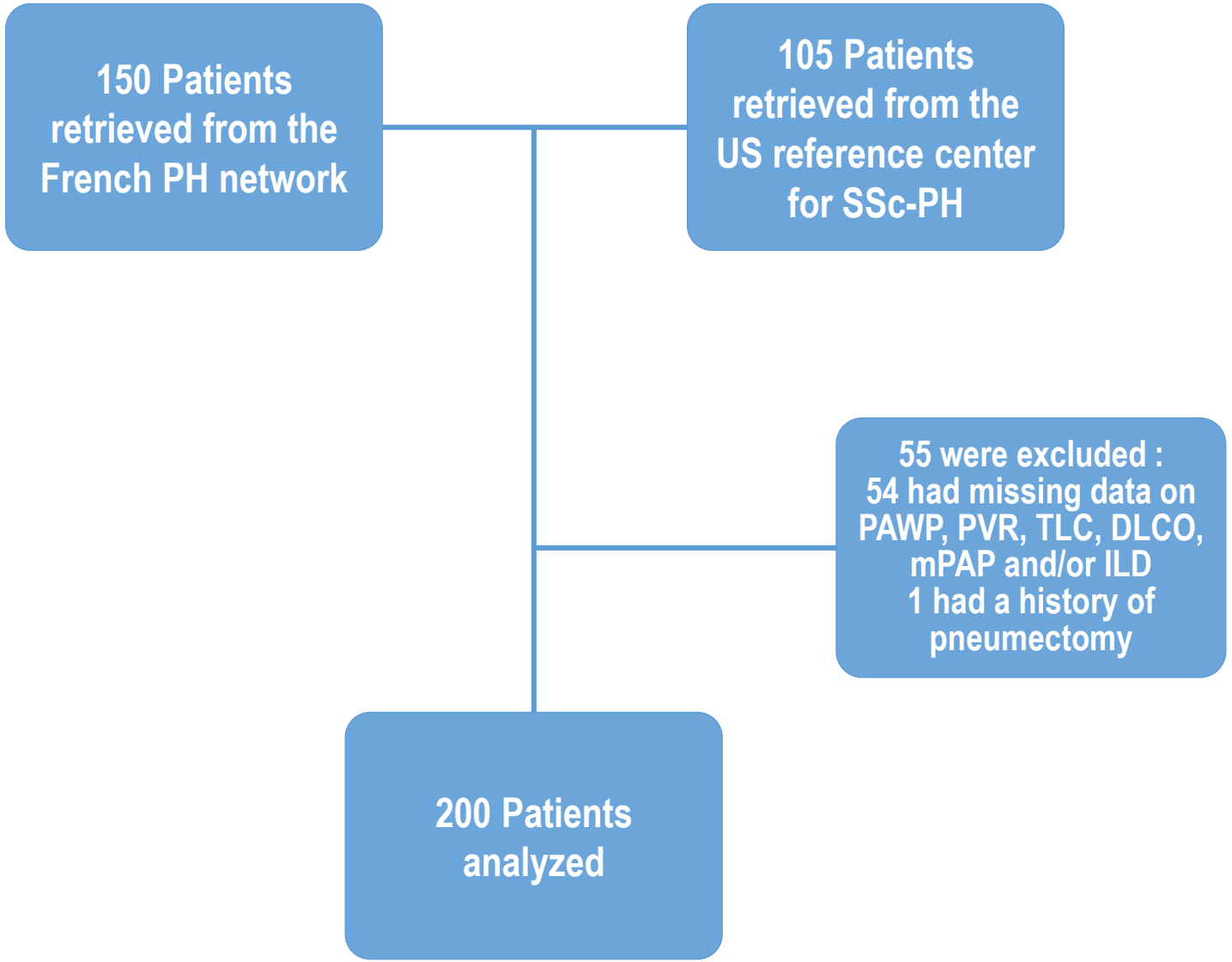
Flowchart of the study



Baseline characteristics

	n	mean ± SD or n (%)
Age, years	200	61.2 ± 11.9
Males	200	47 (23.5)
Diffuse systemic sclerosis	198	52 (26.3)
Limited systemic sclerosis	198	146 (73.7)
Anti-centromere antibodies	128	46 (35.9)
Anti-topoisomerase antibodies	133	24 (18.1)
NYHA functional class III-IV	184	140 (76.1)
DLCO, % of predicted	200	47.1 ± 18.5
FVC, % of predicted	187	79.2 ± 22.9
Six-minute walk distance, meters	169	286 ± 108
No interstitial lung disease	200	94 (47.0)
Limited ILD according to Goh's staging system	200	42 (21.0)
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	n	mean ± SD
mPAP, mmHg	200	40.4 ± 10.6
PCWP, mmHg	200	8.7 ± 3.4
Cardiac index, L/min/m^2	200	2.6 ± 0.8
Pulmonary vascular resistance, WU	200	8.0 ± 4.6

Cluster analysis : 4 clusters C1/C2/C3/C4

- C1 :
  - 94 patients
  - Moderate PH (PVR : 8 ± 3 UW)
  - 98 % no ILD or limited ILD
  - Normal FVC but DLCO : 45±13 %
  - 84 % LcSSc ; 50 % ACA ; 5 % anti-topo 1

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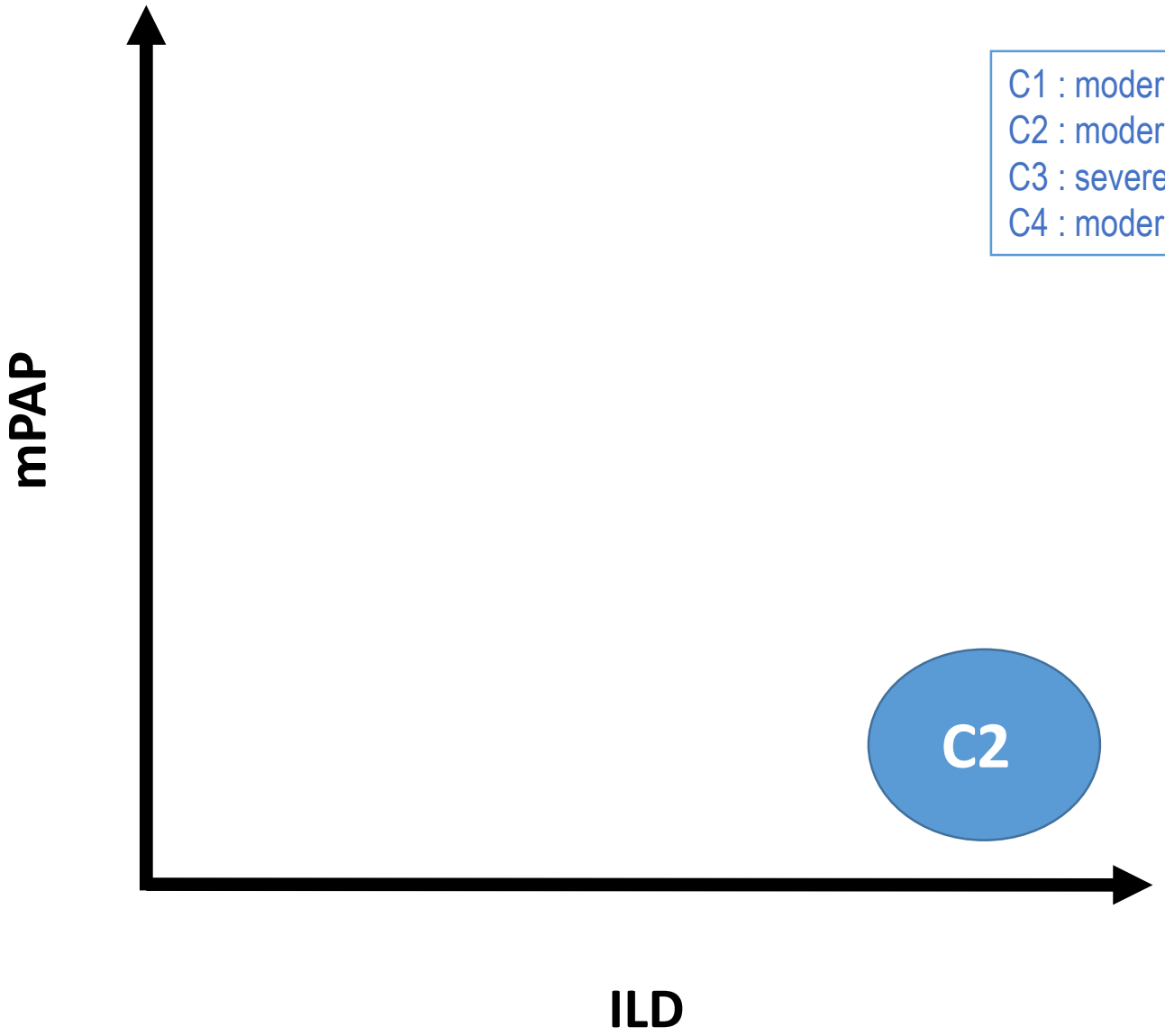
moderate PH due to extensive ILD with low DLCO



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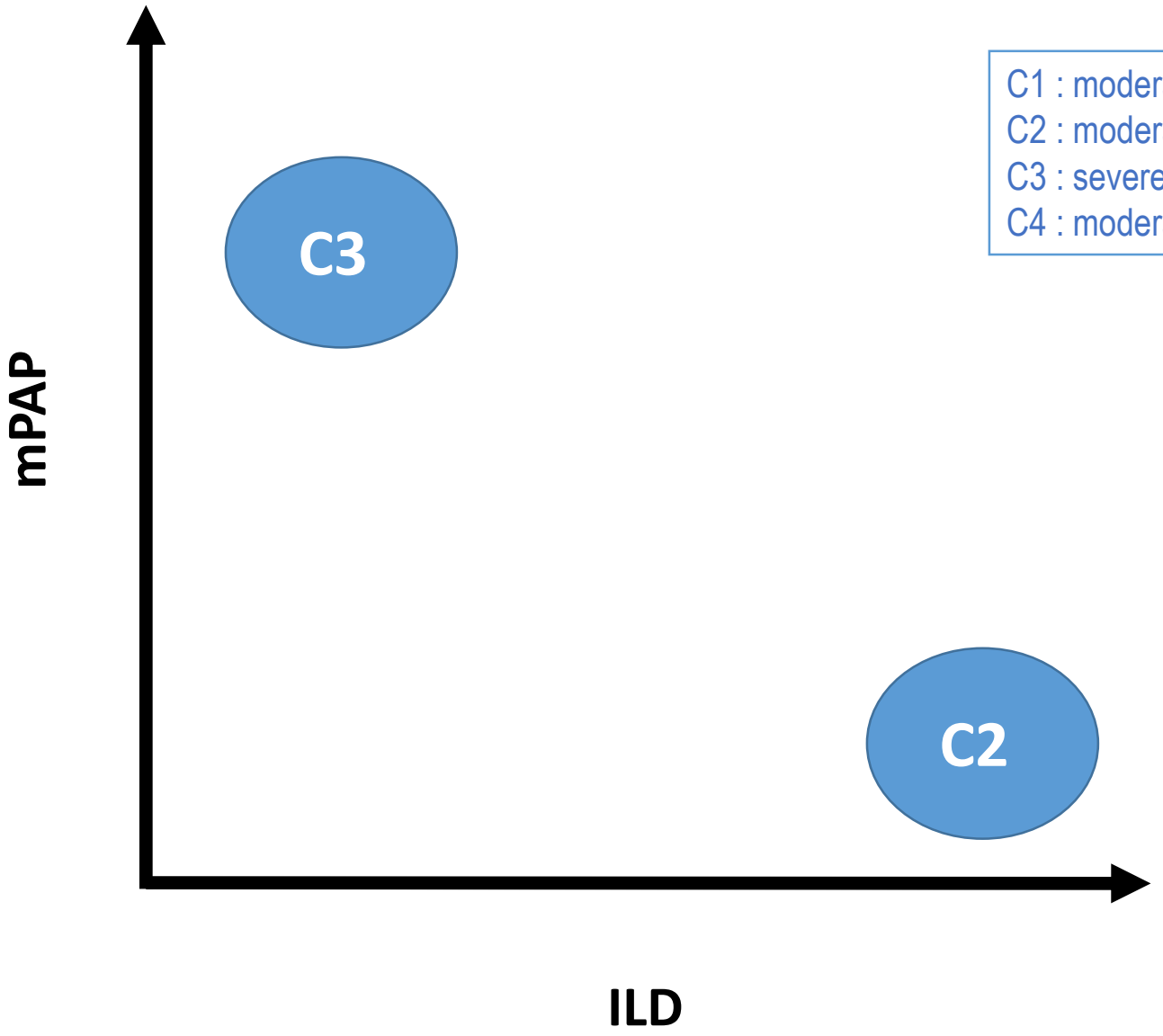

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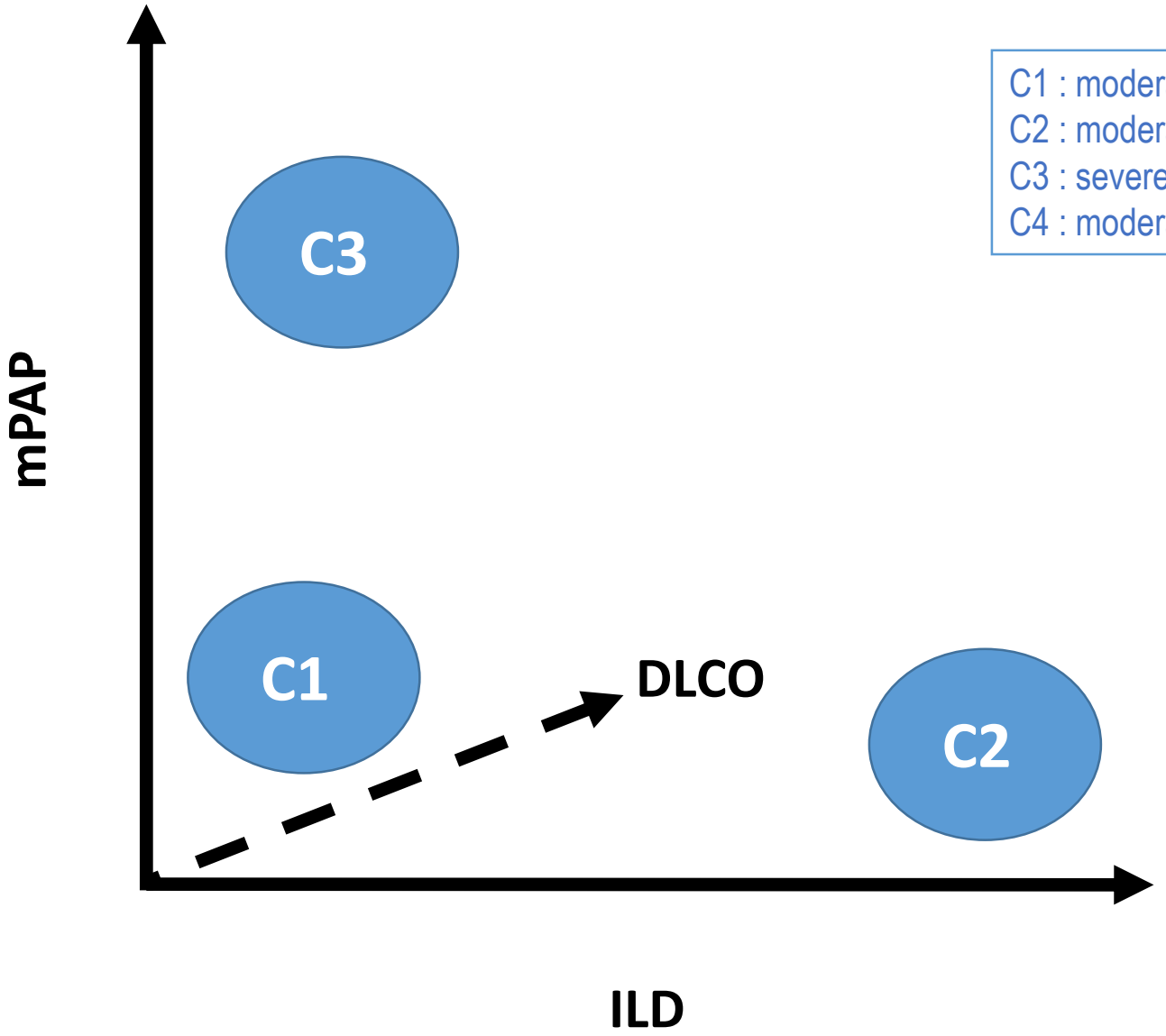

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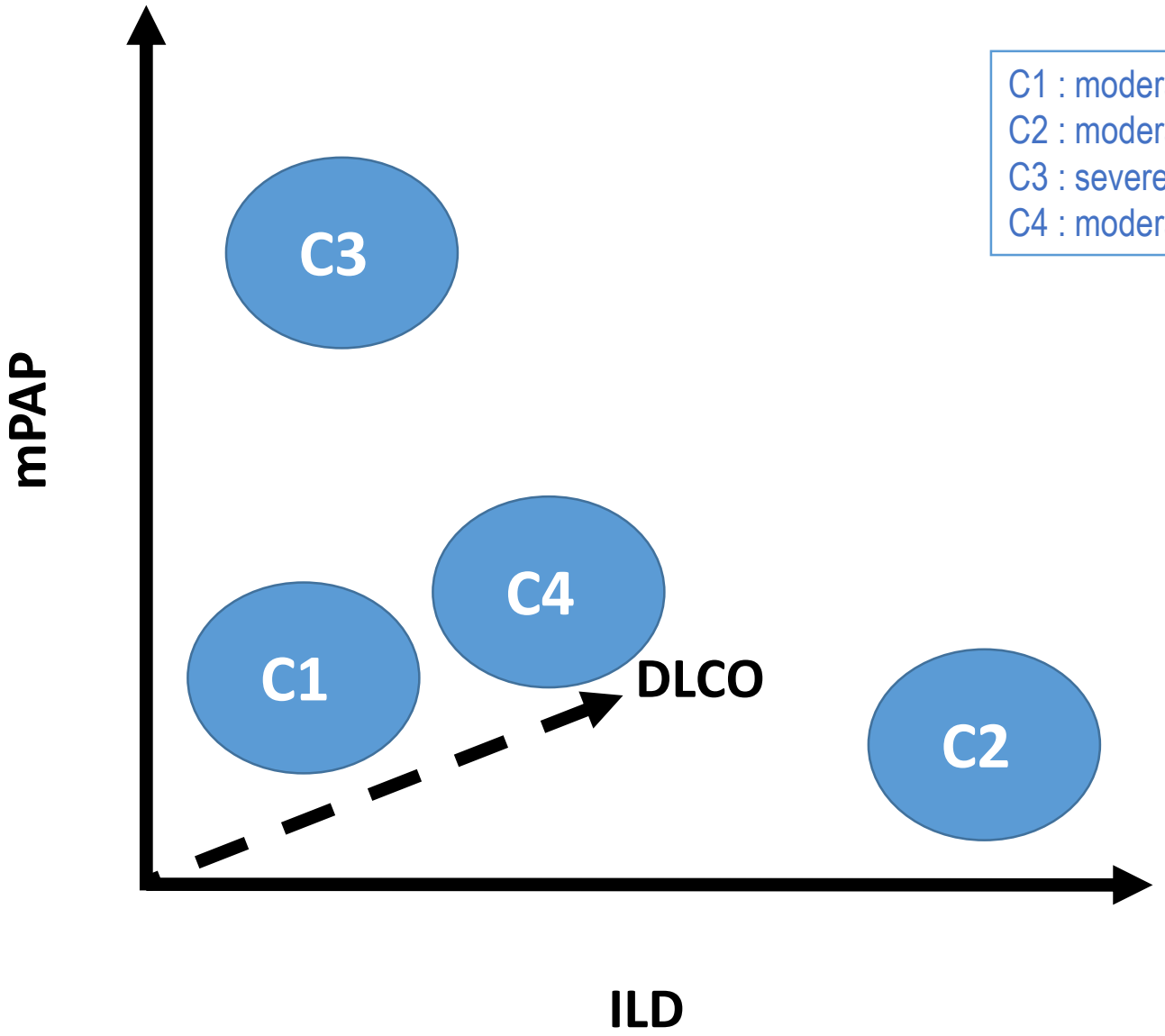

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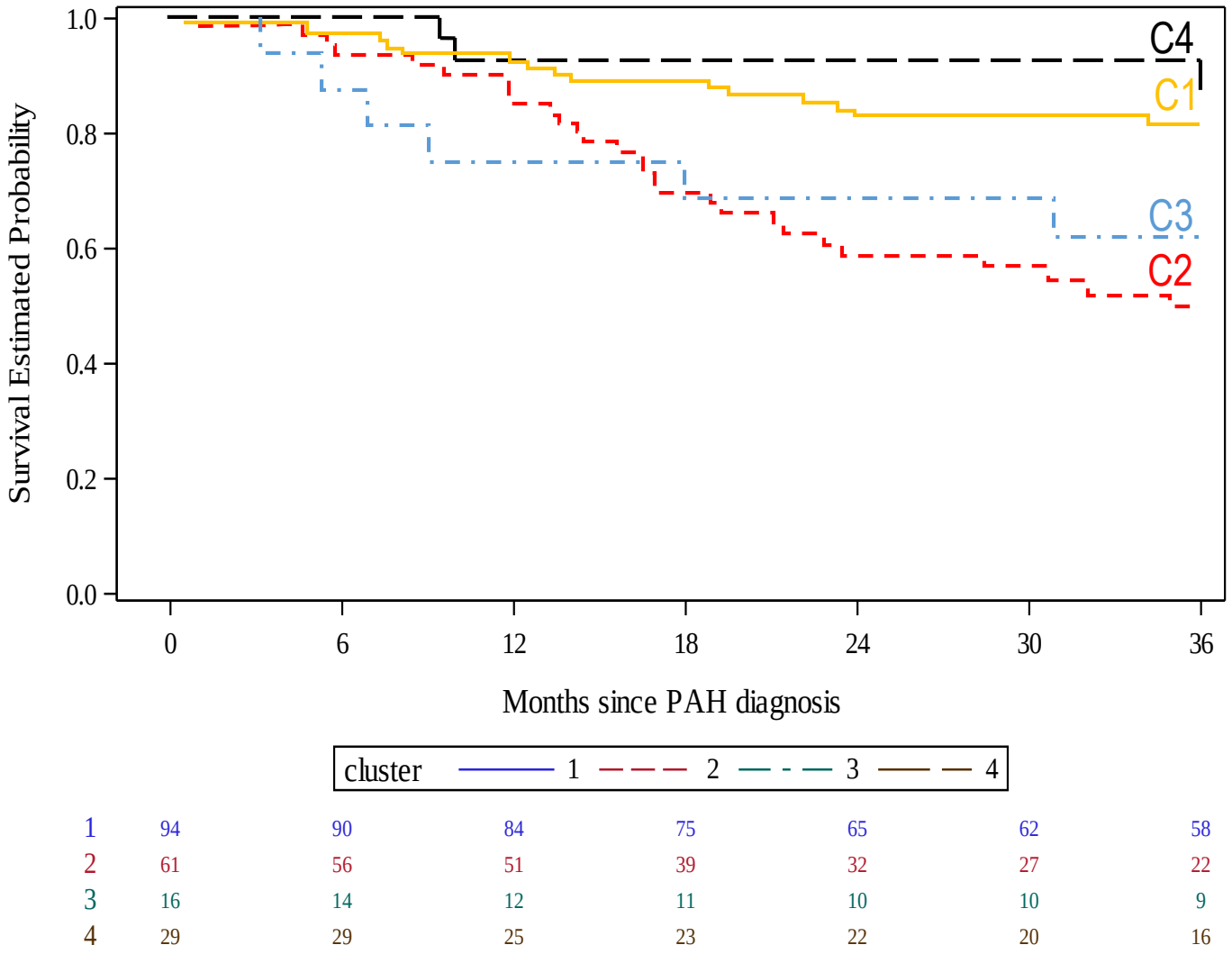

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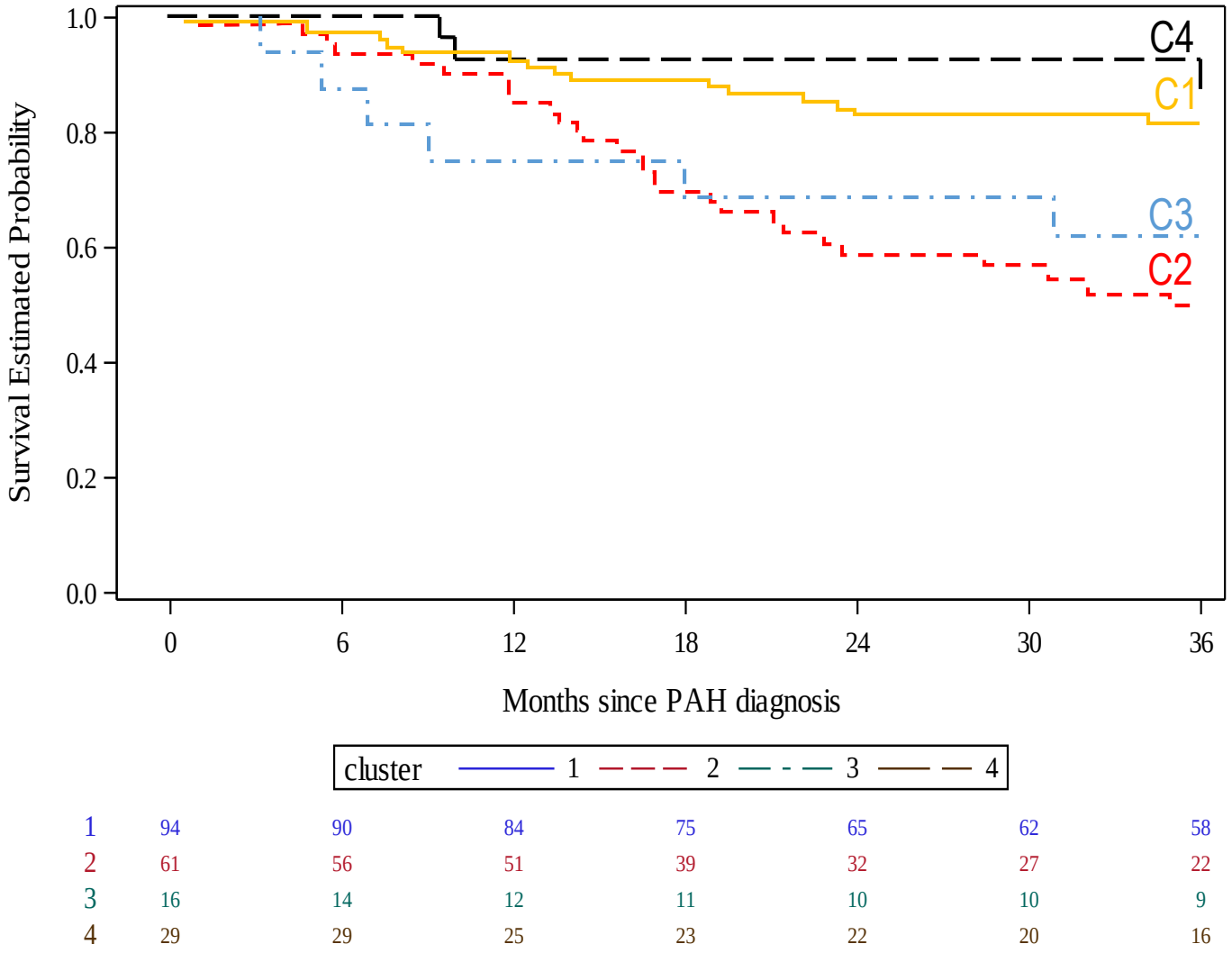

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3-yr survival

- C1 : 81 % [95 % confidence interval 71 - 89]
- C4 : 87 % [64 - 98]
- C2 : 50 % [36 - 62]
- C3 : 62 % [34 - 81]

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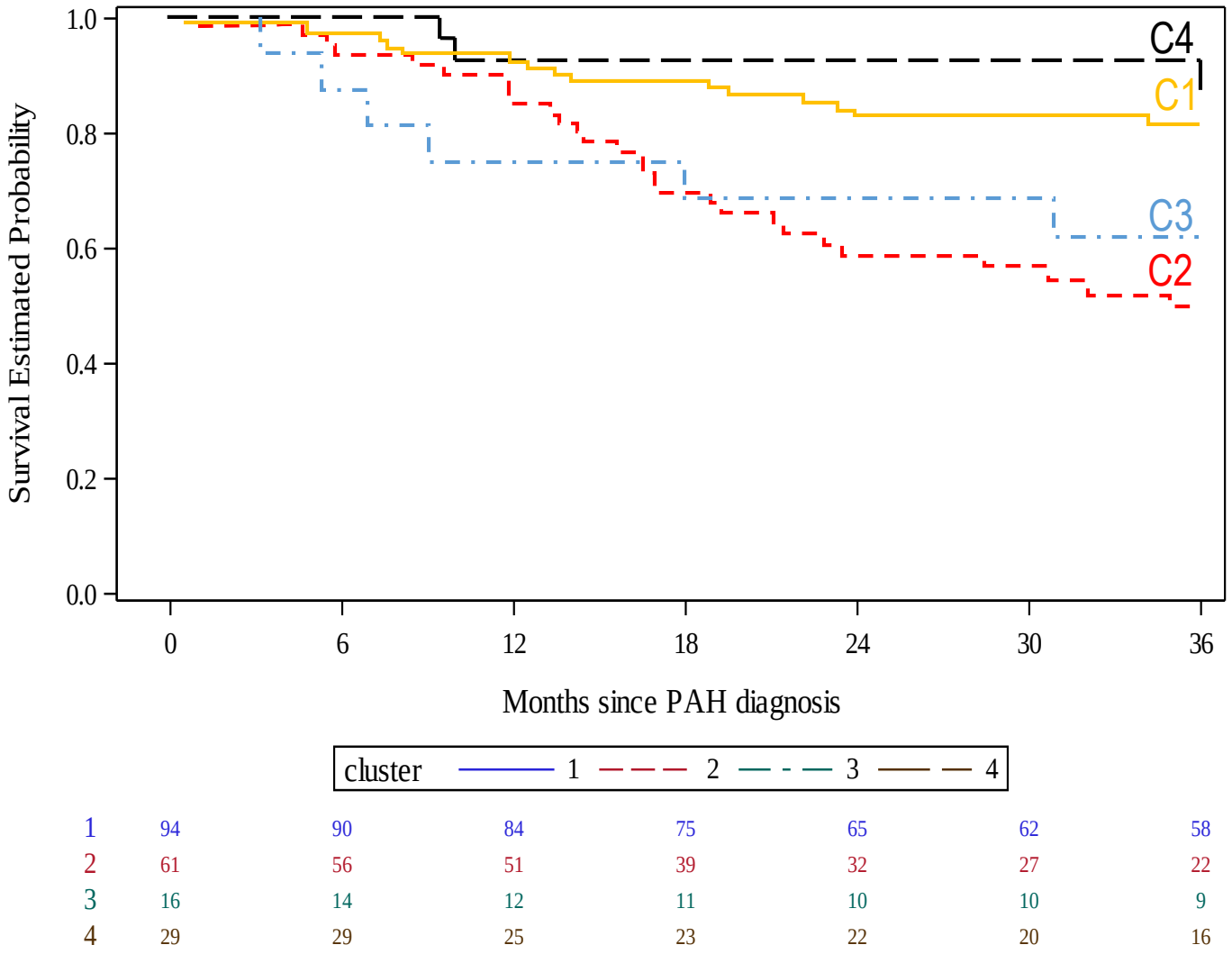

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Age and sex adjusted with C1 as a reference

- C2 : HR à 3,14 [95 % CI 1,66 - 5,94], *p < 0,005*
- C3 : HR à 2,53 [95 % CI 0,99 - 6,49], *p = 0,052*
- C4 : HR à 0,65 [95 % CI 0,19 - 2,27], *p = 0,507*

Discussion-Conclusion

- We found 4 clusters in patients with SSc and precapillary PH
- 2 clusters have a good prognosis : C1 et C4
  - C1 is the most frequent and corresponds to precapillary PAH, low DLCO and no extensive ILD ➔ group 1 & limited ILD or no ILD have the same behavior
  - C4 resembles C1 but DLCO is preserved. Prognosis is even better (87 %) ➔ groupe 1
- 2 clusters have a bad prognosis : C2 et C3

Discussion-Conclusion

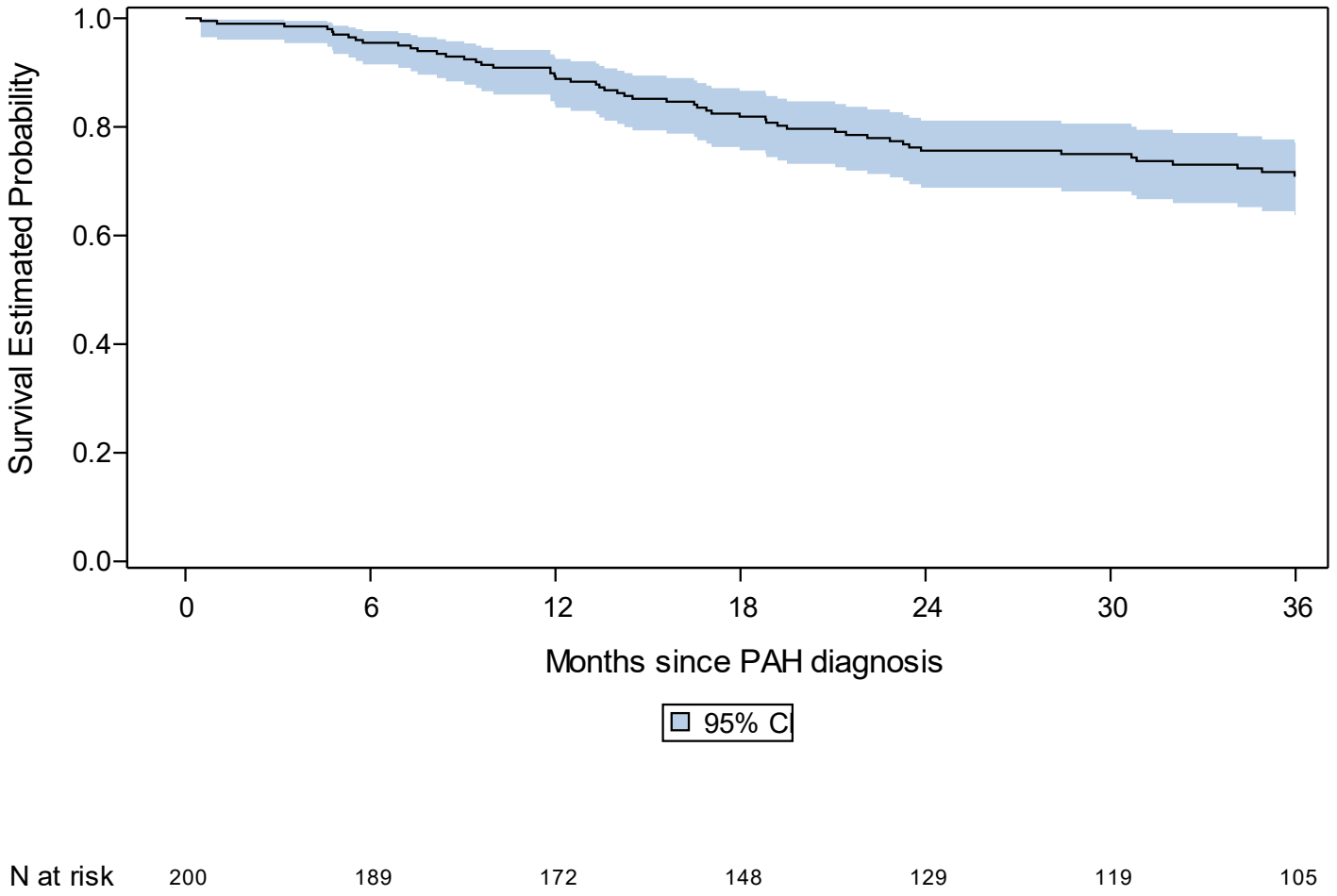
- 2 clusters have a bad prognosis : C2 et C3
  - C2 is characterized by 100 % of extensive ILD (& high percentage of DcSSc and anti-topo isomérase) and the worse 3-yr survival (50 %)
    ➔ the presence of an extensive ILD, whatever the hemodynamics, is a major grouping characteristic (group 3)
  - C3 is characterized by a severe PAH with no extensive ILD and a 3-yr survival of 62%
    (groupe 1)
  - **<u>Although completely different, C2 and C3 share a common bad prognosis</u>**

Discussion-Conclusion

- First study assessing the presence of homogeneous clusters in SSc patients with precapillary PH
- Helpful for the clinician
  - Severe hemodynamics in SSc patient without an extensive ILD
  - Extensive ILD whatever the hemodynamics
    are the 2 clusters with a bad prognosis
  - In these patients, an early evaluation in a transplantation center should be performed
  - The presence of a limited ILD or the absence of ILD seem to have the same signification and not to impact the prognosis
- Remaining questions (not exhaustive) :
  - PVOD ?
  - Occult left ventricular dysfunction ?

backup

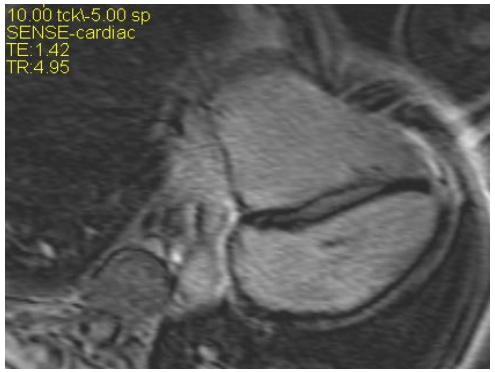
Overall survival : 73.6% at 3 years



PH in sysemic sclerosis : major heterogeneity ≠ idiopathic PH

PVOD

Occult postcapillary PH



Myocardial fibrosis : 20%

Precapillary PH

Mild to severe

LcSSc

DcSSc

Postcapillary PH

Mild to severe

absent

ILD

extensive

Hachulla *et al.* Ann Rheum Dis 2009

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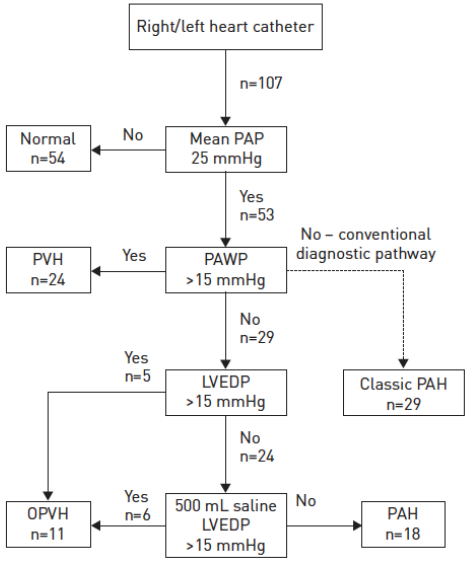
PVOD

20% of

Occult postcapillary PH



Fox B *et al.* Eur Respir J 2013