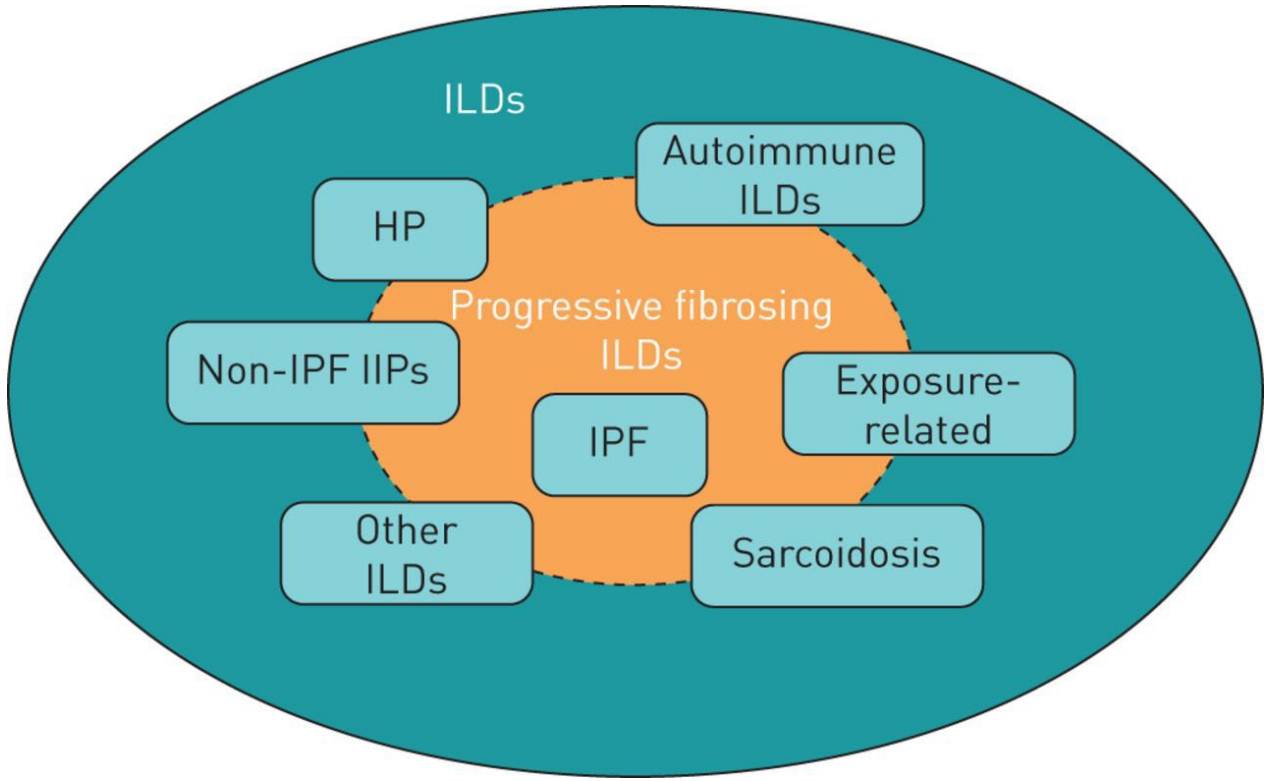
Pulmonary Venous Quantitation Predicts Mortality in Early Lung Fibrosis

Supervisor: Prof. Joseph Jacob

Vichayasit Tantayapong

Fibrosing Interstitial Lung Disease (ILD)

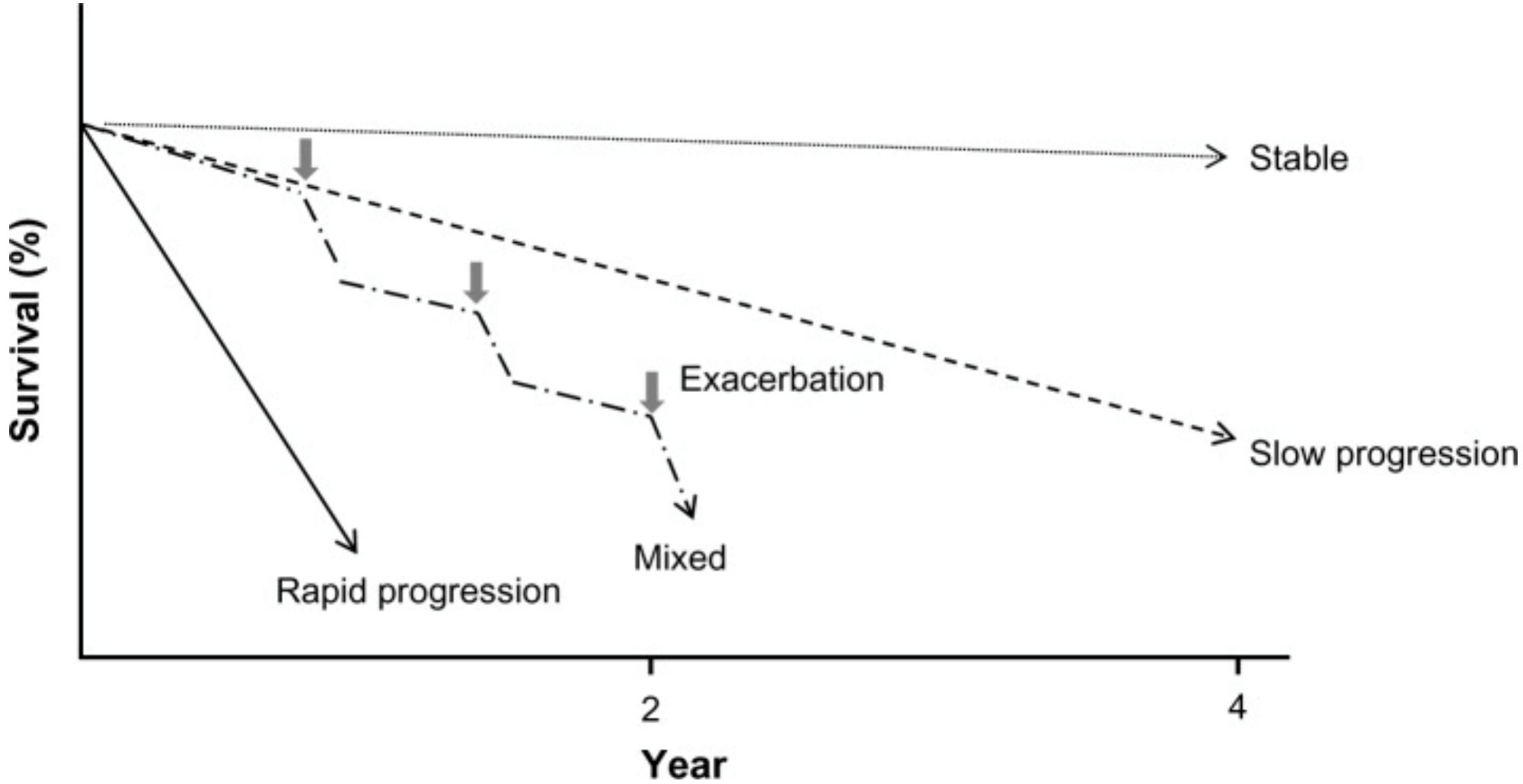


Idiopathic Pulmonary Fibrosis (IPF)

3 – 5 years median survival time from diagnosis

Cottin, V., Wollin, L., Fischer, A., Quaresma, M., Stowasser, S., & Harari, S. (2019). Fibrosing interstitial lung diseases: knowns and unknowns. *European Respiratory Review*, *28*(151). https://doi.org/10.1183/16000617.0100-2018

Clinical course

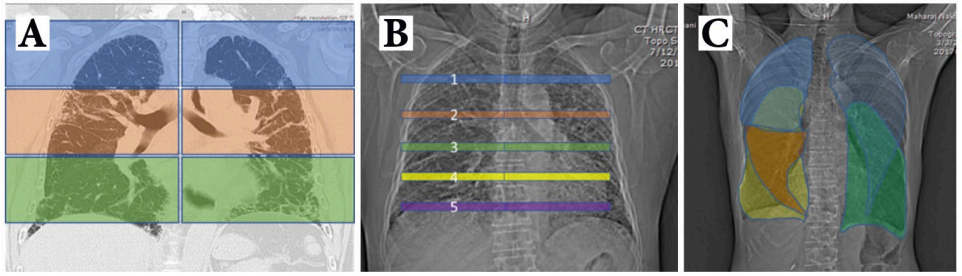


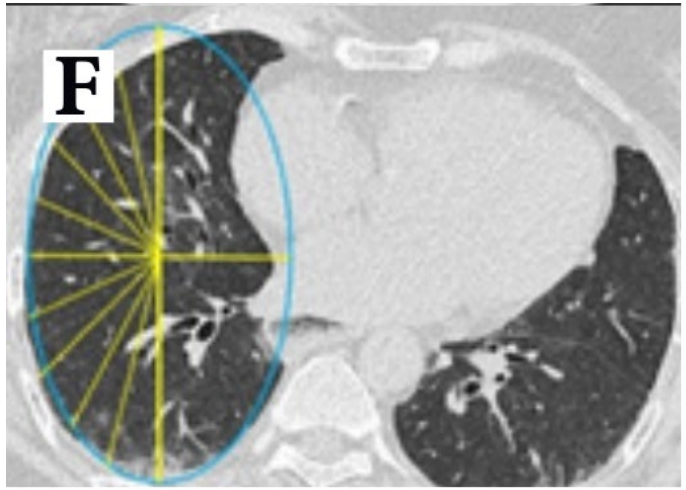
Fujimoto, H., Kobayashi, T., & Azuma, A. (2016). Idiopathic Pulmonary Fibrosis: Treatment and Prognosis. Clinical medicine insights. Circulatory, respiratory and pulmonary medicine, 9(Suppl 1), 179–185. https://doi.org/10.4137/CCRPM.S23321

Prognostic factors

- Clinical conditions
- Pulmonary function tests
  - Forced Vital Capacity (FVC)
  - Diffusion of Carbon Monoxide (DLCO)
- Six minutes walking test
  - Distance walked
  - SpO_2
- High-resolution computed tomography (HRCT)
  - Patterns and fibrosis extent

Visual scoring of ILD extent

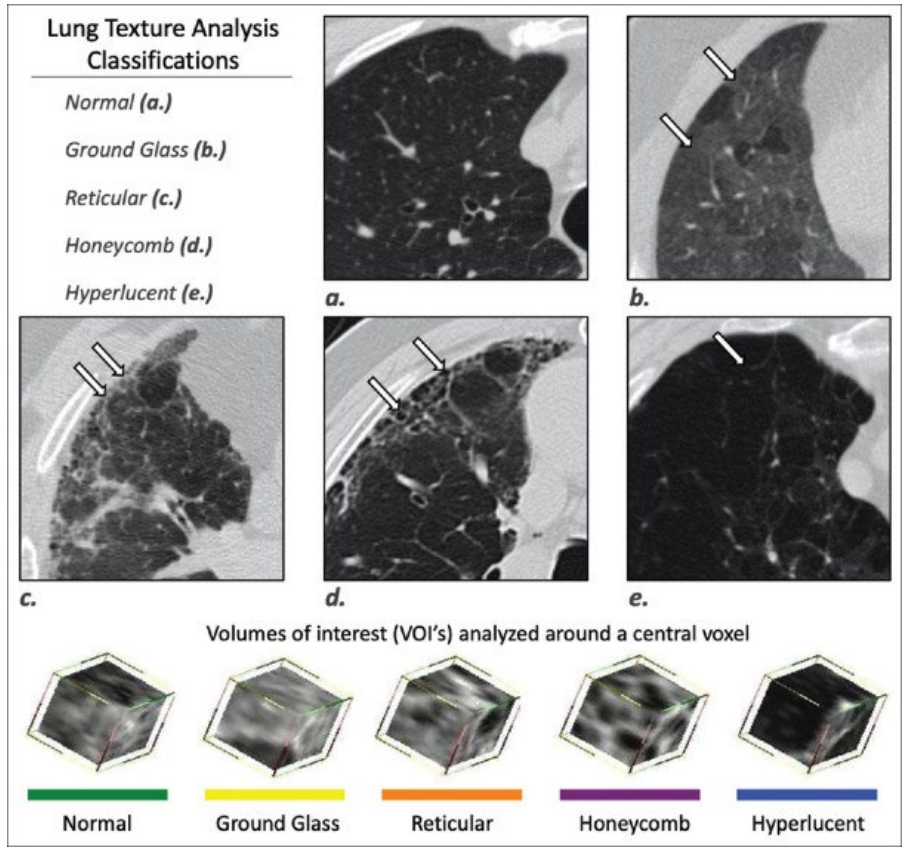


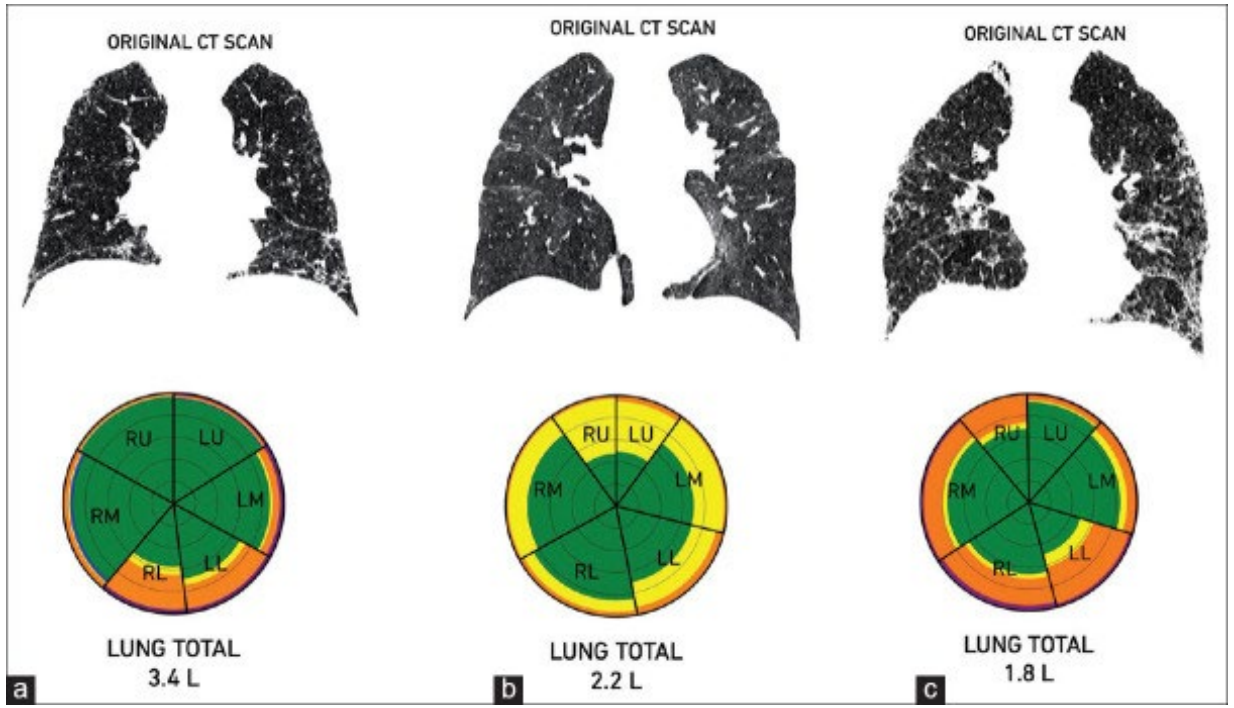


Euathrongchit, J., Phakphoom Thiravit, M. D., Wiwatana Tanomkiat, M. D., Chayanin Nitiwarangkul, M. D., Thanisa Tongbai, M. D., Yutthaphan Wannosopha, M. D., & Thitiporn Suwatanapongched, M. D. (2022). Multidisciplinary working group for interstitial lung disease in Thailand: Part 2 – a concise review of published visual scoring methods for interstitial lung disease. *The ASEAN Journal of Radiology*, *23*(1), 42–55. https://doi.org/10.46475/aseanjr.v23i1.170

CALIPER

Computer-Aided Lung Informatics for Pathology Evaluation and Ratings





Jankharia, B., & Angirish, B. (2021). Computer-Aided quantitative analysis in interstitial lung diseases – A pictorial review using CALIPER. *Lung India : Official Organ of Indian Chest Society*, *38*(2), 161. https://doi.org/10.4103/LUNGINDIA.LUNGINDIA_244_20

Quantitative Analysis

Mortality prediction in idiopathic pulmonary fibrosis: evaluation of computer-based CT analysis with conventional severity measures

Joseph Jacob[1], Brian J. Bartholmai[2], Srinivasan Rajagopalan[3], Maria Kokosi[4], Arjun Nair[1], Ronald Karwoski[3], Simon L.F. Walsh[1], Athol U. Wells[4] and David M. Hansell[1]

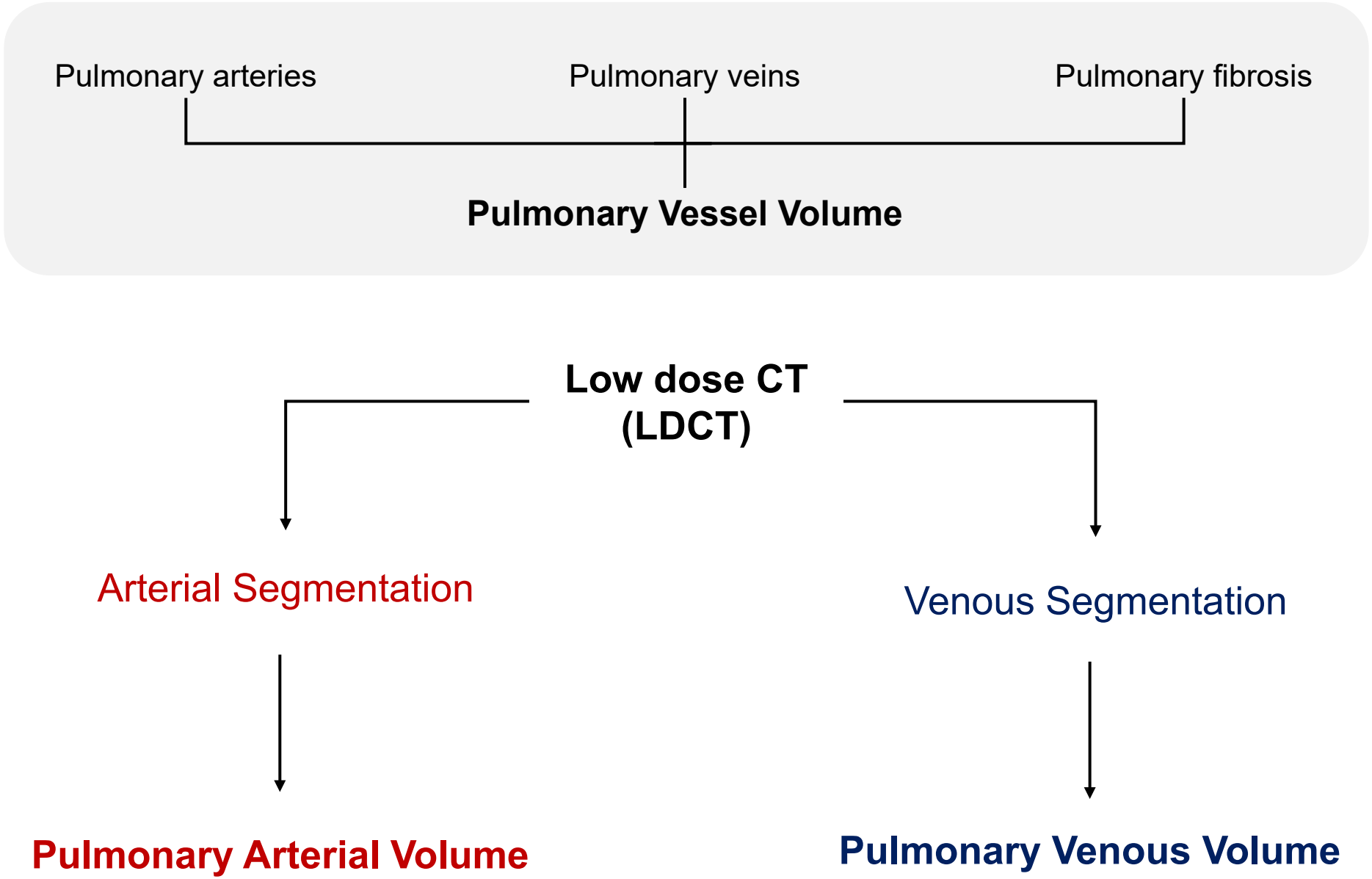
Volumetric quantification of pulmonary vessels outperforms traditional visual scoring metrics in predicting mortality

Pulmonary vessel volume (PVV) is an independent predictor of mortality in fibrotic lung diseases

TABLE 2 Univariate Cox regression analysis demonstrating mortality according to CALIPER indices, visually derived high-resolution computed tomography indices, pulmonary function tests (PFTs) and echocardiography and the Gender, Age, Physiology (GAP) score

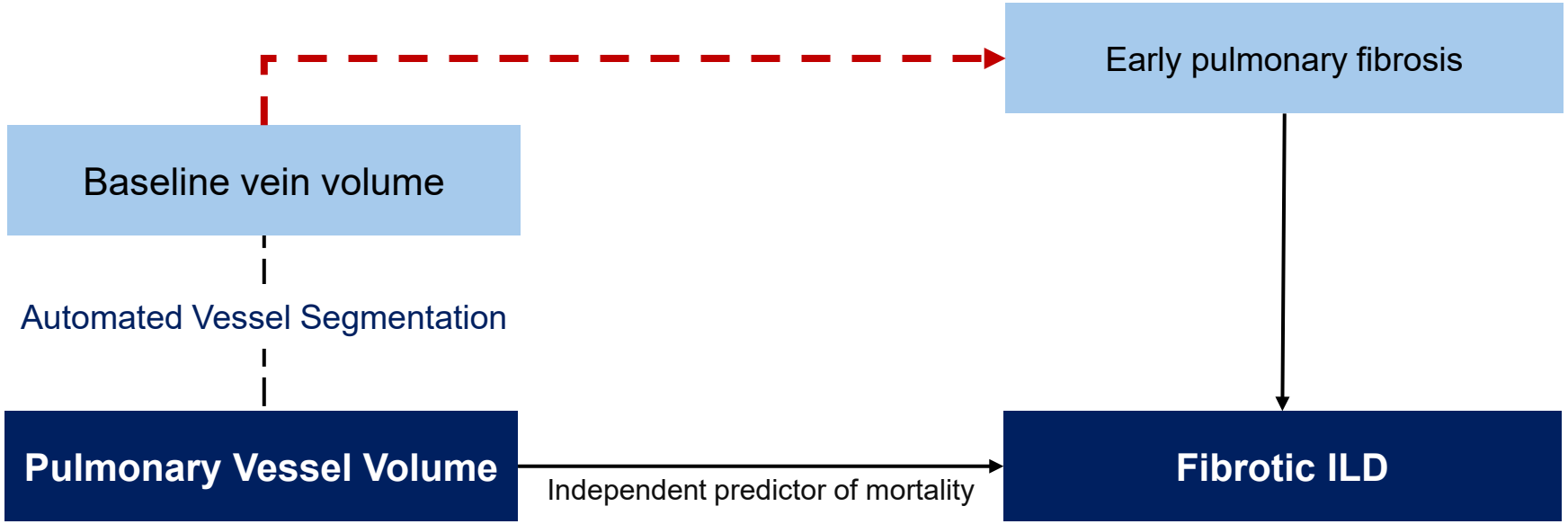
	Subjects n	Hazard ratio (95% CI)	p-value
CALIPER score	283		
Total ILD extent		1.03 (1.03–1.04)	<0.0001
Ground glass opacity		1.03 (1.02–1.04)	<0.0001
Reticular pattern		1.10 (1.07–1.12)	<0.0001
Honeycombing		1.11 (1.03–1.20)	0.006
Grade 1 DA		0.97 (0.97–0.98)	<0.0001
Grade 2 DA			NS
Grade 3 DA			NS
Normal lung			NS
PVV		1.52 (1.40–1.65)	<0.0001
PVV5		3.02 (2.36–3.87)	<0.0001
PVV10		2.29 (1.91–2.75)	<0.0001
PVV>5		1.64 (1.48–1.82)	<0.0001
Visual score	283		
ILD extent		1.03 (1.02–1.04)	<0.0001
Ground glass opacity		1.01 (1.00–1.03)	0.03
Reticular pattern		1.02 (1.01–1.03)	0.002
Honeycombing		1.03 (1.03–1.07)	<0.0001
Consolidation		1.08 (1.04–1.12)	<0.0001
Total emphysema			NS
Mosaicism			NS
TxBx severity (max score 18)		1.11 (1.07–1.16)	<0.0001
Main pulmonary artery diamter mm			NS
Pulmonary artery:aorta ratio			NS
PFTs			
FEV_1	257	0.97 (0.97–0.98)	<0.0001
FVC	257	0.97 (0.96–0.98)	<0.0001
TLC	241	0.96 (0.95–0.97)	<0.0001
D_{LCO}	254	0.94 (0.93–0.95)	<0.0001
K_{CO}	254	0.99 (0.98–1.00)	0.001
CPI	249	1.07 (1.05–1.09)	<0.0001
Echocardiography RVSP mmHg	150	1.02 (1.02–1.03)	<0.0001
GAP score (max score 8)	249	1.45 (1.30–1.62)	<0.0001

ILD: interstitial lung disease; DA: decreased attenuation; PVV: pulmonary vessel volume; PVV5: PVV <5 mm^2 on computed tomography (CT) cross-sectional area; PVV10: PVV <10 mm^2 on CT cross-sectional area; PVV>5: PVV >5 mm^2 on CT cross-sectional area; TxBx: traction bronchiectasis; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity, D_{LCO}: diffusing capacity of the lung for carbon monoxide; K_{CO}: transfer coefficient of the lung for carbon monoxide; CPI: composite physiologic index; RVSP: right ventricular systolic pressure; NS: nonsignificant.


Pulmonary arteries
Pulmonary veins
Pulmonary fibrosis
Pulmonary Vessel Volume
Low dose CT
(LDCT)
Arterial Segmentation
Venous Segmentation
Pulmonary Arterial Volume
Pulmonary Venous Volume

Objective

To develop a model that quantifies the pulmonary venous system and to assess the predictive capability of baseline vein volume from CT scans of ILA patients

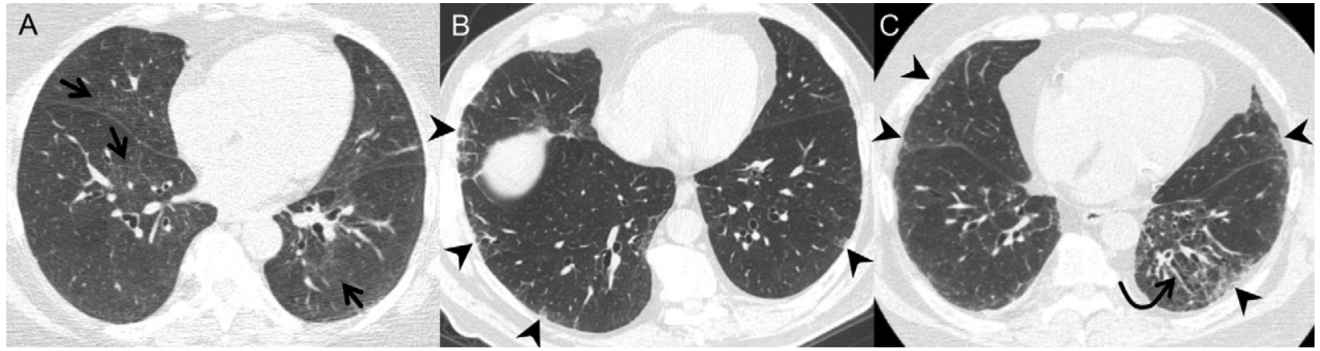


Interstitial Lung Abnormalities (ILA)

Incidental CT findings affecting more than 5% of any lung zone

- ILA is associated with increased mortality (HR = 1.3 to 2.7 in large cohorts)
- 20% of ILAs progress over 2 years, and more than 40% progress over 5 years

ILA may represent early pulmonary fibrosis



Hata, A., Schiebler, M. L., Lynch, D. A., & Hatabu, H. (2021). Interstitial lung abnormalities: State of the art. *Radiology*, *301*(1), 19–34. https://doi.org/10.1148/RADIOL.2021204367/SUPPL_FILE/RY204367SUPPA1.PDF

Population

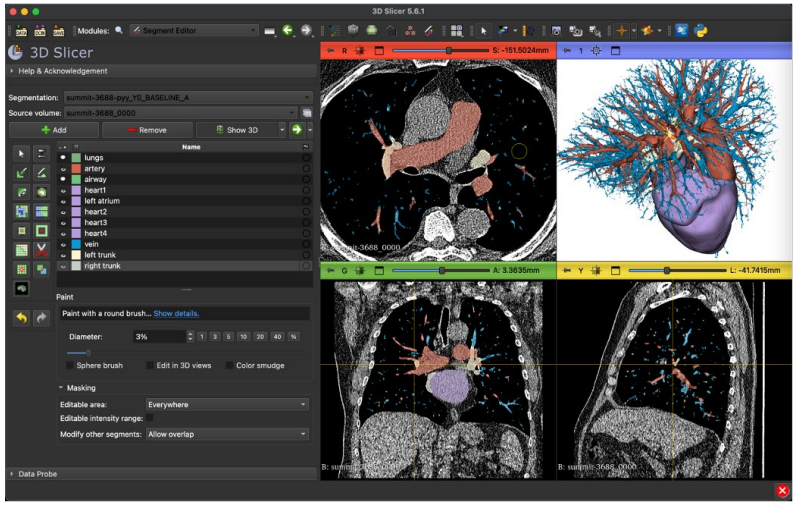
SUMMIT Study: Lung Cancer Screening Study in UK

Individuals aged 55-77, smoking history within the past 20 years ⟶ LDCT scan

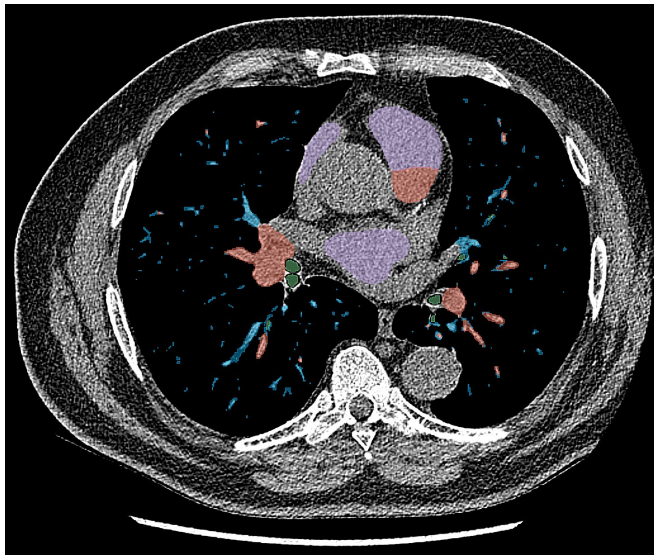
ILA is a common radiological finding in this population

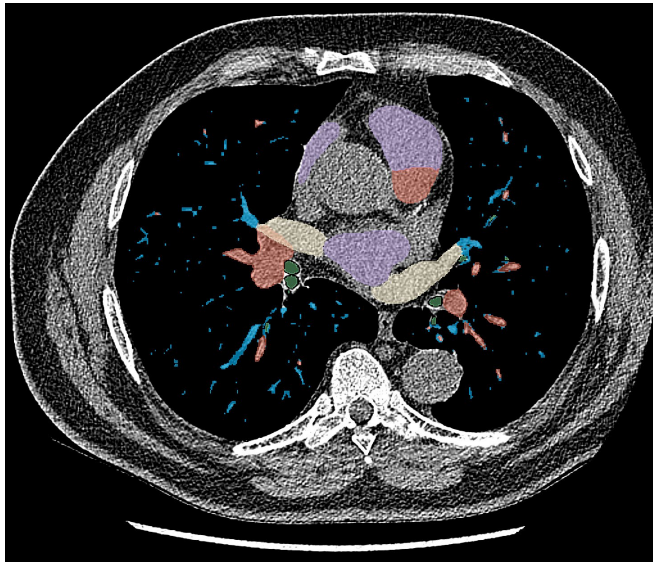
Manual Annotation

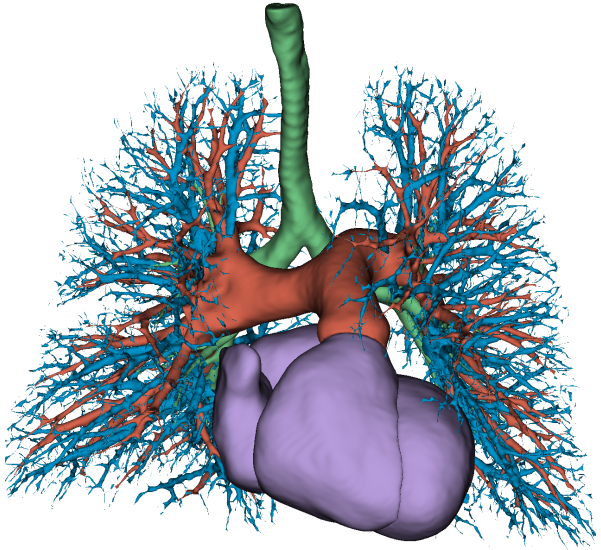
Under supervision of a radiologist

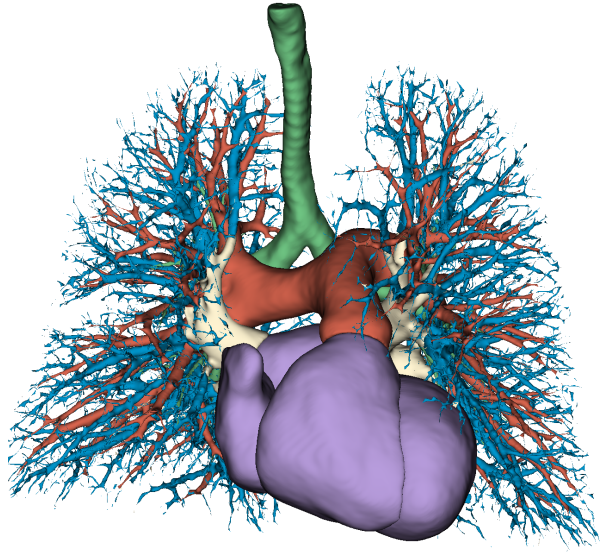


3D Slicer



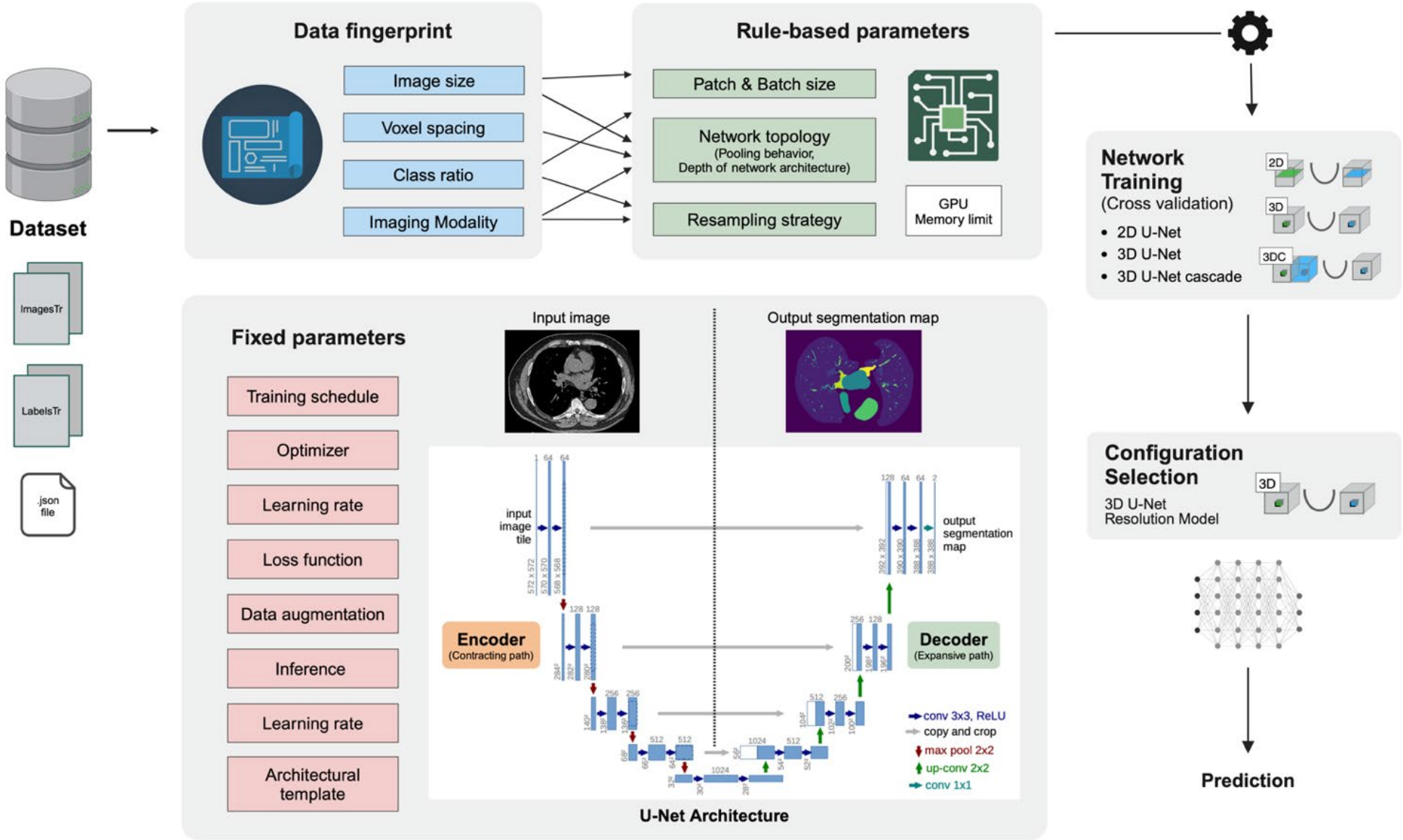






nnU-Net

Self-configuring deep learning-based segmentation method



SUMMIT Study

Manual Annotation → **ILA/Control LDCT** (n = 20)

Manual Annotation → **ILA/Control LDCT** (n = 20)

ILA (n = 417)
Control (n = 404)

Initial Segmentation

nnU-Net

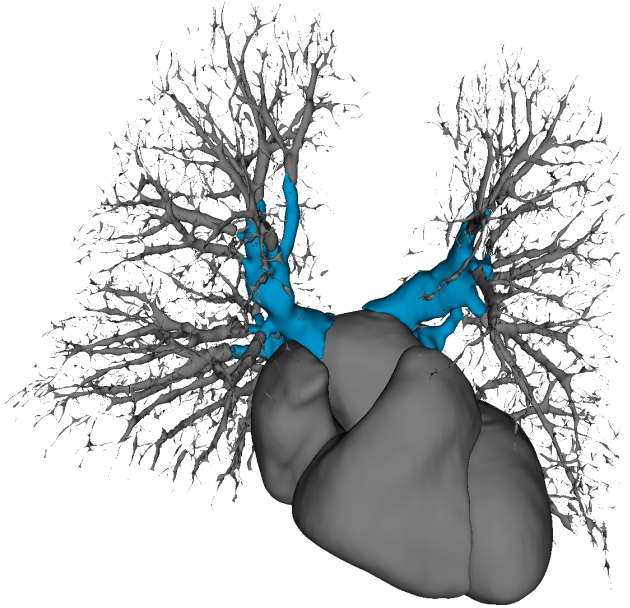
Segmentation Model 1

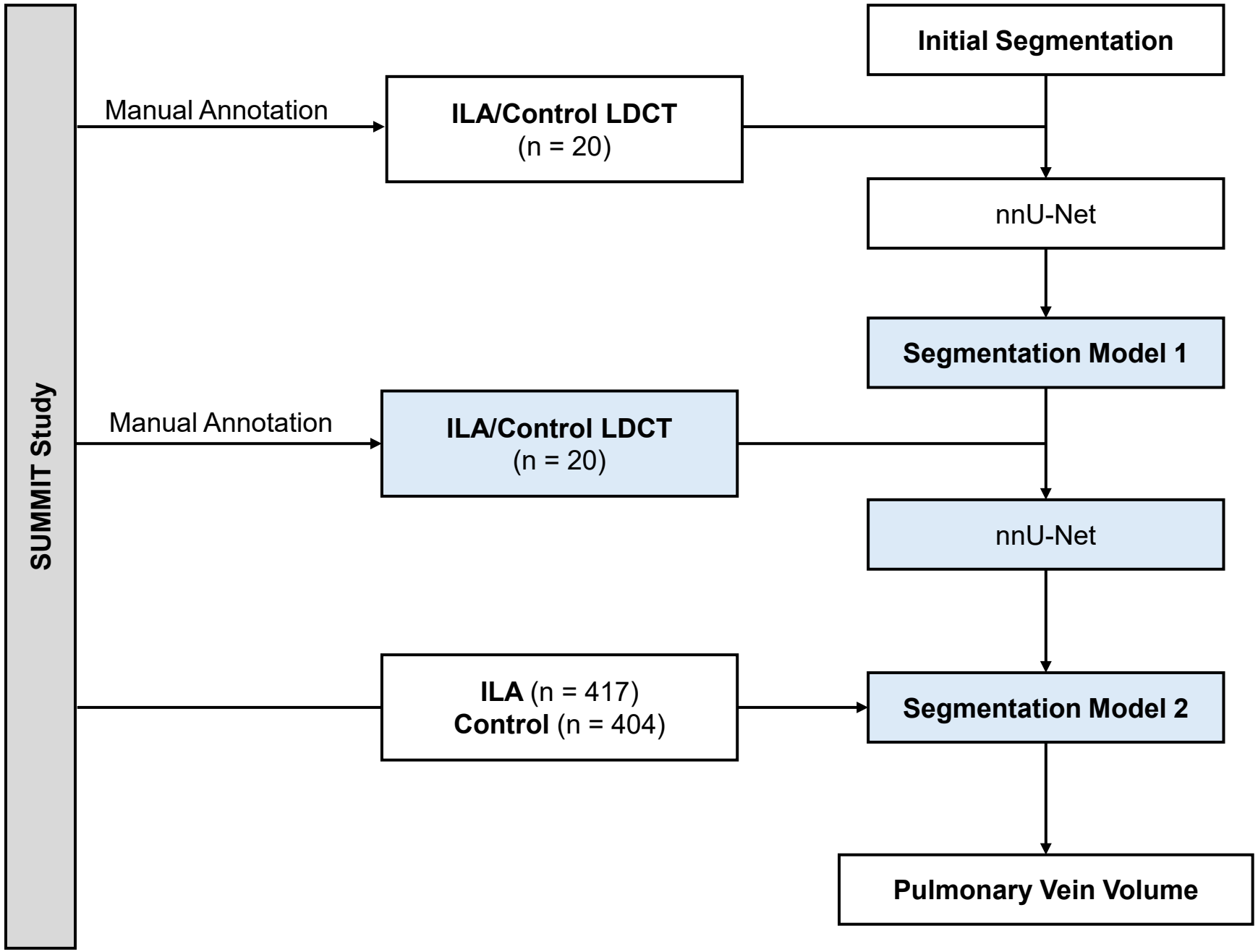
nnU-Net

Segmentation Model 2

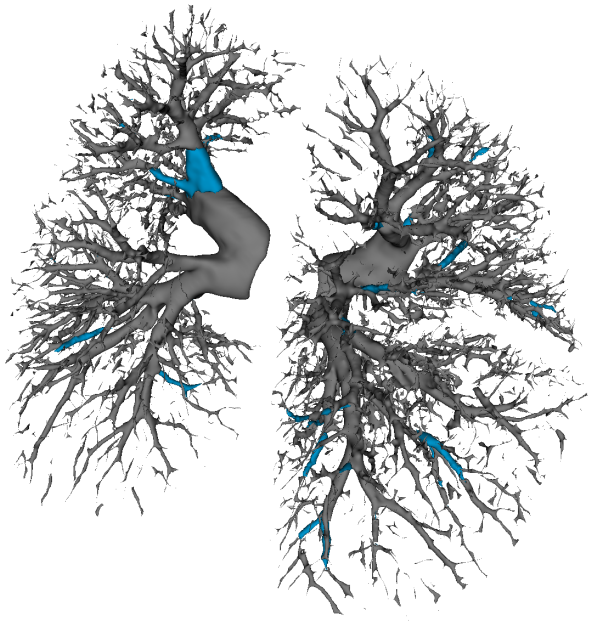
Pulmonary Vein Volume

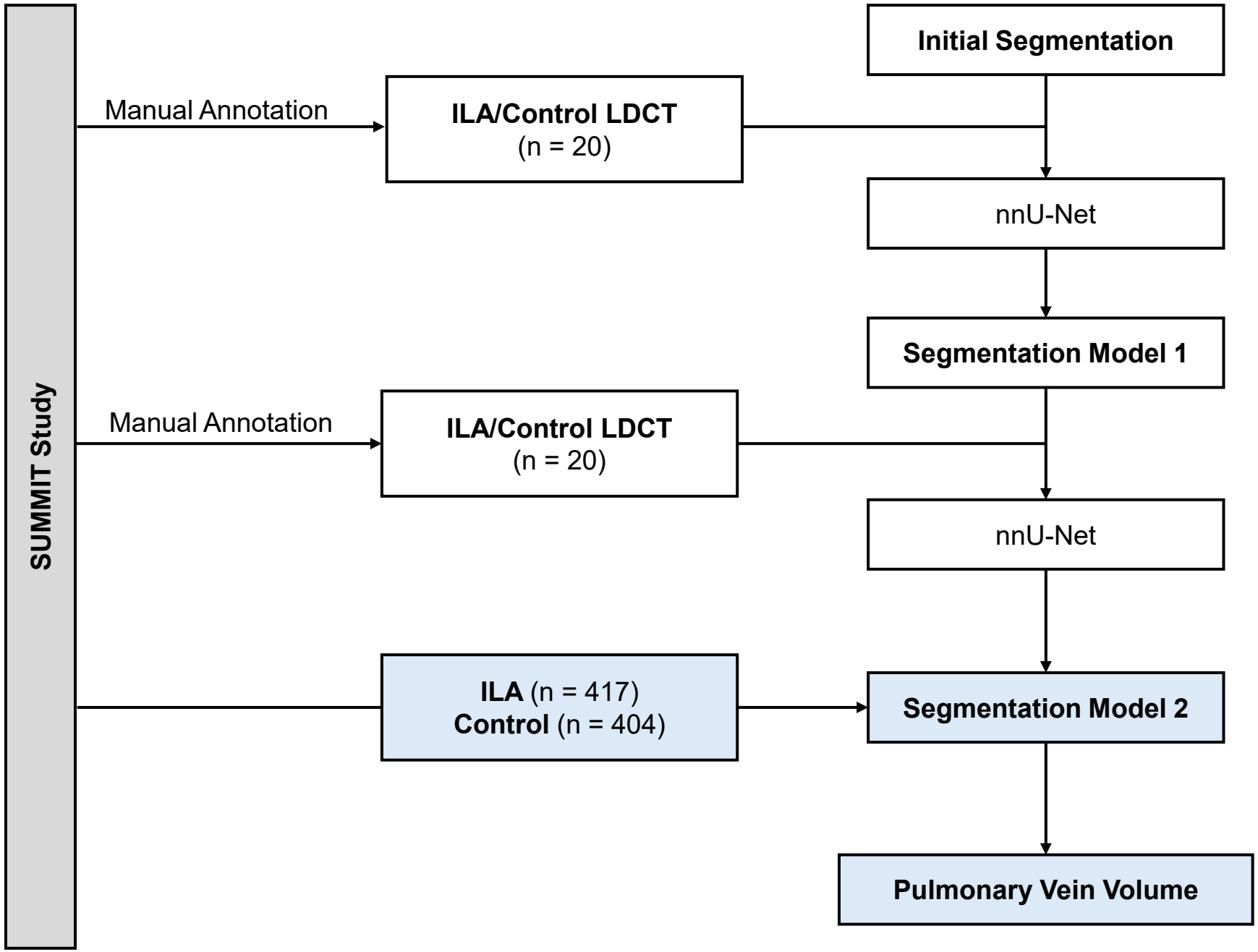
Central Connectivity



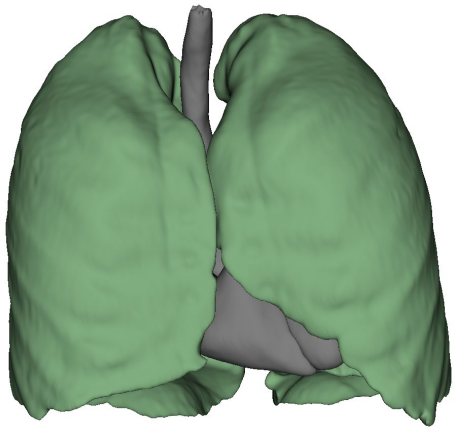


Distal Connectivity





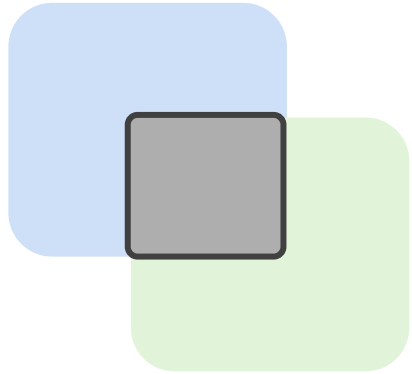
Vein volume expressed as percentage of lung volume



Model Performance

$$\textbf{Dice coefficient} = \frac{2 \times |A \cap B|}{|A| + |B|}$$

$$2 \times$$



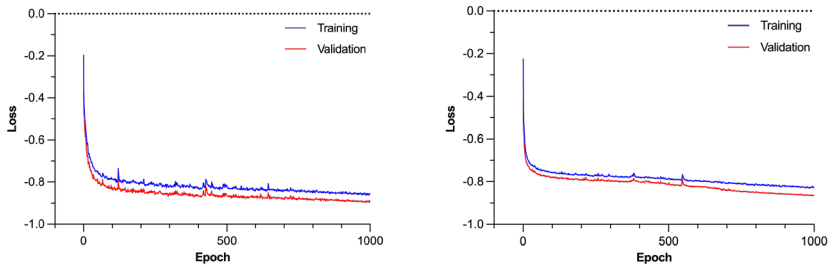
Dice score: 0.0 = No overlap

Dice score: 1.0 = Perfect overlap

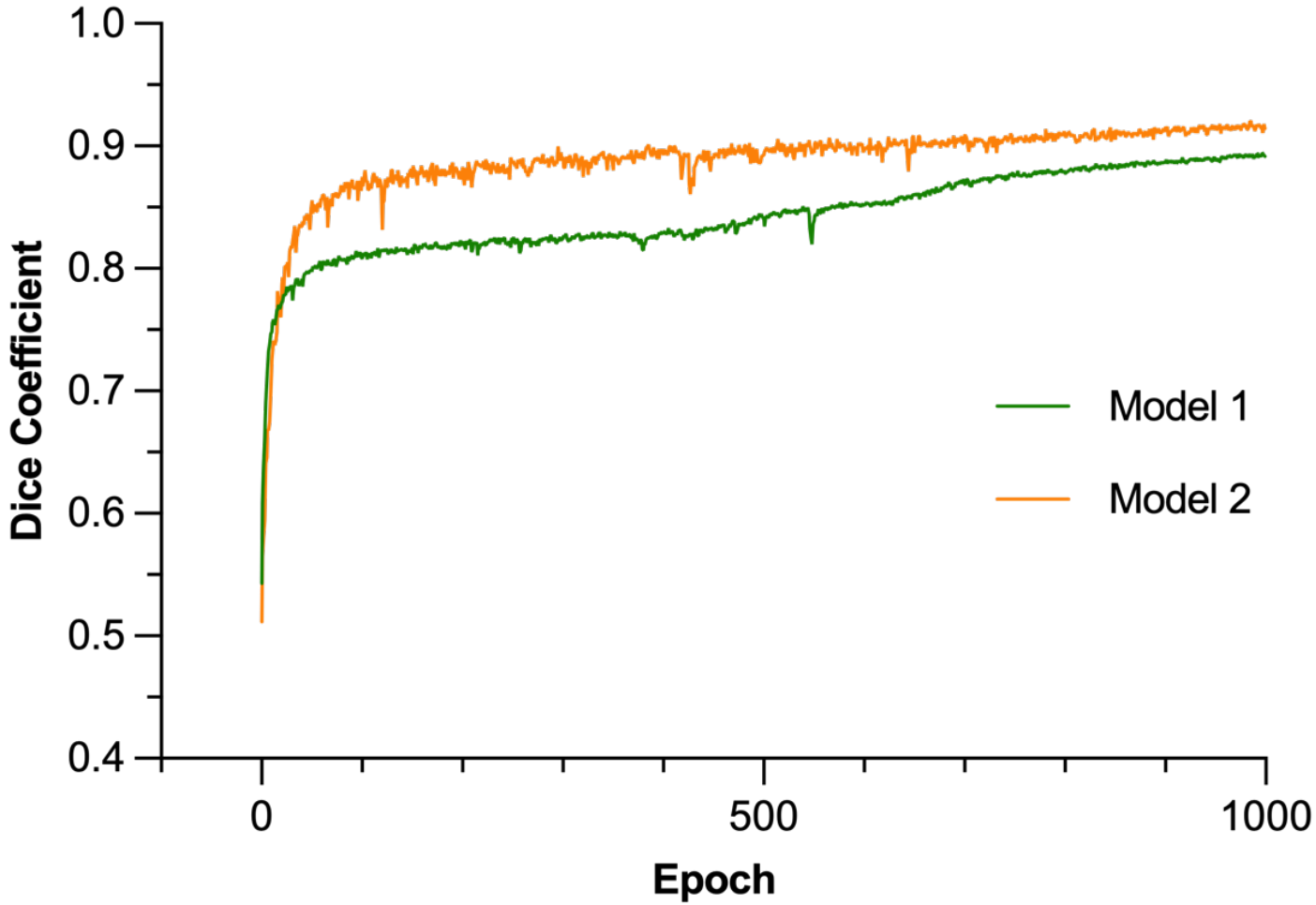
Prediction + Ground Truth

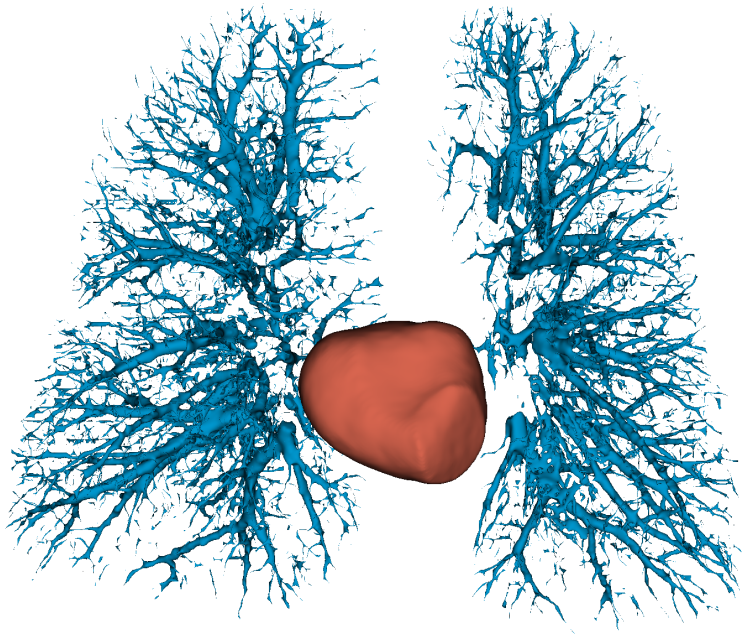
Model Performance

	Dice Coefficient
Model 1	0.8760
Model 2	0.9059

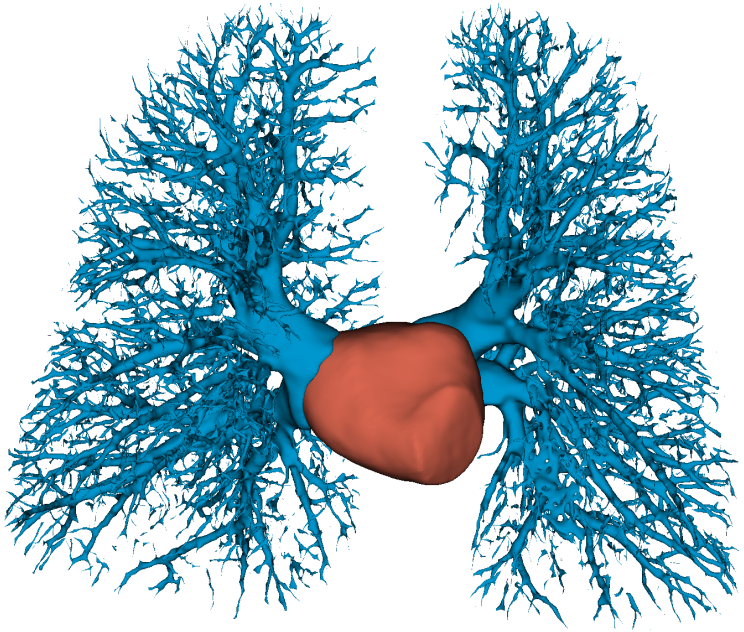


No overfitting or underfitting

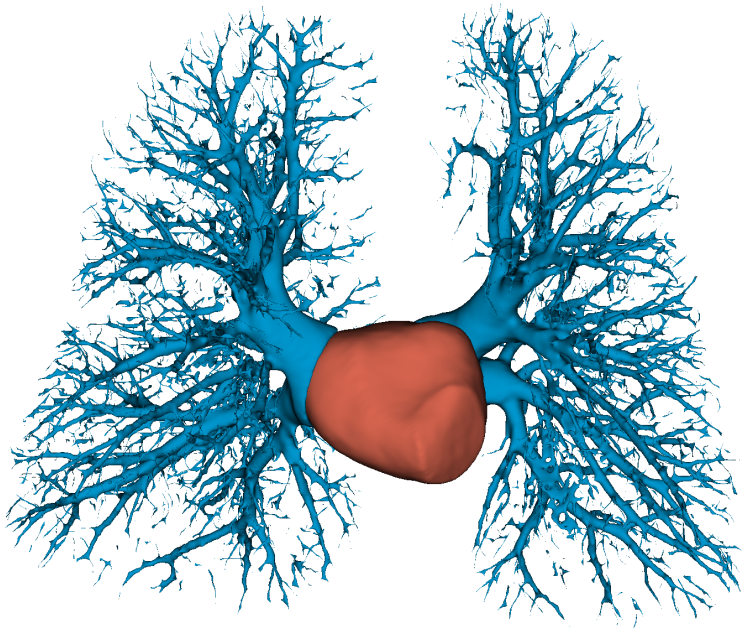




Initial



Model 1



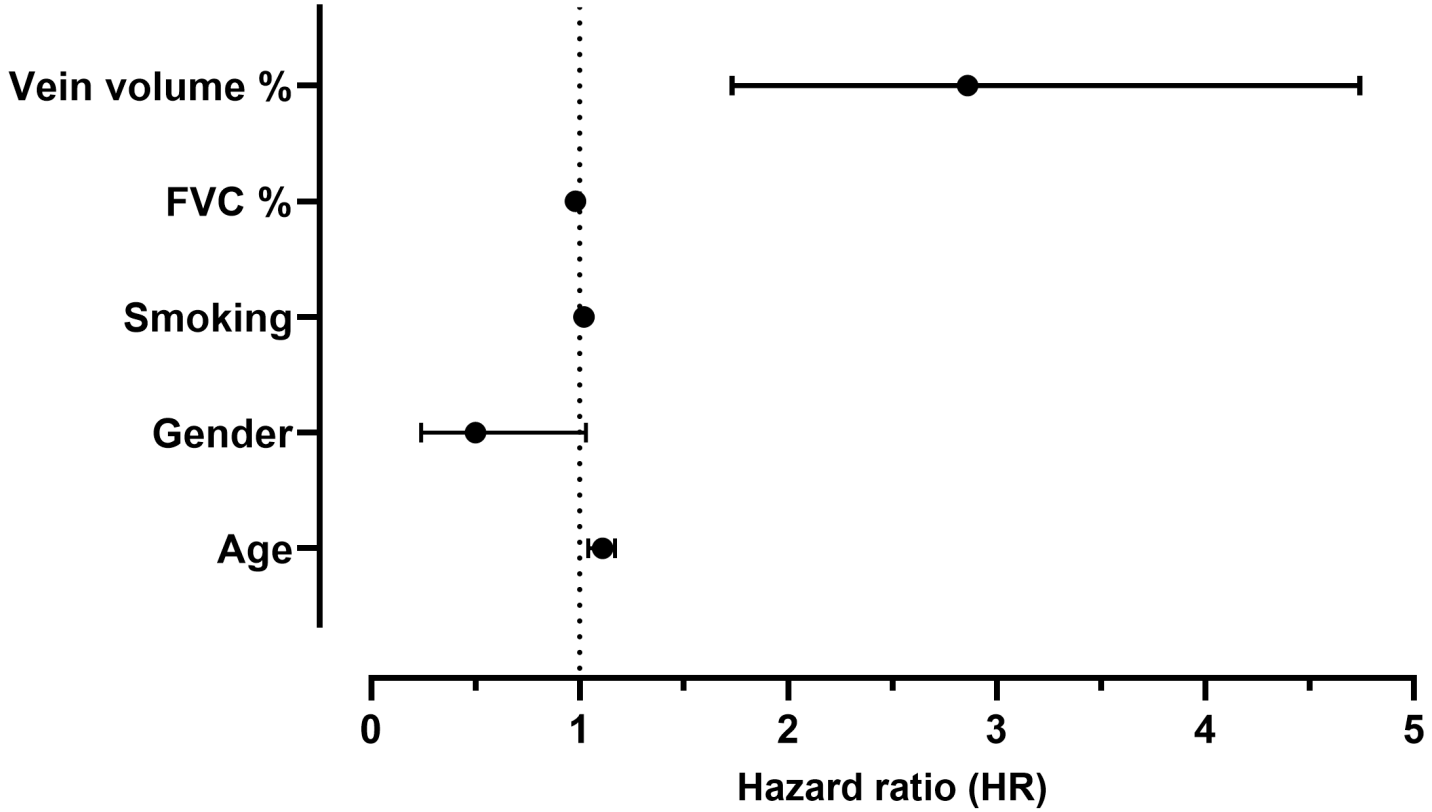
Model 2

Variable	ILA Cases (n = 415)	Control Cases (n = 404)	*p value*
Median age (range)	68 (55-78)	68 (55-78)	
Gender (male/female)	285/130	280/124	
Survival (alive/dead)	376/39	395/9	
Level (mild/moderate/severe)	103/223/89		
Type (ILA/FILA/UILD)	117/136/162		
Median follow-up in years (range)	3.86 (0.36 – 4.34)	3.91 (0.42 – 3.46)	0.002
Median smoking pack years (range)	40.5 (17.5 – 123.0)	40.5 (15.0 – 153.0)	0.844
Predicted FVC % (mean)	87.28 ± 15.80	87.52 ± 18.05	0.925
Vein volume % (mean)	2.09 ± 0.43	1.89 ± 0.34	<0.001

Univariable Cox Regression

(n = 819)

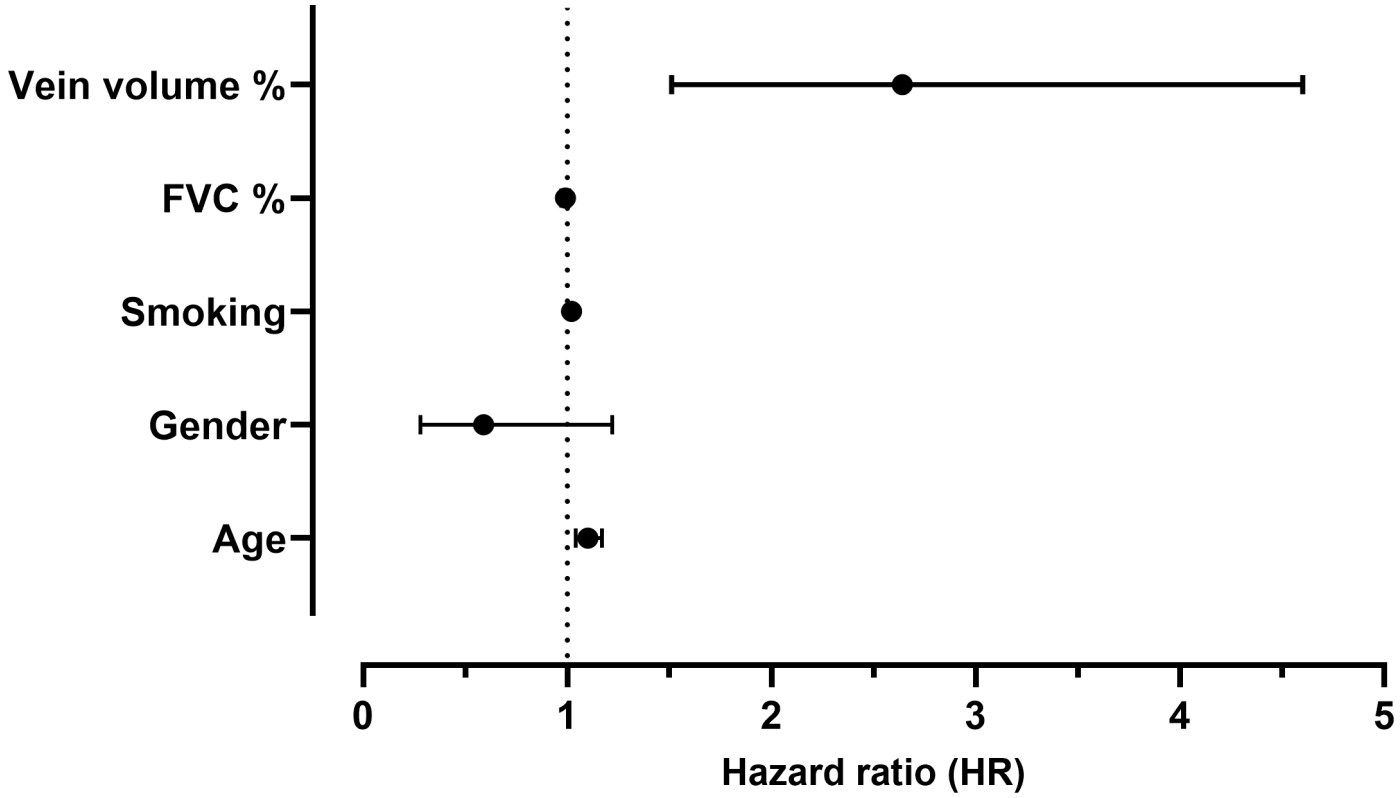
Variable	Hazard ratio	95% CI-lower	95% CI-upper	*p value*
Age	1.11	1.04	1.17	0.0006
Gender	0.50	0.24	1.03	0.0615
Smoking	1.02	1.01	1.03	0.0000
FVC %	0.98	0.97	1.00	0.0319
Vein volume %	2.86	1.73	4.74	0.0000



Multivariable Cox Regression

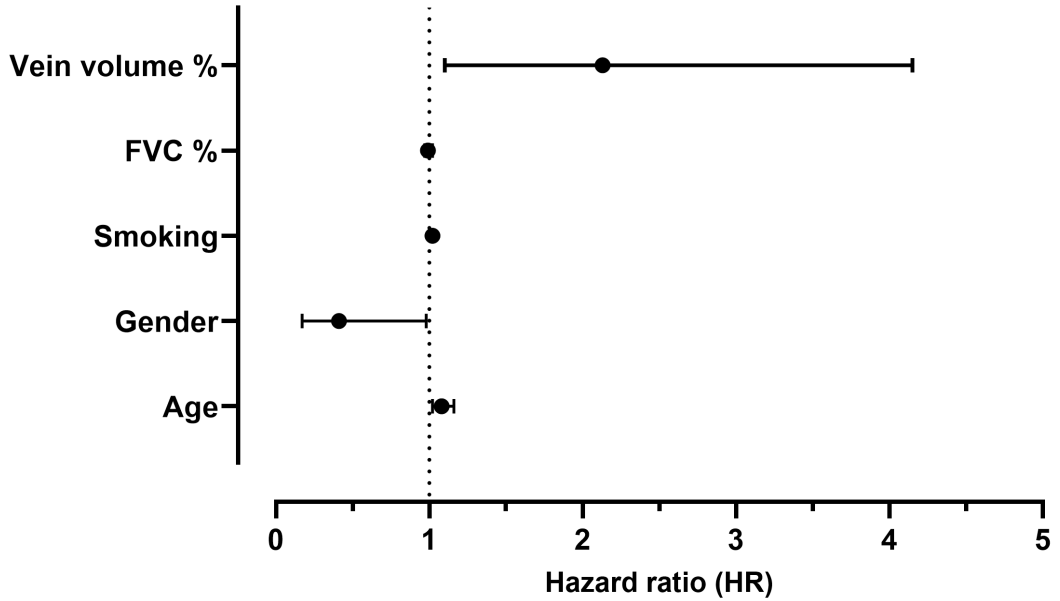
(n = 819)

Variable	Hazard ratio	95% CI-lower	95% CI-upper	*p value*
Age	1.10	1.04	1.17	0.0010
Gender	0.59	0.28	1.22	0.1528
Smoking	1.02	1.01	1.03	0.0000
FVC %	0.99	0.97	1.01	0.2605
Vein volume %	2.64	1.51	4.60	0.0006



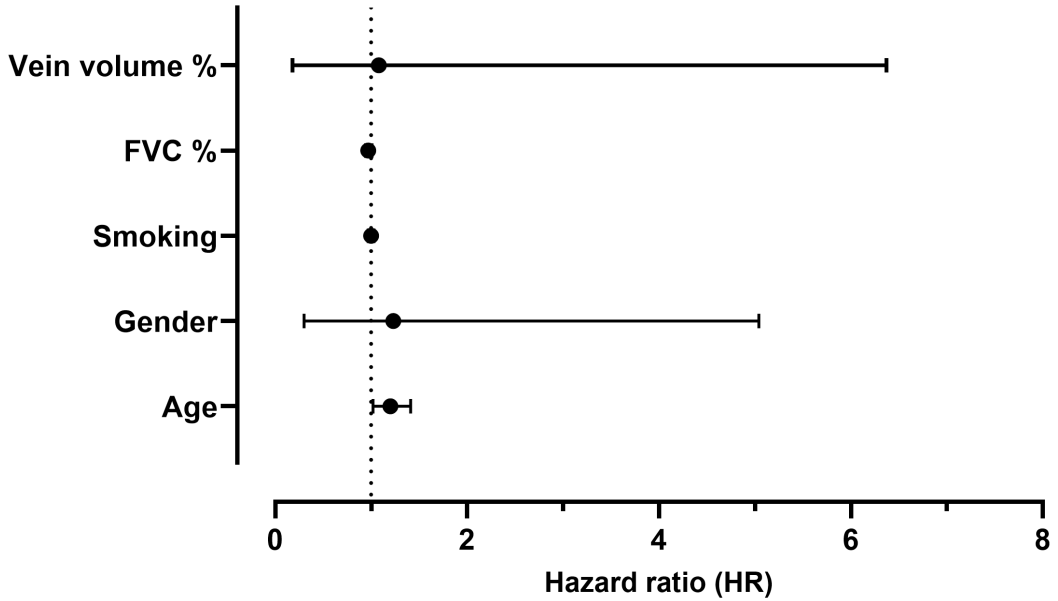
Multivariable Cox Regression ILA Only (n = 415)

Variable	Hazard ratio	95% CI-lower	95% CI-upper	*p value*
Age	1.08	1.02	1.16	0.0117
Gender	0.41	0.17	0.98	0.0455
Smoking	1.02	1.01	1.03	0.0000
FVC %	0.99	0.97	1.02	0.5431
Vein volume %	2.13	1.10	4.15	0.0257



Multivariable Cox Regression Control Only (n = 404)

Variable	Hazard ratio	95% CI-lower	95% CI-upper	*p value*
Age	1.20	1.02	1.41	0.0292
Gender	1.23	0.30	5.04	0.7784
Smoking	1.00	0.97	1.03	0.8852
FVC %	0.97	0.94	1.01	0.1032
Vein volume %	1.08	0.18	6.37	0.9299



Discussion

- Mean vein volumes were significantly higher in ILA cohorts and increased vein volume was independently associated with higher mortality risk

- **Vascular remodeling** as an **early pathological sign of pulmonary fibrosis**
  - Studies found distinct vascularization patterns within spatially interspersed fibrotic foci in IPF
  - **Fibrotic areas**: reduced vascularization and structural arterial alterations
  - **Non-fibrotic regions**: increased vessel profusion and occlusive venopathy

M. Ebina et al., “Heterogeneous Increase in CD34-positive Alveolar Capillaries in Idiopathic Pulmonary Fibrosis,” https://doi.org/10.1164/rccm.200308-1111OC, vol. 169, no. 11, pp. 1203–1208, Dec. 2012, doi: 10.1164/RCCM.200308-1111OC.

Conclusion

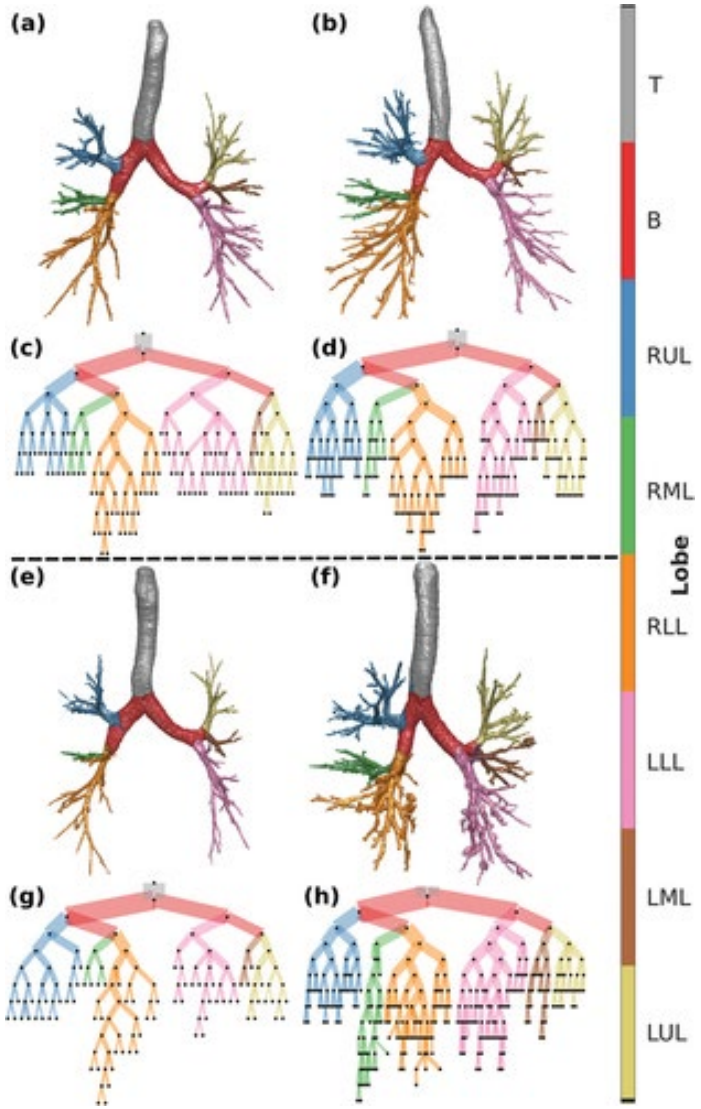
- **Pulmonary vein volume** has the potential to serve as an independent predictor of mortality in the early stages of pulmonary fibrosis

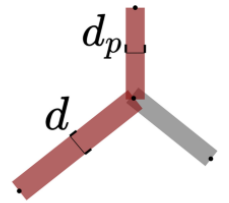
- Quantitative image analysis may allow for derivation of novel biomarkers in fibrosing interstitial lung diseases

Future Work

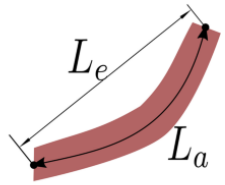
AirQuant

In-house software

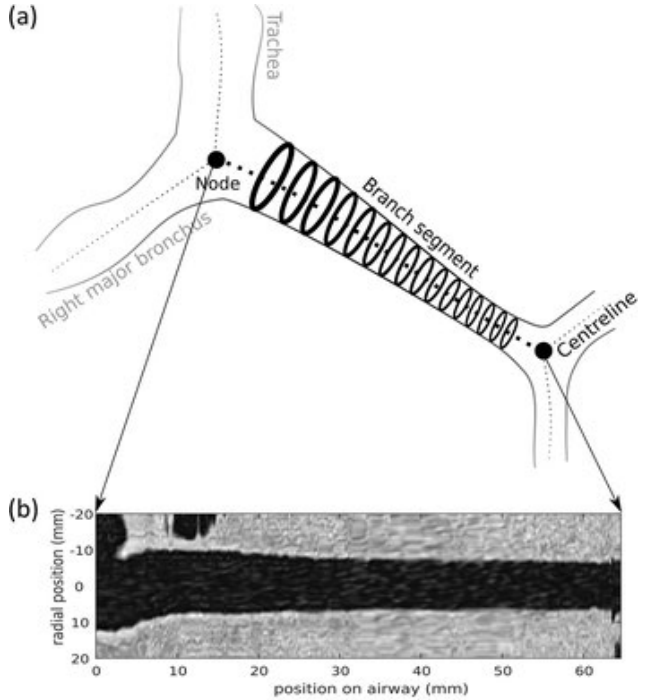




$$intersegmental\,tapering = \frac{d_p - d}{d_p}$$



$$tortuosity = \frac{L_a}{L_e}$$



Pakzad, A., Cheung, WK., Van Moorsel, CHM., Quan, K., Mogulkoc, N., Bartholmai, BJ., … Jacob, J. (2024). Evaluation of automated airway morphological quantification for assessing fibrosing lung disease. *Computer Methods in Biomechanics and Biomedical Engineering: Imaging & Visualization*, *12*(1). https://doi.org/10.1080/21681163.2024.2325361

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