PULMONARY HYPERTENSION CONSIDERATIONS FOR LUNG TRANSPLANT

Bhuvin Buddhdev, MD

Lung Transplant

Co-director, Interstitial Lung Disease and Pulmonary Hypertension Programs

Assistant Professor of Medicine, Creighton University School of Medicine

Norton Thoracic Institute, St joseph's Hospital & Medical Center

2022 ESC/ERS Guidelines for the Diagnosis of PH

Haemodynamic Definitions of PH

Definition	Haemodynamic characteristics
PH	mPAP > 20 mmHg
Pre-capillary PH	mPAP > 20 mmHg PAWP ≤ 15 mmHg PVR > 2 WU
Isolated post-capillary PH	mPAP > 20 mmHg PAWP > 15 mmHg PVR ≤ 2 WU
Combined post- and pre-capillary PH	mPAP > 20 mmHg PAWP > 15 mmHg PVR > 2 WU
Exercise PH	mPAP/CO slope between rest and exercise > 3 mmHg/L/min

There is a need for more rigorous interpretation of hemodynamic values

ESC, European Society of Cardiology; ERS, European Respiratory Society; mPAP, mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure.

Humbert M, et al. Eur Heart J. 2022:ehac237.

Adult Lung Transplants

By Diagnosis (Transplants: January 1992 – June 2018)

	Jan 1992-Dec 2000 (N = 11,796)	Jan 2001-Dec 2009 (N = 21,806)	Jan 2010-Jun 2018 (N = 33,891)	P-value
Diagnosis				<0.0001
- COPD	4162 (37.3%)	7102 (33.1%)	8917 (26.5%)	
- A1ATD	1169 (10.5%)	1131 (5.3%)	1054 (3.1%)	
- CF	1717 (15.4%)	3470 (16.2%)	4771 (14.2%)	
- IPAH	578 (5.2%)	563 (2.6%)	945 (2.8%)	
- IPF	1677 (15.0%)	4899 (22.8%)	9755 (29.0%)	
- Retransplant	394 (3.5%)	921 (4.3%)	1364 (4.1%)	
- Other	1471 (13.2%)	3392 (15.8%)	6822 (20.3%)	

ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION
2022
JHLT. 2022 Oct; 41(10): 1335-1375

Continuous factors are expressed as median (5th – 95th percentiles)

Summary statistics included transplants with non-missing data

ISHLT GUIDELINES FOR REFERRAL FOR PAH

Timing of Referral 2014	Timing of Referral 2021
NYHA Functional Class III or IV symptoms during escalating therapy.	ESC/ERS intermediate or high risk or REVEAL risk score 8 despite appropriate PAH therapy
Rapidly progressive disease	Significant RV dysfunction despite appropriate PAH therapy
Use of parenteral targeted PAH therapy regardless of symptoms or NYHA Functional Class	Need for IV or SC prostacyclin therapy
Known or suspected PVOD or PCH.	Progressive disease despite appropriate therapy or recent hospitalization for worsening of PAH
	Known or suspected high-risk variants such as PVOD/PCH, scleroderma, large and progressive pulmonary artery aneurysms
	Signs of secondary liver or kidney dysfunction due to PAH
	Potentially life-threatening complications such as recurrent hemoptysis

ISHLT GUIDELINES FOR LISTING FOR PAH

Timing of Listing 2014	Timing of Listing 2021
NYHA Functional Class III or IV despite a trial of at least 3 months of combination therapy including prostanoids.	ESC/ERS high risk or REVEAL risk score >10 on appropriate PAH therapy, including IV or SC prostacyclin analogues
Cardiac index of <2 liters/min/m2	Progressive hypoxemia, especially in patients with PVOD or PCH
Mean right atrial pressure of >15 mm Hg	Progressive, but not end-stage, liver or kidney dysfunction due to PAH
6 minute walk test of <350 m.	Life-threatening hemoptysis
Development of significant hemoptysis, pericardial effusion, or signs of progressive right heart failure (renal insufficiency, increasing bilirubin, brain natriuretic peptide, or recurrent ascites).	

LUNG ALLOCATION SCORE (LAS)

2005 - LAS Introduced

- Reduced waitlist mortality except for PAH

Lung Review Board for Exception Request

- PAH highest exceptions requests
- If exception denied, worse outcomes

2015 – CVP, Bilirubin and CI Added

- PAH had largest LAS score gain of 14 points at organ matching
- Reduced waitlist mortality, but risk of death like ILD, rate of transplant like COPD

LUNG ALLOCATION SCORE (LAS)

2021 - LAS Updated

- Removed CVP, CI and Bilirubin
- Would this affect waitlist mortality for PAH?

2022 – Continued Distribution Model

- Help improve waitlist mortality for PAH?

SINGLE LUNG TRANSPLANTS FOR GROUP 3 PH

Single lung transplantation has equivalent long term outcomes to bilateral lung transplantation in patients with pulmonary hypertension associated with advanced lung disease

Walker A. Julliard[1], Keith C. Meyer[1*], Nilto C. De Oliveira[1], Satoru Osaki[1], Glen E. Leverson[1], Richard D. Cornwell[2], David A. Sonetti[2], and James D. Maloney[1]

[1]Department of Surgery, Division of Cardiothoracic Surgery, University of Wisconsin School of Medicine and Public Health, USA

[2]Department of Medicine, Division of Pulmonary and Critical Care Medicine, University of Wisconsin School of Medicine and Public Health, Wisconsin, USA

JULLIARD WA, MEYER KC, DE OLIVEIRA NC, *ET AL*. THE PRESENCE OR SEVERITY OF PULMONARY HYPERTENSION DOES NOT AFFECT OUTCOMES FOR SINGLE-LUNG TRANSPLANTATION.*THORAX* 2016;**71**:478-480.

SINGLE LUNG TRANSPLANTS?

- World Health Association (WHO) Group 3 Pulmonary Hypertension (PH) associated with advanced lung disease.

- Retrospectively examined the outcomes of 474 consecutive patients who underwent BLT or SLT at their center between 1999 and 2013.

- Excluded CF and retransplant, 179 patients with PH were split into 4 groups based on their pulmonary artery pressure values (mild versus severe) and transplant type (BLT versus SLT).

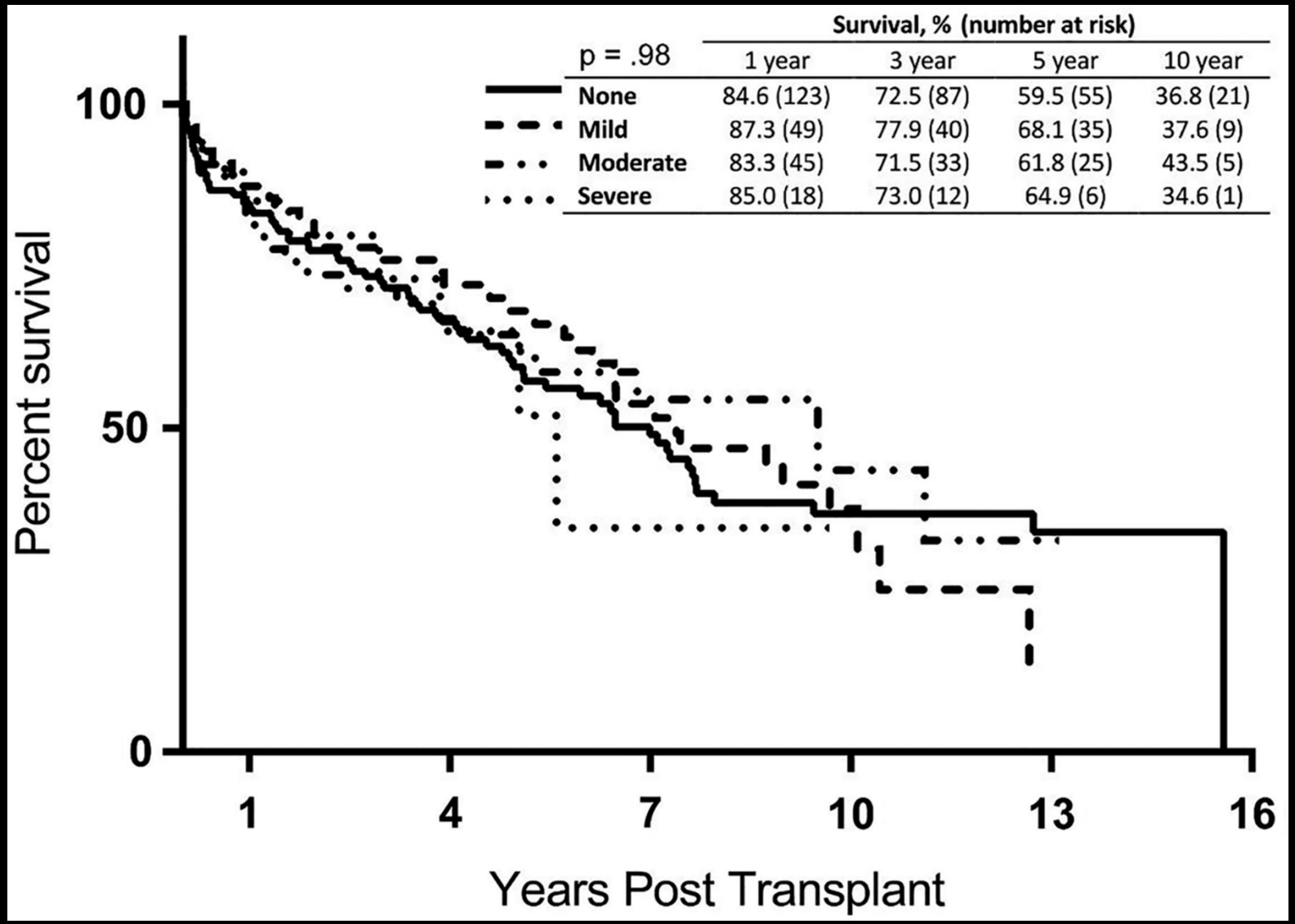
RESULTS

- The incidence of grade 2-3 primary graft dysfunction and mechanical ventilation >48 hours was significantly higher for the BLT versus the SLT recipients.

- However, long-term survival via the Kaplan-Meier method and appropriate log rank tests did not differ significantly among the four cohorts.

- Long term outcomes for patients who undergo SLT for advanced lung disease associated with WHO Group 3 PH did not differ significantly from those for BLT recipients, even if PH was severe

Long-term survival of single-lung transplant recipients with or without secondary pulmonary hypertension.



Julliard WA, Meyer KC, De Oliveira NC, *et al*. The presence or severity of pulmonary hypertension does not affect outcomes for single-lung transplantation. Thorax 2016;**71:**478-480

THORAX

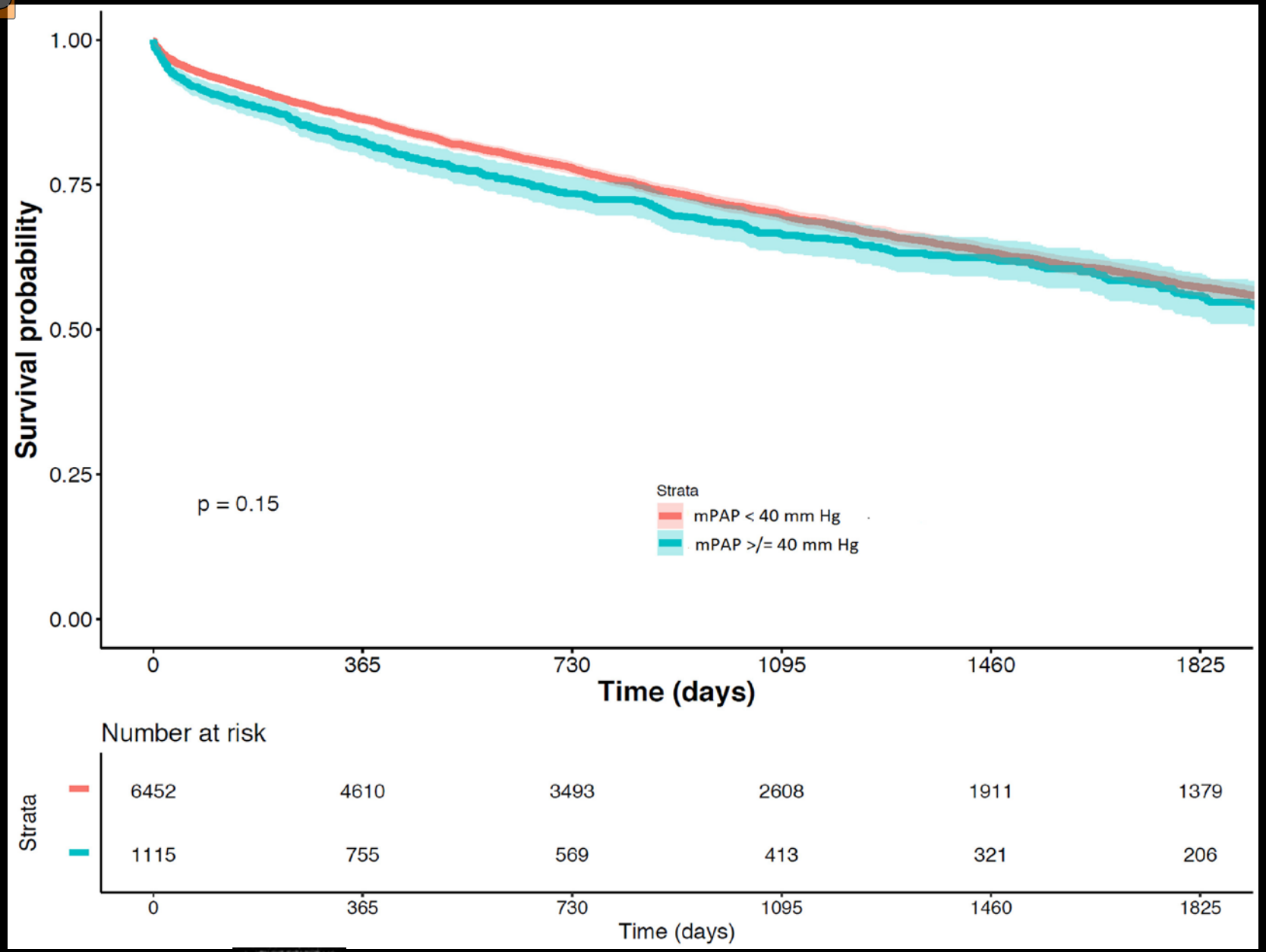
SINGLE LUNG TRANSPLANT?

Single lung transplantation in patients with severe secondary pulmonary hypertension

Basil S. Nasir, MBBCh,[a] Michael S. Mulvihill, MD,[b] Yaron D. Barac, MD, PhD,[b] Muath Bishawi, MD,[b] Morgan L. Cox, MD,[b] Dominick J. Megna, MD,[b] John C. Haney, MD,[b] Jacob A. Klapper, MD,[b] Mani A. Daneshmand, MD,[b] and Matthew G. Hartwig, MD, MHS[b]

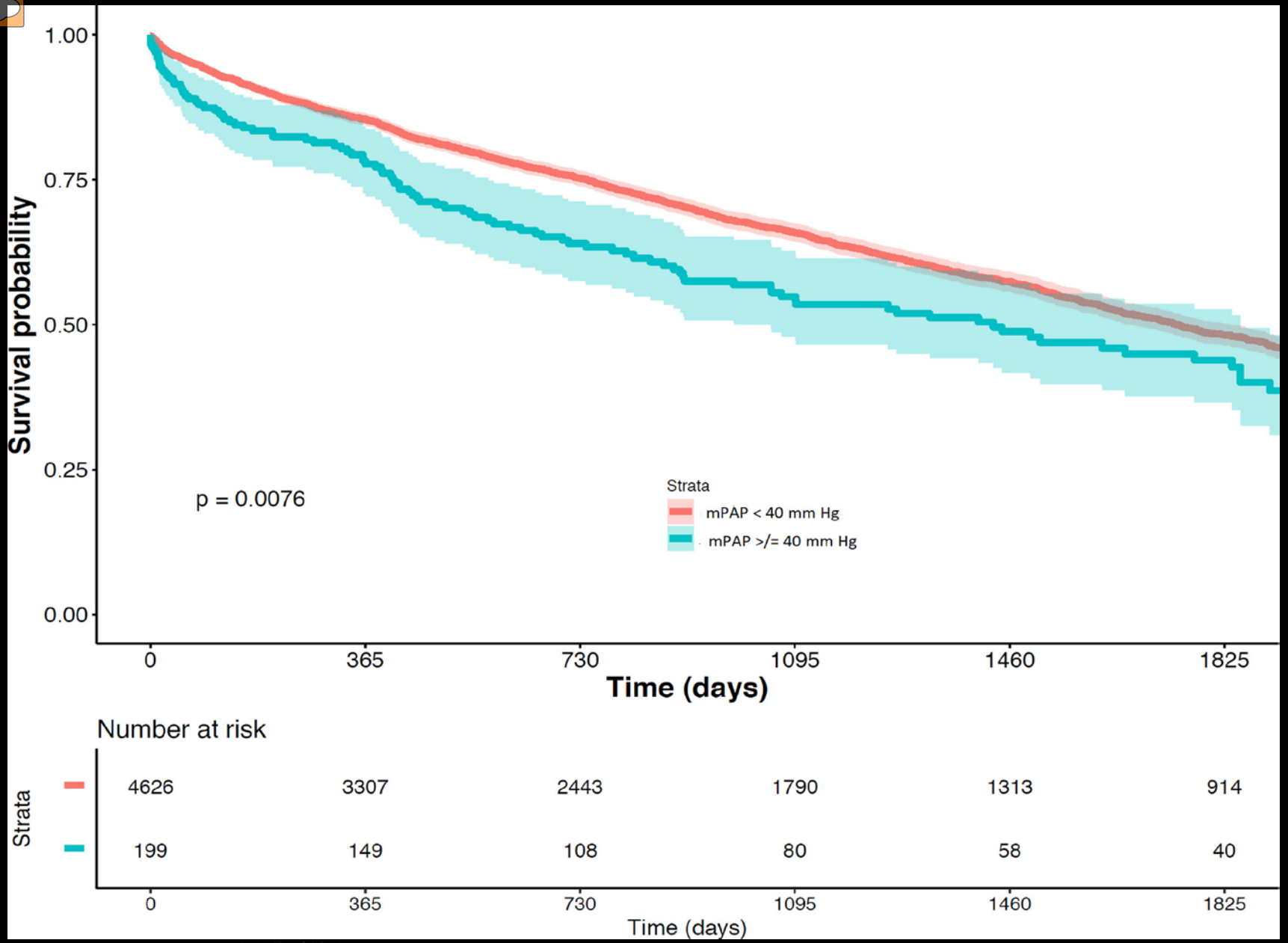
From the [a]Division of Thoracic Surgery, Department of Surgery, Centre Hospitalier de l'Université de Montréal, Montréal, Quebec, Canada; and the [b]Division of Cardiovascular and Thoracic Surgery, Department of Surgery, Duke University Medical Center, Durham, North Carolina.

Nasir BS, Mulvihill MS, Barac YD, Bishawi M, Cox ML, Megna DJ, Haney JC, Klapper JA, Daneshmand MA, Hartwig MG. Single lung transplantation in patients with severe secondary pulmonary hypertension. J Heart Lung Transplant. 2019 Sep;38(9):939-948. doi: 10.1016/j.healun.2019.06.014. Epub 2019 Jul 4. PMID: 31495410.



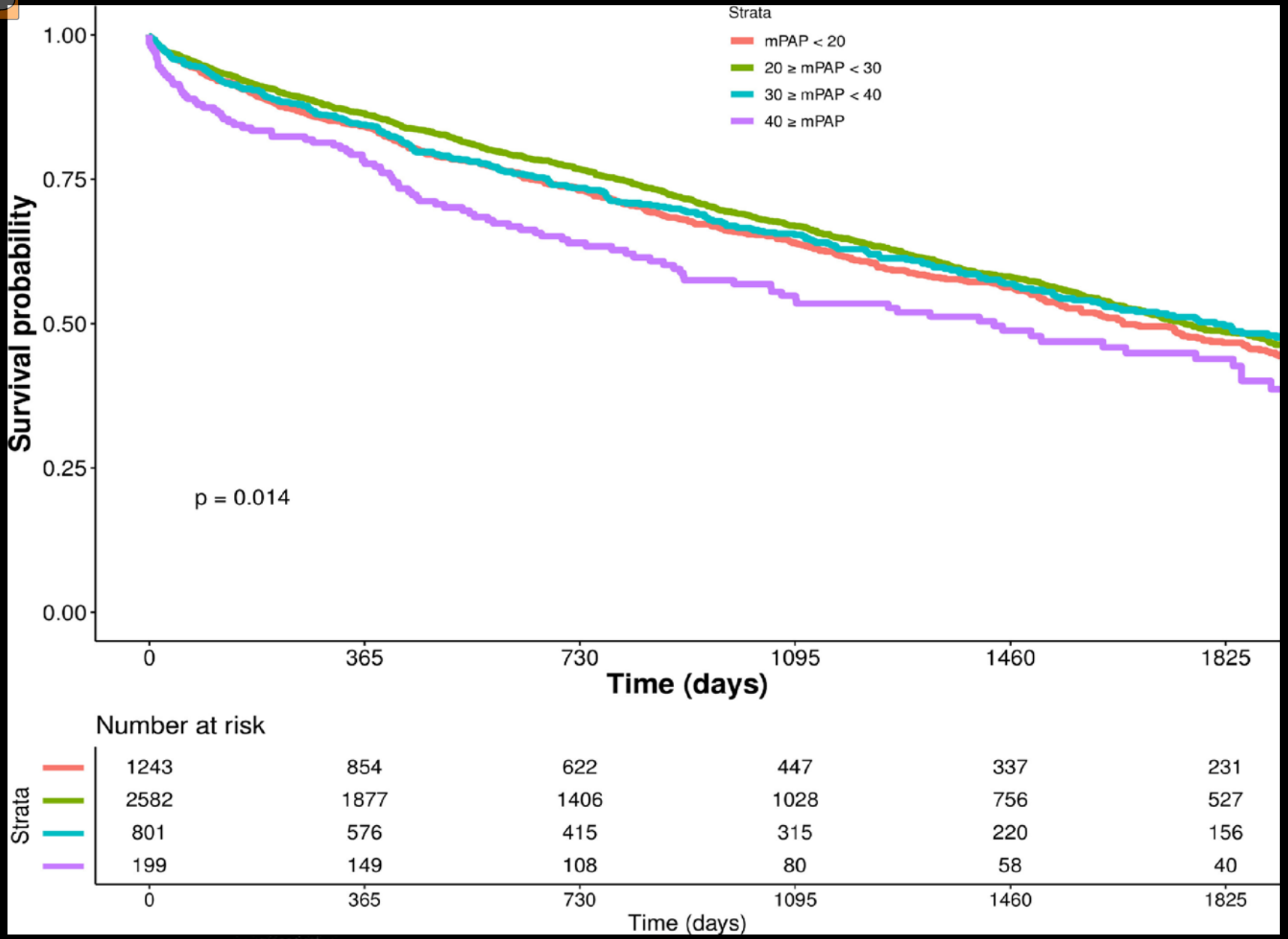
Overall survival in bilateral orthotopic lung transplant (BOLT) recipients stratified by mean pulmonary artery pressure (mPAP).

The Journal of Heart and Lung Transplantation 2019 38939-948DOI: (10.1016/j.healun.2019.06.014)
Copyright © 2019 International Society for Heart and Lung Transplantation Terms and Conditions



Overall survival in single orthotopic lung transplant (SOLT) recipients stratified by mean pulmonary artery pressure (mPAP).

The Journal of Heart and Lung Transplantation 2019 38939-948DOI: (10.1016/j.healun.2019.06.014)
Copyright © 2019 International Society for Heart and Lung Transplantation Terms and Conditions



Overall survival in single orthotopic lung transplant (SOLT) recipients, stratified by increased mean pulmonary artery pressure (mPAP).

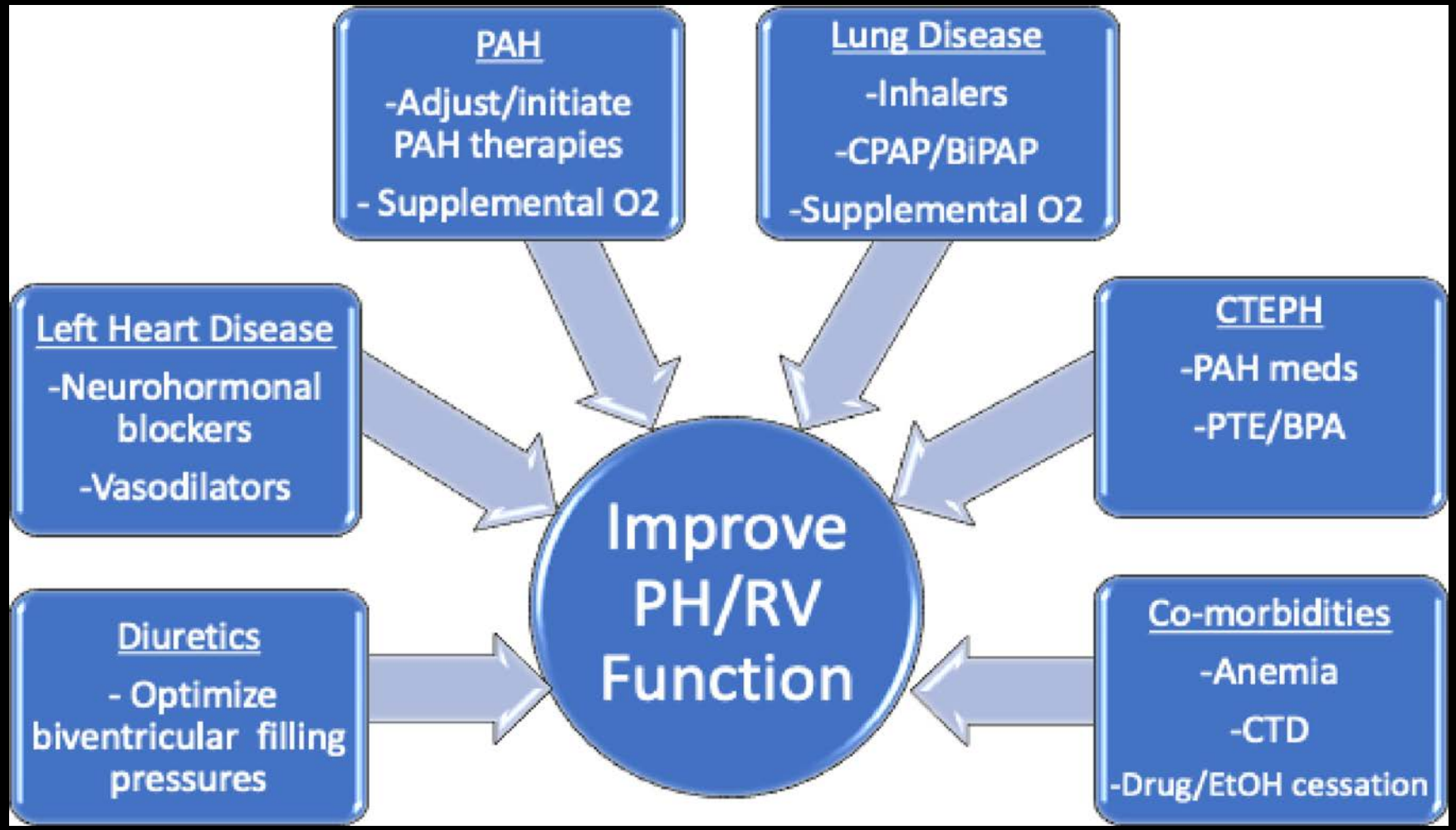
The Journal of Heart and Lung Transplantation 2019 38939-948DOI: (10.1016/j.healun.2019.06.014)
Copyright © 2019 International Society for Heart and Lung Transplantation Terms and Conditions

Successful Lung Transplant for PAH



The Journal of Heart and Lung Transplantation 2022 411135-1194DOI: (10.1016/j.healun.2022.06.013)
Copyright © 2022 International Society for Heart and Lung Transplantation Terms and Conditions

Pre-operative Optimization of PAH patients undergoing Lung Transplant



The Journal of Heart and Lung Transplantation 2022 411135-1194DOI: (10.1016/j.healun.2022.06.013)
Copyright © 2022 International Society for Heart and Lung Transplantation Terms and Conditions

Summary of published data on outcomes of patients with pulmonary arterial hypertension bridged to lung transplant with the use of extracorporeal life support devices

First author [ref.]	Patients who received ECMO support	Patients bridged to transplant	Patients discharged from hospital
de Perrot [30]	6 (4 PA–LA, 2 VA ECMO)	6/6 (100%)	4/6 (66%)
Fuehner [39]	7 (all VA ECMO)	6/7 (86%)	5/6 (71%)
Hoopes [73]	5 (all VA ECMO)	5/5 (100%)	5/5 (100%)
Lang [74]	4 (all VA ECMO)	4/4 (100%)	4/4 (100%)
Rosenzweig [41]	6 (all VA ECMO)	2/2 (100%); 4 received ECMO as bridge to recovery	2/2 (100%); 1/4 (25%) bridge to recovery patients survived for >2 months
Shafii [75]	3 (all VA ECMO)	2/3 (66%)	2/2 (100%)
Crotti [76]	4 (3 VA ECMO, 1 VV ECMO)	4/4 (100%)	3/4 (75%)
Hoetzenecker [77]	13 (9 PA–LA, 4 VA ECMO)	11/13 (85%)	7/11 (63%) survived at 1 year
Savale [56]	13 (all VA ECMO)	13/13 (100%)	8/13 (62%)
Dellgren [78]	2 (both VA ECMO)	2/2 (100%)	1/2 (50%)
Glorion [79]	18 (13 VA ECMO, 3 VV ECMO, 2 PA–LA)	17/18 (94%)	15/17 (88%)
Total	81 (66 ECMO, 15 PA–LA); 77 as bridge to transplant	72/77 (94%)	56/72 (78%)

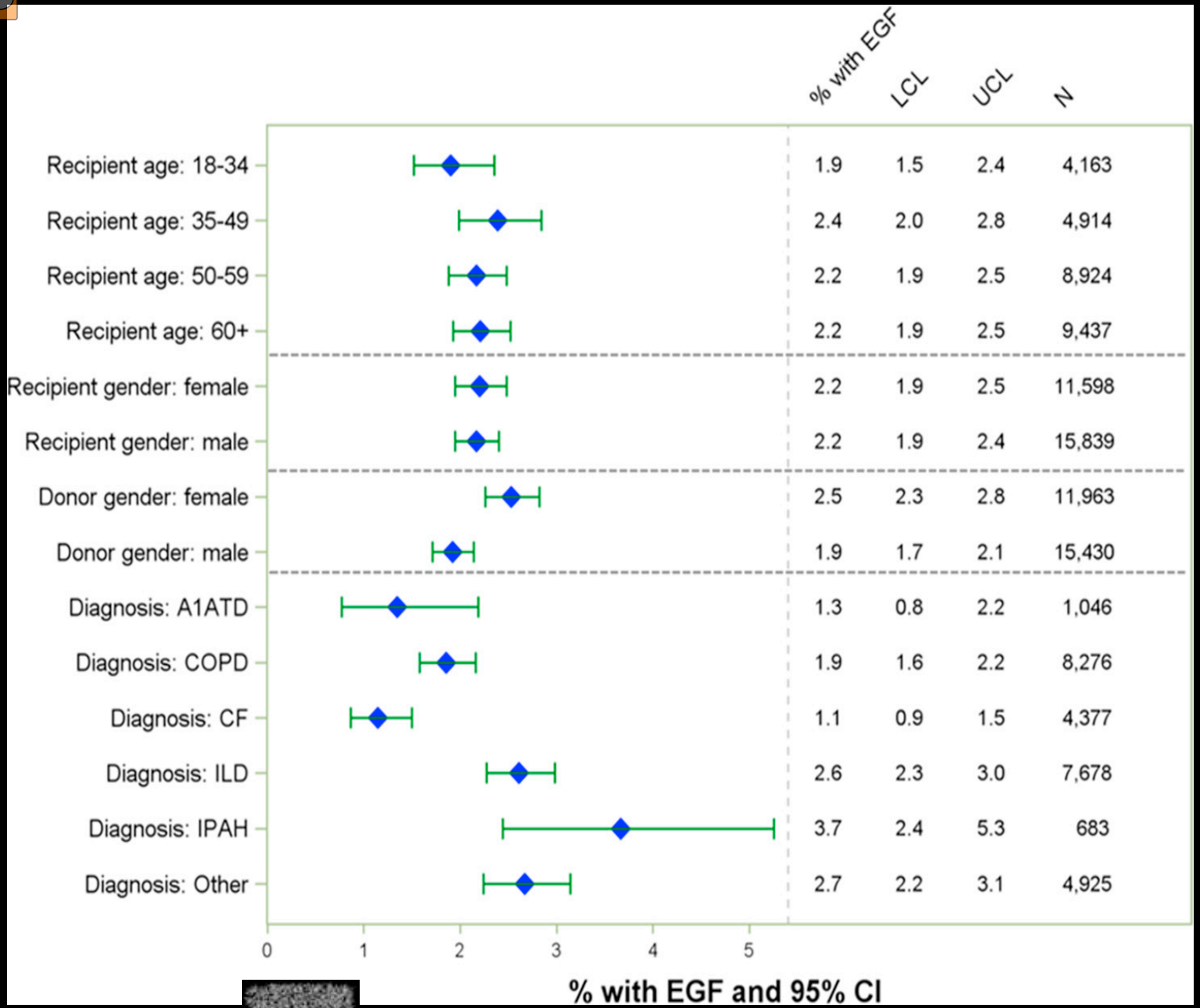
Original Article | Published: 16 September 2017

Extracorporeal membrane oxygenation versus cardiopulmonary bypass during lung transplantation: a meta-analysis

Dimitrios E. Magouliotis ✉, Vasiliki S. Tasiopoulou, Alexis A. Svokos, Konstantina A. Svokos & Dimitris Zacharoulis

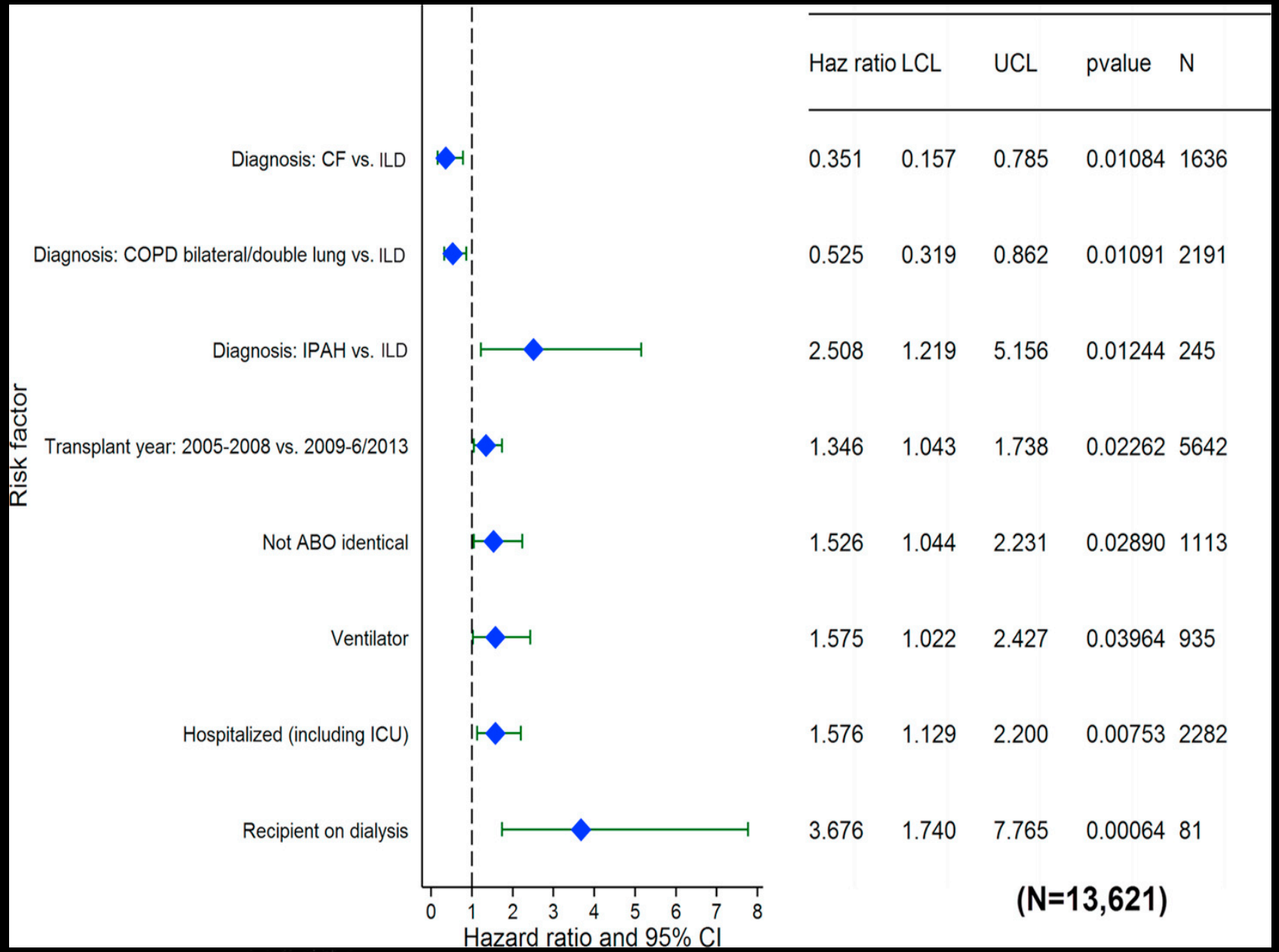
- Seven observational studies met the inclusion criteria incorporating 785 patients. ECMO support showed lower rate of primary graft dysfunction, bleeding, renal failure requiring dialysis, tracheostomy, intraoperative transfusions, intubation time, and hospital stay.
- Total support time was greater for the ECMO-supported group.
- No difference was reported between operative and ischemic time.
- CPB can be used where increased bleeding is anticipated

Magouliotis DE, Tasiopoulou VS, Svokos AA, Svokos KA, Zacharoulis D. Extracorporeal membrane oxygenation versus cardiopulmonary bypass during lung transplantation: a meta-analysis. Gen Thorac Cardiovasc Surg. 2018 Jan;66(1):38-47. doi: 10.1007/s11748-017-0836-3. Epub 2017 Sep 16. PMID: 28918471.



Donor and recipient characteristics for adult primary lung transplants and percentage of patients with early graft failure (EGF) defined by death or retransplant, associated with graft failure, within 30 days after transplant (for 27,438 transplants: January 2005–December 2013).

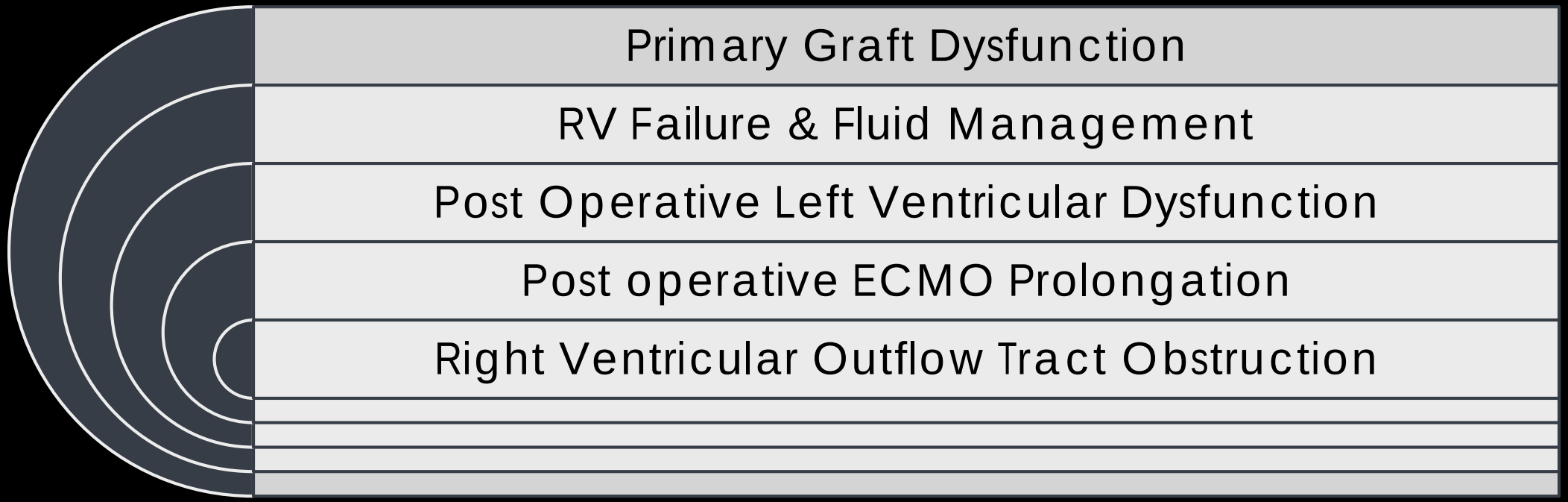
The Journal of Heart and Lung Transplantation 2015 341264-1277DOI: (10.1016/j.healun.2015.08.014)
Copyright © 2015 Terms and Conditions



Adult lung transplant recipient categoric risk factors for early graft failure (EGF), defined by death or retransplant, associated with graft failure, within 30 days after transplant (for 13,621 transplants: January 2005–December 2013)

The Journal of Heart and Lung Transplantation 2015 341264-1277DOI: (10.1016/j.healun.2015.08.014)
Copyright © 2015 Terms and Conditions

POST LUNG TRANSPLANT COMPLICATIONS FOR PAH

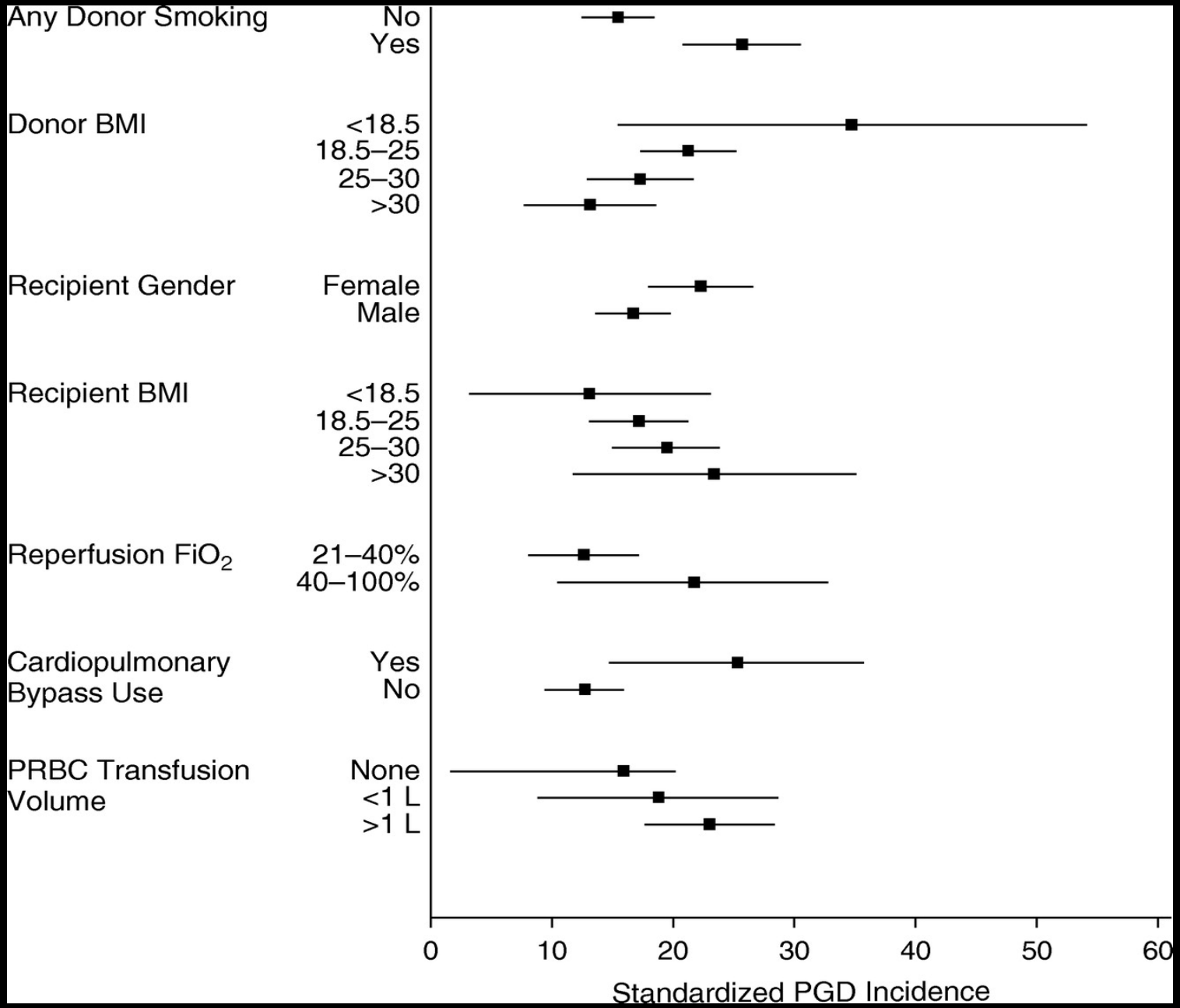


PRIMARY GRAFT DYSFUNCTION

CLINICAL RISK FACTORS AND PROGNOSTIC MODEL FOR PRIMARY GRAFT DYSFUNCTION AFTER LUNG TRANSPLANTATION IN PATIENTS WITH PULMONARY HYPERTENSION

- Conducted a retrospective cohort study of 8226 patients in the multicenter Lung Transplant Outcomes Group with pulmonary hypertension at transplant listing.

Porteous MK, Lee JC, Lederer DJ, Palmer SM, Cantu E, Shah RJ, Bellamy SL, Lama VN, Bhorade SM, Crespo MM, McDyer JF, Wille KM, Localio AR, Orens JB, Shah PD, Weinacker AB, Arcasoy S, Wilkes DS, Ware LB, Christie JD, Kawut SM, Diamond JM; Lung Transplant Outcomes Group. Clinical Risk Factors and Prognostic Model for Primary Graft Dysfunction after Lung Transplantation in Patients with Pulmonary Hypertension. Ann Am Thorac Soc. 2017 Oct;14(10):1514-1522. doi: 10.1513/AnnalsATS.201610-810OC. PMID: 28719755; PMCID: PMC5718566.



Adjusted probability of grade 3 primary graft dysfunction for donor, recipient, and perioperative covariates in Lung Transplants for Pulmonary Hypertension

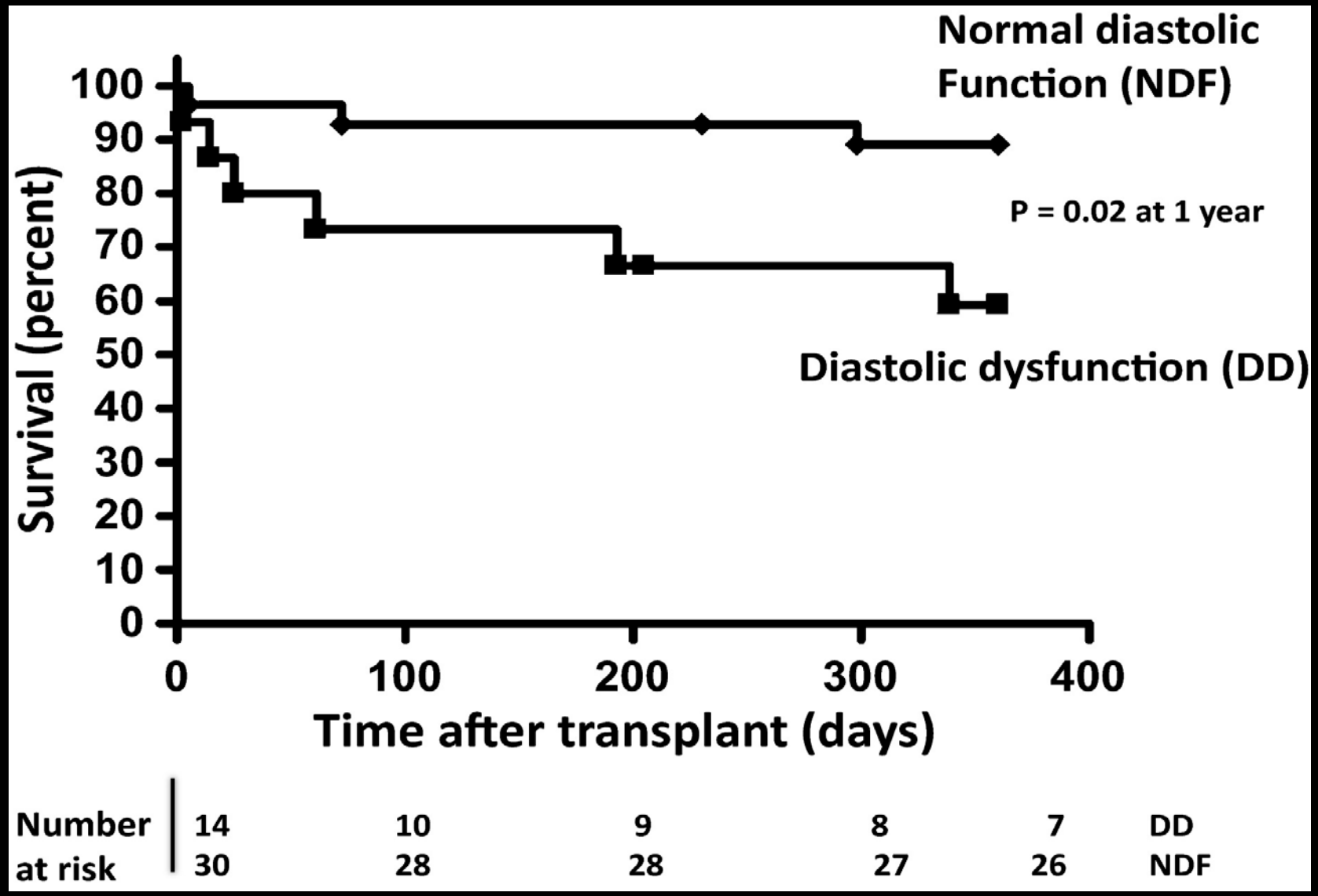
Porteous MK, Lee JC, Lederer DJ, Palmer SM, Cantu E, Shah RJ, Bellamy SL, Lama VN, Bhorade SM, Crespo MM, McDyer JF, Wille KM, Localio AR, Orens JB, Shah PD, Weinacker AB, Arcasoy S, Wilkes DS, Ware LB, Christie JD, Kawut SM, Diamond JM; Lung Transplant Outcomes Group. Clinical Risk Factors and Prognostic Model for Primary Graft Dysfunction after Lung Transplantation in Patients with Pulmonary Hypertension. Ann Am Thorac Soc. 2017 Oct;14(10):1514-1522. doi: 10.1513/AnnalsATS.201610-810OC. PMID: 28719755; PMCID: PMC5718566.

MORE REASONS FOR PGD?

- Most importantly, left ventricular diastolic dysfunction was recently reported to be an independent prognostic risk factor for PGD in patients with PH and may be associated with worse long-term outcomes

1) Avriel A, Klement AH, Johnson SR, de Perrot M, Granton J. Impact of Left Ventricular Diastolic Dysfunction on Lung Transplantation Outcome in Patients With Pulmonary Arterial Hypertension. Am J Transplant. 2017 Oct;17(10):2705-2711. doi: 10.1111/ajt.14352. Epub 2017 Jul 3. PMID: 28508451.

2) Porteous MK, Ky B, Kirkpatrick JN, Shinohara R, Diamond JM, Shah RJ, Lee JC, Christie JD, Kawut SM. Diastolic Dysfunction Increases the Risk of Primary Graft Dysfunction after Lung Transplant. Am J Respir Crit Care Med. 2016 Jun 15;193(12):1392-400. doi: 10.1164/rccm.201508-1522OC. PMID: 26745666; PMCID: PMC4910888.



American J Transplantation, Volume: 17, Issue: 10, Pages: 2705-2711, First published: 16 May 2017, DOI: (10.1111/ajt.14352)

- Kaplan–Meier survival curves illustrating the post–lung transplantation 1-year survival
- According to the diastolic function (hazard ratio 4.45, 95% confidence interval 1.3–22,
- p = 0.02).

RIGHT VENTRICLE FAILURE
&
FLUID MANAGEMENT

Effects on volume changes on cardiac function in right-sided heart failure

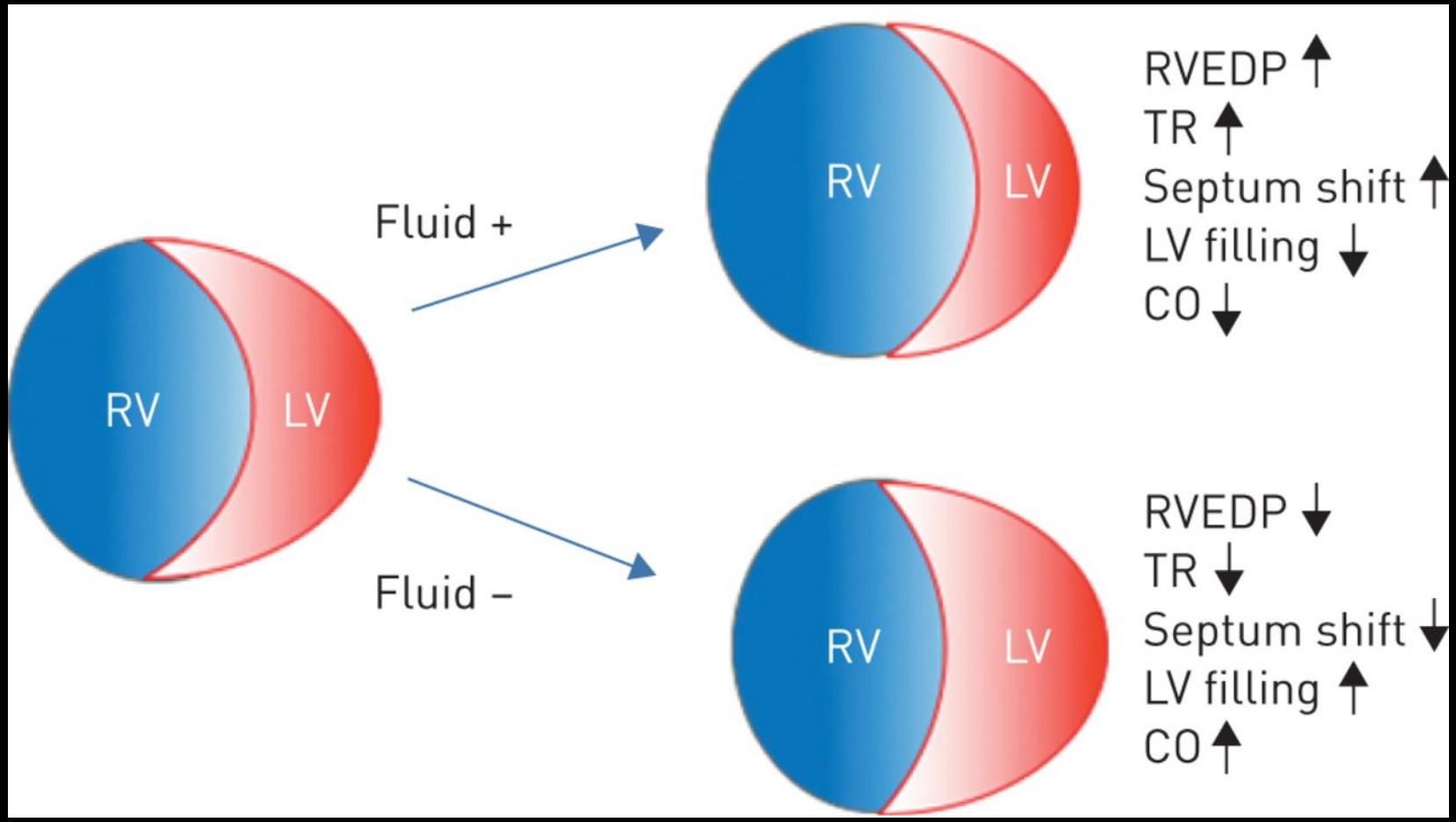
RV: *right ventricle*

LV: *left ventricle*

RVEDP:
right ventricular end-diastolic pressure

TR: *tricuspid regurgitation*

CO: *cardiac output*



RV FAILURE & FLUID MANAGEMENT

- Given the chronic congestive renal impairment, the sole use of diuretics may not be sufficient leading to liberal use of temporary hemofiltration in some patients.

- Up to 45% of patients undergoing lung transplantation for PAH need temporary hemofiltration but without long term sequalae such a permanent hemodialysis or renal transplantation

RV FAILURE & FLUID MANAGEMENT

- Echocardiography is a valid tool to monitor cardiac performance in response to fluid administration in critically ill patients.

- It is important to delay extubation or weaning from ECMO until the patient's fluid status has been normalized.

POST OP LEFT VENTRICULAR DYSFUNCTION

POST OP LEFT VENTRICULAR DYSFUNCTION

- Patients with end stage PAH present with a chronically underfilled LV of reduced dimensions leading to reduced stroke volume.

- Lung transplantation ideally resets the PVR to physiologic conditions which results in improved LV filling and consequent increase in cardiac output.

- Not infrequently, the situation arises that the untrained LV cannot handle this sudden increase of volume load, which can lead to temporary LV failure and pulmonary edema and lower 1-year survival

POST OP ECMO PROLONGATION

PROLONGED VA ECMO POST TRANSPLANT

- A particular benefit of ECMO (over CPB) lies in the possibility to prolong it into the postoperative period to guarantee hemodynamic stability.

Pereszlenyi A, Lang G, Steltzer H, Hetz H, Kocher A, Neuhauser P, Wisser W, Klepetko W. Bilateral lung transplantation with intra- and postoperatively prolonged ECMO support in patients with pulmonary hypertension. Eur J Cardiothorac Surg. 2002 May ;21(5):858-63. doi: 10.1016/s1010-7940(02)00058-1. PMID: 12062275.

PROLONGED VA ECMO POST TRANSPLANT

- Prolonged VA ECMO reduces blood flow through the lungs, gives the heart and lungs the necessary time for slower adaptation to the new conditions and in this way provides optimally controlled reperfusion of the lung allografts

- It offers the possibility for lung protective mechanical ventilation such as low tidal volumes (TV) and plateau pressures thereby avoiding stretch injury associated with higher TV that would otherwise be required without ECMO to support ventilation.

- Routine prophylactic postoperative use of VA ECMO results in excellent outcome and is particularly recommended in patients with PAH

PROLONGED VA ECMO POST TRANSPLANT
HANNOVER, GERMANY

Tudorache I, Sommer W, Kühn C, Wiesner O, Hadem J, Fühner T, Ius F, Avsar M, Schwerk N, Böthig D, Gottlieb J, Welte T, Bara C, Haverich A, Hoeper MM, Warnecke G. Lung transplantation for severe pulmonary hypertension--awake extracorporeal membrane oxygenation for postoperative left ventricular remodelling. Transplantation. 2015 Feb;99(2):451-8. doi: 10.1097/TP.0000000000000348. PMID: 25119128.

Original Clinical Science

Lung Transplantation for Severe Pulmonary Hypertension—Awake Extracorporeal Membrane Oxygenation for Postoperative Left Ventricular Remodelling

Igor Tudorache,[1] Wiebke Sommer,[1] Christian Kühn,[1] Olaf Wiesner,[2] Johannes Hadem,[3] Thomas Fühner,[2] Fabio Ius,[1] Murat Avsar,[1] Nicolaus Schwerk,[4] Dietmar Böthig,[1] Jens Gottlieb,[2,5] Tobias Welte,[2,5] Christoph Bara,[1] Axel Haverich,[1,5] Marius M. Hoeper,[2,5] and Gregor Warnecke[1,5]

PATIENT CHARACTERISTICS

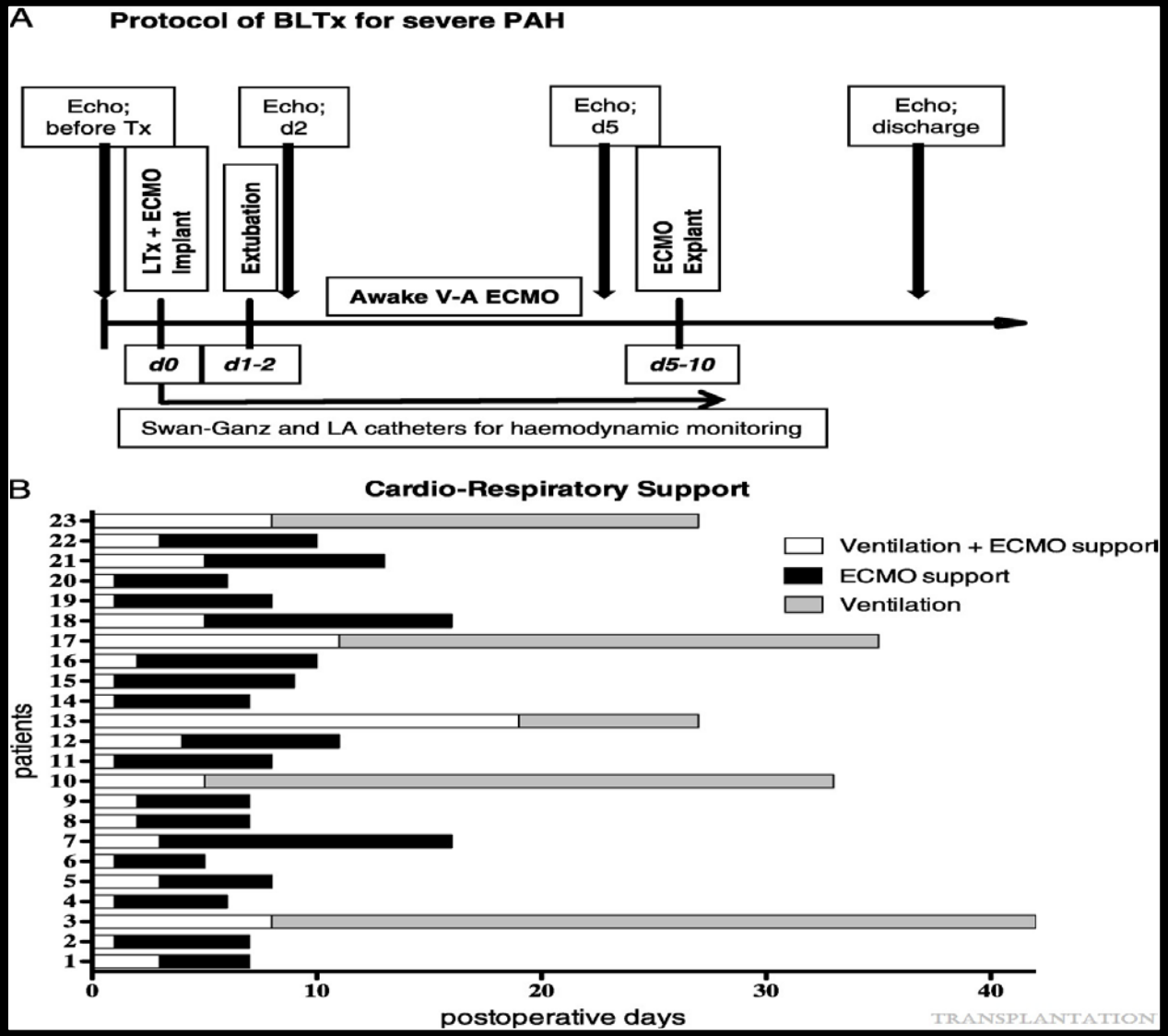
	BLTx-ECMO	BLTx-ventilation	HLTx
Baseline characteristics			
Patients (n)	23	13	17
Age (yr) median (range)	49 (7-62)	42 (17-58)	37 (15-54)
Male/female	8/15	4/9	5/12
Diagnosis (n)			
Idiopathic PAH	17	3	15
PVOD	3	6	2
Sarcoidosis	3	1	—
CTEPH	—	3	—
Hemodynamic details			
mPAP (mm Hg) mean (SD)	66 (17)	59 (8)	74 (21)
PVR (dyn/s/cm^{-5}) mean (SD)	1439 (693)	1131 (473)	1618 (739)
CI (L/min/m^2) mean (SD)	2 (0,7)	2 (1)	2 (1)
LVEF (%) mean (SD)	65 (12)	61 (5)	62 (6)
RVEF (%) mean (SD)	34 (10)	39 (14)	39 (11)
PCWP (mm Hg) mean (SD)	11 (8)	—	—
Other clinical data			
6-min WD (m) mean (SD)	234 (161)	n/a	n/a
NT-proBNP (ng/L) mean (SD)	7258 (8701)	n/a	n/a

PVR, pulmonary vascular resistance; BLTx, bilateral lung transplantation; HLTx, heart-lung transplantation; PAH, pulmonary artery hypertension; PVOD, pulmonary veno-occlusive disease; CTEPH, chronic thrombembolic pulmonary hypertension; mPAP, mean pulmonary artery pressure; RVEF, right ventricular ejection fraction; LVEF, left ventricular ejection fraction; PCWP, pulmonary capillary wedge pressure; WD, walking distance; CI, cardiac index; NT-proBNP, N-terminal pro-brain natriuretic peptide; SD, standard deviation; n/a, not available.

TRANSPLANTATION

TUDORACHE, IGOR; SOMMER, WIEBKE; KÜHN, CHRISTIAN; WIESNER, OLAF; HADEM, JOHANNES; FÜHNER, THOMAS; IUS, FABIO; AVSAR, MURAT; SCHWERK, NICOLAUS; BÖTHIG, DIETMAR; GOTTLIEB, JENS; WELTE, TOBIAS; BARA, CHRISTOPH; HAVERICH, AXEL; HOEPER, MARIUS M.; WARNECKE, GREGOR. TRANSPLANTATION99(2):451-458, FEBRUARY 2015. DOI: 10.1097/TP.0000000000000348

Wolters Kluwer



A) Protocol of BLTx for patients with severe pulmonary hypertension

B) Postoperative cardiorespiratory support in BLTx-ECMO patients.

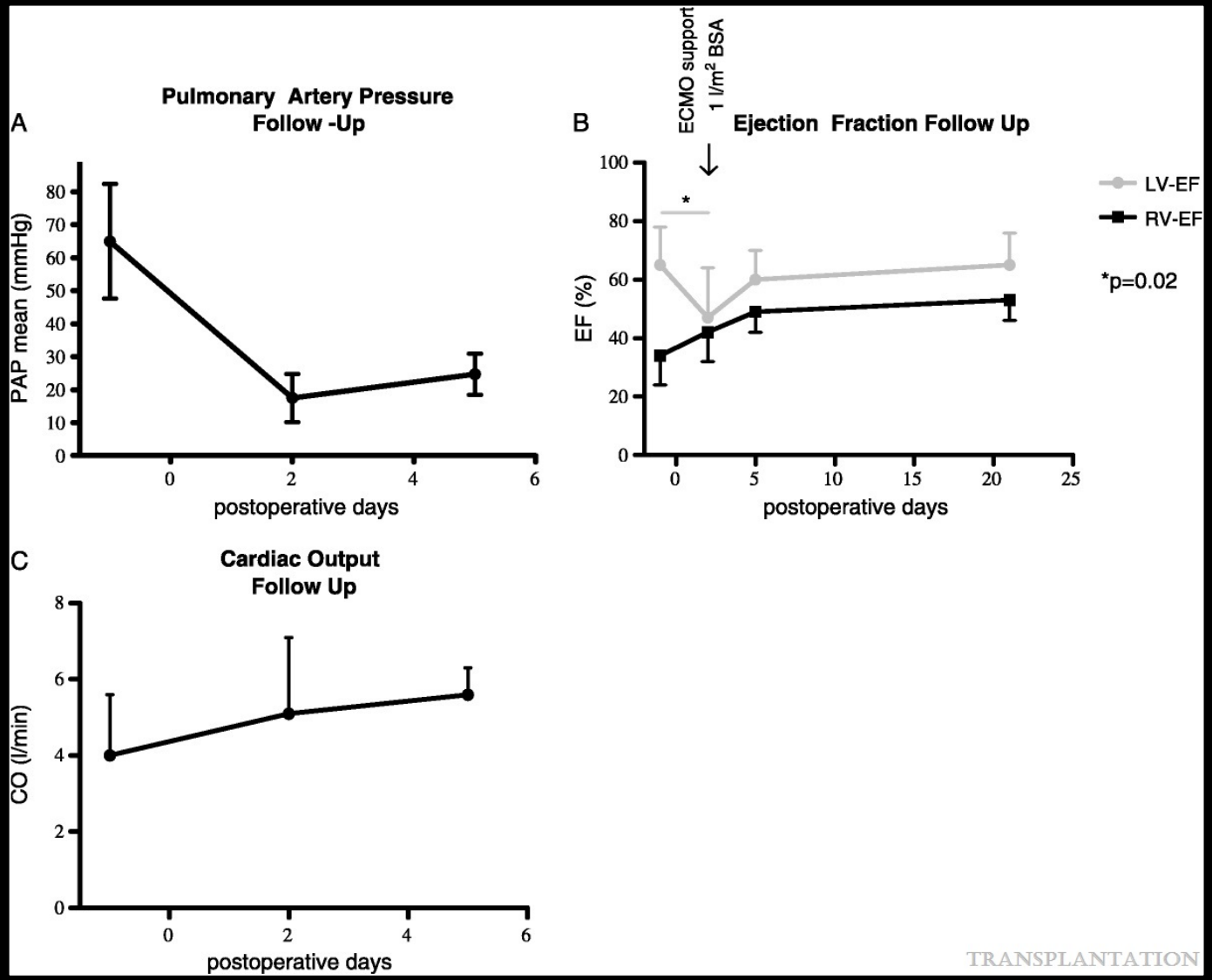
Patient 3: case with postoperative type B dissection; prolonged respiratory weaning

Patients 10, 17, and 23: cases with redo-thoracotomies for bleeding;

Patient 13: 7-year-old patient with inadequate drainage through the pediatric venous cannula of the ECMO on attempting to wean from respirator.

TUDORACHE, IGOR; SOMMER, WIEBKE; KÜHN, CHRISTIAN; WIESNER, OLAF; HADEM, JOHANNES; FÜHNER, THOMAS; IUS, FABIO; AVSAR, MURAT; SCHWERK, NICOLAUS; BÖTHIG, DIETMAR; GOTTLIEB, JENS; WELTE, TOBIAS; BARA, CHRISTOPH; HAVERICH, AXEL; HOEPER, MARIUS M.; WARNECKE, GREGOR
TRANSPLANTATION99(2):451-458, FEBRUARY 2015.DOI: 10.1097/TP.0000000000000348

FOLLOW-UP OF HEMODYNAMIC PARAMETERS IN BLTX-ECMO PATIENTS



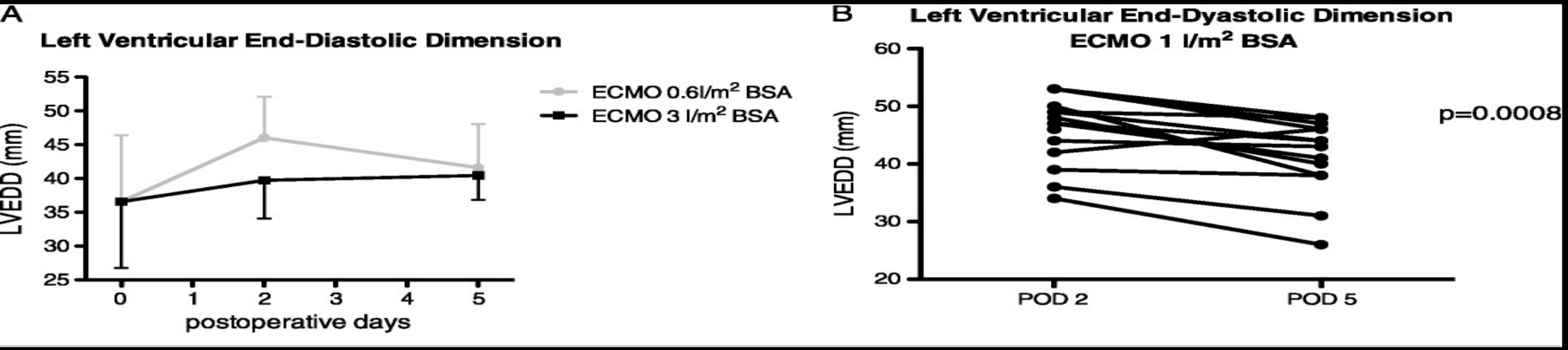
A) PA pressures before transplantation and on days 2 and 5 after transplantation.

B) Left and right ventricular ejection fractions on transthoracic or transesophageal echocardiography before transplantation and on days 2, 5, and ~20 (Data given for days 2 and 5 was obtained at reduced ECMO flow of 1 L/m2 BSA.

C) Cardiac output before transplantation and on days 2 and 5 after lung transplantation as assessed by right heart catheterization.

TUDORACHE, IGOR; SOMMER, WIEBKE; KÜHN, CHRISTIAN; WIESNER, OLAF; HADEM, JOHANNES; FÜHNER, THOMAS; IUS, FABIO; AVSAR, MURAT; SCHWERK, NICOLAUS; BÖTHIG, DIETMAR; GOTTLIEB, JENS; WELTE, TOBIAS; BARA, CHRISTOPH; HAVERICH, AXEL; HOEPER, MARIUS M.; WARNECKE, GREGO TRANSPLANTATION99(2):451-458, FEBRUARY 2015. DOI: 10.1097/TP.0000000000000348

FOLLOW-UP OF LVEDD IN BLTX-ECMO PATIENTS DURING ECMO SUPPORT AND ON REDUCTION OF THE ECMO FLOW



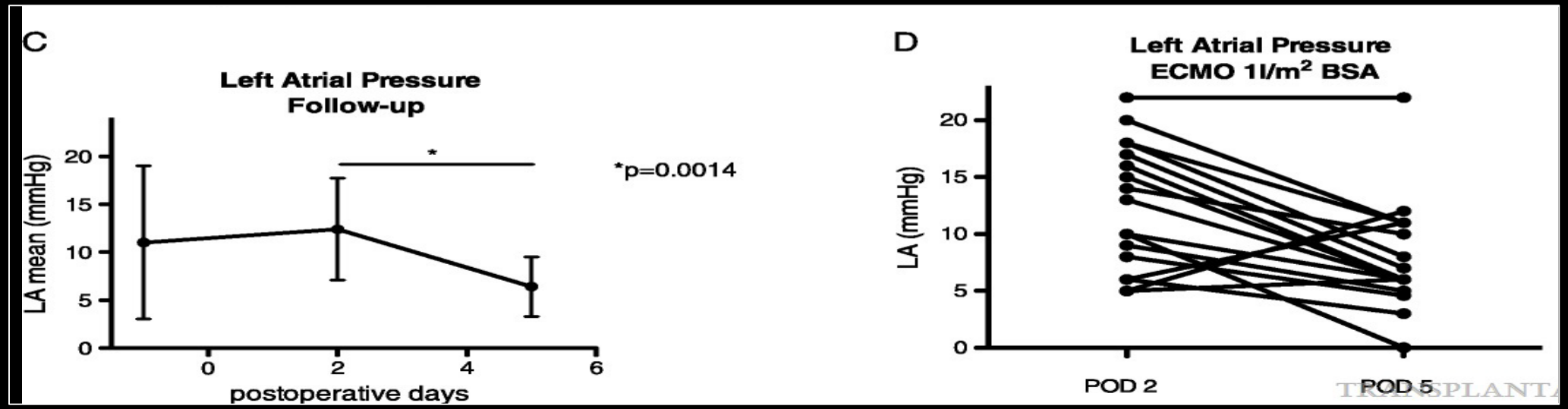
A) LVEDD (left ventricular end-diastolic diameter) before transplantation and 2 and 5 days after transplantation. Data after transplantation is given at full ECMO flow (3 L/m2 BSA, black line) and at reduced ECMO flow (0.6 L/m2 BSA, light gray line). Significant LV dysfunction is evident 2 days after transplantation, but not 5 days after transplantation.

B) Individual patients' LVEDD data pairs are given for 2 and 5 days after transplantation to illustrate the tendency of LV function recovery in most patients.

Wolters Kluwer

TUDORACHE, IGOR; SOMMER, WIEBKE; KÜHN, CHRISTIAN; WIESNER, OLAF; HADEM, JOHANNES; FÜHNER, THOMAS; IUS, FABIO; AVSAR, MURAT; SCHWERK, NICOLAUS; BÖTHIG, DIETMAR; GOTTLIEB, JENS; WELTE, TOBIAS; BARA, CHRISTOPH; HAVERICH, AXEL; HOEPER, MARIUS M.; WARNECKE, GREGO TRANSPLANTATION99(2):451-458, FEBRUARY 2015.DOI: 10.1097/TP.0000000000000348

FOLLOW-UP OF LA PRESSURE IN BLTX-ECMO PATIENTS DURING ECMO SUPPORT AND ON REDUCTION OF THE ECMO FLOW



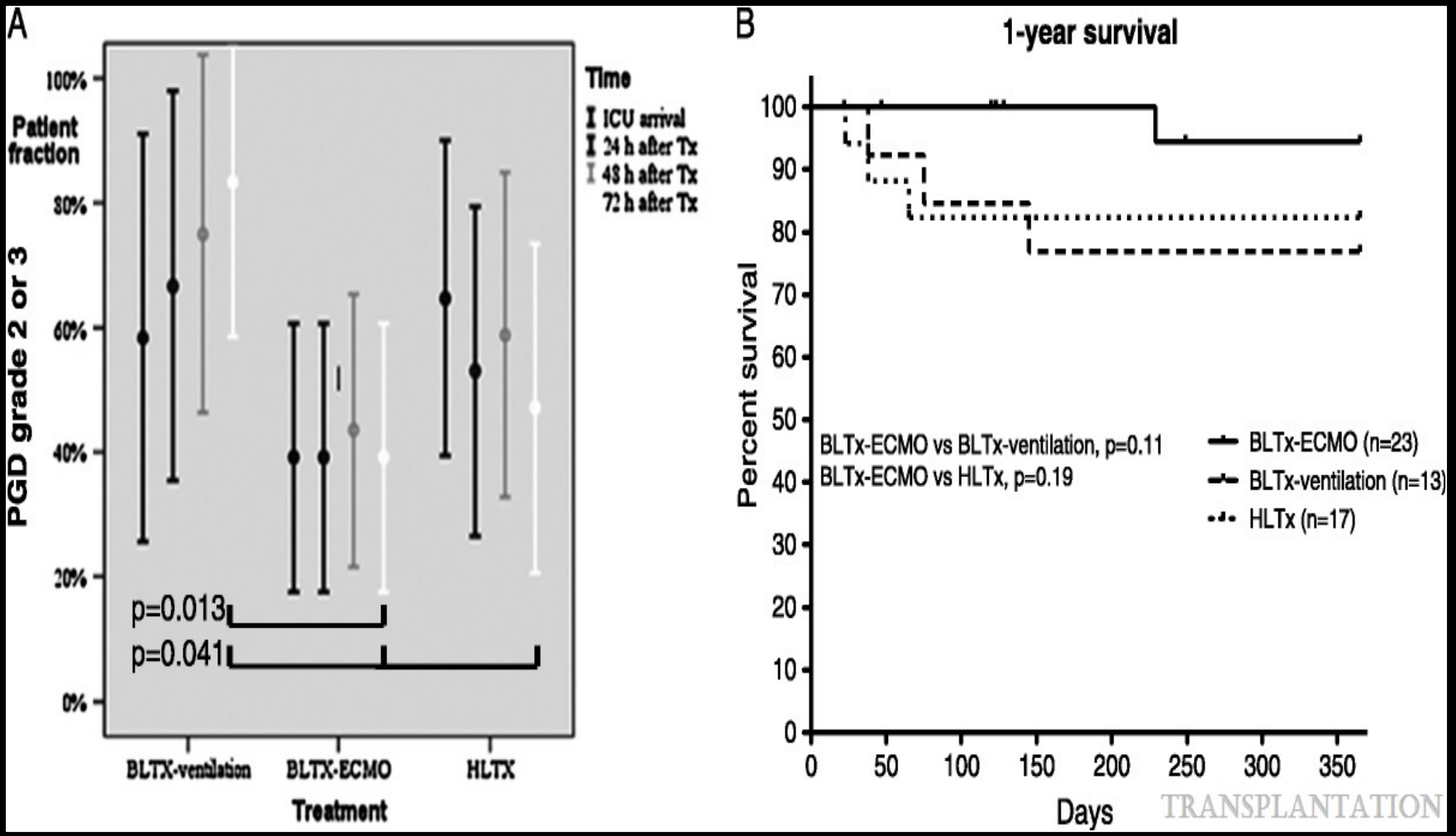
C) LA pressures of BLTx-ECMO patients before transplantation, and 2 and 5 days after lung transplantation are given. Values before transplantation are PCWP values obtained during right heart catheterization. Posttransplantation LA pressures were monitored through an invasive line implanted during BLTx. Measurements on days 2 and 5 after transplantation were performed after ECMO flow reduction to 1 L/m2 BSA. LA pressures of less than 10 mm Hg under reduced ECMO flow conditions were considered an important indicator of LV functional recovery indicating the ECMO might safely be explanted.

D) Individual patients' LA pressure data pairs are given for 2 and 5 days after transplantation to illustrate the tendency of LV function recovery in most patients.

Wolters Kluwer

TUDORACHE, IGOR; SOMMER, WIEBKE; KÜHN, CHRISTIAN; WIESNER, OLAF; HADEM, JOHANNES; FÜHNER, THOMAS; IUS, FABIO; AVSAR, MURAT; SCHWERK, NICOLAUS; BÖTHIG, DIETMAR; GOTTLIEB, JENS; WELTE, TOBIAS; BARA, CHRISTOPH; HAVERICH, AXEL; HOEPER, MARIUS M.; WARNECKE, GREG TRANSPLANTATION99(2):451-458, FEBRUARY 2015.DOI: 10.1097/TP.0000000000000348

PGD AND 1 YEAR SURVIVAL IN ECMO VERSUS MECHANICAL VENTILATION



A) Percentage of patients with PGD grades 2 and 3, stratified by time after transplantation and treatment group. After 72 hr, PGD grade 2 or grade 3 was statistically significantly more often documented in patients of the historic control BLTx-ventilation group as compared to the BLTx-ECMO group.

B) One-year survival of patients with BLTx for severe PH performed using the new awake ECMO weaning protocol (BLTx-ECMO) and of historic controls with BLTx-ventilation or HLTx.

Tudorache, Igor; Sommer, Wiebke; Kühn, Christian; Wiesner, Olaf; Hadem, Johannes; Fühner, Thomas; Ius, Fabio; Avsar, Murat; Schwerk, Nicolaus; Böthig, Dietmar; Gottlieb, Jens; Welte, Tobias; Bara, Christoph; Haverich, Axel; Hoeper, Marius M.; Warnecke, Greg Transplantation99(2):451-458, February 2015.doi: 10.1097/TP.0000000000000348

Wolters Kluwer

PROLONGED VA ECMO POST TRANSPLANT

VIENNA, AUSTRIA

Moser B, Jaksch P, Taghavi S, Muraközy G, Lang G, Hager H, Krenn C, Roth G, Faybik P, Bacher A, Aigner C, Matilla JR, Hoetzenecker K, Hacker P, Lang I, Klepetko W. Lung transplantation for idiopathic pulmonary arterial hypertension on intraoperative and postoperatively prolonged extracorporeal membrane oxygenation provides optimally controlled reperfusion and excellent outcome. Eur J Cardiothorac Surg. 2018 Jan 1;53(1):178-185. doi: 10.1093/ejcts/ezx212. PMID: 28950326; PMCID: PMC5848802.

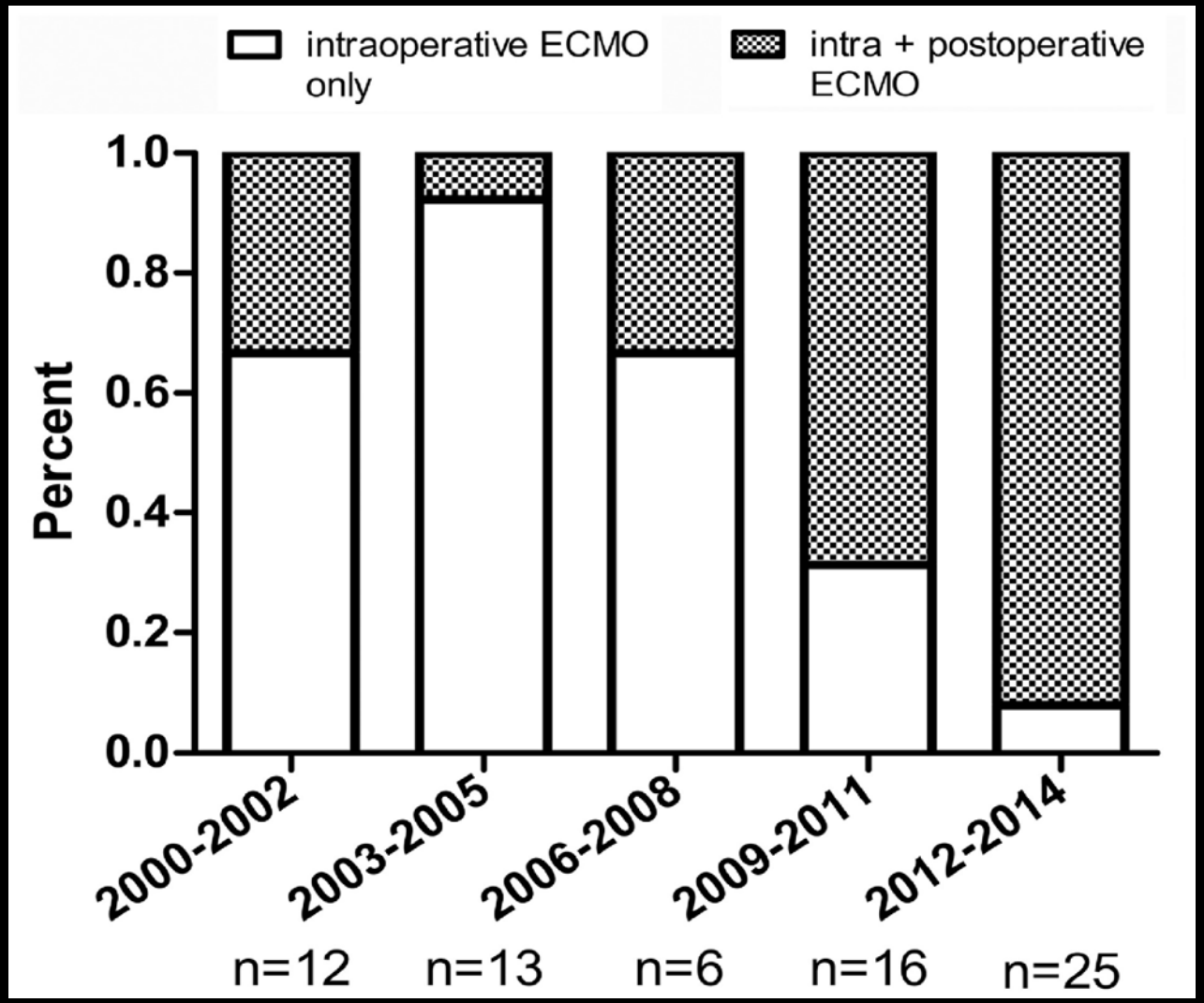
Lung transplantation for idiopathic pulmonary arterial hypertension on intraoperative and postoperatively prolonged extracorporeal membrane oxygenation provides optimally controlled reperfusion and excellent outcome

Bernhard Moser[a,*], Peter Jaksch[a], Shahrokh Taghavi[a], Gabriella Muraközy[a], Georg Lang[a,b], Helmut Hager[c], Claus Krenn[d], Georg Roth[d], Peter Faybik[d], Andreas Bacher[d], Clemens Aigner[a], José R. Matilla[a], Konrad Hoetzenecker[a], Philipp Hacker[a], Irene Lang[e] and Walter Klepetko[a]

[a] Department of Thoracic Surgery, Medical University of Vienna, Vienna, Austria
[b] Department of Thoracic Surgery, National Institute of Oncology, Semmelweis University, Budapest, Hungary
[c] Department of Cardiothoracic and Vascular Anesthesiology and Intensive Care Medicine, Medical University of Vienna, Vienna, Austria
[d] Department of Anesthesiology, General Intensive Care and Pain Medicine, Medical University of Vienna, Vienna, Austria
[e] Division of Cardiology, Department of Internal Medicine II, Medical University of Vienna, Vienna, Austria

Figure 1:

Use of different modes of ECMO (1 January 2000–31 December 2014). Histogram displaying the use of prophylactic postoperative ECMO in patients with iPAH undergoing BLTX (3-year intervals). ECMO: extracorporeal membrane oxygenation; iPAH: idiopathic pulmonary arterial hypertension; BLTX: bilateral lung transplantation.

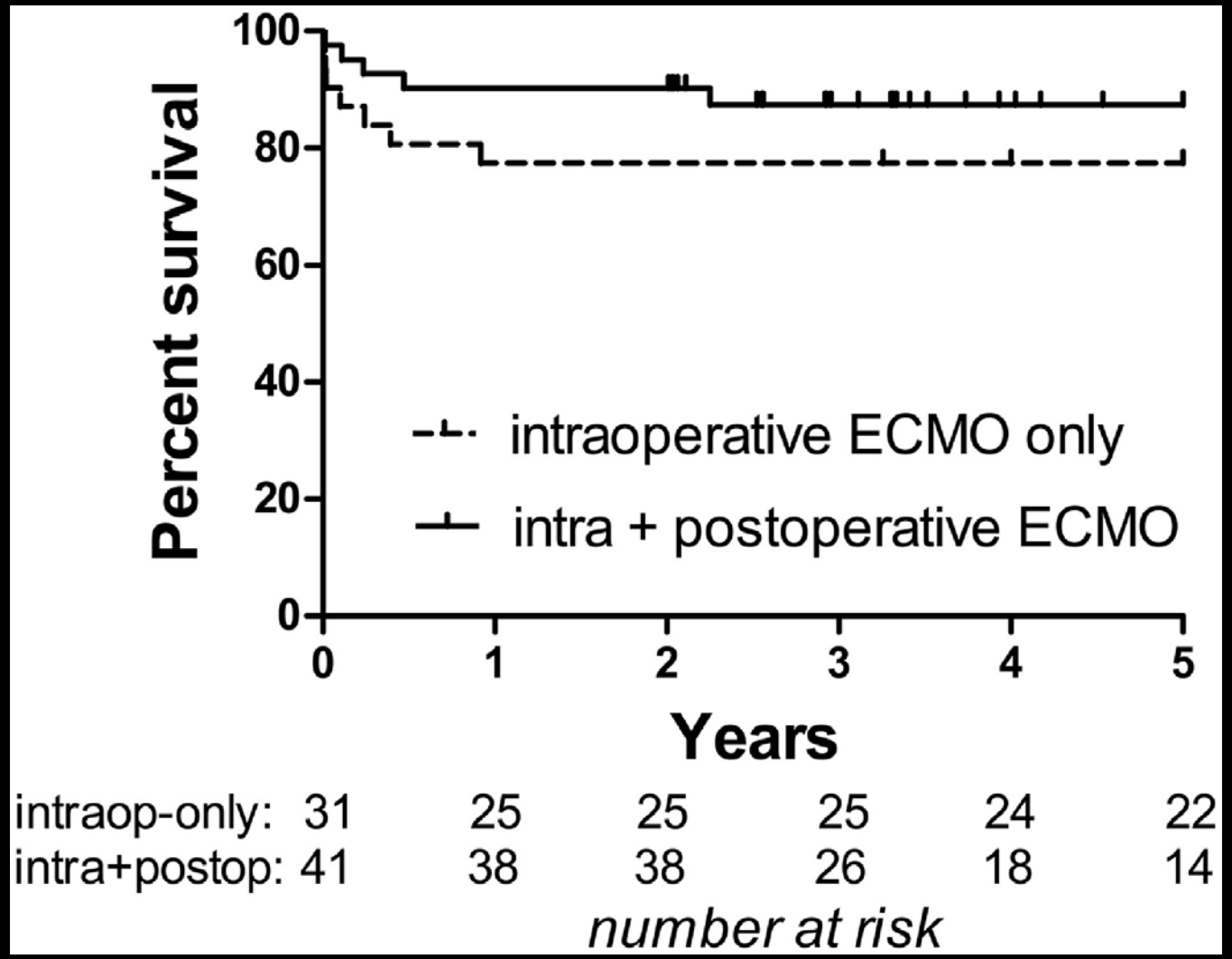


Eur J Cardiothorac Surg, Volume 53, Issue 1, January 2018, Pages 178–185, https://doi.org/10.1093/ejcts/ezx212

The content of this slide may be subject to copyright: please see the slide notes for details.

Figure 2:

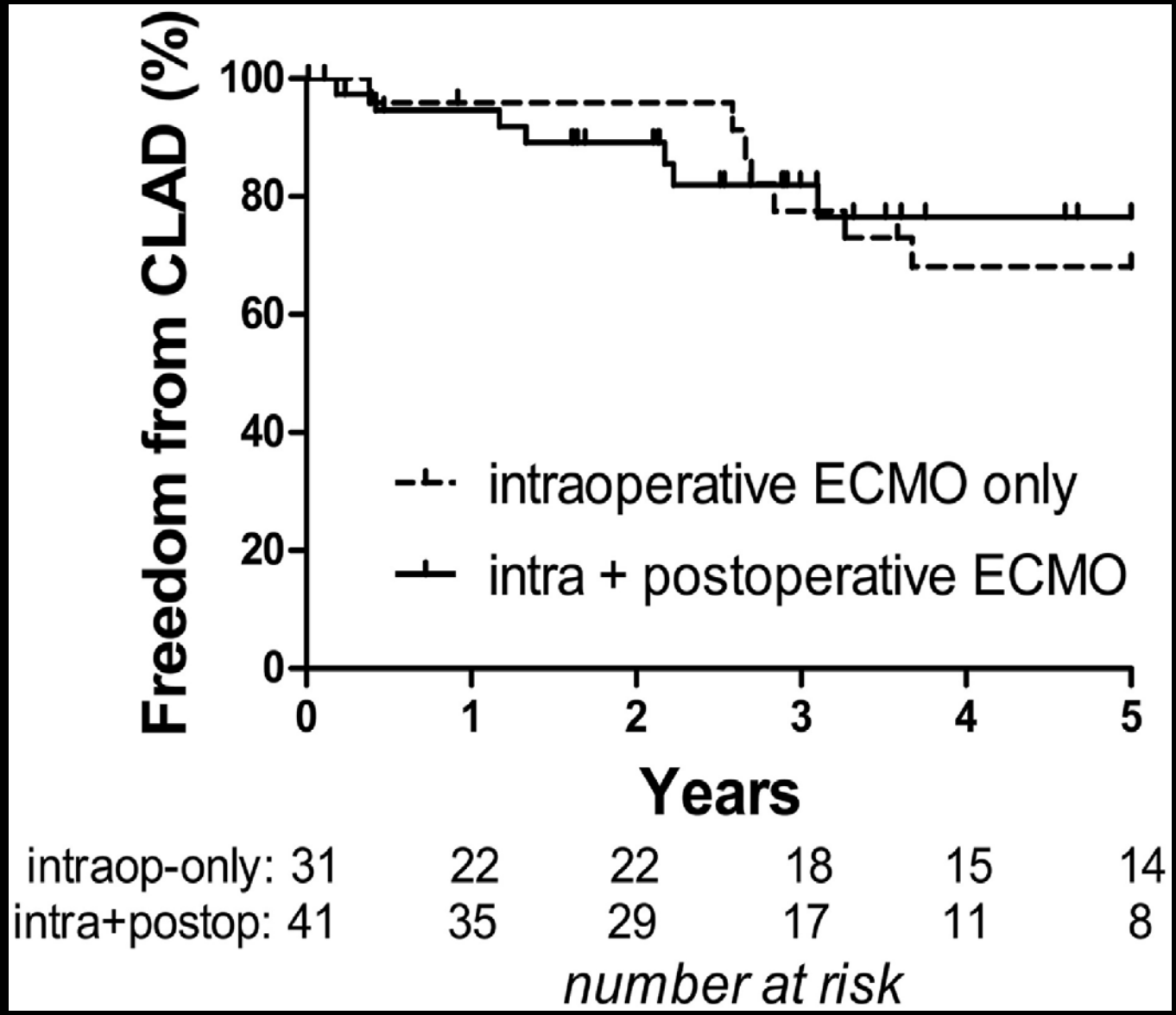
Survival depending on the use of prolonged ECMO. Patients with intraoperative ECMO with prolongation into the postoperative period were compared with a historic control group with intraoperative ECMO only. ECMO: extracorporeal membrane oxygenation.



Eur J Cardiothorac Surg, Volume 53, Issue 1, January 2018, Pages 178–185, https://doi.org/10.1093/ejcts/ezx212

OXFORD UNIVERSITY PRESS

Freedom from CLAD in iPAH patients undergoing BLTX on intraoperative ECMO with prolongation into the postoperative period compared to intraoperative ECMO support only.



Eur J Cardiothorac Surg, Volume 53, Issue 1, January 2018, Pages 178–185, https://doi.org/10.1093/ejcts/ezx212

OXFORD UNIVERSITY PRESS

Complications related to ECMO

n (%)	17 (41.4)
Rethoracotomy for bleeding	7 (17.1)
ECMO-related	
Infection at cannulation site in groin	1 (2.4)
Thrombosis of leg cannula	2 (4.9)
Possibly ECMO-related	
Symptomatic transitory psychotic syndrome	4 (9.7)
Radiological signs of subarachnoidal bleeding[a]	2 (4.9)
Hypoxic brain damage	1 (2.4)

Patients with iPAH undergoing BLTX on intraoperative ECMO with prolongation into the postoperative period.

Moser B, Jaksch P, Taghavi S, Muraközy G, Lang G, Hager H, Krenn C, Roth G, Faybik P, Bacher A, Aigner C, Matilla JR, Hoetzenecker K, Hacker P, Lang I, Klepetko W. Lung transplantation for idiopathic pulmonary arterial hypertension on intraoperative and postoperatively prolonged extracorporeal membrane oxygenation provides optimally controlled reperfusion and excellent outcome. Eur J Cardiothorac Surg. 2018 Jan 1;53(1):178-185. doi: 10.1093/ejcts/ezx212. PMID: 28950326; PMCID: PMC5848802.

LIMITATIONS

- Determination of the optimal extracorporeal support configuration is needed

- Data regarding who would benefit from postoperative ECMO support are lacking.

RIGHT VENTRICULAR OUTFLOW TRACT (RVOT) OBSTRUCTION

- There is one specific exception from the typical hemodynamic pattern after lung transplantation in patients with PAH

RVOT OBSTRUCTION

- Happens with pronounced RV muscular hypertrophy
- Unguided reduction of circulatory volume can exacerbate RVOT obstruction
- The correct treatment in this situation consists of augmented volume status and consideration of beta-blockers. Repeated echocardiographic monitoring is mandatory to identify this condition

Management of Post Lung Transplant for PAH

Lung transplantation for pulmonary hypertension

Effects	Problems	Time	Strategy	Rationale
Reduction of PVR > increase of CO	Overflow of TX lung	Immediately after LTX	BLTX	Provide large pulmonary vascular bed
			Fluid restriction/PEEP	Keep circulatory flow rate low
			Prolonged use of v/a ECMO	Relieve pulmonary circulation from total CO
Reduction of RV size	RV outflow tract obstruction (in cases of muscular hypertrophy)	During weaning	Increase in circulatory volume	Normalize RV filling
			Avoidance of beta-agonists	
Normalization of septal position > normalization of LV filling	Temporary LV failure	During weaning	Diuretic therapy haemofiltration	Normalize fluid balance
			Beta-agonists	Increase inotropy of LV
			Prolonged ventilation	Provide LV sufficient time for adaptation

Haemodynamic effects, resulting problems and postoperative strategies, with permission from ISHLT monograph series editor James K. Kirklin [8].

Moser B, Jaksch P, Taghavi S, Muraközy G, Lang G, Hager H, Krenn C, Roth G, Faybik P, Bacher A, Aigner C, Matilla JR, Hoetzenecker K, Hacker P, Lang I, Klepetko W. Lung transplantation for idiopathic pulmonary arterial hypertension on intraoperative and postoperatively prolonged extracorporeal membrane oxygenation provides optimally controlled reperfusion and excellent outcome. Eur J Cardiothorac Surg. 2018 Jan 1;53(1):178-185. doi: 10.1093/ejcts/ezx212. PMID: 28950326; PMCID: PMC5848802.

Reported outcomes of BLTX for iPAH

Society/institution	BLTX (*n*)	Diagnosis	Era	% Survival				
				30 days	90 days	1 year	3 years	5 years
ISHLT [1]	1550[a]	iPAH	1990–2012	83	78	72	60	52
Paris [15]	67	PH	1986–2008	85		79		52
St Louis [20]	19	iPAH	1991–2009			95	73[b]	61
Vienna [3]	17	PH	1999–2001		100	93	93	93
Pittsburgh [16]	31	iPAH	1982–2006			77		64
Toronto [17]	38[c]	iPAH 34	1997–2010	87		73[b]	49[b]	49[b]
Hannover [18]	28[d]	iPAH 29	1988–1998			52	40	35
Hannover [19]	23[e]	iPAH 17	2005–2013		100	94	n.r.	n.r.

Moser B, Jaksch P, Taghavi S, Muraközy G, Lang G, Hager H, Krenn C, Roth G, Faybik P, Bacher A, Aigner C, Matilla JR, Hoetzenecker K, Hacker P, Lang I, Klepetko W. Lung transplantation for idiopathic pulmonary arterial hypertension on intraoperative and postoperatively prolonged extracorporeal membrane oxygenation provides optimally controlled reperfusion and excellent outcome. Eur J Cardiothorac Surg. 2018 Jan 1;53(1):178-185. doi: 10.1093/ejcts/ezx212. PMID: 28950326; PMCID: PMC5848802.

NOT A TRANSPLANT CANDIDATE?

- For patients with advanced PAH who are ineligible for transplantation, the remaining surgical options are limited. In exceptional cases, balloon atrial septostomy (BAS) may be considered in experienced centers

- If BAS is contraindicated, a transcatheter Potts shunt may be performed in rare cases; however, this procedure is experimental and carries very high levels of risk

RECOMMENDATIONS FOR LUNG TRANSPLANTATION IN PATIENTS WITH PH/PAH

- Repeated risk assessment is pivotal to identify the appropriate time for initiating transplant evaluation
- REVEAL risk score or the ESC/ERS risk prediction strategy should be applied
- Potentially eligible candidates should be referred for evaluation early
- Timing of listing must depend on Risk Score & expected local waiting time
- Bilateral lung transplantation is the method of choice in patients with PH

RECOMMENDATIONS….

- There is no degree of right ventricular dysfunction that precludes bilateral lung transplantation in patients with PAH
- Despite advances in ICU management and ECLS, the ideal recipient is an ambulant outpatient
- VA ECMO and not CPB is recommended for intraoperative cardiopulmonary support during lung transplantation
- Extended use of ECMO support should be considered after lung transplantation in patients with PH to prevent early graft dysfunction and Left ventricular dysfunction
- Given the low number and high risk of lung transplants performed for PAH worldwide, this procedure should be concentrated in specialized centers

THANK YOU!

Expanding the Donor Pool: Lung Transplantation from HCV donors

Errol L. Bush, MD
Associate Professor of Surgery
Surgical Director, Advanced Lung Disease and Lung Transplant Program
Director, Ex vivo Lung Perfusion Program

Dignity Health. Norton Thoracic Institute | Creighton University

2022 Advanced Lung Disease and Lung Transplant Symposium

JOHNS HOPKINS MEDICINE

Lung Transplant Organ Shortage

- Nearly 5,000 people on lung transplant (LT) waitlist (Valapour 2021)
- Waitlist mortality: 15.3% (Kulkarni 2019)
- Number of individuals added to the waitlist per year continues to rise (Valapour 2021)

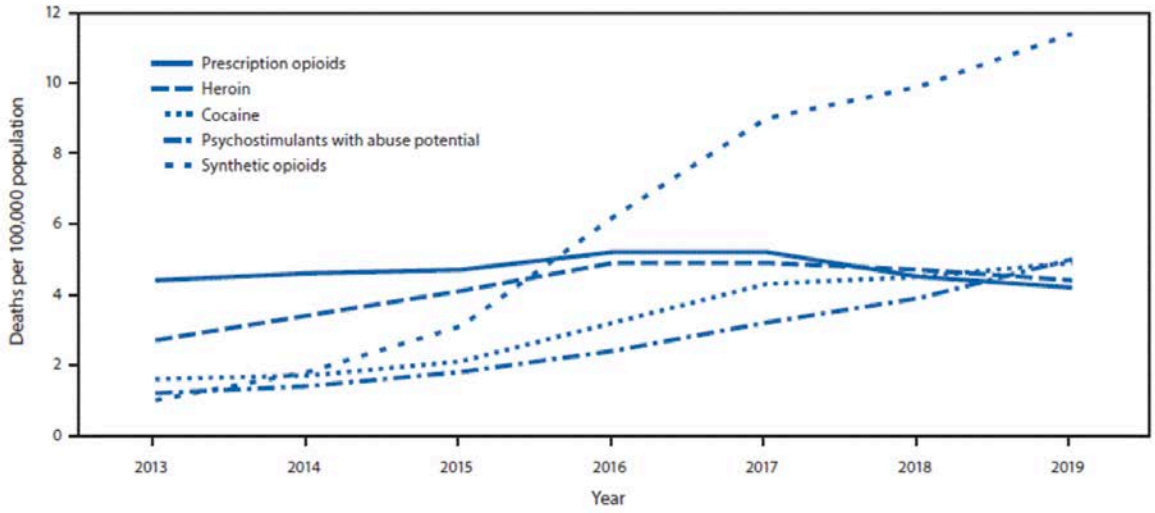
Need to reevaluate potential donor organs

JOHNS HOPKINS MEDICINE

CDC Statistics, 2019

- 70,630 drug overdose deaths in US
  - age-adjusted rate of 21.6 per 100,000 population
    - 56.5% increase above the 2013 rate of 13.8.

FIGURE 1. Age-adjusted rates* of drug overdose deaths† involving prescription opioids,§ heroin,¶ cocaine,** psychostimulants with abuse potential,†† and synthetic opioids other than methadone§§,¶¶ — United States, 2013–2019



Source: National Vital Statistics System, Mortality File. https://wonder.cdc.gov/

Mattson CL.

ORIGINAL RESEARCH

Annals of Internal Medicine

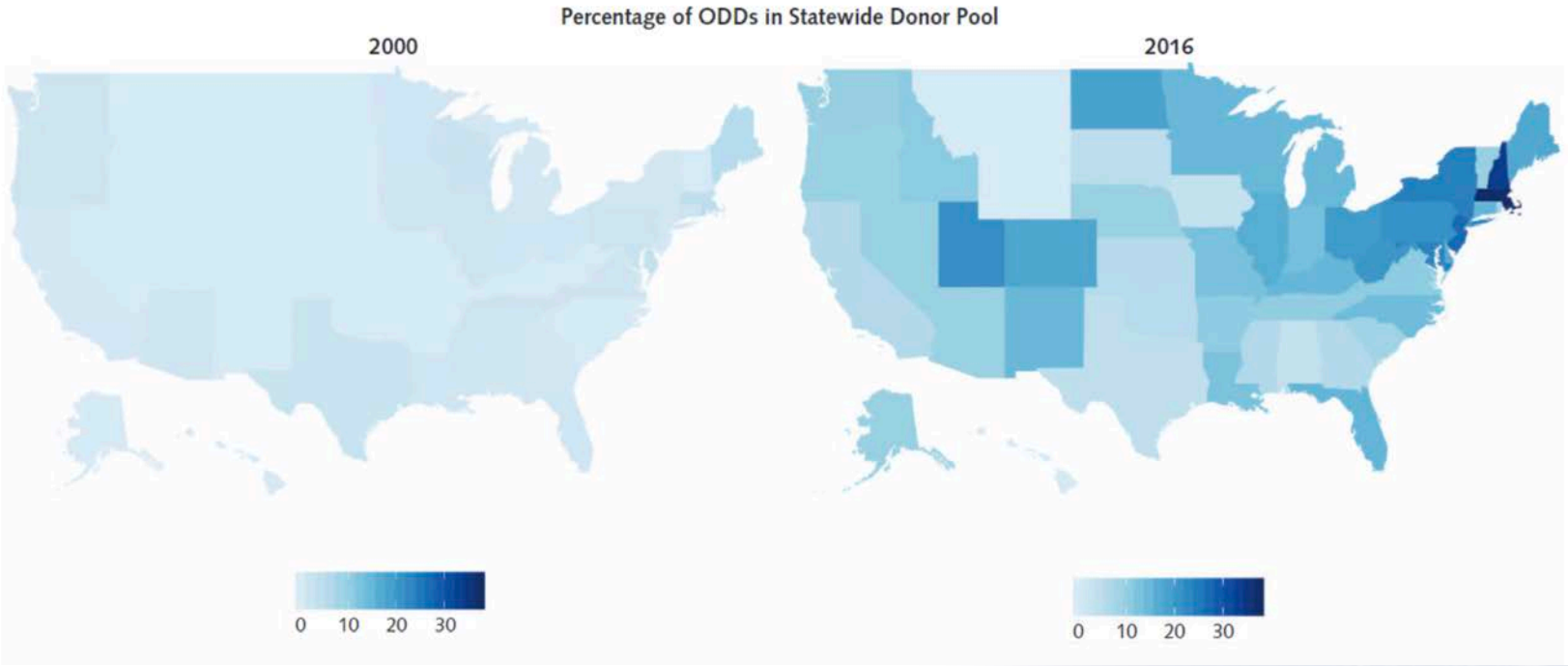
The Drug Overdose Epidemic and Deceased-Donor Transplantation in the United States

A National Registry Study

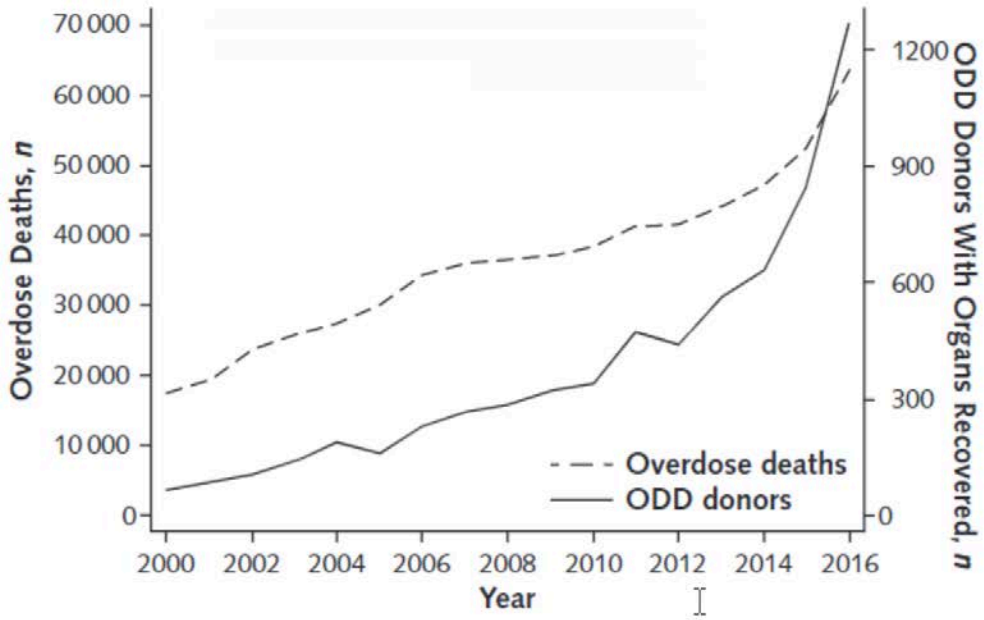
Christine M. Durand, MD*; Mary G. Bowring, MPH*; Alvin G. Thomas, MSPH; Lauren M. Kucirka, MD, PhD; Allan B. Massie, PhD; Andrew Cameron, MD, PhD; Niraj M. Desai, MD; Mark Sulkowski, MD; and Dorry L. Segev, MD, PhD

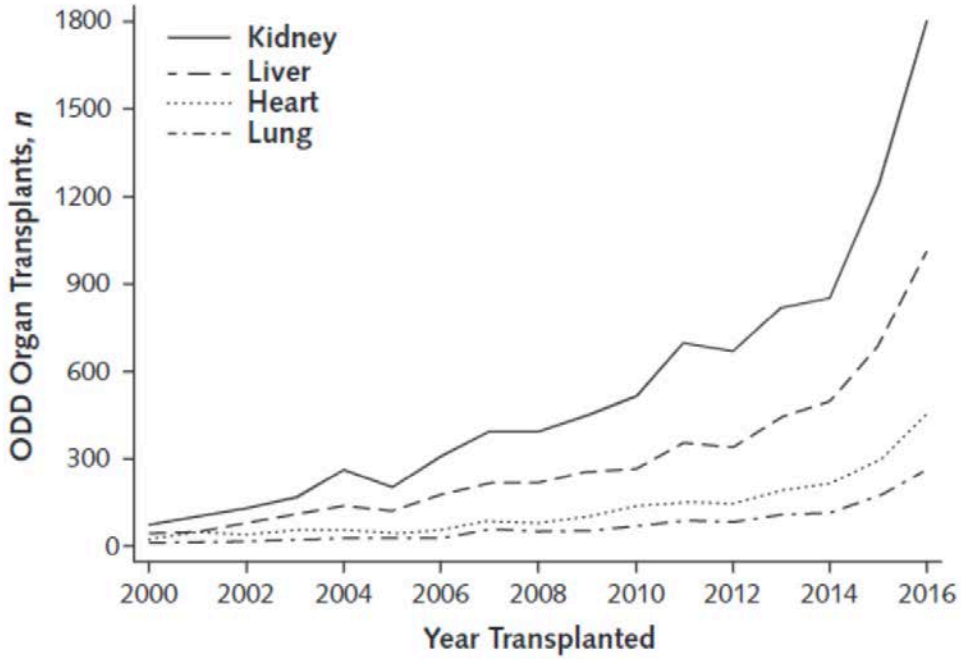
- SRTR, 1 January 2000 to 1 September 2017.
- Participants:
  - 138,565 deceased donors;
  - 337,934 transplant recipients
    - 297 transplant centers.

JOHNS HOPKINS MEDICINE



JOHNS HOPKINS MEDICINE





JOHNS HOPKINS MEDICINE

ORIGINAL RESEARCH

Annals of Internal Medicine

The Drug Overdose Epidemic and Deceased-Donor Transplantation in the United States

A National Registry Study

Christine M. Durand, MD*; Mary G. Bowring, MPH*; Alvin G. Thomas, MSPH; Lauren M. Kucirka, MD, PhD; Allan B. Massie, PhD; Andrew Cameron, MD, PhD; Niraj M. Desai, MD; Mark Sulkowski, MD; and Dorry L. Segev, MD, PhD

- Standardized 5-year patient and graft (kidney/lung) survival similar
  - ODD organ recipients compared with TDD and MDD organ recipients
- Evidence slightly favors ODD organs over non-ODD organs or at least supports noninferiority of ODD organs
- A higher percentage of ODDs were HCV-positive
  - 18.3% vs. 3.2% for TDDs and 4.1% for MDDs

In the beginning

- 1998 UNOS practice survey of LTx programs; Cotler et al.
  - Universal screening of donors and candidates HCV ab+
    - 72% recipient acceptance
    - 55% donor acceptance
    - 8/48 (17%) performed seropositive to seronegative transplants
      - 6/14 serological hepatitis
      - No deaths reported

JOHNS HOPKINS MEDICINE

HEPATITIS C VIRUS INFECTION AFTER LUNG TRANSPLANTATION: DIM PROGNOSIS

M.C. Carreno, U.G. Piedad, L. Maite, V. Andrés, P. Francisca, B. Cesar, M.J. Ferrerio Alvarez; Clinica Puerta de Hierro, Madrid, Spain

- 2001 case report
  - 3 HCV-/- LTx 1993-1999 died within 1 year
    - 3 males
    - COPD, CF, IPF
    - Deaths at 2, 6, 12 months from diagnosis
      - » 2 hepatic failures
  - Concluded
    - Post-transplant acquired HCV had an ominous prognosis with cause related mortality.
    - A conservative approach to accept HCV seropositive donors in LT recipients must be considered.

Hepatitis C and Direct-Acting Antivirals

- Transplants of hepatitis C (HCV)-infected organs into HCV-seronegative recipients → 3x higher mortality
  (Haji 2004, Koenig 2016)
- In 2013, direct-acting antivirals (DAAs) approved by FDA for cure of hepatitis C (HCV)
- Simultaneous rise in HCV-viremic donors due to the opioid epidemic (Durand 2018)

JOHNS HOPKINS MEDICINE

American Journal of Transplantation 2017; 17: 1129–1131
Wiley Periodicals Inc.
© 2016 The American Society of Transplantation and the American Society of Transplant Surgeons
doi: 10.1111/ajt.14137

Case Report

Successful Lung Transplantation From Hepatitis C Positive Donor to Seronegative Recipient

- 44y M with pulmonary fibrosis
  - L SOLT 3years prior, now with CLAD
  - Progressive hypoxia on max HFNC
    - VV ECMO prior to transplant
- Accepted 60y donor Pao2 179, 40pyhx tobacco, HCV NAT+
- EVLP 6 hours
  - HCV 26.5k-> 9.6k in perfusate

JOHNS HOPKINS MEDICINE

- ledipasvir/sofosbuvir started 6 weeks posttransplant (given for 12 weeks)
  - HCV cleared after 1 month therapy

- The patient recovered gradually
  - discharged home 6 weeks after transplantation
  - No episodes of acute rejection in 1st year.
  - Doing well at 16 months posttransplant

American Journal of Transplantation 2017; 17: 1129–1131

Lung Transplantation from Hepatitis C Viremic Donors to Uninfected Recipients

Ahmed Abdelbasit, M.D.
Alim Hirji, M.D.
Kieran Halloran, M.D.
Justin Weinkauf, M.D.
Ali Kapasi, M.D.
Dale Lien, M.D.
Jayan Nagendran, M.D., Ph.D.
Karen Doucette, M.D., M.Sc.(Epi)
University of Alberta
Edmonton, Alberta, Canada

To the Editor:

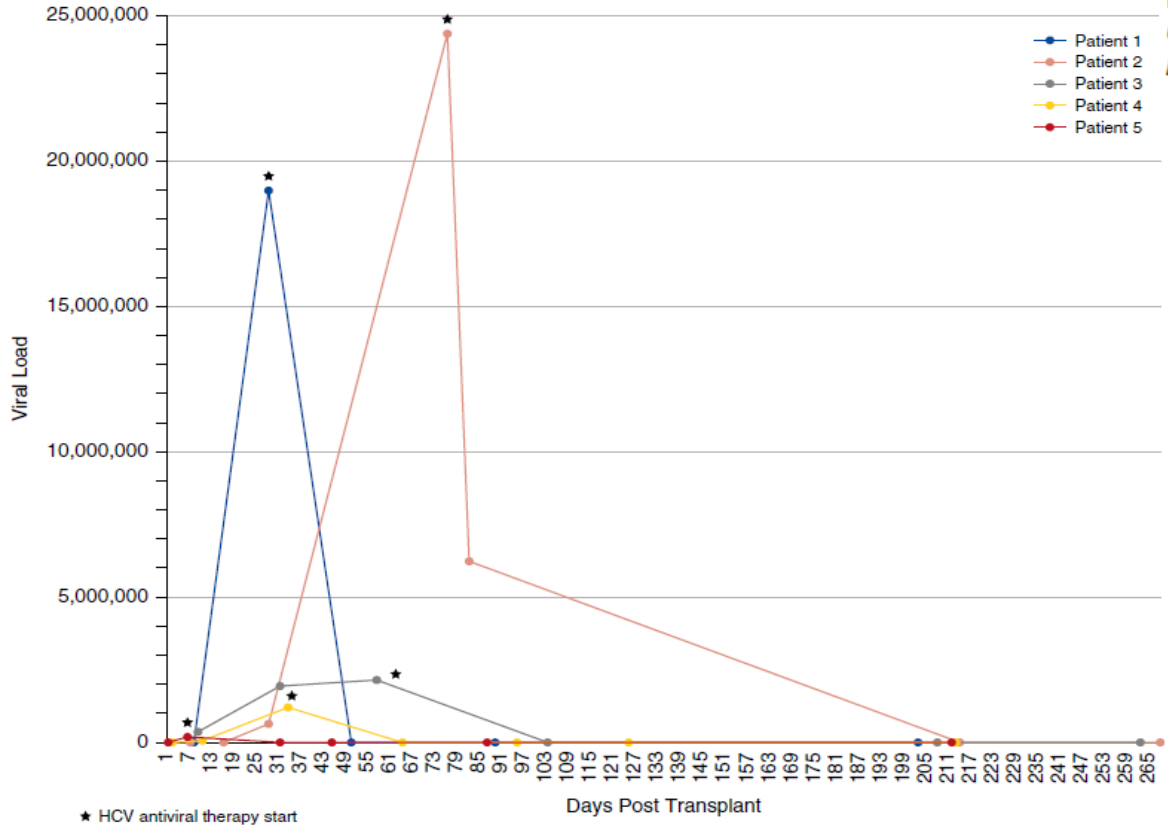


Figure 1. Hepatitis C viral load (in IU/mL) after lung transplant. Stars indicate the start of hepatitis C virus antiviral therapy for each patient. HCV = hepatitis C virus.

JOHNS HOPKINS MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

Heart and Lung Transplants from HCV-Infected Donors to Uninfected Recipients

Ann E. Woolley, M.D., Steve K. Singh, M.D., Hilary J. Goldberg, M.D., Hari R. Mallidi, M.D., Michael M. Givertz, M.D., Mandeep R. Mehra, M.D., Antonio Coppolino, M.D., Amanda E. Kusztos, B.S., Megan E. Johnson, B.A., Kaiwen Chen, B.S., Esther A. Haddad, M.D., John Fanikos, R.Ph., et al., for the DONATE HCV Trial Team*

- Trial of 36 HCV D+/R- LTs
  - Treated with pangenotypic DAA (sofosobuvir/velpatasvir)
    - Daily for 4 weeks
- 95% viremia
- All survived to 6 months and had no detectable HCV
  - HCV undetectable after 2 weeks

JOHNS HOPKINS MEDICINE

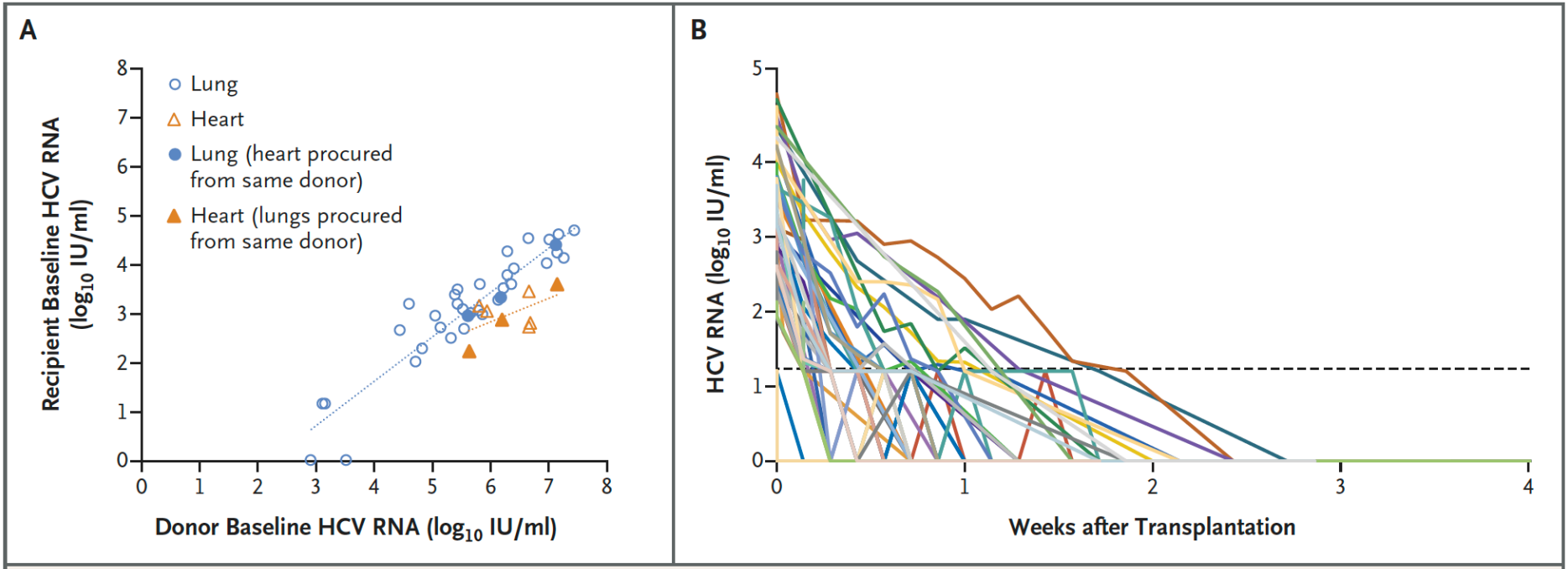


Figure 3. HCV RNA Levels.

Panel A shows the hepatitis C viral loads in the donors and recipients. Donor viral loads were measured at the time of organ procurement, and recipient viral loads were measured immediately after transplantation. There were 41 donors and 44 recipients; both the heart and lungs were procured from 3 donors, whereas a single organ, either the heart or lung, was procured from the other 38 donors. Panel B shows the decreases in the hepatitis C viral load in patients after transplantation. The viral load cleared in all recipients by approximately 2 weeks. The dashed line indicates the lower limit of quantification.

JOHNS HOPKINS MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

Heart and Lung Transplants from HCV-Infected Donors to Uninfected Recipients

Ann E. Woolley, M.D., Steve K. Singh, M.D., Hilary J. Goldberg, M.D., Hari R. Mallidi, M.D., Michael M. Givertz, M.D., Mandeep R. Mehra, M.D., Antonio Coppolino, M.D., Amanda E. Kusztos, B.S., Megan E. Johnson, B.A., Kaiwen Chen, B.S., Esther A. Haddad, M.D., John Fanikos, R.Ph., et al., for the DONATE HCV Trial Team*

- Trial of 36 HCV D+/R- LTs
  - Treated with pangenotypic DAA (sofosobuvir/velpatasvir)
    - Daily for 4 weeks
- 95% viremia
- All survived to 6 months and had no detectable HCV
  - HCV undetectable after 2 weeks
- Possibly higher risk of acute cellular rejection
- Conclusion: HCV D+/R- LT is feasible and safe in the short term (6 months)

And then what?

JOHNS HOPKINS MEDICINE

Featured Article

The impact of hepatitis C viremic donor lung allograft characteristics on post-transplantation outcomes

Ann E. Woolley[1], Laura M. Piechura[2], Hilary J. Goldberg[3], Steve K. Singh[4], Antonio Coppolino[2], Lindsey R. Baden[1], Hari R. Mallidi[2]

[1]Division of Infectious Diseases, [2]Division of Thoracic Surgery, [3]Division of Pulmonary, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; [4]Division of Cardiac Surgery, Trillium Health Partners, University of Toronto, Toronto, Canada

- March 2017-Oct 2018
- 42 and 57 lung transplants were performed from HCV-viremic and HCV-negative donors, respectively.
- The recipient outcomes overall were excellent and did not differ significantly in both cohorts in terms of graft and patient survival at 6 and 12 months.

Ann Cardiothorac Surg 2020;9(1):42-48

JOHNS HOPKINS MEDICINE

Trends in use and three-year outcomes of hepatitis C virus–viremic donor lung transplants for hepatitis C virus–seronegative recipients

Jessica M. Ruck, MD,[a] Laura B. Zeiser, ScM,[a] Alice L. Zhou, MS,[a] Alexis P. Chidi, MD, PhD,[a] Sophia L. Winchester, MPH,[b] Christine M. Durand, MD,[c] Jinny S. Ha, MD, MHS,[a] Pali D. Shah, MD,[d] Allan B. Massie, PhD, MHS,[e] Dorry L. Segev, MD, PhD,[e,f] Christian A. Merlo, MD, MPH,[d] and Errol L. Bush, MD[a]

- Objective
  - Evaluate uptake of HCV D+/R- LT at the individual and center levels
  - Compare longer-term outcomes between HCV D+/R- and D-/R- LT

D+: HCV-viremic donor (reactive nucleic acid test)
D-: HCV-seronegative donor (negative antibody test)
R-: HCV-seronegative recipient
Example: HCV D+/R-: viremic donor, seronegative recipient

(J Thorac Cardiovasc Surg 2022;■:1-9)

JOHNS HOPKINS MEDICINE

Methods

- Scientific Registry of Transplant Recipients (SRTR)
- Adult (≥18 years old) recipients of HCV D+/R- or HCV D-/R- LTs in the United States, 2015-2020
- Trends in use of HCV D+/R- LT
  - Quantified number of HCV D+/R- LT overall and by center
  - High-volume LT centers: ≥20 LT/year
  - High-volume HCV D+/R- LT centers: ≥5 in any year

(J Thorac Cardiovasc Surg 2022;■:1-9)

Methods – Transplant Outcomes

- Covariates: donor (age, sex, race, smoking history), recipient (age, sex, race, Lung Allocation Score [LAS]), and transplant (unilateral vs. bilateral) characteristics
- Analyses: comparisons between HCV D+/R- and D-/R- LT recipients of
  - Acute rejection, ECMO, ventilator support >48 hours, tracheostomy using χ^2 testing
  - Post-transplant length of stay using Wilcoxon rank-sum testing
  - Mortality and all-cause graft failure (ACGF) using Kaplan-Meier curves and multivariable Cox regression

(J Thorac Cardiovasc Surg 2022;■:1-9)

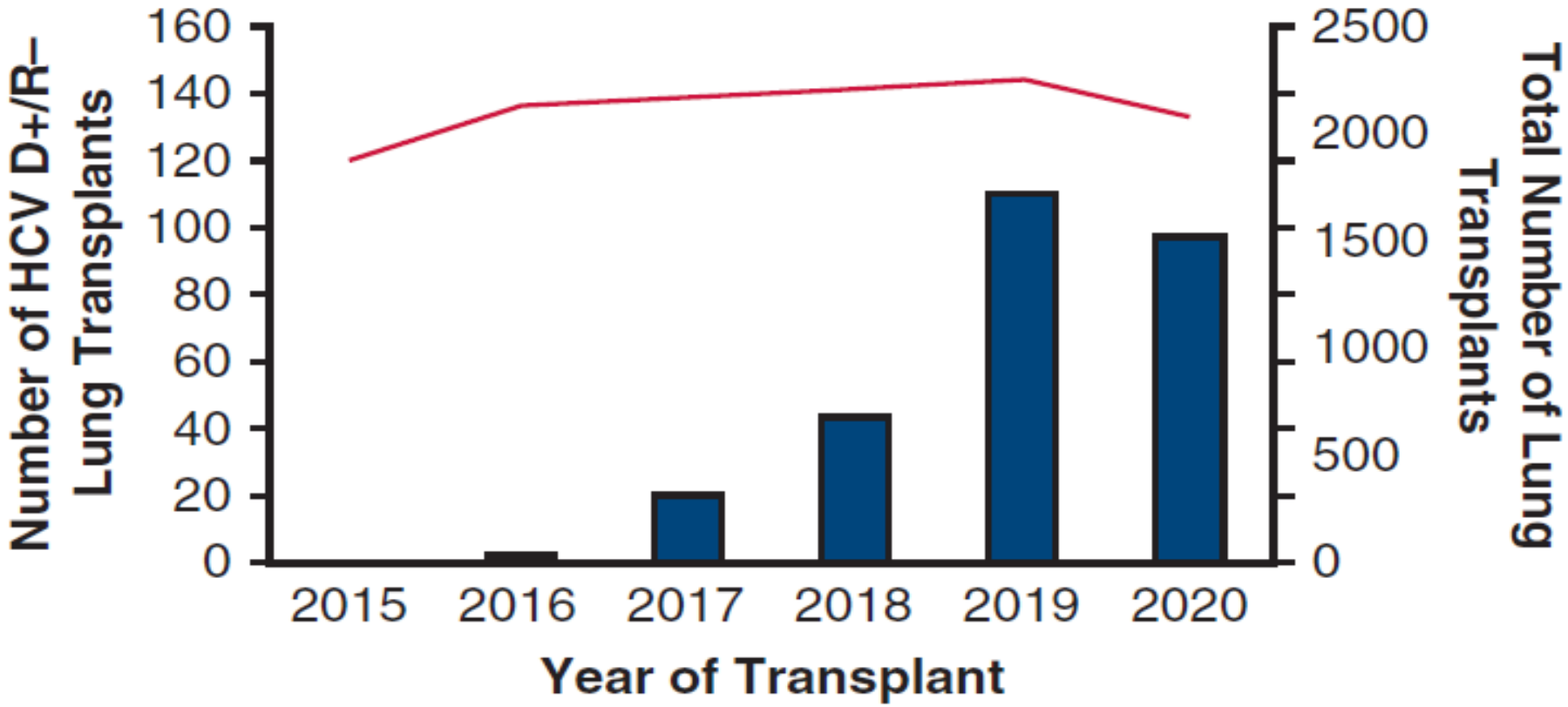
JOHNS HOPKINS MEDICINE

TABLE 1. Donor, recipient, and transplant characteristics by donor and recipient HCV status

Characteristic	HCV D–/R–	HCV D+/R–	*P* value
N	12,736	272	
Donor characteristics			
Age, y, median (IQR)	33 (24, 47)	32 (28, 38)	.18
Male sex	60.8%	52.6%	.006
White race	60.5%	81.6%	<.001
≥20 pack-year smoking history	7.3%	16.9%	<.001
Donation after circulatory death	5.0%	3.7%	.32
Recipient characteristics			
Age, y, median (IQR)	61 (53, 67)	61 (54, 67)	.58
Male sex	59.3%	54.4%	.10
White race	78.6%	84.9%	.04
Blood type			
O	45.1%	45.6%	>.87
A	39.5%	40.1%	
B	11.4%	11.4%	
AB	4.0%	2.9%	
Diagnosis			
Obstructive	23.3%	35.7%	<.001
Pulmonary vascular	4.9%	5.5%	
Cystic fibrosis and immunodeficiency	8.9%	4.0%	
Restrictive	39.6%	33.1%	
Other	23.3%	21.7%	
On ventilator pretransplant	5.0%	2.6%	.07
Waitlist time, d, median (IQR)	48 (14, 149)	57 (21, 203)	.002
Lung allocation score, median (IQR)	41.1 (35.2, 54.0)	36.5 (33.8, 45.9)	<.001
Lung allograft ischemia time, h, median (IQR)	5.4 (4.4, 6.5)	5.9 (4.9, 6.8)	<.001
Bilateral lung transplant	73.9%	82.7%	<.001

HCV, Hepatitis C virus; *HCV D–/R–*, Donor and recipient both HCV-seronegative; *HCV D+/R–*, HCV-viremic donor and HCV-seronegative recipient; *IQR*, interquartile range.

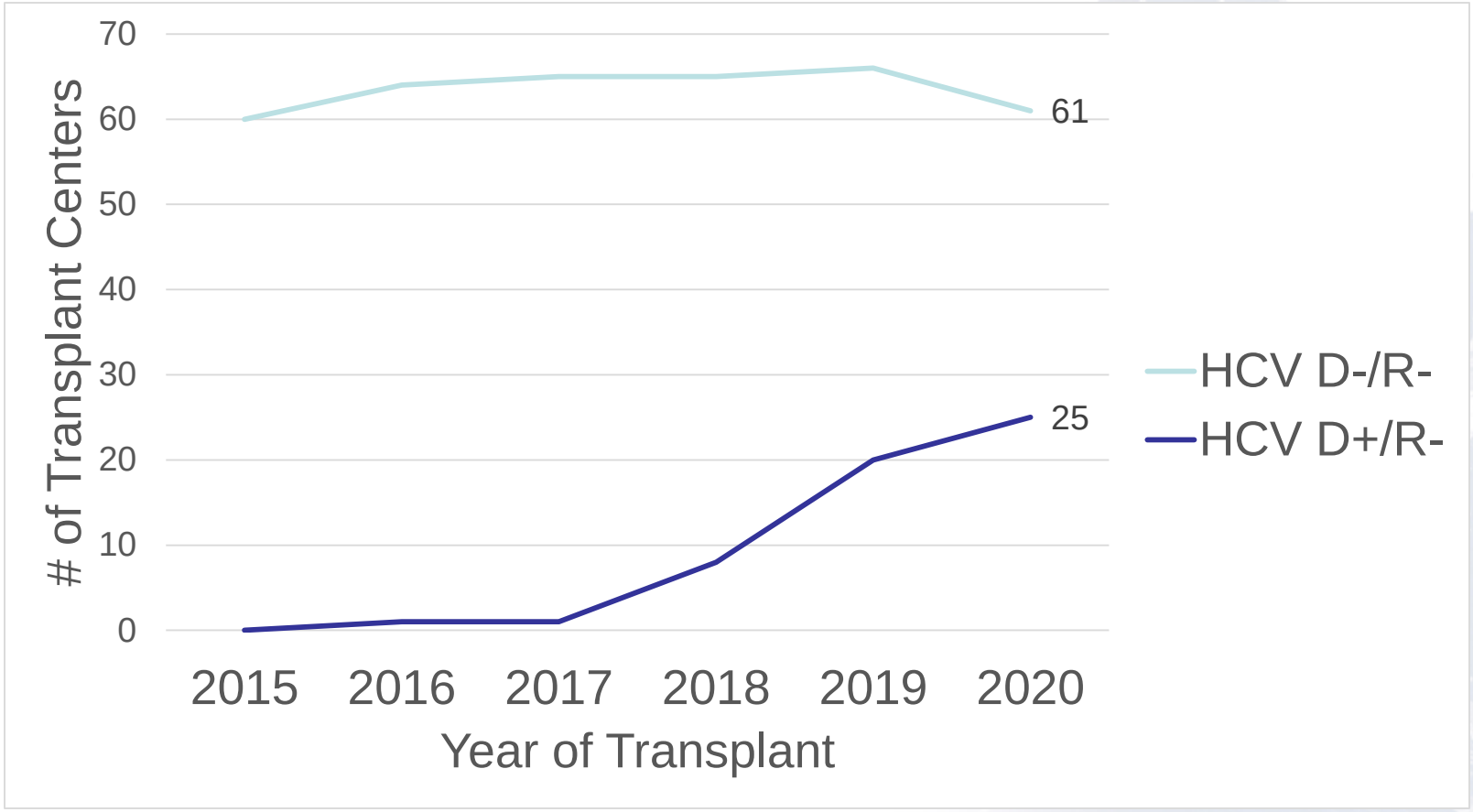
Trends in HCV D+/R- LT



(J Thorac Cardiovasc Surg 2022;■:1-9)

JOHNS HOPKINS MEDICINE

Trends in Centers Performing HCV D+/R- LT



(J Thorac Cardiovasc Surg 2022;■:1-9)

JOHNS HOPKINS MEDICINE

Post-Transplant Outcomes

TABLE E1. Summary of results

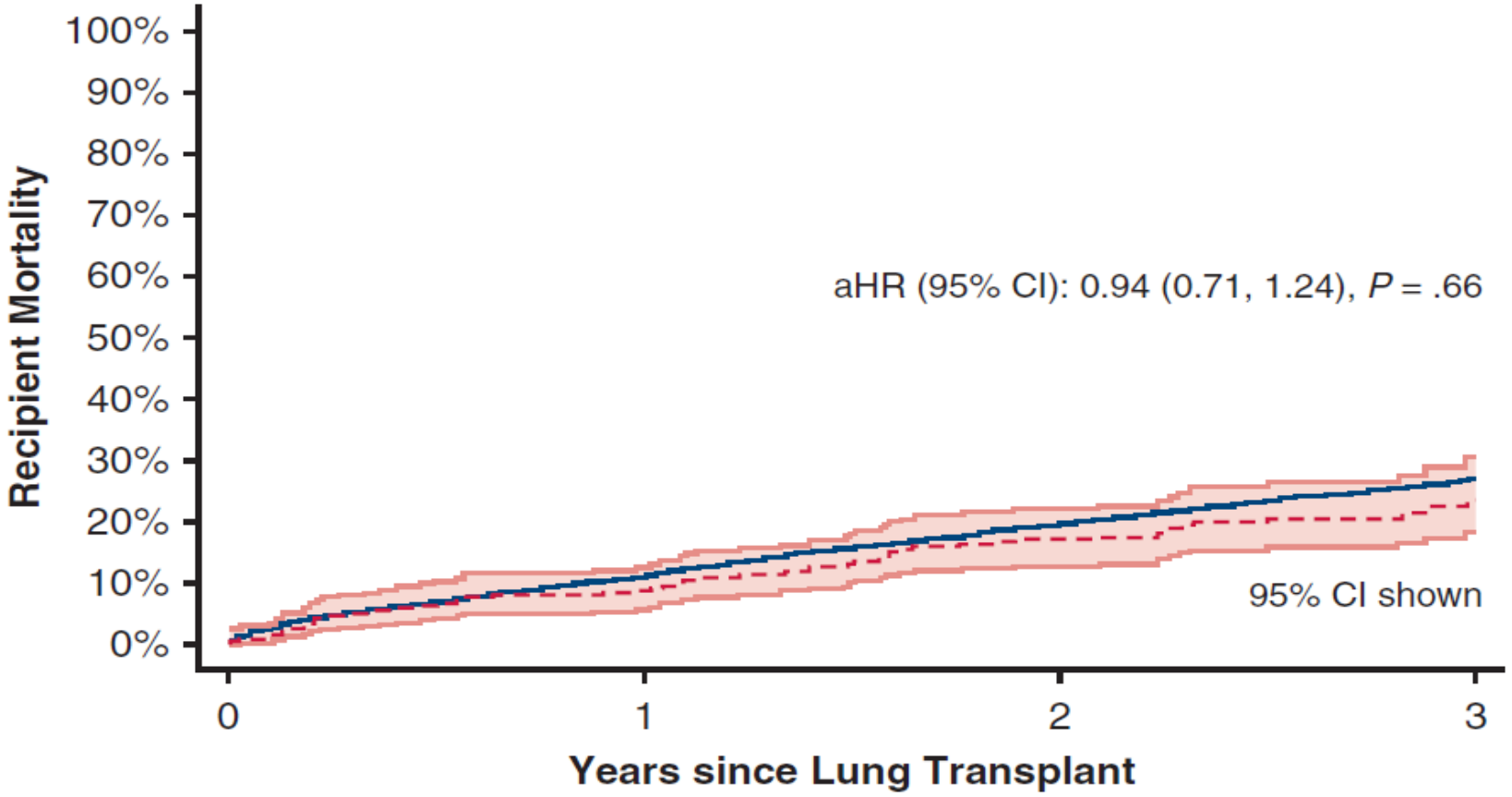
Outcome	HCV D+/R– vs HCV D–/R– LT		
	Estimate	95% CI	*P* value
Posttransplant ECMO	aOR 1.94	0.89-4.22	.10
Prolonged ventilator support >48 h	aOR 0.68	0.52-0.89	.006
Tracheostomy	aOR 0.43	0.13-1.39	.16
Hospital length of stay	–3.8 d	–7.9-0.24	.07
Acute rejection	aOR 0.87	0.54-1.41	.58
Mortality	AHR		
30 d	0.32	0.08-1.28	.11
1 y	0.80	0.52-1.22	.31
3 y	0.94	0.71-1.24	.66
All-cause graft failure	AHR		
30 d	0.31	0.08-1.25	.10
1 y	0.80	0.53-1.22	.30
3 y	0.93	0.71-1.22	.59

All analyses were adjusted for donor age, sex, race, and smoking history; recipient age, sex, race, and LAS; and procedure (single vs bilateral lung transplant). *HCV*, Hepatitis C virus; *HCV D+/R–*, HCV-viremic donor and HCV-seronegative recipient; *HCV D–/R–*, donor and recipient both HCV-seronegative; *LT*, lung transplant; *CI*, confidence interval; *ECMO*, extracorporeal membrane oxygenation; *aOR*, adjusted odds ratio; *aHR*, adjusted hazard ratio; *LAS*, lung allocation score.

(J Thorac Cardiovasc Surg 2022;■:1-9)

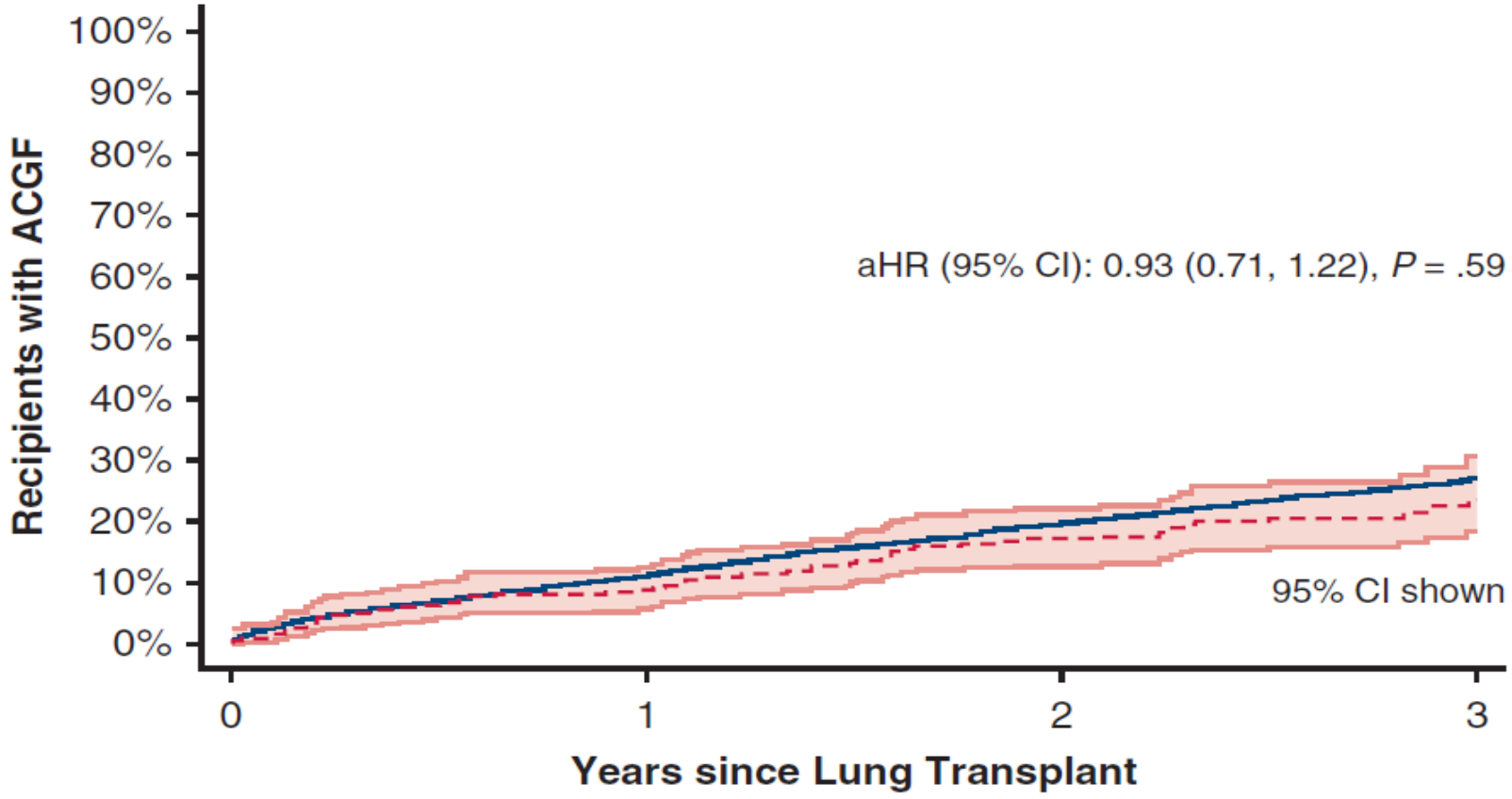
JOHNS HOPKINS MEDICINE

Mortality after HCV D+/R- vs. D-/R- LT



Number at risk				
HCV D–/R–	12,736	11,325	8904	6421
HCV D+/R–	272	249	169	63

ACGF after HCV D+/R- vs. D-/R- LT



Number at risk				
HCV D–/R–	12,736	11,325	8904	6421
HCV D+/R–	272	249	169	63

Conclusions

- Uptake of HCV D+/R- LT rose exponentially, but has plateaued since 2019
- HCV D+/R- LT remains safe and effective out to at least 3 years post-transplant
- HCV D+ lungs represent a source of underutilized donor organs

JOHNS HOPKINS MEDICINE

- Alternative strategies
  - Costs
  - Insurance pre-authorizations
  - Regime tolerance/length
  - Viral load risks

JOHNS HOPKINS MEDICINE

Short-course, direct-acting antivirals and ezetimibe to prevent HCV infection in recipients of organs from HCV-infected donors: a phase 3, single-centre, open-label study

Jordan J Feld, Marcelo Cypel*, Deepali Kumar, Harel Dahari, Rafaela Vanin Pinto Ribeiro, Nikki Marks, Nellie Kamkar, Ilona Bahinskaya, Fernanda Q Onofrio, Mohamed A Zahoor, Orlando Cerrochi, Kathryn Tinckam, S Joseph Kim, Jeffrey Schiff, Trevor W Reichman, Michael McDonald, Carolina Alba, Thomas K Waddell, Gonzalo Sapisochin, Markus Selzner, Shaf Keshavjee, Harry L A Janssen, Bettina E Hansen, Lianne G Singer, Atul Humar*

- 30 patients
  - 13 LTx, 6 Htx, 10 Ktx, 1 KP Tx
  - 18 HCV NAT+ donors
  - 6-12h prior to Tx and dailyx7
    - Ezetimibe and
    - pangenotypic gelcaprevir-pibrentasvir

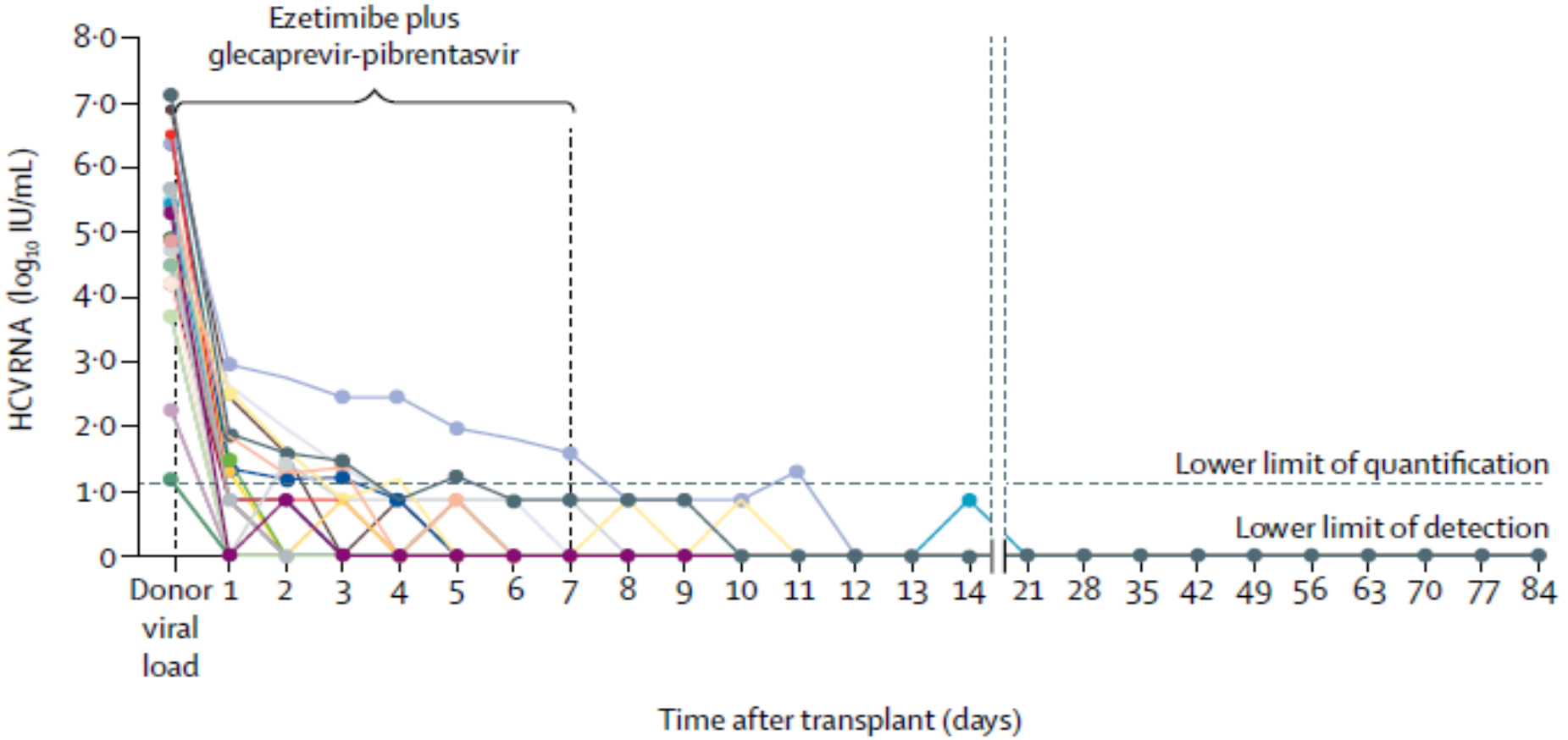


Figure 2: **HCV RNA concentrations in donors and recipients post-transplant**

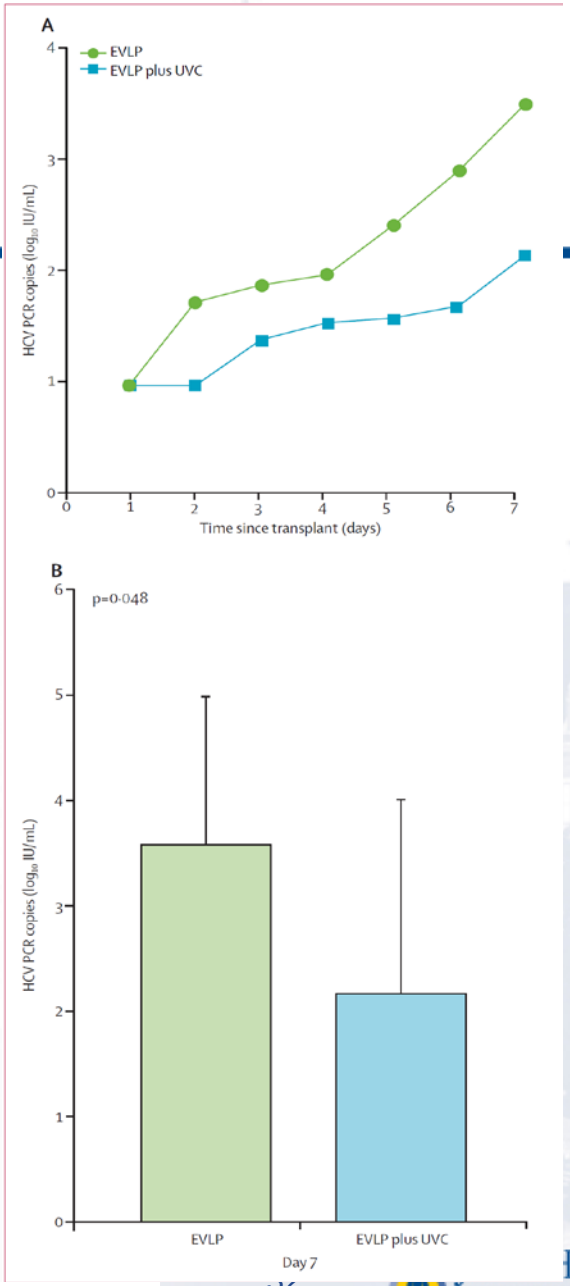
Prevention of viral transmission during lung transplantation with hepatitis C-viraemic donors: an open-label, single-centre, pilot trial

Marcelo Cypel, Jordan J Feld*, Marcos Galasso, Rafaela V Pinto Ribeiro, Nikki Marks, Magdalena Kuczynski, Deepali Kumar, Ilona Bahinskaya, Vanderlei S Bagnato, Cristina Kurachi, Arthur S Slutsky, Jonathan C Yeung, Laura Donahoe, Marc de Perrot, Kazuhiro Yasufuku, Andrew Pierre, Matthew Binnie, Cecilia Chaparro, Tereza Martinu, Manyin Chen, Jussi Tikkanen, Chung-Wai Chow, Aman Sidhu, Thomas K Waddell, Shaf Keshavjee, Lianne G Singer, Atul Humar*

- **22 HCV NAT+ donor lungs**
  - **Treated before implantation**
    - **EVLP alone or**
    - **EVLP + UVC perfusate irradiation**
    - **EVLP 4-6 hours**
  - **Recipients**
    - **12 weeks of oral sofosbuvir/velpatasvir**
      - **starting at least 2 weeks after transplantation.**

Results

- 20 (91%) developed HCV viremia within the first week
- negative HCV PCR within 6 weeks of treatment initiation
- UVC
  - significantly lower recipient viral loads in blood within the first week after transplantation
  - prevented transmission in two (18%)
- One patient died PsA sepsis
- Two patients presented with HCV relapse within 3 months



Conclusion

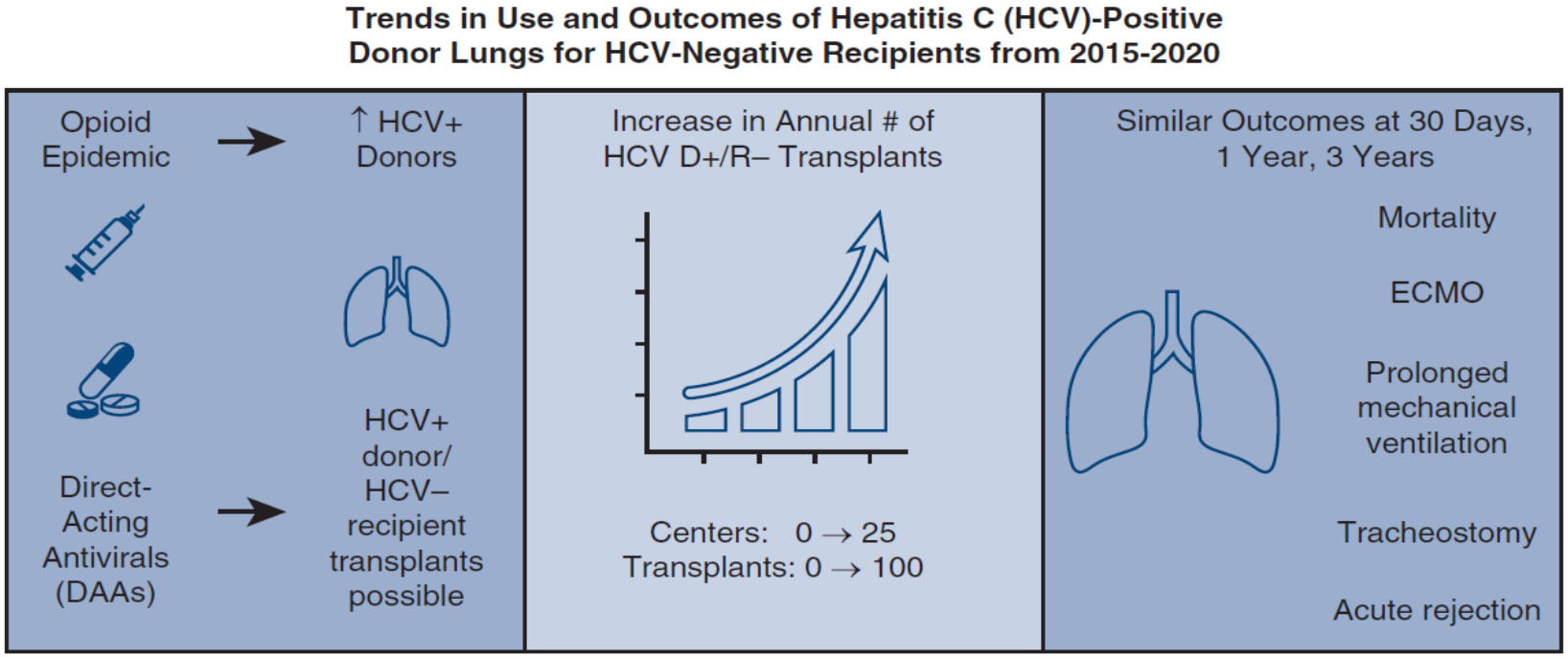


FIGURE 1. Trends in use and outcomes of HCV-positive donor lungs for HCV-negative recipients from 2015 to 2020. *HCV*, Hepatitis C virus.

(J Thorac Cardiovasc Surg 2022;■:1-9)

JOHNS HOPKINS MEDICINE



Hcv recipient

- Sahi 2007, Cleveland Clinic
  - 465 transplants, 6 HCV -/+
  - No significant difference in patient or graft survival was noted



Updates and Clinical Cases in Connective Tissue Disease Interstitial Lung Disease and Hypersensitivity Pneumonitis

Sachin Chaudhary, MD
Director, Interstitial Lung Disease Program
University of Arizona

THE UNIVERSITY OF ARIZONA

Disclosures:

Investigator initiated grant to study IPF:

- Boehringer Ingelheim

Consulting:

- ❿ Genentech
- ❿ Boehringer Ingelheim
- ❿ Veracyte

Objectives:

Progressive Pulmonary Fibrosis

Scleroderma ILD

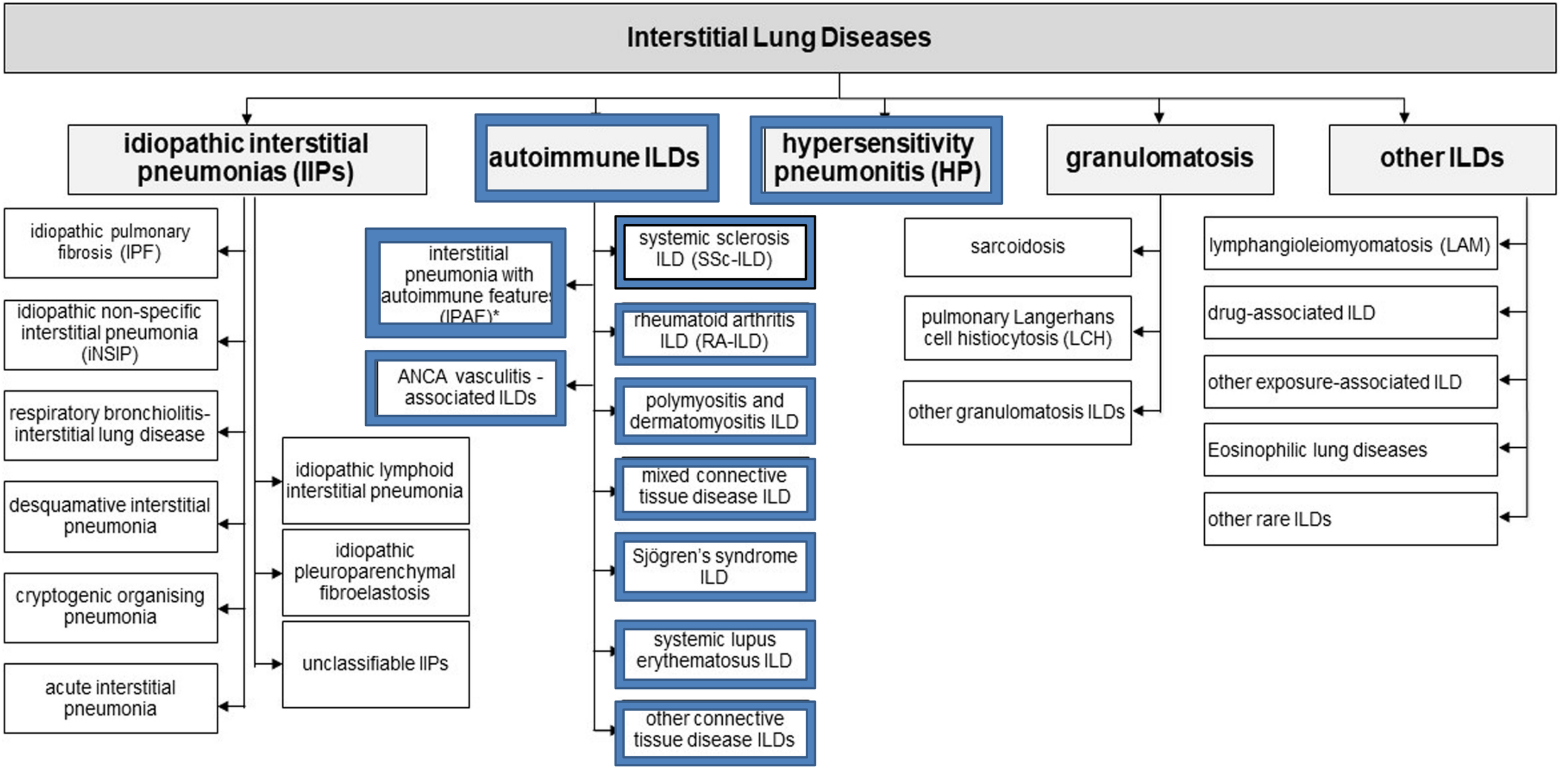
Rheumatoid arthritis – ILD

Idiopathic Inflammatory Myositis – ILD

IPAF

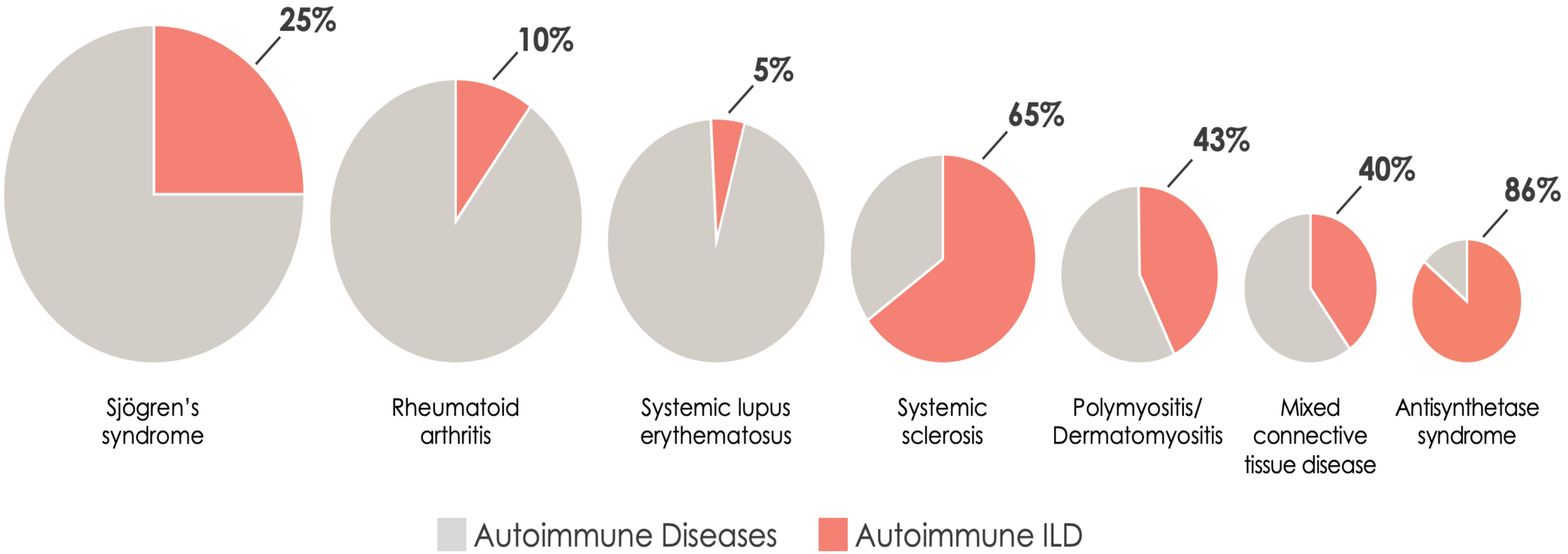
Hypersensitivity Pneumonitis

THE UNIVERSITY OF ARIZONA



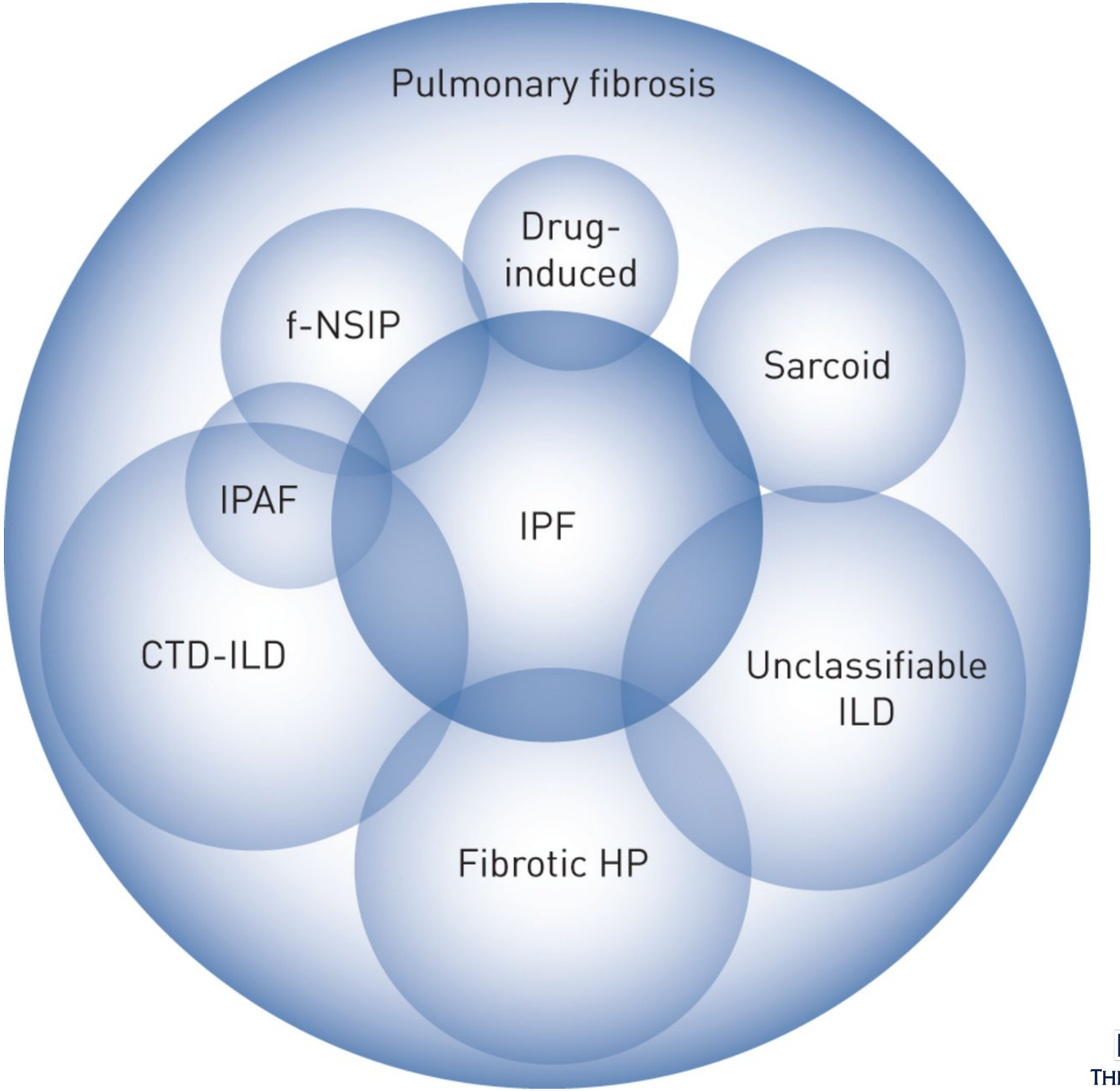
Vincent Cottin, Claudia Valenzuela, Diagnostic approach of fibrosing interstitial lung diseases of unknown origin, La Presse Médicale, Volume 49, Issue 2, 2020, 104021, ISSN 0755-4982, https://doi.org/10.1016/j.lpm.2020.104021.

ILD is common among autoimmune diseases:



THE UNIVERSITY OF ARIZONA

The overlap in longitudinal disease behavior between idiopathic pulmonary fibrosis (IPF) and other disorders



THE UNIVERSITY OF ARIZONA

Progressive Pulmonary Fibrosis

THE UNIVERSITY OF ARIZONA

AMERICAN THORACIC SOCIETY DOCUMENTS

Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

Ganesh Raghu, Martine Remy-Jardin, Luca Richeldi, Carey C. Thomson, Yoshikazu Inoue, Takeshi Johkoh, Michael Kreuter, David A. Lynch, Toby M. Maher, Fernando J. Martinez, Maria Molina-Molina, Jeffrey L. Myers, Andrew G. Nicholson, Christopher J. Ryerson, Mary E. Strek, Lauren K. Troy, Marlies Wijsenbeek, Manoj J. Mammen, Tanzib Hossain, Brittany D. Bissell, Derrick D. Herman, Stephanie M. Hon, Fayez Kheir, Yet H. Khor, Madalina Macrea, Katerina M. Antoniou, Demosthenes Bouros, Ivette Buendia-Roldan, Fabian Caro, Bruno Crestani, Lawrence Ho, Julie Morisset, Amy L. Olson, Anna Podolanczuk, Venerino Poletti, Moisés Selman, Thomas Ewing, Stephen Jones, Shandra L. Knight, Marya Ghazipura, and Kevin C. Wilson; on behalf of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax

This official clinical practice guideline was approved by the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax February 2022

THE UNIVERSITY OF ARIZONA

The definition of PPF is based on a combination of worsening respiratory symptoms, physiological or radiological evidence of disease progression

In a patient with ILD of known or unknown etiology (other than IPF) who has radiological evidence of pulmonary fibrosis, PPF is defined as **at least two of the following three criteria** occurring **within the past year** with no alternative explanation

- Worsening respiratory symptoms
- Physiological evidence of disease progression
- Radiological evidence of disease progression

THE UNIVERSITY OF ARIZONA

Raghu G *et al. Am J Respir Crit Care Med* 2022;205:e18–47

Physiological evidence of disease progression is based on an absolute decline in FVC and/or DL_{CO} within 1 year of follow-up

- Absolute decline in FVC of ≥5% within 1 year of follow-up
- Absolute decline in DLCO (corrected for Hb) of ≥10% within 1 year of follow-up

Worsening respiratory symptoms

Physiological evidence of disease progression

Radiological evidence of disease progression

THE UNIVERSITY OF ARIZONA

Raghu G *et al. Am J Respir Crit Care Med* 2022;205:e18–47

Radiological evidence of disease progression is based on the appearance or increased extent of fibrotic features on CT

One or more of:

A. Increased extent or severity of traction bronchiectasis and bronchiolectasis
B. New ground-glass opacity with traction bronchiectasis
C. New fine reticulation
D. Increased extent or increased coarseness of reticular abnormality
E. New or increased honeycombing
F. Increased lobar volume loss

Worsening respiratory symptoms

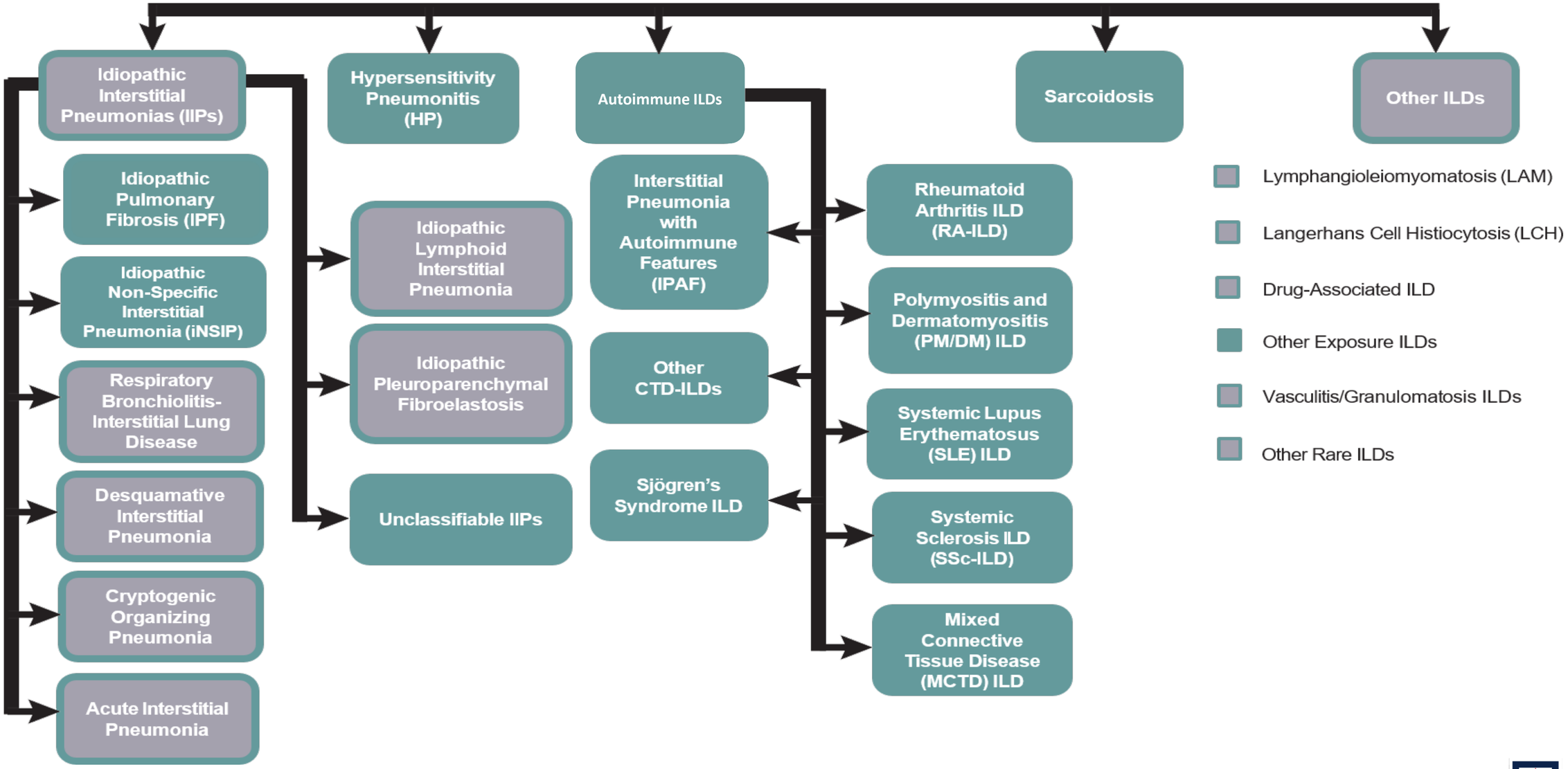
Physiological evidence of disease progression

Radiological evidence of disease progression

THE UNIVERSITY OF ARIZONA

Raghu G *et al. Am J Respir Crit Care Med* 2022;205:e18–47

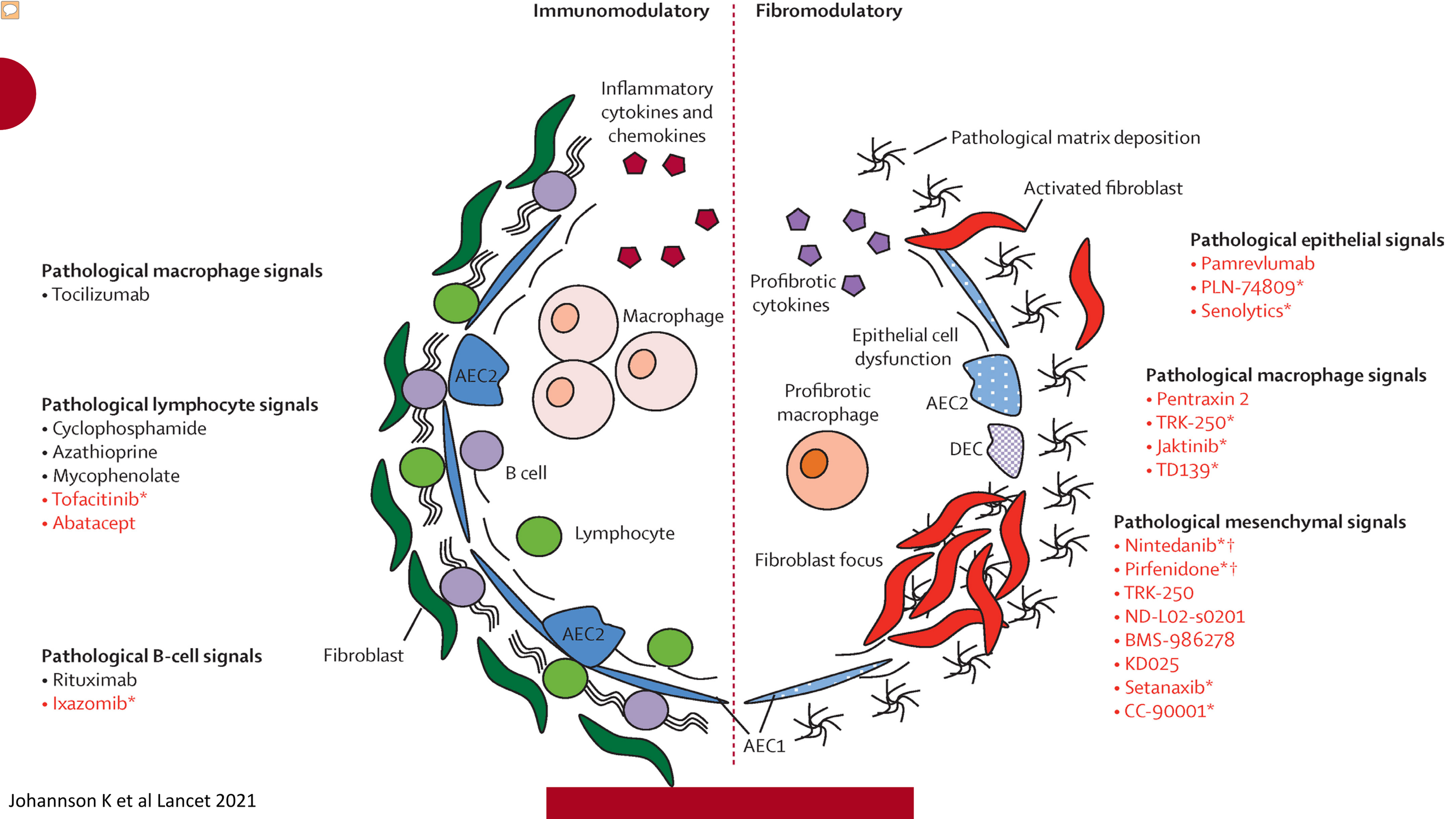
Interstitial Lung Diseases (ILDs)



[a]Targets in teal are associated with a progressive fibrosing phenotype. [b]IPAF is not an established clinical diagnosis.

1. ATS/ERS. *AJRCCM.* 2002;165:277-304. 2. Fischer A et al. *Eur Respir J*. 2015;46:976-987. 3. Flaherty KR et al. *BMJ Open Respir Res*. 2017;4:e000212.
4. Ryerson CJ, Collard HR. *Curr Opin Pulm Med*. 2013;19:453-459. 5. Travis WD et al. *AJRCCM.* 2013;188(6):733-748. 6. Cottin V et al. *Eur Respir Rev.* 2018;27:180076.

THE UNIVERSITY OF ARIZONA



Johannson K et al Lancet 2021

Immunomodulatory therapies in CTD-ILD and HP

Azathioprine

- Suppresses the immune system by inhibiting DNA synthesis.
- There are no published randomized trial data showing efficacy of azathioprine for managing ILDs.

Cyclophosphamide

- Cyclophosphamide can be administered orally or intravenously, **with greater toxicity orally** due to the risk of urothelial malignancy.
- **Scleroderma Lung Study 1**, patients with SSc-ILD treated with oral cyclophosphamide had significantly **less** loss of FVC than did patients given placebo after 12 months, suggesting that cyclophosphamide is an effective treatment for SSc-ILD.
- Associated with **favorable outcomes** in ILD associated with **inflammatory myopathies**, ANCA Vasculitis

THE UNIVERSITY OF ARIZONA

Immunomodulatory therapies in CTD-ILD and HP

Mycophenolate mofetil

- **Lymphocytes** are a relatively specific target of mycophenolate mofetil.

- Efficacy of mycophenolate mofetil for managing SSc-ILD was compared with that of oral cyclophosphamide, it was shown that patients receiving 3 g per day of mycophenolate mofetil had a **2·2% improvement in FVC** 2 years after initiating therapy, compared with baseline, with the majority of improvement occurring within the first 12 months.

- Retrospective case studies have reported that mycophenolate mofetil can stabilize or improve lung function in patients with **hypersensitivity pneumonitis** and those with **CTD-ILD including inflammatory myopathies**

THE UNIVERSITY OF ARIZONA

Immunomodulatory therapies in CTD-ILD and HP

Tocilizumab

- Blocks IL-6 signaling
- **Tocilizumab is approved for treatment of SSc-ILD**
- Two randomized, double-blind placebo-controlled trials have studied the efficacy of tocilizumab for treatment of early scleroderma
- Both studies reported that patients with SSc-ILD treated with tocilizumab had less of a decline in FVC over 48 weeks than did the control group (−0·4% *vs*−4·6%)
- Sporadic reports that it might be useful for treating RA-ILD and anti-synthetase syndrome

THE UNIVERSITY OF ARIZONA

Immunomodulatory therapies in CTD-ILD and HP

Rituximab

- Binds to CD20 expressed on B cells.

- Uncontrolled studies have reported an association between the use of rituximab and improved lung function in patients with SSc-ILD, inflammatory myopathies, and hypersensitivity pneumonitis.

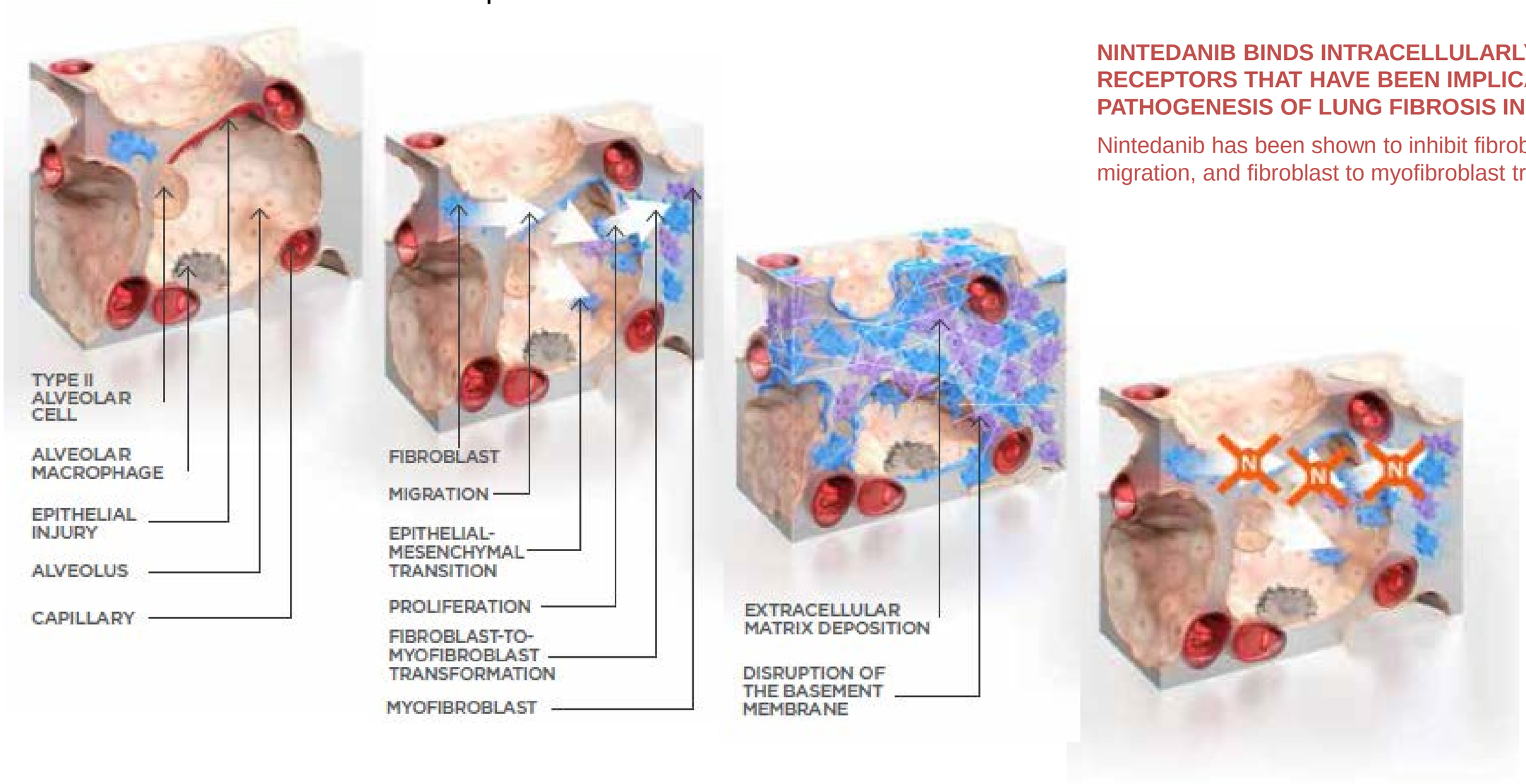
THE UNIVERSITY OF ARIZONA

Antifibrotics

THE UNIVERSITY OF ARIZONA

Nintedanib Is a Tyrosine Kinase Inhibitor That Inhibits Pathways Involved in Lung Fibrosis

- Fibrosis in Chronic Fibrosing ILDs With a Progressive Phenotype Is Thought to Arise From Fibroblast Proliferation and Excess Deposition of Extracellular Matrix[2]



NINTEDANIB BINDS INTRACELLULARLY TO KEY RECEPTORS THAT HAVE BEEN IMPLICATED IN THE PATHOGENESIS OF LUNG FIBROSIS IN ILDs

Nintedanib has been shown to inhibit fibroblast proliferation, migration, and fibroblast to myofibroblast transformation.[1]

Kolb M et al. *Respir Rev*. 2019;20:57.

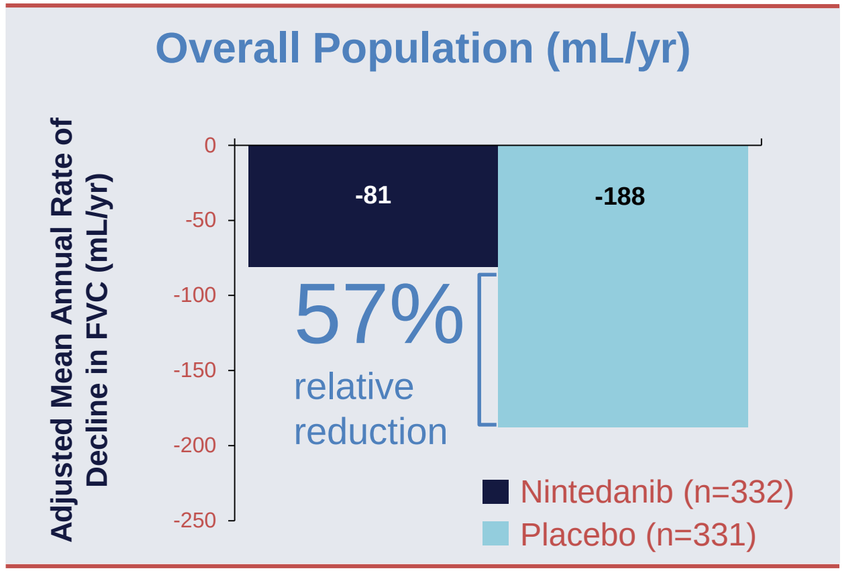
INBUILD: Clinical ILD diagnoses documented on case report form (n=663) (1/3)

Hypersensitivity pneumonitis	173 (26.1)
Idiopathic non-specific interstitial pneumonia	125 (18.9)
Unclassifiable idiopathic interstitial pneumonia	114 (17.2)
Rheumatoid arthritis-associated ILD	89 (13.4)
Systemic sclerosis-associated ILD	39 (5.9)
Exposure-related ILD	39 (5.9)
Mixed connective tissue disease-associated ILD	19 (2.9)
Sarcoidosis	12 (1.8)
Other ILDs*	53 (8.0)
Pleuroparenchymal fibroelastosis	10 (1.5)
Sjögren's syndrome	7 (1.1)
Desquamative interstitial pneumonia	5 (0.8)
Interstitial pneumonia with autoimmune features	5 (0.8)

Flaherty KR et al. Eur Respir J

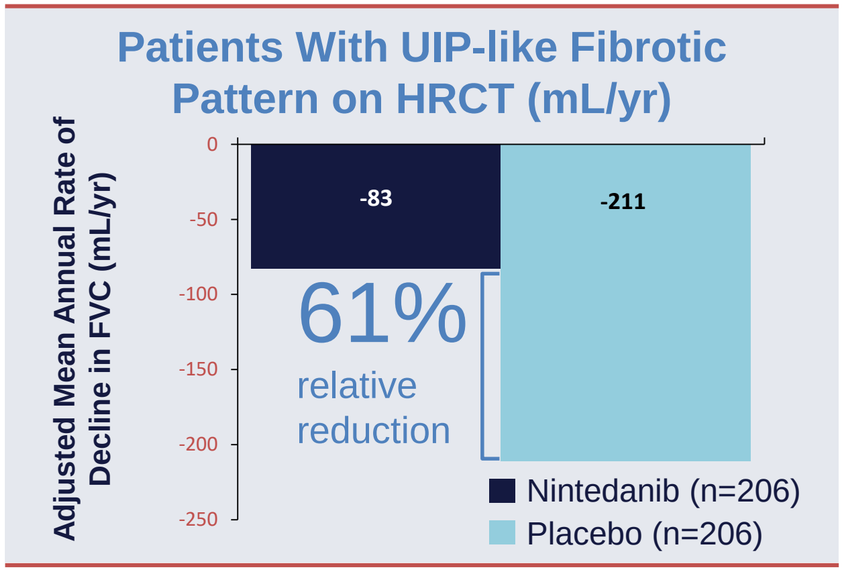
INBUILD

Adjusted Annual Rate of Decline in FVC (mL/year) over 52 weeks



Difference: 107.0 mL/yr

***P*<0.001** (95% CI: 65.4-148.5)



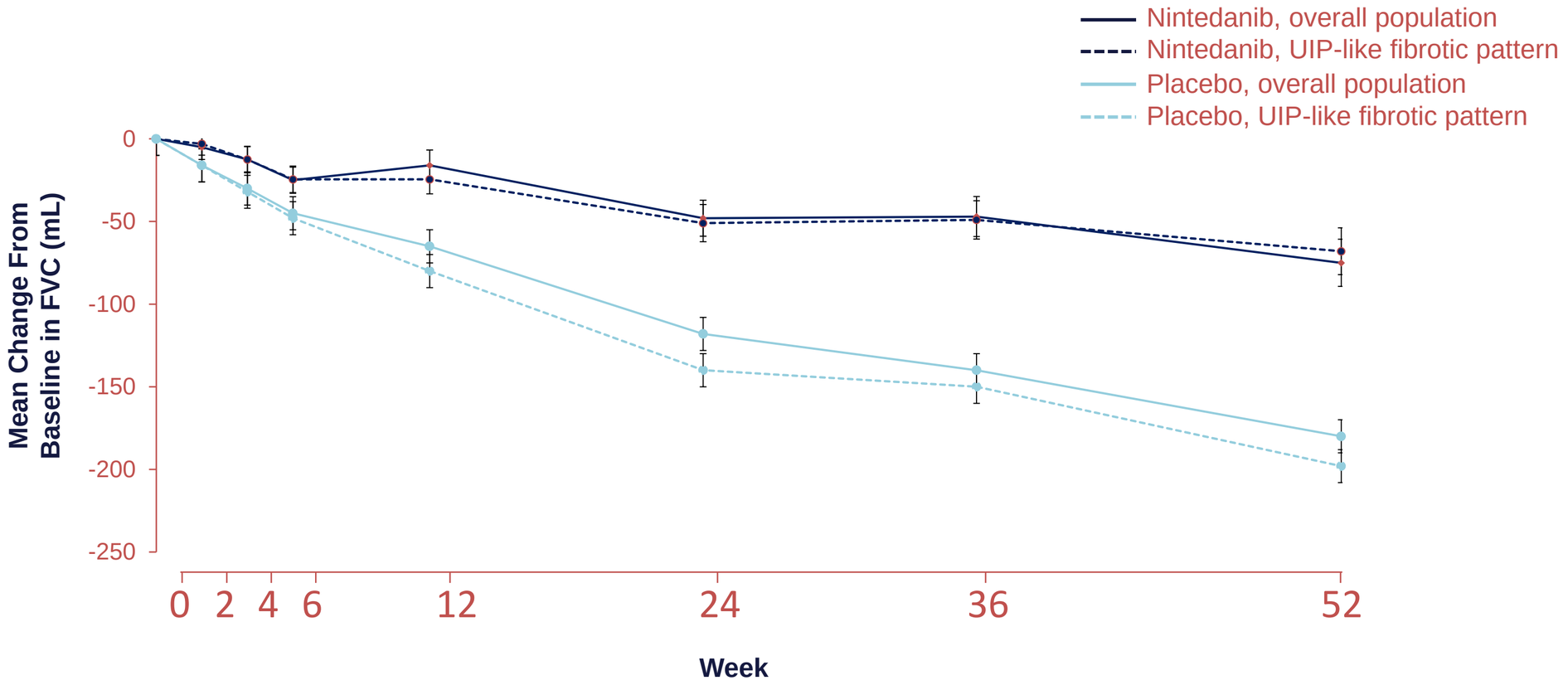
Difference: 128.2 mL/yr

***P*<0.001** (95% CI: 70.8-185.6)

Annual rate of decline in FVC was significantly lower among patients who received Nintedanib than among those who received placebo

Flaherty KR et al. *N Engl J Med.* 2019;381(18):1718-1727

Observed Change From Baseline in FVC (mL) Over 52 Weeks



INBUILD

Flaherty KR et al. N Engl J Med. 2019;381(18):1718-1727

Systemic Sclerosis (SSc) - ILD

THE UNIVERSITY OF ARIZONA

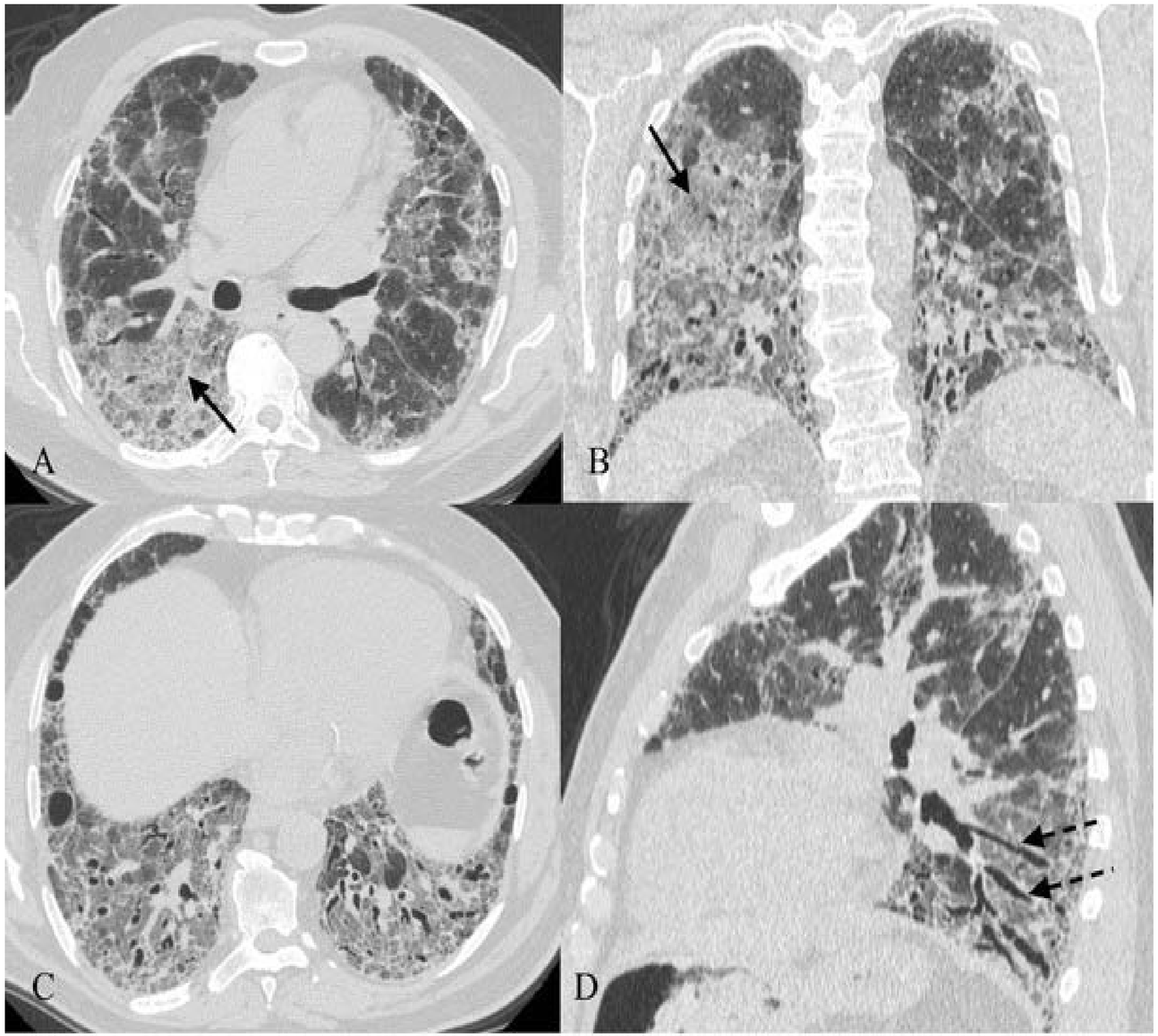
Case:

42 Y old female who presented to our ILD center with chief complaints of SOB and exertional dyspnea. Raynaud's phenomenon

Serologies
ANA 1:1200 (speckled)
Scl - 70 : Positive
TPO: 20.0 (High)

PFT's
FVC 3.25 (63%)
FEV1/FVC ratio (85%)
TLC 5.26 (55%)
DLCO 22.0 (40%)

HRCT



THE UNIVERSITY OF ARIZONA

Risk Factors:

Women **4X** more likely to develop disease but **Males have higher prevalence of SSc-ILD**

African – Americans are at a higher risk and much severe disease

Prevalence of SSc is 13.5–44.3 per 100,000 individuals in North America

Annual incidence 56 cases per million adults per year

Disease onset typically between 30-60 years

THE UNIVERSITY OF ARIZONA

Extent of skin involvement determines the specific sub-classification:

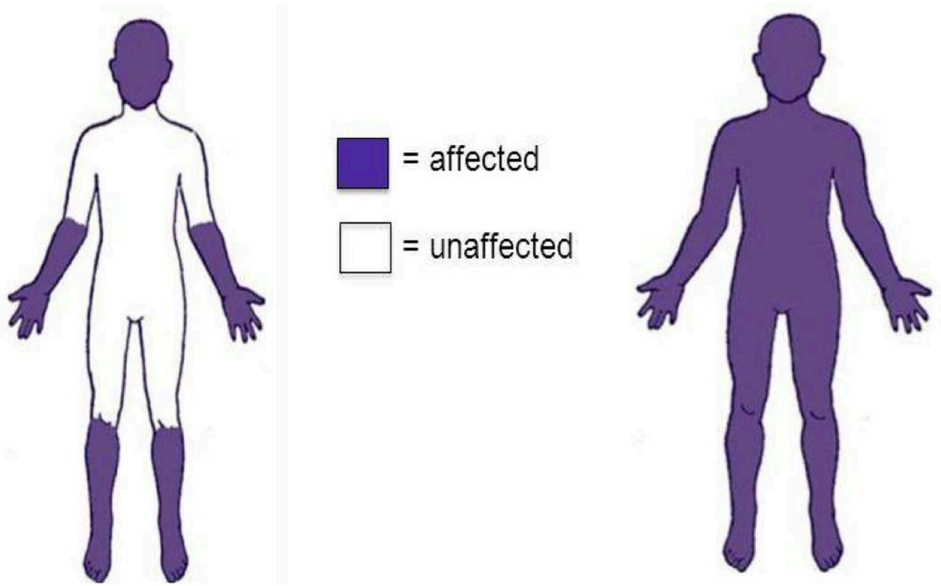
EUSTAR (EULAR Scleroderma Trials and Research) database SSc-ILD

Limited Cutaneous systemic sclerosis (lcSSc)
Skin thickening distal to the elbows, knees or face

Diffuse Cutaneous systemic sclerosis (dcSSc)
Skin thickening that extends proximal to the elbows or involves the trunk

Sine Scleroderma
Occurrence of Raynaud's, visceral fibrosis, + antibodies but no pulmonary fibrosis

Up to 65% of patients with SSc will develop ILD



THE UNIVERSITY OF ARIZONA

Risk factors in SSc ILD are associated with:

Autoantibodies – Present in all SSc-ILD patients

Anti-Scl-70 is strongly associated with development of ILD

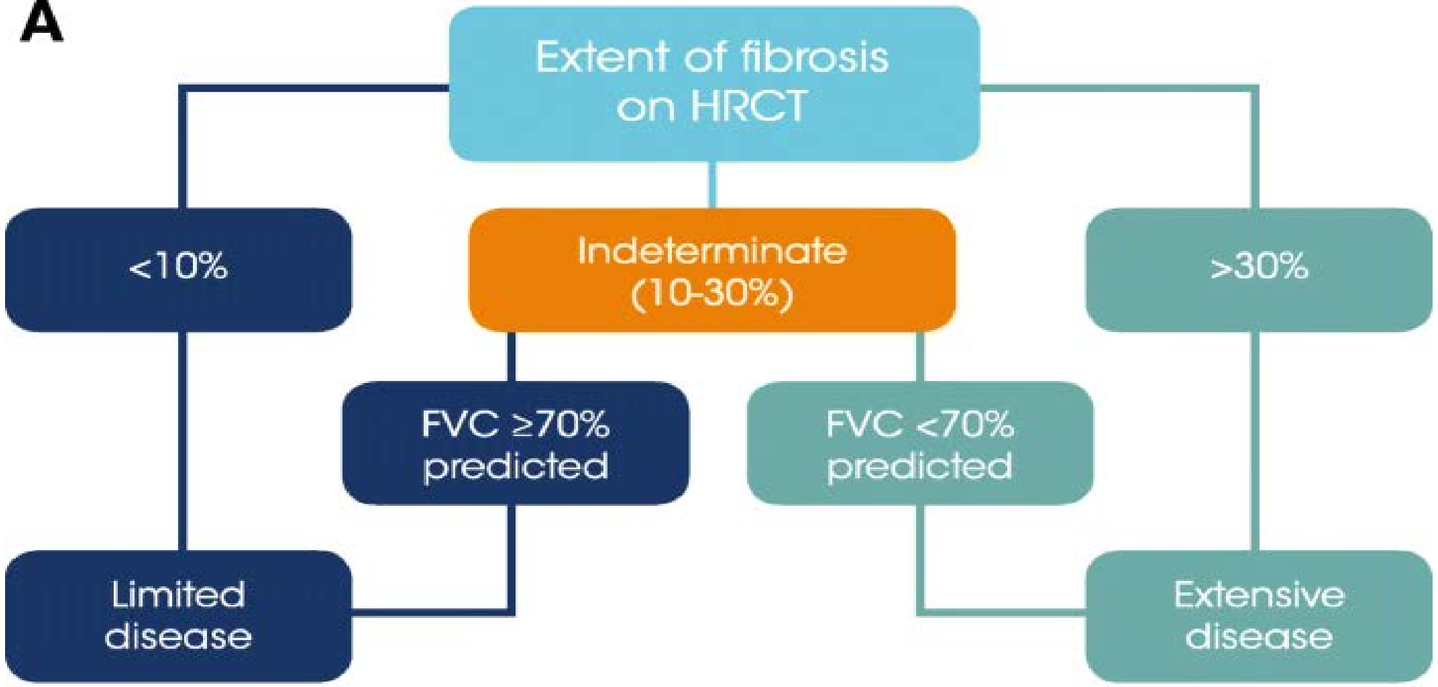
- Over 85% of these individuals will develop ILD

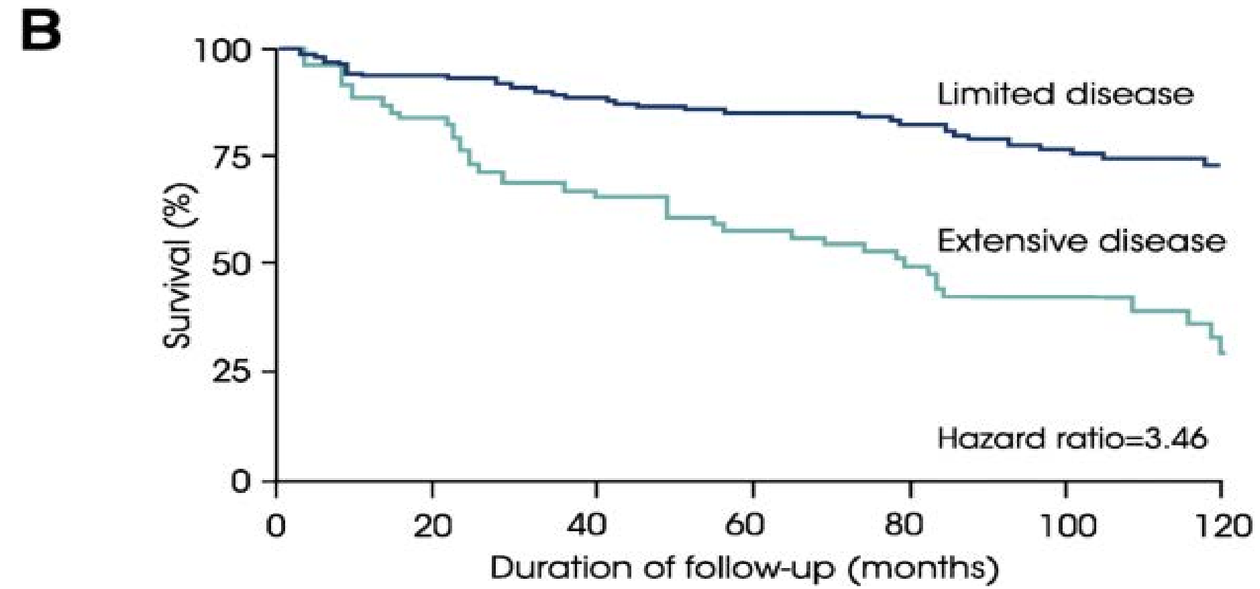
SSc-ILD is more common in diffuse cutaneous variant

Fibrotic NSIP is the most predominant pattern

THE UNIVERSITY OF ARIZONA

Staging system
Goh Criteria

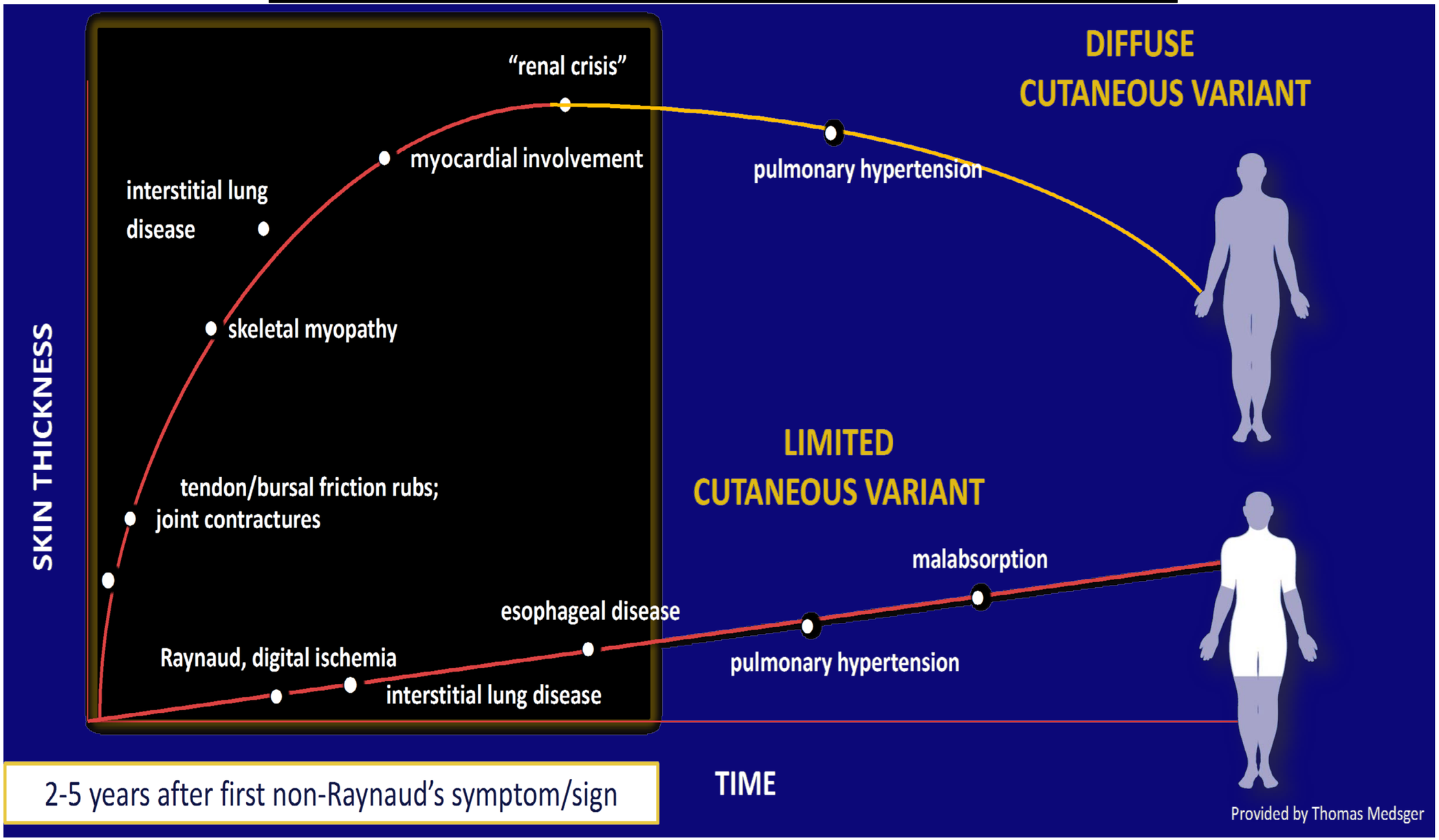




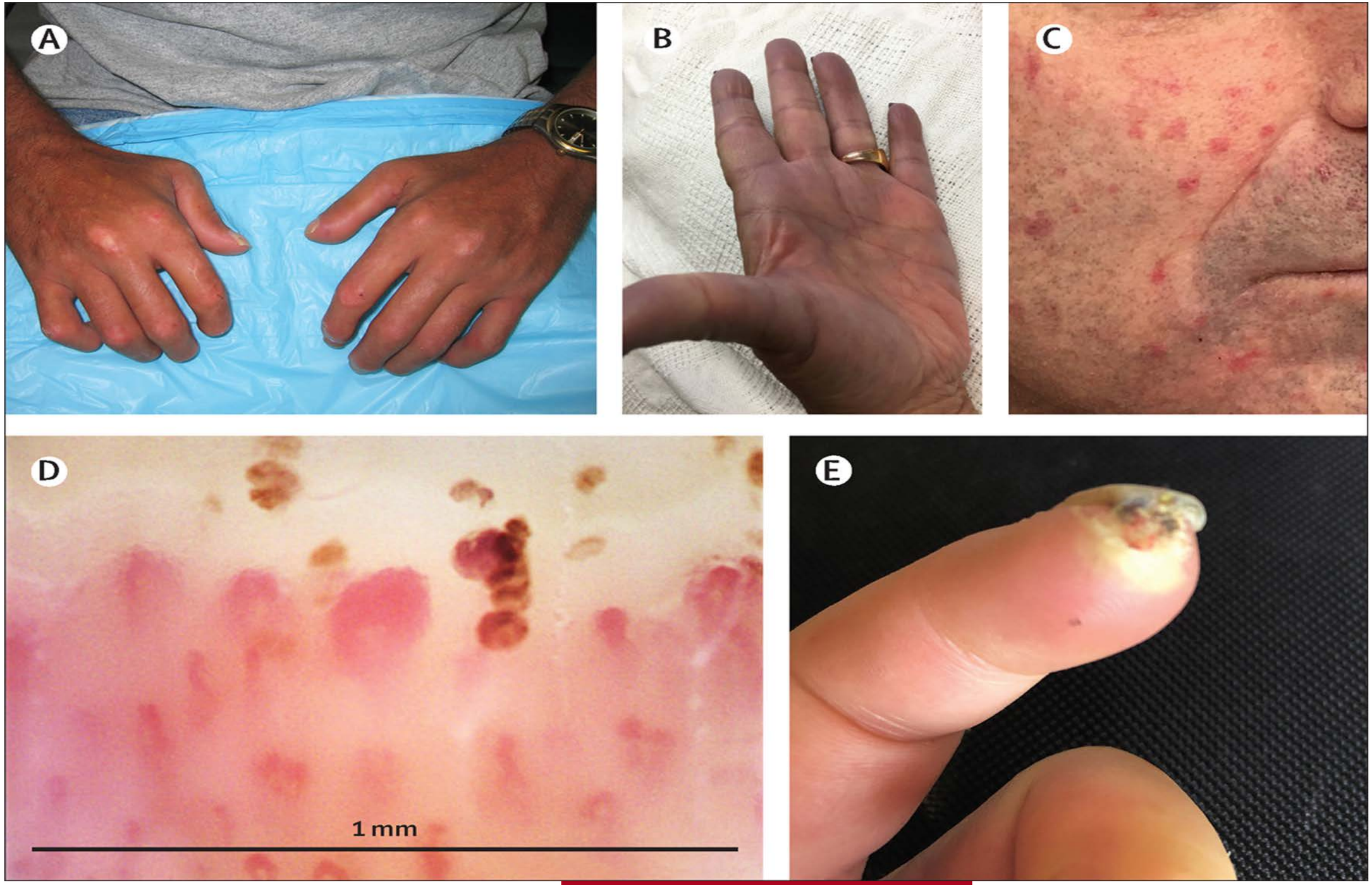
Am J Respir Crit Care Med 2008;177:1248–54. The *American Journal of Respiratory and Critical Care Medicine*

THE UNIVERSITY OF ARIZONA

Usual Timing of Problems in Systemic Sclerosis



THE UNIVERSITY OF ARIZONA



THE UNIVERSITY OF ARIZONA

Treatment of SSc- ILD

THE UNIVERSITY OF ARIZONA

Timeline of randomized controlled trials in systemic sclerosis–associated interstitial lung disease

Scleroderma Lung Study I (7)
- Cyclophosphamide (CYC) vs. placebo (PBO)
- Primary endpoint: CYC improved mean adjusted FVC compared to PBO at 12 months
- Improvement in mRSS, dyspnea, and QOL scores

2006

SENSCIS (5)
- Nintedanib vs. PBO
- Allowed background therapy
- Primary endpoint: nintedanib with slower annual rate of FVC decline compared to PBO at 52 weeks
- No improvement in mRSS, dyspnea, or QOL scores

2019

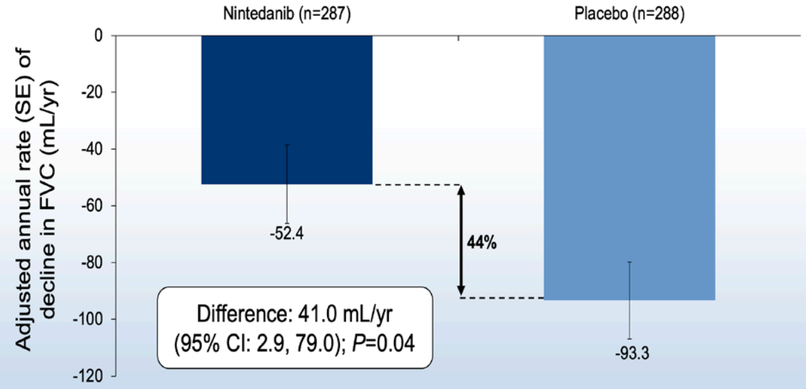
2016

Scleroderma Lung Study II (6)
- CYC vs. mycophenolate mofetil (MMF)
- Primary endpoint: no difference in adjusted FVCpp at 24 months between MMF and CYC
- Both arms with improved mRSS, dyspnea, and QOL scores*

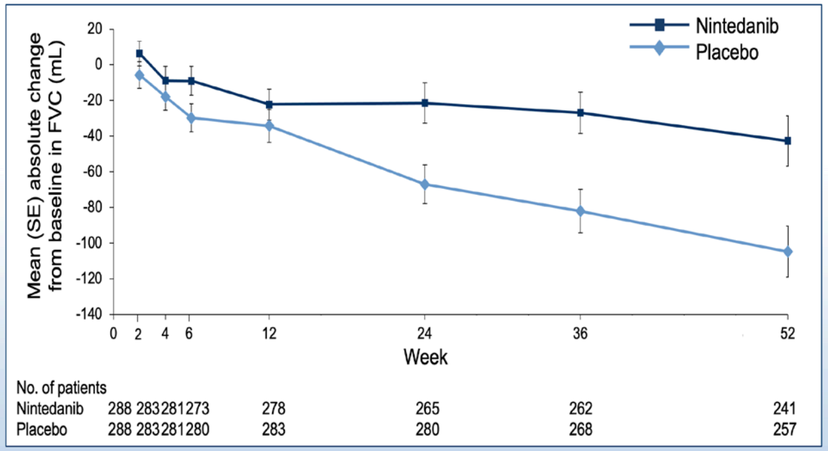
2020

focuSSced (8)
- Tocilizumab vs. PBO
- Not an ILD only study
- Primary endpoint: no significant impact on mRSS from tocilizumab at 48 weeks
- Secondary endpoint: improvement in adjusted FVC compared to PBO at 48 weeks
- No improvement in mRSS, dyspnea, or QOL scores

SENSCIS®: annual rate of decline in FVC (mL/yr) over 52 weeks (primary endpoint)



SENSCIS®: change from baseline in FVC (mL) over 52 weeks



THE UNIVERSITY OF ARIZONA

Biological therapies:

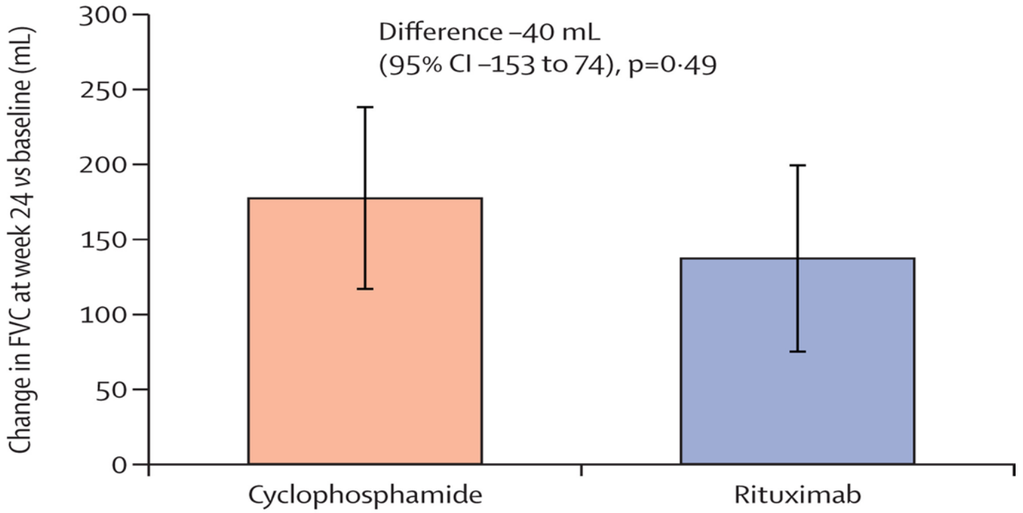
Rituximab:

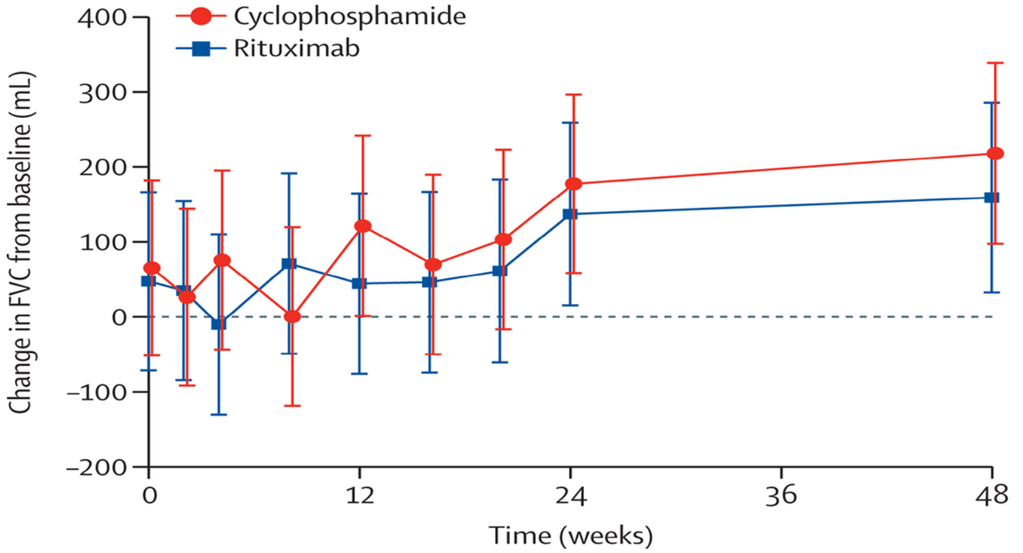
- Rituximab has been used as rescue therapy in patients with progressive SSc-ILD.

- **RECITAL trial:** Randomized, double-blind, double-dummy, phase 2b trial comparing intravenous cyclophosphamide with rituximab in patients with connective tissue disease-associated ILD, including patients with SSc-ILD.

  Rituximab was not superior to cyclophosphamide to treat patients with CTD-ILD, although participants in both treatment groups had increased FVC at 24 weeks

- **EvER-ILD trial:** Comparing 6 months of mycophenolate mofetil (2 g/day) with mycophenolate mofetil (2 g/day) plus rituximab (France)





THE UNIVERSITY OF ARIZONA

The Lancet Respiratory Medicine DOI: (10.1016/S2213-2600(22)00359-9

Biological therapies:

Tocilizumab:

- **faSScinate clinical trial:** Phase 2, Skin scores seemed to improve, **fewer patients** on **Tocilizumab** experienced **a decline of 10%** or more in FVC during the study, and no patients had a clinically significant decline during the 48-week follow-up.

- **FocuSSed trial:** Phase 3, Findings for the secondary endpoint of FVC% predicted indicate that Tocilizumab might preserve lung function in people with early SSc-ILD.

THE UNIVERSITY OF ARIZONA

Antifibrotic therapies:

SENSCIS trial: Rate of FVC decline reduced by 44% in the group receiving Nintedanib

INBUILD trial: This trial focused on patients with progressive fibrosing ILD. **Nintedanib** reduced the annual FVC decline rate by almost 60%. (6% of these patients enrolled had SSc-ILD)

Scleroderma Lung Study III: Upfront combination therapy (MMF+Pirfenidone) led to more rapid improvement in the FVC% (0-6 months) but with a similar overall improvement over 18 months as compared to MMF + placebo. Study was underpowered.

THE UNIVERSITY OF ARIZONA

High-dose immunosuppressant therapy with autologous stem cell transplantation:

ASSIST trial: Phase 2 trial that compared ASCT to intravenous cyclophosphamide for 6 months. % of FVC predicted improved significantly compared with the control group with an accompanying reduction in the volume of diseased lung on HRCT

ASTIS trial: 156 patients were randomly assigned to receive ASCT or pulse cyclophosphamide. DLCO did not change, the FVC and TLC were significantly higher in the transplant group at the end of the 2-year follow-up.

SCOT trial: 75 patients with SSc and renal or pulmonary disease, or both, were randomly assigned to receive either myeloablation and ASCT or 12 months of intravenous cyclophosphamide.
More patients in the transplant group developed complications from therapy than in the other group, they showed a better event-free survival and were more likely to have improved or stabilized pulmonary function and fewer episodes of respiratory failure at 54 months.

EULAR recommends consideration of ASCT in selected patients with rapidly progressive SSc at risk of organ failure, and the disease is now considered a standard of care indication for ASCT by the American Society for Blood and Marrow Transplantation.

THE UNIVERSITY OF ARIZONA

Rheumatoid Arthritis - ILD

THE UNIVERSITY OF ARIZONA

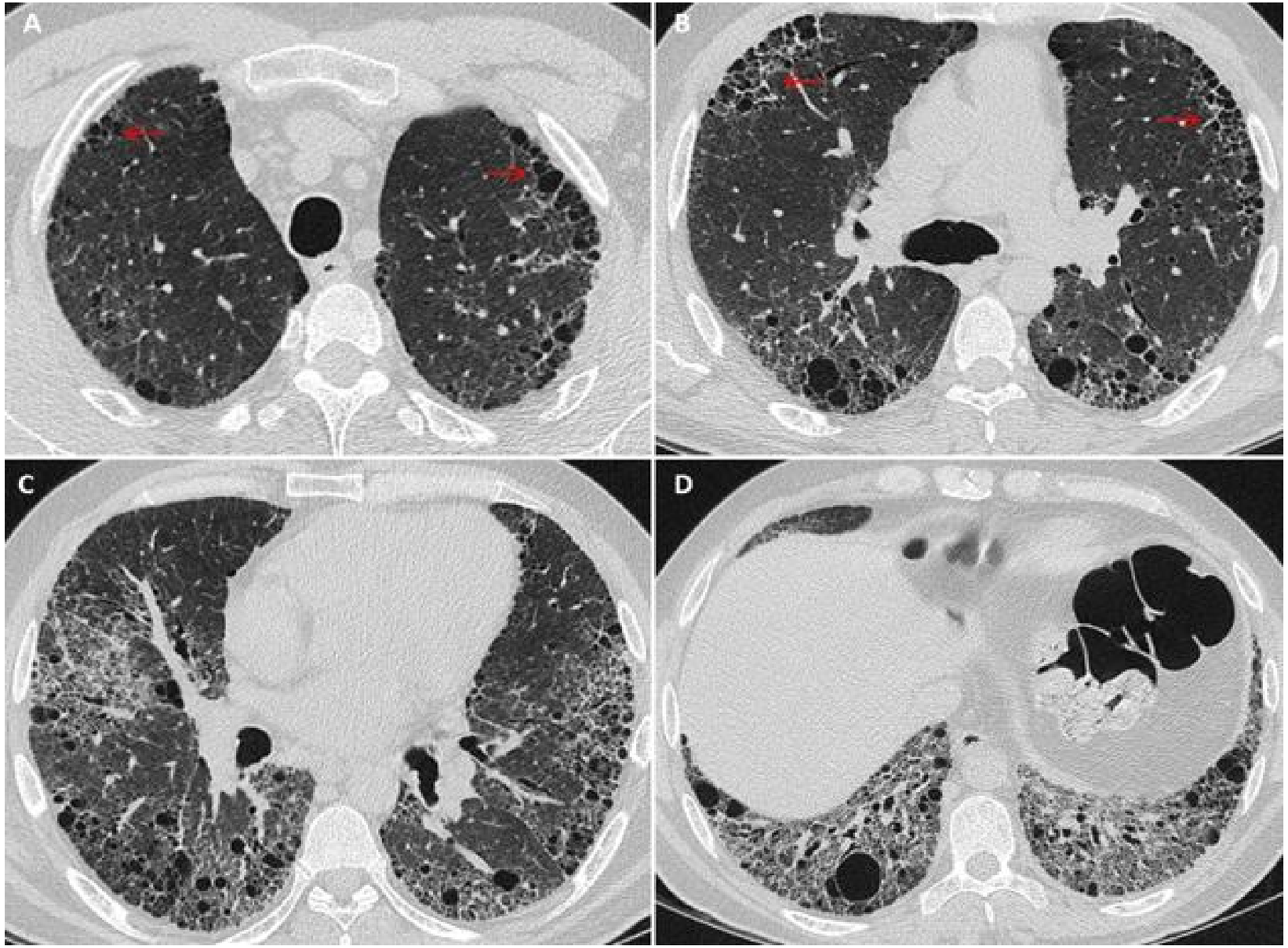
Case:

70 Y old male, former smoker comes in with progressive SOB

Serologies:
RF: Positive
CRP: High
CCP: Positive

PFT's:
FVC 3.25 (69%)
FEV1/FVC ratio (87%)
TLC 4.15 (46%)
DLCO 12.97 (39%)

HRCT



THE UNIVERSITY OF ARIZONA

Rheumatoid arthritis

Prevalence	3 - 30%
Radiologic Pattern	**UIP** >NSIP > COP RB-ILD
Beyond lungs	Joints Eyes Nodules Vasculitis









Hyldgaard et.al. Ann Rheum Dis 2017: 76(10): 1700-1706; Doylt TJ et.al, Chest 2014: 145(3): 454-463
ACR image bank

Epidemiology/Risk Factors

Most common extra-articular manifestation of RA is the lung

- Can affect up to 60% of patients during their clinic course (on HRCT)
- Clinically significant ILD in nearly 10% of patients
- Autopsy study of 81 patients with long-standing RA – **35%** with evidence of ILD.

RA-ILD affects men > women (up to 2:1), even though RA affects women > men.

Risk Factors

- Genetic: HLA-DRB1 allele, MUC5B, TERT, RTEL1, PARN, and SFTPC
- Smoking
- Seropositivity of RF or anti-CCP antibodies

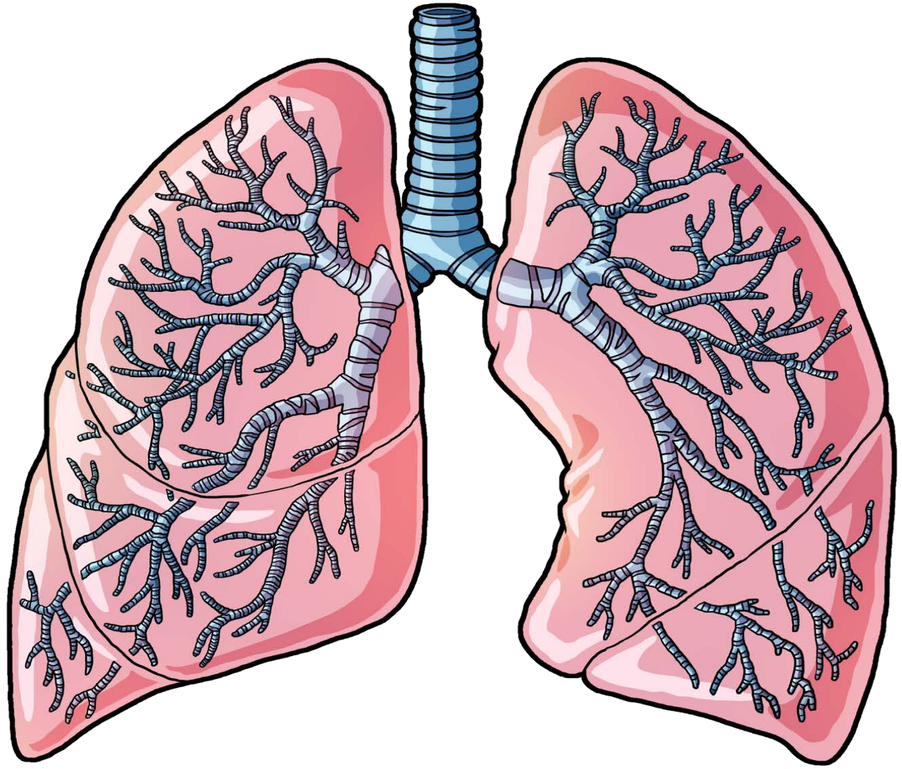
THE UNIVERSITY OF ARIZONA

Pulmonary manifestations in RA-ILD

Upper airways Disease:
- Cricoarytenoid arthritis
- Rheumatoid nodules on the vocal cords
- Vasculitis of the recurrent laryngeal nerve or the vagus nerve

Lower airways disease:
- Follicular Bronchiolitis
- Bronchiolitis obliterans
- Bronchiectasis

Parenchymal disease:
- UIP
- NSIP
- OP
- LIP
- Rheumatoid Nodules



Pleural disease:
- Pleuritis
- Pleural effusion
- Pleural Nodules

Comorbidities:
- Caplan Syndrome
- Amyloidosis

Drug toxicity:
LFN, MTX, SSZ and others

THE UNIVERSITY OF ARIZONA

Idiopathic Inflammatory Myositis - ILD

THE UNIVERSITY OF ARIZONA

Case:

67 Y old female who presented with progressive SOB

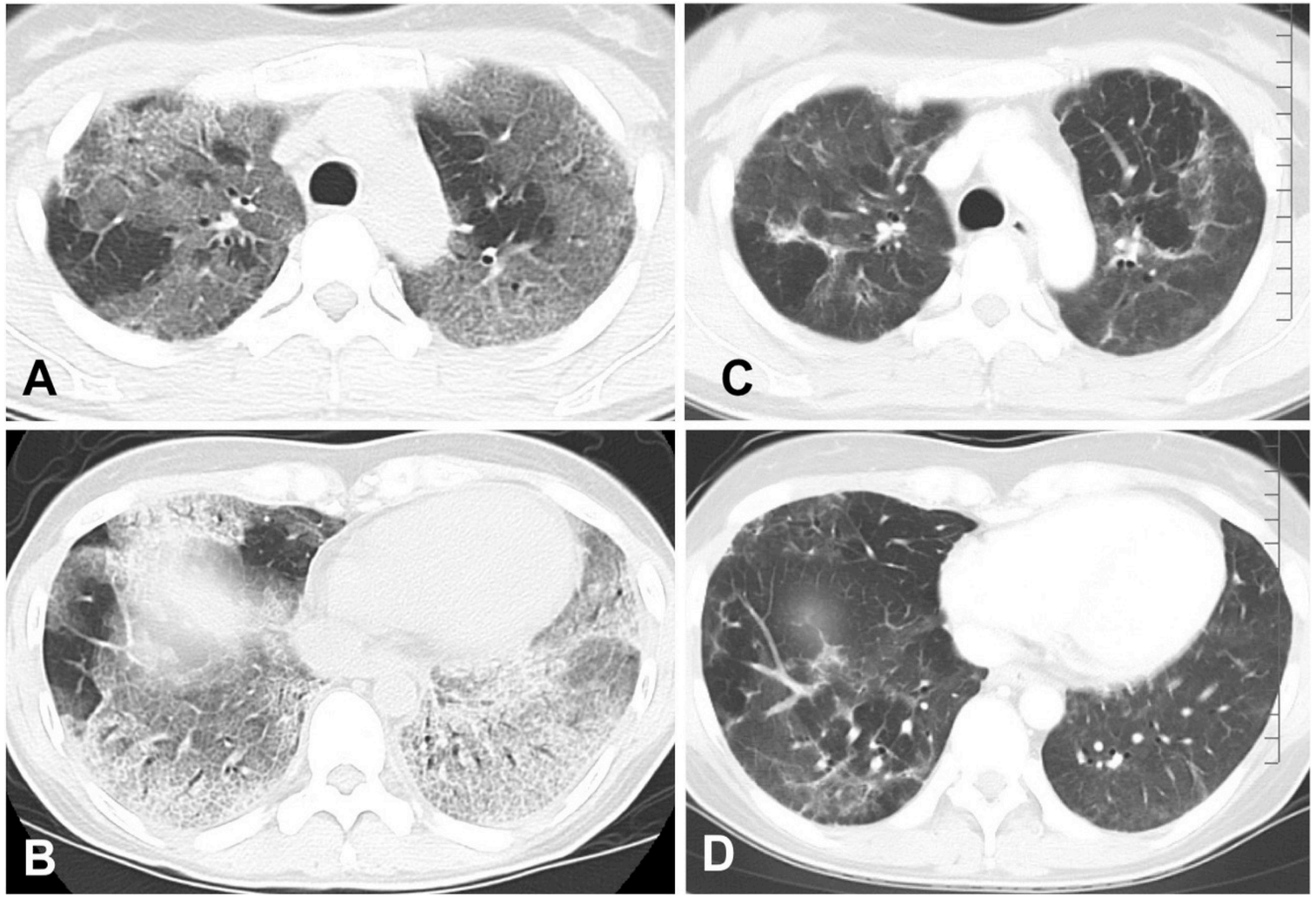
Serologies:

ANA- 1:1450
Scl-70 – Positive
Myositis panel:
PL – 12 Positive

PFT's

FVC 2.01 (45%)
FEV1/FVC ratio 87%
TLC 3.46 (45%)
DLCO 9.76 (34%)

HRCT



Before

After

THE UNIVERSITY OF ARIZONA

Idiopathic inflammatory myopathies:

Idiopathic inflammatory myopathies (IIM), collectively referred to as myositis, are a heterogenous group of autoimmune connective tissue disease characterized by:

- Symmetrical, proximal muscle weakness
- Serologies
- Neurophysiological and or histological evidence of muscle inflammation with extra-muscular manifestations, including rash and (ILD).

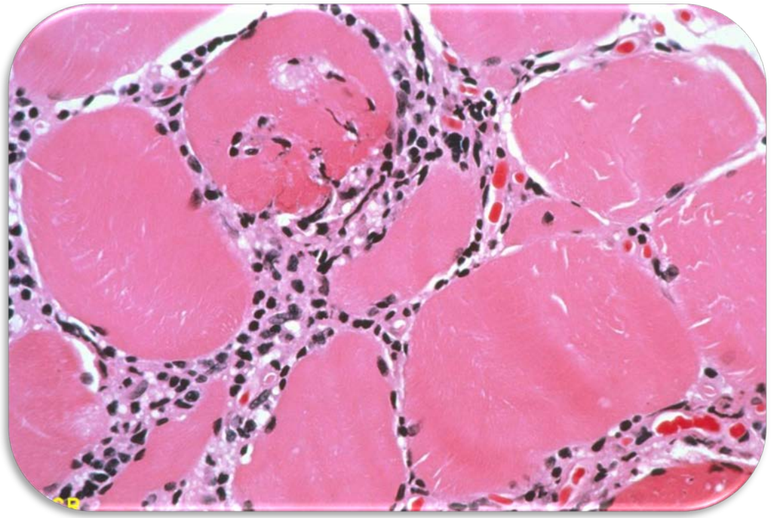
THE UNIVERSITY OF ARIZONA

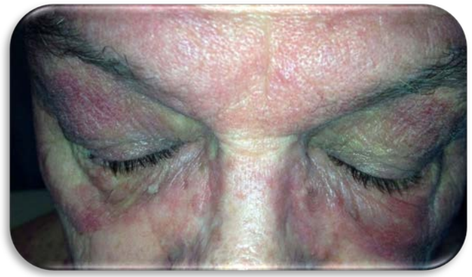
Idiopathic inflammatory myositis

Prevalence	17-35%
Radiologic Pattern	**NSIP** >UIP OP
Beyond lungs	Skeletal muscles (diaphragm) Skin Joints











Barba et al. Semin Respir Crit Care Med 2019;40:255–270
ACR Image Bank

Serological risk factors – 3 key phenotypes

Phenotype/ILD	Clinical Manifestations	Antibodies
Anti-synthetase **(NSIP/OP)**	Myositis, arthritis, ILD, mechanic's hands, Gottron's lesion, fever, Raynaud's	Anti-Jo1 **Anti-PL7** **Anti-PL12** Anti-EJ Anti-OJ Anti-KS Anti-Ha Anti-Zo
Anti-MDA5 **(AIP)**	Rapidly progressive ILD > acute | subacute ILD, mucocutaneous ulcerating lesions, clinically amyopathic DM	**Anti-MDA5**
Anti-PM-Scl **NSIP/OP**	Scleroderma, myositis, Raynaud's, mechanic fingers, arthritis	**Anti-PM-Scl**

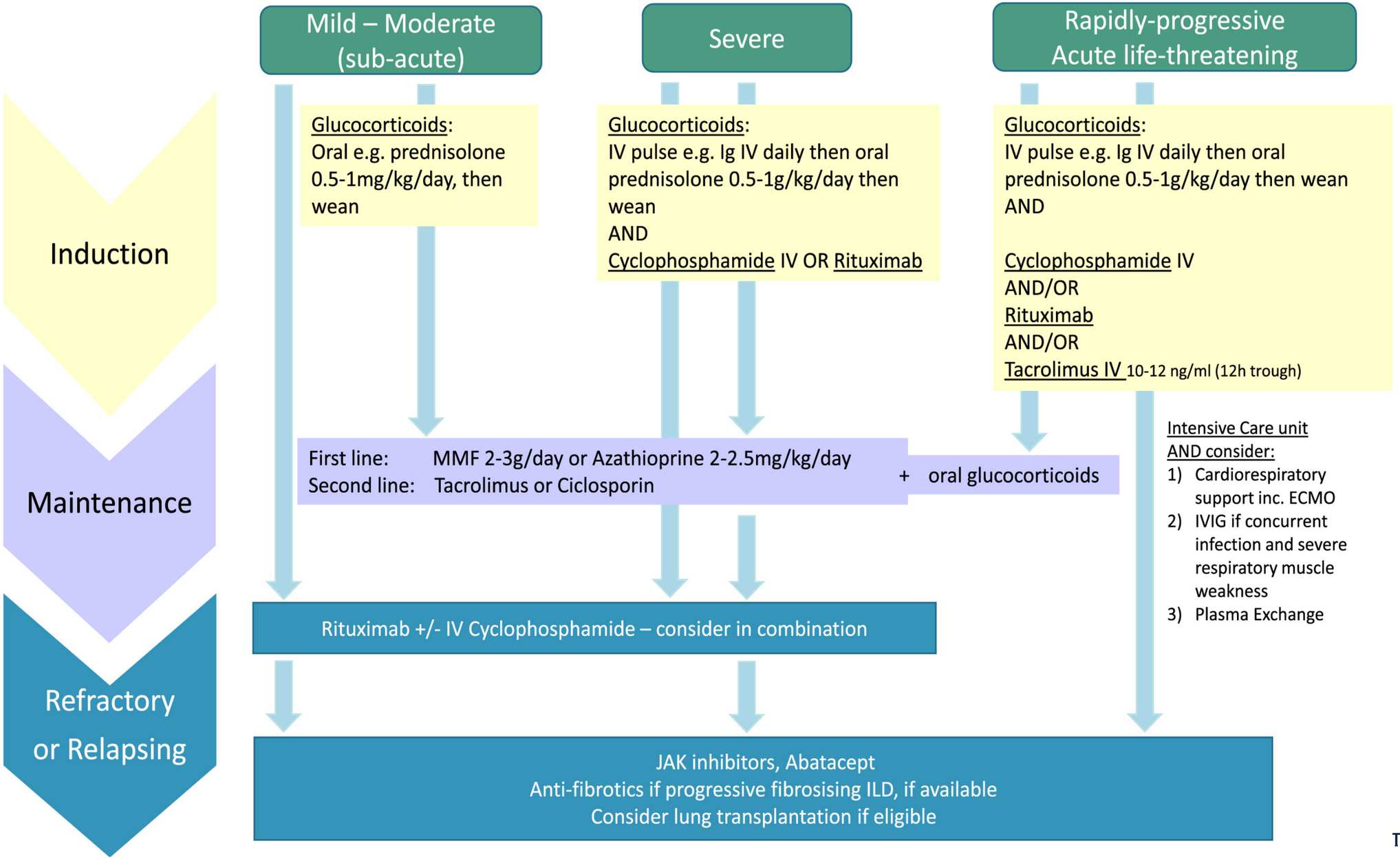
THE UNIVERSITY OF ARIZONA

Clinical course of ILD in myositis can be described as:

- **Rapidly progressive (RP-ILD):** Disease progresses over the course of days or weeks and may be refractory to standard immunomodulatory regimes
- **Acute or Sub-acute sub-type:** Disease progresses over the course of weeks or months and usually responds favorably to immunosuppressive treatment
- **Chronic sub-type:** Where the disease could be stable on therapy or demonstrate slow progression

THE UNIVERSITY OF ARIZONA

Framework for overall management of myositis-ILD

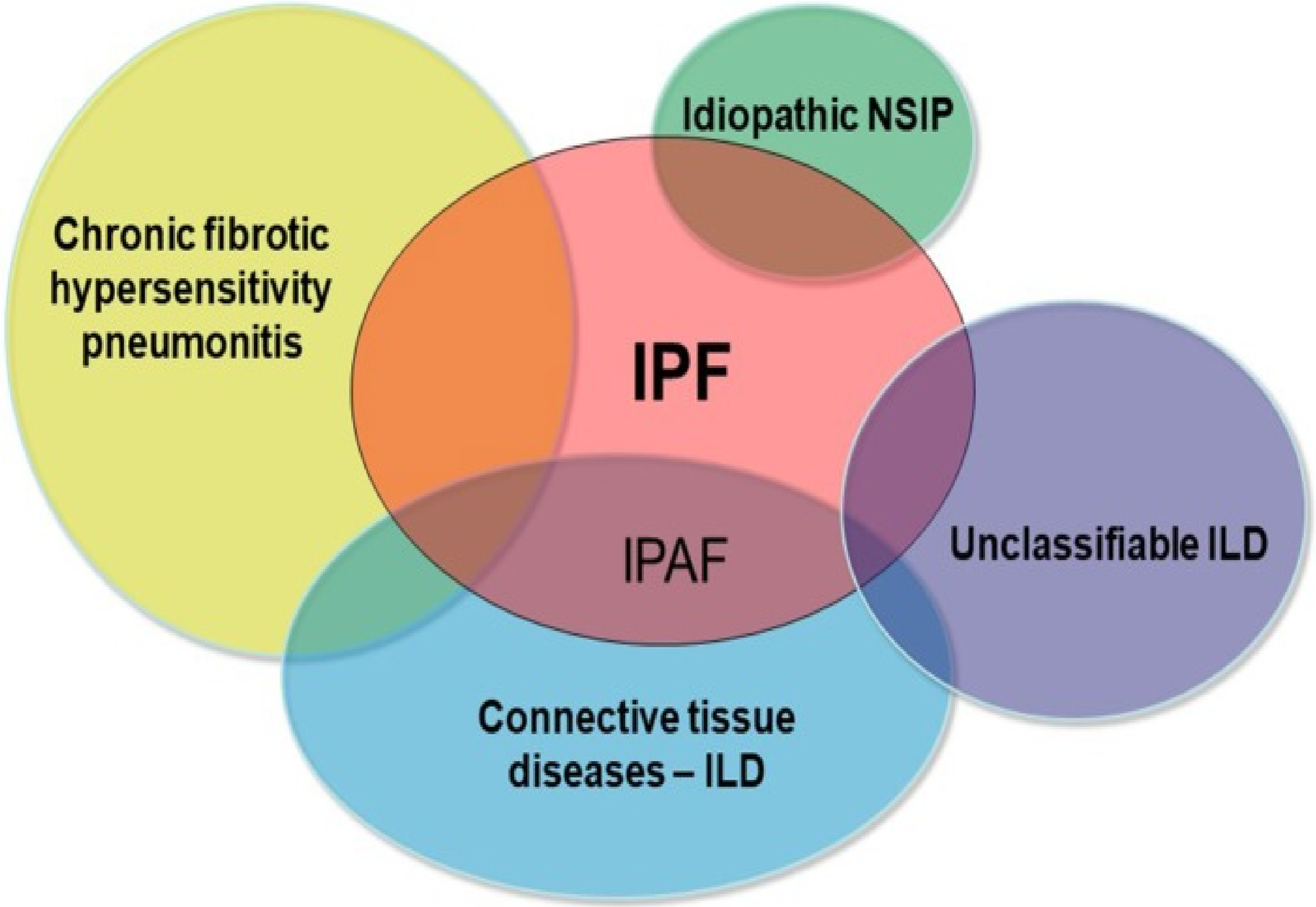


THE UNIVERSITY OF ARIZONA

https://doi.org/10.1016/j.berh.2022.101769

Idiopathic Pneumonitis with Autoimmune Features (IPAF)

THE UNIVERSITY OF ARIZONA



THE UNIVERSITY OF ARIZONA

Idiopathic Pneumonitis with Autoimmune Features (IPAF)

A designation of IPAF should be used to identify individuals with IIP and features suggestive of, but not definitive for, a CTD

Classification criteria organized around the presence of a combination of features from three domains:

- **Clinical** domain consisting of specific extra-thoracic features
- **Serologic** domain consisting of specific autoantibodies, and
- **Morphologic** domain consisting of specific chest imaging, histopathologic or pulmonary physiologic features

THE UNIVERSITY OF ARIZONA

IPAF clinical domain

1. Distal digital fissuring (i.e., “mechanic hands”)
2. Distal digital tip ulceration
3. Inflammatory arthritis or poly-articular morning joint stiffness $\geqslant$60 min
4. Palmar telangiectasia
5. Raynaud’s phenomenon
6. Unexplained digital edema
7. Unexplained fixed rash on the digital extensor surfaces (Gottron’s sign)

IPAF serologic domain

1. ANA ⩾1:320 titer, diffuse, speckled, homogeneous patterns or
   - ANA nucleolar pattern (any titer) or
   - ANA centromere pattern (any titer)
2. Rheumatoid factor ⩾2× upper limit of normal
3. Anti-CCP
4. Anti-dsDNA
5. Anti-Ro (SS-A)
6. Anti-La (SS-B)
7. Anti-ribonucleoprotein
8. Anti-Smith
9. Anti-topoisomerase (Scl-70)
10. Anti-tRNA synthetase (e.g., Jo-1, PL-7, PL-12; others are EJ, OJ, KS, Zo, tRS)
11. Anti-PM-Scl
12. Anti-MDA-5

IPAF Radiologic domain

- Suggestive radiology patterns by HRCT (see text for descriptions): NSIP, OP, NSIP with OP overlap, or LIP

- Histopathology patterns or features by surgical lung biopsy: NSIP, OP, NSIP with OP overlap, or LIP, interstitial lymphoid aggregates with germinal centers, diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles)

- Multi-compartment involvement (in addition to interstitial pneumonia):
  - Unexplained pleural effusion or thickening
  - Unexplained pericardial effusion or thickening
  - Unexplained intrinsic airways disease# (by PFT, imaging or pathology)
  - Unexplained pulmonary vasculopathy

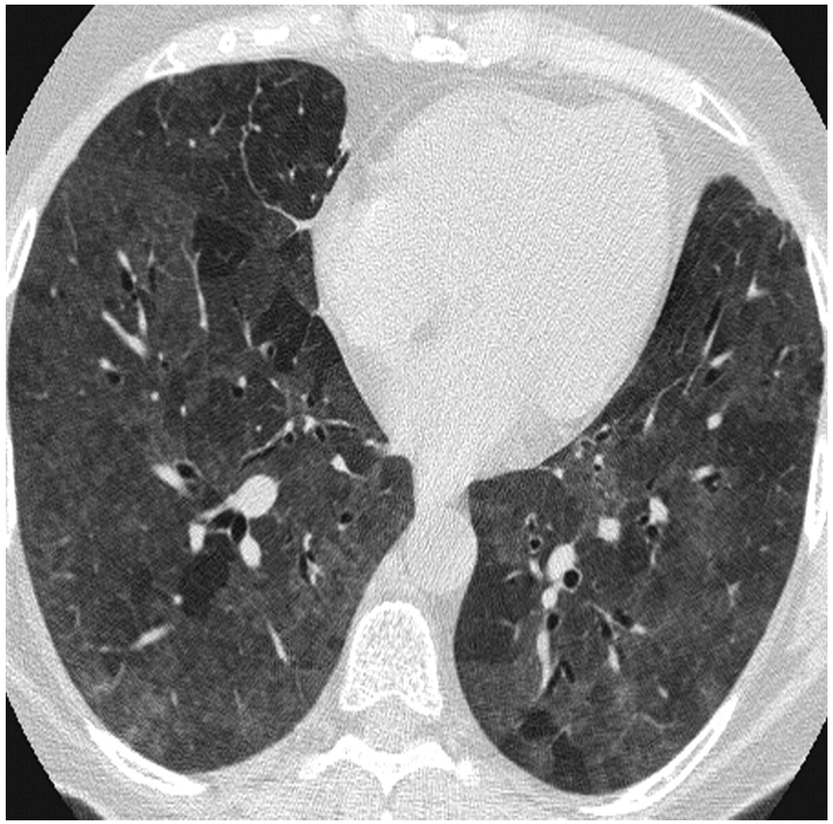
Hypersensitivity Pneumonitis:

THE UNIVERSITY OF ARIZONA

Case

61 y African-American female, golfer, never smoker presents with 6 months progressive SOB, cough

- Takes no medications, worked in sales
- Denies CTD symptoms
- **Owns two cockatiels**
- Lives in home build in 1904
- Scattered crackles throughout all lung fields with occasional squeaks
- Hypoxemic with exertion to SaO2 88%
- PFTs
  - TLC 50% predicted
  - FVC 48% predicted
  - DLCO 48% predicted
  - **BAL: 50% Lymphs**





THE UNIVERSITY OF ARIZONA

Epidemiology:

Varies with Geography, Occupation and Season

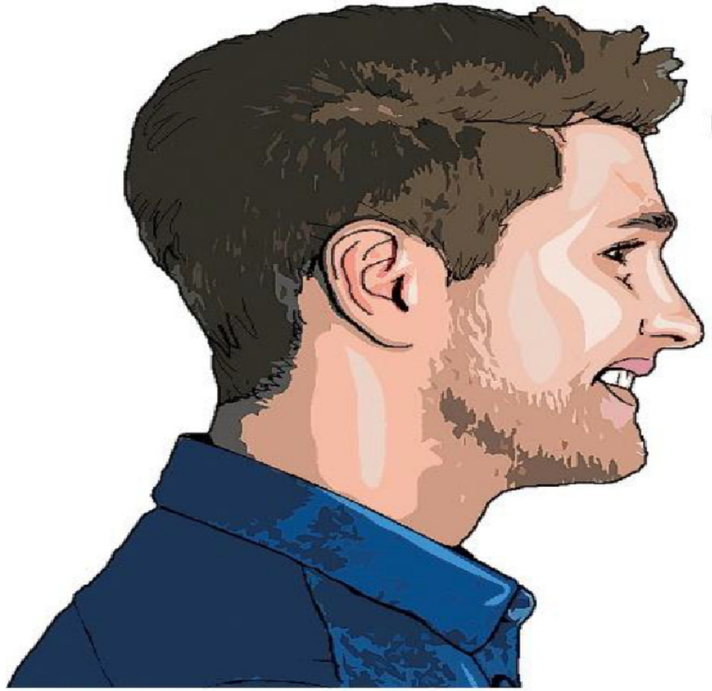
Farmers and bird-related HP the most common forms globally

U.S. one-year prevalence rate: **1.7-2.7/100,000 persons**

- **Increases with age**: Age 0-9: 0.9/100,000 persons
  Age >65: 11.2/100,000 persons

- **About half of HP cases** may present as **chronic disease** with 1/3 to half of those being classified as fibrotic HP

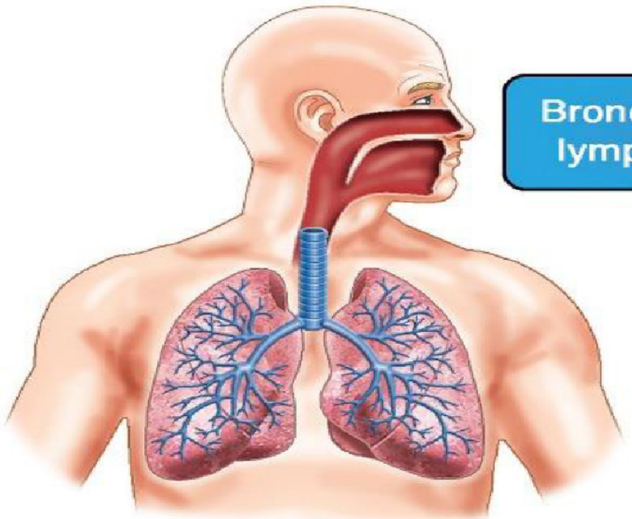
THE UNIVERSITY OF ARIZONA



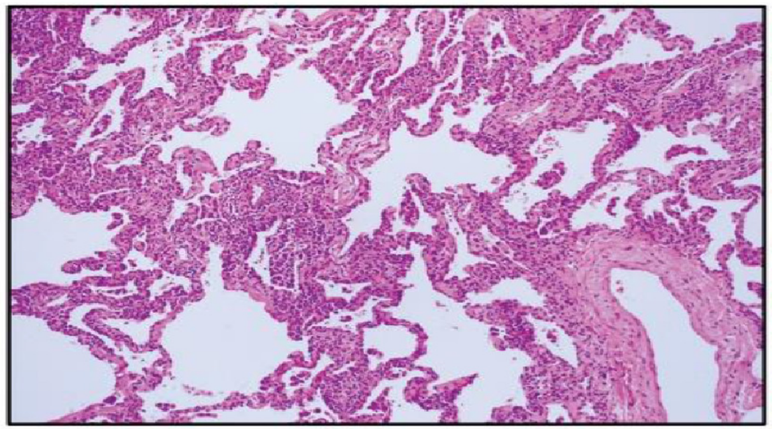
The doctor now says that my breathing problem could be from asthma, sarcoid, IPF or NSIP.



I still think you're allergic to me.



Bronchoalveolar lavage lymphocytosis ≥ 30%



There is thickening of the alveolar septae by intense lymphocytic interstitial infiltrates

The diagnosis of hypersensitivity pneumonitis is made with compatible clinical symptoms, an inciting (inducing) antigen, the abnormal high resolution CT scan, pulmonary function testing, evidence of IgG antibodies to the antigen, and for some patients, lung biopsy.

https://doi.org/10.1016/j.anai.2022.09.002 *Annals of Allergy, Asthma & Immunology* 2022 129544-545DOI 10.1016/j.anai.2022.09.002)

- In HP, the nodules (2-7 mm) are centrilobular on CT examination and may be described as airway centered, peribronchiolar, or “bronchiolocentric”

- HP has long been recognized to have a pattern of BAL lymphocytosis with **a consensus cutoff of 30%** or more because healthy, nonsmoking people may have 10% to 15% lymphocytes and **smokers have up to 30% lymphocytosis on BAL.**

- BAL lymphocytosis may **not** be present in patients with **extensive fibrotic HP**

THE UNIVERSITY OF ARIZONA

AMERICAN THORACIC SOCIETY DOCUMENTS

Diagnosis of Hypersensitivity Pneumonitis in Adults

An Official ATS/JRS/ALAT Clinical Practice Guideline

Ganesh Raghu, Martine Remy-Jardin, Christopher J. Ryerson, Jeffrey L. Myers, Michael Kreuter, Martina Vasakova, Elena Bargagli, Jonathan H. Chung, Bridget F. Collins, Elisabeth Bendstrup, Hassan A. Chami, Abigail T. Chua, Tamera J. Corte, Jean-Charles Dalphin†, Sonye K. Danoff, Javier Diaz-Mendoza, Abhijit Duggal, Ryoko Egashira, Thomas Ewing, Mridu Gulati, Yoshikazu Inoue, Alex R. Jenkins, Kerri A. Johannson, Takeshi Johkoh, Maximiliano Tamae-Kakazu, Masanori Kitaichi, Shandra L. Knight, Dirk Koschel, David J. Lederer, Yolanda Mageto, Lisa A. Maier, Carlos Matiz, Ferran Morell, Andrew G. Nicholson, Setu Patolia, Carlos A. Pereira, Elisabetta A. Renzoni, Margaret L. Salisbury, Moises Selman, Simon L. F. Walsh, Wim A. Wuyts, and Kevin C. Wilson; on behalf of the American Thoracic Society, Japanese Respiratory Society, and Asociación Latinoamericana de Tórax

This guideline is dedicated to the memory of Prof. Jean-Charles Dalphin† (June 2, 1956–October 17, 2019)

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE WAS APPROVED BY THE AMERICAN THORACIC SOCIETY, JAPANESE RESPIRATORY SOCIETY, AND ASOCIACIÓN LATINOAMERICANA DE TÓRAX MAY 2020

Diagnosis and Evaluation of Hypersensitivity Pneumonitis
CHEST Guideline and Expert Panel Report



August 2021 Vol 160, Issue 2

Diagnosis and Evaluation of Hypersensitivity Pneumonitis

CHEST Guideline and Expert Panel Report

Check for updates

Evans R. Fernández Pérez, MD, FCCP; William D. Travis, MD, FCCP; David A. Lynch, MB, BCh; Kevin K. Brown, MD, FCCP; Kerri A. Johannson, MD, MPH; Moisés Selman, MD; Jay H. Ryu, MD, FCCP; Athol U. Wells, MD; Yuh-Chin Tony Huang, MD, MHS, FCCP; Carlos A. C. Pereira, MD, FCCP; Mary-Beth Scholand, MD, FCCP; Ana Villar, MD, PhD; Naohiko Inase, MD, PhD; Richard B. Evans, MD, MPH, FCCP; Stephen A. Mette, MD, FCCP; and Lindsy Frazer-Green, PhD

THE UNIVERSITY OF ARIZONA

- Historically termed “Extrinsic Allergic Alveolitis” and categorized as:

-Acute
-Subacute
-Chronic

Traditional	ATS/ACCP guideline recommendation May 2020/Aug 2021
Acute	**Nonfibrotic**
Subacute/Chronic	**Fibrotic**

THE UNIVERSITY OF ARIZONA

HP – Pharmacotherapy

Progressive FHP

- Immunomodulatory therapy (e.g., corticosteroids, MMF, AZA)
- Antifibrotic therapy (i.e., Nintedanib, Pirfenidone?)
- Combined immunomodulatory and antifibrotic therapy

Severe and/or progressive non-FHP

- Immunomodulatory therapy (e.g., Steroids, MMF, AZA)

HP acute exacerbation

- Immunomodulatory therapy (i.e., Corticosteroids)

THE UNIVERSITY OF ARIZONA

Antigen Identification and Avoidance

Microbial:



- Prevention/remediation leaking and flooding
- Removing stagnant water sources (e.g., AC drip pans)
- Removing humidifiers, hot tubs, vaporizers, swamp coolers
- Maintain relative humidity <60 (ideally 30-50%)
  - Dehumidifiers
  - Mold/flooding cleanup and remediation – AIHA, CDC and EPA.gov

Avian:

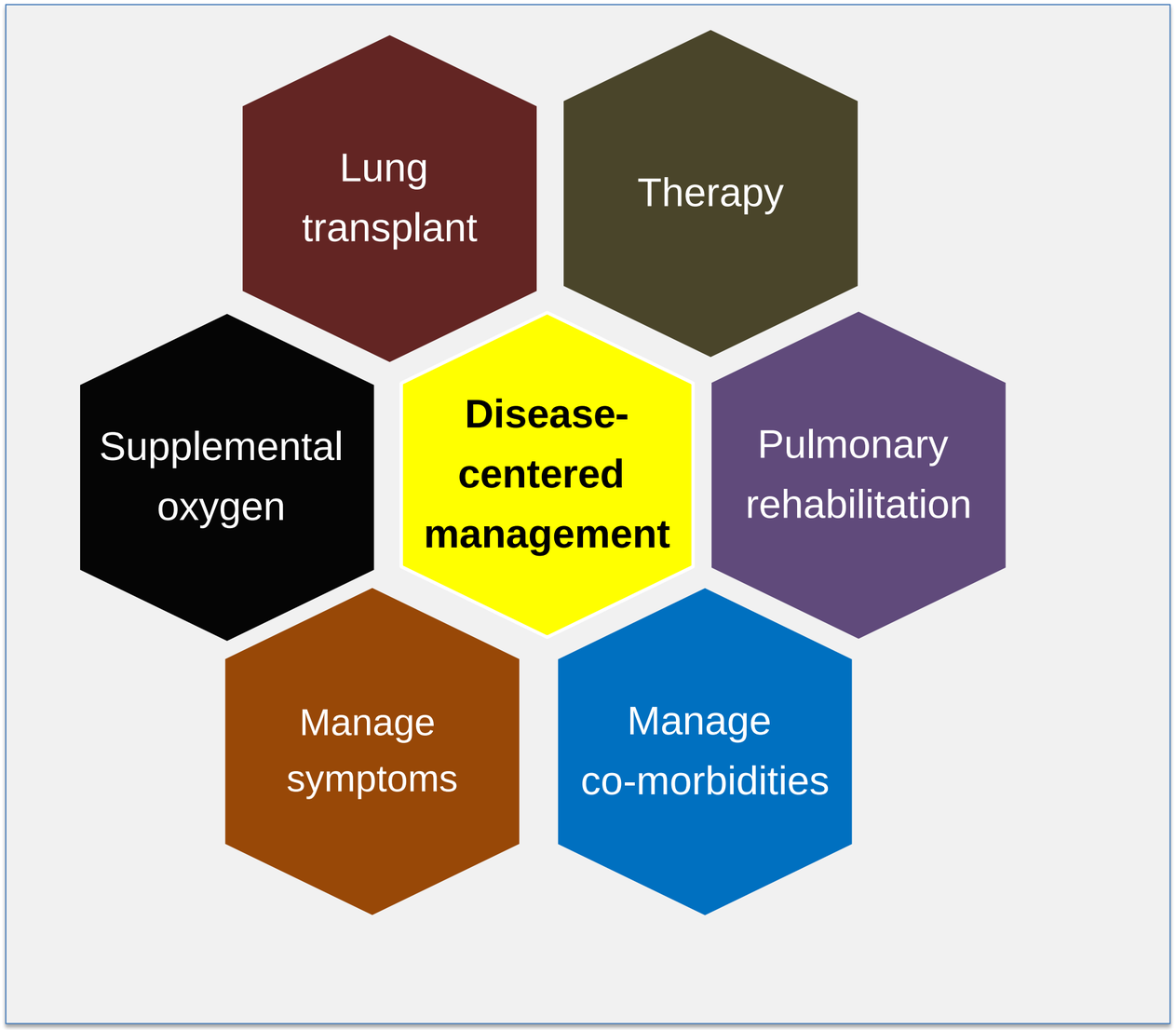
- Removal of birds, feather pillows/furniture/down



Education/consider consultation OM/certified hygienist – contractor

Temporary relocation - occupational or domestic

Management Options for Patients with ILD's

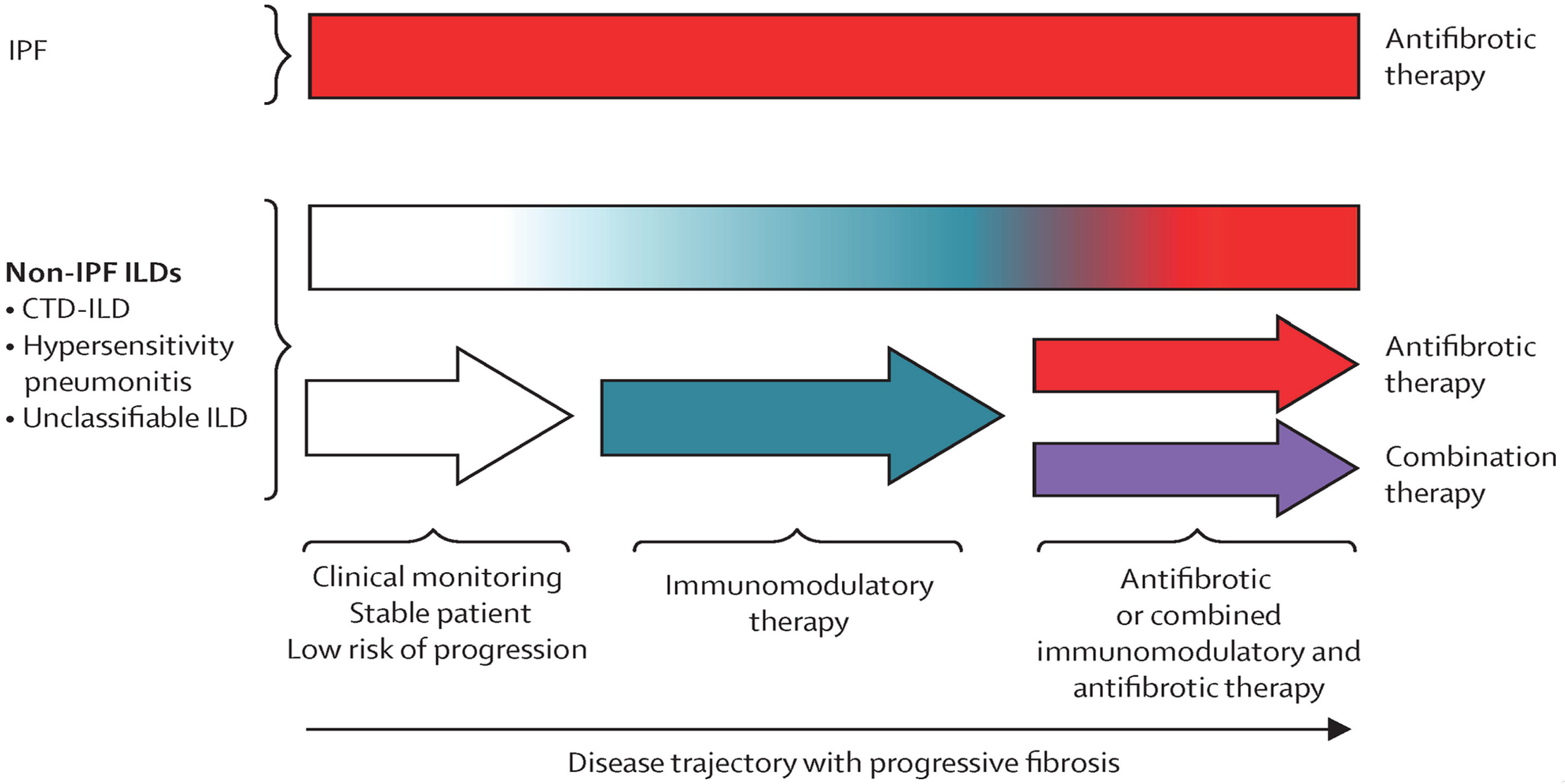


1.Raghu G, Richeldi L. *Respir Med*. 2017;129:24-30.
2.van Manen MJG et al. *Ther Adv Respir Dis*. 2017;11(3):157-169
3. Raghu G et al. *Am J Respir Crit Care Med.* 2011;183:788-824.
4. Raghu G et al. *Am J Respir Crit Care Med*. 2015;192(2).

Summary

THE UNIVERSITY OF ARIZONA

Conceptual framework for the treatment of Progressive ILD's



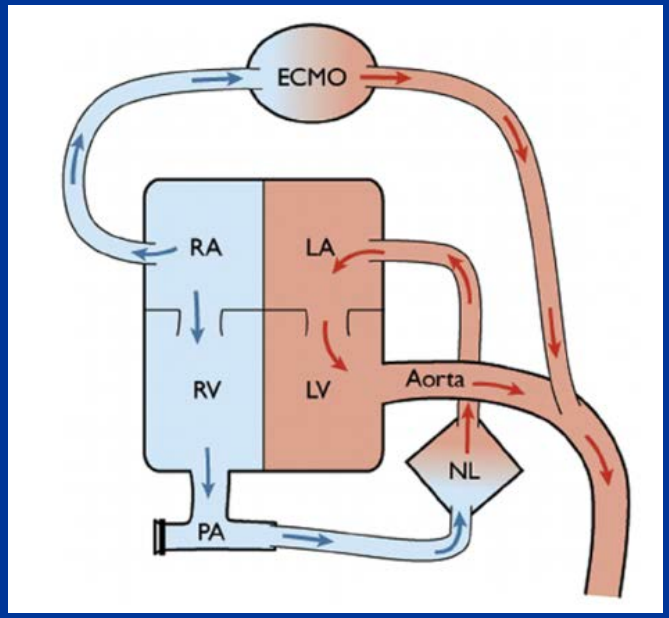
THE UNIVERSITY OF ARIZONA

Johannson K et al Lancet 2021



THE UNIVERSITY OF ARIZONA

ECMO Bridging to Lung Transplantation in the Covid Era



Matthew G. Hartwig, MD, MHS
Professor of Surgery with tenure
Division of Cardiovascular and Thoracic Surgery
Duke University Health System

Duke Surgery





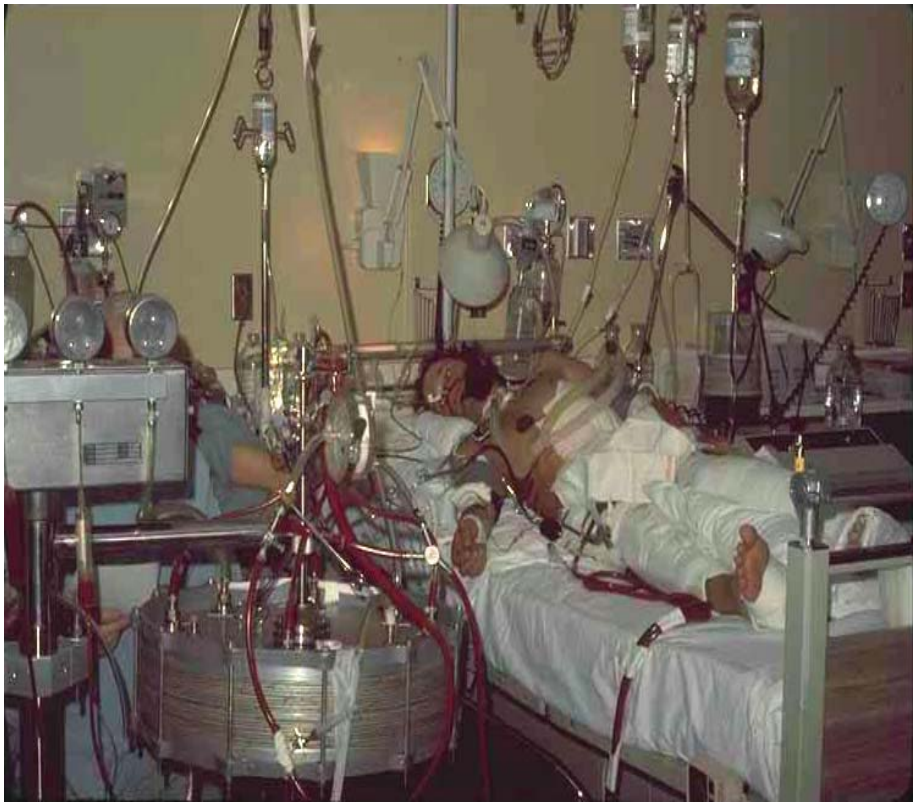
Disclosure Slide

- Research relationships with CFF, Lung Bioengineering, Transmedics, Paragonix and Biomedinnovations.
- Consultant or advisory board for Intuitive, CSL Behring, paragonix and Qx Pharmaceuticals on topics related to lung transplantation
- None of those are related to this talk



ECMO, Then

- The original ECMO circuit made for short bridging conversations



J. Donald Hill, MD and Maury Bramson, BME, Santa Barbara, CA 1971



World J. Surg. 1, 177–184, 1977

World Journal of Surgery

© 1977 by the Société Internationale de Chirurgie

Lung Transplantation 1977

FRANK J. VEITH, M.D. and SPENCER K. KOERNER, M.D.

Department of Surgery, and the James Hilton Manning and Emma Austin Manning Laboratory, Montefiore Hospital and Albert Einstein College of Medicine, New York, New York, U.S.A.



29/F. J. Veith, S. K. Koerner	1/7/72	COPD	Right lung	6 months	Massive hemoptysis from eroded bronchial artery
30/F. J. Veith, S. K. Koerner	5/6/72	COPD	Left lung	15 days	Aspiration pneumonia from necrotic bronchial mucosa
31/M. Molins	3/30/67	Bronchiectasis, COPD	Right lung	6 days	Respiratory insufficiency, pneumonia
32/M. Molins	9/28/67	Carcinoma left lung, COPD	Left lung	1 day	Respiratory insufficiency, pneumothorax
33/K. Davidson	12/12/71	Toxic pneumonitis (paraquat)		5 days	? Paraquat toxicity
34/M. Noirclerc	7/7/72	CLD		No survival	Cardiac arrest
35/M. Noirclerc	5/14/73	CLD		9 days	Acute gastric dilation
36/F. J. Veith, S. K. Koerner	12/4/73	COPD		2 days	Respiratory insufficiency, ? hyperacute rejection, bleeding
37/A. Thomas, W. F. Blaisdell	8/22/75	Posttraumatic pulmonary insufficiency; failed ECMO	Left lung	10 days	Sepsis, bronchial leak, space problem

*CLD, chronic lung disease; COPD, chronic obstructive lung disease; ECMO, extracorporeal membrane oxygenation.

Veith Trans Proc, 1977;9:203-08



Early ECMO experience in lung transplant

- 1975 first case of ECMO bridge to transplant was performed for post-traumatic respiratory failure.
- Successfully weaned from ECMO after txp but died 10 days later from combination of sepsis, bronchial leak and size mismatch.
- 1982 ECMO bridge to transplant for paraquat poisoning; successfully weaned from ECMO but paraquat poisoning recurred and back on ECMO. Re-txp done 19 days later (lived 93 days until developed complications of tracheal-innominate artery fistula).



ECMO, Now

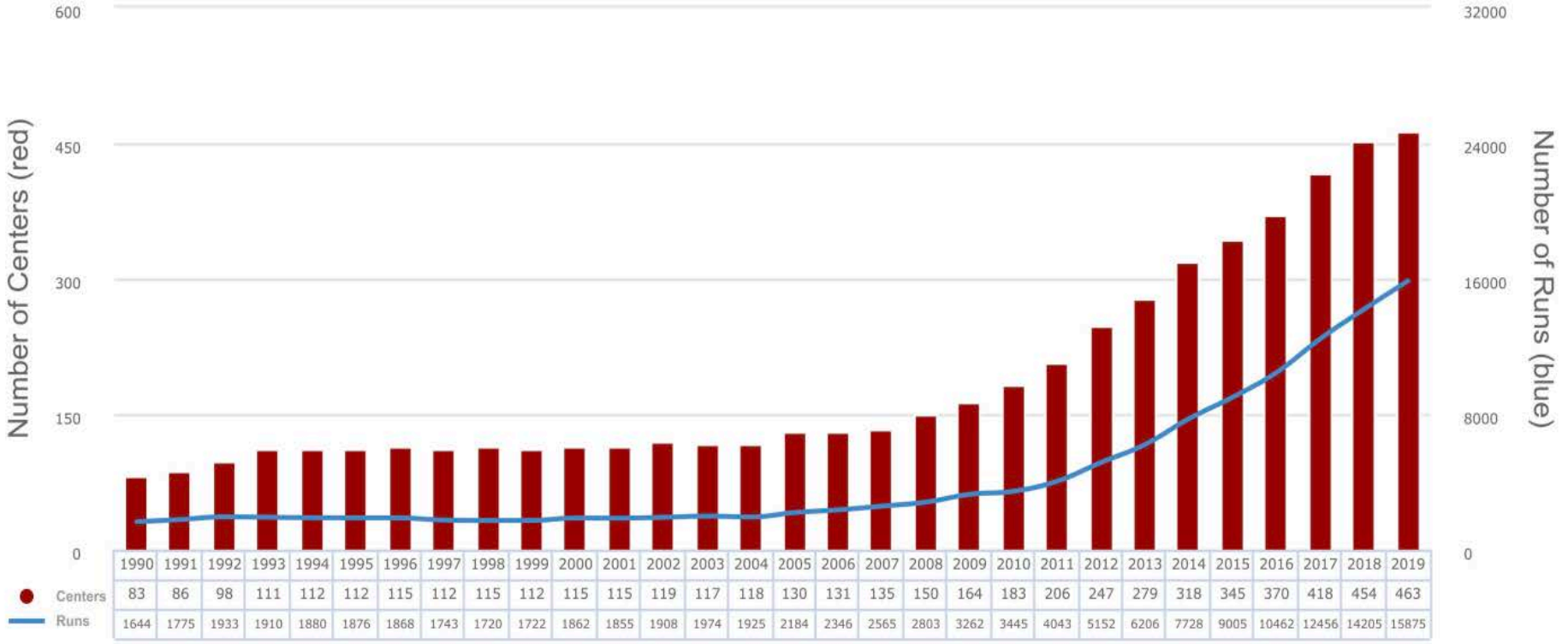
- Today's ECMO circuit has changed the conversation



Schmid et al. J Heart Lung Transplant 2012;31:9–15.



ECMO, Now



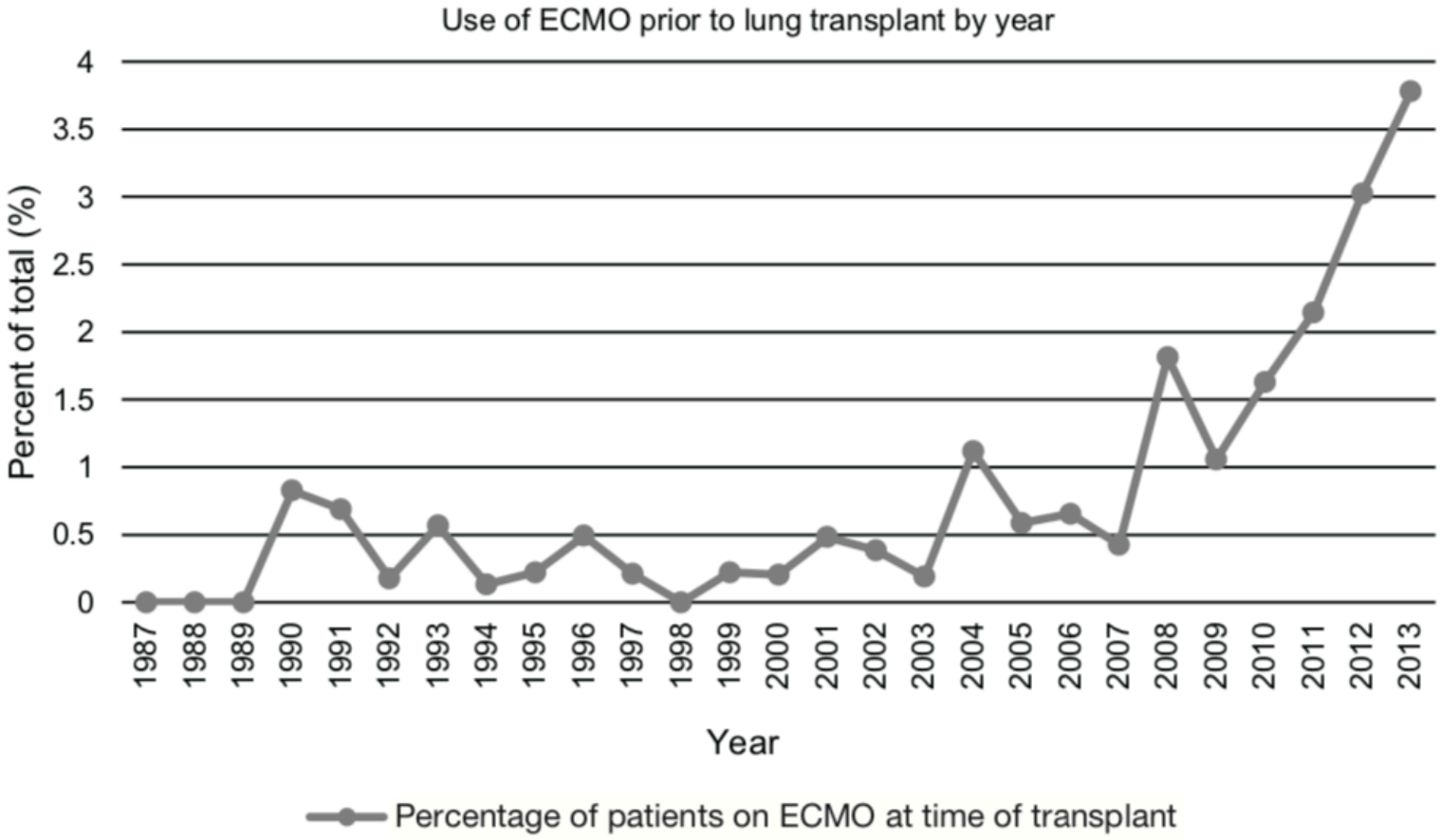
	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Centers	83	86	98	111	112	112	115	112	115	112	115	115	119	117	118	130	131	135	150	164	183	206	247	279	318	345	370	418	454	463
Runs	1644	1775	1933	1910	1880	1876	1868	1743	1720	1722	1862	1855	1908	1974	1925	2184	2346	2565	2803	3262	3445	4043	5152	6206	7728	9005	10462	12456	14205	15875

(c) 2020 Extracorporeal Life Support Organization



ECMO: Then and Now

Journal of Thoracic Disease, Vol 6, No 8 August 2014





Use of Extracorporeal Membrane Oxygenation as a Bridge to Primary Lung Transplant: 3 Consecutive, Successful Cases and a Review of the Literature

Andrew Jackson, MBBS, Jonathan Cropper, MSc, Roger Pye, MBBS, Frank Junius, MBBS, Monique Malouf, MBBS, and Allan Glanville, MBBS, MD

Many transplant centers have considered extracorporeal membrane oxygenation (ECMO) to be a contraindication to lung transplantation, due to historically poor outcomes. However, recent advances in the technical aspects of ECMO have enabled patients to be supported with relative safety for several weeks until a donor lung becomes available. We present 3 young patients with acute (in 1 case, acute on chronic), severe respiratory failure that was refractory to conventional ventilation, who were placed on venovenous ECMO. In each case, a clinical decision was made that the patient's respiratory failure was irreversible and they were successfully managed with urgent lung transplantation. J Heart Lung Transplant 2008;27:348–52. Copyright © 2008 by the International Society for Heart and Lung Transplantation.

J Heart Lung Transplant 2008;27:348–52. Copyright © 2008 I



Use of Extracorporeal Membrane Oxygenation as a Bridge to Primary Lung Transplant: 3 Consecutive, Successful Cases and a Review of the Literature

Andrew Jackson, MBBS, Jonathan Cropper, MSc, Roger Pye, MBBS, Frank Junius, MBBS, Monique Malouf, MBBS, and Allan Glanville, MBBS, MD

- 3 cases successfully bridge to transplant
  - 15 year old post-influenza staph pneumonia/ARDS
  - 18 year old post-influenza candida pneumonia/ARDS
  - 26 year old with ILD developed ARDS following urosepsis

J Heart Lung Transplant 2008;27:348-52. Copyright © 2008



Extracorporeal life support as a bridge to lung transplantation–experience of a high-volume transplant center

Konrad Hoetzenecker, MD, PhD,[a,b] Laura Donahoe, MD,[a] Jonathan C. Yeung, MD, PhD,[a] Sassan Azad, CRA,[a] Eddy Fan, MD,[c] Niall D. Ferguson, MD,[c] Lorenzo Del Sorbo, MD,[c] Marc de Perrot, MD,[a] Andrew Pierre, MD,[a] Kazuhiro Yasufuku, MD, PhD,[a] Lianne Singer, MD,[a] Thomas K. Waddell, MD, PhD,[a] Shaf Keshavjee, MD,[a] and Marcelo Cypel, MD, MSc, FRCSC[a]

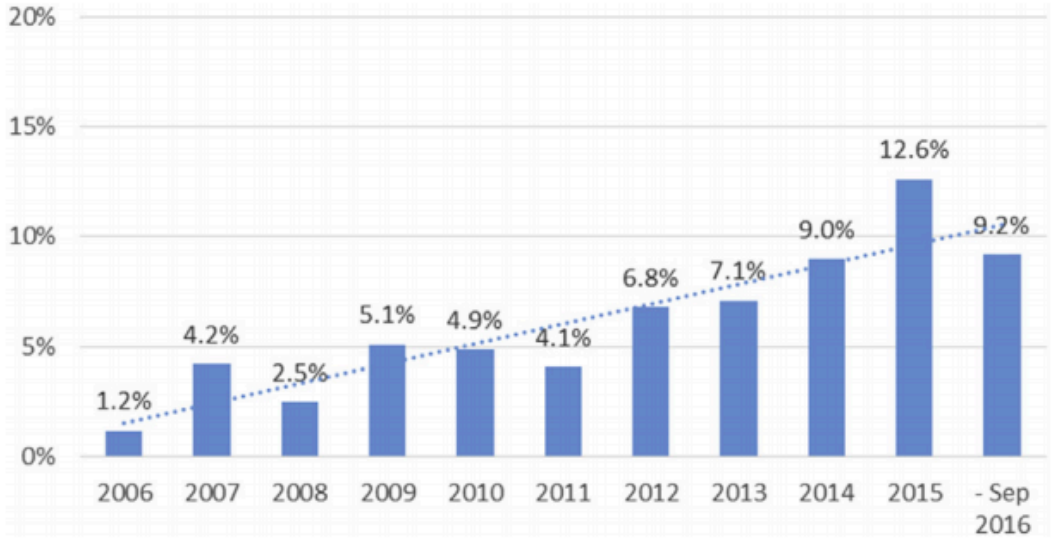
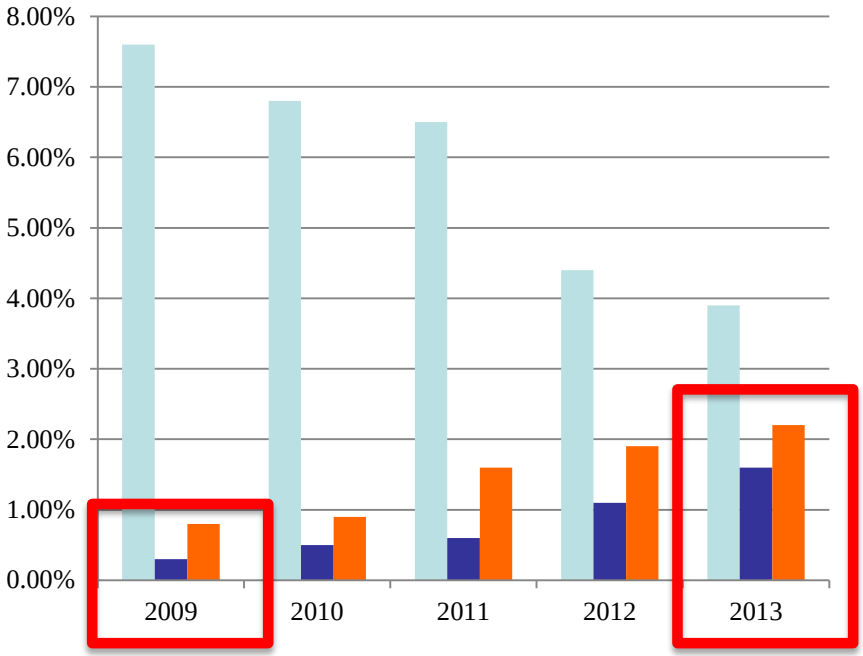


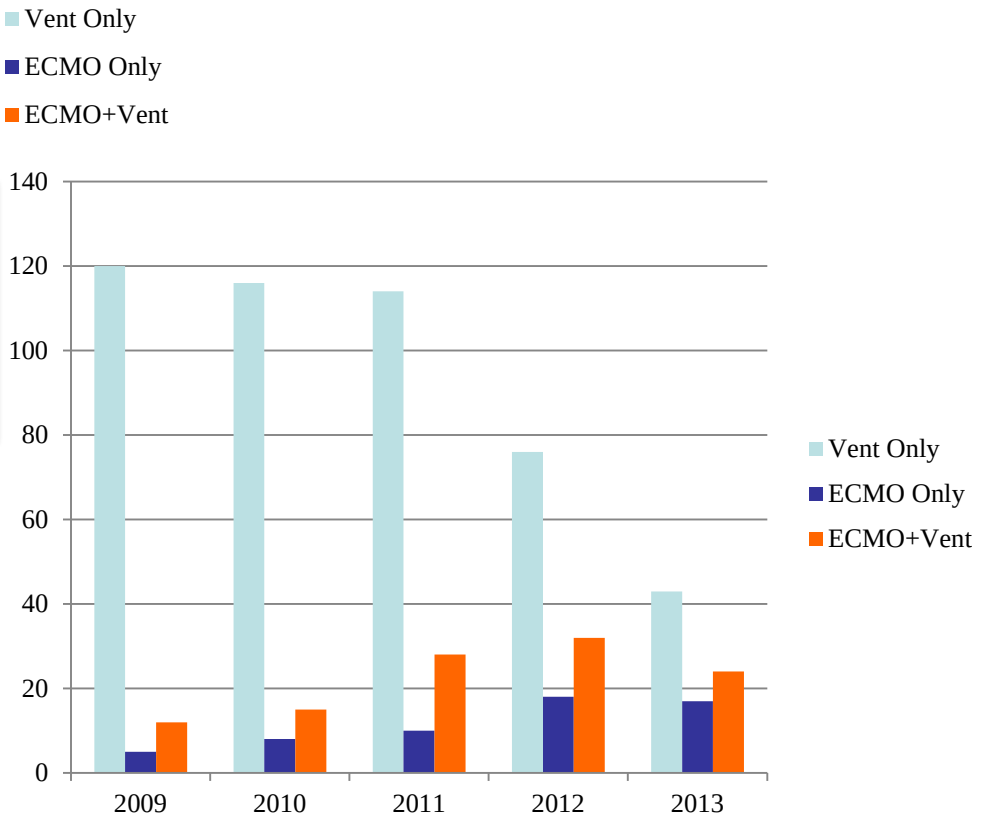
FIGURE 1. The percentage of patients bridged to transplant by extracorporeal life support in our institution. The proportion of extracorporeal life support bridging gradually increased over the years to approximately 10% of all lung transplant recipients.

J Thorac Cardiovasc Surg 2018;155:1316-28



Increasing use of ECMO bridge to Transplant







Extracorporeal Membrane Oxygenation in Awake Patients as Bridge to Lung Transplantation

Thomas Fuehner[1], Christian Kuehn[2], Johannes Hadem[3], Olaf Wiesner[1], Jens Gottlieb[1], Igor Tudorache[2], Karen M. Olsson[1], Mark Greer[1], Wiebke Sommer[2], Tobias Welte[1], Axel Haverich[2], Marius M. Hoeper[1], and Gregor Warnecke[2]

[1]Department of Respiratory Medicine, [2]Department of Cardiothoracic, Transplant and Vascular Surgery, and [3]Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany

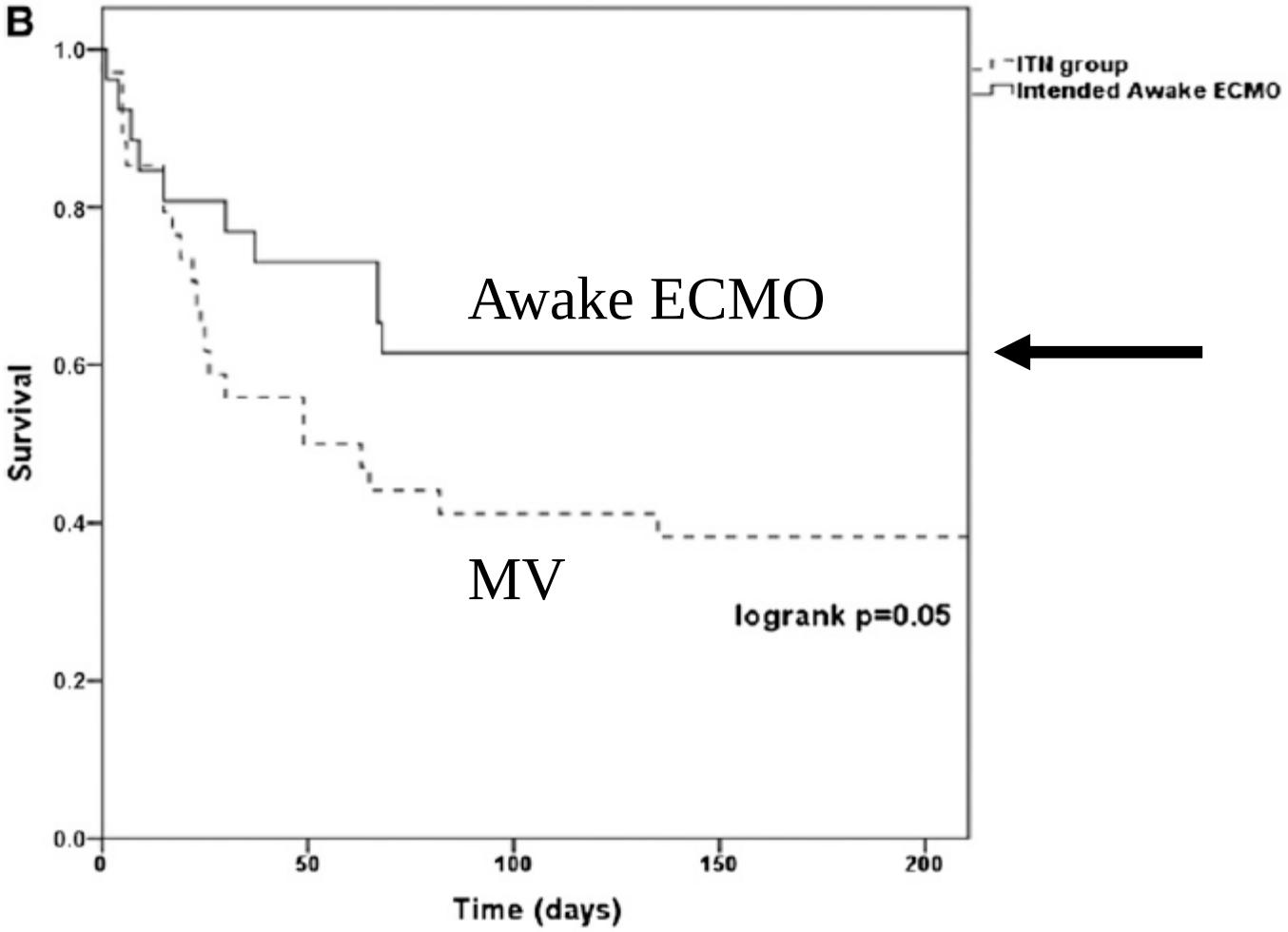
TABLE 1. COMPARISON OF PATIENT CHARACTERISTICS AND OUTCOMES IN THE AWAKE ECMO GROUP AND THE MECHANICAL VENTILATION GROUP

	Mechanical Ventilation Group	Awake ECMO Group	*P* Value
Baseline characteristics			
Patients, n	34	26	
Age, yr, median (range)	36 (18–59)	44 (23–62)	0.13

Am J Respir Crit Care Med Vol 185, Iss. 7, pp 763–768, Apr 1, 2012
Copyright © 2012 by the American Thoracic Society



Survival ECMO BTT vs Intubation group



Am J Respir Crit Care Med Vol 185, Iss. 7, pp 763–768, Apr 1, 2012
Copyright © 2012 by the American Thoracic Society



Active Rehabilitation During Extracorporeal Membrane Oxygenation as a Bridge to Lung Transplantation

Kyle J Rehder MD, David A Turner MD, Matthew G Hartwig MD, W Lee Williford RRT, Desiree Bonadonna CCP LP, Richard J Walczak Jr CCP, R Duane Davis MD, David Zaas MD, and Ira M Cheifetz MD FAARC

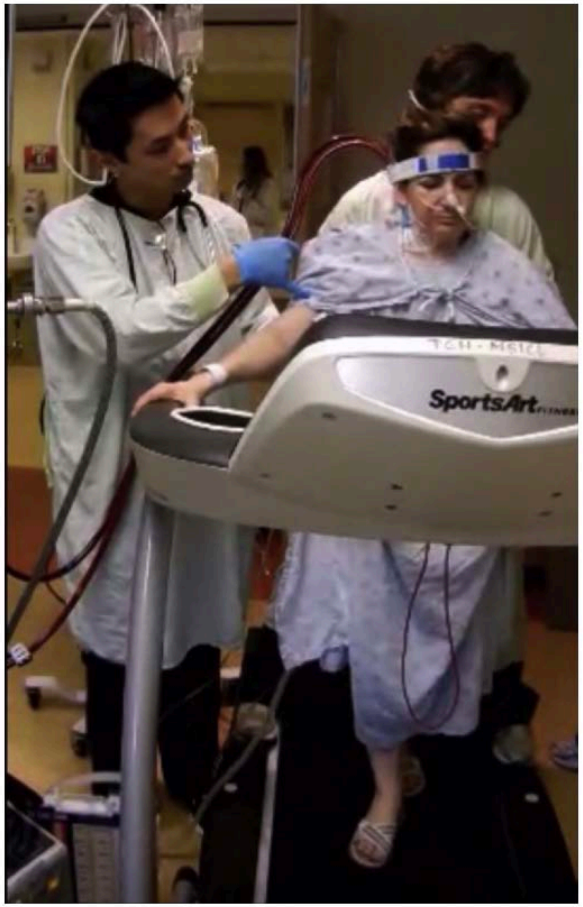
Table 4. Comparison of Outcomes by Cohort

	Control Cohort mean (range)	Rehabilitation Cohort mean (range)	*P*
FEV_1 (% predicted) at 3 months[27]	36 (25–44)	35 (21–43)	.65
FEV_1 (% predicted) at 12 months[27]	59 (43–66)	52 (34–70)	.66
Best FEV_1 (% predicted), any time in the first 12 months[27]	60 (43–69)	57 (43–70)	.80
Walk distance at discharge, m	213 (0–457)	780 (91–1,829)	.14
Total hospital stay, d	98 (51–151)	49 (31–63)	.05
Total ICU stay, d	49 (39–60)	27 (22–33)	.01
Days until free of mechanical ventilation for 48 h, post-transplant, d	34 (22–54)	4 (1–11)	.01
ICU stay post-transplant, d	45 (34–56)	11 (6–21)	.01
Days until tracheostomy removal, post-transplant, d	73 (44–104)	30 (13–46)	.04
Hospital stay, post-transplant, d	80 (45–110)	26 (13–33)	.01

[Respir Care 2013;58(8):1291–1298



Ambulatory ECMO



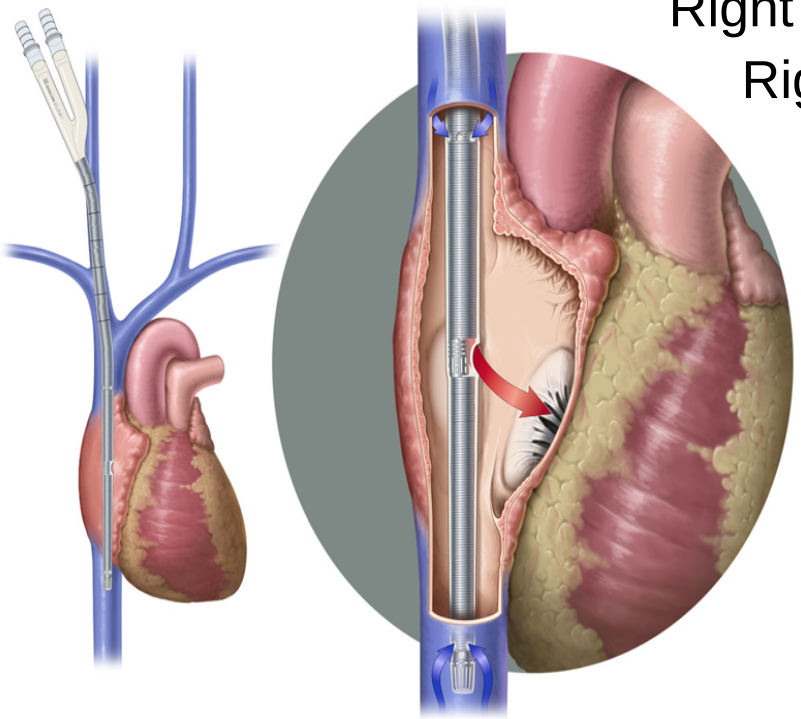
VIDEO 1. A patient bridged awake and mobilized with a single dual-lumen cannula. Video available at: http://www.jtcvsonline.org/article/S0022-5223(17)32720-4/fulltext.





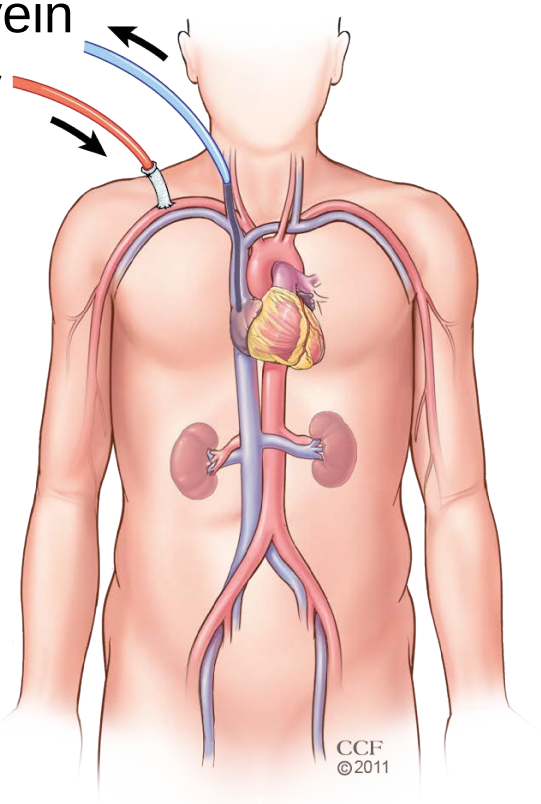
ECMO: Now

- Appropriate cannulation strategies allow for possible ambulation while on VV or VA ECMO.



Right internal jugular vein

Right axillary artery





Extracorporeal life support as a bridge to lung transplantation–experience of a high-volume transplant center

Konrad Hoetzenecker, MD, PhD,[a,b] Laura Donahoe, MD,[a] Jonathan C. Yeung, MD, PhD,[a] Sassan Azad, CRA,[a] Eddy Fan, MD,[c] Niall D. Ferguson, MD,[c] Lorenzo Del Sorbo, MD,[c] Marc de Perrot, MD,[a] Andrew Pierre, MD,[a] Kazuhiro Yasufuku, MD, PhD,[a] Lianne Singer, MD,[a] Thomas K. Waddell, MD, PhD,[a] Shaf Keshavjee, MD,[a] and Marcelo Cypel, MD, MSc, FRCSC[a]

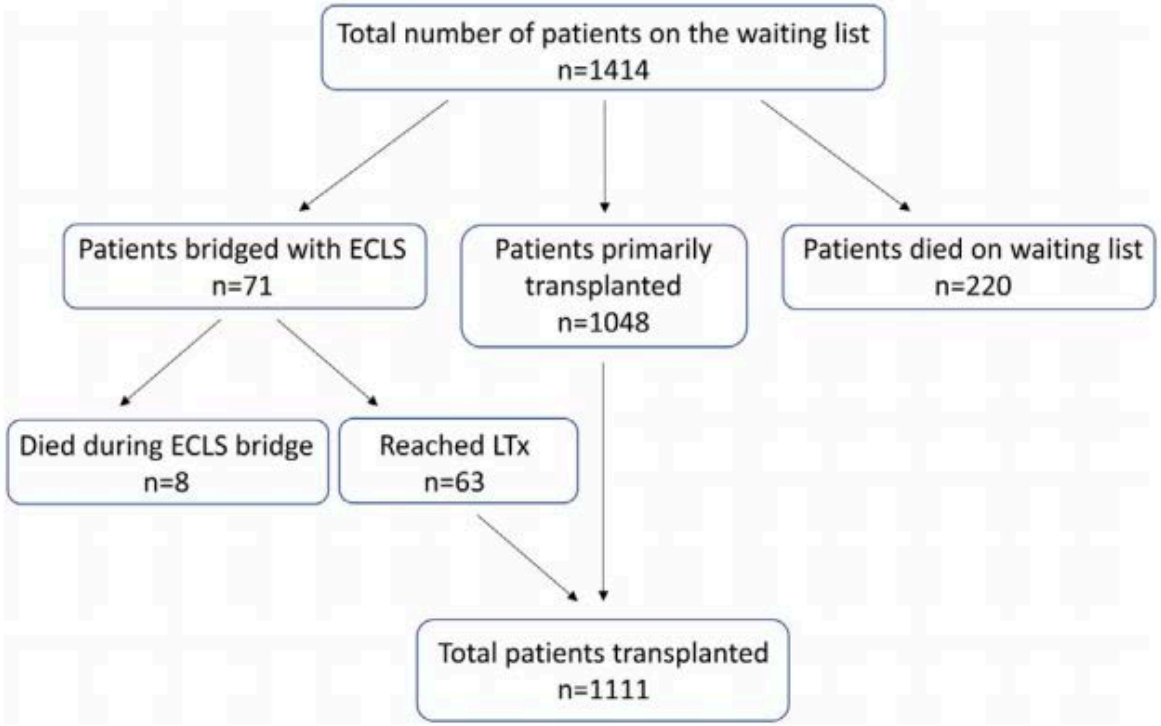
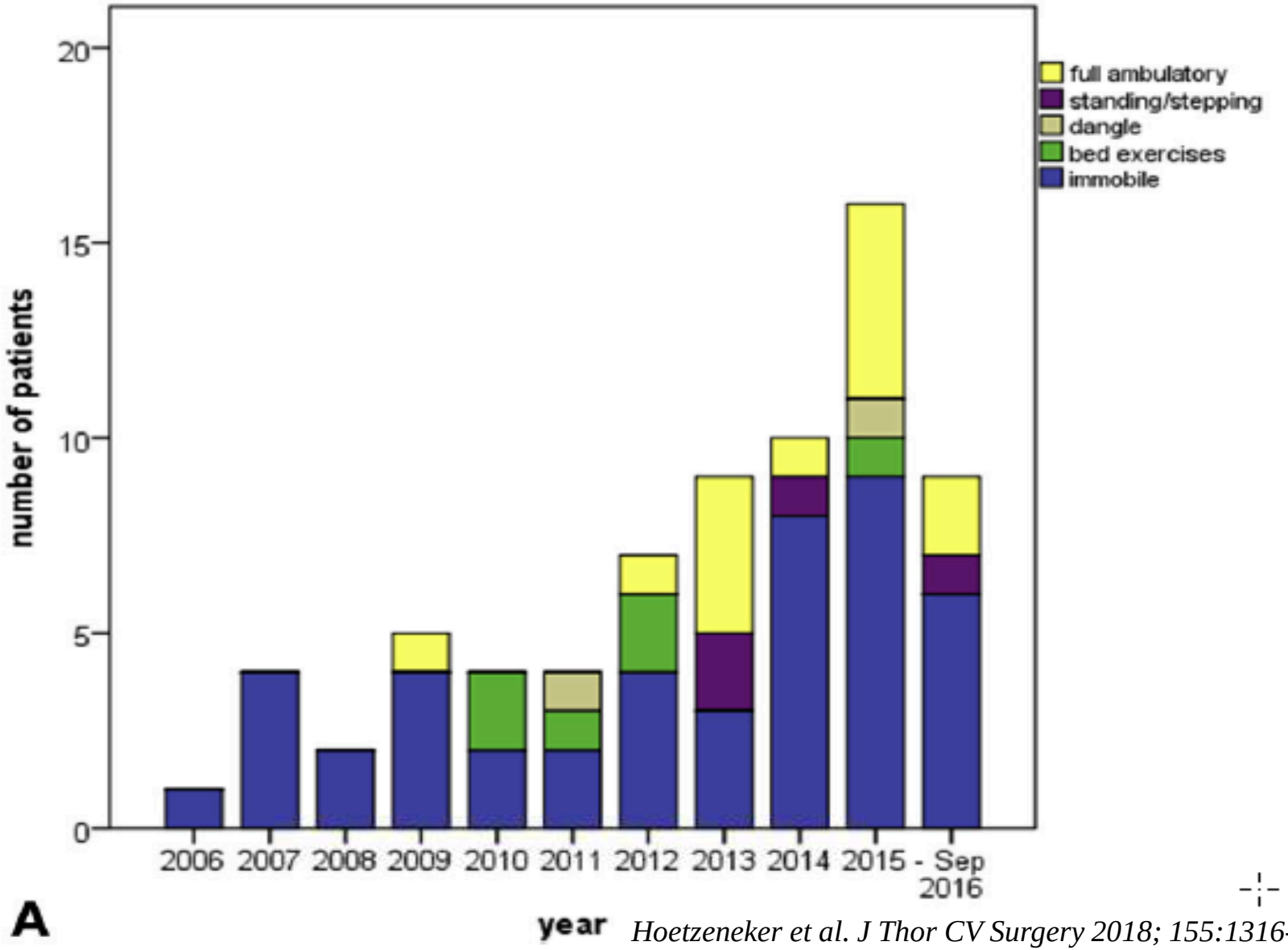


FIGURE E1. Flow chart of patients included in the study. *ECLS*, Extracorporeal life support; *LTx*, lung transplantation.

J Thorac Cardiovasc Surg 2018;155:1316-28



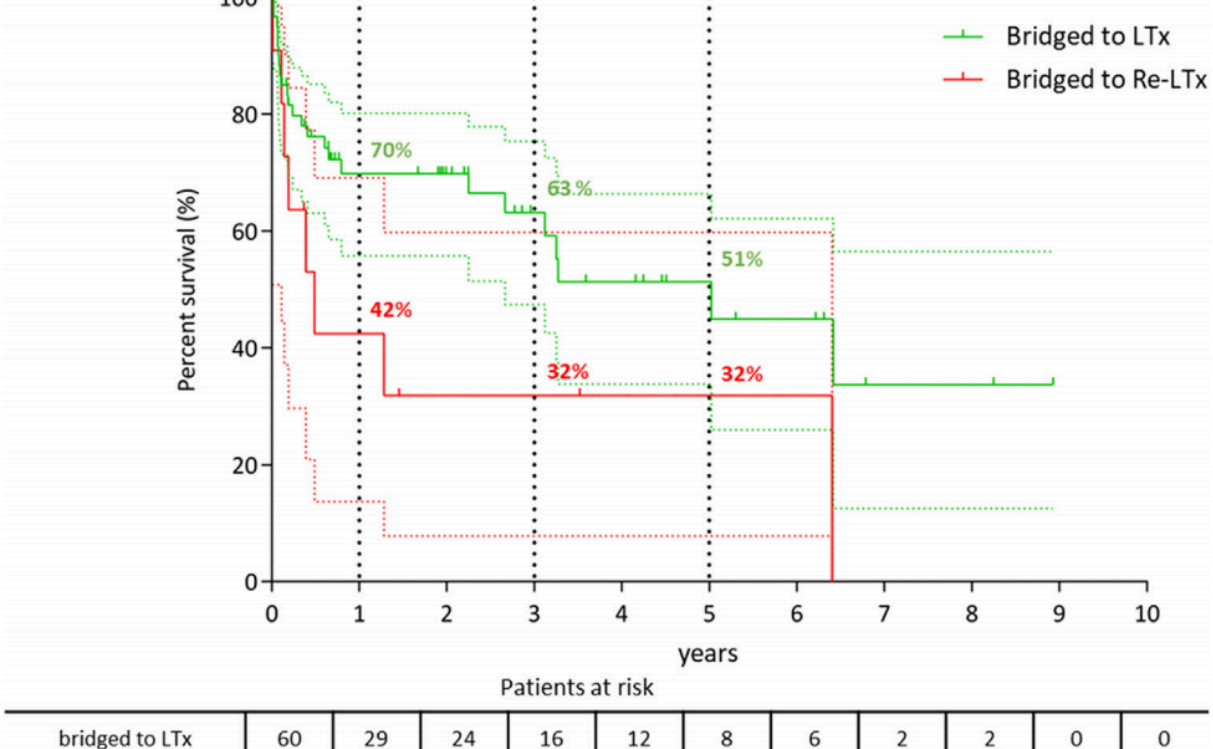


Hoetzeneker et al. J Thor CV Surgery 2018; 155:1316-28



Extracorporeal life support as a bridge to lung transplantation—experience of a high-volume transplant center

Konrad Hoetzenecker, MD, PhD,[a,b] Laura Donahoe, MD,[a] Jonathan C. Yeung, MD, PhD,[a] Sassan Azad, CRA,[a] Eddy Fan, MD,[c] Niall D. Ferguson, MD,[c] Lorenzo Del Sorbo, MD,[c] Marc de Perrot, MD,[a] Andrew Pierre, MD,[a] Kazuhiro Yasufuku, MD, PhD,[a] Lianne Singer, MD,[a] Thomas K. Waddell, MD, PhD,[a] Shaf Keshavjee, MD,[a] and Marcelo Cypel, MD, MSc, FRCSC[a]



Patients at risk

bridged to LTx	60	29	24	16	12	8	6	2	2	0	0
Bridged to Re-LTx	11	4	2	2	1	1	1	0	0	0	0

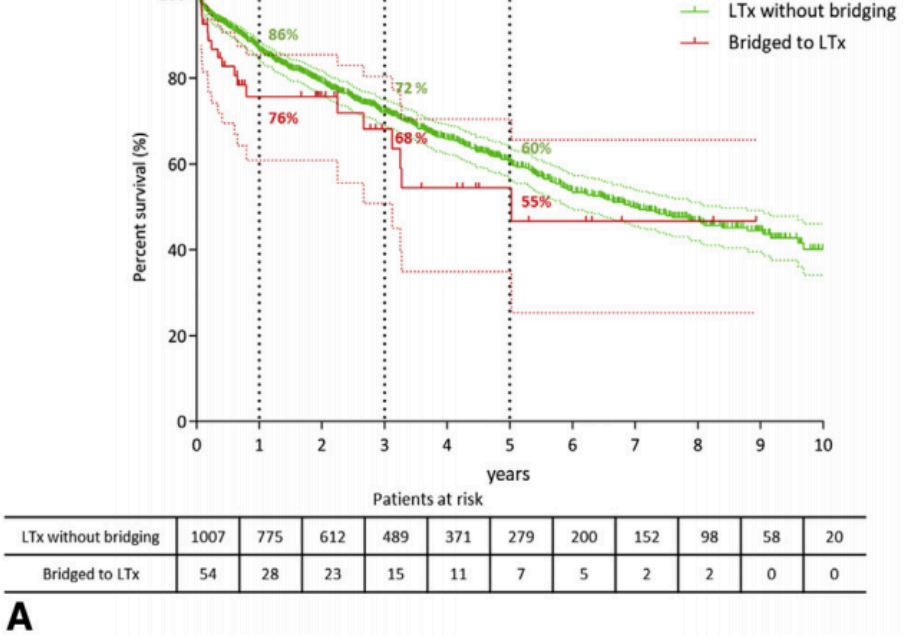
FIGURE 4. Survival curves of bridged patients by intention to treat. Patients bridged to their first transplant had good outcome with 1-year, 3-year, and 5-year survival of 70%, 63%, and 51%. Survival was significantly lower for patients bridged to retransplantation (1-year, 42%; 3-year, 32%; 5-year, 32%; $P = .041$). *LTx*, Lung transplantation.

J Thorac Cardiovasc Surg 2018;155:1316-28



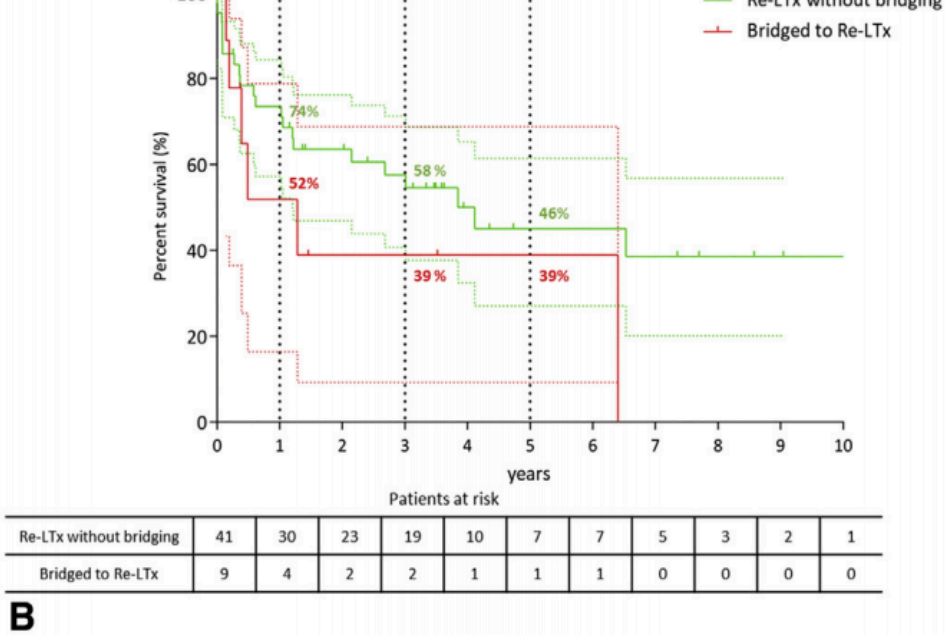
Extracorporeal life support as a bridge to lung transplantation–experience of a high-volume transplant center

Konrad Hoetzenecker, MD, PhD,[a,b] Laura Donahoe, MD,[a] Jonathan C. Yeung, MD, PhD,[a] Sassan Azad, CRA,[a] Eddy Fan, MD,[c] Niall D. Ferguson, MD,[c] Lorenzo Del Sorbo, MD,[c] Marc de Perrot, MD,[a] Andrew Pierre, MD,[a] Kazuhiro Yasufuku, MD, PhD,[a] Lianne Singer, MD,[a] Thomas K. Waddell, MD, PhD,[a] Shaf Keshavjee, MD,[a] and Marcelo Cypel, MD, MSc, FRCSC[a]



LTx without bridging	1007	775	612	489	371	279	200	152	98	58	20
Bridged to LTx	54	28	23	15	11	7	5	2	2	0	0

A



Re-LTx without bridging	41	30	23	19	10	7	7	5	3	2	1
Bridged to Re-LTx	9	4	2	2	1	1	1	0	0	0	0

B

FIGURE 5. Survival curves for transplanted patients. Patients successfully bridged to their first transplant had only a slightly impaired prognosis compared with nonbridged transplant recipients (A). Survival was lower for retransplantations, both in the bridged and in the nonbridged group (B). *LTx*, Lung transplantation.

J Thorac Cardiovasc Surg 2018;155:1316-28



Extracorporeal life support as a bridge to lung transplantation–experience of a high-volume transplant center

Konrad Hoetzenecker, MD, PhD,[a,b] Laura Donahoe, MD,[a] Jonathan C. Yeung, MD, PhD,[a] Sassan Azad, CRA,[a] Eddy Fan, MD,[c] Niall D. Ferguson, MD,[c] Lorenzo Del Sorbo, MD,[c] Marc de Perrot, MD,[a] Andrew Pierre, MD,[a] Kazuhiro Yasufuku, MD, PhD,[a] Lianne Singer, MD,[a] Thomas K. Waddell, MD, PhD,[a] Shaf Keshavjee, MD,[a] and Marcelo Cypel, MD, MSc, FRCSC[a]

TABLE 1. Modes of extracorporeal life support and their indications for bridging

	Hypercapnic failure	Hypoxemic failure	IPAH: decompensated RV	IPAH: biventricular failure
Pumpless AV Novalung	Yes	No	No	No
Hemolung	Yes	No	No	No
VV ECMO (single dual-lumen cannula)	Yes	Mostly (mild-moderate)	No	No
VV ECMO	Yes	Yes (severe)	No	No
PA/LA Novalung	No	No	Yes	No
VA ECMO	Yes	Yes (only when with concomitant cardiac failure)	Yes (temporary)	Yes

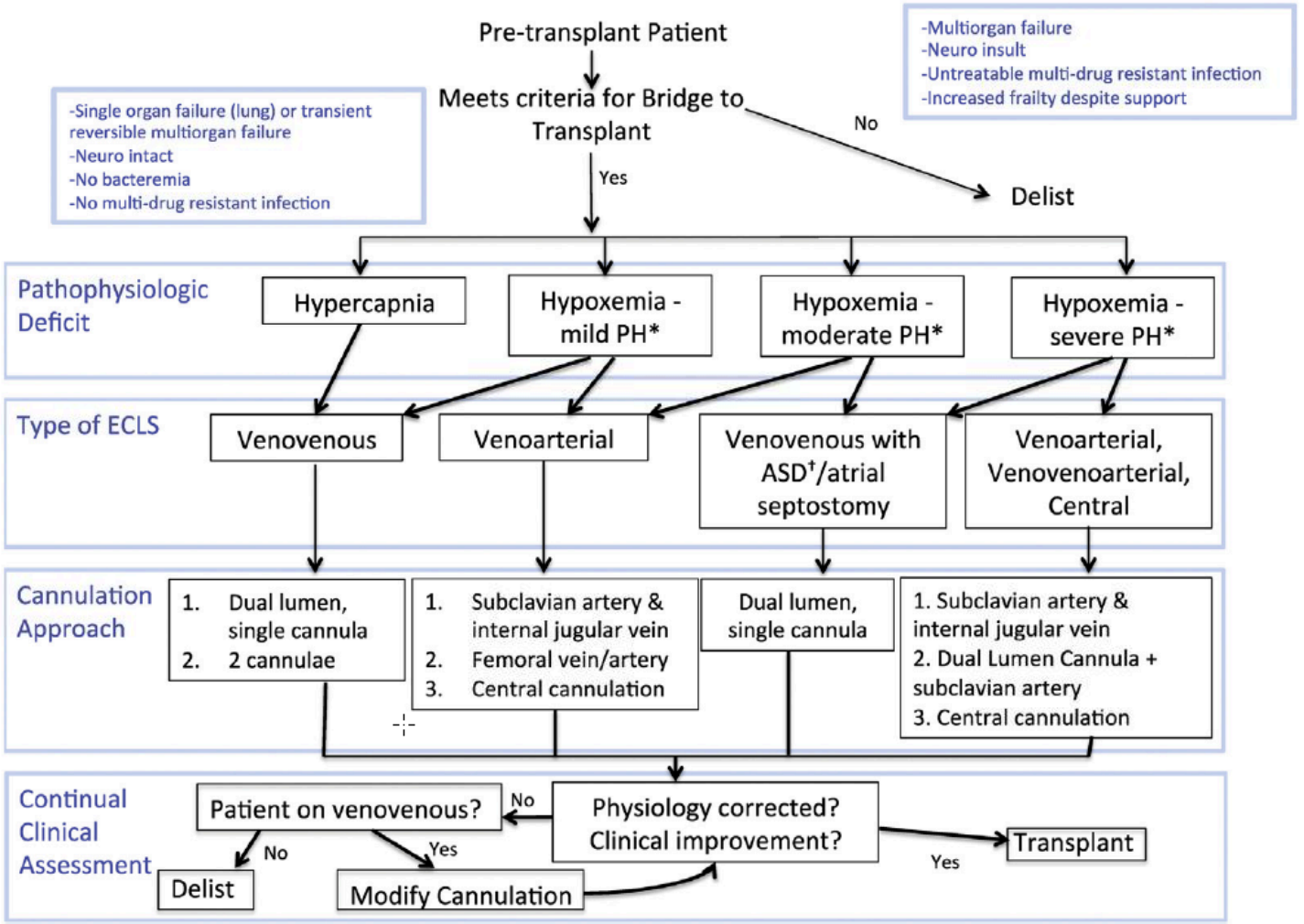
IPAH, Idiopathic pulmonary arterial hypertension; *RV*, right ventricle; *AV*, arteriovenous; *VV*, venovenous; *ECMO*, extracorporeal membrane oxygenation; *PA*, pulmonary artery; *LA*, left atrium; *VA*, venoarterial.

J Thorac Cardiovasc Surg 2018;155:1316-28



Proposed bridge to transplant algorithm

*Fig 1. Bridge to transplantation decision algorithm. *Pulmonary hypertension (PH). †Atrial septal defect (ASD). (ECLS = extracorporeal life support.)*



Biscotti et al. Ann Thorac Surg 2017;104:412–9



Other things to consider prior to bridging

- Age of recipient is major predictor of success
  - Age over 60 in particular with increased hazard ratio 3.0 compared to < 40 years old.

Influence of age on survival in adult patients on extracorporeal membrane oxygenation before lung transplantation
Hayes, Don et al.
The Journal of Heart and Lung Transplantation , Volume 34 , Issue 6 , 832 - 838

- Active rehab optimal, but awake ECMO better than alternative

- Avoid re-transplantation bridging if possible



The Recipient Stratification Risk Analysis in Bridging Patients to Lung Transplant on ECMO (STABLE Score)

- SRTR Database Analysis
  - 2004-2018
  - 630 ECMO BTT
  - Excluded Re-do LTx

(Ann Thorac Surg 2020;110:1175-84)



STABLE Score

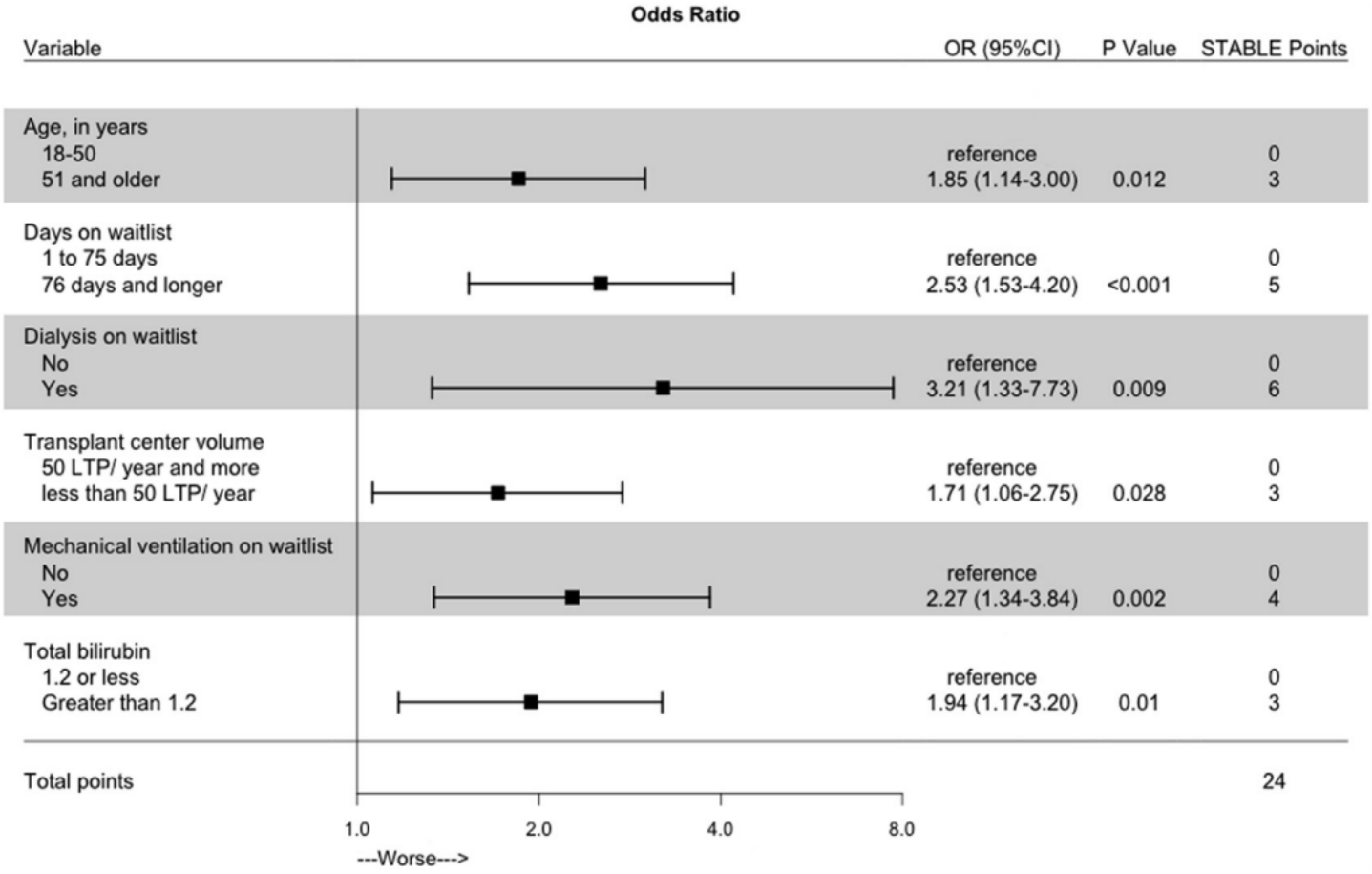
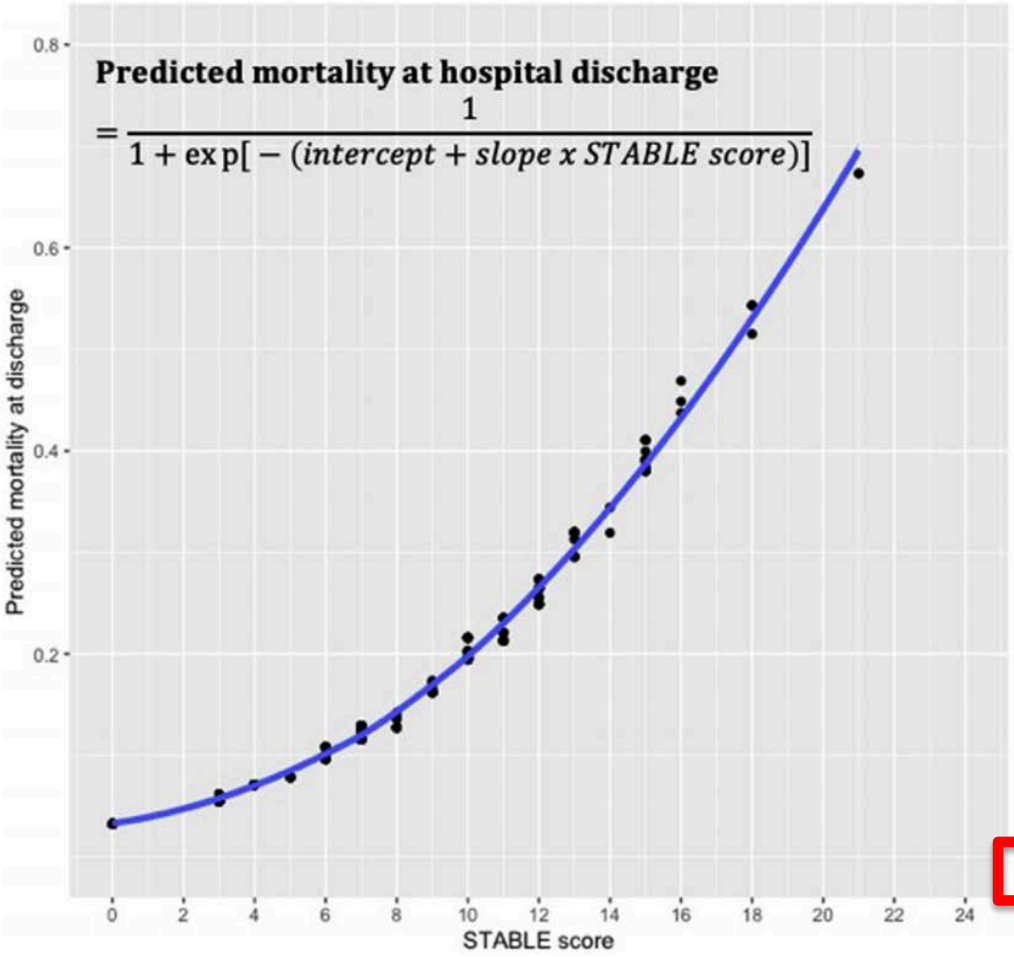


Figure 2. Multivariable logistic regression used to generate the Recipient Stratification Risk Analysis in Bridging Patients to Lung Transplant on ECMO (STABLE) recipient risk score. (OR, odds ratio; LTP, lung transplantation.)

(Ann Thorac Surg 2020;110:1175-84)



STABLE Score



STABLE score	Predicted mortality
0	3.27%
1	3.95%
2	4.77%
3	5.74%
4	6.89%
5	8.26%
6	9.86%
7	11.75%
8	13.93%
9	16.45%
10	19.34%
11	22.55%
12	26.15%
13	30.10%
14	34.37%
15	38.90%
16	43.64%
17	48.50%
18	53.38%
19	58.21%
20	62.88%
21	67.32%
22	71.47%
23	75.29%
24	78.74%

Figure 5. Predicted mortality from the risk score model. The equation predicting in-hospital mortality is given along with the predicted mortality for each 1-point increase in Recipient Stratification Risk Analysis in Bridging Patients to Lung Transplant on ECMO (STABLE) score.

(Ann Thorac Surg 2020;110:1175-84)



Bilateral pneumonectomy to treat uncontrolled sepsis in a patient awaiting lung transplantation

Marcelo Cypel, MD,[a,b] Thomas Waddell, MD,[a,b] Lianne G. Singer, MD,[a,c] Lorenzo del Sorbo, MD,[d] Eddy Fan, MD,[d] Matthew Binnie, MD,[a,c] Niall D. Ferguson, MD,[d] and Shaf Keshavjee, MD,[a,b] Toronto, Ontario, Canada

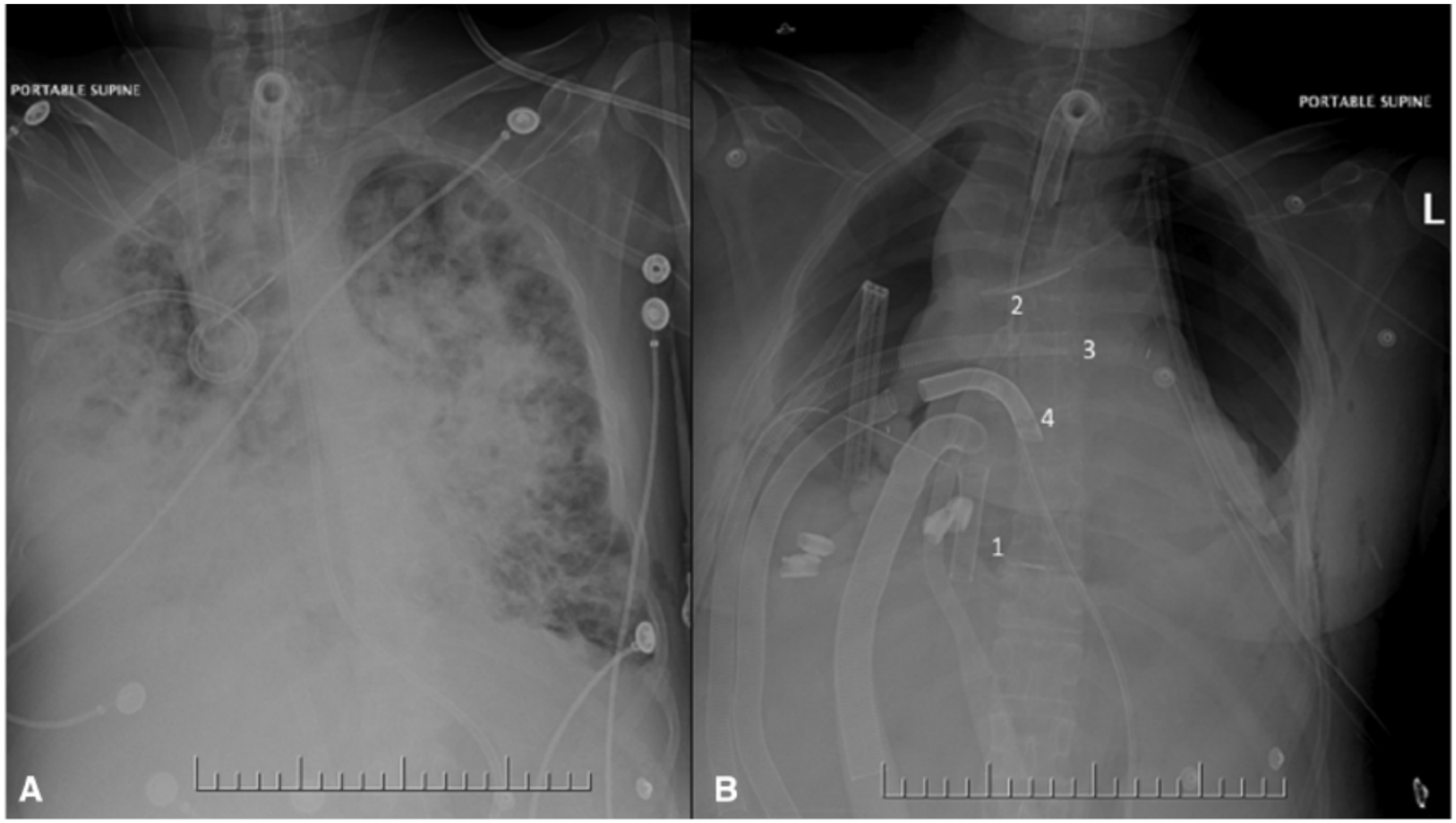


FIGURE 1. A, Severe pneumonia in the background of end-stage cystic fibrosis. B, Patient in the intensive care unit with no lungs for 6 days. *1*, Right atrial venous drainage cannula; *2*, aortic return cannula; *3*, pulmonary arterial cannula; *4*, pulmonary vein arterial cannula (left atrial).

J Thorac Cardiovasc Surg 2017;153:e67-9



Bilateral pneumonectomy to treat uncontrolled sepsis in a patient awaiting lung transplantation

Marcelo Cypel, MD,[a,b] Thomas Waddell, MD,[a,b] Lianne G. Singer, MD,[a,c] Lorenzo del Sorbo, MD,[d] Eddy Fan, MD,[d] Matthew Binnie, MD,[a,c] Niall D. Ferguson, MD,[d] and Shaf Keshavjee, MD,[a,b] Toronto, Ontario, Canada

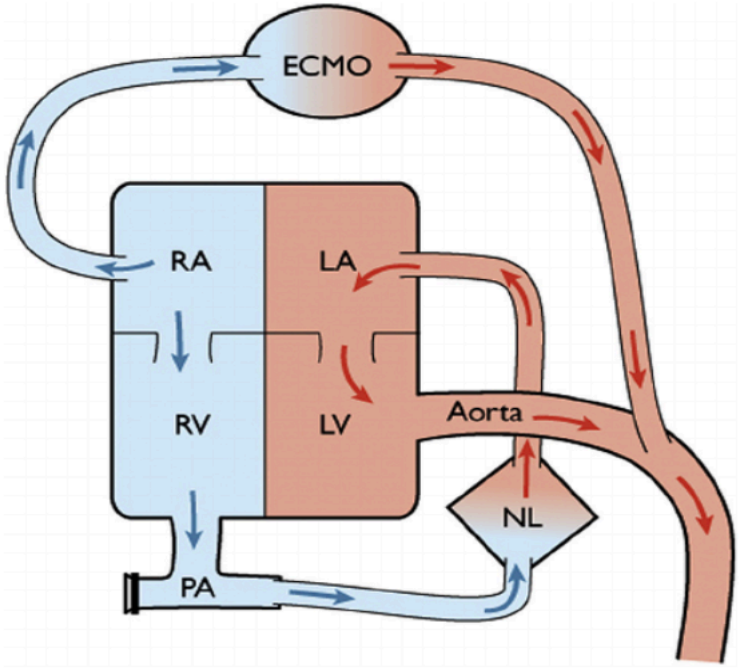


FIGURE 2. Diagram of mechanical support before transplantation in the absence of lungs. Flow is directed from the right ventricle to the aorta in a standard veno-arterial extracorporeal membrane oxygenation configuration. Residual flow passing from the right atrium to the pulmonary artery is then shunted and oxygenated via the Novalung to the left atrium, allowing the right ventricle to provide pulsatility against a low-resistance system. *ECMO*, Extracorporeal membrane oxygenation; *RA*, right atrium; *LA*, left atrium; *RV*, right ventricle; *LV*, left ventricle; *PA*, pulmonary artery; *NL*, Novalung.

J Thorac Cardiovasc Surg 2017;153:e67-9



The Science and Ethics of ECMO Candidacy

Patient DS: 30 y/o CF from Northeast transferred on bipap for acute decompensation and emergent listing with history of colonization with MDR Burkohlderia, pseudomonas, and MRSA.

- Worsening respiratory status requiring intubation followed by VV ECMO
- Transition to Avalon cannula in left SCV and tracheostomy
- Actively rehabbing on ECMO, listed for transplant, but developed persistently positive blood cultures with Burkholderia.
- Inactivated until blood cultures clear, but they wouldn't clear



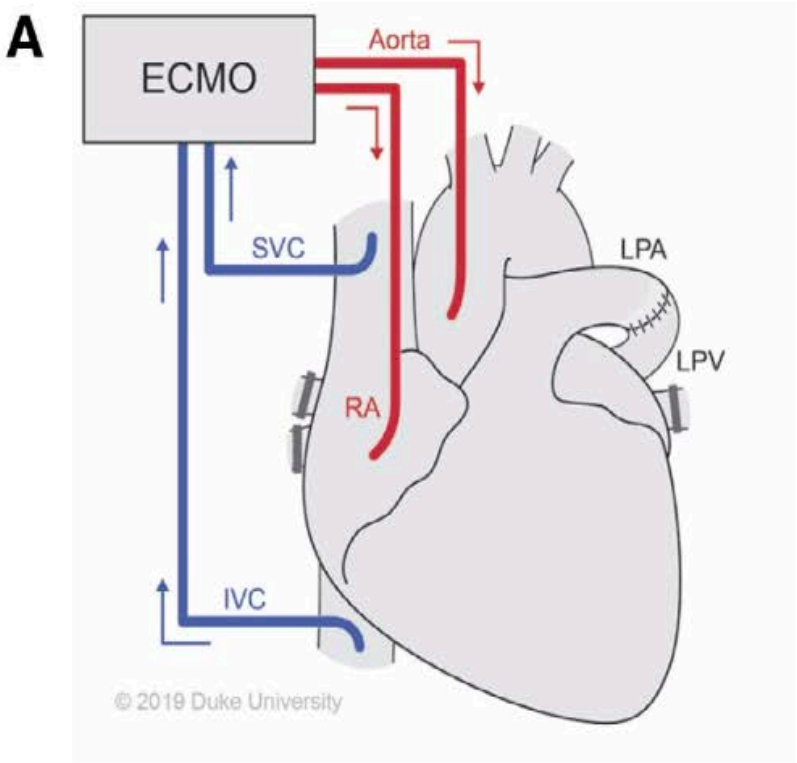
The Science and Ethics of ECMO Candidacy

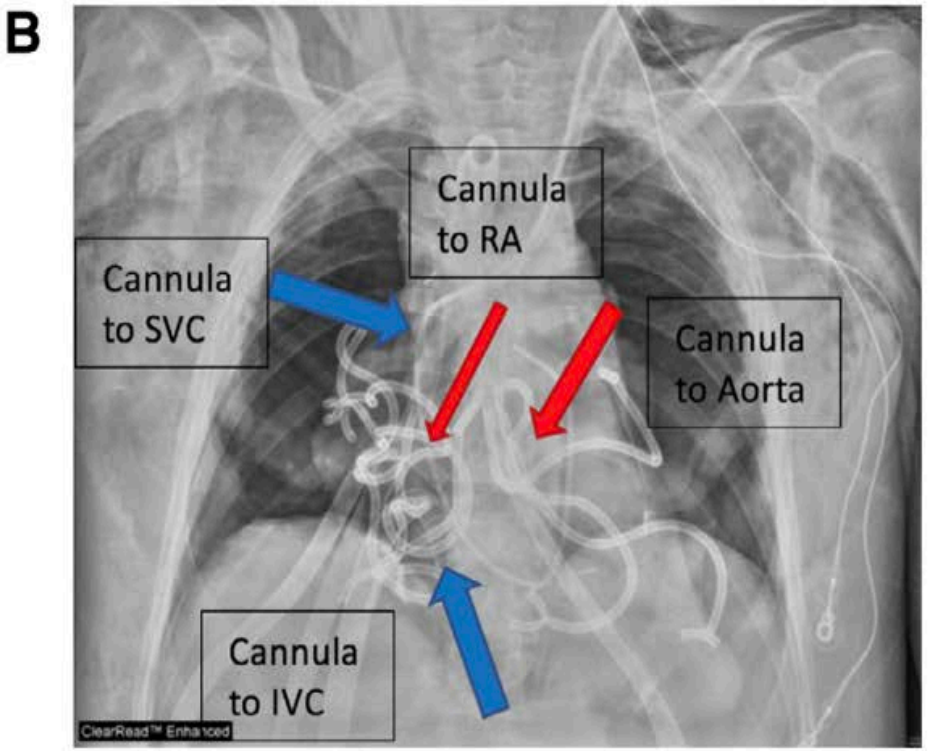


Pre-tx Left SCV Avalon ECMO



The Science and Ethics of ECMO Candidacy



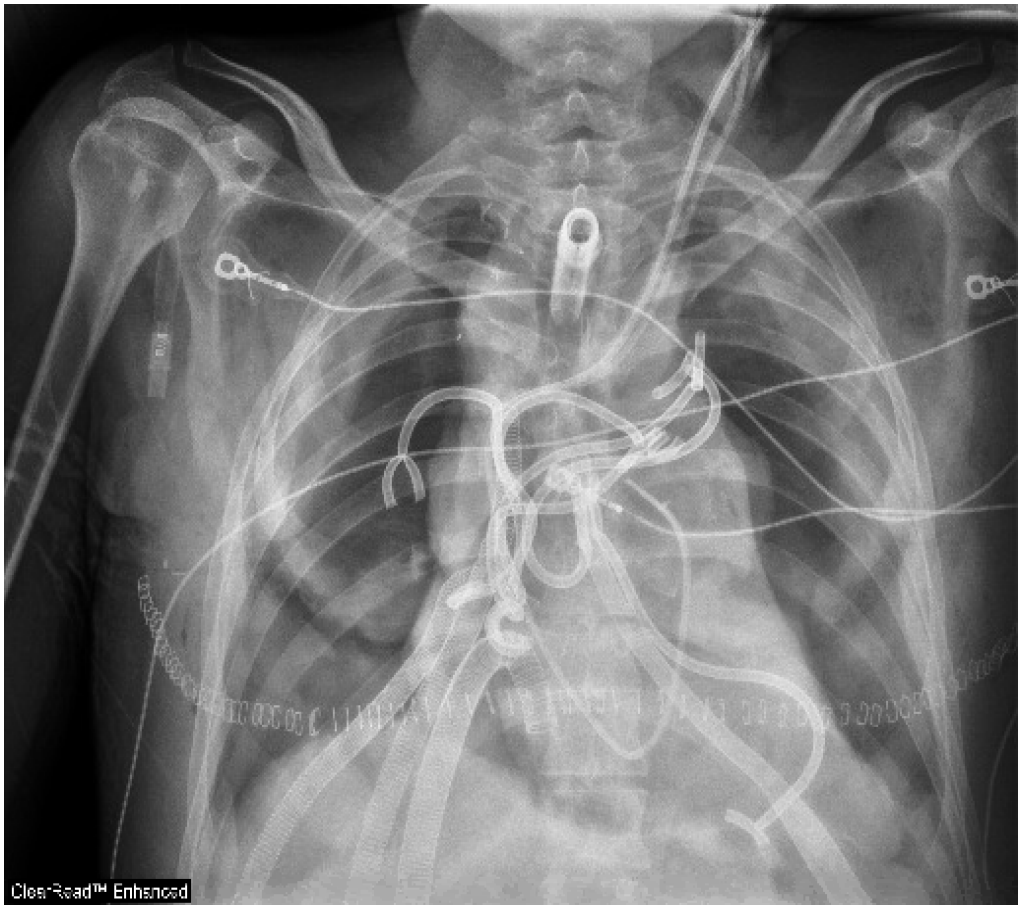


Intraop ECMO Cannulation Strategy

The Journal of Heart and Lung Transplantation, Vol 38, No 11, November 2019



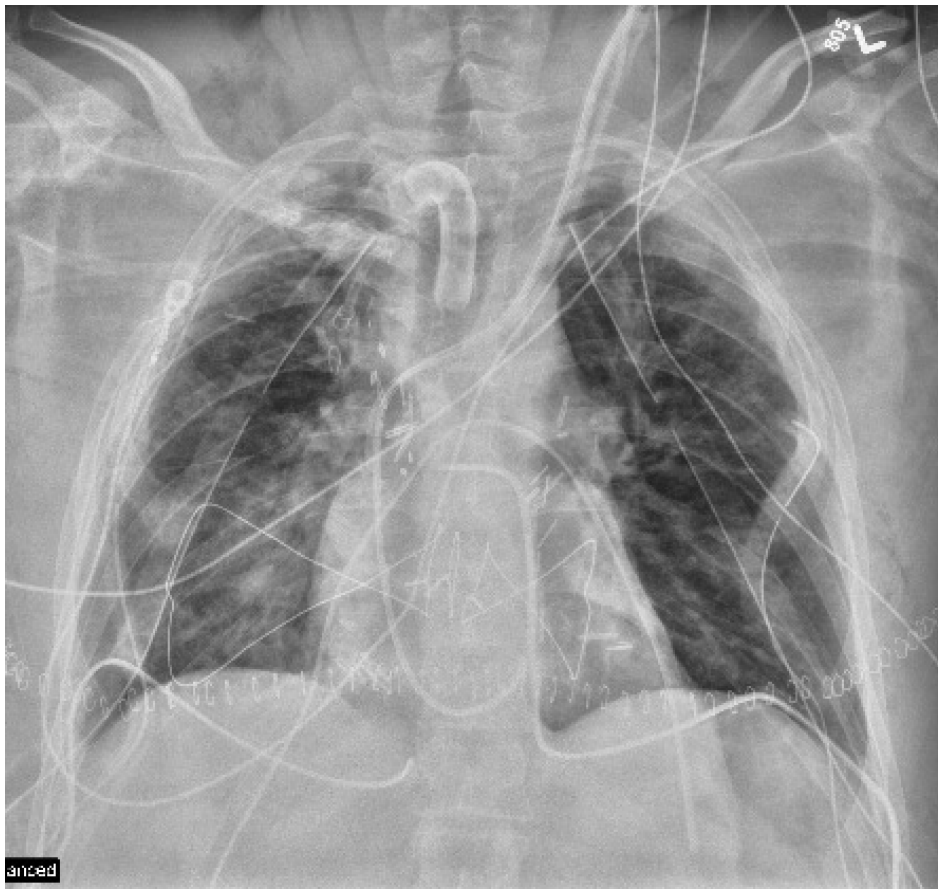
The Science and Ethics of ECMO Candidacy



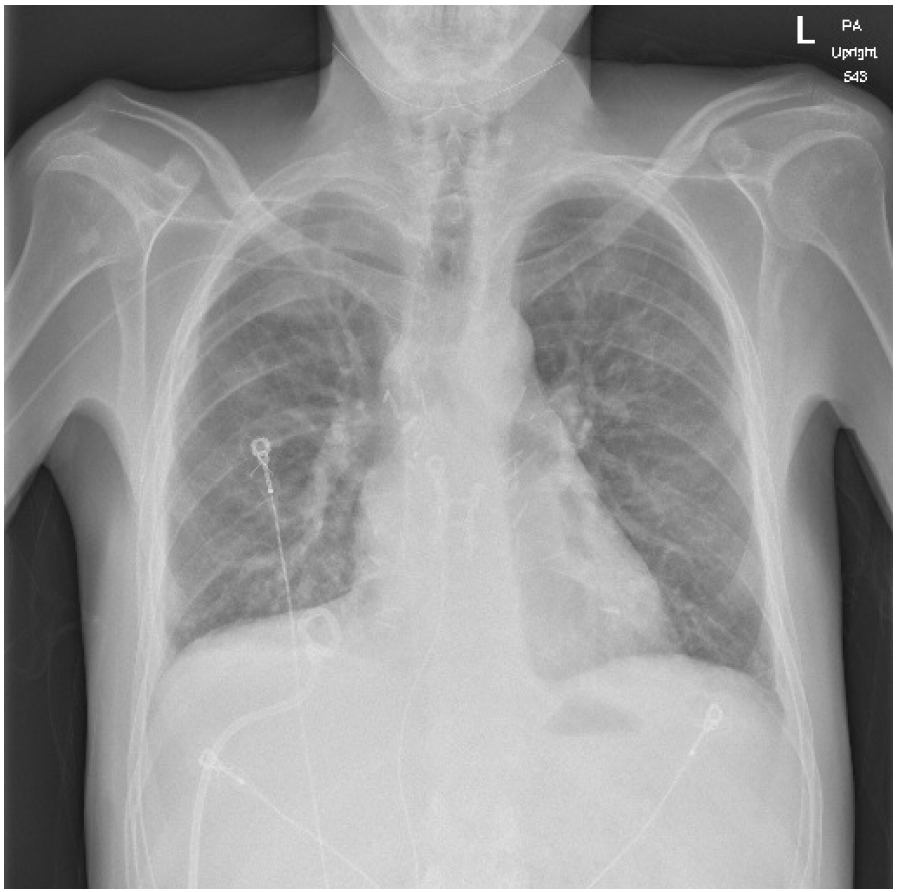
Pre-tx, post bilateral pneumonectomies on VAV ECMO with LPA-LPV fistula



The Science and Ethics of ECMO Candidacy



Post-Tx Postop



Post-Tx 3 months



The Science and Ethics of ECMO Candidacy



Post-Tx 6 months Postop
With new baby



Has Covid-19 C ECMO BTT?





Has Covid-19 Changed ECMO BTT?
ECMO BTT for ARDS Pre-Covid

ORIGINAL ARTICLE

AJT

Lung transplantation for acute respiratory distress syndrome: A multicenter experience

Anna E. Frick[1,2] | Christiaan T. Gan[3] | Robin Vos[4,5] | Stefan Schwarz[1] | Felix Kraft[6] | Daria Kifjak[7] | Arne P. Neyrinck[2] | Dirk E. Van Raemdonck[4,8] | Walter Klepetko[1] | Peter Jaksch[1] | Erik A. M. Verschuuren[3] | Konrad Hoetzenecker[1]

Am J Transplant. 2022;22:144–153.



Has Covid-19 Changed ECMO BTT?
ECMO BTT for ARDS Pre-Covid

ORIGINAL ARTICLE

AJT

Lung transplantation for acute respiratory distress syndrome: A multicenter experience

Anna E. Frick[1,2] | Christiaan T. Gan[3] | Robin Vos[4,5] | Stefan Schwarz[1] | Felix Kraft[6] | Daria Kifjak[7] | Arne P. Neyrinck[2] | Dirk E. Van Raemdonck[4,8] | Walter Klepetko[1] | Peter Jaksch[1] | Erik A. M. Verschuuren[3] | Konrad Hoetzenecker[1]

- 3 large centers in Eurotransplant
  - 1998-2020 (22 years)
  - 13 patients transplanted for ARDS

Am J Transplant. 2022;22:144–153.



Has Covid-19 Changed ECMO BTT?
ECMO BTT for ARDS Pre-Covid

TABLE 1 Recipient characteristics

Number of patients	13
Recipient	
Age, years	29.2 (±3.6)
Gender, female (%)	8 (61.5)
BMI	23.1 (±1.2)
Underlying disease, *n* (%)	
Cytomegalovirus	1 (7.7)
H1N1 influenza	4 (30.8)
H3N1 influenza	1 (7.7)
Covid-19 infection	1 (7.7)
ARDS after abdominal sepsis	1 (7.7)
Pneumonia	5 (38.5)
At time of listing	
MV, *n* (%)	13 (100)
MV, days	43 (34–56.5)
ECLS support, *n* (%)	11 (84.6)
ECLS support, days	35 (16–42.5)

Am J Transplant. 2022;22:144–153.



Has Covid-19 Changed ECMO BTT?
ECMO BTT for ARDS Pre-Covid

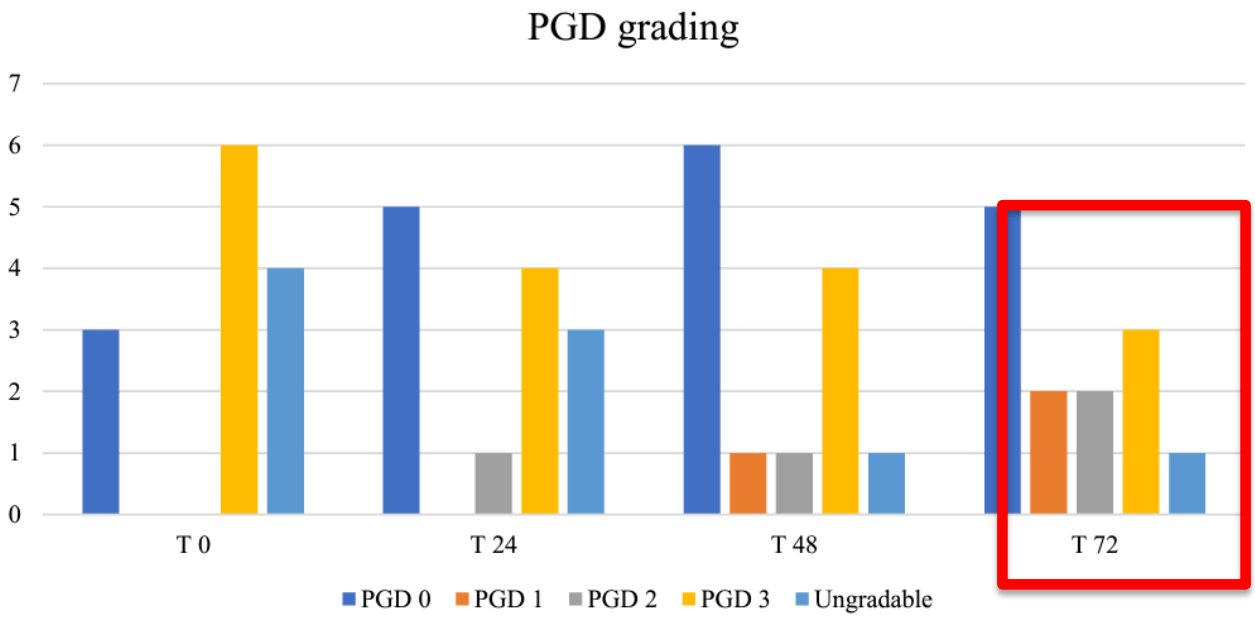


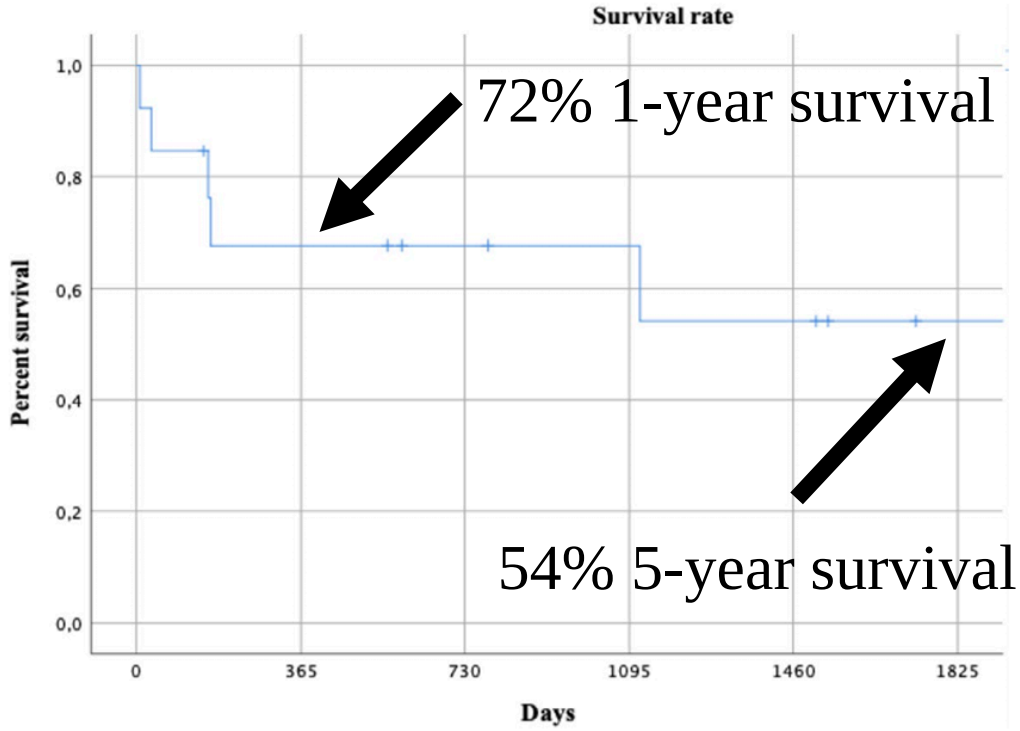
FIGURE 1 PGD grading: PGD grading according to the ISHLT guidelines[21] within the first 72 h postoperative for all 13 patients. Four out of 13 (30.8%) patients with a prolonged prophylactic ECMO support were graded as PGD "ungradable" at T 24 h. PGD grade 3 was seen in 6 (46.2%) patients. Graft function improved significantly thereafter and only three patients remained in PGD 3 at T72 h

Am J Transplant. 2022;22:144–153.



Has Covid-19 Changed ECMO BTT?
ECMO BTT for ARDS Pre-Covid

FIGURE 2 Survival curve 1998–2020: Kaplan–Meier survival curve of all 13 ARDS patients who received a lung transplantation demonstrates 1-year and 5-year survival rates of 71.6% and 54.2%, respectively [Color figure can be viewed at wileyonlinelibrary.com]



Am J Transplant. 2022;22:144–153.



Has Covid-19 Changed ECMO BTT?
ECMO BTT for Covid-19 ARDS

Lung transplantation for severe COVID-19-related ARDS

Ryoung-Eun Ko[1], Dong Kyu Oh[2], Sun Mi Choi [3], Sunghoon Park[4], Ji Eun Park[5], Jin Gu Lee[6], Young Tae Kim[7], Kyeongman Jeon [8], and ; on behalf of the Korean Lung Transplantation Study Group

Therapeutic Advances in Respiratory Disease
Volume 16, 2022



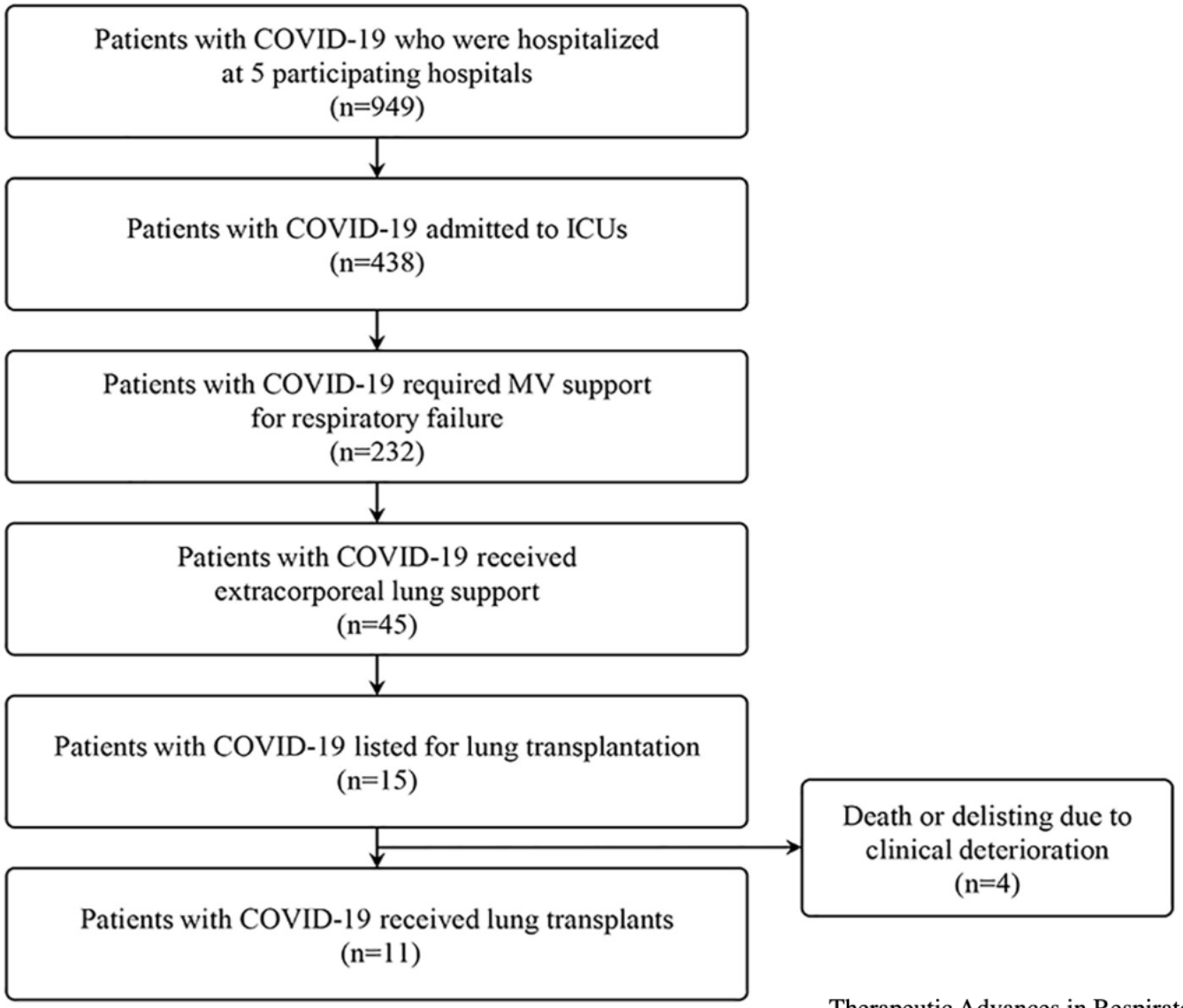


Figure 1. Study flow.

Therapeutic Advances in Respiratory Disease
Volume 16, 2022



Has Covid-19 Changed ECMO BTT?
ECMO BTT for Covid-19 ARDS

Table 5. Comparison of clinical characteristics and outcomes between COVID-19 patients and other causes patients who received extracorporeal membrane oxygenation as a bridge to lung transplantation.

	Patients with COVID-19-associated ARDS (*N* = 11)	Control (*N* = 27)	*p*
Gender, male	6 (54.5)	21 (77.8)	0.238
Age, years	60.0 (57.5–62.5)	58.0 (53.0–62.0)	0.287
Body mass index, kg/m^2	23.7 (20.4–25.3)	21.4 (18.7–23.4)	0.122
Time from intubation to LT, days	67.0 (54.5–83.5)	18.0 (7.0–26.5)	<0.001
Time from listing to LT, days	26.0 (9.0–38.0)	27.0 (10.5–40.5)	0.961
Time from ECMO to LT, days	49.0 (32.0–66.0)	11.0 (6.0–18.0)	<0.001
Characteristics of LT			
Bilateral lung transplantation	11 (100.0)	26 (96.3)	1.000
Operation time, min	510 (447–541)	575 (474–690)	0.097
Total ischemic time, right, min	199 (142–292)	280 (231–363)	0.053
Total ischemic time, left, min	319 (222–351)	331 (250–372)	0.384
Number of intraoperative packed RBC	10.0 (3.5–12.5)	9.0 (6.5–12.0)	0.821
Number of intraoperative FFP	2.0 (1.0–6.5)	3.0 (0.0–6.0)	0.961

Therapeutic Advances in Respiratory Disease
Volume 16, 2022



Has Covid-19 Changed ECMO BTT?
ECMO BTT for Covid-19 ARDS

Table 5. Comparison of clinical characteristics and outcomes between COVID-19 patients and other causes patients who received extracorporeal membrane oxygenation as a bridge to lung transplantation.

	Patients with COVID-19-associated ARDS (*N* = 11)	Control (*N* = 27)	*p*
PGD at 72 h			
PGD 0	9 (81.8)	25 (92.6)	0.435
PGD 1	0 (0.0)	0 (0.0)	
PGD 2	1 (9.1)	2 (7.4)	
PGD 3	1 (9.1)	0 (0.0)	
Complications			
Acute kidney injury required renal replacement therapy	3 (27.3)	7 (25.9)	1.000
Bleeding requiring chest reopening	2 (18.2)	6 (22.2)	1.000
Bleeding requiring medical management	2 (18.2)	1 (3.7)	0.196
Infection	7 (63.6)	4 (14.8)	0.005
Airway complication	3 (27.3)	2 (7.4)	0.134
Postoperative prolonged ECMO	4 (36.4)	8 (29.6)	0.714
Length of stay in ICU, days	88.0 (75.0–98.5)	33.0 (23.0–43.5)	<0.001
Hospital survival			0.395
Alive	10 (90.9)	20 (74.1)	
Expired	1 (9.1)	7 (25.9)	

Therapeutic Advances in Respiratory Disease
Volume 16, 2022



Has Covid-19 Changed ECMO BTT? ECMO BTT for Covid-19 ARDS

Hospitalized patients with irreversible lung injury from COVID-19 have higher morbidity but similar 1-year survival after lung transplant compared to hospitalized patients transplanted for restrictive lung disease

Deepika Razia, MD,[a] Michael T. Olson, BS,[b] Katherine Grief, RN,[a] Rajat Walia, MD,[a,c] Ross M. Bremner, MD, PhD,[a,c] Michael A. Smith, MD,[a,c] and Sofya Tokman, MD[a,c]

From the [a]Norton Thoracic Institute, St. Joseph's Hospital and Medical Center, Phoenix, Arizona; [b]University of Arizona College of Medicine – Phoenix Campus, Phoenix, Arizona, USA; and the [c]Creighton University School of Medicine, Phoenix Regional Campus, Phoenix, Arizona.

https://doi.org/10.1016/j.healun.2022.09.002



Has Covid-19 Changed ECMO BTT? ECMO BTT for Covid-19 ARDS

Table 1 Baseline and Preoperative Characteristics in the Study Groups

Variable	Hospitalized patients transplanted for CARDS N = 11	Hospitalized patients transplanted for RLD N = 121	*p*-value[b]
Age at transplant, years[a]	47 (42.5, 56.7)	62.4 (56.4, 68.3)	**0.001**
Interval between initial hospitalization and transplant, days[a]	100 (85, 121)	14 (9, 21)	**<0.001**
Interval between listing and transplant, days[a]	5 (4, 11)	5 (3, 11)	0.482
Ventilator support just prior to transplant, yes	10 (90.9)	42 (34.7)	**<0.001**
Vasopressor dependence immediately before transplant, yes	8 (72.7)	47 (38.8)	0.054
ECMO as bridge to transplant	8 (72.7)	34 (28.1)	**0.002**

https://doi.org/10.1016/j.healun.2022.09.002



Has Covid-19 Changed ECMO BTT? ECMO BTT for Covid-19 ARDS

Table 2 Perioperative Outcomes in the Study Groups

Variable	Hospitalized patients transplanted for CARDS N = 11	Hospitalized patients transplanted for RLD N = 121	*p*-value[b]
Severe intrathoracic adhesions, yes	8 (72.7)	31 (28.4)	**0.003**
Posttransplant duration of mechanical ventilation			**0.045**
≤5 days	3 (27.3)	71 (58.7)	
>5 days	8 (72.7)	50 (41.3)	
Posttransplant ECMO rescue, yes	0 (0)	4 (3.3)	0.540
Primary graft dysfunction grade 3, 72 hours	4 (36.4)	12 (9.9)	**0.017**
Intubated at 72 hours, yes	9 (81.8)	56 (46.3)	**0.037**

https://doi.org/10.1016/j.healun.2022.09.002



Has Covid-19 Changed ECMO BTT? ECMO BTT for Covid-19 ARDS

Table 6 Posttransplant Outcomes in Propensity-Matched Groups

Variable	Hospitalized LTRs transplanted for CARDS N = 10	Hospitalized LTRs transplanted for RLD N = 10	*p*-value[b]
Length of inpatient hospital stay after transplant, days[a]	48 (26, 61)	23.5 (12, 34)	**0.037**
Severe intrathoracic adhesions, yes	7 (70)	4 (44.4)	0.260
Posttransplant duration of mechanical ventilation			0.639
≤5 days	3 (30)	4 (40)	
>5 days	7 (70)	6 (60)	
Posttransplant ECMO rescue, yes	0 (0)	0 (0)	N/A
Primary graft dysfunction grade 3, 72 hours	4 (40)	1 (20)	0.439
Intubated at 72 hours, yes	9 (90)	4 (80)	0.591
Total blood products transfused during first 2 weeks posttransplant[a]	11 (8, 17)	29 (3, 42)	0.252

https://doi.org/10.1016/j.healun.2022.09.002



When is Permanent Truly Irreversible? ECMO BTT for Covid-19 ARDS

ECMO Long Haulers: A Distinct Phenotype of COVID-19–Associated ARDS With Implications for Lung Transplant Candidacy

Manish R. Mohanka, MD,[1] John Joerns, MD,[1] Adrian Lawrence, MD,[1] Srinivas Bollineni, MD,[1] Vaidehi Kaza, MD,[1] Sreekanth Cheruku, MD,[2] Matthew Leveno, MD,[1] Catherine Chen, MD,[1] Lance S. Terada, MD,[1] Corey D. Kershaw, MD,[1] Fernando Torres, MD,[1] Matthias Peltz, MD,[3] Michael A. Wait, MD,[3] Amy E. Hackmann, MD,[3] and Amit Banga, MD, FCCP, MBA[1]

(*Transplantation* 2022;106: e202–e211)

W

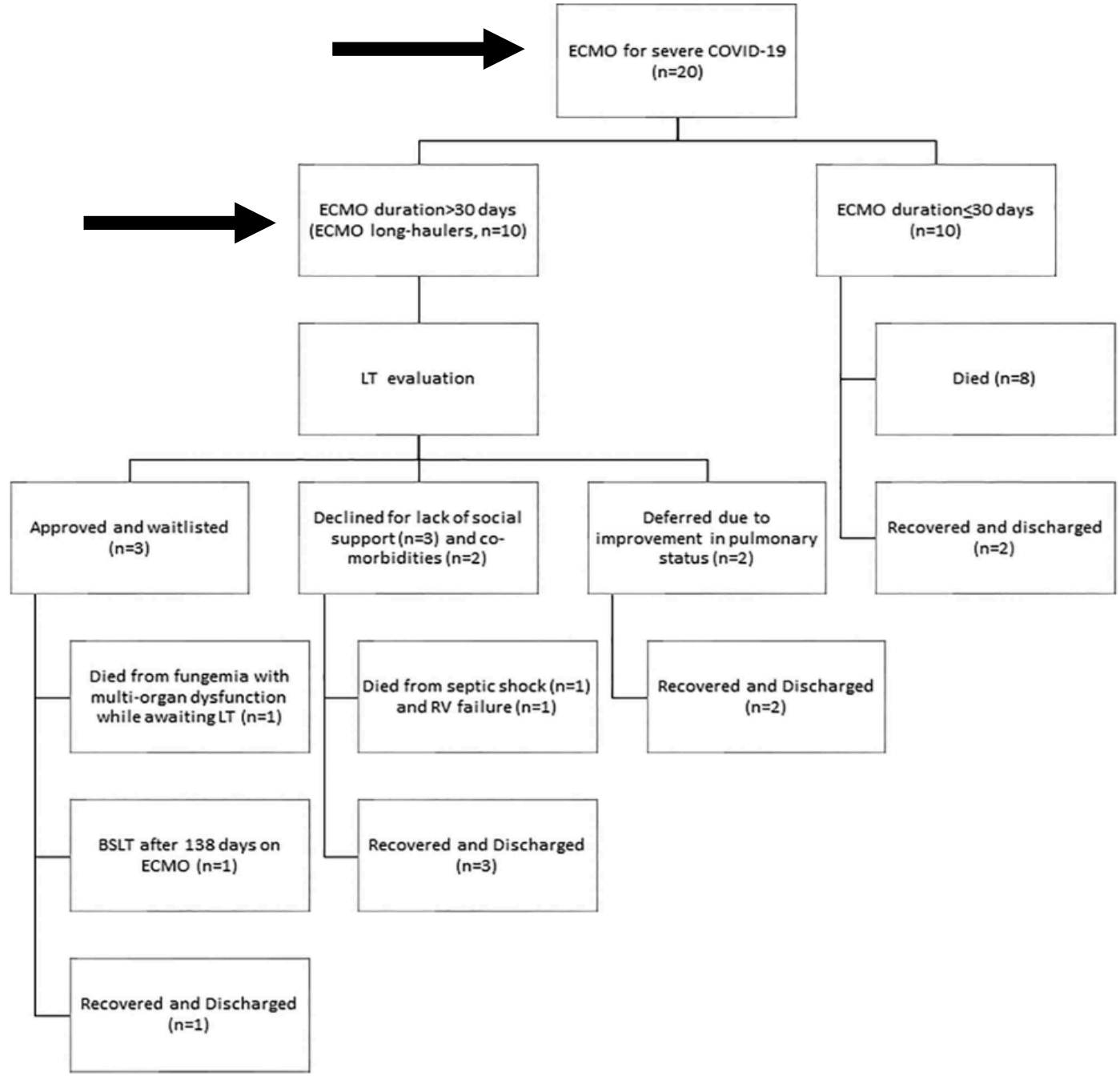


FIGURE 1. Flowchart of the patients included in the study and their outcomes. BSLT, bilateral sequential lung transplantation; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; LT, lung transplantation; RV, right ventricular.

e202–e211)



When is Permanent Truly Irreversible?
ECMO BTT for Covid-19 ARDS: Duke Experience

- Prior to COVID pandemic, our average VV ECMO run for ARDS was 7 days.
- Our average ECMO run during COVID was nearly 30 days.
- We had eleven patients require support for over 60 days…ECMO long-haulers



When is Permanent Truly Irreversible?
ECMO BTT for Covid-19 ARDS: Duke Experience

- Outcomes for the 11 patients who required ECMO support for over 60 days.
  - Of these patients, 8 survived to hospital discharge
  - One of the 8 patients required a lung transplant for ECMO liberation

Duke Surgery



The Journal of Thoracic and Cardiovascular Surgery JTCVS

Submit Log in Registe

CONSENSUS STATEMENT | ARTICLES IN PRESS

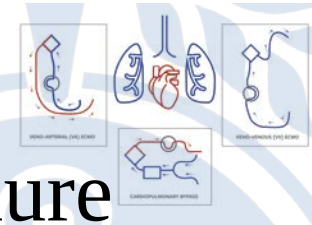
Purchase Subscribe

The American Association for Thoracic Surgery (AATS) 2022 Expert Consensus Document: The use of mechanical circulatory support in lung transplantation

Expert Consensus Panel: • Matthew Hartwig, MD (Co-Chair) • Victor van Berkel, MD, PhD (Co-Chair) • ... Isabelle Opitz, MD • Varun Puri, MD • Dirk Van Raemdonck, MD, PhD • Show all authors

Published: October 26, 2022 • DOI: https://doi.org/10.1016/j.jtcvs.2022.06.024





Consensus Statements
Section 1a: Pre-operative Pulmonary Failure

1) VV ECMO is the preferred initial option for bridging strategies in patients with isolated hypoxia and/or hypercapnia in the absence of hemodynamic instability or RV dysfunction. (CoR: 2a, LoE: C-LD)

2) In patients supported with VV ECMO as a bridge to lung transplantation, periodic evaluation of RV function (by clinical assessment or otherwise) should be performed to evaluate the need for alternative support strategies. (CoR: 1, LoE: C-EO)

3) While undergoing extracorporeal pulmonary support as bridge to lung transplantation, ambulation and rehabilitation should be aggressively pursued to improve bridge success rates and post-transplant outcomes. (CoR: 1, LoE: C-LD)

4) Femoral venous cannulation should not be considered a contraindication to ambulation and rehabilitation in patients supported with VV ECMO as a bridge to lung transplantation. (CoR: 2a, LoE: C-LD)

5) While extracorporeal circulatory support is the preferred strategy for bridging to transplant to promote physical therapy, bridging with mechanical ventilation alone can be utilized in highly select cases where deconditioning can be avoided. (CoR: 1, LoE: C-LD)

6) In select circumstances where hypercapnic respiratory failure is the predominant issue, extracorporeal CO2 removal (ECCO2R) can effectively be used as a bridging strategy. (CoR: 2a, LoE: C-LD)



Consensus Statements
Section 1b: Pre-operative Cardiopulmonary Support

7) VA ECMO as bridge to lung transplantation is a valuable option in selected patients with end-stage PAH evolving with RV failure, despite the risk of impaired short-term outcomes. (CoR: 1, LoE: B-NR)

8) Both femoral and subclavian arterial cannulation could be considered (based on lung oxygenation and cardiac output) for VA-ECMO bridging for lung transplantation. (CoR: 1, LoE: B-NR)

9) In patients with combined circulatory and respiratory failure, the use of VAV-ECMO, as opposed to VA-ECMO only, is a valuable option to prevent differential upper-body hypoxia in patients with peripheral femoral artery cannulation. (CoR: 2a, LoE: C-EO)





Consensus Statements
Section 1c: Special Circumstances for Pre-op Bridging

10) Selected patients with COVID-related ARDS supported with ECMO can be considered for transplantation in the absence of any signs of lung recovery. (CoR: 2a, LoE: C-EO)

11) Patients considered for transplantation for COVID-ARDS should fulfill other standard criteria for listing and demonstrate the potential for post-transplant rehabilitation. (CoR: 1, LoE: C -EO)

12) Patients with pulmonary hypertension should be considered for bridge with mechanical support when clinical signs of right heart failure are evident, such as need for inotropes, poor mixed venous saturation, and early signs of kidney and liver dysfunction. (CoR: 1, LoE: C-LD)

13) In exceptional circumstances, bilateral pneumonectomies and central ECMO initiation can be considered in patients with uncontrolled pulmonary sepsis as a bridge to transplantation. (CoR: 2b, LoE: C-EO)





Conclusions

Improvements in ECMO/ECLS Technologies open the door for complex bridging strategies

- ECMO bridging “pre- and post- pan” is possible with success well-documented
- For Covid-19 ARDS the optimal timing remains to be determined and likely is in evolution with changes in natural immunity, vaccinations, and therapies
- We didn’t talk about COST
- We didn’t talk about COMPLICATIONS
- Eventually, we need to talk about the ethical and emotional cost to healthcare providers and families as well

Idiopathic Pulmonary Fibrosis(IPF) and Progressive Pulmonary Fibrosis (PFF): An Update on Diagnosis and Treatment

December 2, 2022

Tristan Huie, MD
Interstitial Lung Disease Clinic
National Jewish Health
Denver, CO

Disclosure

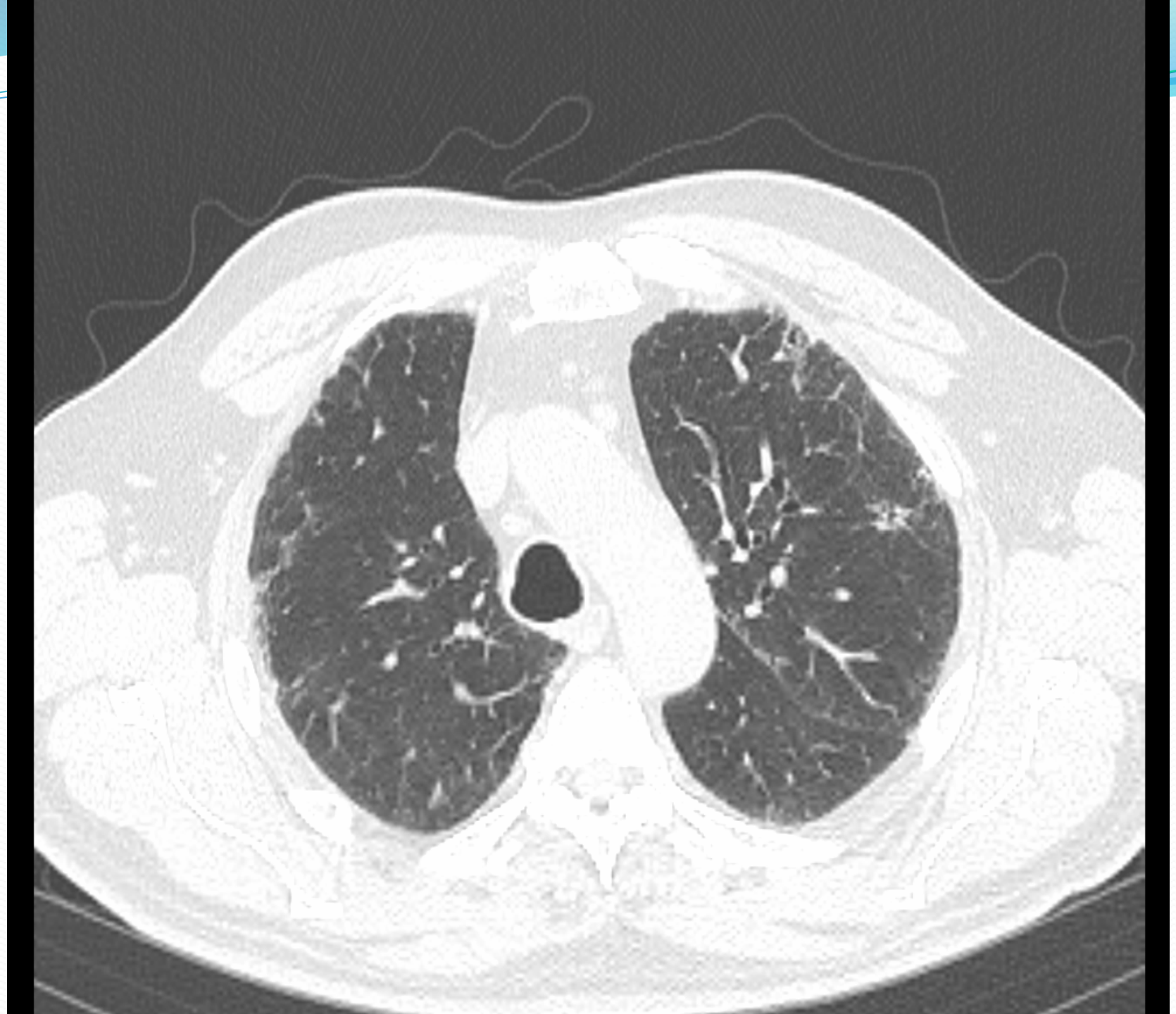
- I serve as a site investigator for clinical trials and registry trials for the following companies:
  - Boerhinger Ingelheim
  - Roche/Genentech

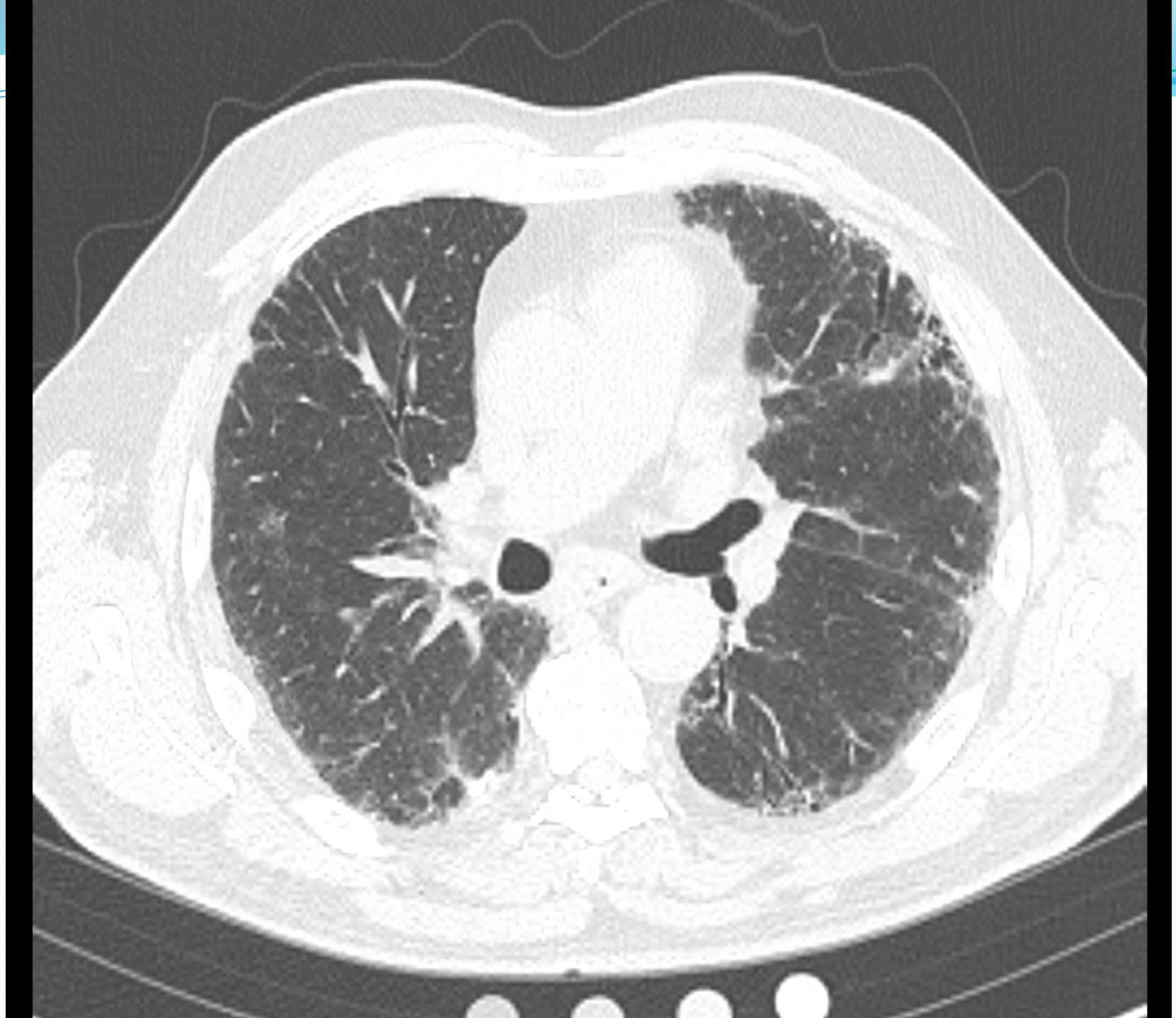
Objectives

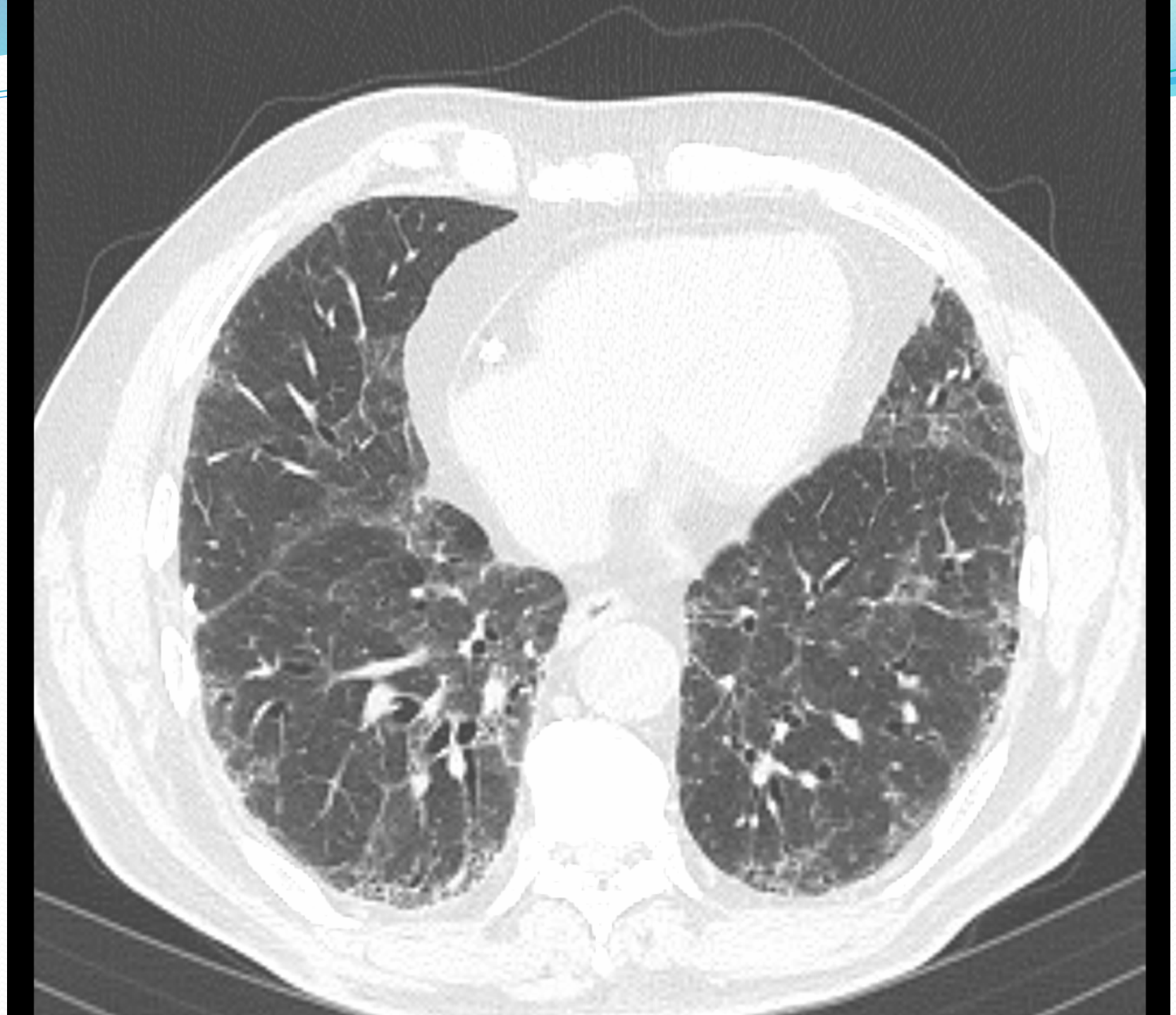
- Review the diagnostic approach to interstitial lung disease
- Evaluate the emerging role of cryobiopsy and genomic classifier
- Review the features of progressive pulmonary fibrosis
- Highlight treatment options

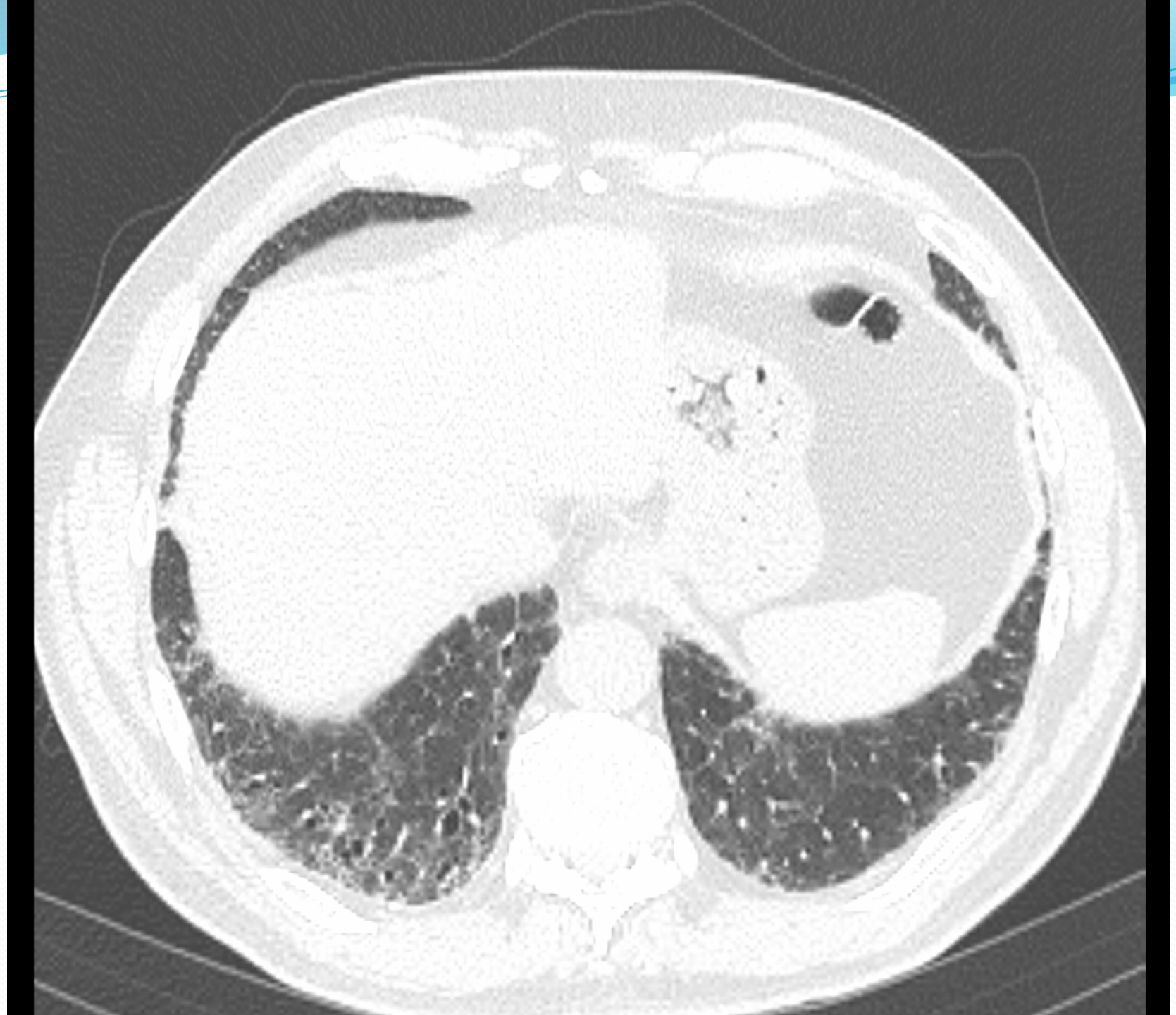
Case: AB

- 64 yo man with bicuspid aortic valve, mild aortic stenosis, hyperlipidemia, and diverticulosis presents with several years of dry cough and progressive dyspnea. Associated fatigue. Intermittent reflux.
- No symptoms to suggest CTD. No prior history of drugs associated with ILD. Soc hx: 30 pk yr history; quit 15 years ago
- He works in telecommunications as a manager. Had a cockatiel 20 years ago. No relevant exposures at work or in the home.
- Exam with basilar crackles; 3/6 systolic murmur. No synovitis, rash.
- Autoimmune serologies normal.
- Mild restriction with FVC 70%; DLCO 64% pred









Next step?

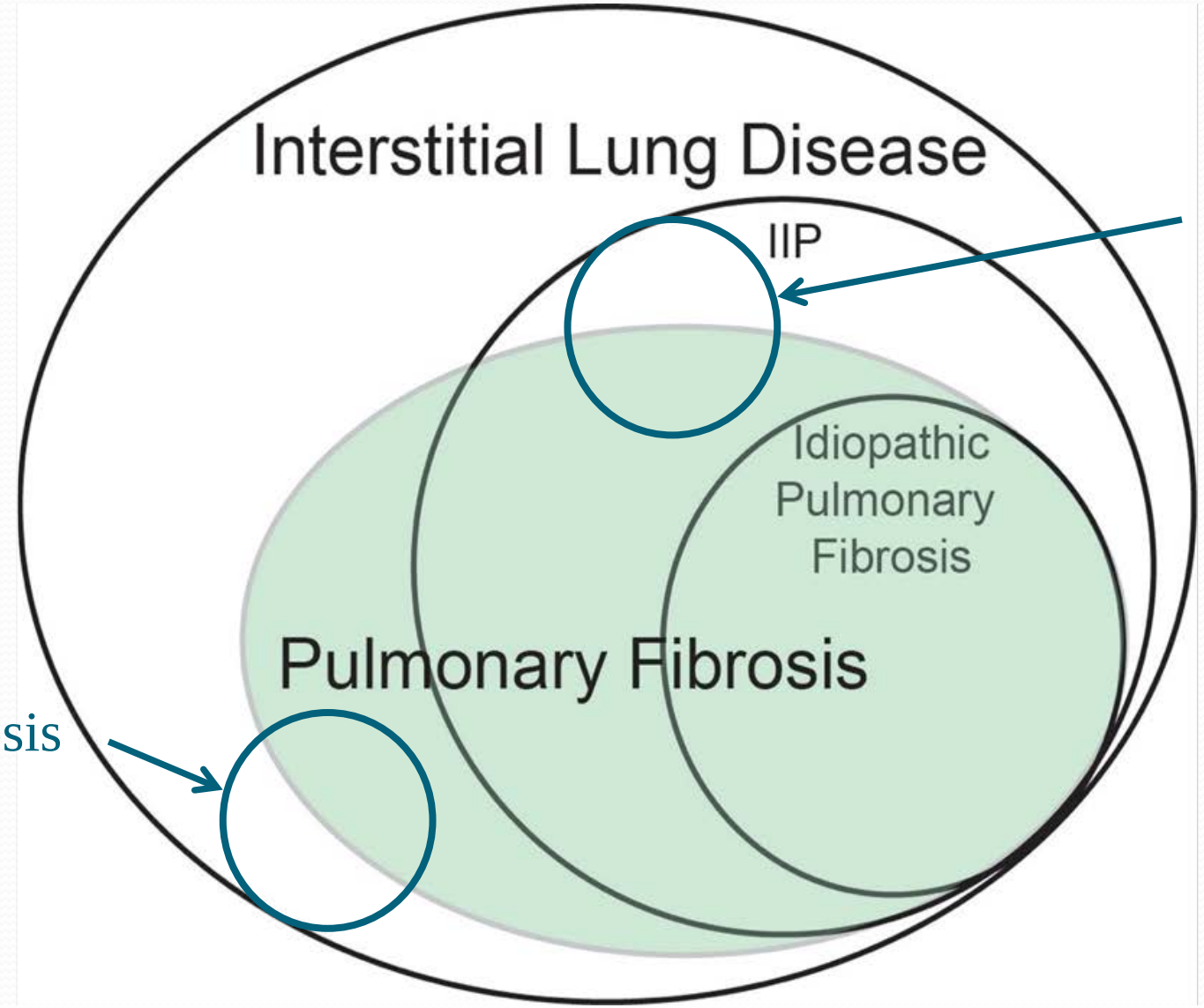
Next step?

A. Order hypersensitivity pneumonitis panel

B. Refer for surgical lung biopsy

C. Present at a multidisciplinary ILD conference

D. Make a diagnosis and start therapy



Sarcoid

HP
Asbestosis
CT-ILD

Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

-Updated in 2022; reflects new data since 2018 guidelines

-Used rigorous evidence-based approach

Raghu AJRCCM 2022

Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

-Updated in 2022; reflects new data since 2018 guidelines

-Used rigorous evidence-based approach

Revised:

- Revisited imaging and path patterns
- Diagnostic criteria
- Diagnostic and treatment approaches
  - Reflux medications
  - Role for Transbronchial Lung Cryobiopsy

Added:

- Addressed reflux surgery
- Role of genomic classifier
- Defined Progressive Pulmonary Fibrosis (PFF)

Raghu AJRCCM 2022

Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults

An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline

-Applied GRADE methodology recommendations that apply to patients, clinicians, policymakers

-Provided additional guidance

Strong Recommendation:

- It is the right course for >95% of patients
- "Just do it"
- You would tell a colleague who didn't follow rec that they did the wrong thing
- May be appropriate performance measure

Conditional Recommendation:

- Right course for >50% of patients
- "Slow down, think about it, discuss it with patient"
- You wouldn't correct a colleague—this is style/equipoise
- Not a performance measure

Raghu AJRCCM 2022

Diagnostic Approach

- Clinical-Radiologic-Pathologic Approach
- Etiology?
- Pattern of injury?

Etiology

- Autoimmune & Systemic Dz
- Drugs
- Environmental & Occupational
- Familial
- Idiopathic

Etiology

History

- Systemic diseases
- Occupational & Environmental History
- Drug & Medication History
- Family History

Review of Systems

- Extra-pulmonary manifestations

Examination

- Pulmonary exam
- Extra-pulmonary signs

Laboratories

- Extra-pulmonary organ dysfunction
- Auto-immune serologies
- Immune function

Why Etiology Alone Isn't Enough

Rheumatoid Arthritis	
UIP	Emphysema
NSIP	Bronchiectasis
Organizing Pneumonia	Bronchiolitis
DAD	Nodules
LIP	Alveolar hemorrhage/vasculitis
DIP	Pleural disease
PPFE	Drug toxicity

Why Pathology Alone Isn't Enough

	UIP	Granulomatous
Idiopathic	IPF	Sarcoid
Autoimmune	RA-ILD	GPA
Drug	Chemo/XRT	Methotrexate
Occupational	Asbestosis	Beryllium
Familial	FPF	Familial Sarcoid

Pattern

Pattern

- HRCT
- Pathology

- Idiopathic pulmonary fibrosis is diagnosed with a pattern of usual interstitial pneumonia (UIP) without an identifiable cause

HRCT Patterns

UIP	Probable UIP	Indeterminate	Alternative Diagnosis
Subpleural and basal predominant reticular abnormality	Subpleural and basal predominant reticular abnormality	Subpleural and basal predominant	CT features: Cysts Mosaic attenuation GGO Centrilobular nodules Nodules Consolidation
Honeycombing	*No honeycombing Traction bronchiectasis or bronchioloectasis	Subtle reticulation	Distribution: Peribronchovascular Perilymphatic Upper or mid-lung Subpleural sparing
No features to strongly suggest an alternative diagnosis		Features do not suggest any specific etiology	Other: Pleural plaques Dilated esophagus Extensive LAD

HRCT Patterns – Likelihood of UIP on biopsy?

UIP	Probable UIP	Indeterminate	Alternative Diagnosis

Lynch Lancet Resp Med 2018
Raghu AJRCCM 2022

HRCT Patterns – Likelihood of UIP on biopsy?

UIP	Probable UIP	Indeterminate	Alternative Diagnosis
94-100%			

Lynch Lancet Resp Med 2018
Raghu AJRCCM 2022

HRCT Patterns – Likelihood of UIP on biopsy?

UIP	Probable UIP	Indeterminate	Alternative Diagnosis
94-100%	88-94%		

Lynch Lancet Resp Med 2018
Raghu AJRCCM 2022

HRCT Patterns – Likelihood of UIP on biopsy?

UIP	Probable UIP	Indeterminate	Alternative Diagnosis
94-100%	88-94%	70-80%	

Lynch Lancet Resp Med 2018
Raghu AJRCCM 2022

HRCT Patterns – Likelihood of UIP on biopsy?

UIP	Probable UIP	Indeterminate	Alternative Diagnosis
94-100%	88-94%	70-80%	<=60%

Lynch Lancet Resp Med 2018
Raghu AJRCCM 2022

HRCT Patterns – Likelihood of UIP on biopsy?

UIP	Probable UIP	Indeterminate	Alternative Diagnosis
94-100%	88-94%	70-80%	<=60%
Confident >90%	Provisional High Confidence 70-89%	Provisional Low Confidence 51-69%	Low (or very low) Confidence <=50%

- Depends on pre-test probability
  - Older man with a smoking history vs young woman

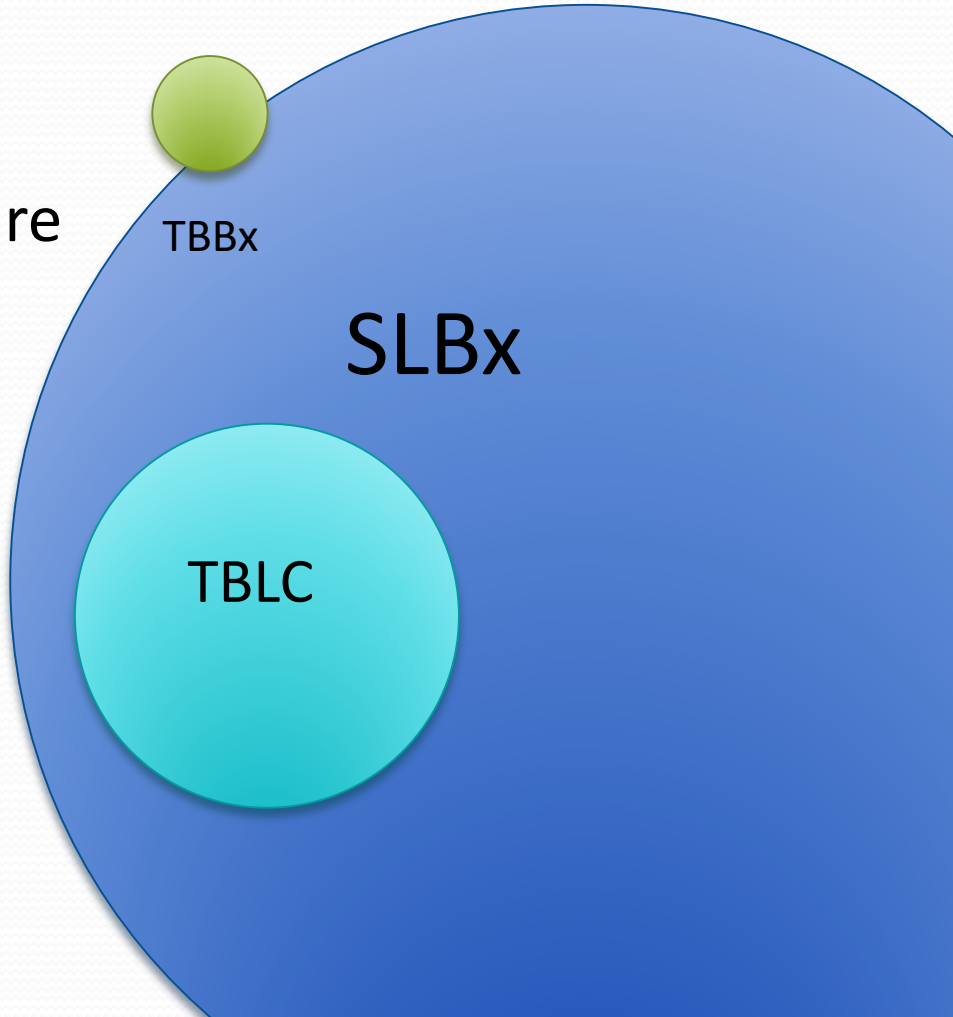
Lynch Lancet Resp Med 2018
Raghu AJRCCM 2022

Bronchoscopy

- Bronchoalveolar lavage may suggest alternate diagnosis—send cell counts!
- Diagnosis of ILD requires assessment of architecture of the lung
- Higher yield with airway centered diseases

  (e.g. sarcoid, HP)
- TBBx usually not diagnostic for IPF:

  ~36% (95% CI 33.4-38.9%)
- Generally safe



Transbronchial Lung Cryobiopsy (TBLC)

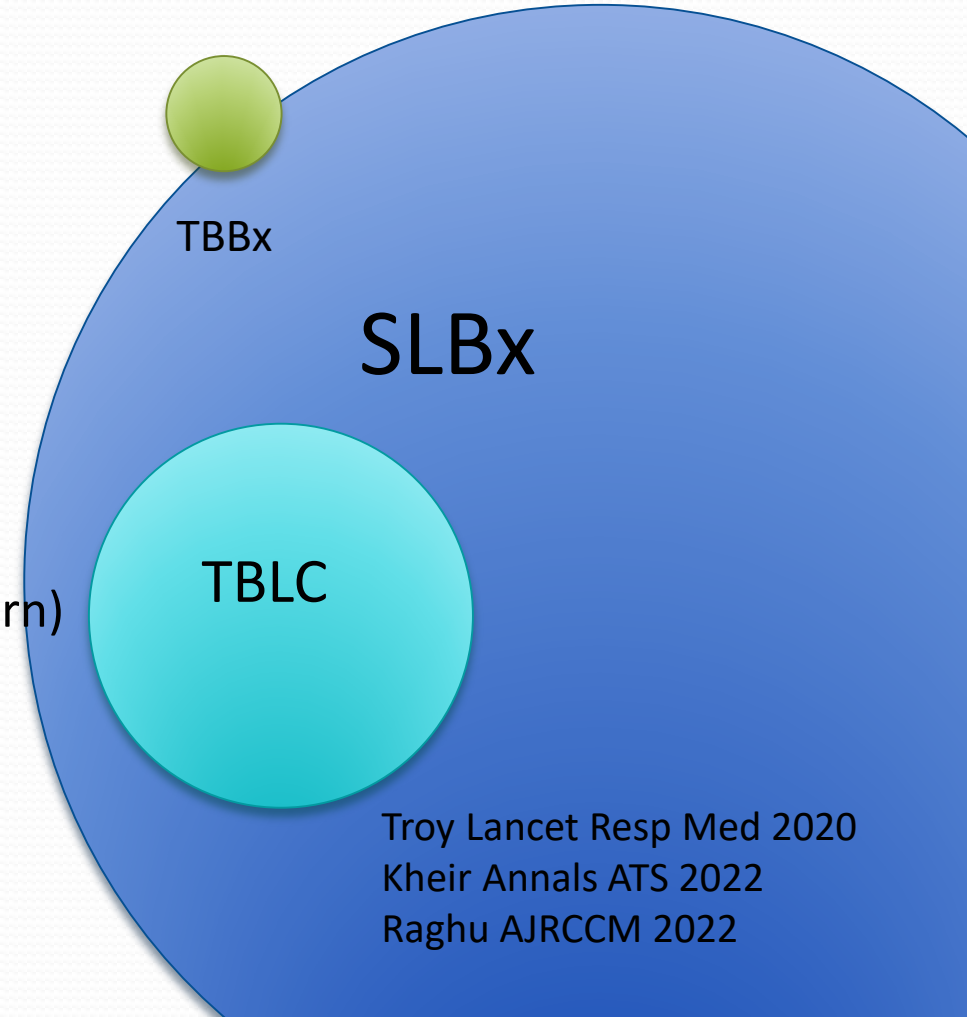
Cryoprobe obtains much larger biopsy than TBBx:

- Mean specimen area:
  15.1 mm^2 (2.2-54.5mm^2) vs 5.8mm^2 (0.58-20.1mm^2)
- Variable technique
- Safety concerns in inexperienced hands
  - PTX 8% (95% CI, 6-11)
  - Bleeding 30% (95% CI, 20-41)

80% of cases with specific diagnosis

- Limited comparison with SLBx and MDD
- Biopsy from a single lobe generally (may miss discordant pattern)
- Samples more centrally—more likely to result in "Prob UIP"
- Similar contraindications as surgical lung biopsy

TBLC may be regarded as an acceptable alternative to surgical lung biopsy in experienced centers (conditional rec; very low quality evidence.



Genomic classifier

- Lung tissue is obtained from transbronchial forceps biopsy
- Whole transcriptome RNA sequencing with gene expression analysis to classify UIP vs not UIP.
- Meta-analysis of four studies (195 patients):
  - Sensitivity 68% (CI 55-73%); specificity 92% (CI 81-95%)
  - Confidence in IPF dx improved with use of genomic classifier (43->93%; 59->89%)
- **No recommendation for use due to insufficient agreement among committee (41 vs 59%); moderate quality evidence for test characteristics; very low for confidence, agreement**
- High specificity helpful; low sensitivity results in false negatives; unclear utility of test; unknown distinction between UIP due to IPF vs other; relatively poor availability

Raghu Lancet Resp Med 2019
Kheir Annals ATS 2022
Raghu AJRCCM 2022

IPF Phenotypes

- Combined pulmonary fibrosis and emphysema (CPFE)
- Pleuroparenchymal fibroelastosis with UIP (PPFE+UIP)

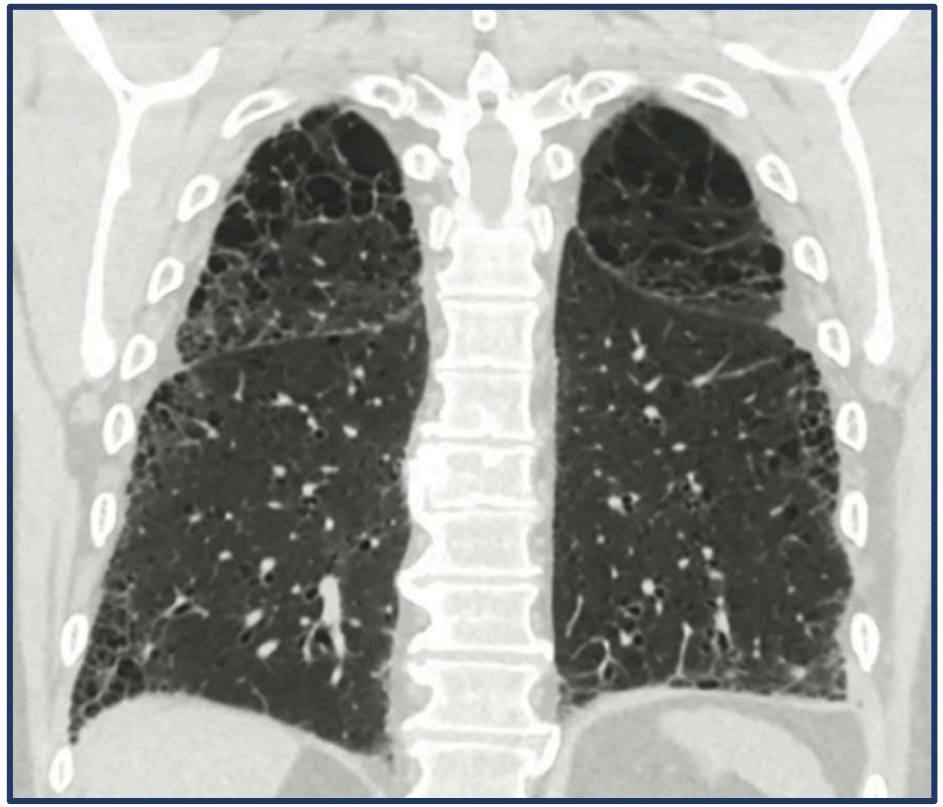
Lynch Lancet Resp Med 2018
Raghu AJRCCM 2022

IPF Phenotypes - CPFE

- Substantial emphysema present in 1/3 of IPF pts
- Risk associated with tobacco; but also CTD, HP, pneumoconiosis

- Preserved FVC; markedly reduced DLCO
  - Longitudinal FEV1 may be more predictive
- High risk of pulmonary hypertension, lung camcer
- Likely worse prognosis
- Overlap with Smoking-related Fibrosis; air-space enlargement with fibrosis

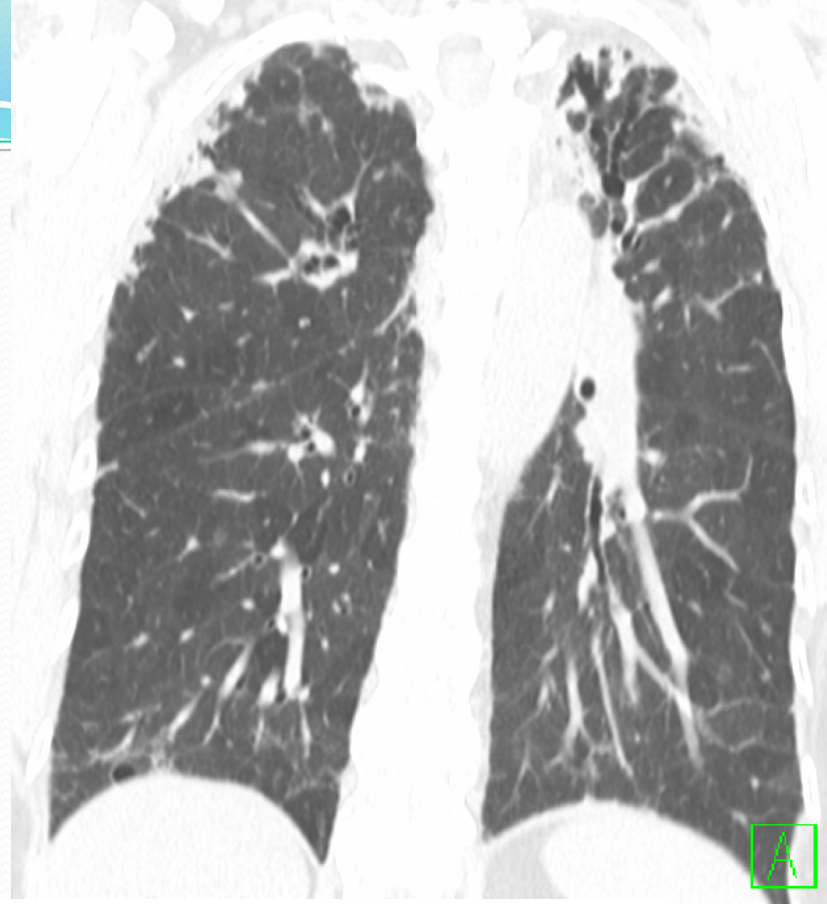
- Generally excluded from clinical trials
- ATS/ERS/JRS/ALAT Research Statement



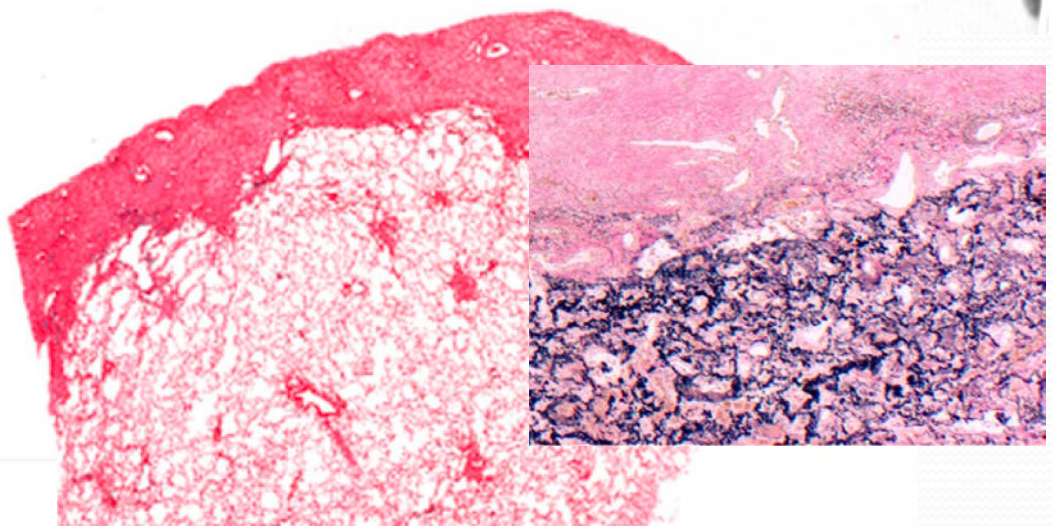
Cottin AJRCCM 2022

IPF Phenotypes - PPFE

- PPFE is increasingly recognized pattern of ILD
  - Upper lobe predominant subpleural fibrosis
  - Subset with lower lobe UIP
- PPFE may be found in 6-8% of IPF patients



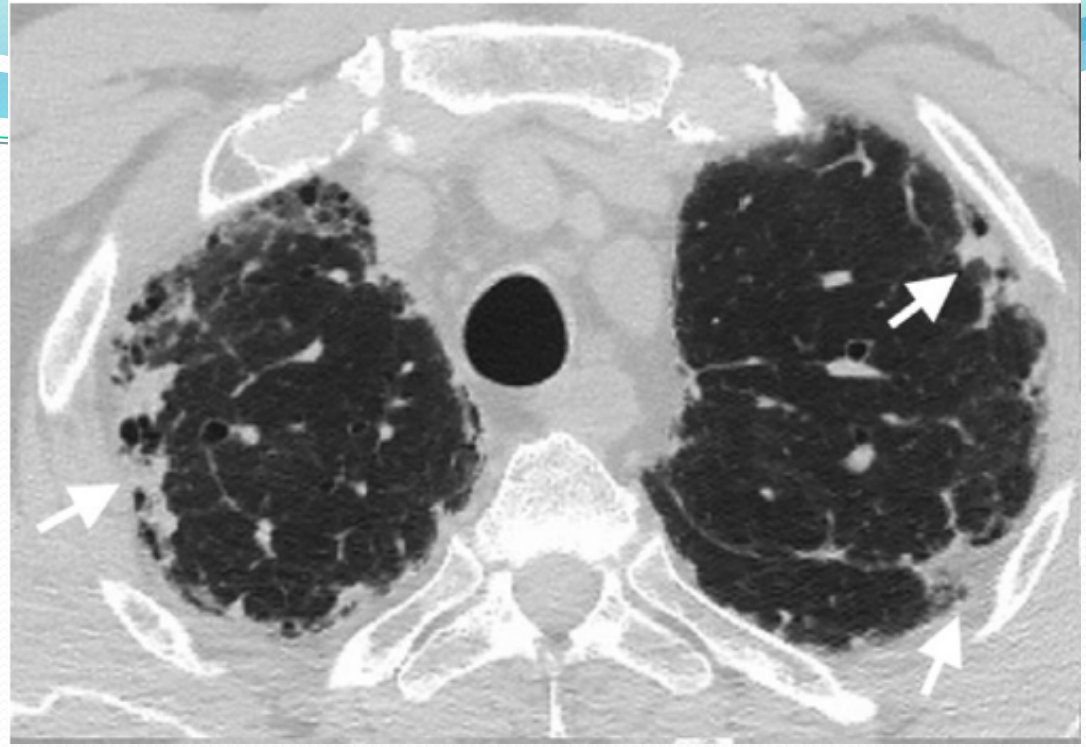
- May be associated with more rapid decline in function
- Increased risk of pneumothorax
- Increased mortality
- Current recs to treat as IPF

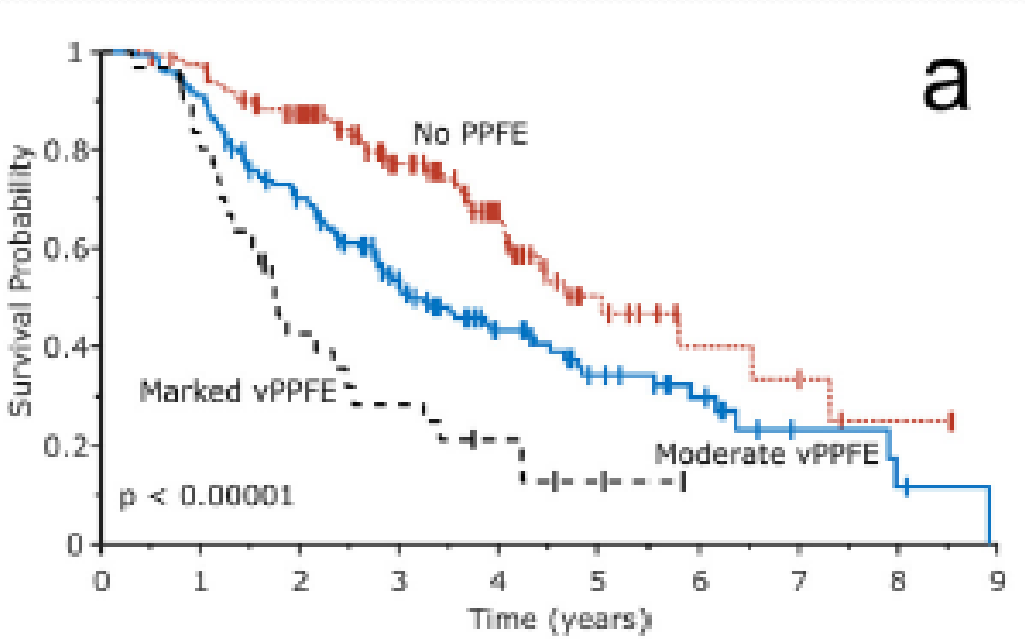


Raghu AJRCCM 2022; Lynch Lancet Resp Med 201

IPF Phenotypes - PPFE

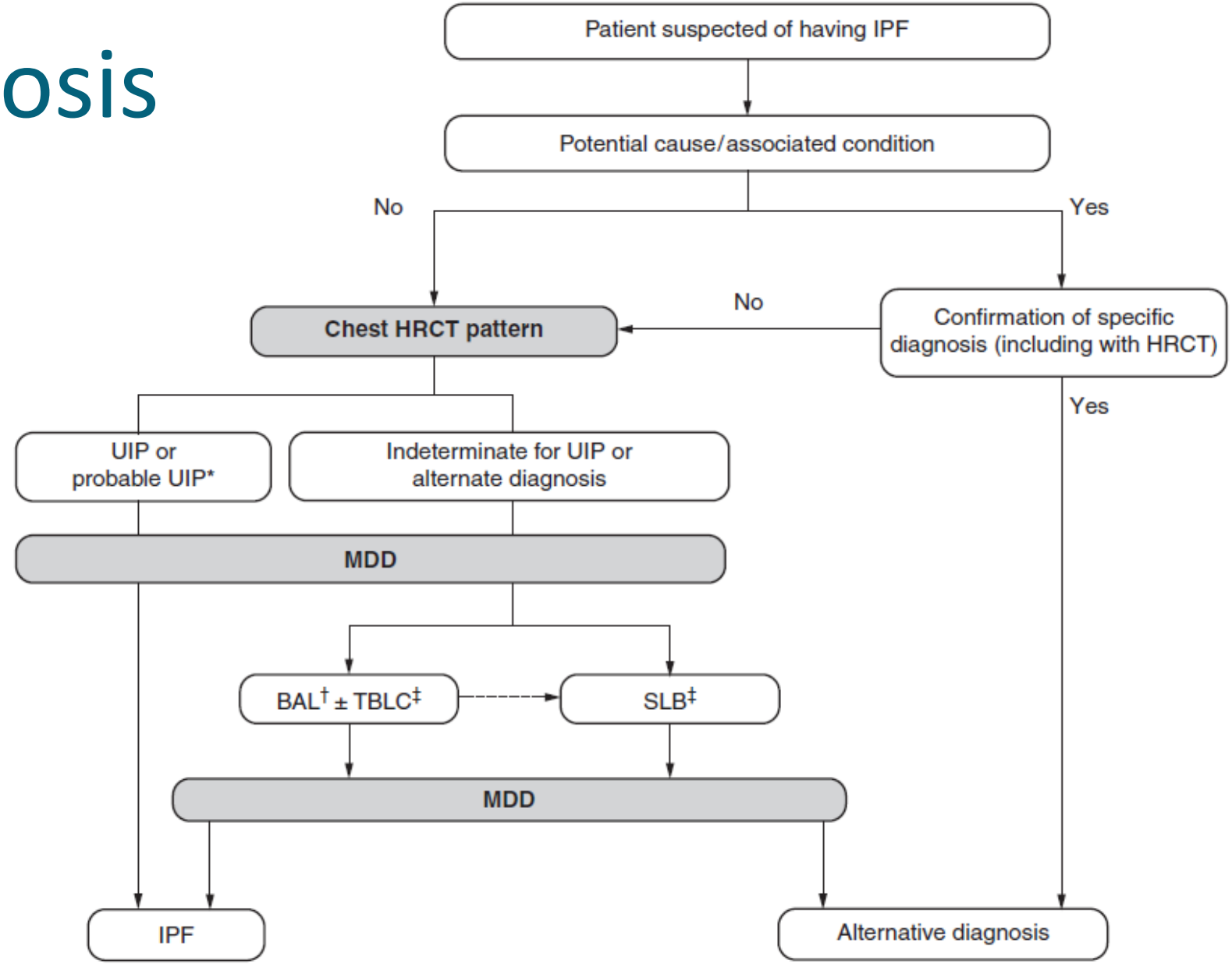
- Retrospective evaluation of 3 IPF cohorts (n=287) looked for PPFE changes visually and with quantitative imaging
- PPFE imaging changes prevalence 49% in derivation cohort; 79% in validation cohort
- Associated with more rapid loss of FVC; increased mortality compared to IPF without PPFE





Gudmundsson eClinMed 2021

Diagnosis



Raghu AJRCCM 2022

Diagnosis

IPF suspected*		Histopathology pattern†			
		UIP	Probable UIP	Indeterminate for UIP or biopsy not performed	Alternative diagnosis
HRCT pattern	UIP	IPF	IPF	IPF	Non-IPF dx
	Probable UIP	IPF	IPF	IPF (Likely)‡	Non-IPF dx
	Indeterminate	IPF	IPF (Likely)‡	Indeterminate§	Non-IPF dx
	Alternative diagnosis	IPF (Likely)‡	Indeterminate§	Non-IPF dx	Non-IPF dx

Raghu AJRCCM 2022

IPF Treatment – no changes!

- Antifibrotic therapy should be strongly considered.
- Pirfenidone and nintedanib slow progression.
- Most patients tolerate therapy.
- Dose adjustment and drug holidays can help attenuate adverse effects.

- **Conditional recommendation for use with moderate confidence**

Raghu AJRCCM 2022; 2015

IPF Treatment – Gastroesophageal Reflux (GER)

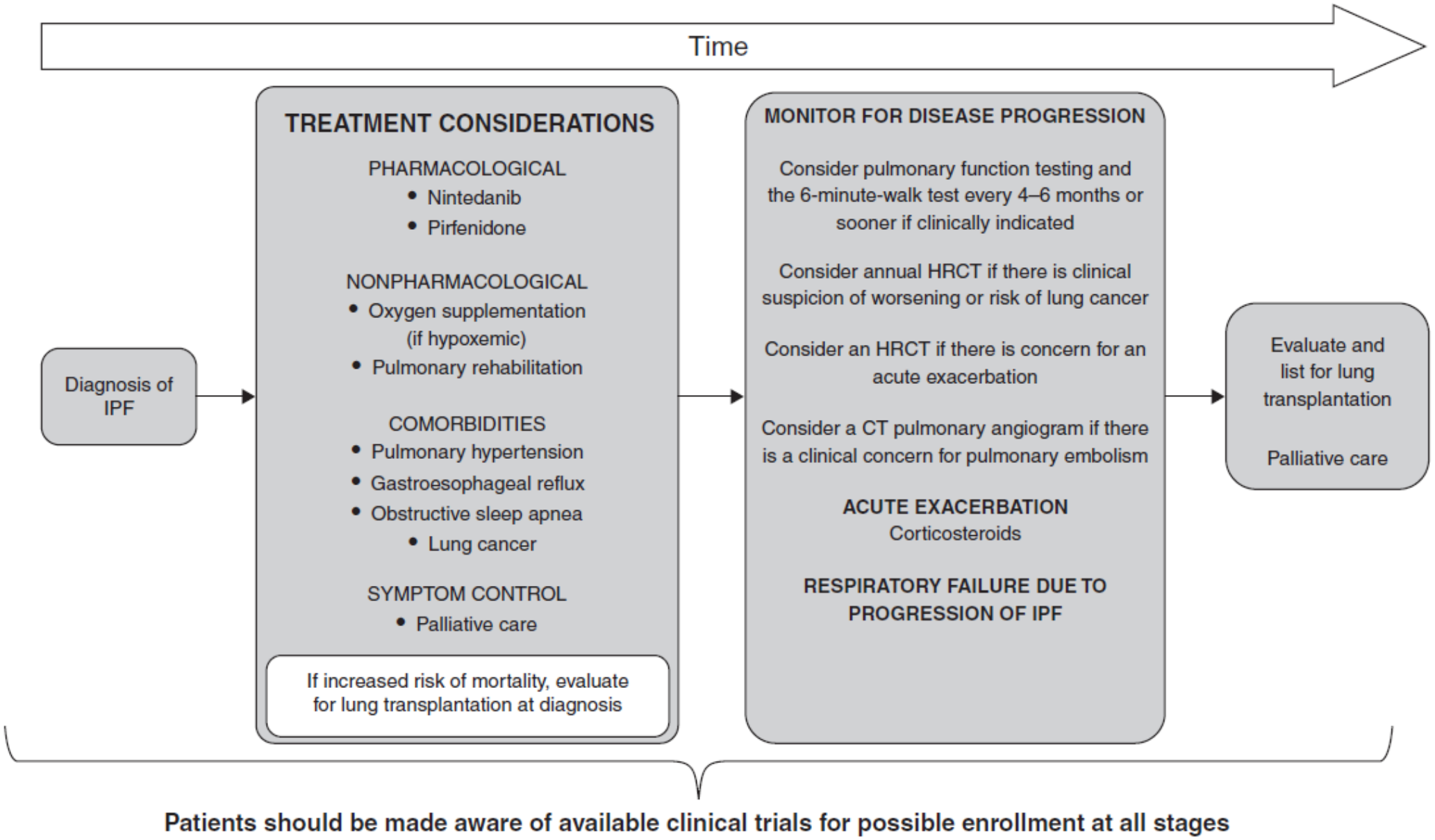
- Previously antireflux meds were recommended for treatment of IPF.
- New data since 2015 guidelines:
  - No studies directly assessed for GER in study subjects
  - 15 studies evaluated antacids in IPF.
  - One prospective pilot RCT enrolled 45 patients. No significant difference in primary outcome of cough frequency. A trend toward improved physiology.
- No benefits in terms of mortality, disease progression, exacerbations or adverse effects.
- **Conditional recommendation to not treat; very low quality evidence**
- This does not address treatment of symptomatic reflux.

Dutta Thorax 2019
Khor Ann ATS 2022
Raghu AJRCCM 2022

IPF Treatment – Antireflux surgey

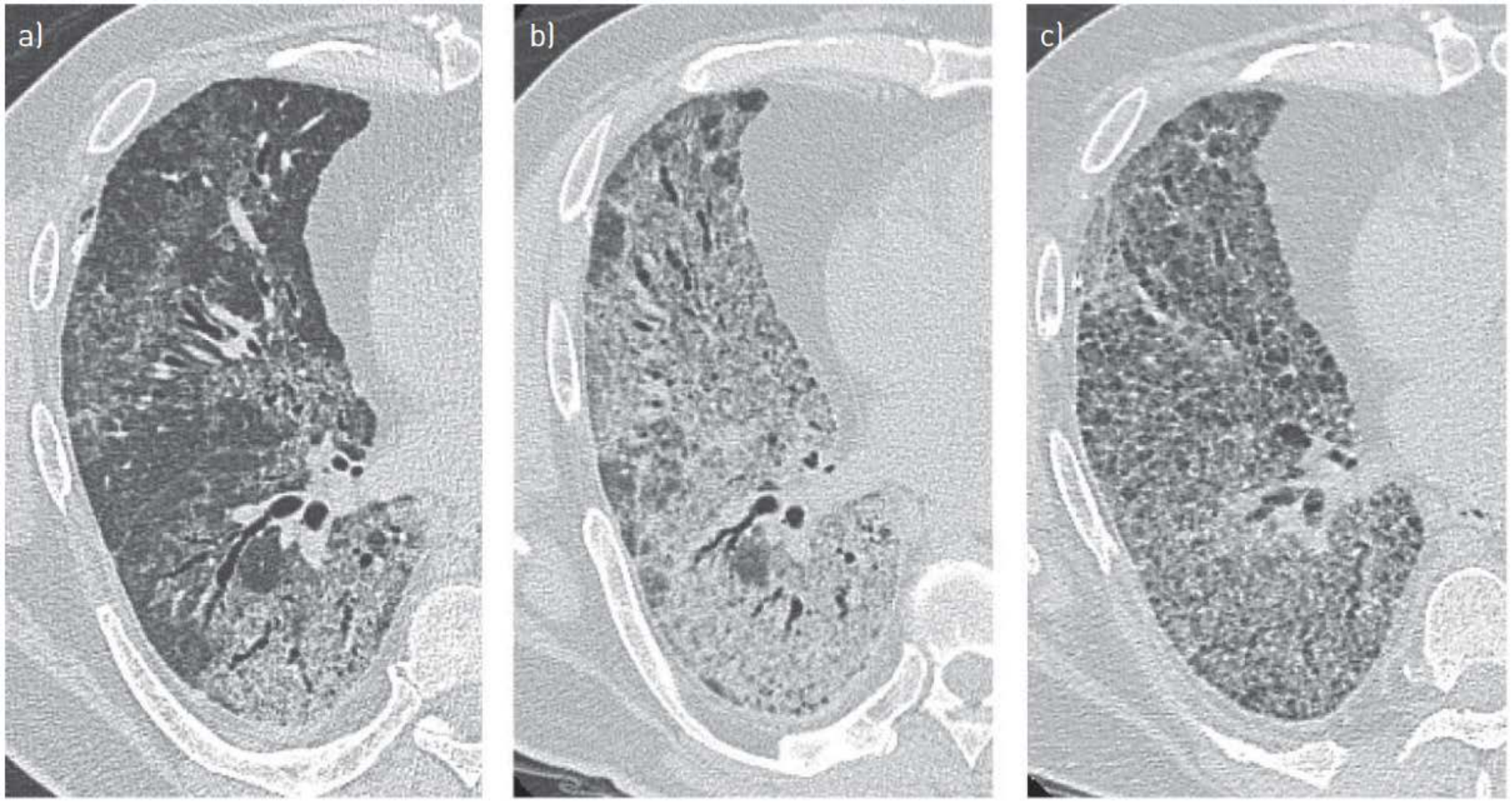
- New data since 2015 guidelines:
  - Randomized trial of antireflux surgery (WRAP-IPF)
  - Enrolled 58 patients
  - No significant difference in multiple measures of disease progression; mortality, exacerbation rates.
  - Meta-analysis also included 2 observational studies and one case series.
- **Conditional recommendation to not treat; very low quality evidence.**
- This does not address treatment of symptomatic reflux.

Raghu Lancet Resp Med 2018
Khor Ann ATS 2022
Raghu AJRCCM 2022



Raghu AJRCCM 2022

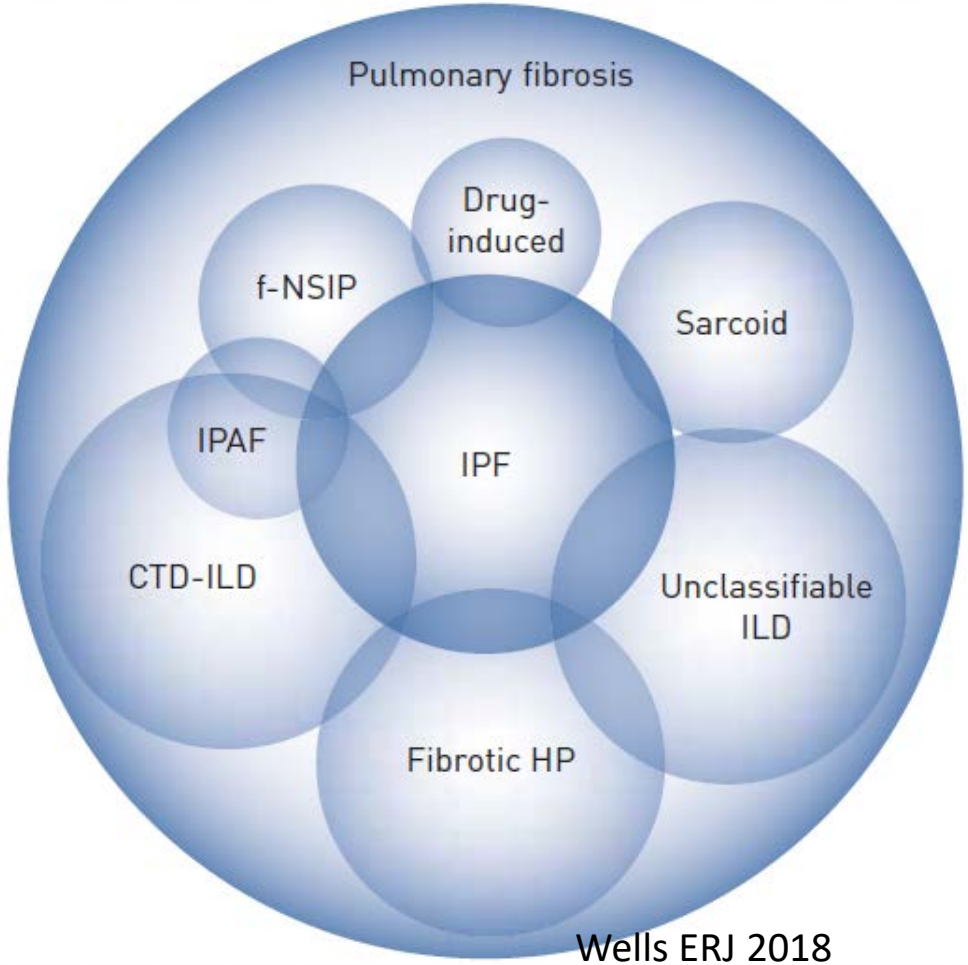
Progressive Pulmonary Fibrosis



Cottin Eur Respir Rev 2018

Progressive Pulmonary Fibrosis

- Heterogeneity of PF frustrated attempts to understand pathogenesis and find treatment
- The definition of IPF narrowed substantially
- Approved drugs for IPF left many patients without access to therapy
- It is recognized that patients with UIP due to rheumatoid or fHP progress similarly to patients with IPF.
- Progressive Fibrosing ILD phenotype suggested
- Builds on IIP guidelines recommendation to group via disease trajectory



Wells ERJ 2018
Cottin Eur Respir Rev 2018
Travis AJRCCM 2013

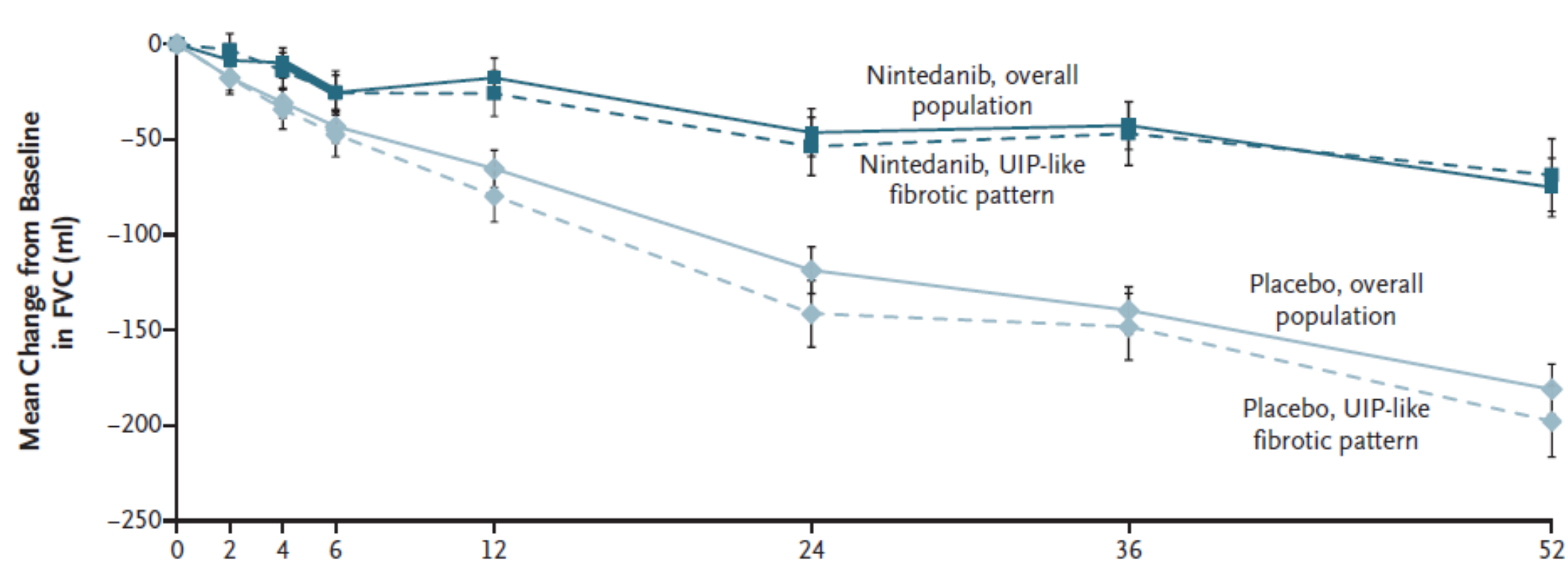
Progressive Pulmonary Fibrosis

- IMPULSIS trial enrolled 663 patients with PF-ILD
- Patients had to progress within prior 2 years; 2/3 had UIP pattern of fibrosis

End Point	Nintedanib (N=332)	Placebo (N=331)	Difference (95% CI)
Primary end point			
Rate of decline in the FVC at 52 wk — ml/yr†			
Overall population	−80.8±15.1	−187.8±14.8	107.0 (65.4 to 148.5)‡
Patients with a UIP-like fibrotic pattern	−82.9±20.8	−211.1±20.5	128.2 (70.8 to 185.6)‡
Patients with other fibrotic patterns	−79.0±21.6	−154.2±21.2	75.3 (15.5 to 135.0)§

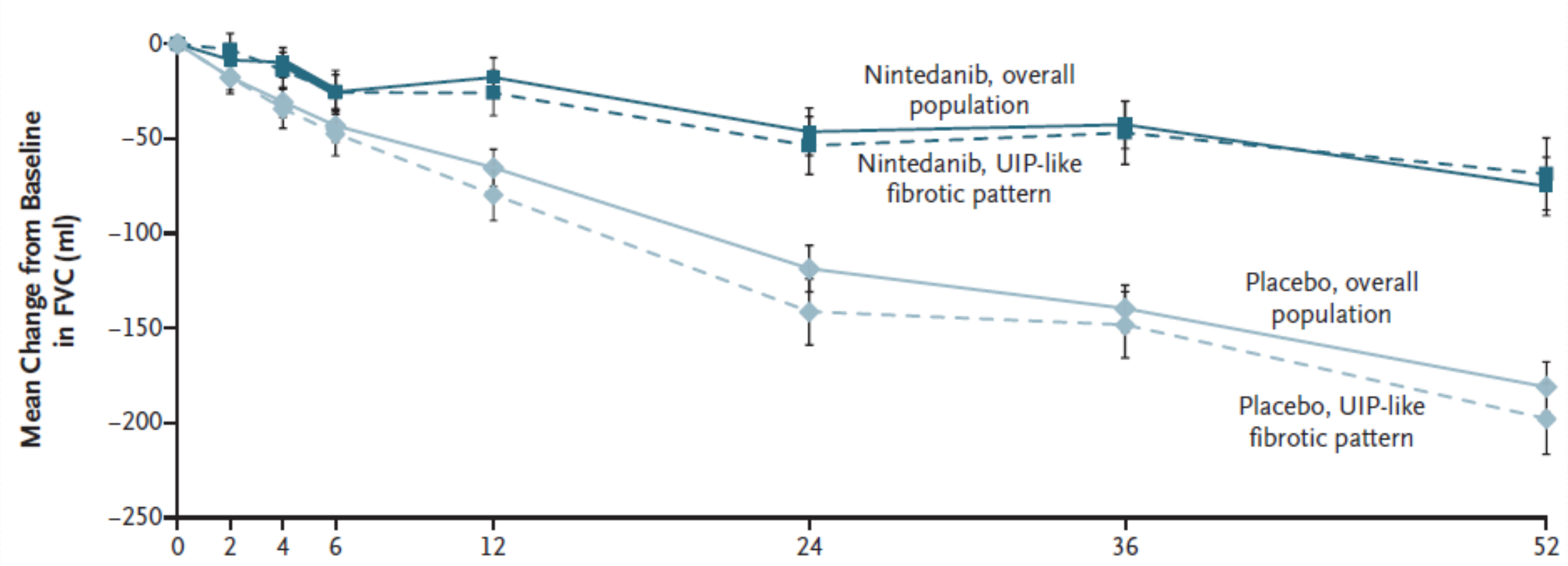
Flaherty NEJM 2019

Progressive Pulmonary Fibrosis



Flaherty NEJM 2019

Progressive Pulmonary Fibrosis



Flaherty NEJM 2019

Progressive Pulmonary Fibrosis

Definition requires 2 of 3 criteria within past year:

- Worsening respiratory symptoms
- Worsening physiology
- Imaging progression

No alternative explanation!

<u>Worsening PFTs:</u>

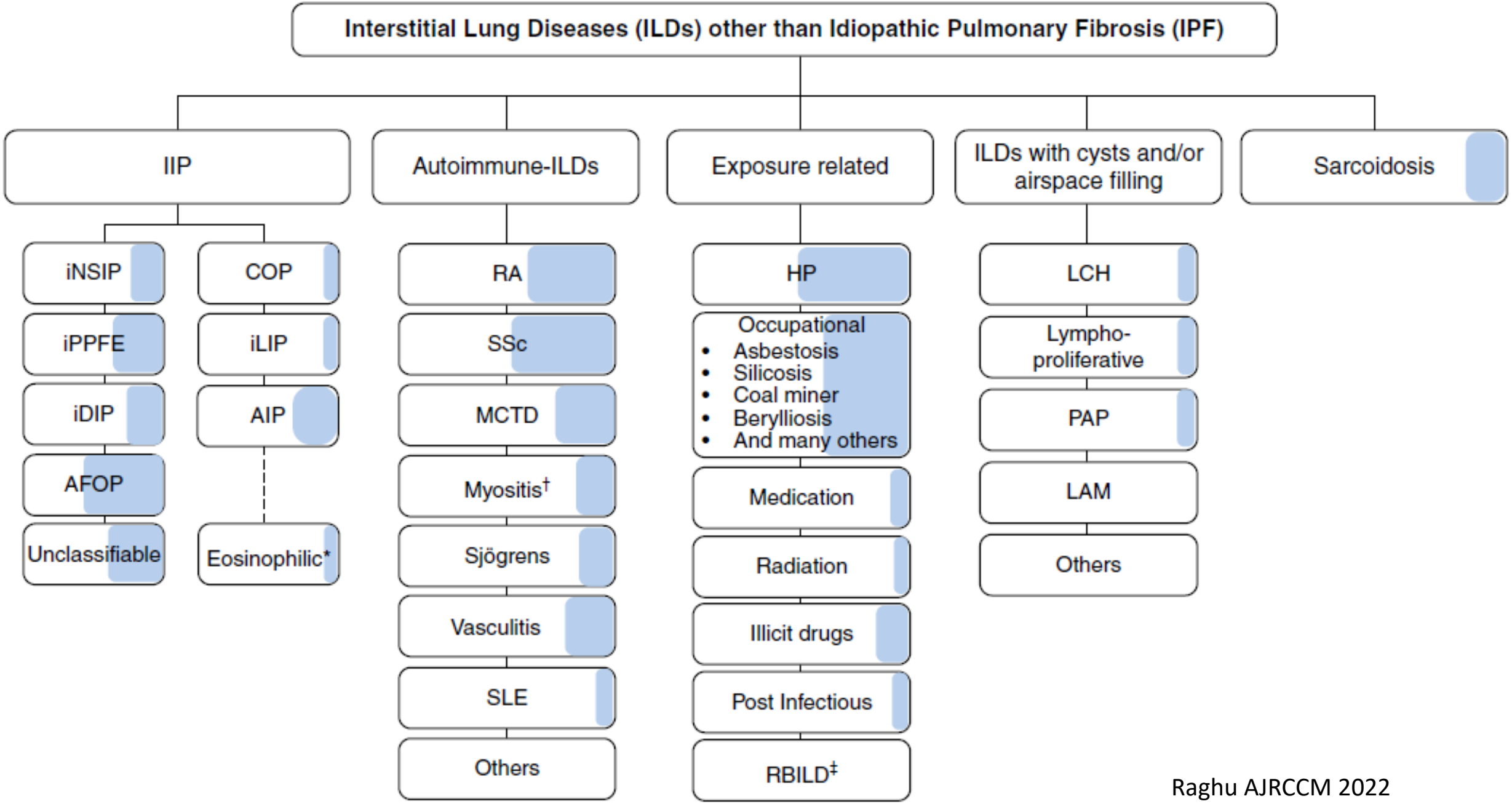
- Absolute decline in FVC >=5%
- Absolute decline in DLCO >=10%
  - Ensure not worsening pulm HTN

<u>Imaging progression:</u>

- Increased extent/severity of traction bronchiectasis/bronchiolectasis
- Increased GGO with traction
- New fine reticulation
- Increased extent/coarseness of reticulation
- New or increased honeycombing
- Increased lobar volume loss

*Use of Quantitative HRCT coming

Raghu AJRCCM 2022



Raghu AJRCCM 2022

Progressive Pulmonary Fibrosis

Pirfenidone

- Systematic review identified two prospective RCTs:
- 253 patients with fibrotic unclassifiable ILD followed for 24 weeks; primary outcome was change in FVC measured by home spirometer. No difference.
- RELIEF trial enrolled 127 patients with fHP, CTD, NSIP, asbestosis. It was terminated early due to slow enrollment. Findings suggest a benefit of pirfenidone in slowing loss of FVC.
- Meta-analysis suggested a benefit of pirfenidone in slowing disease progression, but very low certainty due to methodologic concerns.

2022 Guidelines recommend more research into effectiveness and safety in non-IPF with PPF and specific types of non-IPF ILD with PPF

Maher Lancet Resp Med 2020
Behr Lancet Resp Med 2021
Ghazipura Annals ATS 2022
Raghu AJRMCCM 2022

Progressive Pulmonary Fibrosis

Nintedanib

- Systematic review identified one prospective RCT (INBUILD) and a post-hoc analysis of INBUILD that assessed response in individual type of ILD manifesting PFF.
- Meta-analysis suggested a benefit of nintedanib in slowing disease progression, but no effect on mortality. Effect, but very low certainty due to methodologic concerns.

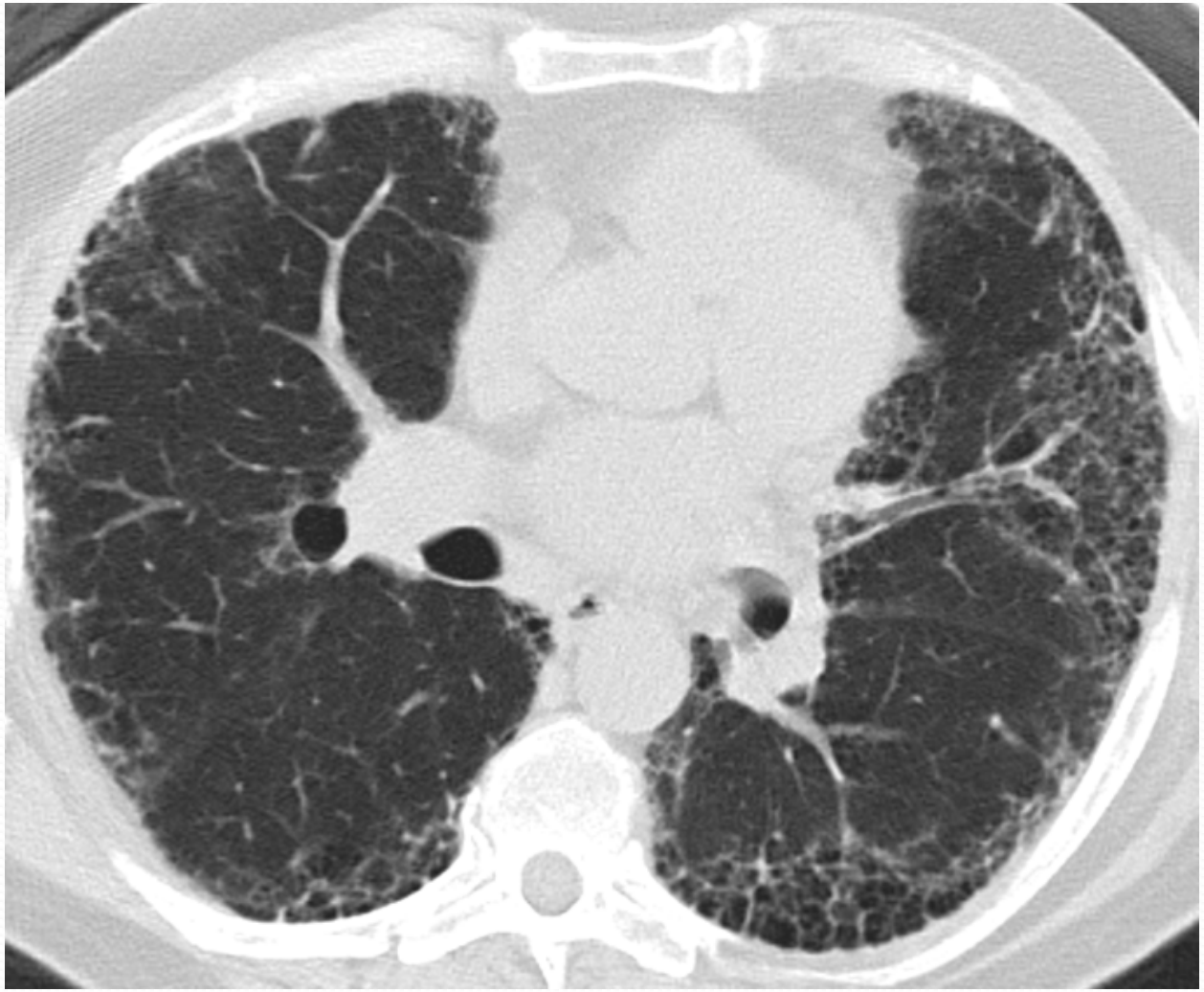
2022 Guidelines make a *conditional* recommendation to use nintedanib in PPF based on low quality evidence. They also recommend more research.

Flaherty NEJM 2019
Wells Lancet Resp Med 2020
Ghazipura Annals ATS 2022
Raghu AJRMCCM 2022

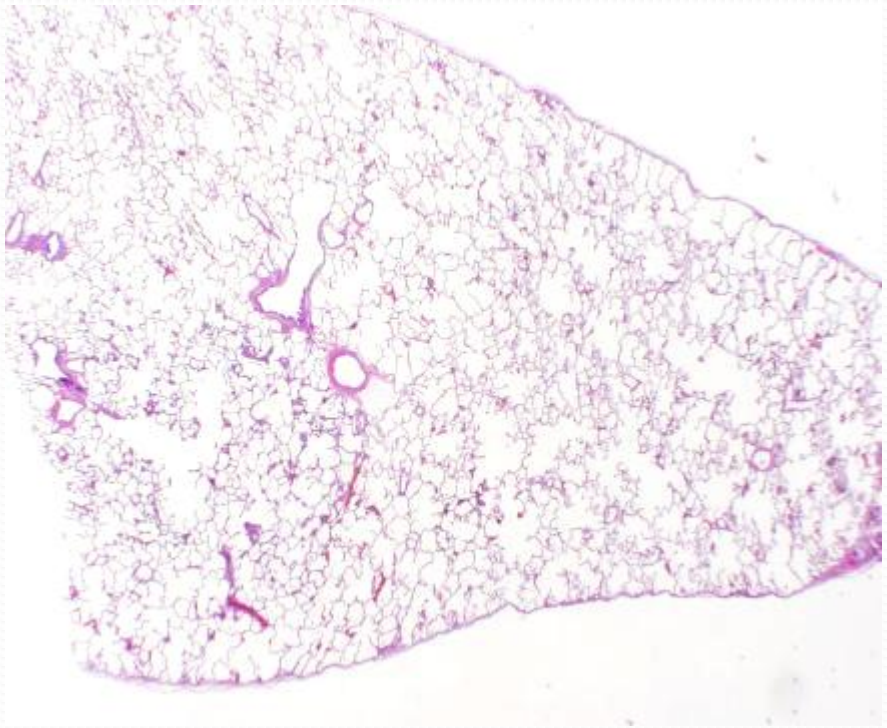
Summary

- Diagnostic approach to IPF remains multidisciplinary
- Pre-test probability is important
- Evolving role for TBLC, genomic classifier
- Progressive pulmonary fibrosis is a disease behavior that warrants close monitoring, treatment

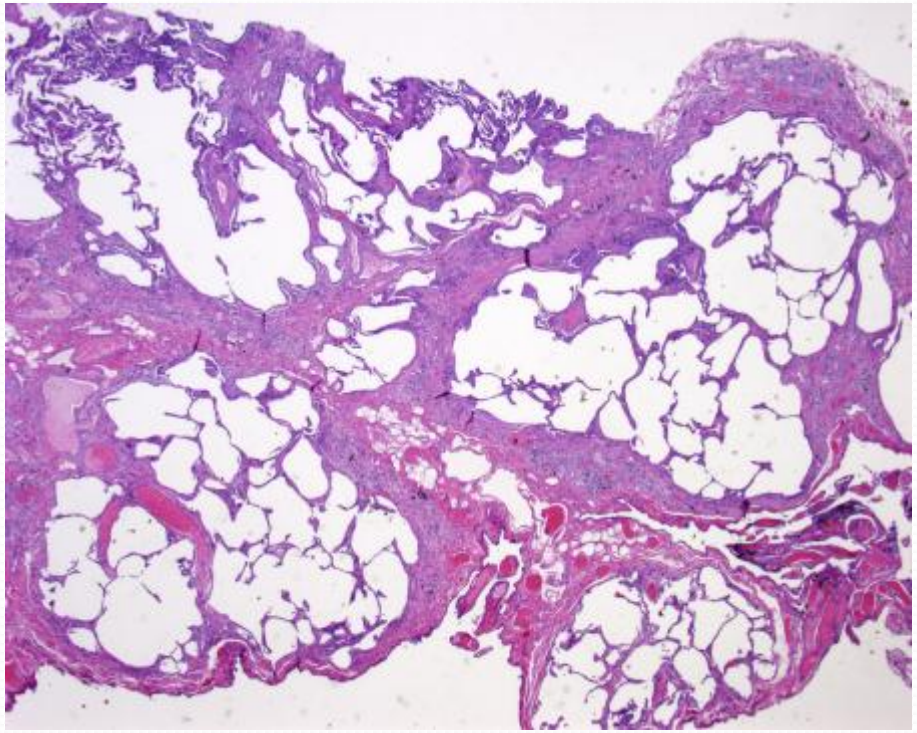
Idiopathic Pulmonary Fibrosis (IPF)



Idiopathic Pulmonary Fibrosis (IPF)

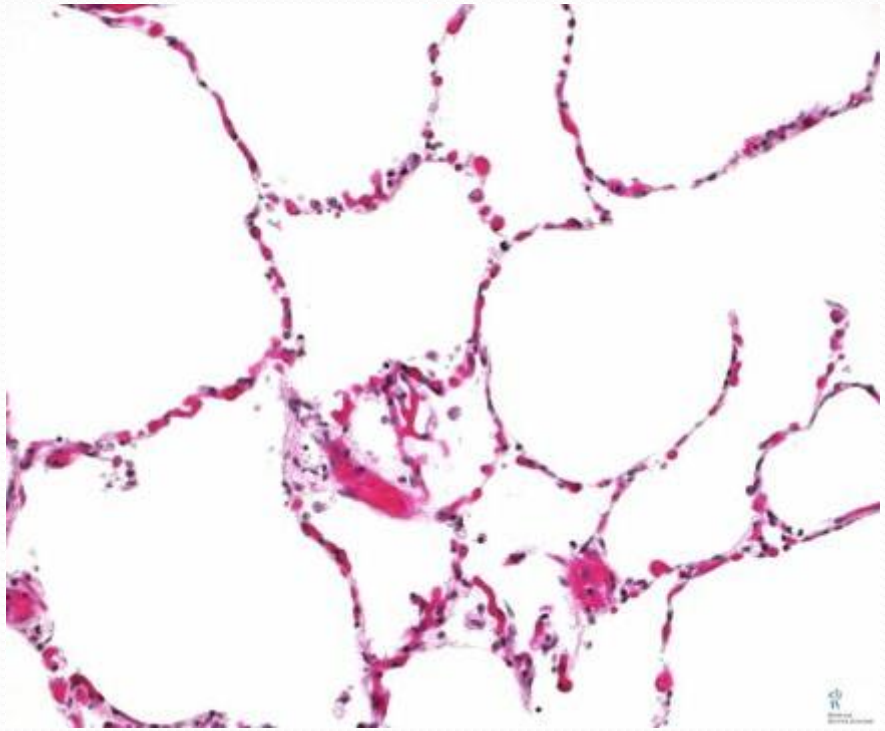


Normal Lung

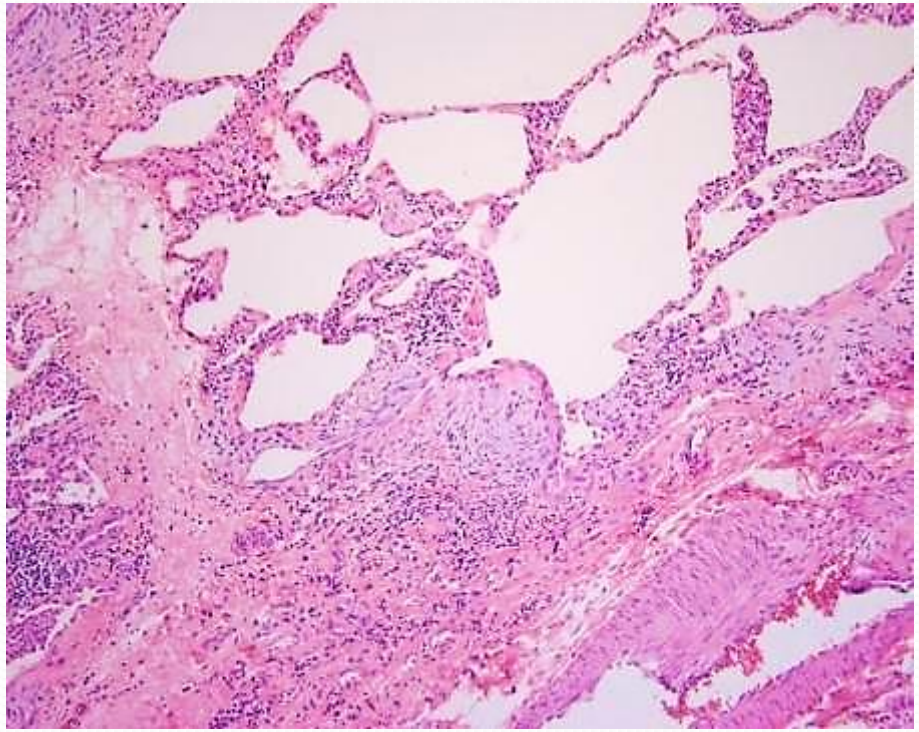


Usual Interstitial Pneumonia

Idiopathic Pulmonary Fibrosis (IPF)



Normal Lung



Usual Interstitial Pneumonia

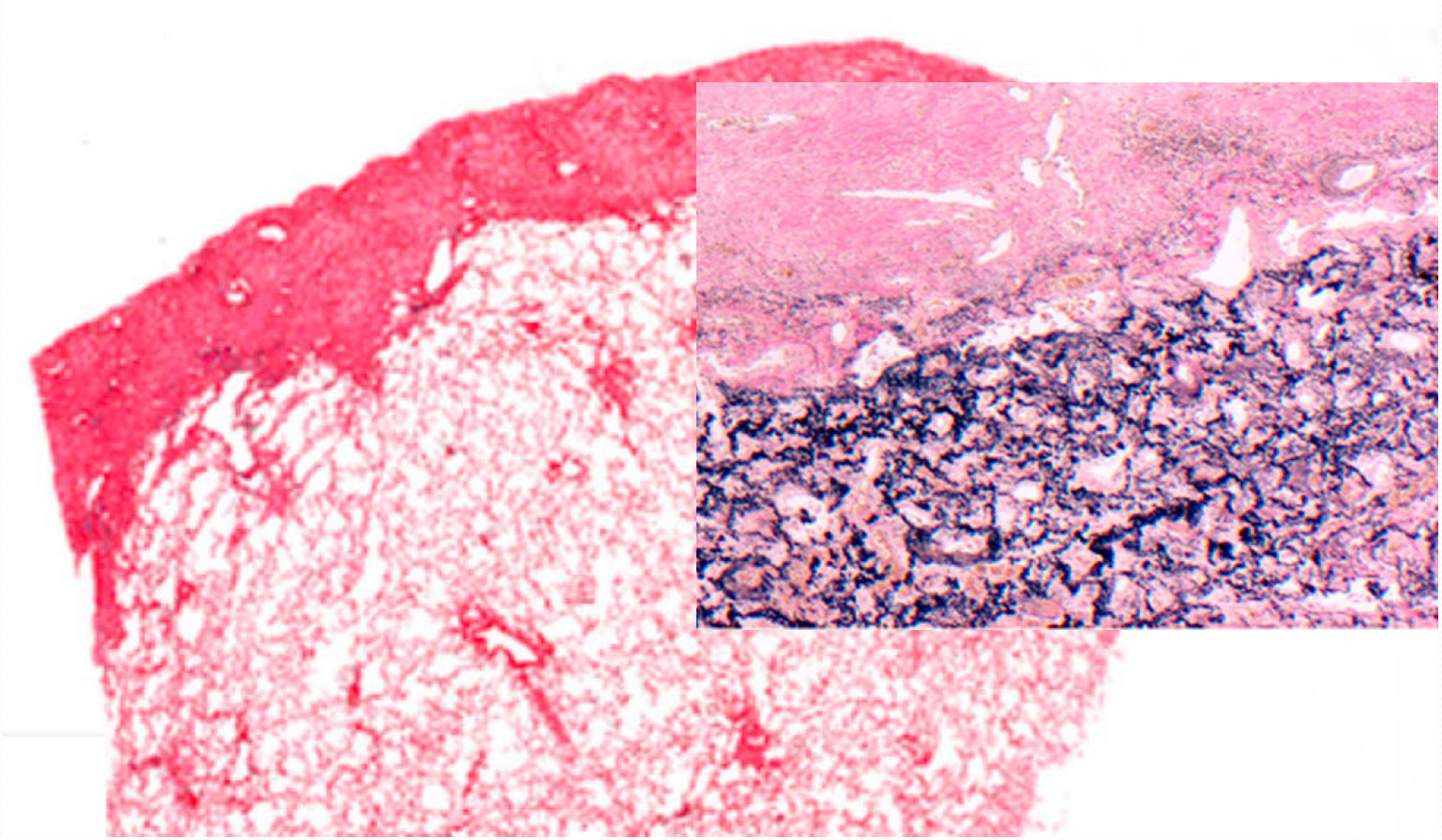
Pleuroparenchymal Fibroelastosis



Pleuroparenchymal Fibroelastosis



Pleuroparenchymal Fibroelastosis



National Jewish Health®



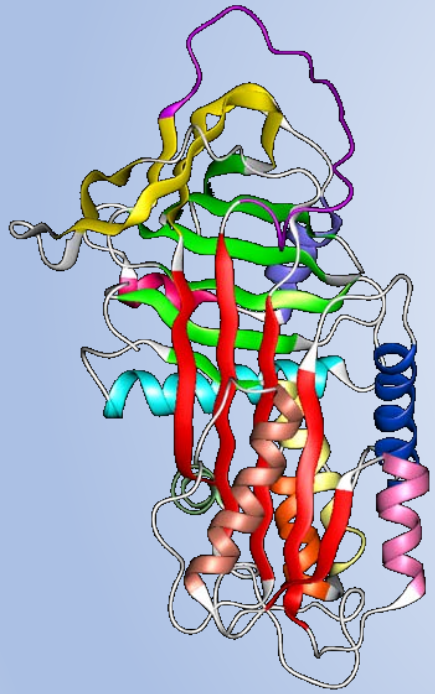
Alpha-1 Antitrypsin Deficiency

Robert A. Sandhaus, MD, PhD

Disclosures

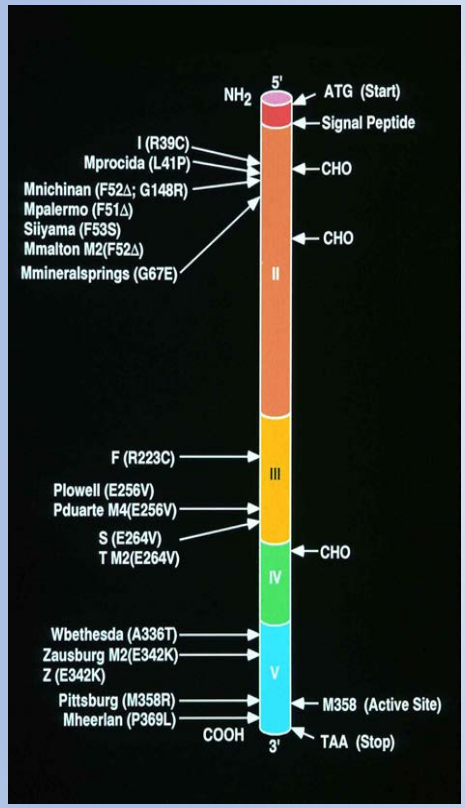
- Employment: National Jewish Health, the Alpha-1 Foundation, AlphaNet, and AlphaNet Canada
- Grants to National Jewish Health, the Alpha-1 Foundation, or AlphaNet from NIH/NHLBI, Grifols, CSL Behring, Takeda, Vertex, Mereo
- Advisory or consulting agreements with Vertex, InhibRx, Grifols, CSL Behring, Takeda, Mereo, Intellia, Novo Nordisk, AstraZeneca, Arrowhead, Dicerna, Evolve, Koro Bio, Peak Bio

Alpha-1 Antitrypsin (AAT): *The Protein*



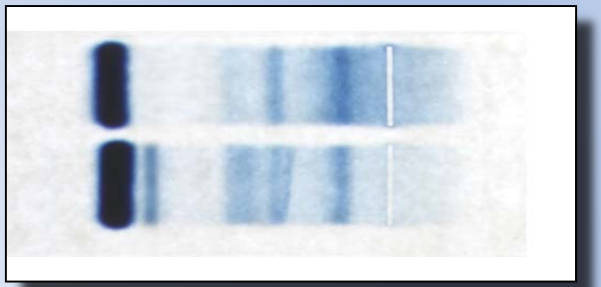
- 52,000 MW protein coded for by single gene on the long arm of chromosome 14
- Synthesis predominantly in hepatocytes
- Transported to blood where it bathes all tissues
- The body's major SERPIN
  - **SER**ine **P**rotease **IN**hibitor
- Primary target: neutrophil elastase
- Acute phase reactant
- Anti-inflammatory properties

Alpha-1 Antitrypsin *Deficiency* (AATD or Alpha-1): *The Condition*



- Genetic condition causing decreased levels (or function) of AAT in blood and tissues
- Over 200 different mutations identified
  - ~ ⅓ associated with deficiency or dysfunction
- Usually estimated to be 100,000 people in the US and a similar number in Europe
- Over 20 million carriers of a single abnormal AAT gene in the US
- Predisposes to lung, liver, other diseases
- **<u>But</u> people can have severe Alpha-1 and no disease**

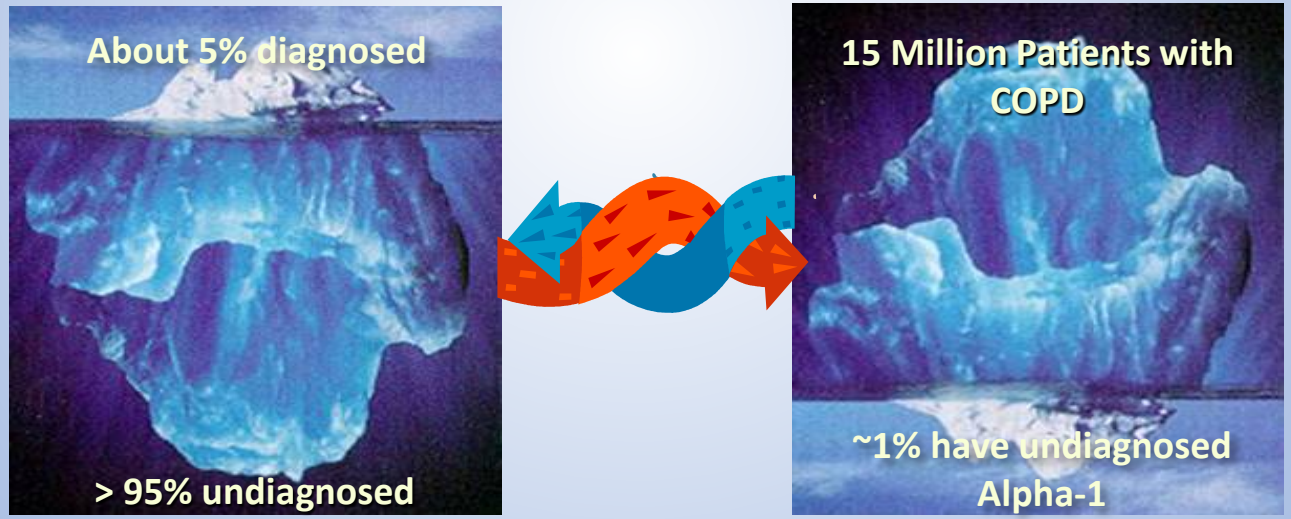
A Brief History of Alpha-1



- 1963 - Alpha$_1$-Antitrypsin Deficiency first described
- 1964 - Role of elastase in emphysema
- 1967 - Discovery of neutrophil elastase (Janoff)
- 1969 - Neonatal cirrhosis (Sharp)
- 1970s - Neutrophil elastase causes emphysema (me)
  - Alpha-1 antitrypsin blocks neutrophil elastase (me)
  - Cigarette smoke destroys alpha$_1$-antitrypsin function (me)
- 1980s - Deficiency and liver disease due to poor exit of AAT from liver cells
- 1987 - First augmentation therapy approved, followed by three more
- 2015 - Effectiveness accepted?

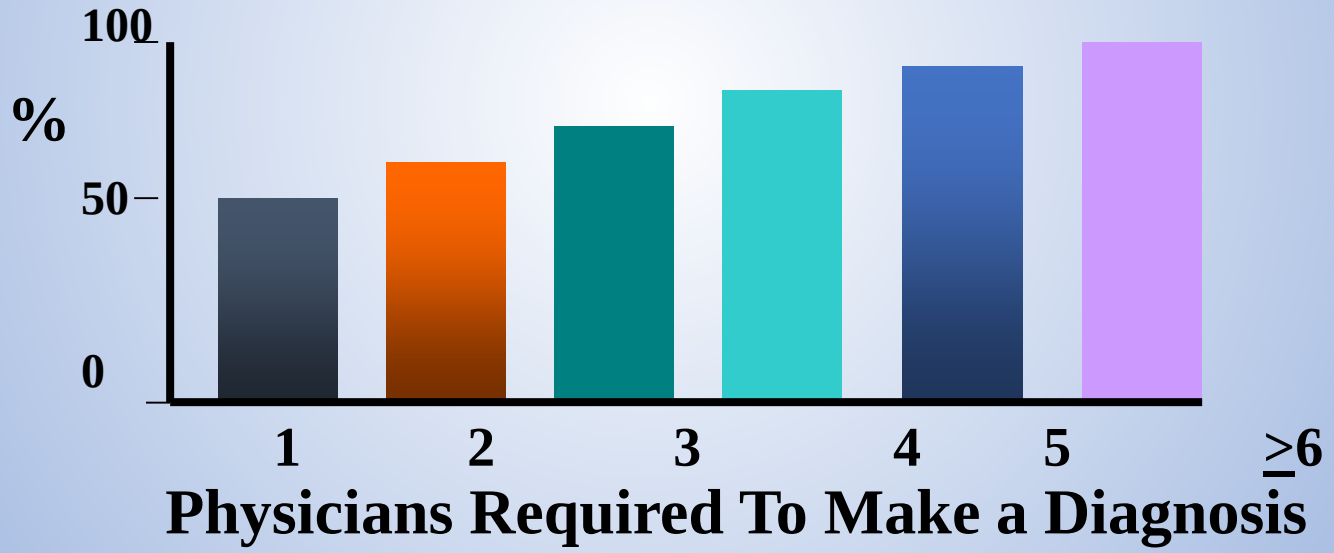
How many Alphas are out there?

- ~~100,000 with severe deficiency in~~ US
- At least 150,000 with severe deficiency and COPD! (Perhaps as many as 300,000)

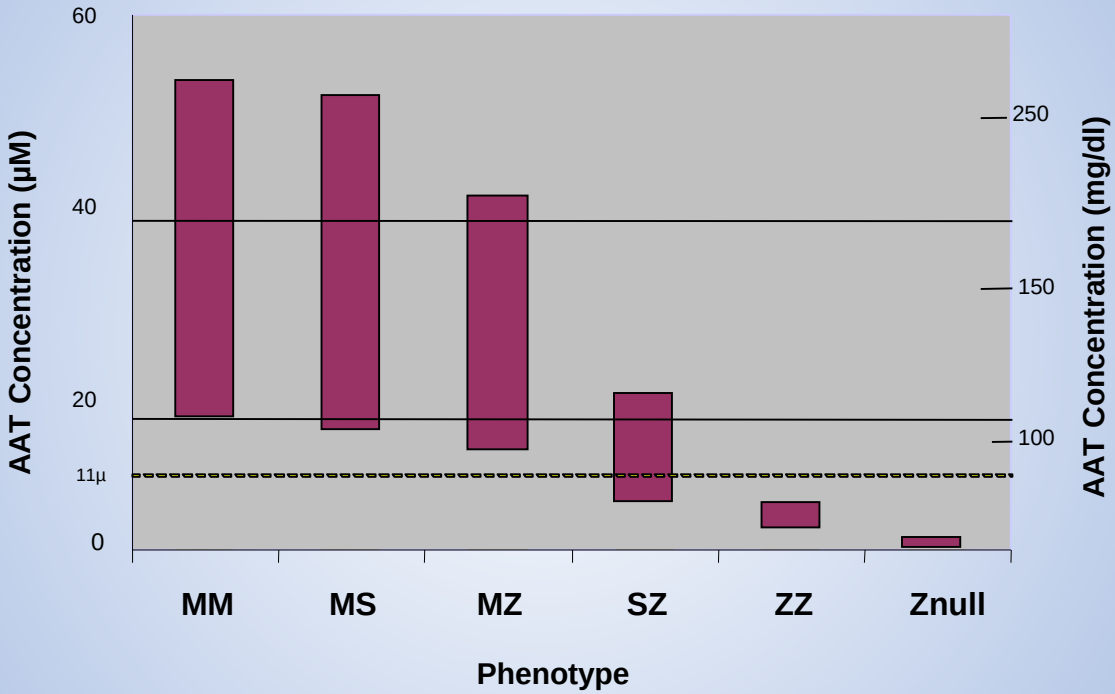


AATD Clinical Presentation

Mean Age at first symptoms **35 years**
Mean Age at diagnosis **41 years**



Stoller, Clev Clinic J Med 1994; 61:461

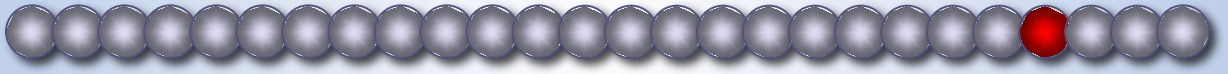

60
40
20
11µ
0
AAT Concentration (µM)
250
150
100
AAT Concentration (mg/dl)
MM
MS
MZ
SZ
ZZ
Znull
Phenotype

The Genome and Alpha-1



~ 14,000 base pairs

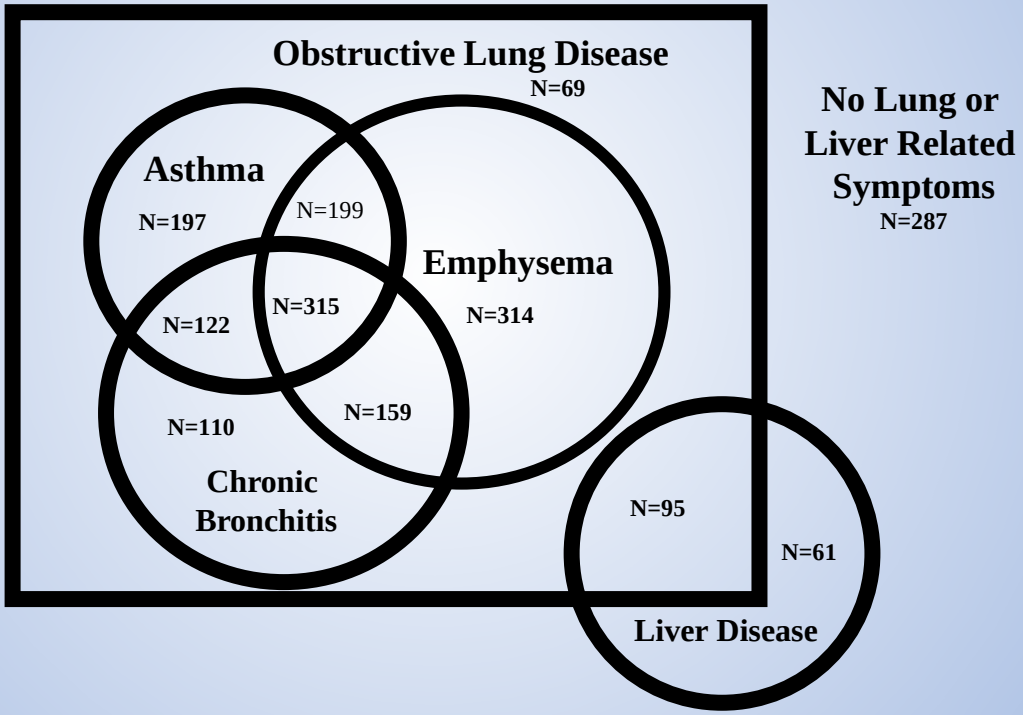




394 amino acids

Co-dominant allelic expression

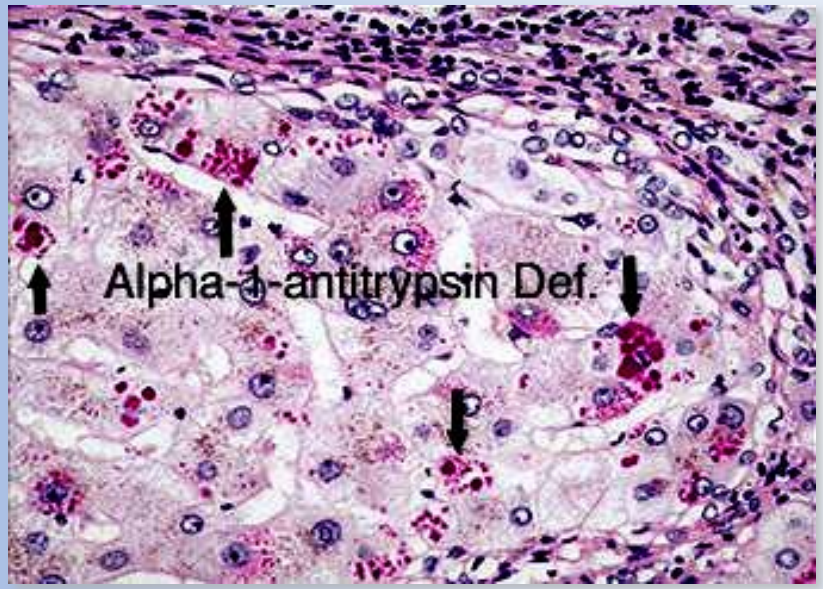
Diagnoses Reported in Severe AAT Deficiency
(N=1851)



Strange C, et al. Respiration 2006, 73(2):185

Diseases Associated with Alpha-1

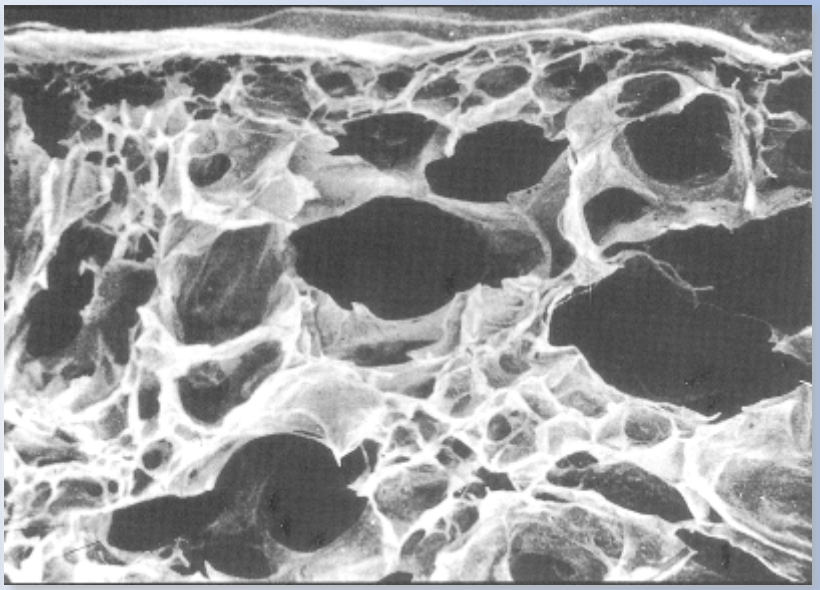
Liver



Childhood and adult liver disease

- Fulminant liver failure
- Cirrhosis

Lung



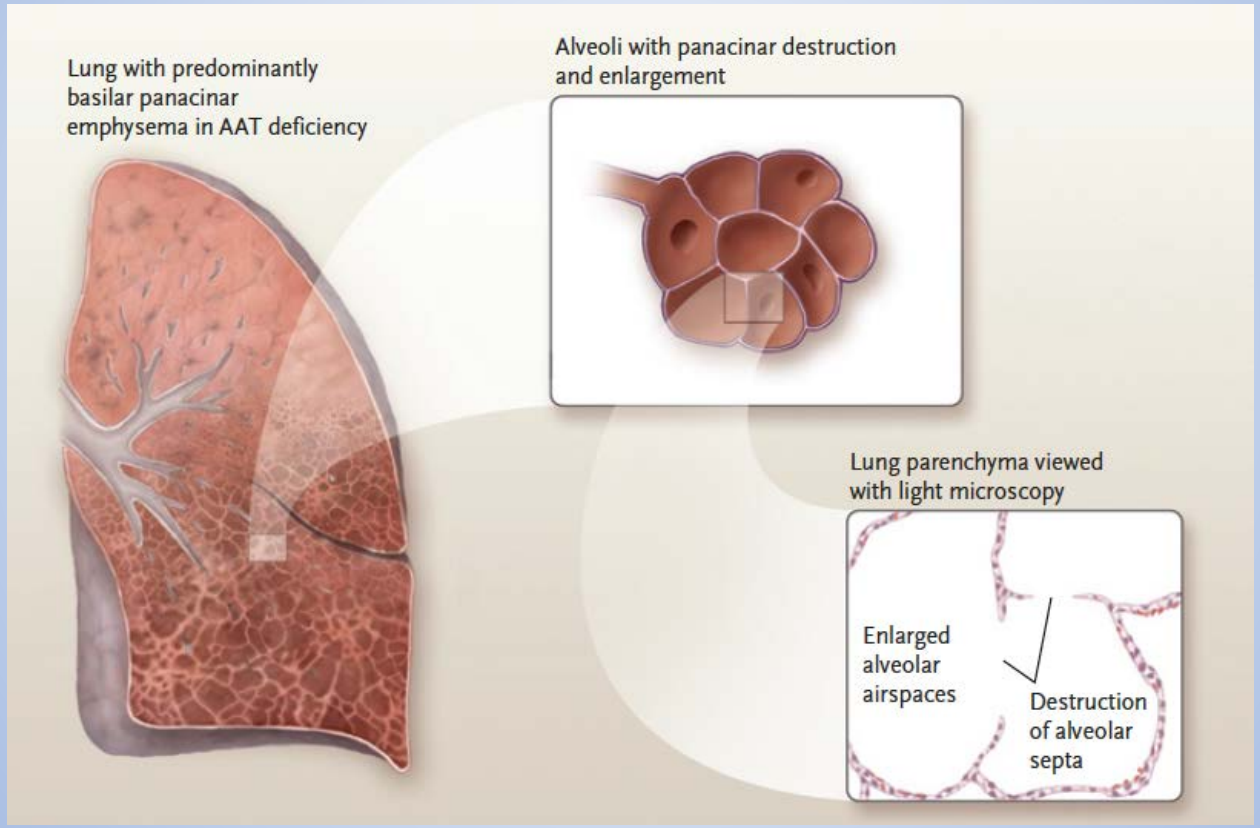
Lung disease – "AAT-COPD"

- Emphysema
- Bronchiectasis

Diseases Associated with Alpha-1

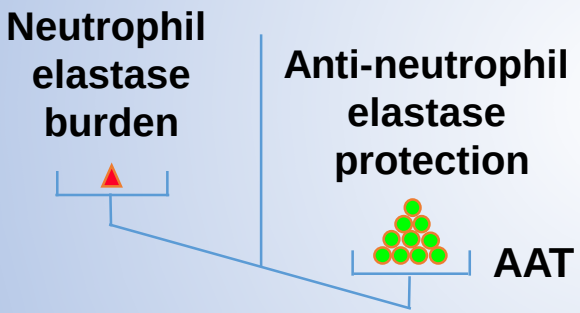
- Others
  - Vasculitis
    - Necrotizing panniculitis
    - Granulomatosis with polyangiitis (formerly Wegener's)
  - Hepatocellular carcinoma
  - Susceptibility to atypical TB

The Lung in Alpha-1

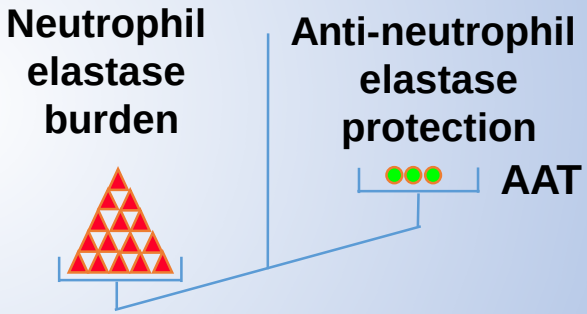


Protease-Antiprotease Balance

Normal

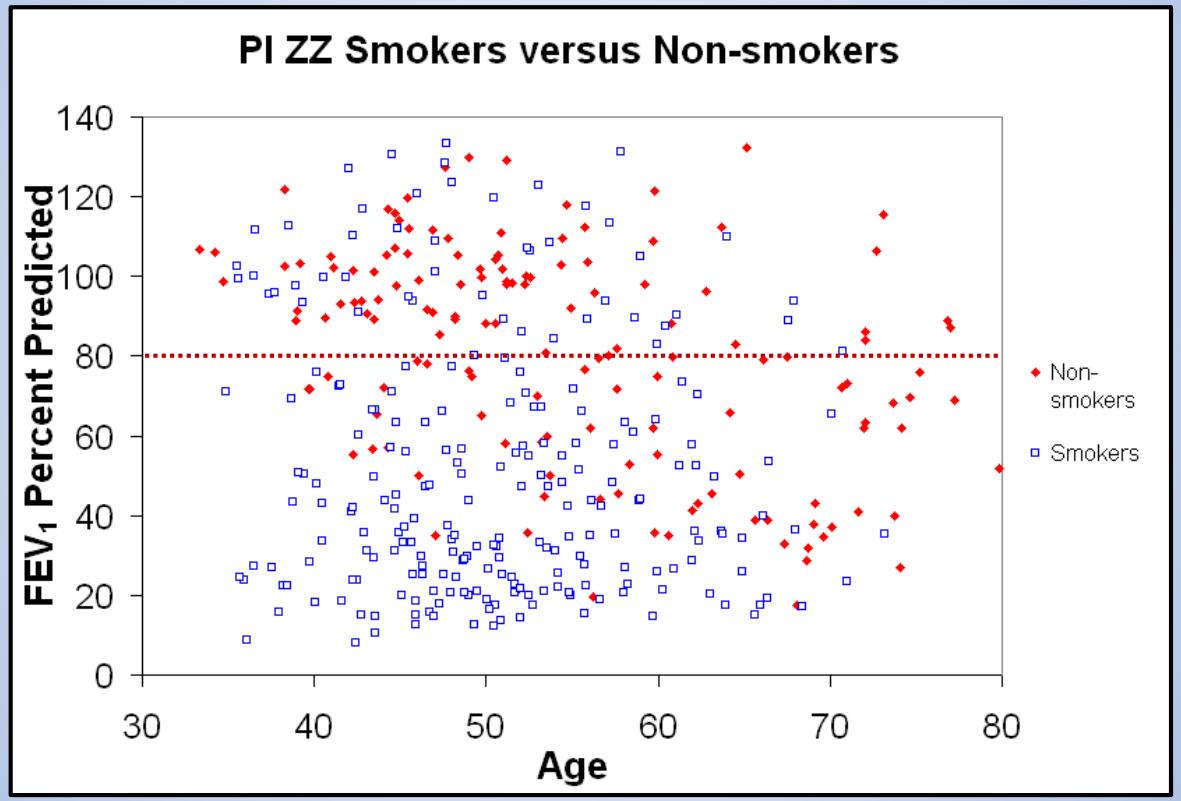


AAT Deficiency



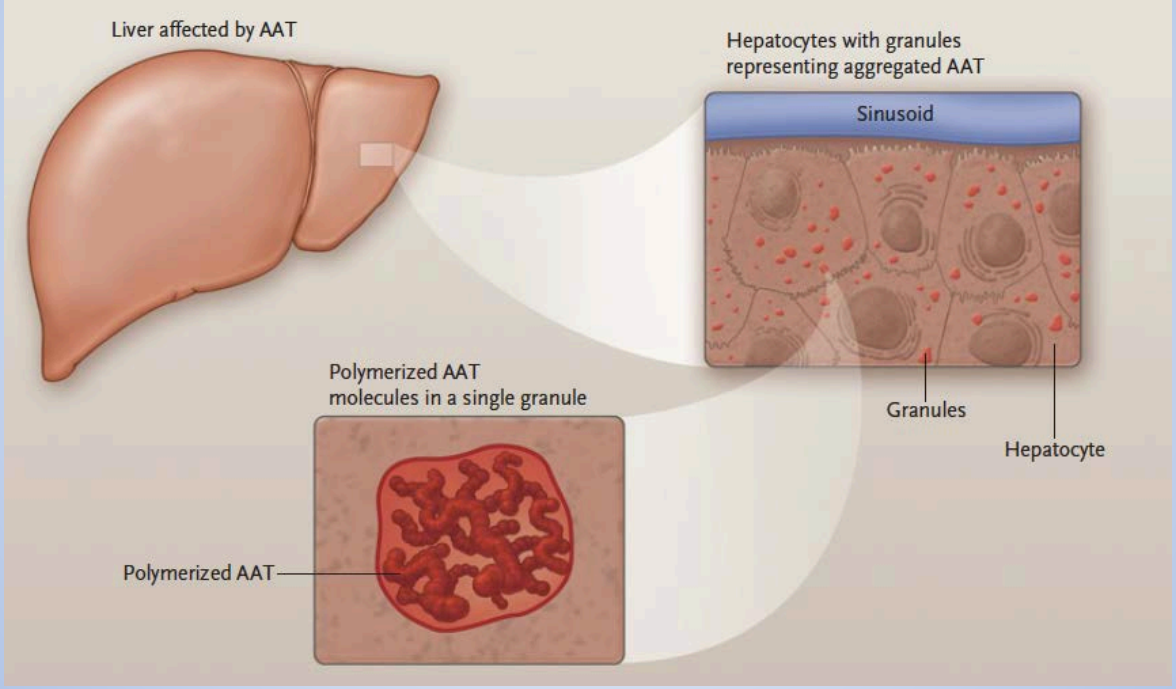
Lung damage is the result of both a burden of neutrophil elastase and a lack of sufficient AAT

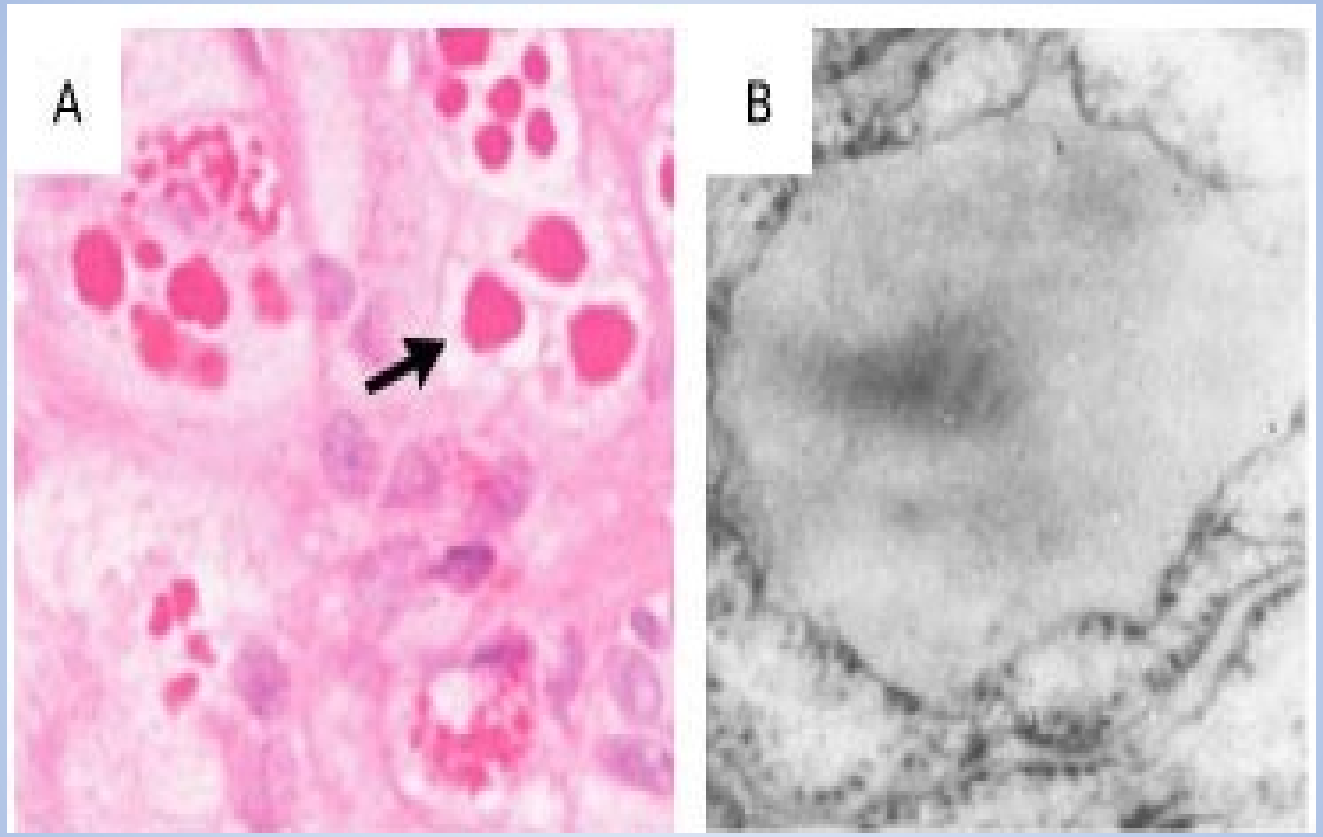
Impact of Smoking in AATD



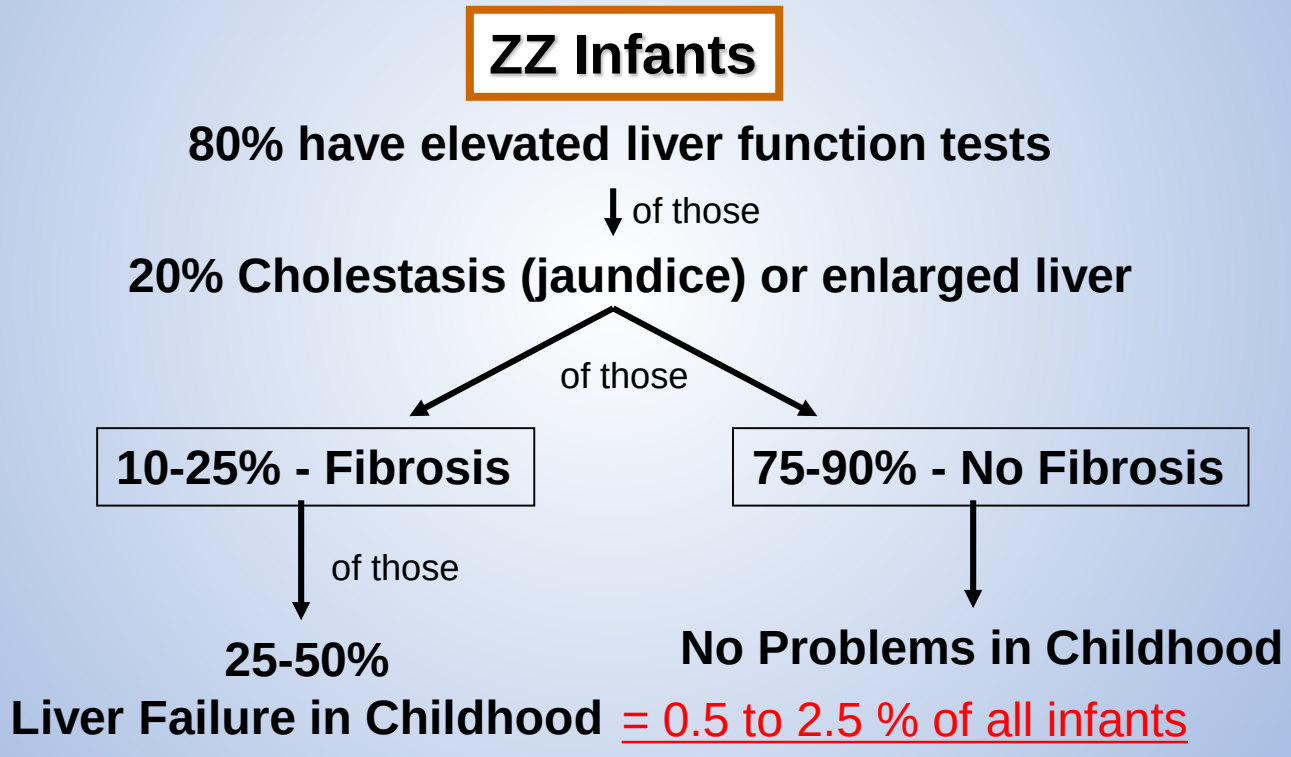
Demeo, DL, et al. Thorax 2007; 62:806

The Liver in Alpha-1




A
B

Of All Babies Born with Alpha-1



American Thoracic Society/European Respiratory Society Statement: Standards for the Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency

This Joint Statement of the American Thoracic Society and the European Respiratory Society was approved by the ATS Board of Directors, December 2002, and by the ERS Executive Committee, February 2003

CONTENTS

Executive Summary

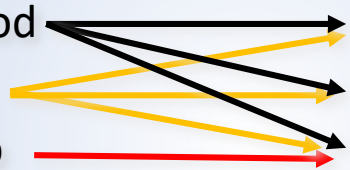
Introduction 820
Goals, Organization of the Project, and Timeline 820
Summary of Main Recommendations Regarding Diagnosis and Management by the Alpha-1 Antitrypsin Deficiency Task Force 820
Clinical Recognition of AAT Deficiency 820
Genetic Testing for AAT Deficiency 821
Liver Disease 821
Other Conditions 822
Efficacy of Augmentation Therapy 822
General Management of Obstructive Lung Disease . . 822
Surgical Procedures 836
Special Situations 837
Future Directions of Research in AAT Deficiency 837
Some Specific Research Needs in AAT Deficiency 838
Appendix 1. Primary Evidence Table: Summary of Studies Addressing Clinical Features of PI*ZZ Alpha-1 Antitrypsin Deficiency 840
Appendix 2. General Population-based Studies: Prevalence of PI Variants and Risk of Associated Lung Disease 841
Appendix 3. Chronic Obstructive Pulmonary Disease Population Studies: Prevalence of PI Variants and Risk of Associated Lung Disease 842
Appendix 4. Serial Case Studies in PI*ZZ: Risk

Major contribution of the 2003 Standards Document

- Who should be tested?
  - **All individuals with COPD**
  - Adult asthmatics with incomplete reversibility on maximal therapy
  - Bronchiectasis without other risk factors
  - Siblings of AAT deficient individual
  - Fam Hx of AAT deficiency or early onset COPD
  - Cirrhosis without apparent risk factors

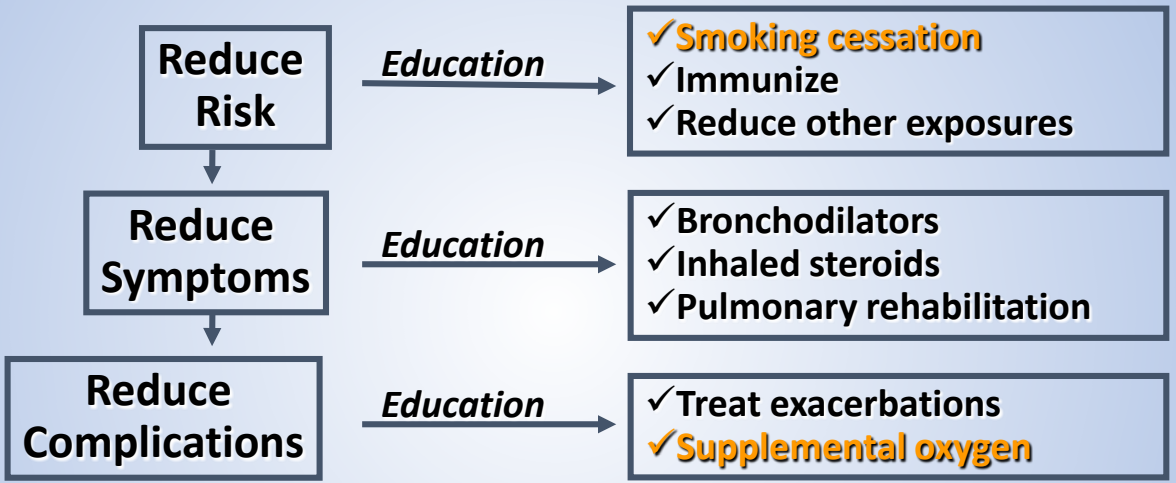
Making the Diagnosis

- Simple to diagnose
  - Tube of blood
  - Finger stick
  - Buccal swab



  - Level
  - Pi-typing (phenotyping)
  - Genotyping
- All can be used for sequencing the *serpina1* gene
- **Alpha-1 is a laboratory diagnosis, not a clinical diagnosis**
- Problems
  - Differences between the various testing methods difficult to appreciate by those who order it

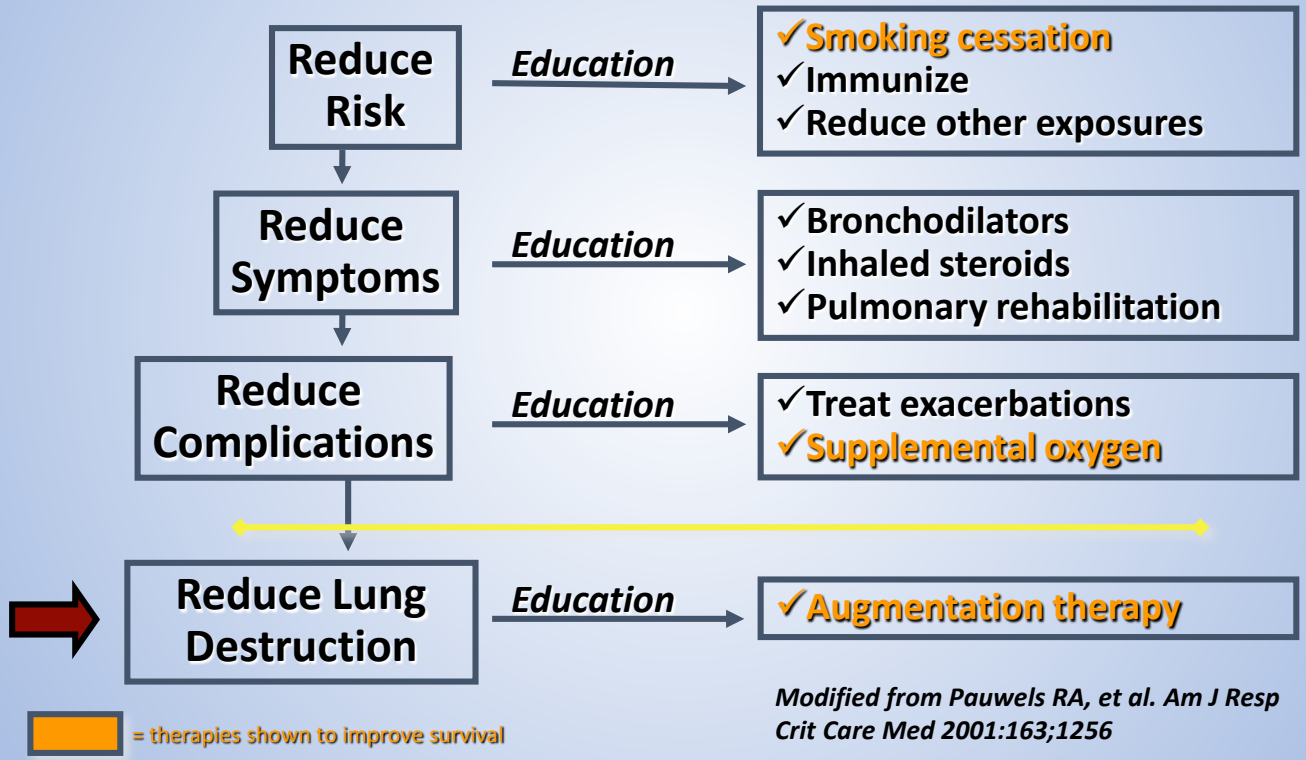
COPD is Treatable!



= therapies shown to improve survival

Modified from Pauwels RA, et al. Am J Resp Crit Care Med 2001:163;1256

Alpha-1 COPD is Treatable!



Modified from Pauwels RA, et al. Am J Resp Crit Care Med 2001:163;1256

Augmentation Therapy for Alpha-1

- 1980s NIH evaluated purified AAT administration
  - Attempt to interest plasma companies
  - Re-attempt
- 1987 Prolastin (Cutter=> Miles=> Bayer=> Talecris=> Grifols)
- 2003 Aralast (Alpha Therapeutics=> Baxter/Grifols=> Baxter=> Baxalta=> Shire=> Takeda)
- 2004 Zemaira (Armor=> Cention=> Aventis Behring=> ZLB Behring=> CSL Behring)
- 2010 Glassia (American Red Cross/Kamada => Baxter => Baxalta => Shire => Takeda)

- (Prolastin-C Liquid, Aralast-NP)

Augmentation Therapy for Alpha-1

- Biochemical efficacy has been repeatedly demonstrated
- 2 small randomized, blinded clinical trials
- 1 well-powered randomized, blinded trial
- Evidence of efficacy in 8 trials (mostly case controlled)
  - Some misinterpretation of these studies
- Expensive
- A pooled blood product
- 2016 Clinical Practice Guidelines: Consider for Alpha-1 patients with evidence of emphysema
- Augmentation therapy improves survival

Intravenous augmentation treatment and lung density in severe α1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial

*Kenneth R Chapman, Jonathan G W Burdon, Eeva Piitulainen, Robert A Sandhaus, Niels Seersholm, James M Stocks, Berend C Stoel, Liping Huang, Zhenling Yao, Jonathan M Edelman, Noel G McElvaney, on behalf of the RAPID Trial Study Group**

Summary

Background The efficacy of α1 proteinase inhibitor (A1PI) augmentation treatment for α1 antitrypsin deficiency has not been substantiated by a randomised, placebo-controlled trial. CT-measured lung density is a more sensitive measure of disease progression in α1 antitrypsin deficiency emphysema than spirometry is, so we aimed to assess the efficacy of augmentation treatment with this measure.

Methods The RAPID study was a multicentre, double-blind, randomised, parallel-group, placebo-controlled trial of A1PI treatment in patients with α1 antitrypsin deficiency. We recruited eligible non-smokers (aged 18–65 years) in 28 international study centres in 13 countries if they had severe α1 antitrypsin deficiency (serum concentration <11 μM) with a forced expiratory volume in 1 s of 35–70% (predicted). We excluded patients if they had undergone, or were on the waiting list to undergo, lung transplantation, lobectomy, or lung volume-reduction surgery, or had selective IgA deficiency. We randomly assigned patients (1:1; done by Accovion) using a computerised pseudorandom number generator (block size of four) with centre stratification to receive A1PI intravenously 60 mg/kg per week or placebo for 24 months. All patients and study investigators (including those assessing outcomes) were unaware of treatment allocation throughout the study. Primary endpoints were CT lung density at total lung capacity (TLC) and functional residual capacity (FRC) combined, and the two separately, at 0, 3, 12, 21, and 24 months, analysed by modified intention to treat (patients needed at least one evaluable lung density measurement). This study is registered with ClinicalTrials.gov, number NCT00261833. A 2-year open-label extension study was also completed (NCT00670007).

Findings Between March 1, 2006, and Nov 3, 2010, we randomly allocated 93 (52%) patients A1PI and 87 (48%) placebo, analysing 92 in the A1PI group and 85 in the placebo group. The annual rate of lung density loss at TLC and

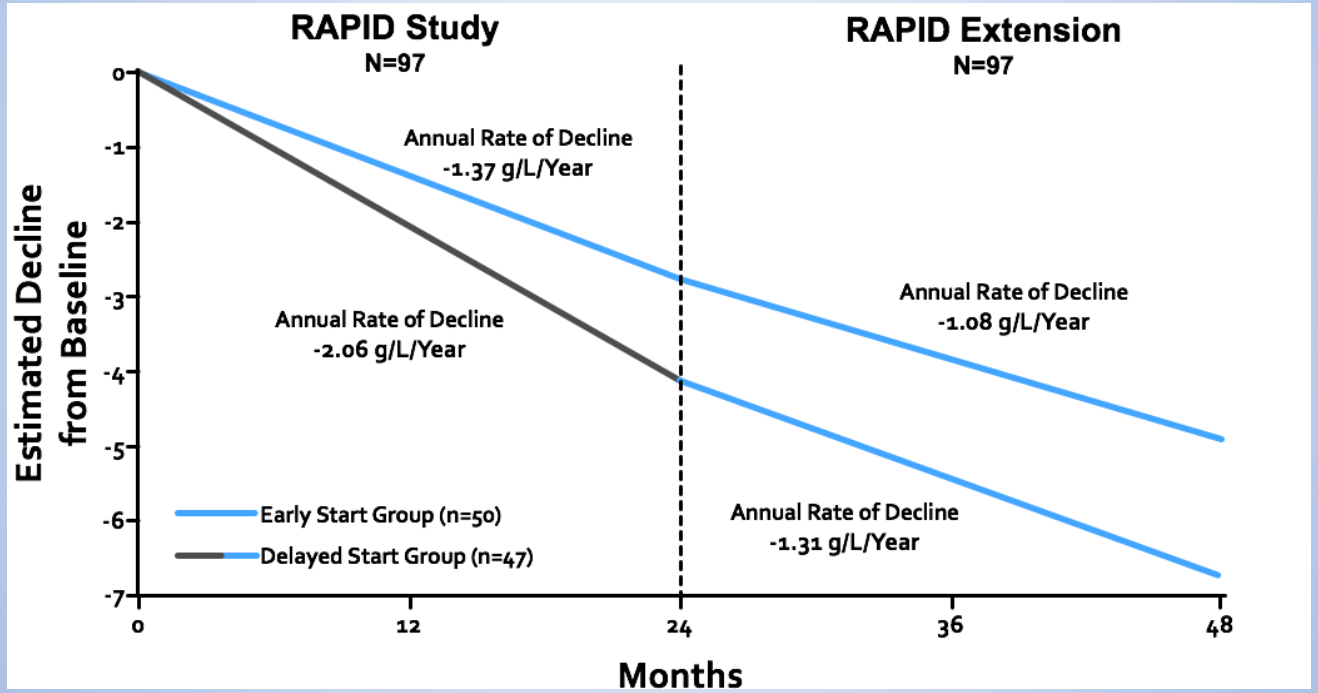
Published Online
May 28, 2015
http://dx.doi.org/10.1016/S0140-6736(15)60860-1

See Online/Comment
http://dx.doi.org/10.1016/S0140-6736(15)60036-8

*Members listed at end of paper

Asthma and Airway Centre, University Health Network, Toronto Western Hospital, and Division of Respiratory Medicine, Department of Medicine, University of Toronto, Toronto, ON, Canada (Prof K R Chapman MD); **St Vincent's Hospital, Fitzroy, Melbourne, VIC, Australia** (J G W Burdon MD); **Skåne University Hospital, Lund University, Malmö, Sweden** (E Piitulainen MD); **National Jewish Health, Denver, CO, USA** (Prof R A Sandhaus MD);

RAPID Study and Extension



Chronic Obstructive Pulmonary Diseases:
Journal of the COPD Foundation

Clinical Practice Guidelines

The Diagnosis and Management of Alpha-1 Antitrypsin Deficiency in the Adult

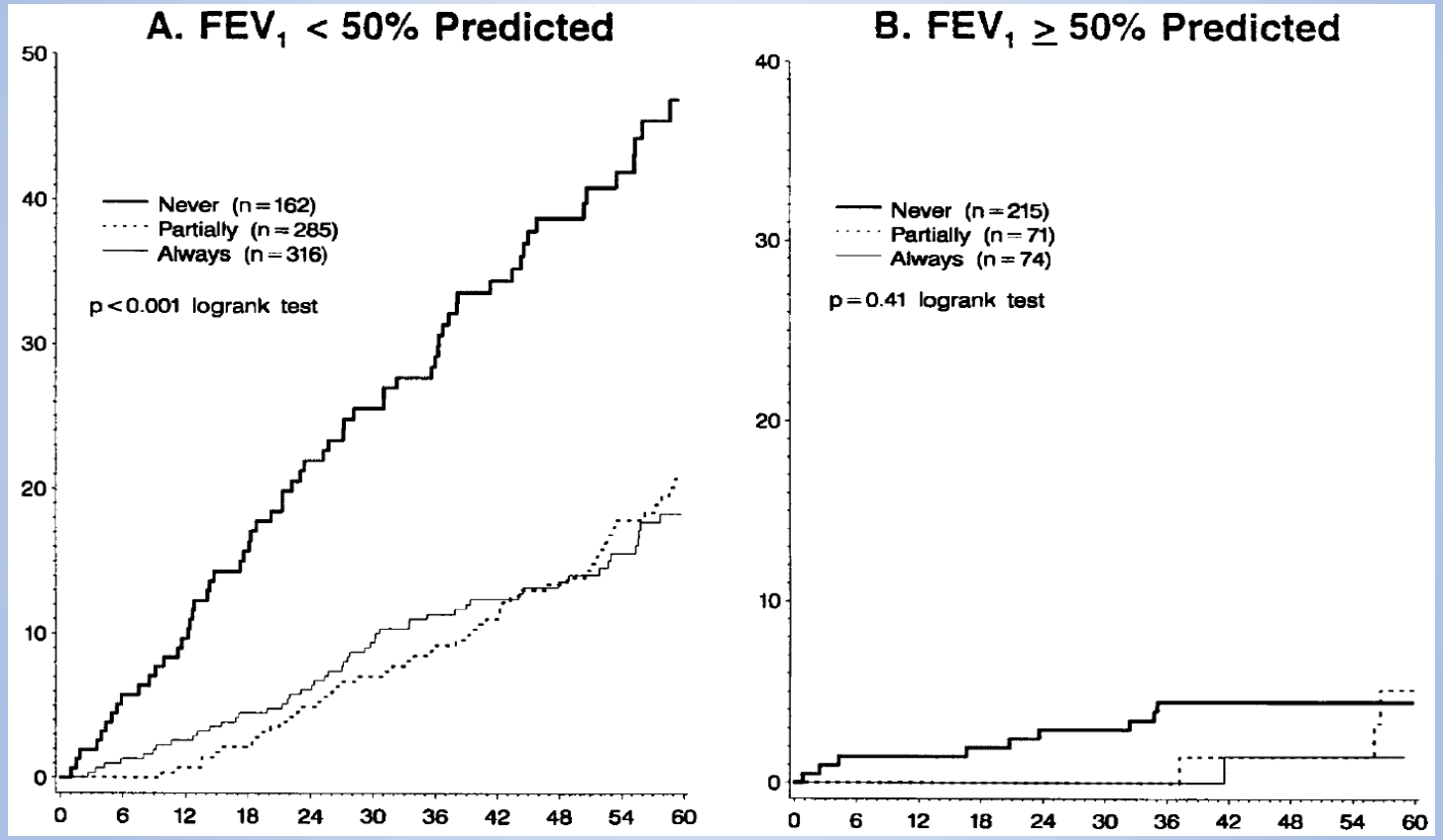
Co-chairs: Robert A. Sandhaus, MD, PhD[1] and Gerard Turino, MD[2]
Writing Committee: Mark L. Brantly, MD[3] Michael Campos, MD[4] Carroll E. Cross, MD[5]
Kenneth Goodman, PhD[6] D. Kyle Hogarth, MD[7] Shandra L. Knight, MS[8] James M. Stocks, MD[9]
James K. Stoller, MD, MS[10] Charlie Strange, MD[11] Jeffrey Teckman, MD[12]

Abstract

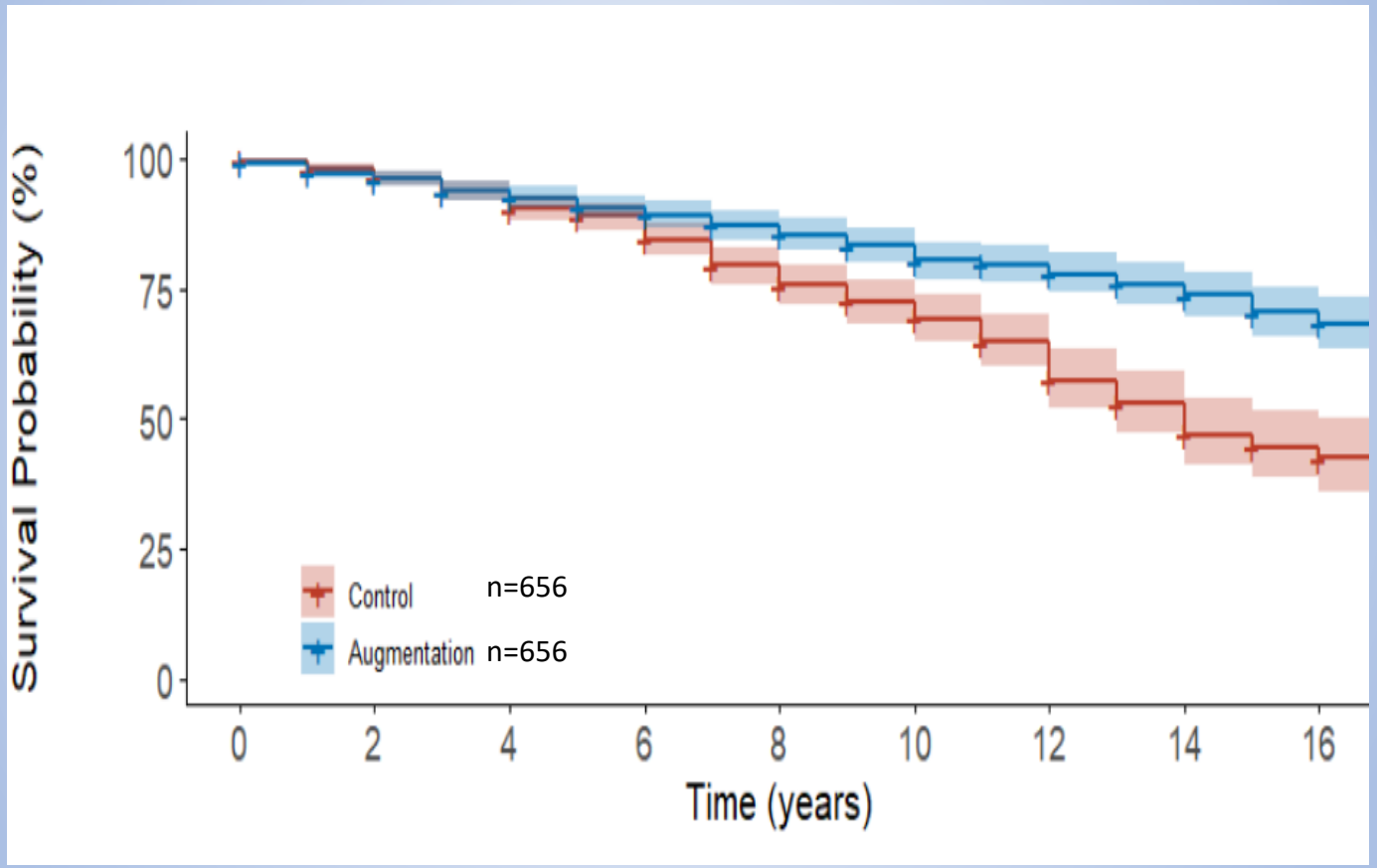
Background: The diagnosis and clinical management of adults with alpha-1 antitrypsin deficiency (AATD) have been the subject of ongoing debate, ever since the publication of the first American Thoracic Society guideline statement in 1989.[1] In 2003, the "American Thoracic Society (ATS)/European Respiratory Society (ERS) Statement: Standards for the Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency" made a series of evidence-based recommendations, including a strong recommendation for broad-based diagnostic testing of all symptomatic adults with chronic obstructive pulmonary disease (COPD).[2] Even so, AATD remains widely under-recognized. To update the 2003 systematic review and clinical guidance, the Alpha-1 Foundation sponsored a committee of experts to examine all relevant, recent literature in order to provide concise recommendations for the

JCOPF, July 2016

Survival

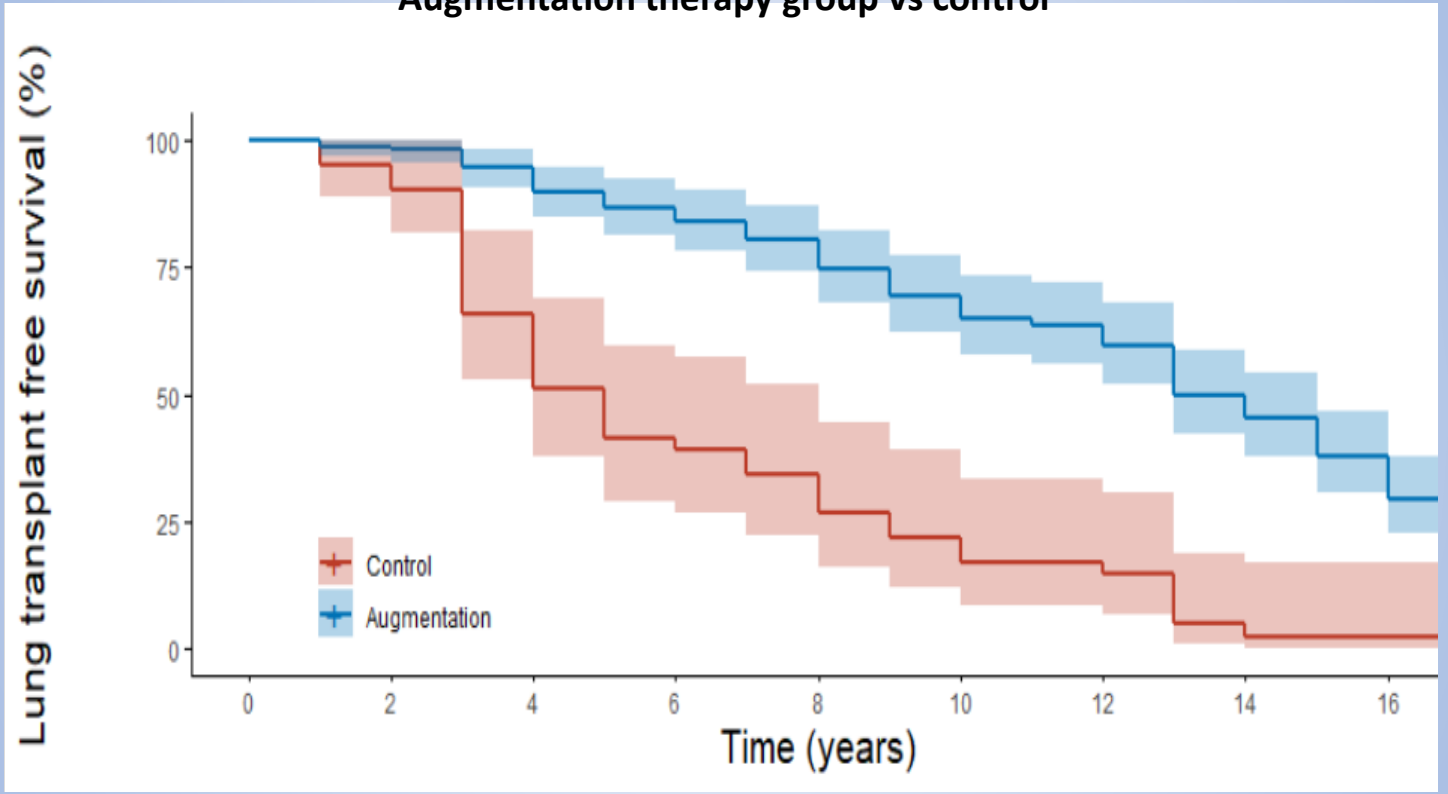

A. FEV1 < 50% Predicted
Never (n=162)
Partially (n=285)
Always (n=316)
p<0.001 logrank test
0
10
20
30
40
50
0 6 12 18 24 30 36 42 48 54 60
B. FEV1 ≥ 50% Predicted
Never (n=215)
Partially (n=71)
Always (n=74)
p=0.41 logrank test
0
10
20
30
40
0 6 12 18 24 30 36 42 48 54 60

Kaplan-Meier survival plot for augmentation therapy group vs control (matched)



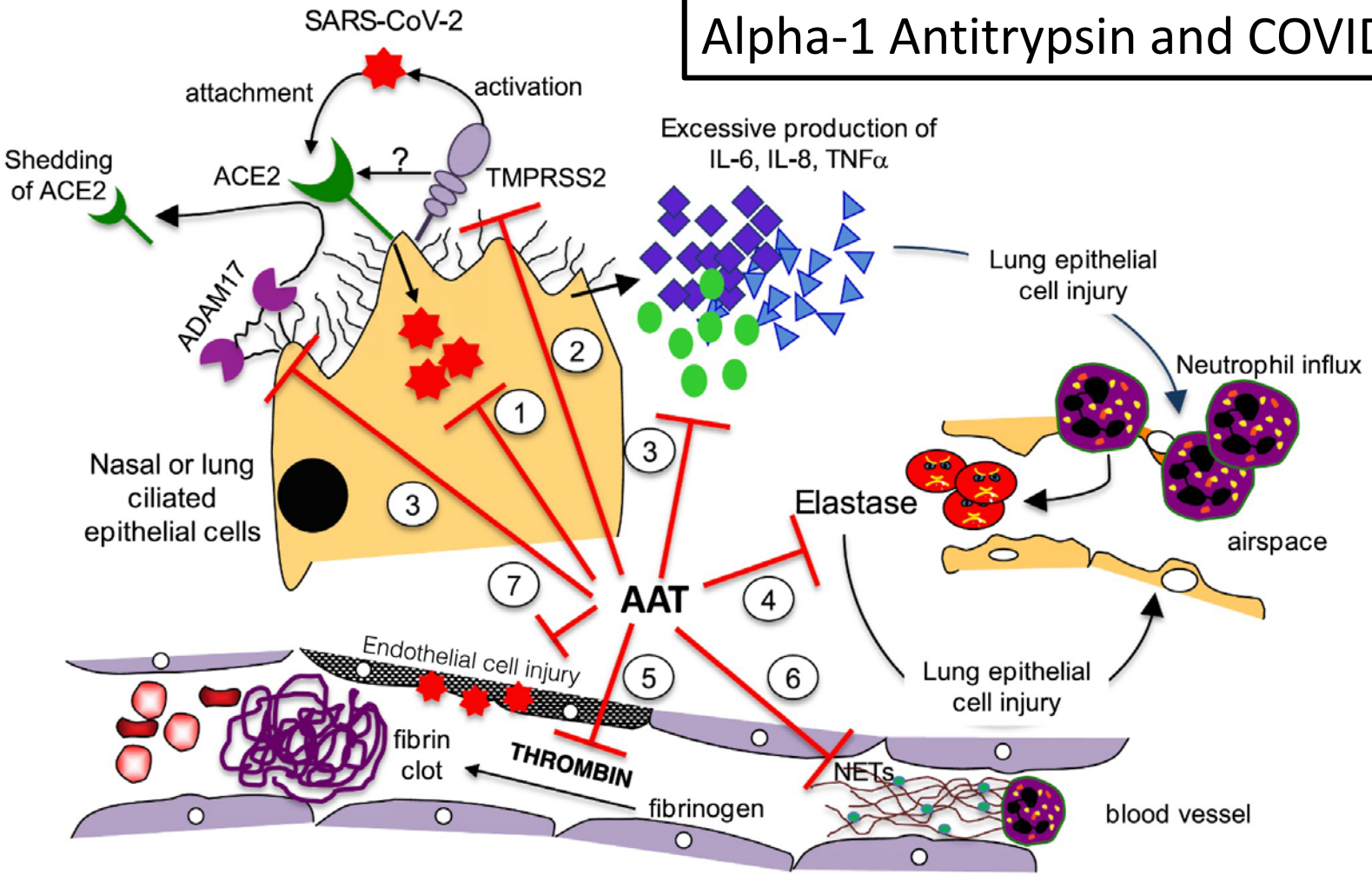
P. Ellis, K. Holm, R. Choate, D. Mannino, R. Stockley, R. Sandhaus, A. Turner: ERS 2019

Kaplan-Meier plot of time to lung transplant
Augmentation therapy group vs control



P. Ellis, K. Holm, R. Choate, D. Mannino, R. Stockley, R. Sandhaus, A. Turner: ERS 2019

Alpha-1 Antitrypsin and COVID



A1ATD Therapeutics In Clinical Trials

Phase, Estimated Completion Date*, Therapy Type, as of 8-Oct-22

ALPHA-1 FOUNDATION

Phase 1	Phase 2	Phase 3	
Not To Time Scale		KAMADA P3 - 2/23	Inhaled AAT
		GRIFOLS P3 - 6/25	IV AAT Dosing
	Mereo BioPharma P2 – Complete 3/22 (Mereo), 8/23 (UAB)		Oral Anti-protease
	(w/ Takeda) arrowhead pharmaceuticals P2 – 9/23 (RCT), 8/24 (open label)		RNA Interference
	(subsidiary of Novo Nordisk) Dicerna™ P2 - 12/23		RNA Interference
	INHIBRX P2 to start 1Q23		Recombinant AAT
(was Ph-Pharma)	PEAK BIO "P2 ready", awaiting financing		Oral Anti-protease
GRIFOLS P1, 2/23			Subcutaneous AAT

*As recorded in ClinicalTrials.gov or Clinicaltrialsregistry.eu

Publicly-Announced* A1ATD Programs In Preclinical Development as of 10/22

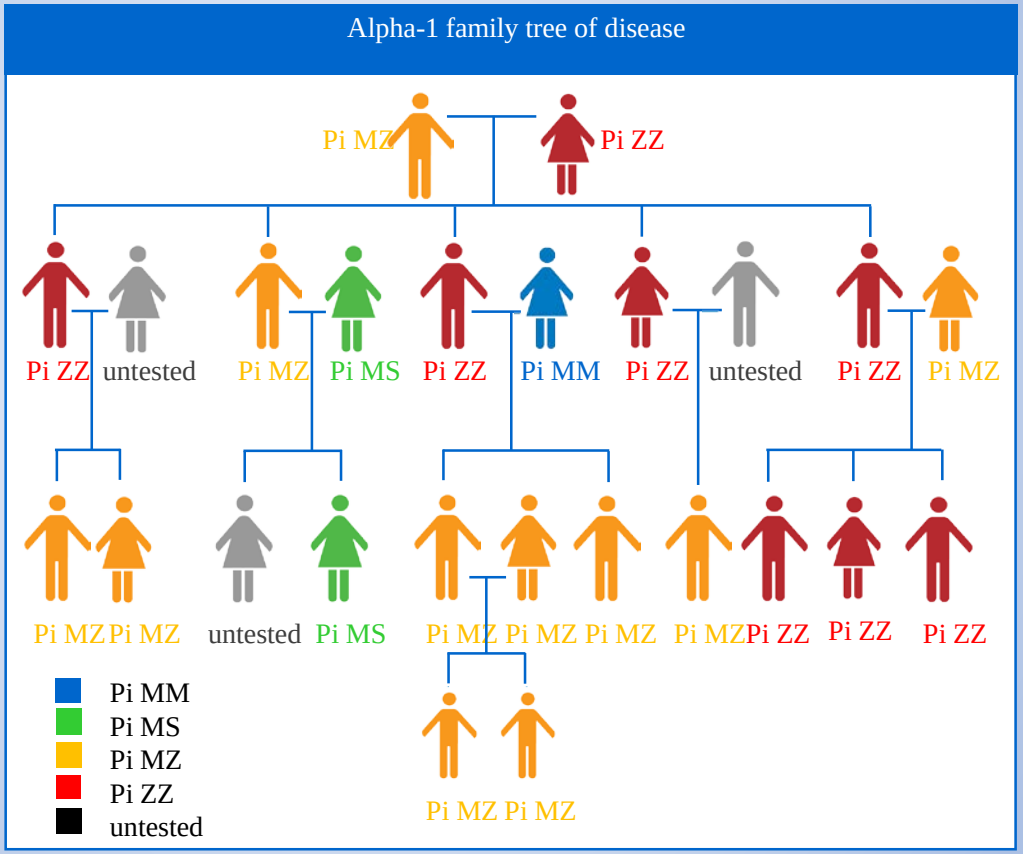
ALPHA-1 FOUNDATION

Discovery/Optimization	IND-Enabling (w/ Expected Filing Date)		
ADARx PHARMACEUTICALS; KORRO BIO	WAVE LIFE SCIENCES	2023	ADAR
Beam THERAPEUTICS; LogicBio THERAPEUTICS	(NTLA-3001) Intellia THERAPEUTICS	2023	Gene Editing
	(NTLA-2003) Intellia THERAPEUTICS		Gene Knockout
ApicBio; epic bio			Silence & Replace w/ AAV vector
	BIOMARIN	2H23	Small Molecule – Polymer Clearance
	VERTEX	2H22	Small Molecule - Corrector
evolve biologics			IV AAT Adv. Tech

*Sources: Company Websites, Investor Presentations

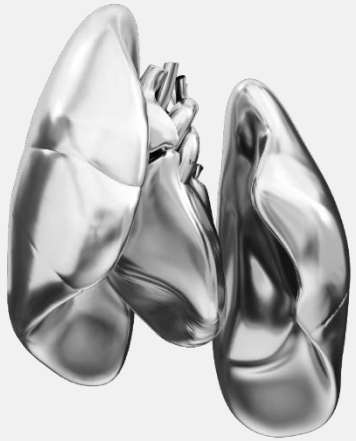
You're Not Just Identifying a Patient—You're Discovering an Entire Family at Risk for Lung and/or Liver Disease

- The model shown is based on an actual family that has been tested for Alpha-1



Summary

- **Alpha-1 antitrypsin deficiency (Alpha-1):**
  - **The most common genetic cause of COPD and a frequent cause of liver disease**
  - **Accounts for about 1% of all COPD, although most remain undiagnosed**
  - **Specific plasma-derived therapy is available that improves survival and quality of life**
  - **The diagnosis of Alpha-1 is a laboratory diagnosis, *not* a clinical diagnosis**
  - **All patients with COPD should be tested for Alpha-1**
  - **Many new therapies are in clinical trials**



Toronto
Lung
Transplant
Program

Recipient Evaluation for Lung Transplantation

Pushing the Envelope

Lianne G Singer, MD, FRCPC
Professor of Medicine, University of Toronto
Division Head, Pulmonary and Critical Care Medicine, University Health Network

lianne.singer@uhn.ca
@liannesinger



Toronto
Lung
Transplant
Program

Presenter Disclosure

Faculty: Lianne Singer

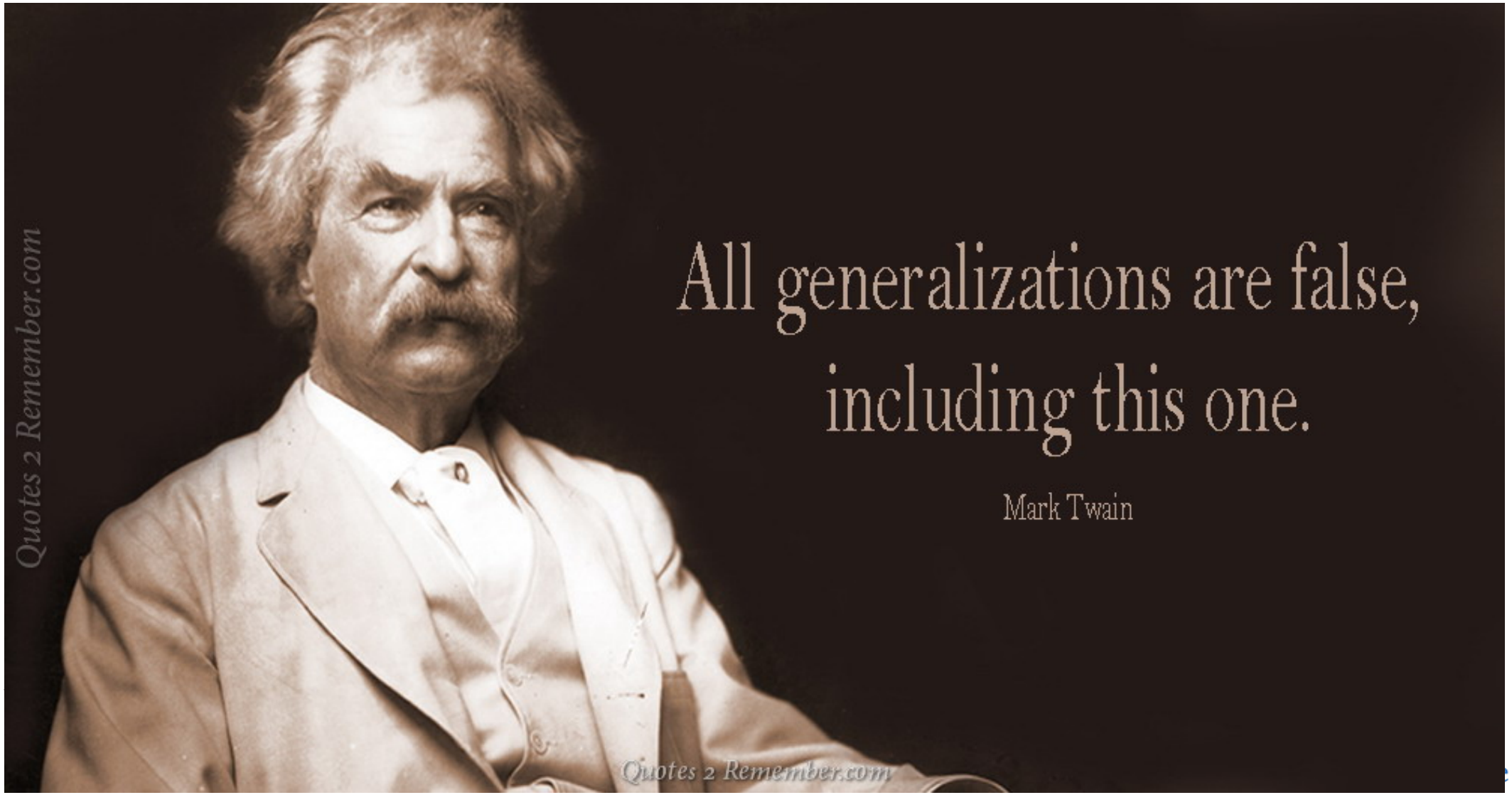
Relationships with commercial interests:

No relevant relationships

UHN Ajmera Transplant Centre

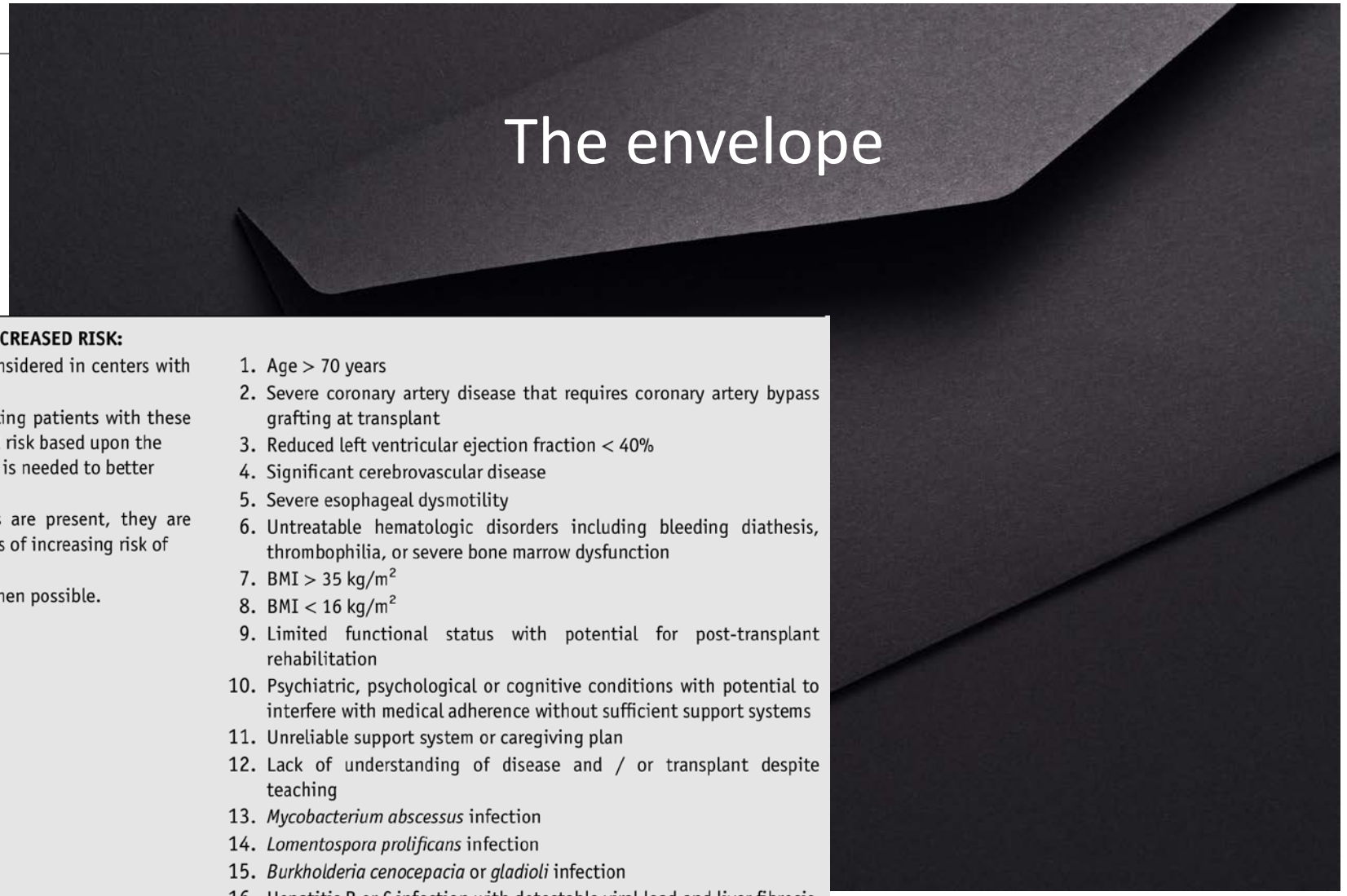
Toronto
Lung
Transplant
Program

Disclaimer



Toronto Lung Transplant Program

The envelope



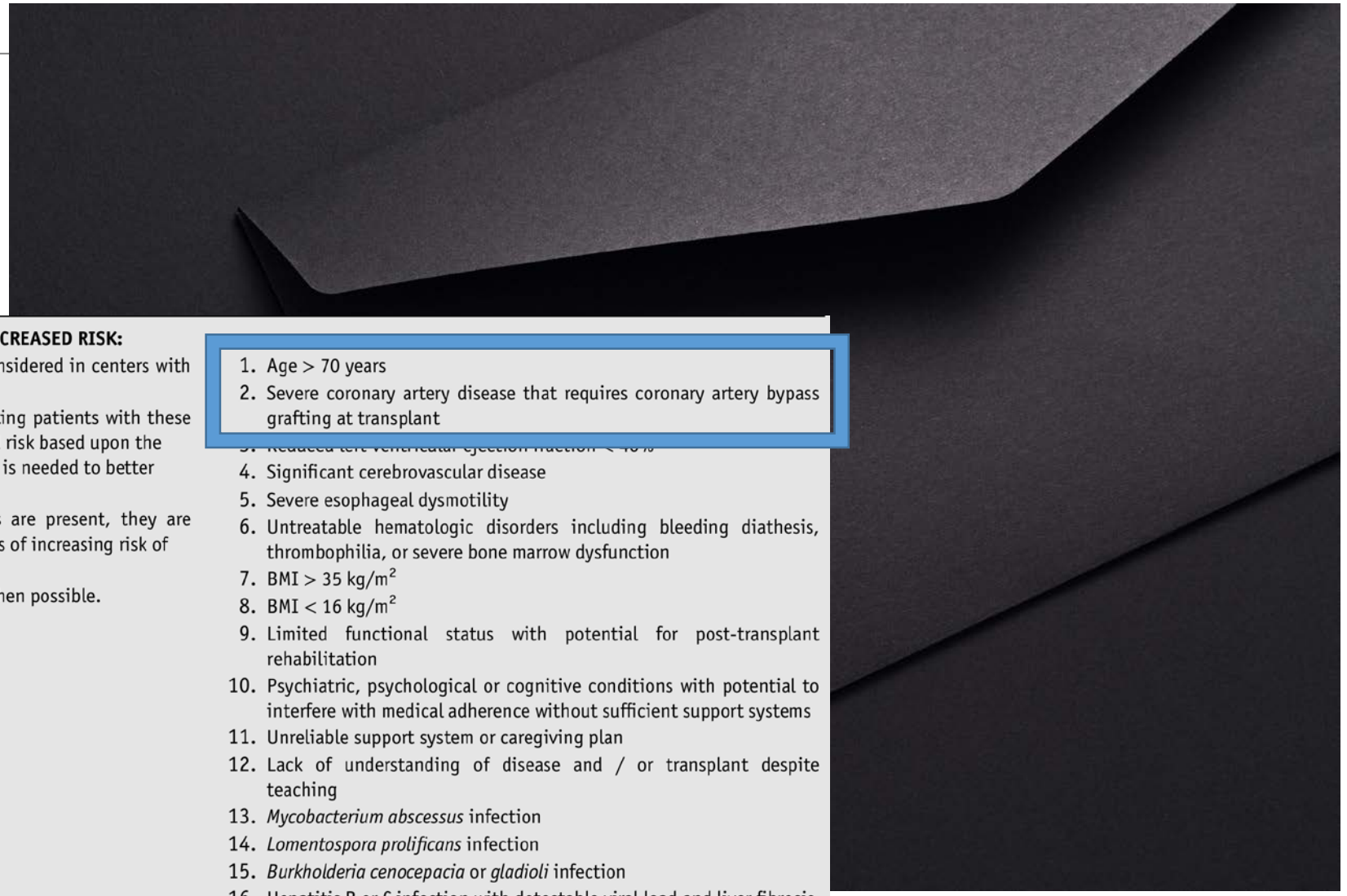
RISK FACTORS WITH HIGH OR SUBSTANTIALLY INCREASED RISK:

- Candidates with these conditions may be considered in centers with expertise specific to the condition.
- We may not have data to support transplanting patients with these risk factors or there is substantially increased risk based upon the currently available data, and further research is needed to better inform future recommendations.
- When more than one of these risk factors are present, they are thought to be possibly multiplicative in terms of increasing risk of adverse outcomes.
- Modifiable conditions should be optimized when possible.

1. Age > 70 years
2. Severe coronary artery disease that requires coronary artery bypass grafting at transplant
3. Reduced left ventricular ejection fraction < 40%
4. Significant cerebrovascular disease
5. Severe esophageal dysmotility
6. Untreatable hematologic disorders including bleeding diathesis, thrombophilia, or severe bone marrow dysfunction
7. BMI > 35 kg/m^2
8. BMI < 16 kg/m^2
9. Limited functional status with potential for post-transplant rehabilitation
10. Psychiatric, psychological or cognitive conditions with potential to interfere with medical adherence without sufficient support systems
11. Unreliable support system or caregiving plan
12. Lack of understanding of disease and / or transplant despite teaching
13. *Mycobacterium abscessus* infection
14. *Lomentospora prolificans* infection
15. *Burkholderia cenocepacia* or *gladioli* infection
16. Hepatitis B or C infection with detectable viral load and liver fibrosis
17. Chest wall or spinal deformity expected to cause restriction after transplant
18. Extracorporeal life support
19. Retransplant <1 year following initial lung transplant
20. Retransplant for restrictive CLAD
21. Retransplant for AMR as etiology for CLAD

UHN Ajmera Transplant Centre

Toronto Lung Transplant Program



RISK FACTORS WITH HIGH OR SUBSTANTIALLY INCREASED RISK:

- Candidates with these conditions may be considered in centers with expertise specific to the condition.
- We may not have data to support transplanting patients with these risk factors or there is substantially increased risk based upon the currently available data, and further research is needed to better inform future recommendations.
- When more than one of these risk factors are present, they are thought to be possibly multiplicative in terms of increasing risk of adverse outcomes.
- Modifiable conditions should be optimized when possible.

1. Age > 70 years
2. Severe coronary artery disease that requires coronary artery bypass grafting at transplant
3. Reduced left ventricular ejection fraction < 40%
4. Significant cerebrovascular disease
5. Severe esophageal dysmotility
6. Untreatable hematologic disorders including bleeding diathesis, thrombophilia, or severe bone marrow dysfunction
7. BMI > 35 kg/m^2
8. BMI < 16 kg/m^2
9. Limited functional status with potential for post-transplant rehabilitation
10. Psychiatric, psychological or cognitive conditions with potential to interfere with medical adherence without sufficient support systems
11. Unreliable support system or caregiving plan
12. Lack of understanding of disease and / or transplant despite teaching
13. *Mycobacterium abscessus* infection
14. *Lomentospora prolificans* infection
15. *Burkholderia cenocepacia* or *gladioli* infection
16. Hepatitis B or C infection with detectable viral load and liver fibrosis
17. Chest wall or spinal deformity expected to cause restriction after transplant
18. Extracorporeal life support
19. Retransplant <1 year following initial lung transplant
20. Retransplant for restrictive CLAD
21. Retransplant for AMR as etiology for CLAD

UHN Ajmera Transplant Centre



Toronto
Lung
Transplant
Program

Case 1

- 69 M referred for rapidly progressive ILD
- PMHx hypertension, dyslipidemia, OSA
- Presented with hypoxemic respiratory failure, intubated
- Hx chronic cough × years, worsening over 4-5 months
- Fibrosis on CT
- Married, working full time as electrical engineer

- Would you evaluate for transplant?
- Our team decision – not while intubated, reconsider if recovers

UHN Ajmera Transplant Centre



Toronto Lung Transplant Program

Case 1

- 5 month admission – extubated to high flow O2, new onset A fib, new ECG changes and troponin elevation
- Echo N LVEF, RVSP 48
- Cath mean PAP 22, severe 3 vessel CAD with chronic total occlusion of LAD

- Would you consider for transplant?

UHN Ajmera Transplant Centre



Toronto Lung Transplant Program

Case 1

- CABG with transplant considered – lung tx team felt too high risk
- Underwent stenting to RCA, circumflex, OM2, proximal LAD, mid LAD with Resolute Onyx DESs
- DAPT + apixaban – rectal bleed, negative workup. Large inguinal hernia.
- Subcentimeter spiculated lung nodule, negative PET
- Pulmonary rehab, 6MW increase from 195 to 300 m (on 15 L/min mask)

- Would you list for transplant?

UHN Ajmera Transplant Centre



Toronto
Lung
Transplant
Program

Case 1

- Listed for lung transplant at age 70, 14 months after initial referral, Plavix DCed 6 months after multivessel PCI
- Determined not a candidate for bridging – discussed with patient at listing, opted for DNR/DNI if worsened before transplant
- 6MWD at listing 382 m (N), desat to 82% on 15 L/min oxymask

UHN Ajmera Transplant Centre



Toronto
Lung
Transplant
Program

Case 1

- Bilateral lung tx 5 months after listing
- 15 hours in ICU, 20 days in hospital, discharged home
- Explant UIP +/- coexisting chronic HP, no malignancy
- FEV1 79% pred, 6MWD 487 m (107% pred) at 5 months post tx
- Minor issues-compression fracture, edema, needs hernia repair

UHN Ajmera Transplant Centre

Toronto Lung Transplant Program

Higher risk transplant – key considerations

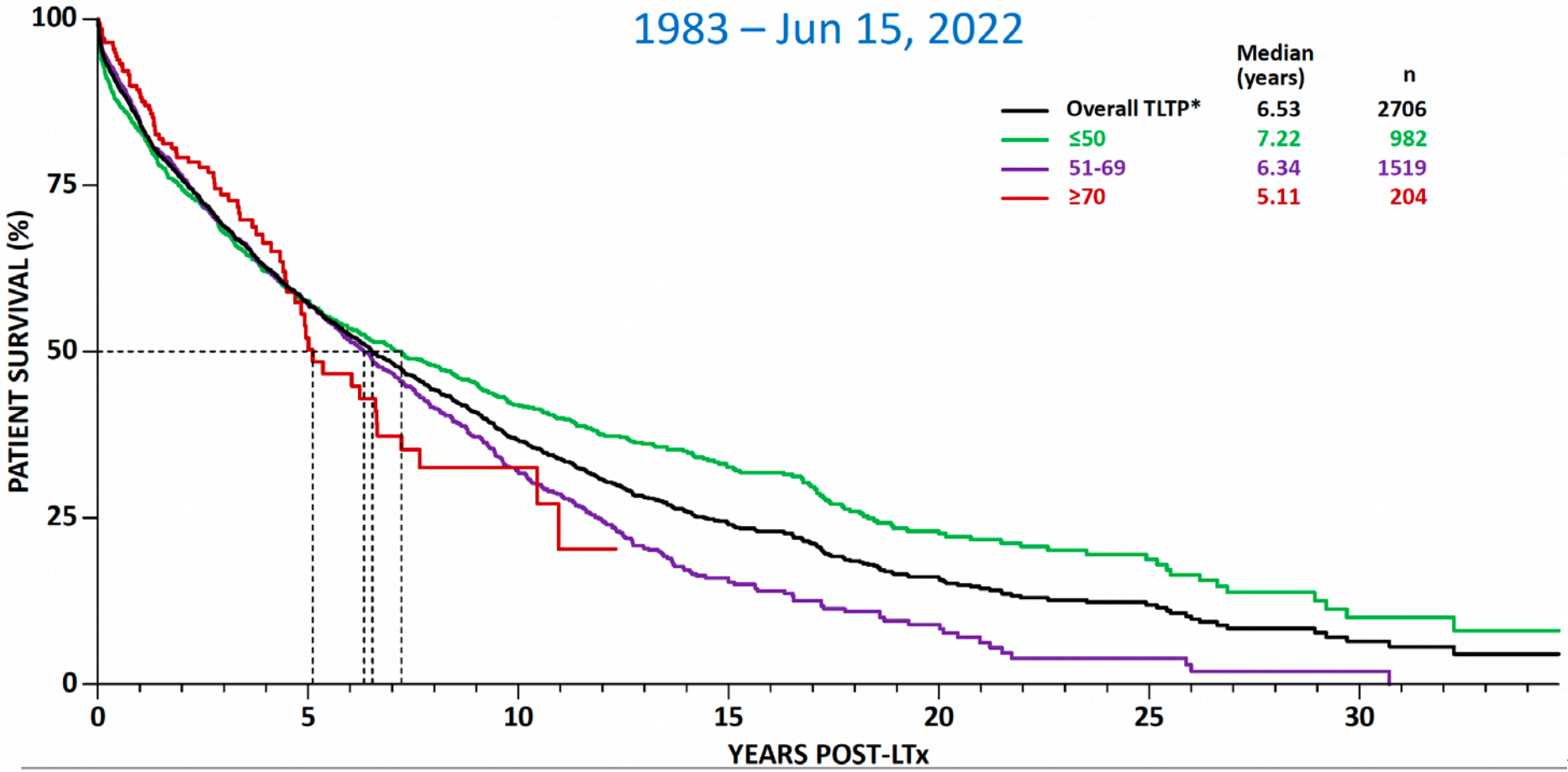
- Build expertise and trust with referring teams – satellite clinic in this case
- Fully informed patient – awaited extubation and recovery, accept this may not happen
- Partnership with interventional cardiology program
- Rehabilitation – prepares for transplant, allows ongoing assessment
- Decide on bridging strategy ahead of listing – discuss advance directive
- Palliative care referral for all candidates
- Regular rediscussion at team meetings

UHN Ajmera Transplant Centre

Toronto Lung Transplant Program

Patient Survival by Recipient Age at Transplant: Over 70 yo

1983 – Jun 15, 2022



*Retransplants excluded (4% of TLTP)
Log-rank p = 5.9e-05 (All categories; Does not include combined curves)

UHN Ajmera Transplant Centre



Toronto Lung Transplant Program

HRQL – benefit of transplant

HRQL measure	Effect of transplant at age 50, units (95% CI)	Effect on tx benefit per decade of age, units (95% CI)	P for age tx interaction effect
SGRQ	-46.5 (-48.4 to -44.5)	1.2 (-0.1 to 2.4)	0.06
SF-36 PCS	17.7 (16.5 to 18.9)	-1.1 (-1.9 to -0.3)	0.008
SF-36 MCS	7.8 (6.5 to 9.1)	-0.5 (-1.2 to 0.3)	0.22
EQ-5D	0.27 (0.24 to 0.30)	-0.01 (-0.03 to 0.01)	0.28
Standard gamble	0.48 (0.44 to 0.51)	0.03 (0.01 to 0.05)	0.02
Visual analog scale	44.3 (42.0 to 46.6)	-1.6 (-3.1 to -0.2)	0.03

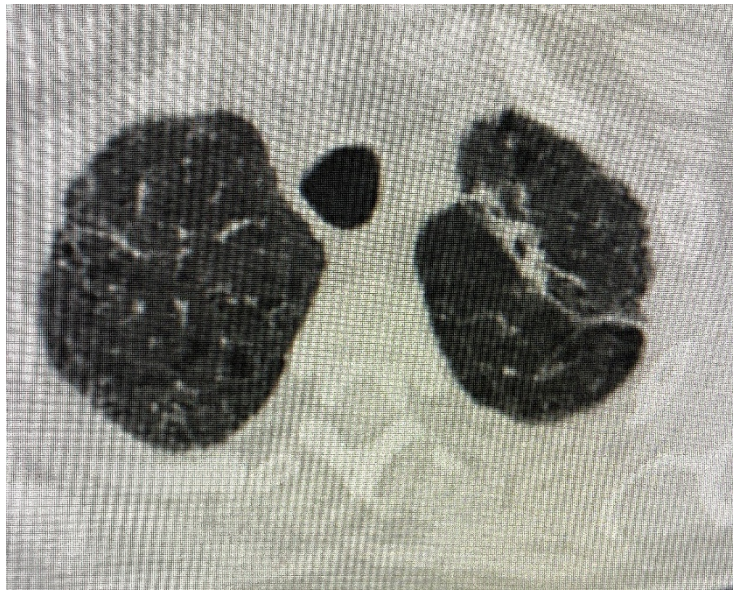
Singer et al, AJRCCM 192:8 (2015), pp. 965-973

UHN Ajmera Transplant Centre

Toronto Lung Transplant Program

Case 2- 73 yo, CPFE

CT Feb 2019



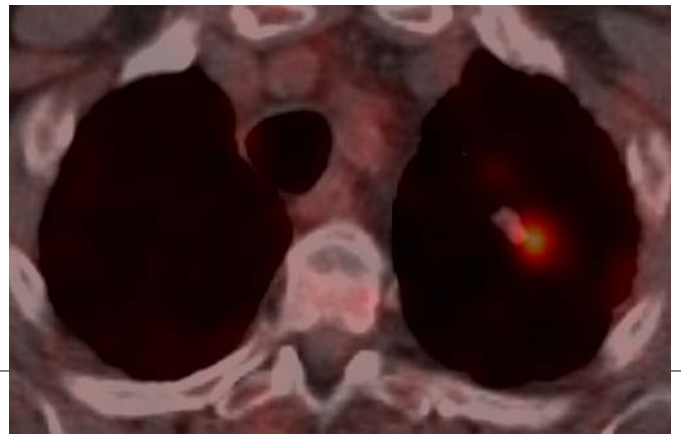
CT Jun 2020



CT Nov 2020



PET Aug 2020
SUVmax 8.0
Highly suggestive for lung cancer



Spiculated nodule LUL
7 mm 2019
to 11x8 mm June 2020
1.9cm x 2.3cm Nov 2020
EBUS negative

UHN Ajmera Transplant Centre

Sub-ablative radiovaccination: a new paradigm in radiation



Toronto

Palliative radiation

Control the tumor

Sub-ablative radiation
3 fractions, 4-12 Gy per fraction

Combined with immunotherapy

Abscopal effect in stage IV

Combined with R0 Surgery

In situ vaccination in early stage

Ablative radiation

Eradicate the tumor

Courtesy of Marc de Perrot

De La Maza, de Perrot, et al. *Clin Cancer Res* 2017;23:5502-13
Murakami, de Perrot, et al. *Science Transl Med* 2021 Apr 14

UHN Ajmera Transplant Centre

NORTh STAR trial

End stage lung disease with stage 1 lung cancer
Multifocal lung cancer
Lung metastasis

Interstitial lung disease (ILD)

Phase 1a, dose escalation (3+3), homogenous RT

1. **3 x 4 Gy (homogenous radiation dose)**
2. **3 x 6 Gy (homogenous radiation dose)**
3. **3 x 8 Gy (homogenous radiation dose)**

Phase 1b using MTD with heterogeneous radiation dose distribution for tumor >2cm

Other lung pathology than ILD

Phase 1a, dose escalation (3+3), homogenous RT

1. **3 x 8 Gy (homogenous radiation dose)**
2. **3 x 10 Gy (homogenous radiation dose)**
3. **3 x 12 Gy (homogenous radiation dose)**

Phase 1b using MTD with heterogeneous radiation dose distribution for tumor >2cm

List for lung transplantation
1 week after the end of radiation

Primary endpoints:

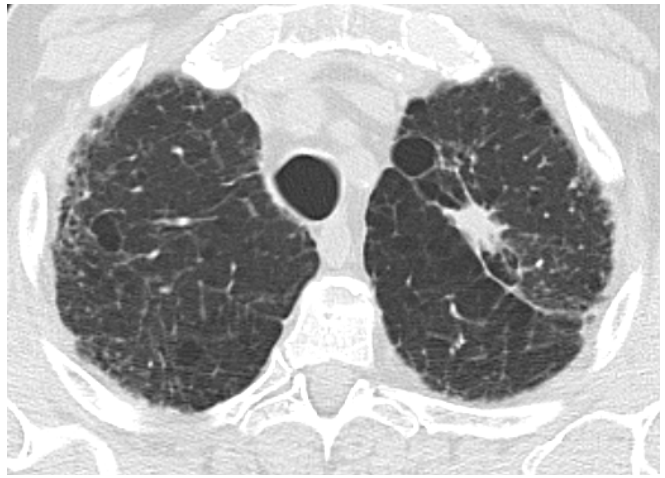
1. Feasibility determined by ability to list patients for transplantation one week after the end of radiation
2. Safety determined by the absence of grade 3 or greater (G3+) complications related to radiation

Toronto Lung Transplant Program

Case 2

Left single LTx Oct 2021

CT May 2021



CT Aug 2021



Radiation:
12 Gy in 3 fractions
From 5 Jul to 9 Jul 2021

Pathology:

- 2.0 cm mass left upper lobe
- Scar with extensive smooth muscle hyperplasia, secondary fibroelastosis with stromal and epithelial reactive changes to suggest treatment effect.
- It is unclear if this represents a neoplastic process with pathological complete response or something else.

Clear CT at 1 year follow up

UHN Ajmera Transplant Centre

Toronto Lung Transplant Program

Case 3

67 yo, IPF

Listed for bilateral lung transplant

Growing nodule in LUL, suspicious for lung cancer

PET shows activity in LUL tumor with SUVmax 8.9

Second nodule in LUL SUVmax 3.4

RUL nodule SUVmax 2.8



LUL nodule SUXmax 8.9 | Satellite nodule LUL | RUL nodule

HN Ajmera Transplant Centre



Toronto Lung Transplant Program

Case 3

LUL nodule radiated 12 Gy in 3 fractions 25 to 29 Oct 2021

Transplanted 24 Dec 2021

LUL lung nodule: adenocarcinoma, solid type, 80% response rate (20% residual active disease)

LUL satellite nodule: non-necrotizing granulomatous inflammation

RUL nodule: necrotizing granulomatous inflammation, +ve for M avium

Clear CT at 9 month assessment

UHN Ajmera Transplant Centre



Toronto Lung Transplant Program

Customizing immune suppression

IMMUNOSUPPRESSION

Months	Postop	0 - 3	3 - 6	6 - 9	9 - 12	> 12
High IS (+VXM, AMR, recurrent ACR)						
Antithymocyte globulin	3-5 mg/kg	(after PLEX/IVIg)				
CSA trough level (C) Ontario		200 - 240		160 - 200		120 - 160
CSA trough level (C) Out-of-Province		250 - 300		200 - 250		150 - 200
Tacrolimus trough level (T)		15 - 20		10 - 15		7 - 12
Cell cycle inhibitor		Cellcept 1 - 1.5 g bid or Myfortic 720 - 900 mg bid Use highest tolerable dose if ACR/AMR				
Prednisone (mg/kg/d)		0.25	0.2	0.15		0.1
Standard IS (PRA+ at tx, dnDSA)						
CSA trough level (C) Ontario		200-240		160-200		120-160
CSA trough level (C) Out-of-Province		250-300		200-250		150-200
Tacrolimus trough level		15 - 20		10 - 15		7 - 12
Cell cycle inhibitor		Cellcept 1 g bid or Myfortic 720 mg bid (M) Azathioprine 1.5-2 mg/kg/d (A)				
Prednisone (mg/kg/d)		0.25	0.2	0.15		0.1
Low IS (>age 60, malignancy, severe infection)						
Basiliximab (for CNI deferral)	20 mg day 0,4	(if CNI start delayed)				
CSA trough level (C) Ontario		160-200		120-160		80-120
CSA trough level (C) Out-of-Province		200-250		150-200		100-150
Tacrolimus trough level		10 - 15		7 - 12		
Cell cycle inhibitor		Cellcept 750 g bid or Myfortic 540 mg bid (M) Azathioprine 1-1.5 mg/kg/d (A)				
Prednisone (mg/kg/d)		0.25	0.2	0.15		0.1

UHN Ajmera Transplant Centre



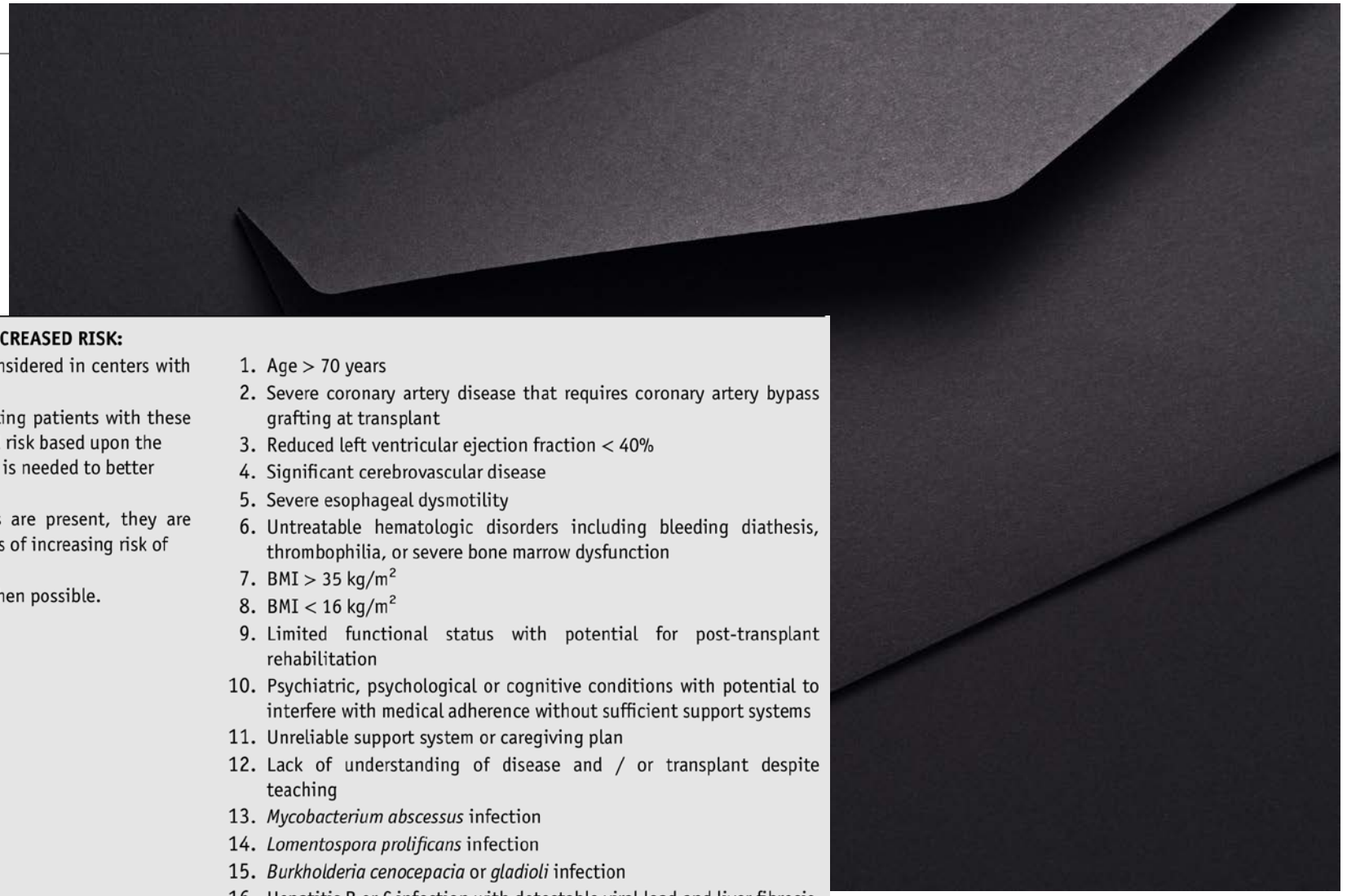
Toronto Lung Transplant Program

Immunosuppressive strategy

T=Tacrolimus, M-Mycophenolate, A=Azathioprine

Patient characteristics / Risk factor	Age >60	Age <60	Heart-lung TX	CF B.cepacia+	Chronic kidney disease
Standard	Low	Standard-A	Standard-M	Low	Low CNI Standard
Re-tx	Low CNI Standard CCI	Low CNI Standard CCI	Low CNI Standard CCI	Low	Low CNI Standard
Cancer	Low	Low	Low-M	Low	Low
Infection	Low	Low	Low-M		Low
Kidney disease	Low	Low CNI Standard CCI	Low-M	Low	
PRA+ without DSA	Low-M	Standard-M	Standard-M	Low-M	Low-M
+ve VCM/ACM	High	High	High	Avoid	Avoid
De novo DSA	Standard-M	High	High	Standard-M	Standard-M
Risk epitope mismatch	Standard-M	Standard-M	Standard-M	Low-M	Standard-M
AMR post TX	High	High	High	High	High
Recurrent/refractory ACR	High-T	High-T	High-T	High	High

Toronto Lung Transplant Program



RISK FACTORS WITH HIGH OR SUBSTANTIALLY INCREASED RISK:

- Candidates with these conditions may be considered in centers with expertise specific to the condition.
- We may not have data to support transplanting patients with these risk factors or there is substantially increased risk based upon the currently available data, and further research is needed to better inform future recommendations.
- When more than one of these risk factors are present, they are thought to be possibly multiplicative in terms of increasing risk of adverse outcomes.
- Modifiable conditions should be optimized when possible.

1. Age > 70 years
2. Severe coronary artery disease that requires coronary artery bypass grafting at transplant
3. Reduced left ventricular ejection fraction < 40%
4. Significant cerebrovascular disease
5. Severe esophageal dysmotility
6. Untreatable hematologic disorders including bleeding diathesis, thrombophilia, or severe bone marrow dysfunction
7. BMI > 35 kg/m^2
8. BMI < 16 kg/m^2
9. Limited functional status with potential for post-transplant rehabilitation
10. Psychiatric, psychological or cognitive conditions with potential to interfere with medical adherence without sufficient support systems
11. Unreliable support system or caregiving plan
12. Lack of understanding of disease and / or transplant despite teaching
13. *Mycobacterium abscessus* infection
14. *Lomentospora prolificans* infection
15. *Burkholderia cenocepacia* or *gladioli* infection
16. Hepatitis B or C infection with detectable viral load and liver fibrosis
17. Chest wall or spinal deformity expected to cause restriction after transplant
18. Extracorporeal life support
19. Retransplant <1 year following initial lung transplant
20. Retransplant for restrictive CLAD
21. Retransplant for AMR as etiology for CLAD

UHN Ajmera Transplant Centre



Toronto Lung Transplant Program

Case 4

- 37-year-old female (G2P1) presented with a planned pregnancy at 21-weeks' gestation with new onset dyspnea and hypoxemia
- Uneventful pregnancy 12 years earlier
- Mother had lung tx for PAH in early 30s, brother sudden death late 20s
- Echo and heart cath – severe PAH with RV dysfunction
- 24 hrs after cath – severe hypoxemia pO2 in 70s, early bubbles on echo c/w PFO

UHN Ajmera Transplant Centre



Toronto
Lung
Transplant
Program

Case 4- Options

Termination of pregnancy

- Given gestational age - surgical dilatation and evacuation or medical induction of labor
- No criminal restrictions on abortion in Canada
- High risk of hemorrhage due to anticoagulation, maternal decompensation
- Not desired by pt

Extracorporeal support

- High rate of major complications

UHN Ajmera Transplant Centre



Toronto Lung Transplant Program

Case 4

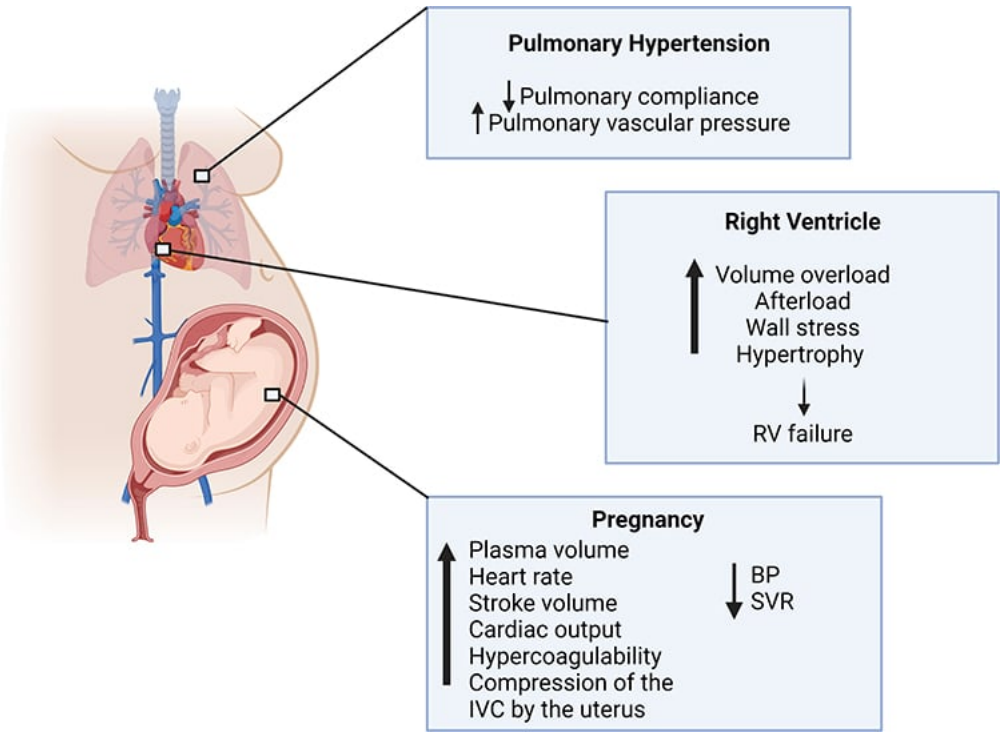
- Initially VV ECMO to improve hypoxemia - femoral drainage cannula, internal jugular return cannula
- Initiation of epoprostenol and sildenafil
- Two episodes of profound hypotension – urgent reconfiguration
- 22 weeks' GA - awake open cannulation of left femoral artery for VA-ECMO to allow for induction of general anesthetic
- Pumpless pulmonary artery to left atrium (PA-LA) circuit using the NovaLung membrane, removal of VV and VA ECMO, closed sternotomy
- PA-LA: safe, durable, allows mobilization, oxygenation, offloads RV

UHN Ajmera Transplant Centre

Toronto Lung Transplant Program

Case 4

- Stable on pumpless PA-LA Novalung until 25+3 week's GA – became increasingly hypoxemic, unable to mobilize
- Pump inserted in PA-LA circuit to improve RV offloading, essentially providing RVAD support
- Stable until 28+6 weeks' GA – desaturation
- Caesarean delivery of healthy 1.04 k boy on PA-LA support, stable throughout delivery



Afify H, et al. Pulmonary Hypertension in Pregnancy: Challenges and Solutions. *Integr Blood Press Control*. 2022;15:33-41

UHN Ajmera Transplant Centre



Toronto
Lung
Transplant
Program

Case 4

- 3 weeks postpartum – bilateral lung transplant
- Central VA ECMO – removal of PA-LA Novalung – discontinuation of VA ECMO
- Positive virtual and flow crossmatch – Rx PLEX, IVIg periop and monthly for 3 months, RATG
- Peripheral VA ECMO required for PGD
- Decannulated after 3 days, discharged after 1 month
- Baby discharged after 12 weeks, at corrected GA of 41 weeks
- On follow up – persistent strong DR and DQ DSA with AMR, acceptable lung function

UHN Ajmera Transplant Centre

Toronto Lung Transplant Program

STAR EXCLUSIVE

She was pregnant and needed new lungs. In a world first, here's how Toronto doctors saved a dying mom — and her baby

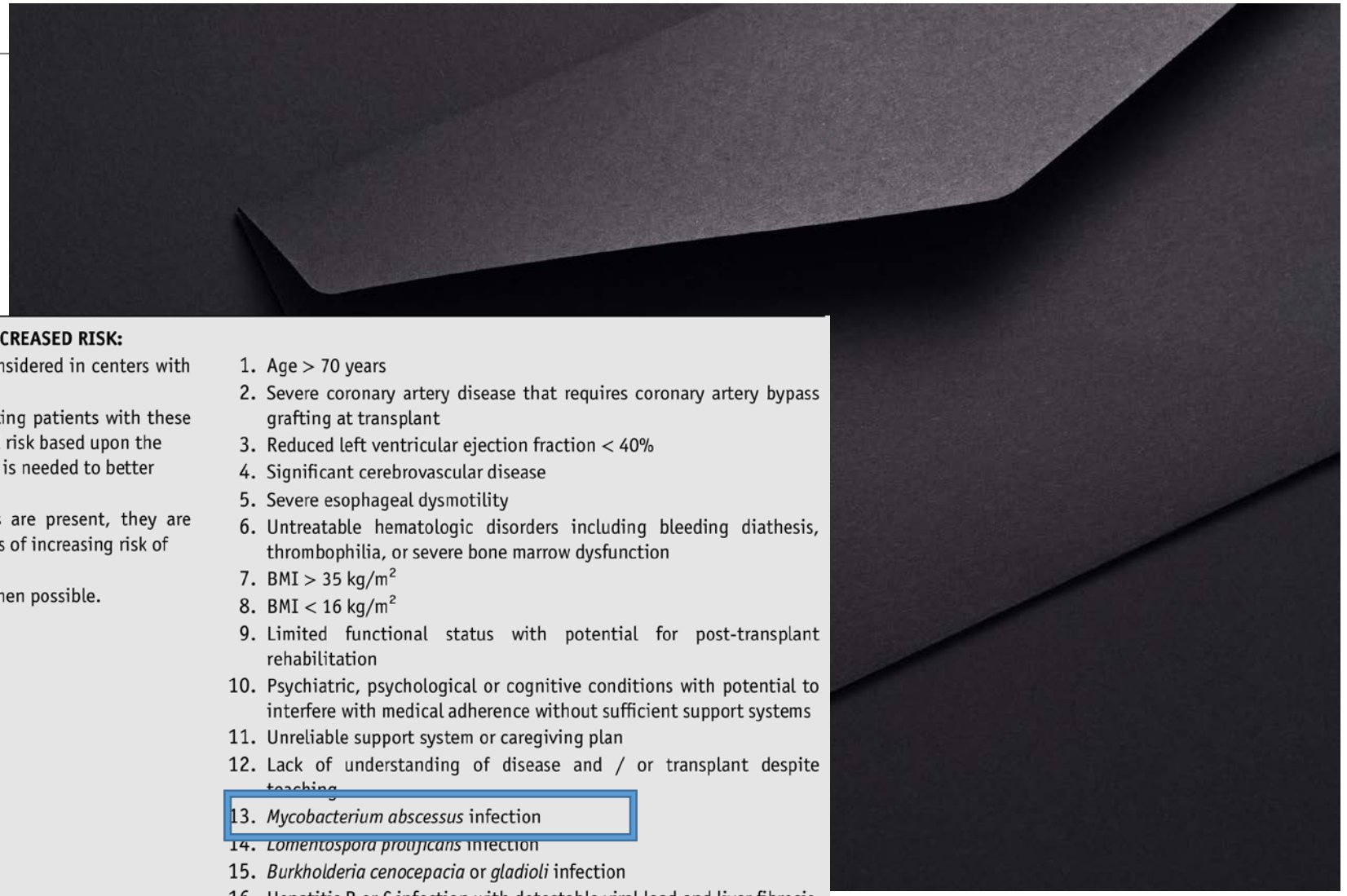
This was a medical case that would test the skills and daring of a physician team willing to push boundaries to save the lives of a mother and her unborn baby.





ntre

Toronto Lung Transplant Program



RISK FACTORS WITH HIGH OR SUBSTANTIALLY INCREASED RISK:

- Candidates with these conditions may be considered in centers with expertise specific to the condition.
- We may not have data to support transplanting patients with these risk factors or there is substantially increased risk based upon the currently available data, and further research is needed to better inform future recommendations.
- When more than one of these risk factors are present, they are thought to be possibly multiplicative in terms of increasing risk of adverse outcomes.
- Modifiable conditions should be optimized when possible.

1. Age > 70 years
2. Severe coronary artery disease that requires coronary artery bypass grafting at transplant
3. Reduced left ventricular ejection fraction < 40%
4. Significant cerebrovascular disease
5. Severe esophageal dysmotility
6. Untreatable hematologic disorders including bleeding diathesis, thrombophilia, or severe bone marrow dysfunction
7. BMI > 35 kg/m^2
8. BMI < 16 kg/m^2
9. Limited functional status with potential for post-transplant rehabilitation
10. Psychiatric, psychological or cognitive conditions with potential to interfere with medical adherence without sufficient support systems
11. Unreliable support system or caregiving plan
12. Lack of understanding of disease and / or transplant despite teaching
13. *Mycobacterium abscessus* infection
14. *Lomentospora prolificans* infection
15. *Burkholderia cenocepacia* or *gladioli* infection
16. Hepatitis B or C infection with detectable viral load and liver fibrosis
17. Chest wall or spinal deformity expected to cause restriction after transplant
18. Extracorporeal life support
19. Retransplant <1 year following initial lung transplant
20. Retransplant for restrictive CLAD
21. Retransplant for AMR as etiology for CLAD

UHN Ajmera Transplant Centre



Toronto Lung Transplant Program

Case 5

46 yo woman

- DLTx 2007 for COPD (prior lower lobe LVRS), peak FEV1 3.5 (100% pred)
- Slow progressive decline in lung function since 2013, CLAD-BOS
- Probable pulmonary nocardia 2018 – Rx imipenem and TMP-SMX
- M abscessus pulmonary disease Apr 2020 – cavitating nodules, sputum smear +ve, BAL smear neg, culture positive– Rx cefoxitin, imipenem, inhaled amikacin, moxifloxacin – subsequent multiple BALs negative stain and culture
- Invasive pulmonary aspergillosis Aug 2020 – intolerant to vori, progressed on Posaconazole – Rx caspo and isavuconazole
- Recurrent cutaneous HSV infections

UHN Ajmera Transplant Centre



Toronto Lung Transplant Program

Case 5

Multidisciplinary approach was key

- Infectious diseases
- Nausea- weight loss – dietician and GI
- Palliative care – symptom management
- Psychiatry – anxiety and depression
- Physiotherapy – improve deconditioning
- Multiple team discussions – detailed review of first post tx course before initiating second evaluation

Ultimately relisted after progress in rehab, despite ongoing nutritional issues

UHN Ajmera Transplant Centre



Toronto
Lung
Transplant
Program

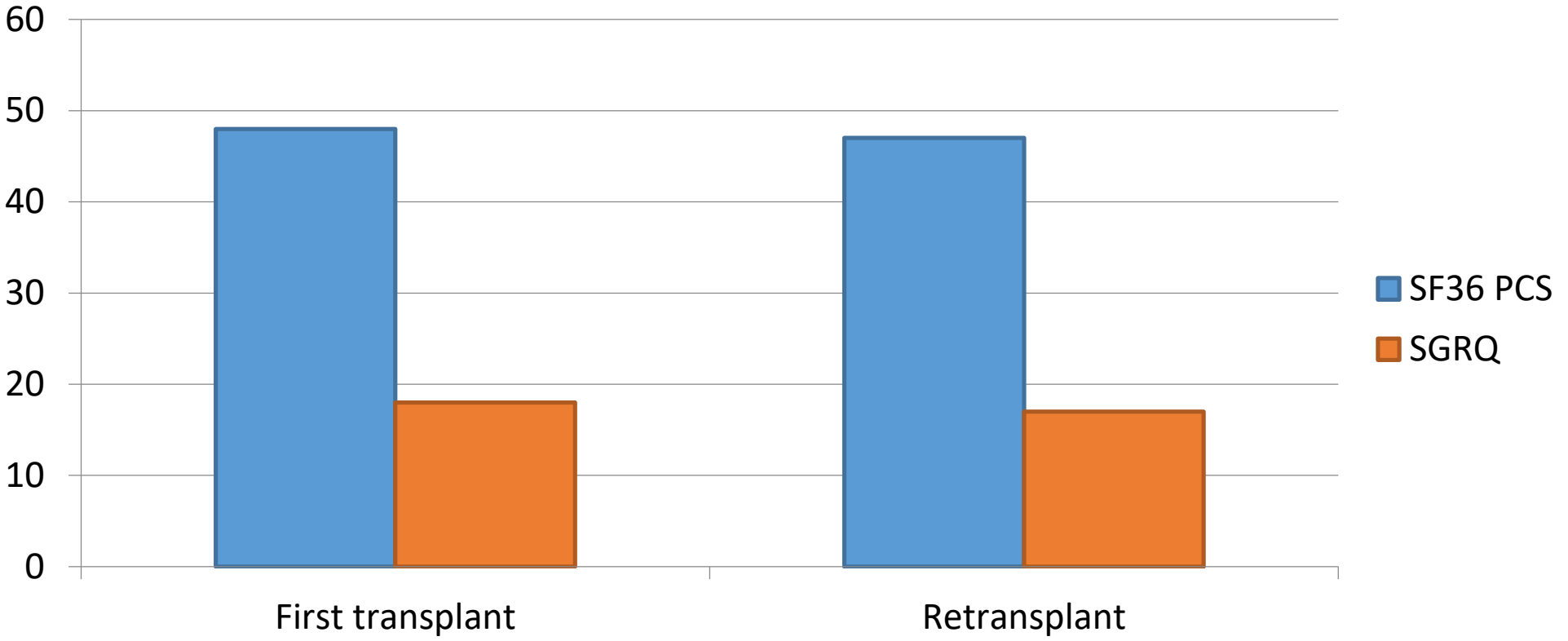
Case 5

- Redo bilateral lung tx June 2021 (>14 yrs post first transplant)
- PRA +, virtual and flow crossmatch negative
- Uncomplicated, 17-day admission, discharged home
- Explant: obliterative bronchiolitis, early RAS, chronic aspergillosis, no AFB
- Continued antimycobacterial and antifungal medications for 3 months post-tx
- In follow up – CMV viremia, COVID, PJP (not taking atovaquone prophylaxis)
- At last follow up – FEV1 2.7 L (90% pred), N BMI, working part time

UHN Ajmera Transplant Centre

Toronto Lung Transplant Program

Maximum HRQL after first lung transplant vs. retransplant (n=21)



Halloran et al – Clin Transplant 2018

UHN Ajmera Transplant Centre



Toronto Lung Transplant Program

”Common DSA” avoidance

Characteristic	Primary transplant n = 38	Retransplant n = 38	*P*-value
HLA antibodies[a], [n_F = 20, n_R = 25]			
Repeat HLA mismatch (%) [n_R = 21]	-	14 (67)	.76
Donor-specific antibody (DSA), (%)	11 (55)	12 (48)	
At time of transplant	7 (37)	7 (37)	
De novo post-transplant	4 (21)	5 (26)	
DSA common to 1st donor antigens (%)	-	5 (24)	

HLA lab can help!

UHN Ajmera Transplant Centre



Toronto Lung Transplant Program

Case 6

- 43 y M severe COPD
- History of smoking (abstinent 7-8 months), crack, IV heroin – abstinent for > 1 year
- Unemployed, on social assistance. Remote work in waste collection. 9 years of incarceration for thefts to support habit.
- Living for past year with ex-wife, her current husband, his daughter, stepson, grandchildren. Prior to that marginally housed and inconsistent medical treatment.
- Meds include methadone 80 mg/d (take home dose 6 days/wk), oxygen – good adherence in past year.
- Very disabled with poor quality of life
- 6MW 354 m on 6 L/min

UHN Ajmera Transplant Centre



Toronto
Lung
Transplant
Program

Case 6

- Psych assessment – identified negative but also positive prognostic factors; moderate risk of relapse
- Recommended stay on methadone; careful periop analgesia planning, shore up supports, addiction counselling
- Social work – supported by uncle and partner, ”good candidate” SIPAT=20, cleared for transplant
- No medical issues on evaluation
- Listed for lung transplant

UHN Ajmera Transplant Centre



Toronto Lung Transplant Program

Case 6

- Bilateral transplant 4 weeks after listing
- Epidural, IV PCA, ketamine – uneventful recovery
- Discharged on hydromorphone prn, gabapentin, methadone, followed by transitional pain clinic
- Excellent initial lung function
- Stress managing frequent hospital visits and missing some (lives 1 hr away with social assistance for transportation), local methadone appointments
- Unable to reduce hydromorphone use, running out between appointments
- Sternal wire protrusion and malunion – wire removal, debridement and plating
- Plate /screws dislodged – reoperation with debridement and plate removal, osteomyelitis with CNST

UHN Ajmera Transplant Centre



Toronto Lung Transplant Program

Case 6

- Multiple admissions for pneumonia (bacterial, influenza, aspiration, Aspergillus)
- Respiratory failure and intubation after fentanyl overdose, aspiration pneumonia and PE – improved and had pulmonary rehab
- Housing instability, nonadherence
- Progressive CLAD-RAS
- Died in hospice

UHN Ajmera Transplant Centre



Toronto
Lung
Transplant
Program

Issues

- Fragmentation of care – multiple pain clinic providers, methadone prescriber
- Sternal issues
- Distance
- Limitations of social assistance – transportation, nutrition unaffordable
- Addiction is a terrible disease

UHN Ajmera Transplant Centre



Toronto Lung Transplant Program

Factors that may implicitly or explicitly affect listing decisions

- Size of program – ability to dilute bad outcomes
- Program relationships with hospital, payers, regulatory authorities, referring physicians
- Resources available to manage complicated recipients
- Collective experience of the program – especially recent similar cases
- Who is at the candidacy review meeting
- Allocation system itself – patients unlikely to get transplant are not listed

UHN Ajmera Transplant Centre



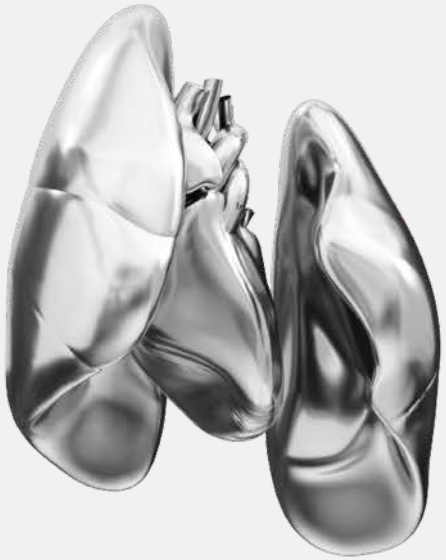
Toronto Lung Transplant Program

Managing patient selection challenges

- Make sure all team voices are heard
- Have a process to resolve disputes
- Get input from experts – current care team, lung disease specialists, mental health/addiction, bioethics, oncology
- Be clear on your program's philosophy and how much risk is acceptable

UHN Ajmera Transplant Centre





Toronto Lung Transplant Program



COVID-Related Lung Disease Long Term Sequalae

JOSHUA SOLOMON, MD

ASSOCIATE PROFESSOR OF MEDICINE

NATIONAL JEWISH HEALTH

DENVER, CO

Case #1

74yo woman admitted to the hospital COVID (+) with COVID PNA.

She developed ARDS and was ventilated for 17 days.

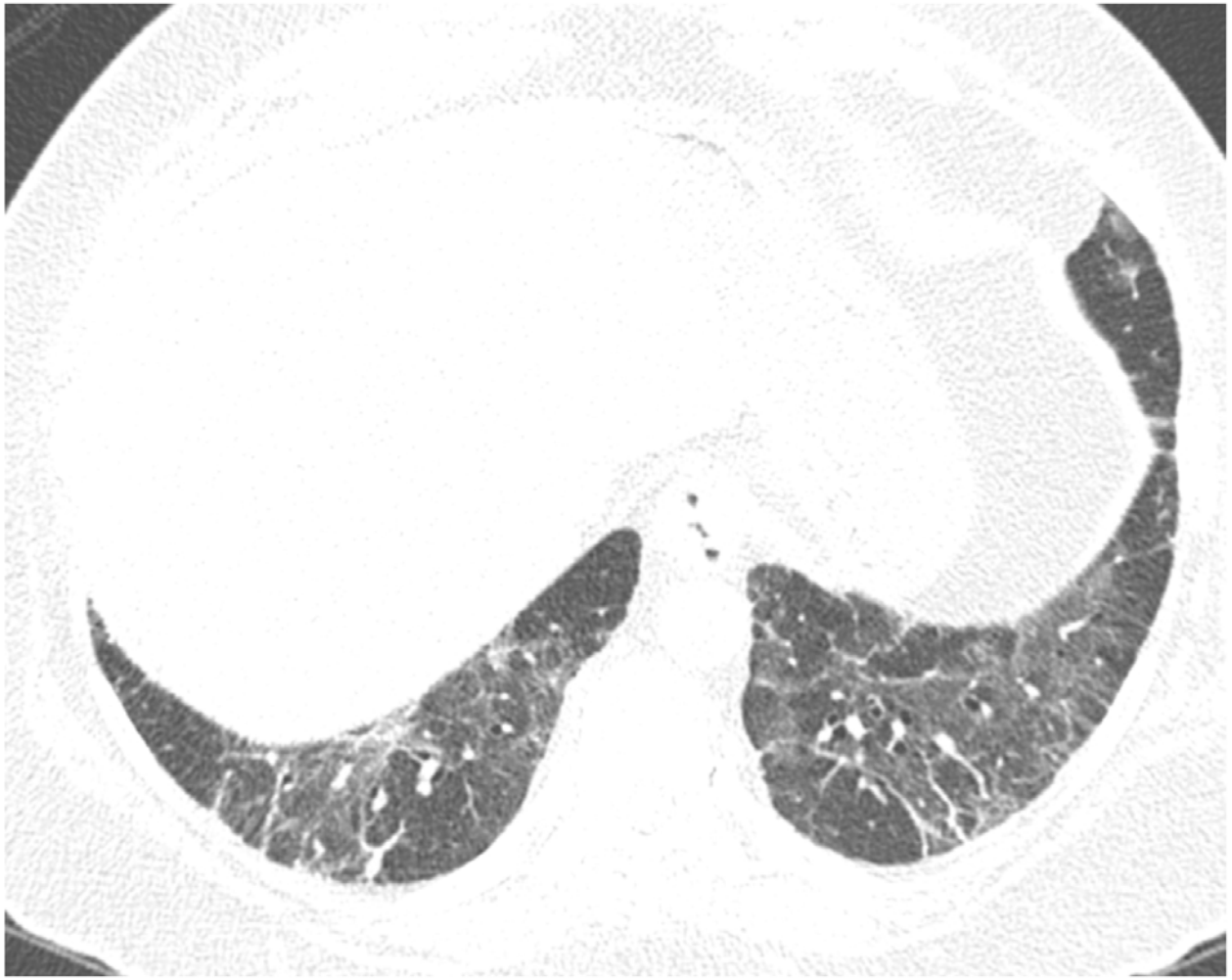
She was proned until her PF ratio was >150 and received low tidal-volume ventilation.

She was treated with dexamethasone and Remdesvir.

CT scan at admission



CT scan at 2 months



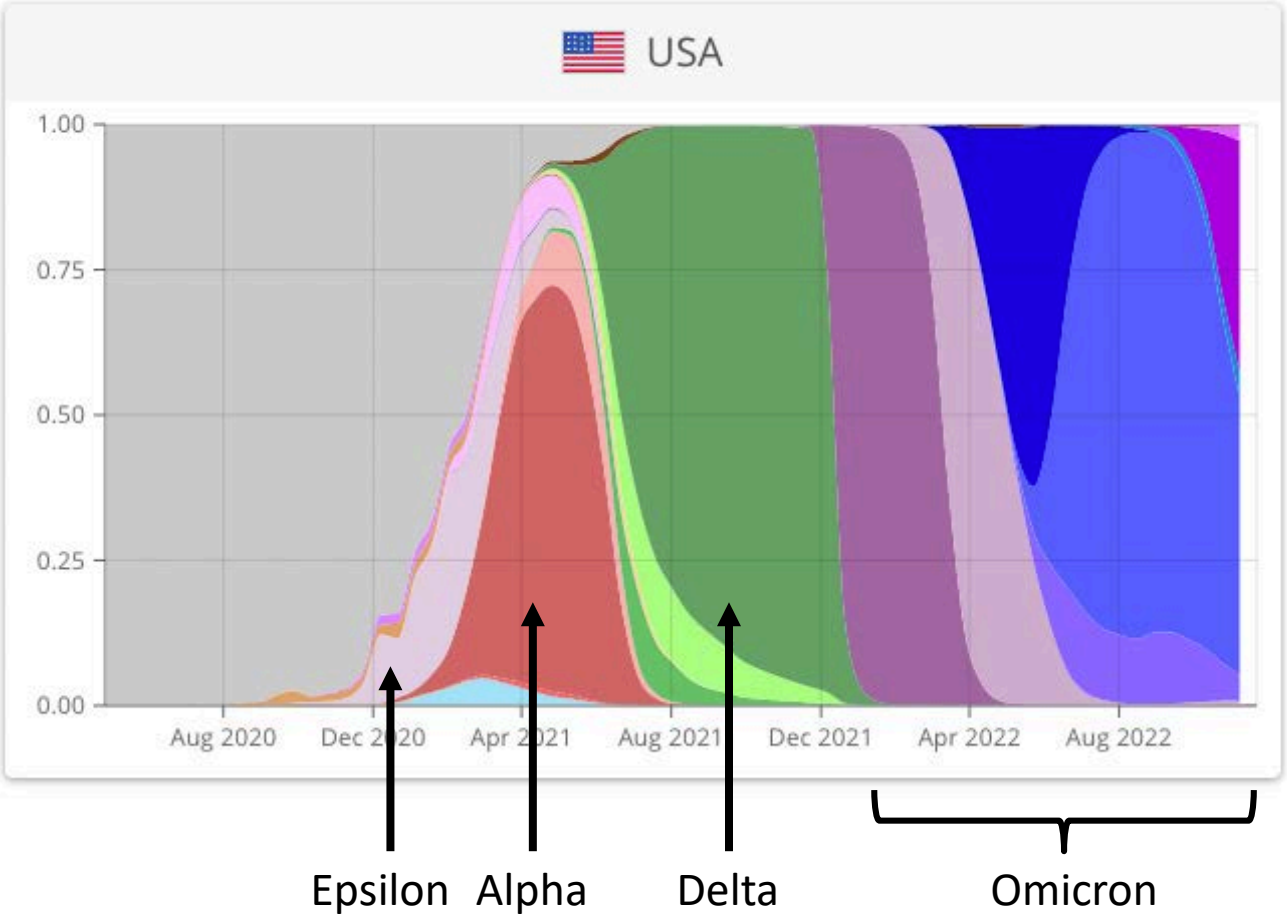
CT scan at 7 months



Background - COVID-19

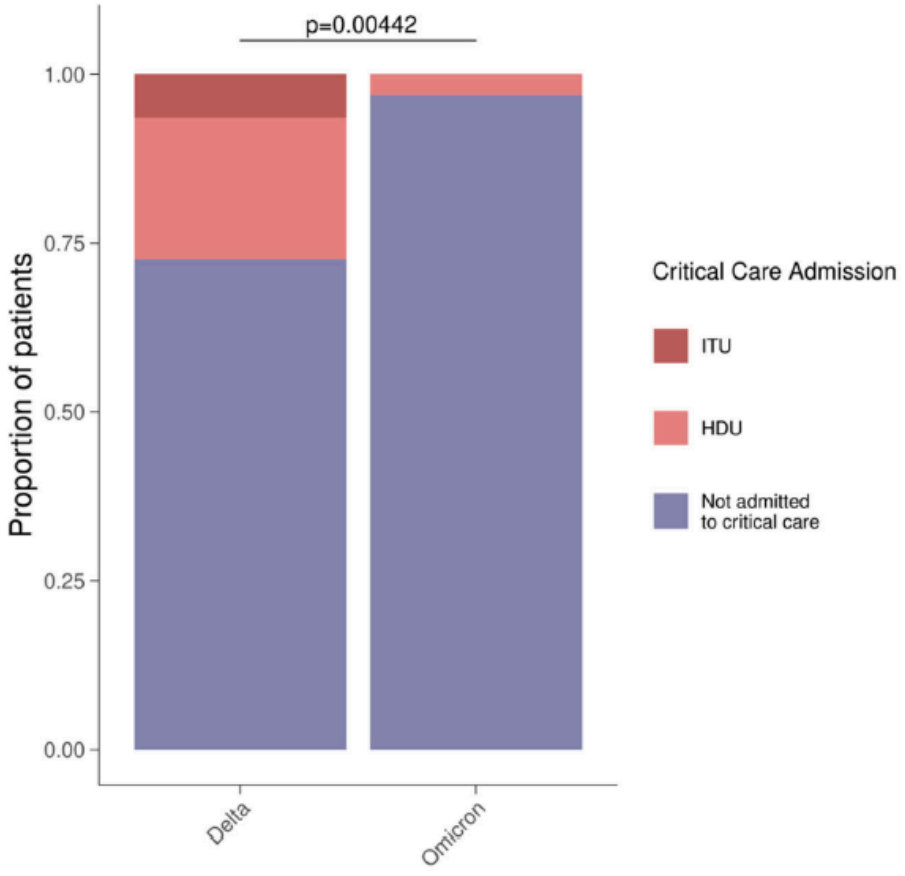
- First patients admitted to hospital in Wuhan, China in December 2019
- There have been 98,000,000 cases/1,075,000 deaths in the US as of ***Nov 30th, 2022***
- We noticed early in the pandemic that some recovering patients had respiratory symptoms

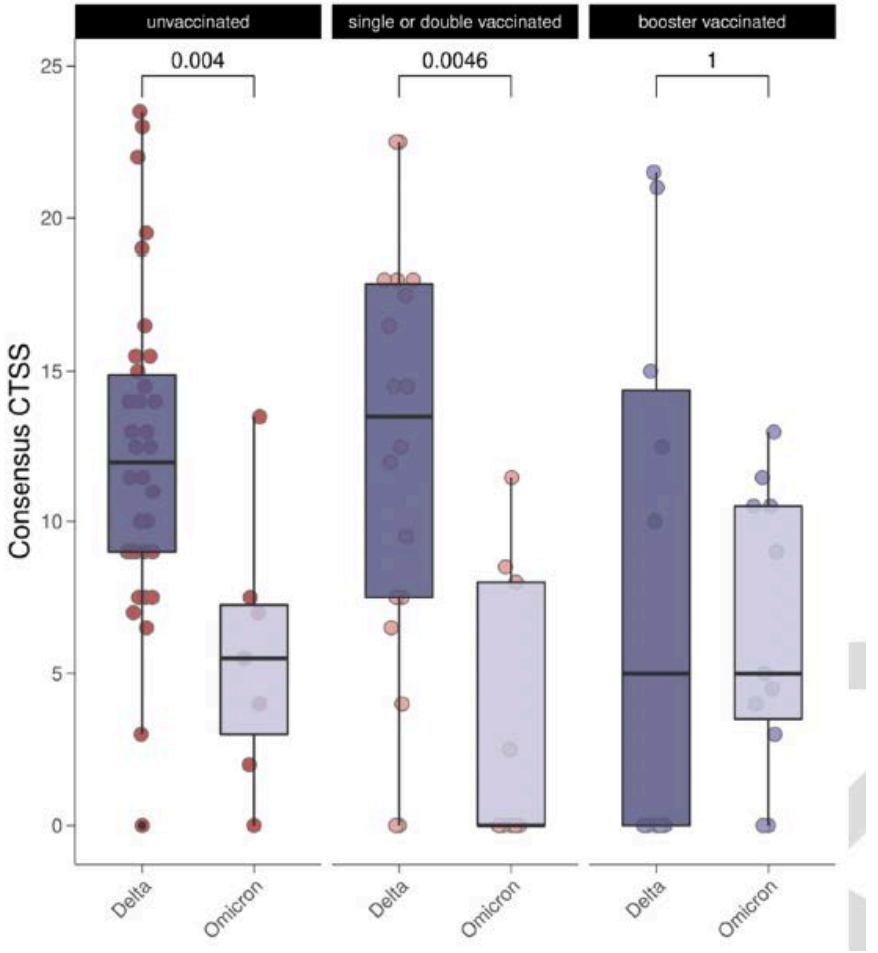
COVID Lung Involvement by strain



https://covariants.org/

Omicron vs. Delta





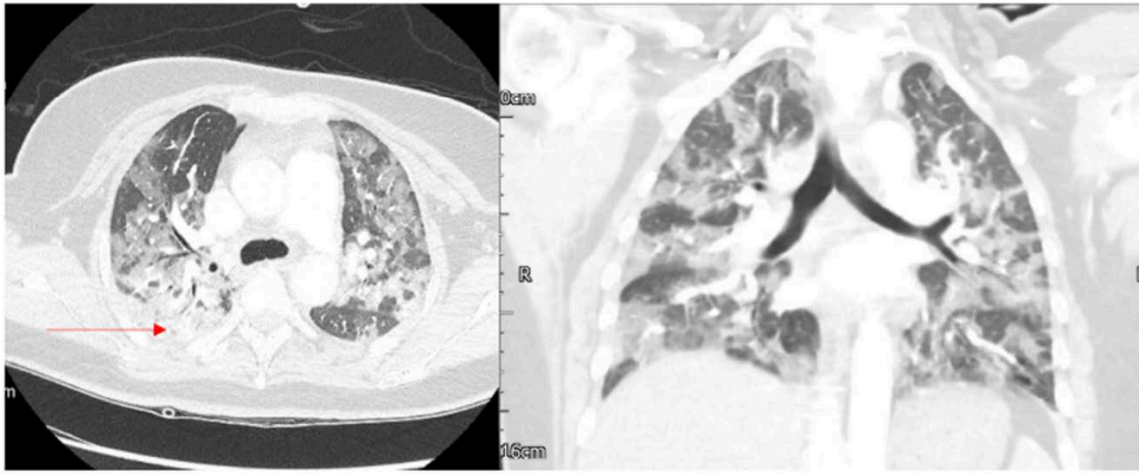
Tsakok et al. Rad Jun 2022

Why less lung disease with Omicron?

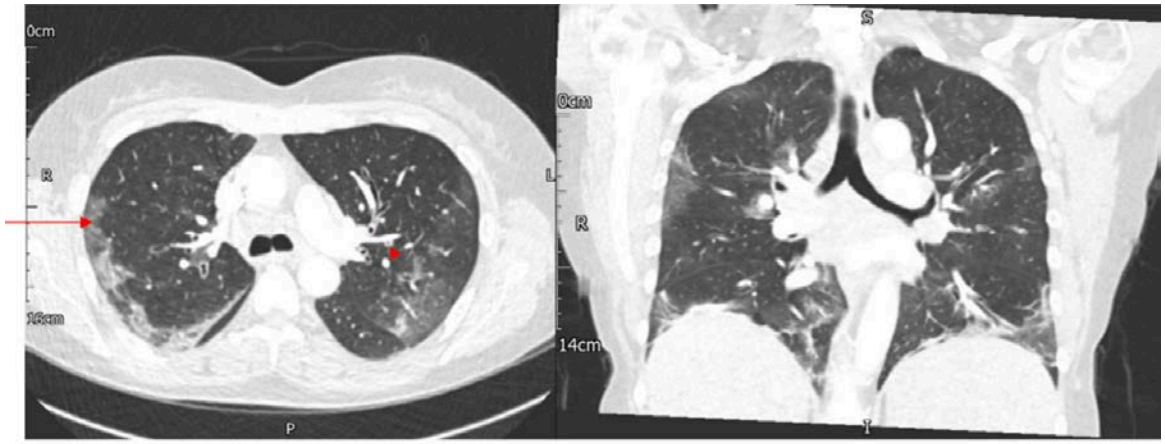
- Noted early less lung involvement/lower levels in lung tissue in multiple animal models
  - Halfman et al. Nature Mar 2022
- Less binding to lung receptor TMPRSS2
  - Peacock et al. bioRxiv May 2022
- Fares better in upper airway
- Later variants (BA.4 and 5) are more efficient in lung tissue

Acute COVID Lung Involvement

Delta



Omicron



Tsakok et al. Rad Jun 2022

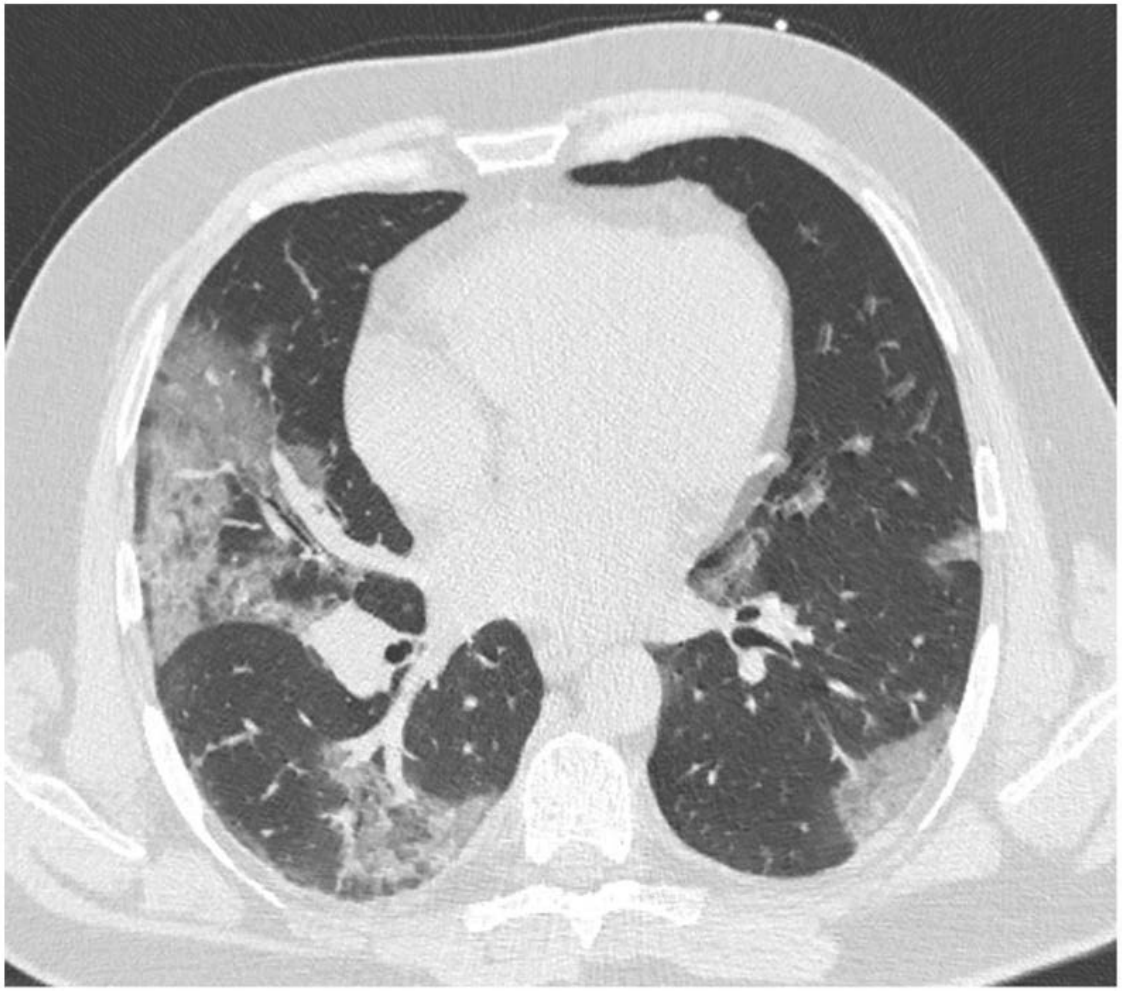
Acute COVID Lung Involvement

- 14% of symptomatic infected develop either:
  - Dyspnea
  - Tachypnea
  - Hypoxia
  - Lung opacities

- 5% of symptomatic infected develop either:
  - Respiratory Failure
  - Septic Shock
  - Multiorgan dysfunction

Wu et al. JAMA 2020

Acute COVID-Lung



Kwee et al. Radiographics 2020

Acute COVID-Lung



”Halo Sign”

Seen in up to 25% of acute COVID CT scans

Hu et al. EJR 2020
Meiler et al. EJR 2020

Viral PNA and Fibrosis

- SARS-CoV 2003
  - First 2 weeks into illness reticulations first noticed
  - Though GGO improved, 55% with reticulations at 4 wks.
  - 30 to 40% with abnormalities at 6 to 12 months
    - Those with abnormalities at 12 months had at 15 years
  - Fibrosis more common in *older, longer length of stay, higher LDH.*



Ooi et al. Rad 2004
Chan, Resp 2003
Antonio et al. Rad 2003

Viral PNA and Fibrosis

- MERS-CoV 2012
  - 33% with residual reticular opacities at median 43 days after recovery
  - Subjects were *older, longer ICU stay, higher LDH*
- Similar findings in influenza/H1N1



Das et al. Indian J Rad Imag 2017

Post-COVID Lung Disease

Prevalence varies and depends on:

- What population you are studying (everyone or just those with symptoms)
- How sick they were in the hospital (no oxygen, high flow oxygen, ventilator)
- Interval after infections (weeks or months)
- Variant of SARS-CoV-2

Post-COVID Lung Disease

"Clinical Phenotypes" noted early in pandemic

1. Radiographic abnormalities + symptoms
2. Radiographic abnormalities without symptoms
3. Breathlessness and normal radiograph

Etiology of Post-COVID Lung

Likely some combination of:

1. ARDS injury to the lung
2. Lung injury from mechanical ventilation
3. Direct viral injury to the lung

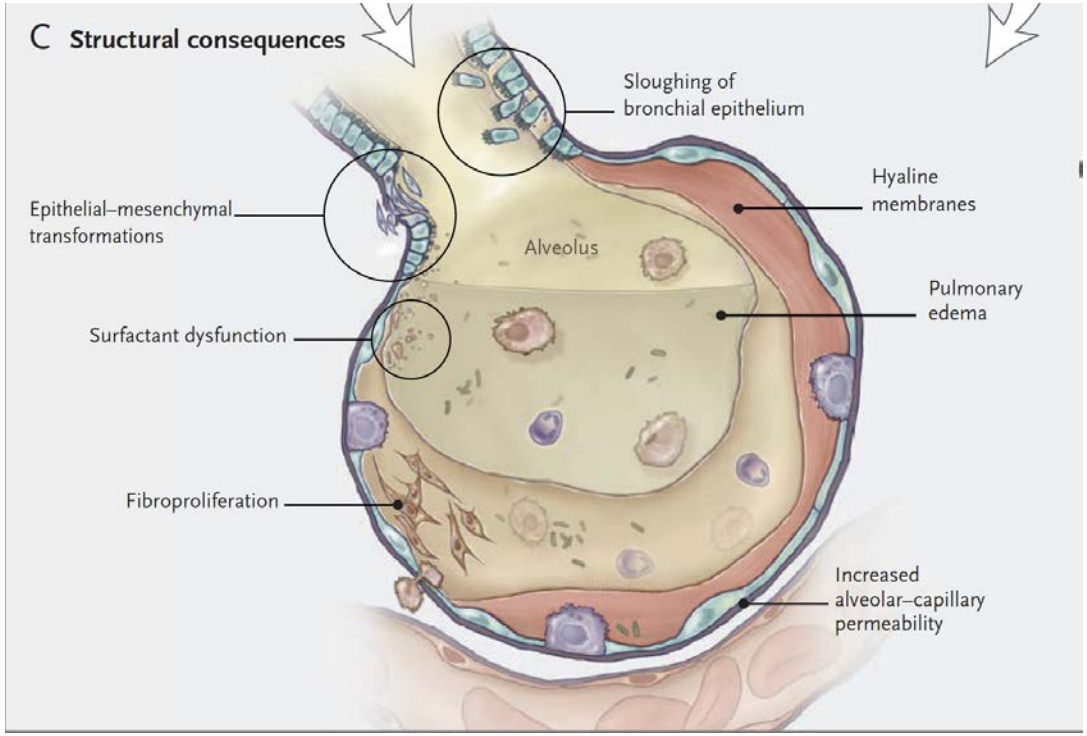
ARDS and Fibrosis

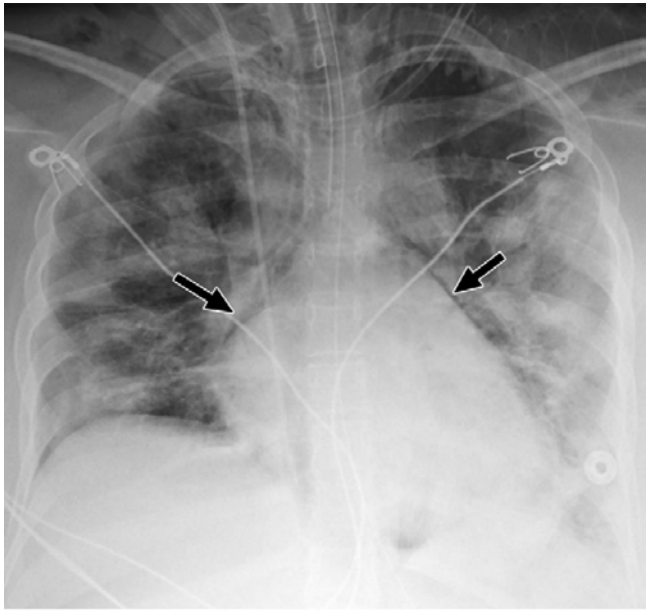
- Subset of ARDs survivors have persistent fibrotic changes
  - Correlate with restrictive physiology
  - Correlate with worse health and pulmonary QOL
  - Predicts mortality
  - Non-progressive



Ichikado, BMJ Open 2012

Ventilator-induced lung injury





COVID ARDS Barotrauma - 15%
Non-COVID ARDS Barotrauma - 10%

Slutsky et al. NEJM 2013

McGuinness et al. Rad 2020

Autoimmune disease

Cigarette Smoke

Infections

Drugs

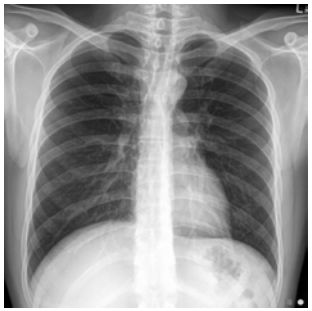
Radiation

Lung Injury

Environmental

ARDS

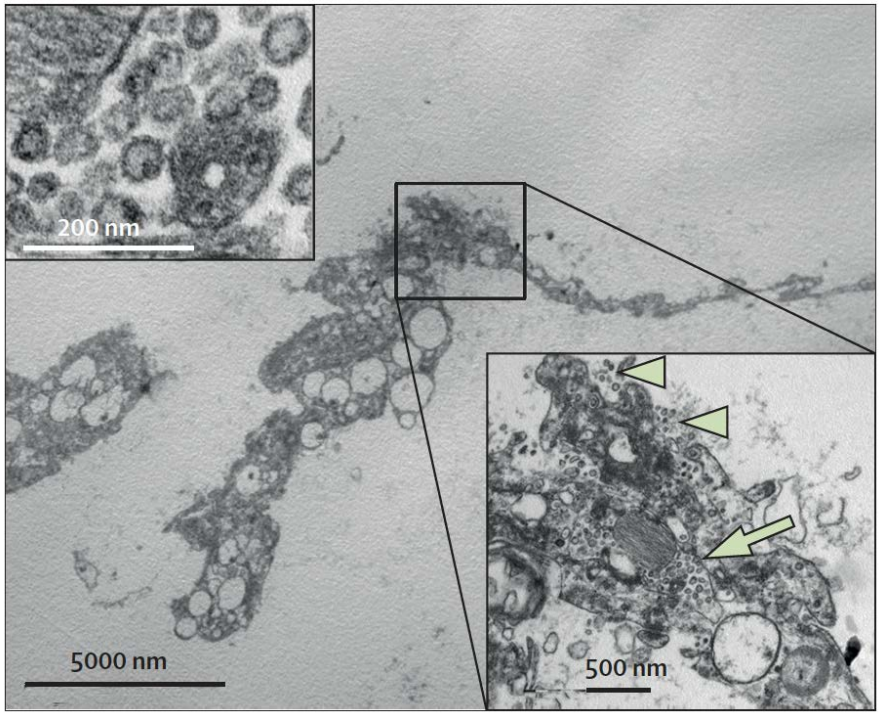
Normal Healing ---------- Abnormal Healing



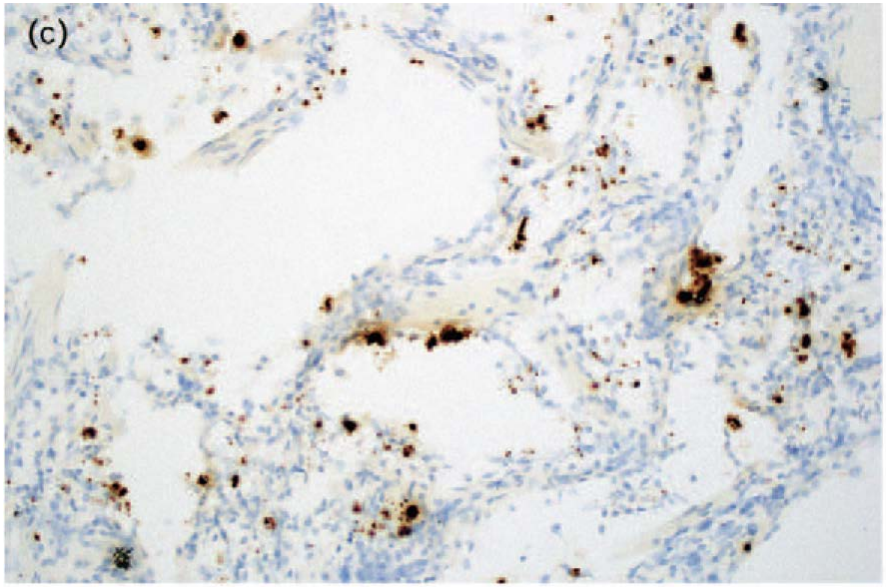
Genetics??



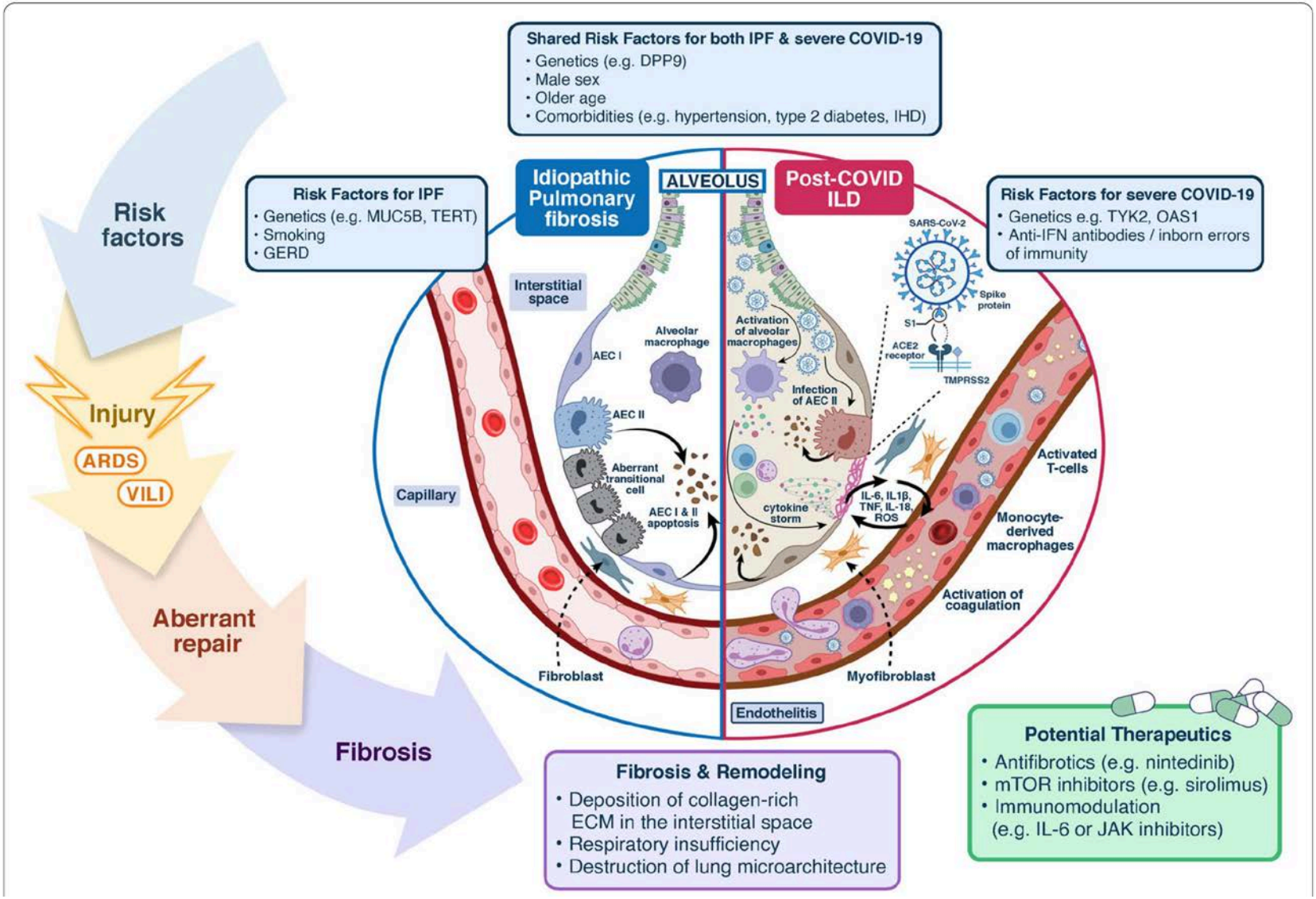
Direct injury from SARS-CoV-2



Carsana et al. LID 2020



Borczuk et al. Curr Opin 2021



MEHTA et al. Int Care 2022

Post-COVID Lung - 2 to 4 weeks

- At four weeks, 50% have persistent abnormalities - septal thickening and GGO

  Zhao et al. AJR 2020

- At four weeks, 75% of patients who were hospitalized have PFT abnormalities (most commonly reduced DLCO)

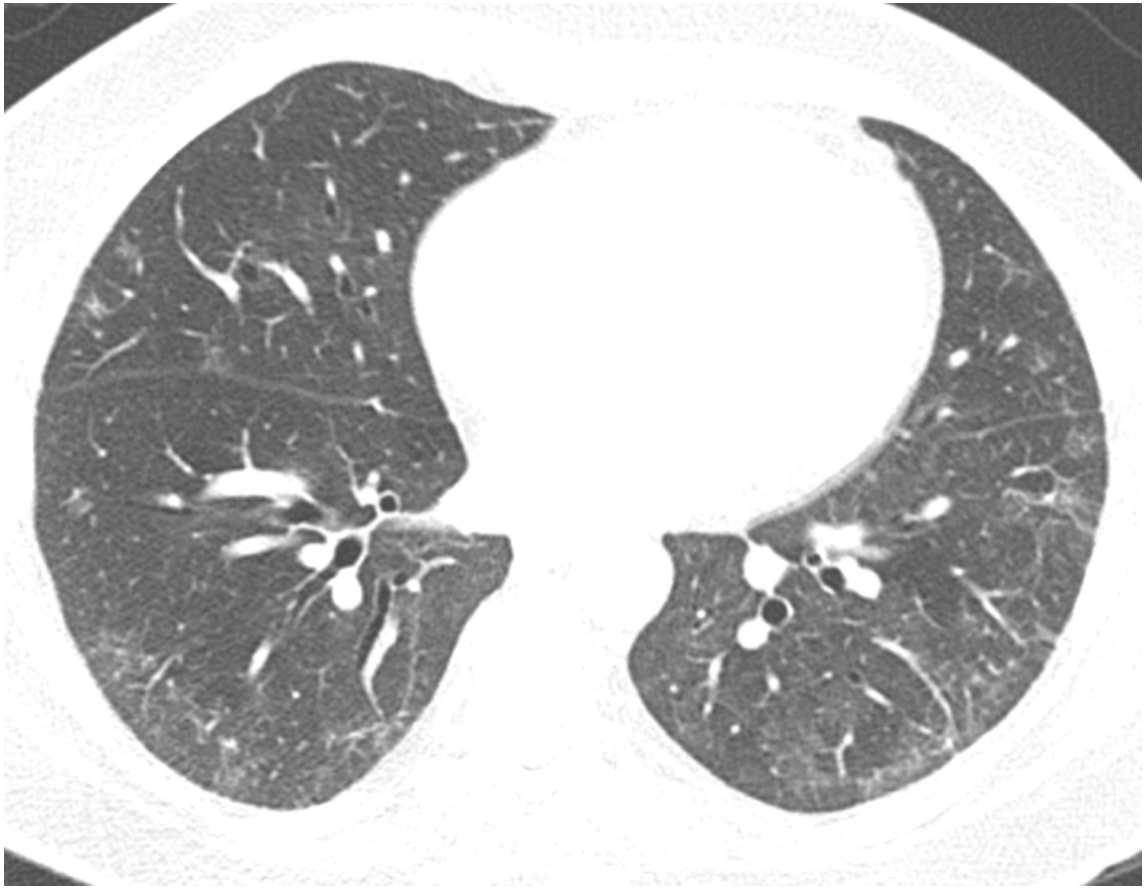
  Huang et al. Resp Res 2020

Hospital admission scan



Solomon et al. Rad 2021

Follow-up scan over 1 month



Solomon et al. Rad 2021

Post-COVID Lung - 3 months

- 42% with abnormal baseline CT have residual changes
  - *25% were never hospitalized*
  - Most commonly GGO and subpleural parenchymal bands

    Tabatabaei et al. Em Rad 2020
- In those requiring ventilation, fibrosis seen in 67%

  Morin at al. JAMA 2020.
- Abnormalities are in areas of previous GGO

Post-COVID Lung - 3 months



Solomon et al. Rad 2021

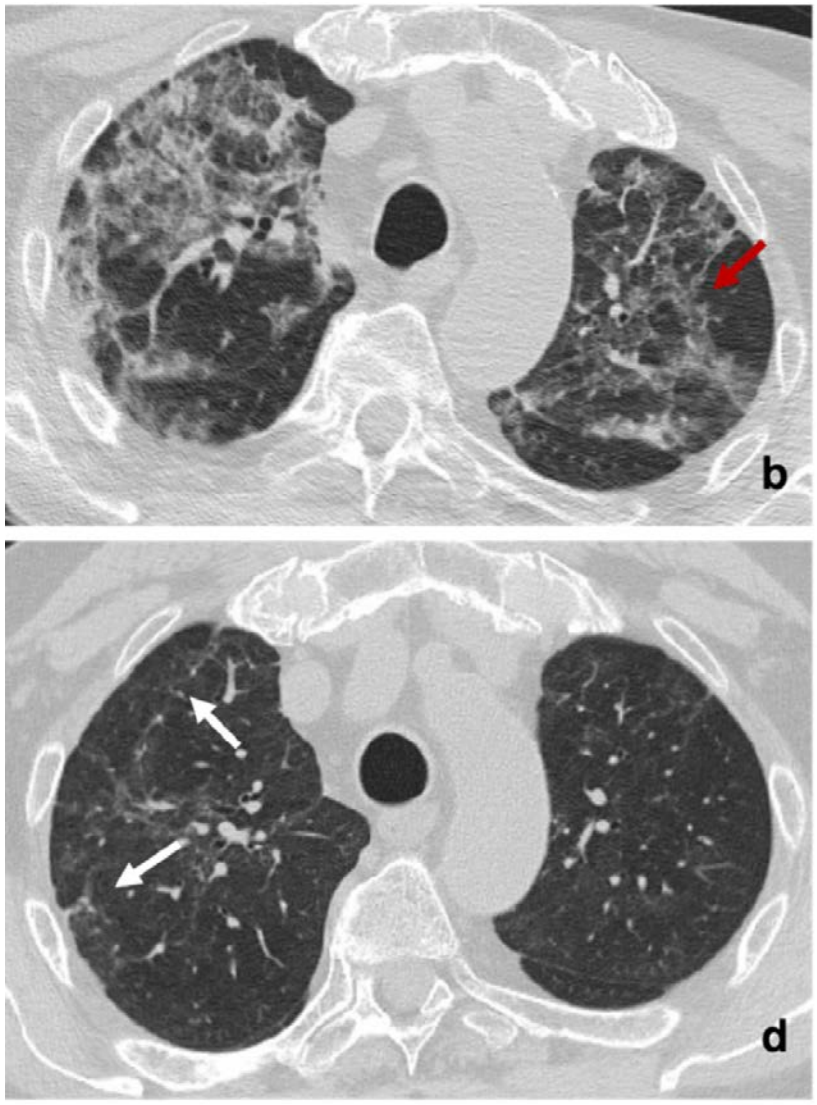
Post-COVID Lung – 4 to 6 months

- At 4 months, 76% of intubated and 58% of non-intubated patients had abnormalities
  - 19% had fibrotic changes predominately subpleural

    Morin et al, JAMA 2021

- At 6 months, 35% of those who had severe COVID pneumonia had fibrosis (traction bronchiectasis and/or honeycombing)

    Han et al. Rad 2021



Post-COVID Lung - 6 months

- 118 patients with moderate to severe COVID pneumonia
- 72% with fibrotic changes at 6 months
- Baseline lung severity score and quantitative CT were highly predictive of fibrosis at 6 months

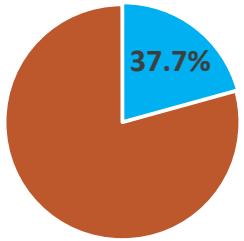
Caruso et al. Rad 2021

Post-COVID Lung – 12 months

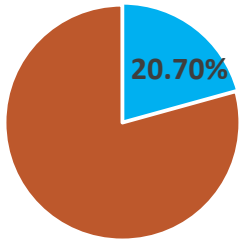
- Meta-analysis showing 32.6% with any residual abnormality

GGO	21%
Fibrotic changes	21%
Bronchiectasis	10%
Septal Thickening	8%
Reticular Opacity	5.5%
Consolidation	2.6%

Severe/Critical COVID



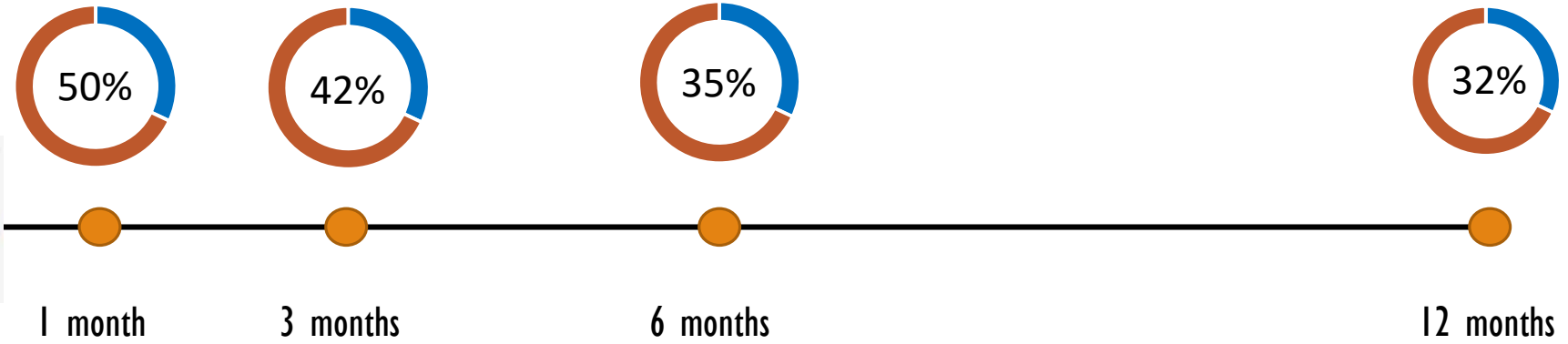
Mild/Moderate COVID



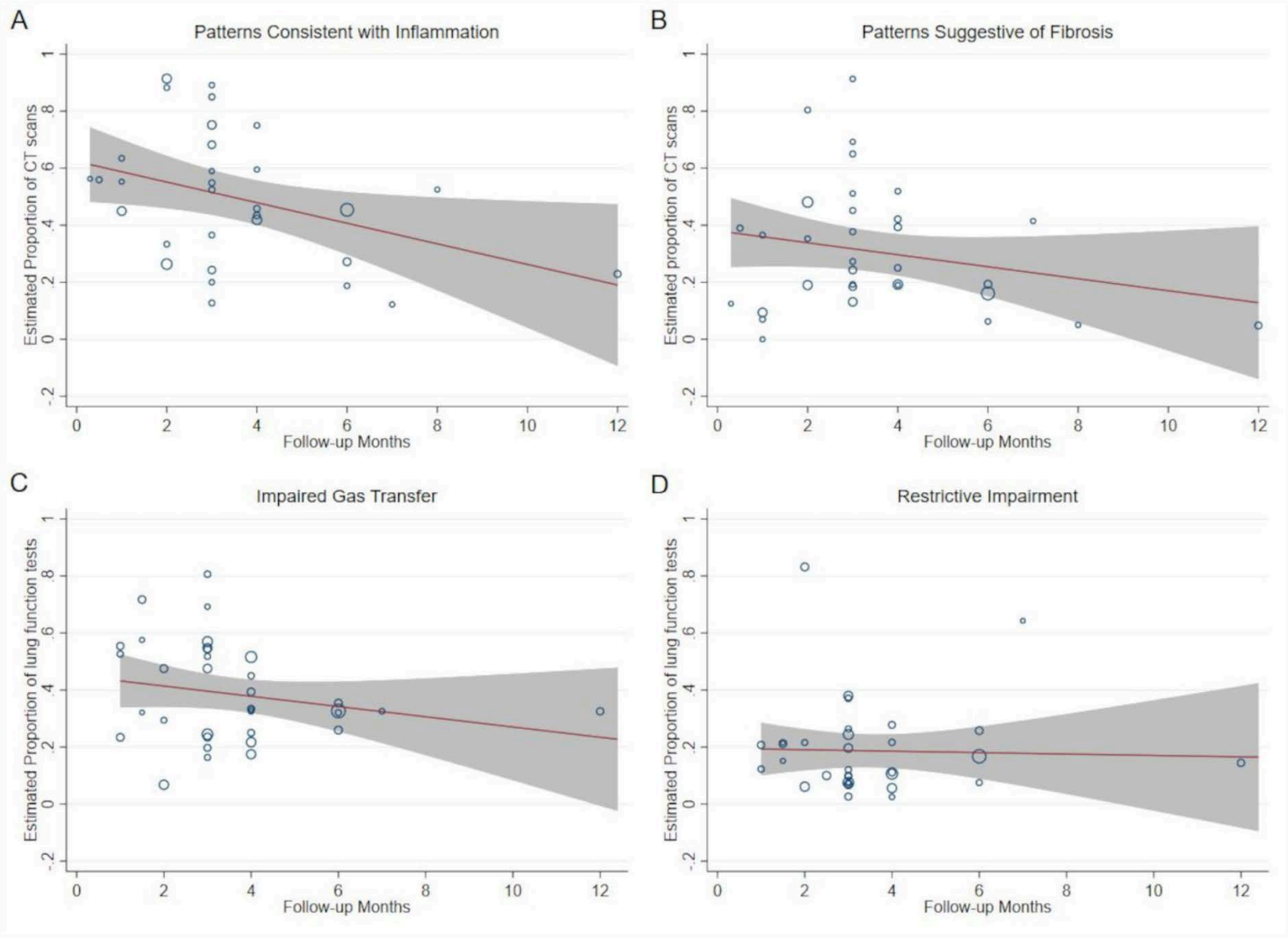
Watanabe et al. Resp Mar 2022

Post-COVID Lung - Summary





SARS-Cov-1 = 30 to 40% at one year



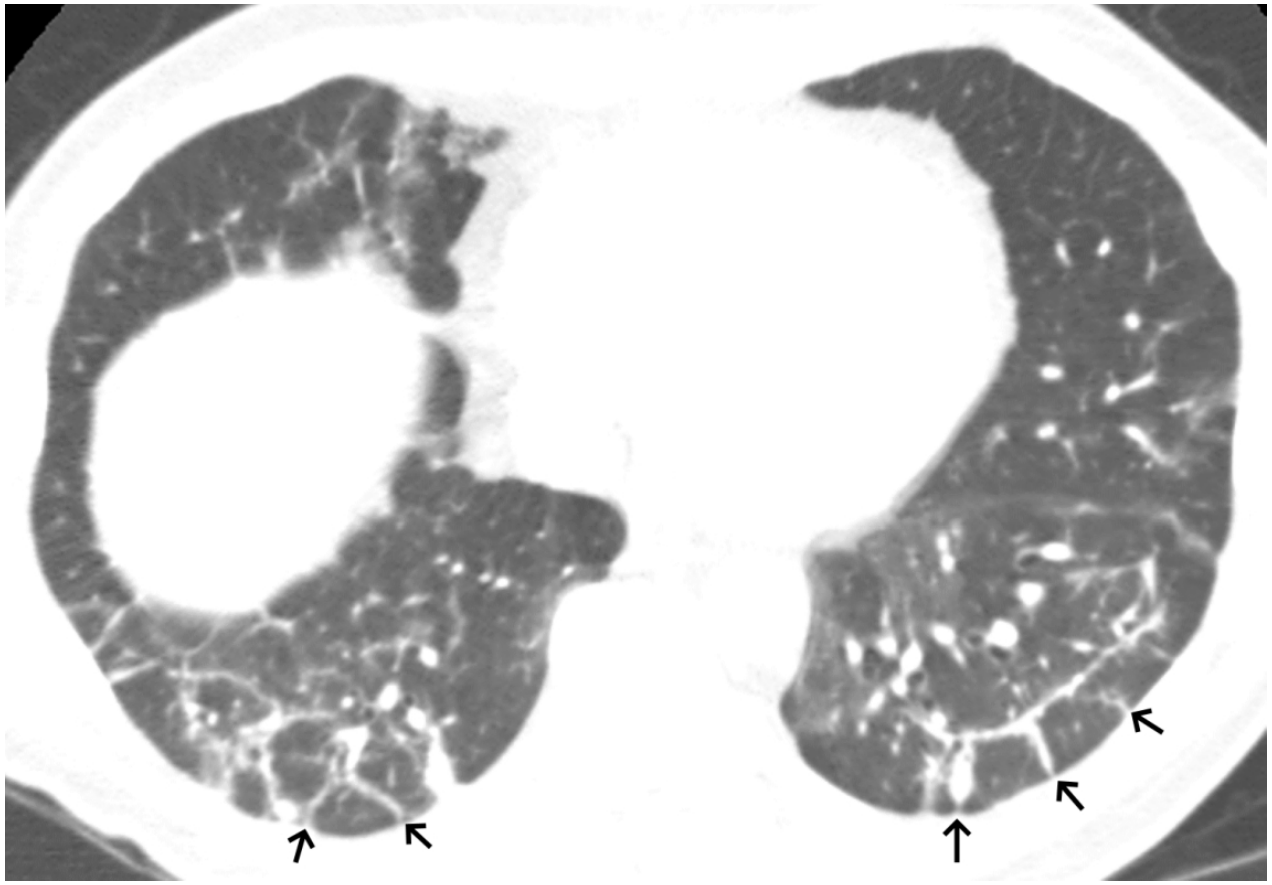
Fabbri et al. Thorax 2022

Post-COVID persistent GGO

- A subset have slowly resolving GGOs
- Some evidence that this represents either organizing pneumonia (OP) or acute and fibrinous organizing pneumonia (AFOP)
- A third will resolve in one to two months
- Steroids may speed resolution

Myall et al. Annals ATS 2021

Post-COVID persistent GGO



Solomon et al. Rad 2021

Post-COVID persistent GGO





Solomon et al. Rad 2021

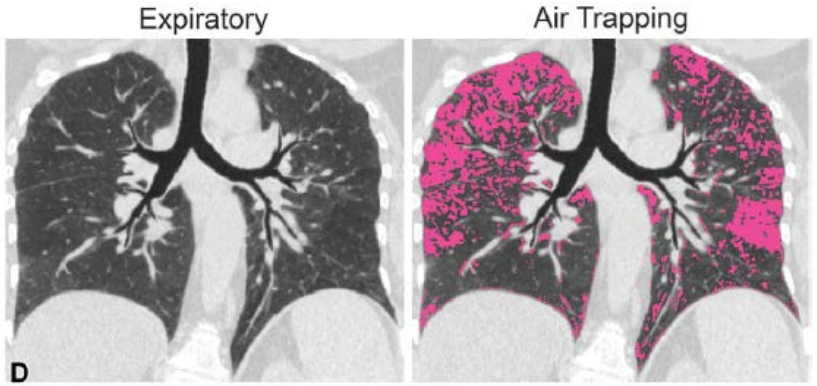
Post-COVID Airways

Timeframe	Type	Ct Findings
Acute/Subacute	Large	Bronchial wall thickening
		Bronchial dilation (reversible)
	Small	Air Trapping
Chronic	Large	Peripheral, central or diffuse bronchiectasis with residual opacities
		Anterior bronchiectasis with fibrosis and cysts (ARDS)
	Small	Mosaic attenuation
		Air Trapping
		Ventilation defects with abnormal diffusion

Kanne et al. Rad 2022

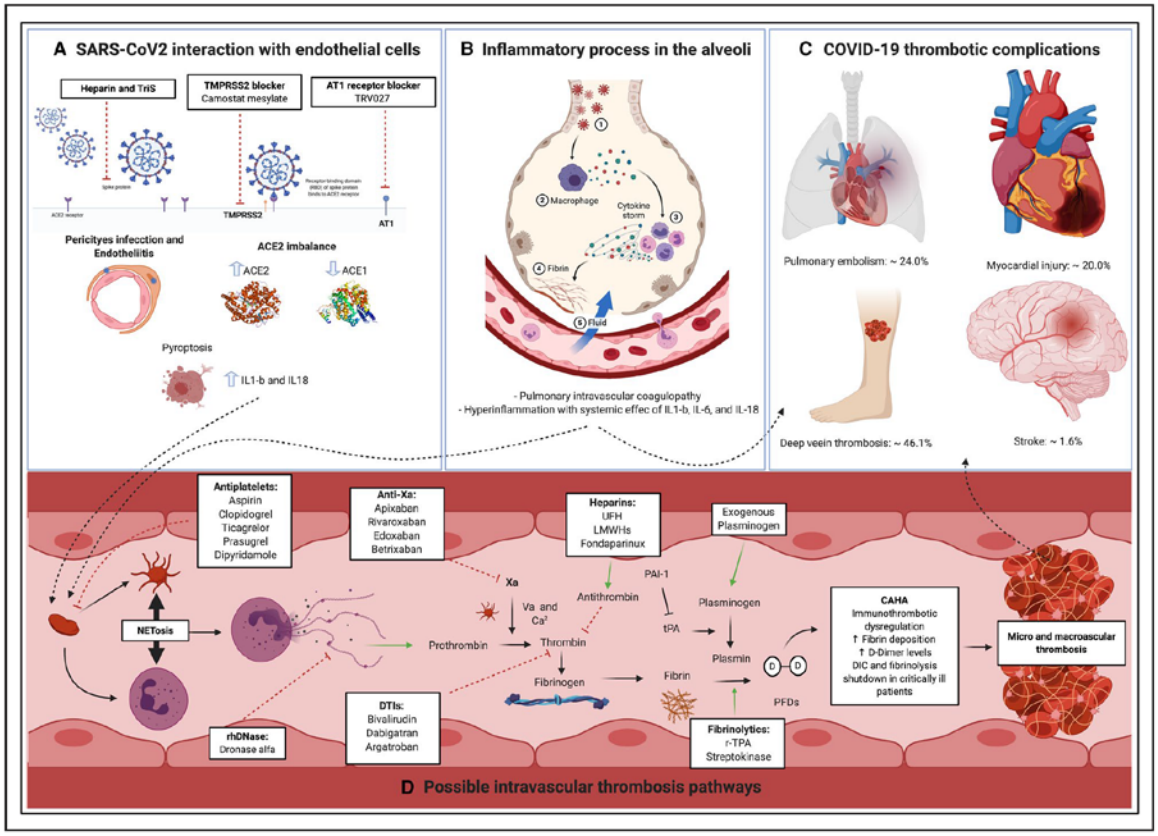
Post-COVID Small Airways

Population	Incidence	Notes
6 months post COVID[1]	29%	Higher in more severe PNA
30 days post COVID with symptoms[2]	77%	Higher in older males
30 days post COVID with symptoms[3]	58%	Similar values in outpatients and inpatients, used quant CT



1. Jia et al. Sci Rep 2022
2. Franquet et al. Eur Rad 2022
3. Cho et al. Rad 2022

Post-COVID PE

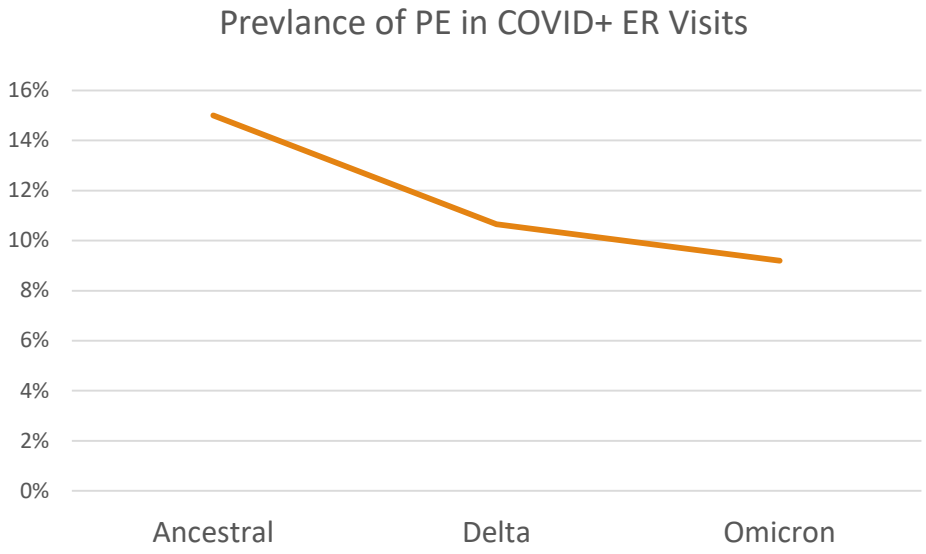


Ortez-Paz et al. JAHA 2021

- DVT in 14.8% and PE in 16.5% of all hospitalized patients
  Suh et al. Rad 2021
- Rate of PE in ICU may be higher - 49% in one series
  Kwee et al. Eur Rad 2021

Post-COVID PE

VTE Prevalence	Population
14.1%	Hospitalized, prophylaxis
40.3%[1]	US screening
9.5%	No screening



Vaccinated	10.6%
Unvaccinated	9.17%

P=0.02

Nopp et al. Res Pract Thromb 2020

Law et al. Emer Rad 2022

Post-COVID PE

PE - 27 to 30%

Leonard-Larnat et al. Rad 2020
Poyiadji et al. Rad 2020

Unclear thromboembolic risk

Suh et al. Rad 20201

VTE risk at 42 days 0.48%?

Increased risk in first 19 days after hospitalization…

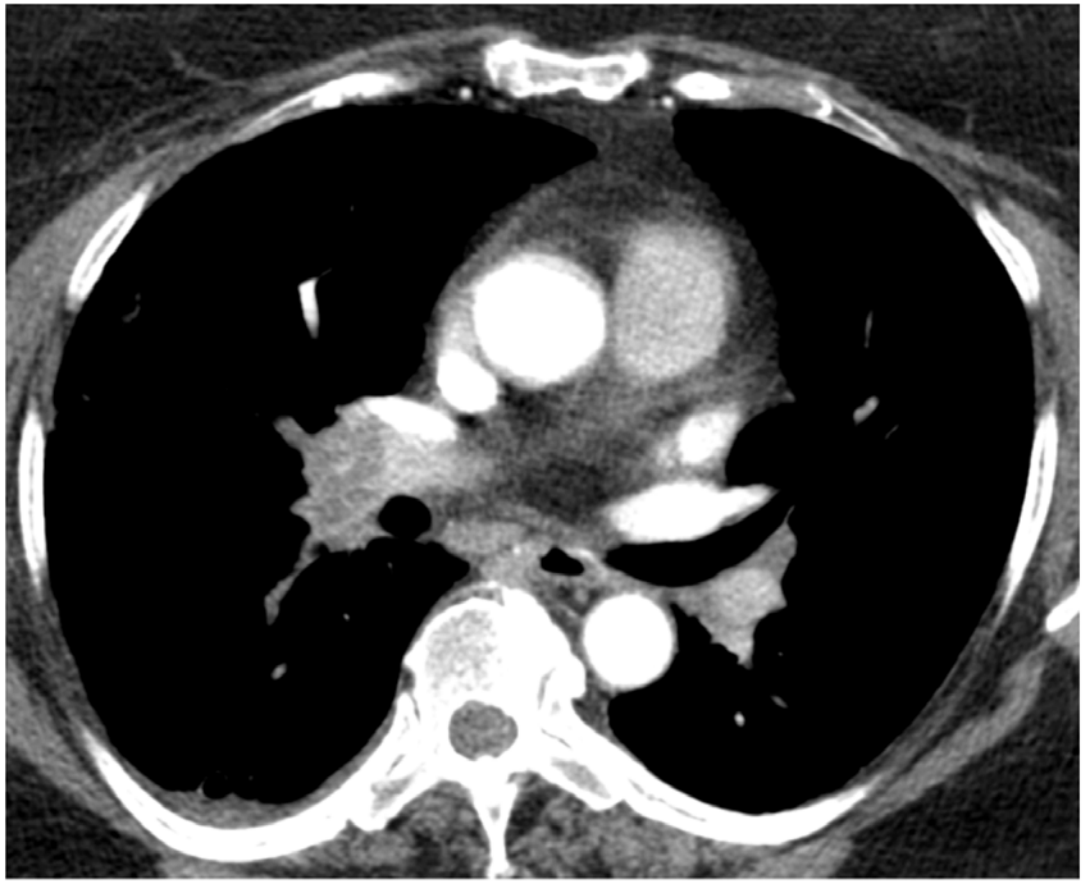
Scudiero et al. Thromb Res 2021

DVT – 2.5% at day 30

Patell et al. Blood 2020.

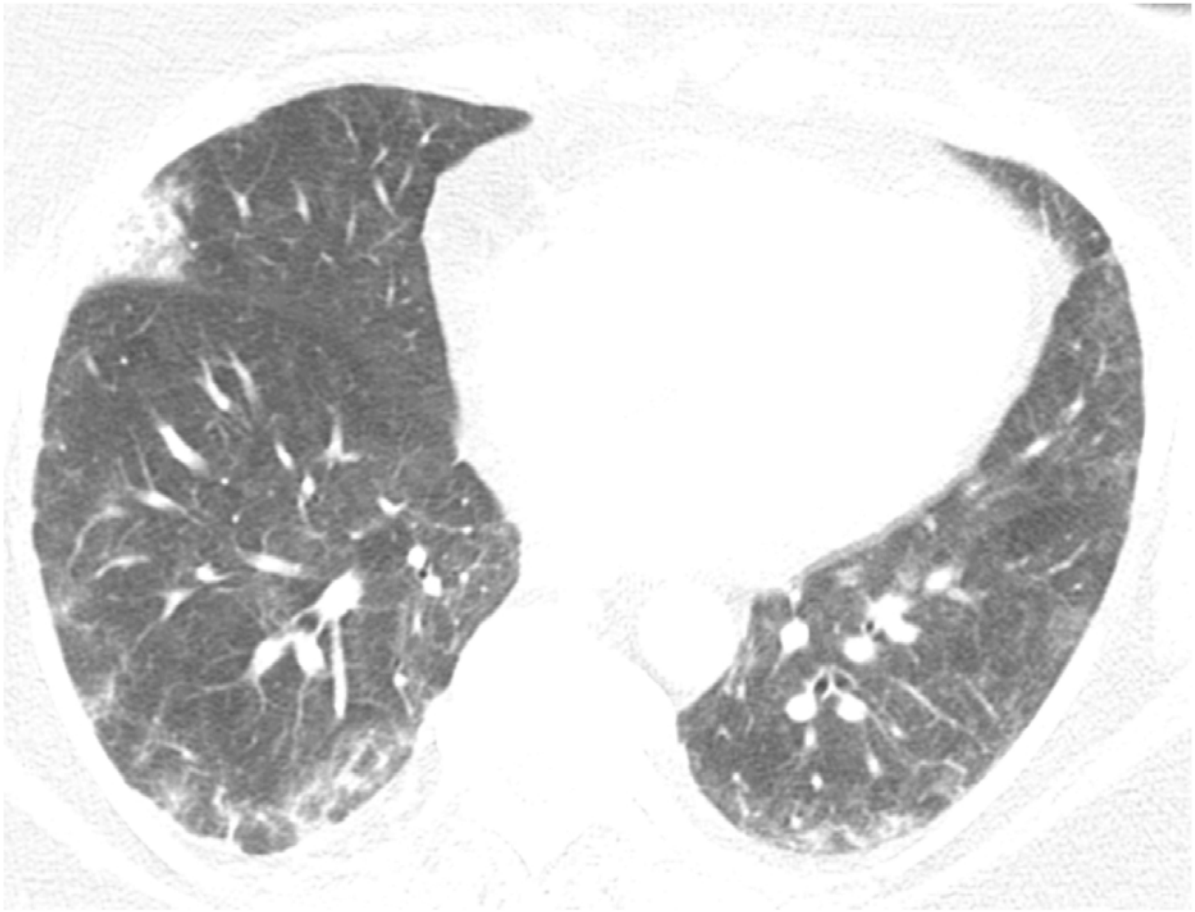
No higher thromboembolic risk

Roberts et al. Blood 2020



Post-COVID Pulmonary Embolism

Solomon et al. Rad 2021



Post-COVID Pulmonary Embolism

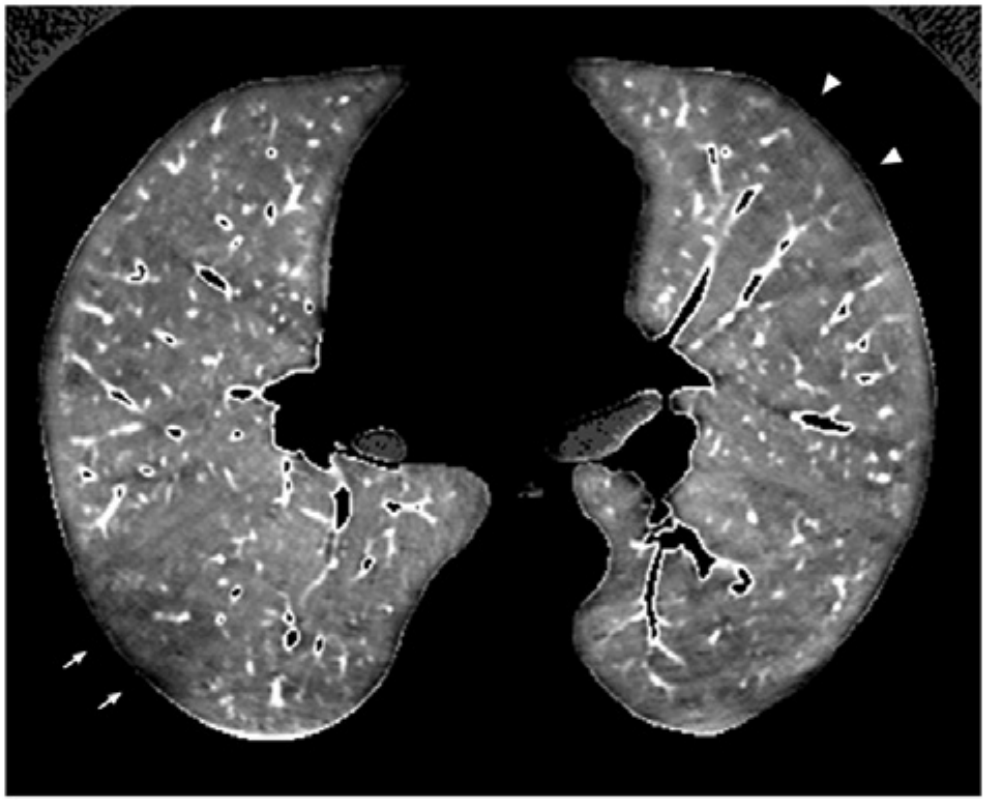
Solomon et al. Rad 2021



Post-COVID Pulmonary Embolism

Solomon et al. Rad 2021

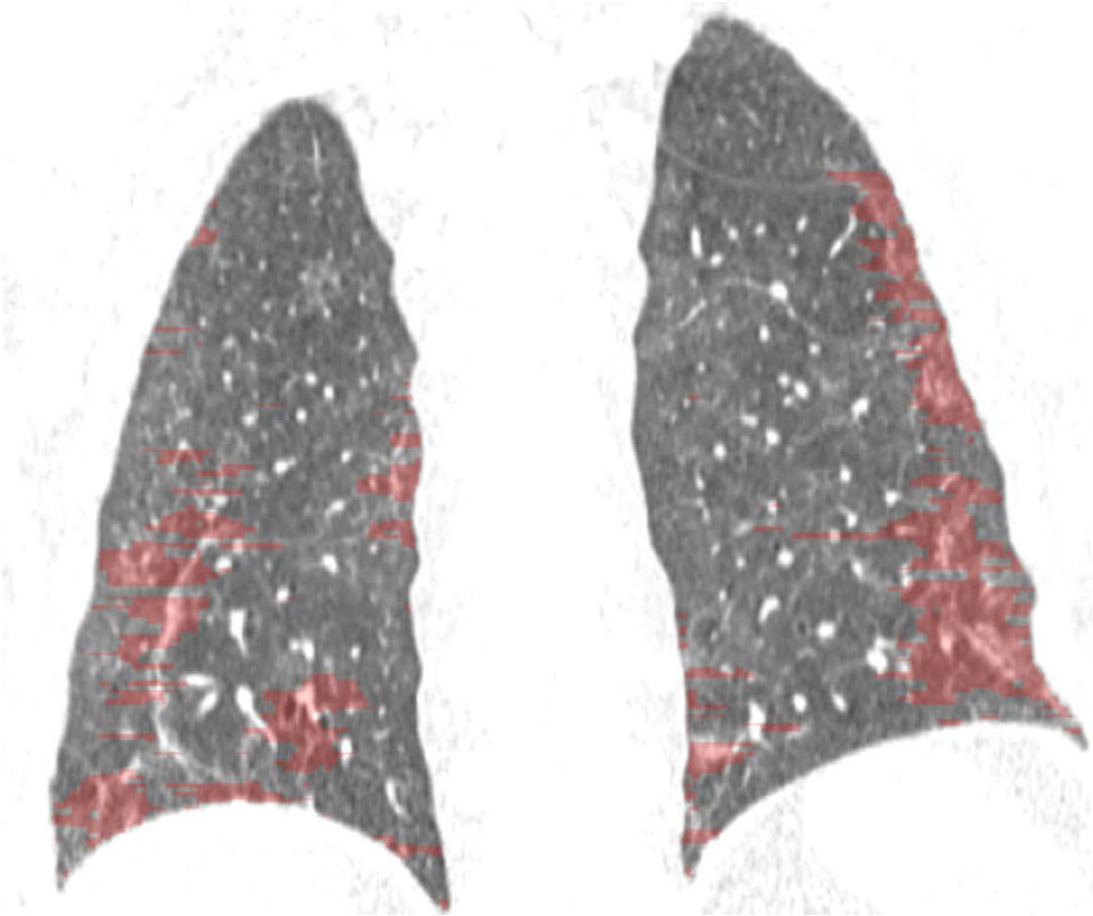
Post-COVID Perfusion Abnormalities



- A study looking at dual-energy CT in 55 symptomatic patients after COVID pneumonia
- 5% had unsuspected clot
- 58% had perfusion defects (4 with normal lung parenchyma) suggestive persistent microvascular abnormality

Remy-Jardin et al. Eclin Med 2021

Quant CT in Post-COVID Evaluation

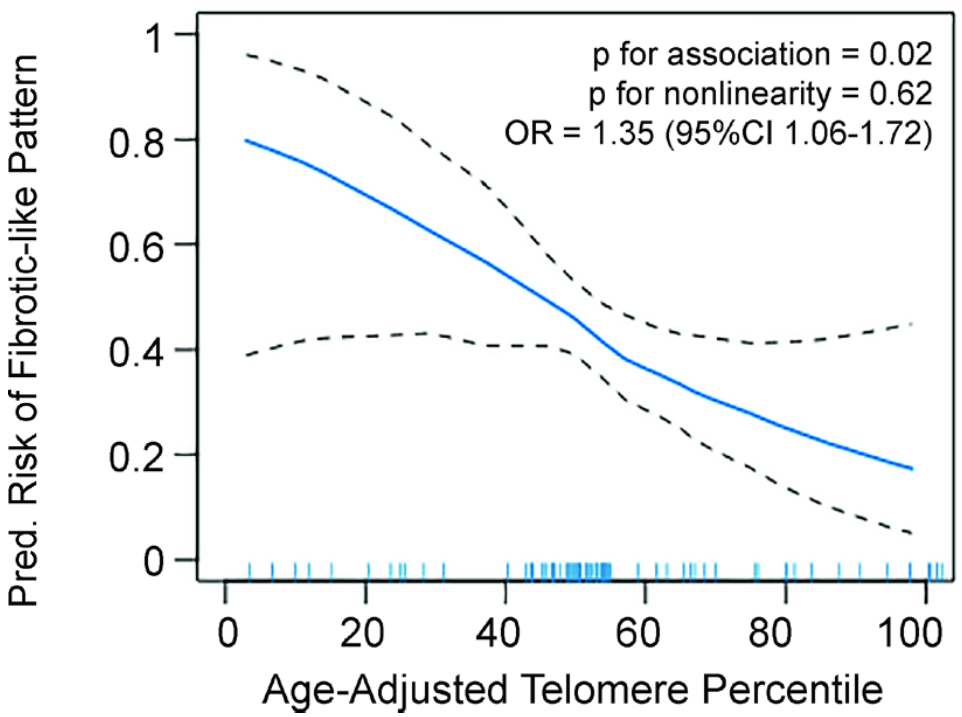


- QCt early in the course of infection independently predicts ICU admission and mortality
  Li et al. Clin Imag 2021
  Chabi et al. Diag 2021
- QCt metrics of pneumonia decline over time in recovery
  Liu et al. Front Med 2021
  Kassin et al. Sci Rep 2021
- DTA fibrosis predicts progression in ILD and can discriminate between GGO and fibrosis in COVID
  Humphries at al, Rad 2017

Risk Factors for Post COVID lung

Extent on acute CT	Need for hospitalization	Need for oxygen in hospital	Need for ventilation in hospital
CRP	LDH	IL-6	Dimer
WBC	Albumin	Male Sex	Co morbidities
Older age	Longer hospital stay	Duration of ventilation	ARDS

Risk Factors for Post COVID lung



- Telomerase mutations associated with IPF - 15% of familial pulmonary fibrosis patients have mutations
  Tsakiri et al. PNAS 2007
- Telomere length has been associated with survival in IPF
  Stuart et al. Lancet Resp 2014
- Leukocyte telomerase length is *independently associated* with post-COVID fibrosis.

McGroder et al. Thorax 2021

Treatments

Complete

Fuzheng Huayu
Low dose Prednisone
Strong **lungs** through Song
LYT-100
Zilucoplan
Angiotension-(1-7)

Enrolling

EV-Pure and WJ-Pure	MON002
Canrenoate K	BIO300
Sirolimus	Nintedanib
Pirfenidone	APX-115
Ozone	Whole Blood Exosomes
bovhyaluronidase azoxymer	Wharton's jelly derived mesenchymal stem cells

“Soft”Recommendations

- High resolution CT imaging on post-COVID patients with respiratory symptoms
- Strong consideration for PE evaluation for those with breathlessness not explained by lung disease
- Treatment of persistent GGOs with immunosuppressive agents
- Do not rush to use drugs without any data to support them
- Expiratory films and treatment of airways disease
- Convince people not to get COVID….

Case #2

78yo admitted COVID + on 12/7/20

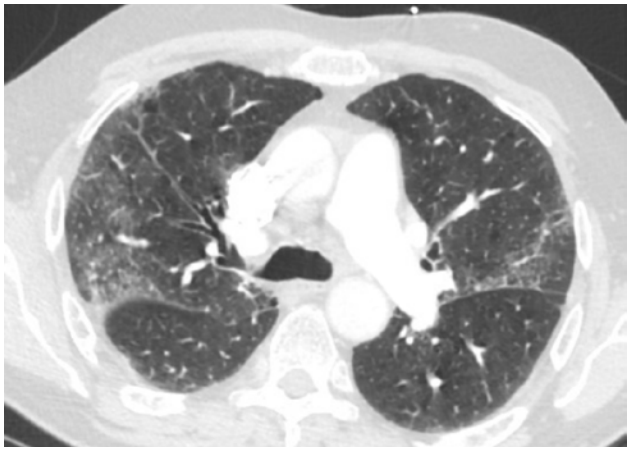
- PMH of COPD

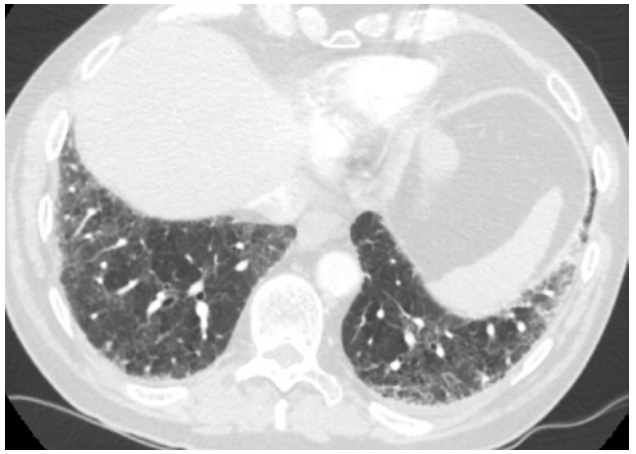
Not ventilated – 15L max O2 during stay

Hospitalized x 30 days

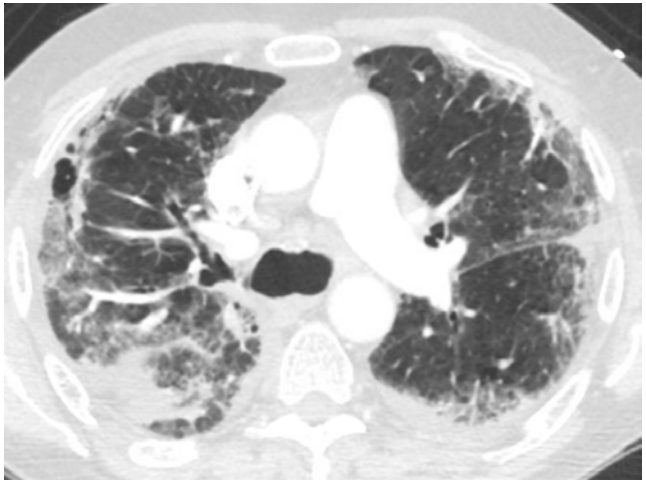
Got dexamethasone, had PE

12/8/20



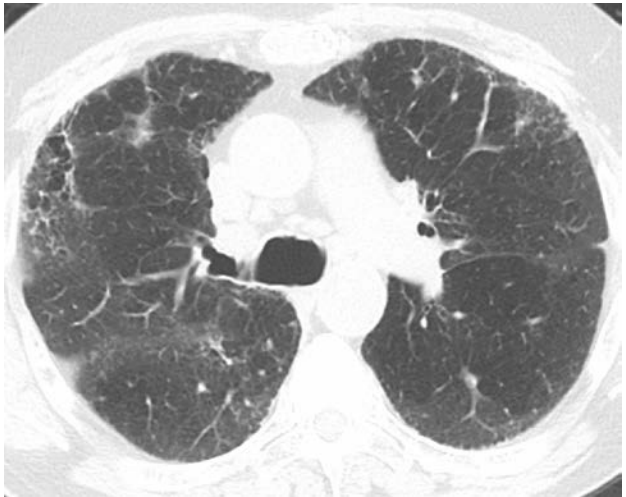


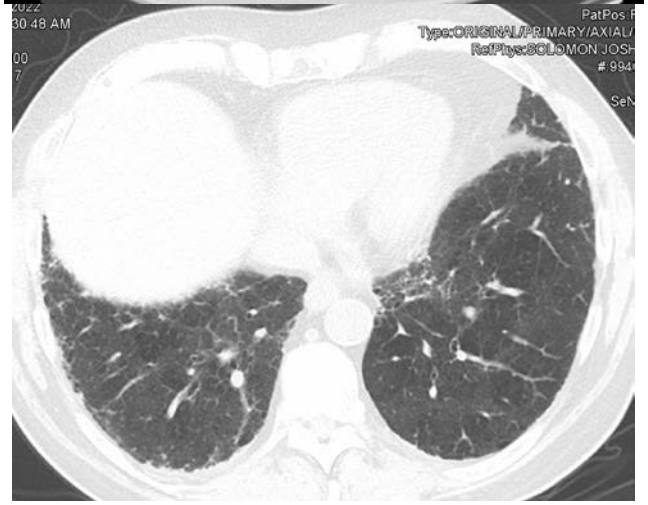
1/6/21



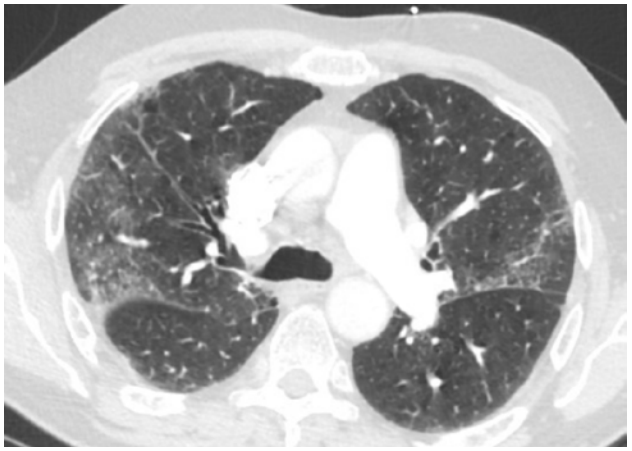


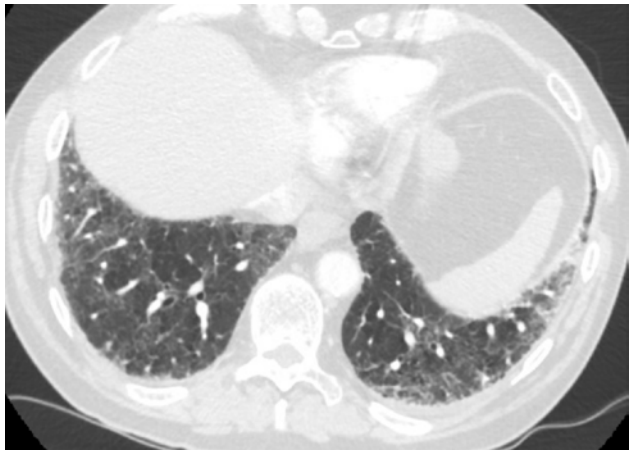
9/1/22



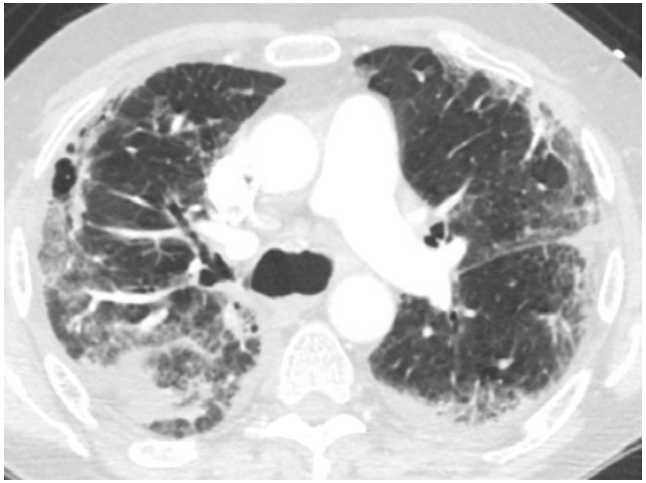


12/8/20



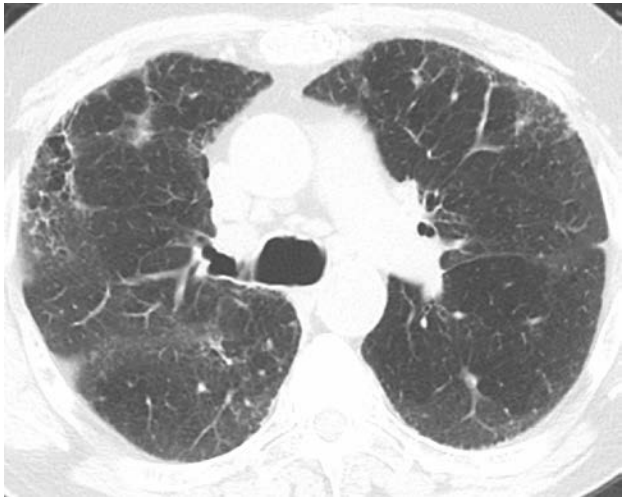


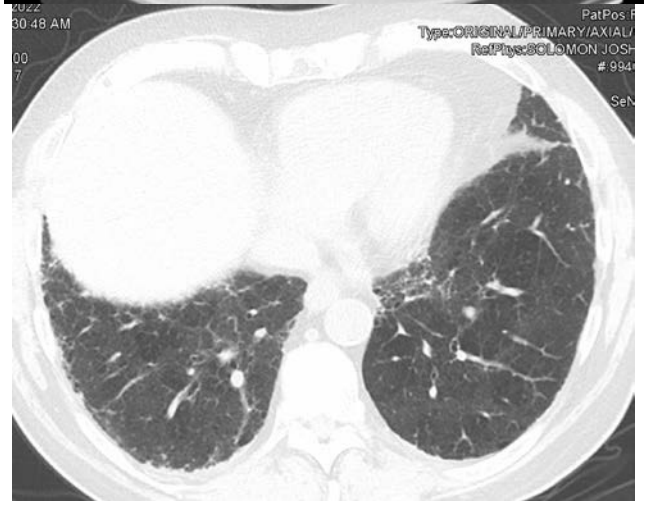
1/6/21





9/1/22





Case #3

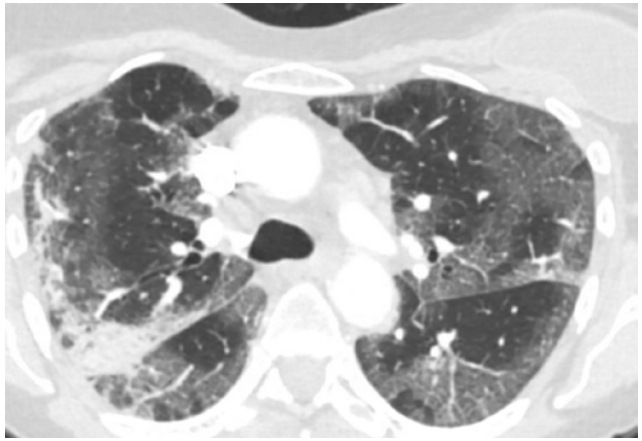
58yo healthy active female, no health problems

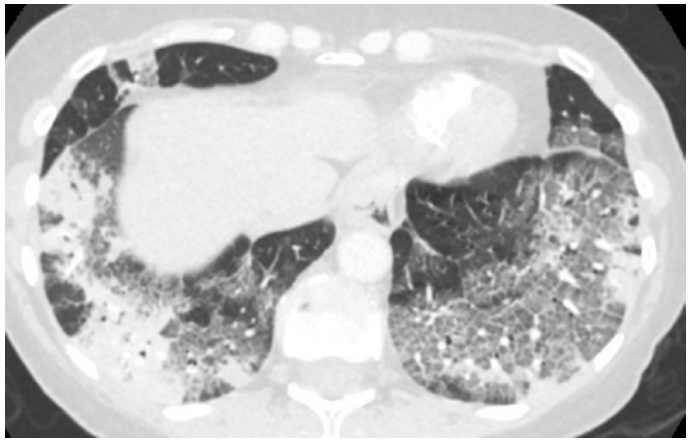
Covid Oct 10th, 2021

Hospital stay

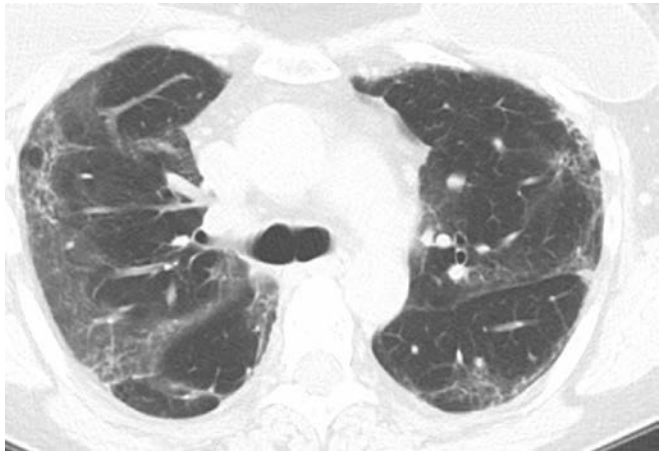
- HHF - no ventilation
- Dexamethasone
- 22 days in hospital, lost 17 lbs., got dexamethasone
- Had bilateral PEs

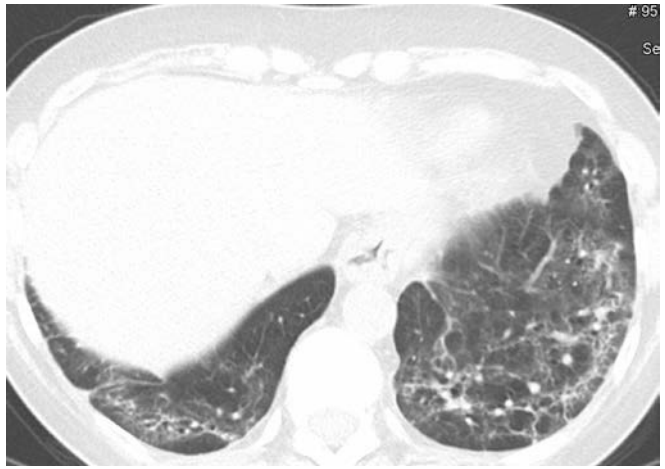
10/26/21



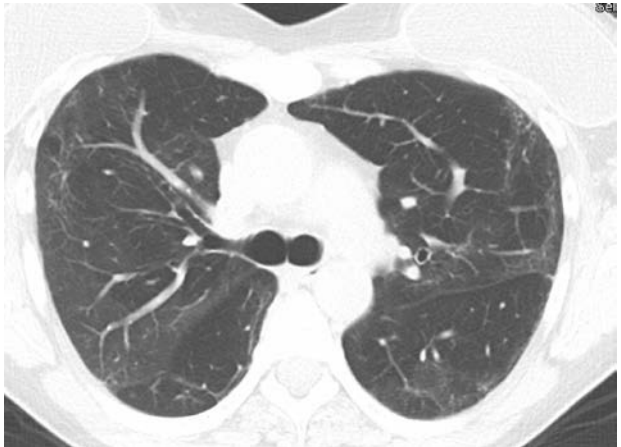


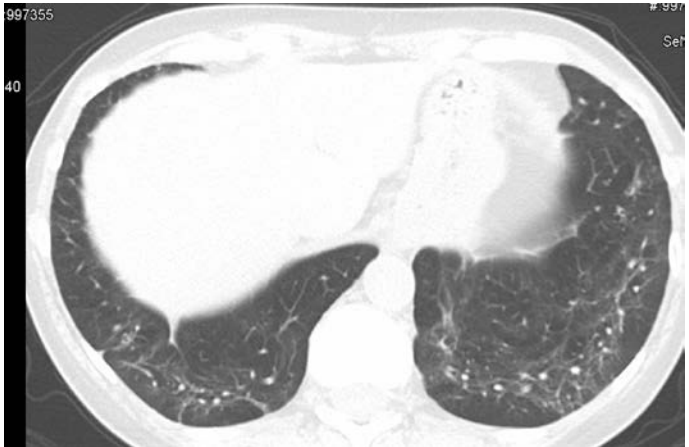
12/7/21



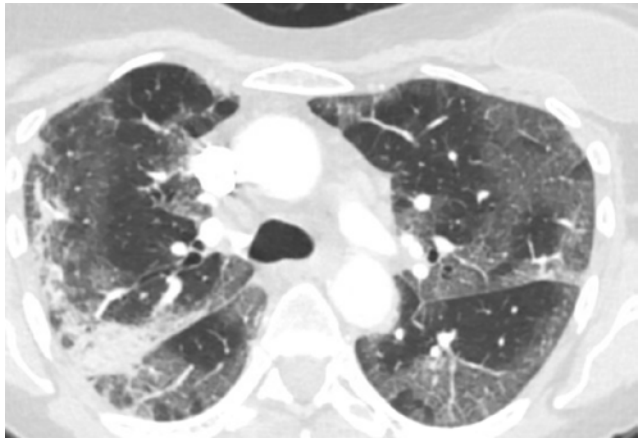


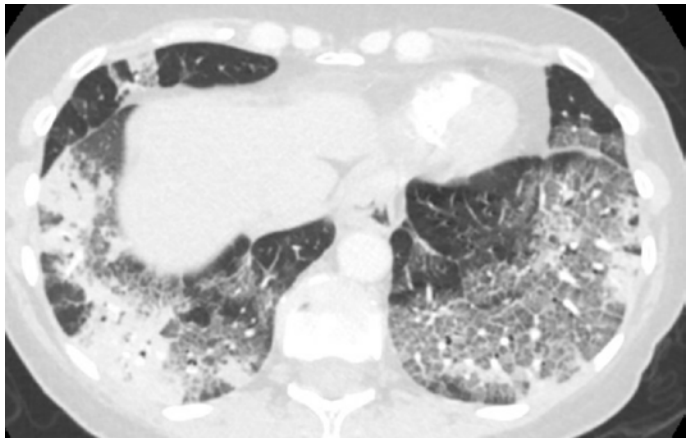
9/22/22



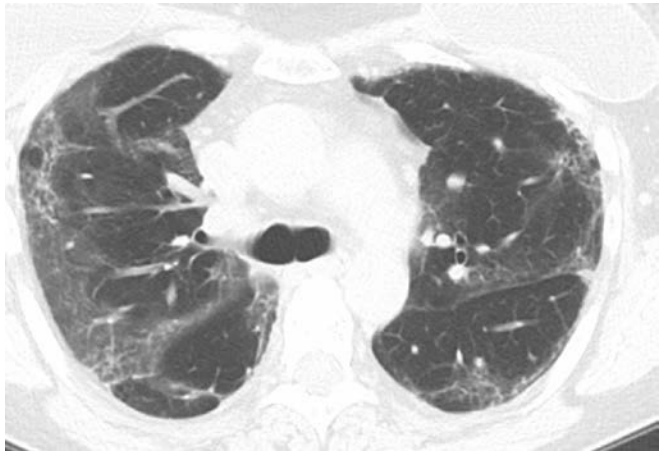


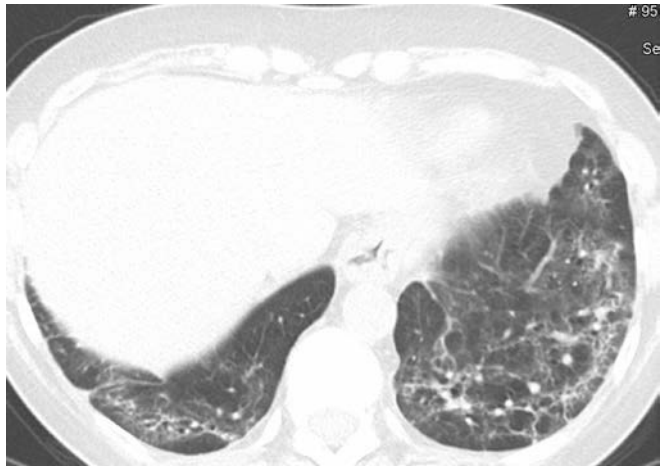
10/26/21





12/7/21





9/22/22

Outcomes	ILD n=46	No ILD n=92	Odds Ratio (95% CI)	p value
Hospital Admission†	34 (74)	53 (58)	2.1 (0.9-4.6)	0.07
ICU Level of Care	16 (47)	12 (23)	3.0 (1.2-7.9)	0.02
Mechanical Ventilation	13 (81)	11 (92)	0.4 (0.03-3.1)	NS
Length of Stay, days	7 (5-13)	7 (5-14)	NA	NS
Discharged	17 (50)	45 (85)	0.2 (0.06-0.5)	<0.001
Home	9 (28)	31 (58)	0.3 (0.1-0.7)	0.008
Skilled Nursing Facility	8 (25)	14 (26)	0.9 (0.3-2.6)	NS
Death	15 (33)	12 (13)	3.2 (1.3-7.3)	0.01

Esposito et al. AJRCCM 2020

Conclusions

- Post-COVID lung disease is common, especially in those hospitalized on respiratory support
- Data suggest that most of these radiographic changes resolve over time
- Patients can have inflammation, fibrosis, airways disease and pulmonary embolisms
- Treatment are not yet established though immunosuppression may help with inflammatory lung disease

MAYO CLINIC

LUNG FIBROSIS

WHAT IS IT, WHAT DOES IT MEAN AND HOW IS IT RELATED TO COVID-19

Henry D. Tazelaar, M.D.
Geraldine Colby Zeiler Professor of Cytopathology
Mayo Clinic Alix College of Medicine
Mayo Clinic Arizona

2022 Advanced Lung Disease and Lung Transplant Symposium
Scottsdale, AZ, Feb 18-20, 2022



©2021 Mayo Foundation for Medical Education and Research

LEARNING OBJECTIVES

At the end of the lecture, participants

1.Will be able to list the types of fibrosis which affect the lung

2. Understand the clinical significance of different types of lung fibrosis

3. List some of the pathologic changes in the lung due to COVID-19

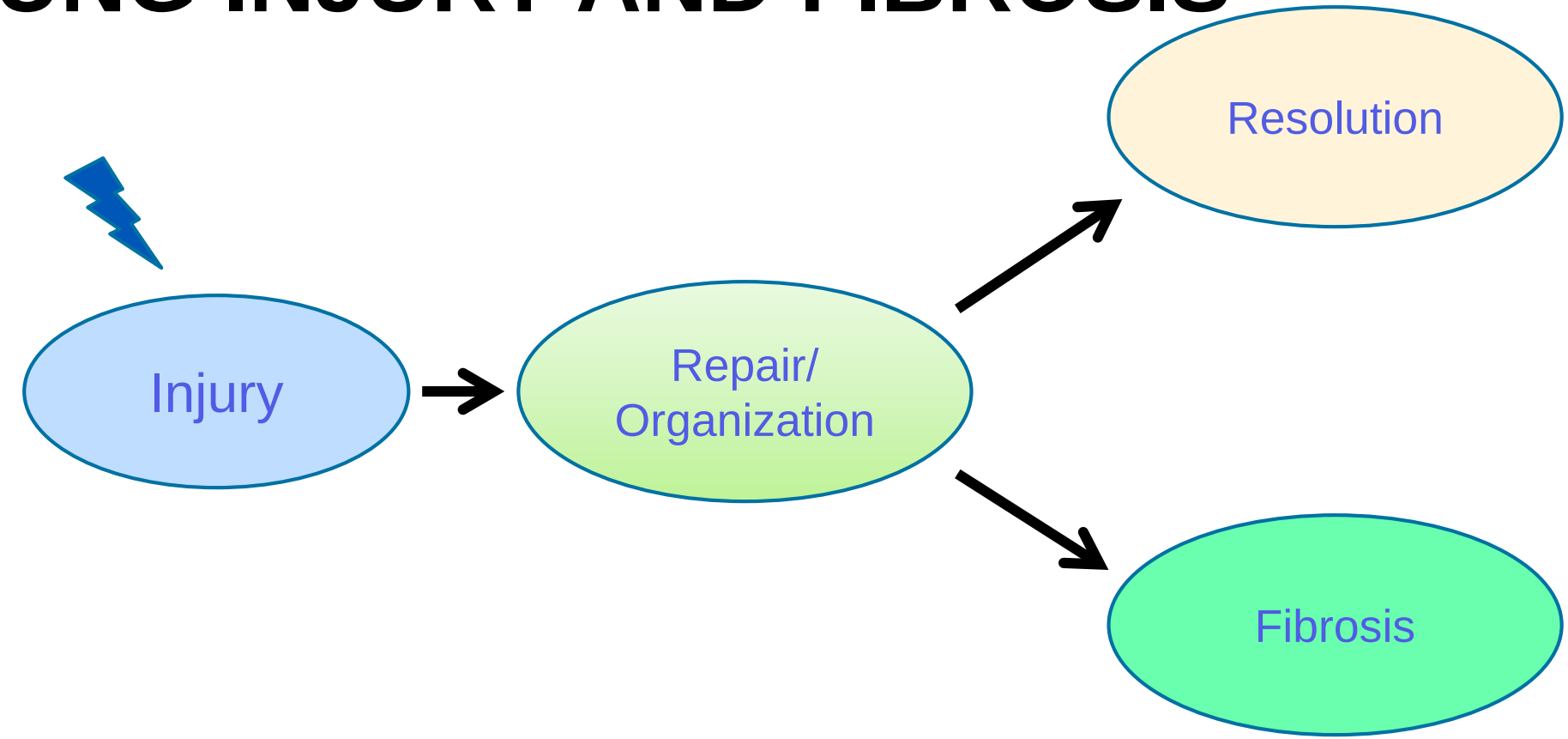
©2021 Mayo Foundation for Medical Education and Research

OUTLINE

- Lung injury and fibrosis (“fibrosis”)
- COVID-19 related pathology

©2021 Mayo Foundation for Medical Education and Research

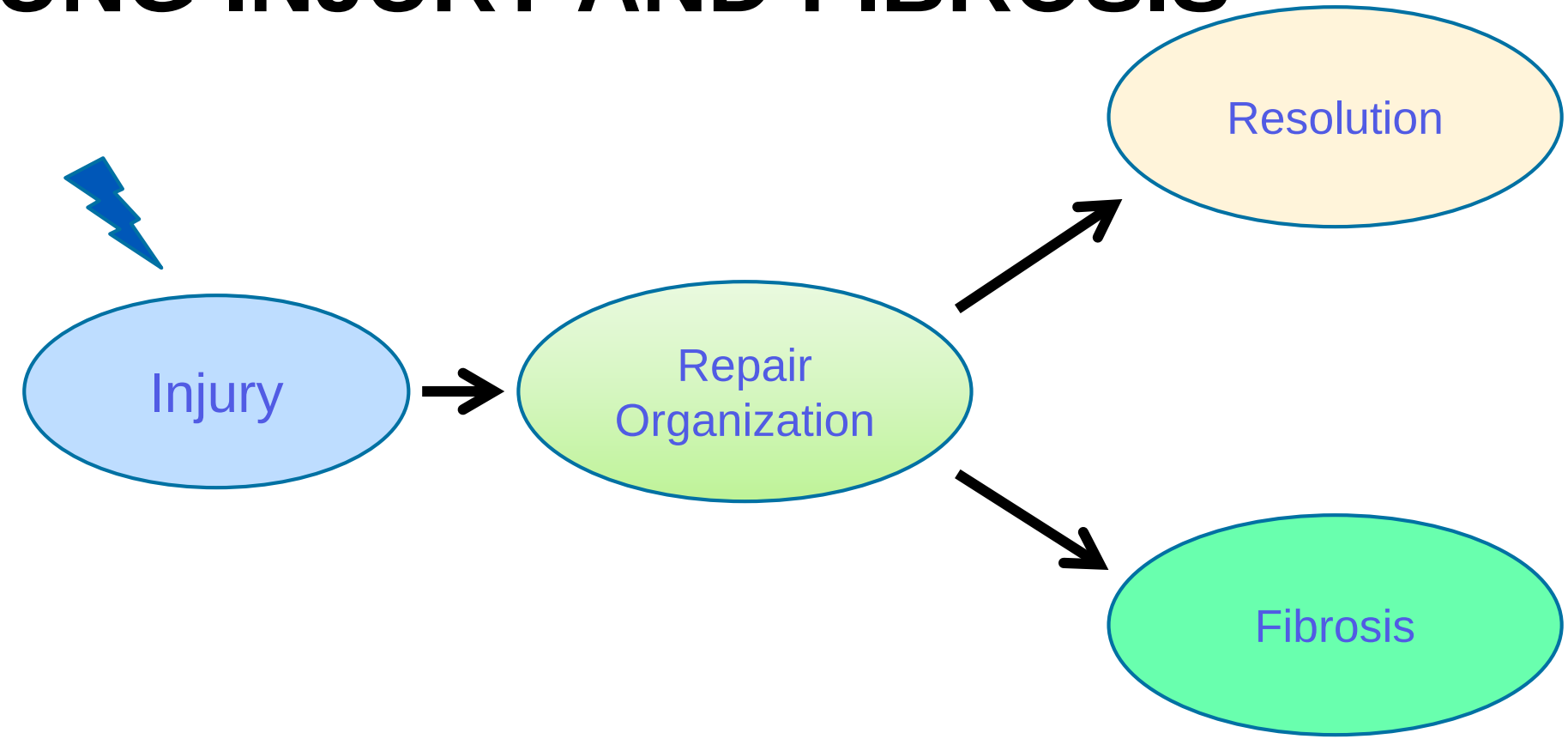
LUNG INJURY AND FIBROSIS



Organization = the conversion of coagulated blood, exudate or dead tissue into fibrous or virtually normal tissue

©2021 Mayo Foundation for Medical Education and Research

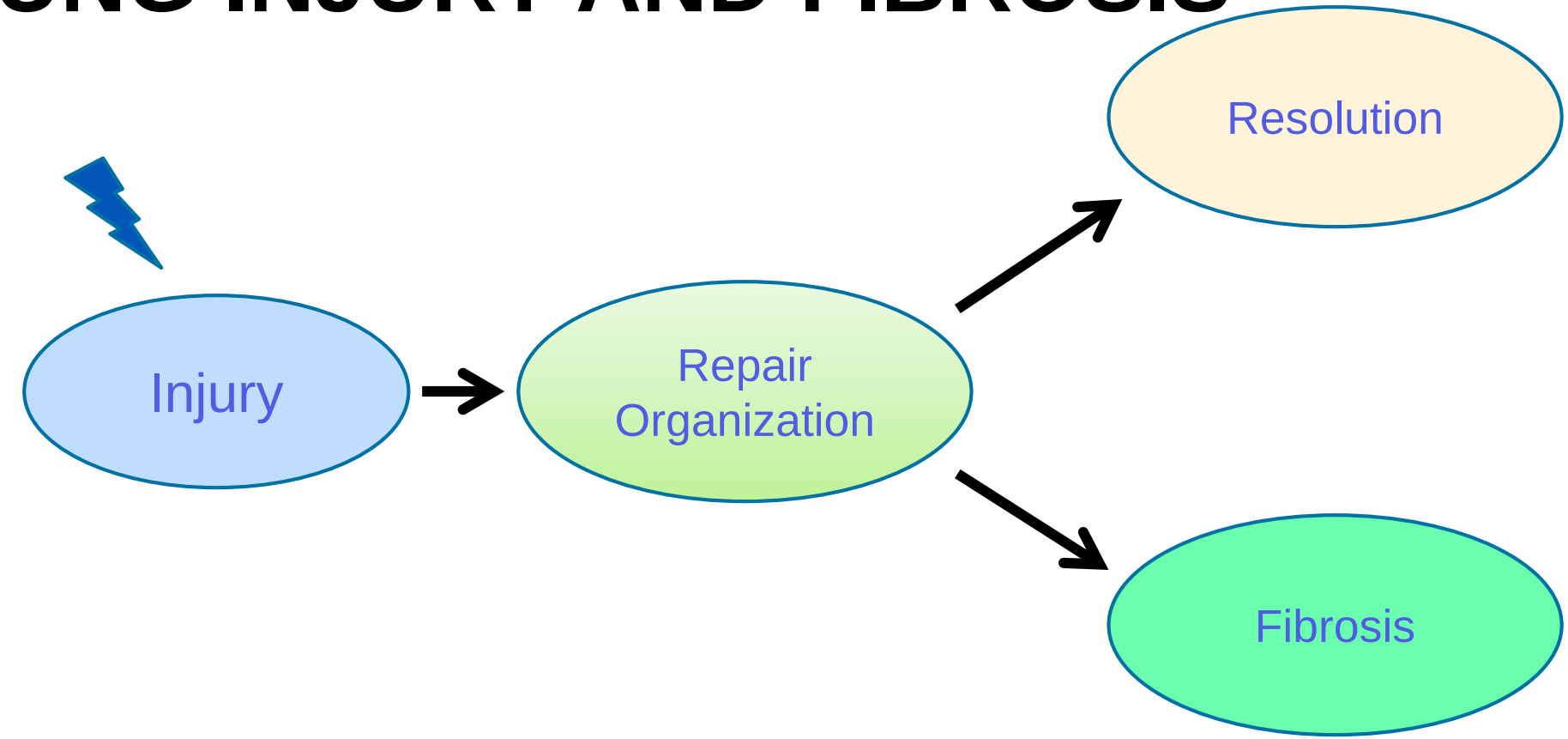
LUNG INJURY AND FIBROSIS



Fibrosis = formation of excess connective tissue in an organ

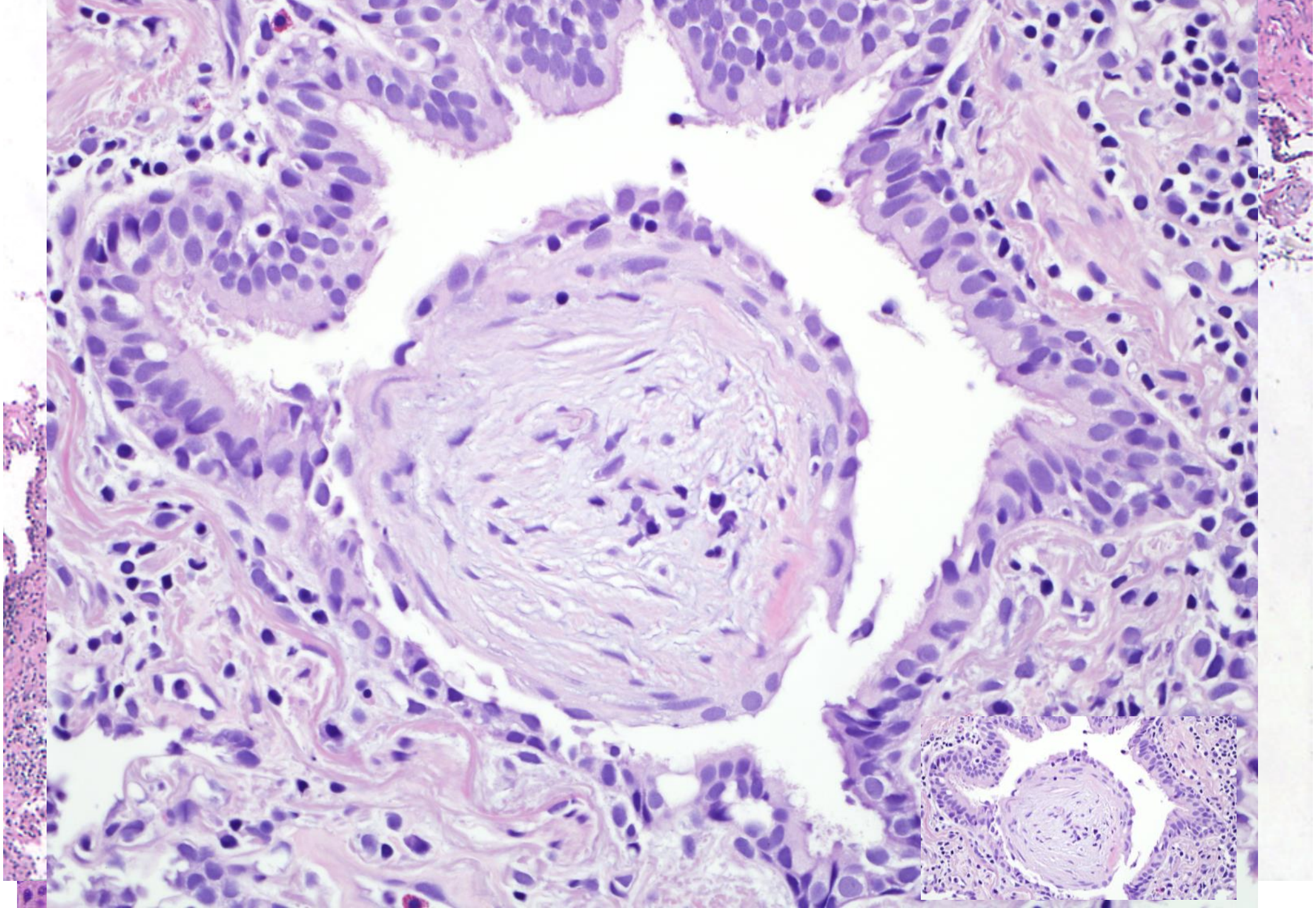
©2021 Mayo Foundation for Medical Education and Research

LUNG INJURY AND FIBROSIS



Organization ≠ Fibrosis

©2021 Mayo Foundation for Medical Education and Research



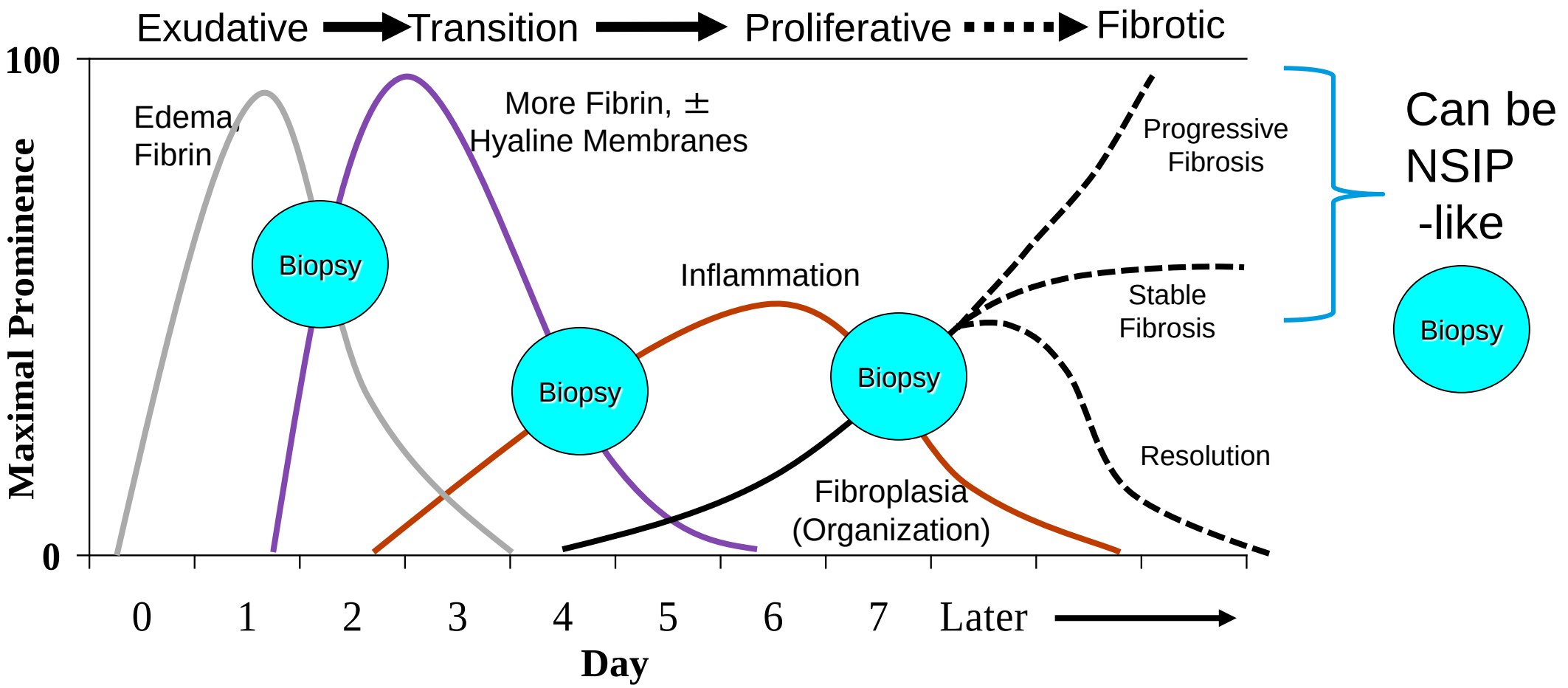
FIBROSIS

- Term used to denote
  - Dense collagen deposition

    AND
  - Organization: “fibrosis”

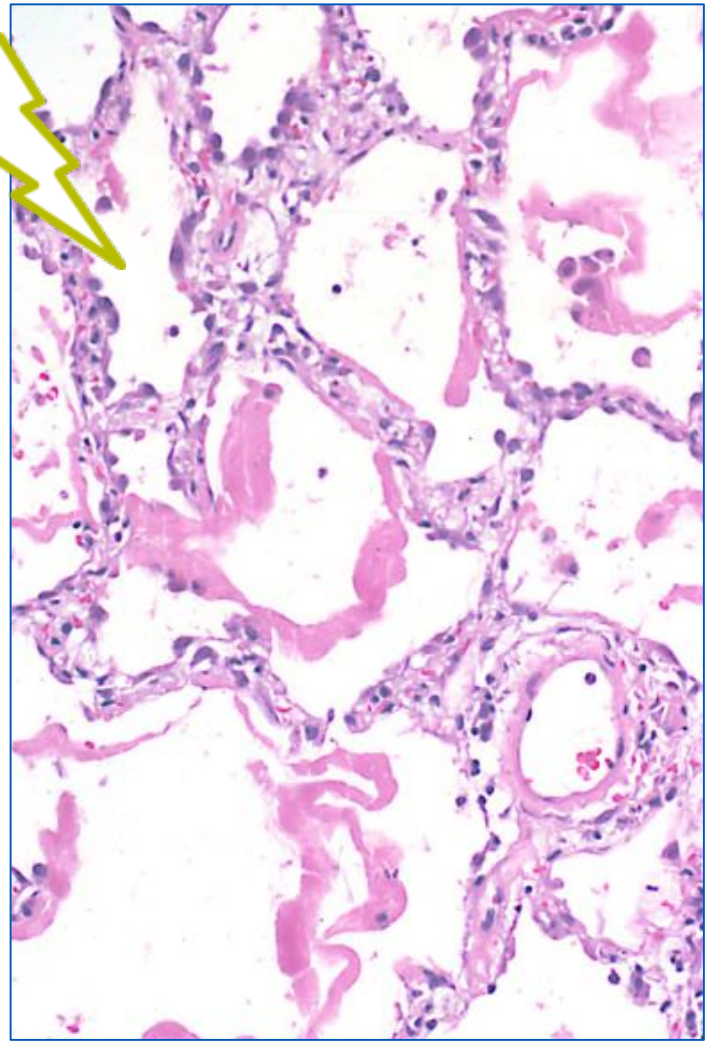
©2021 Mayo Foundation for Medical Education and Research

Pathology of Acute Lung Injury/DAD

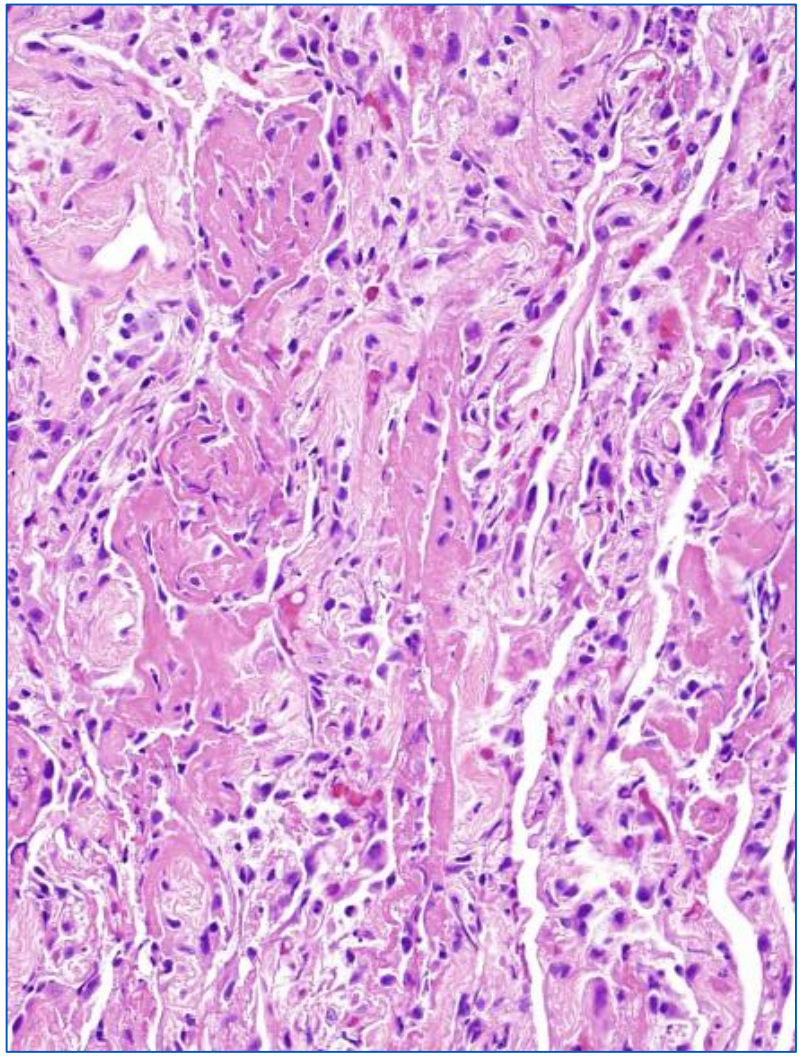


©2021 Mayo Foundation for Medical Education and Research

DIFFUSE ALVEOLAR DAMAGE

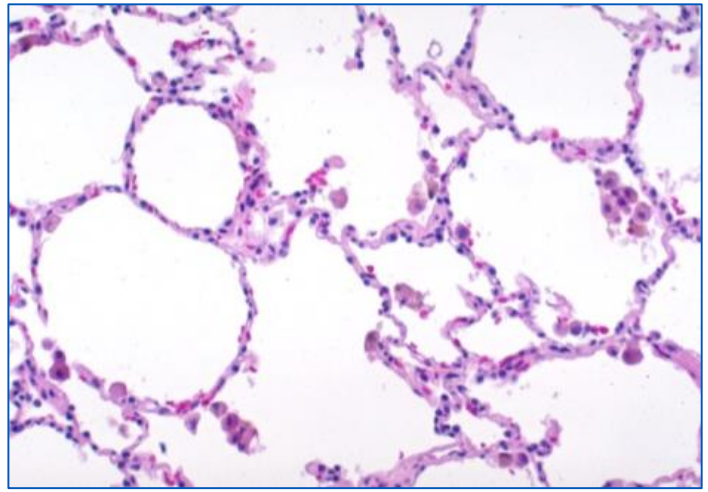


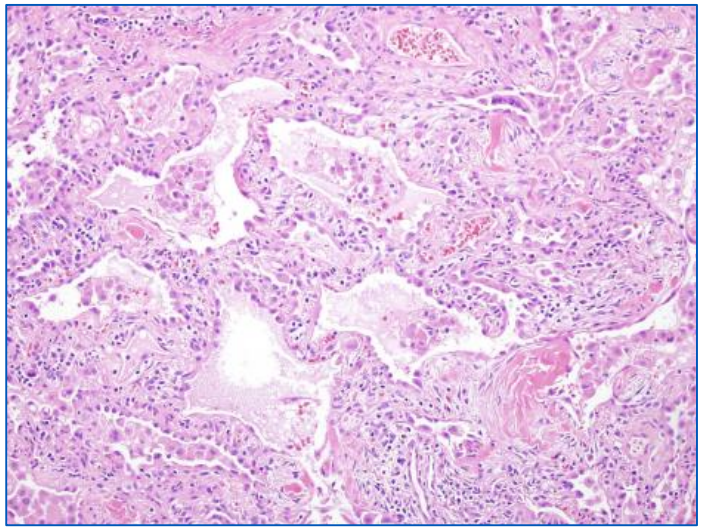
Acute injury with hyaline membranes



Repair: airspace and interstitial organization

Resolved/healed

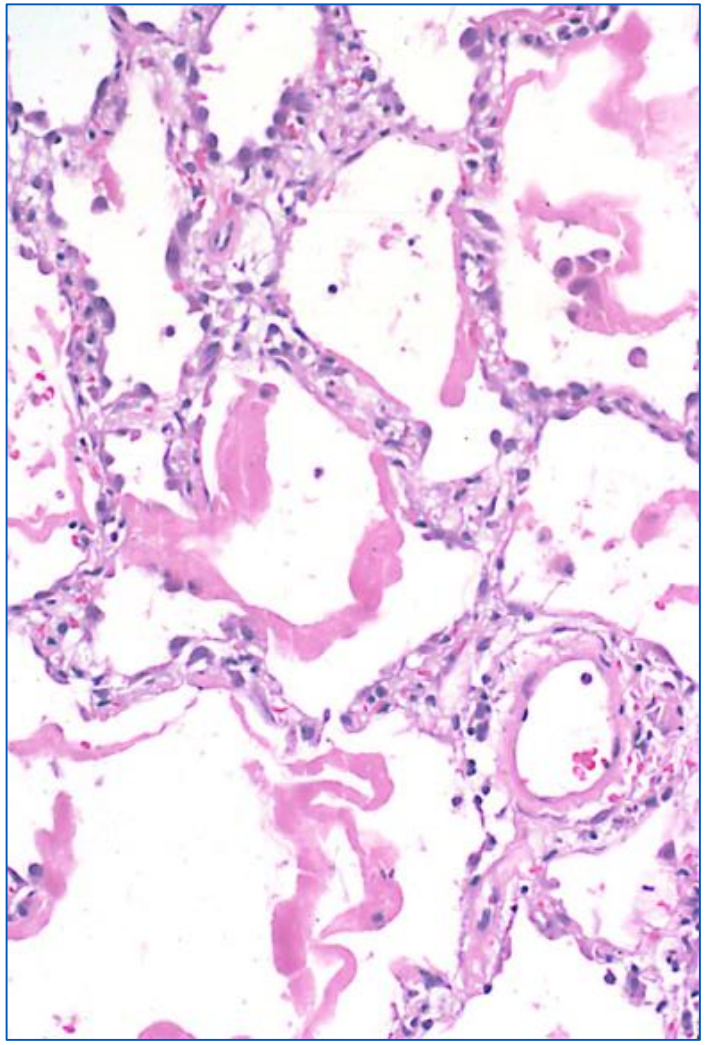




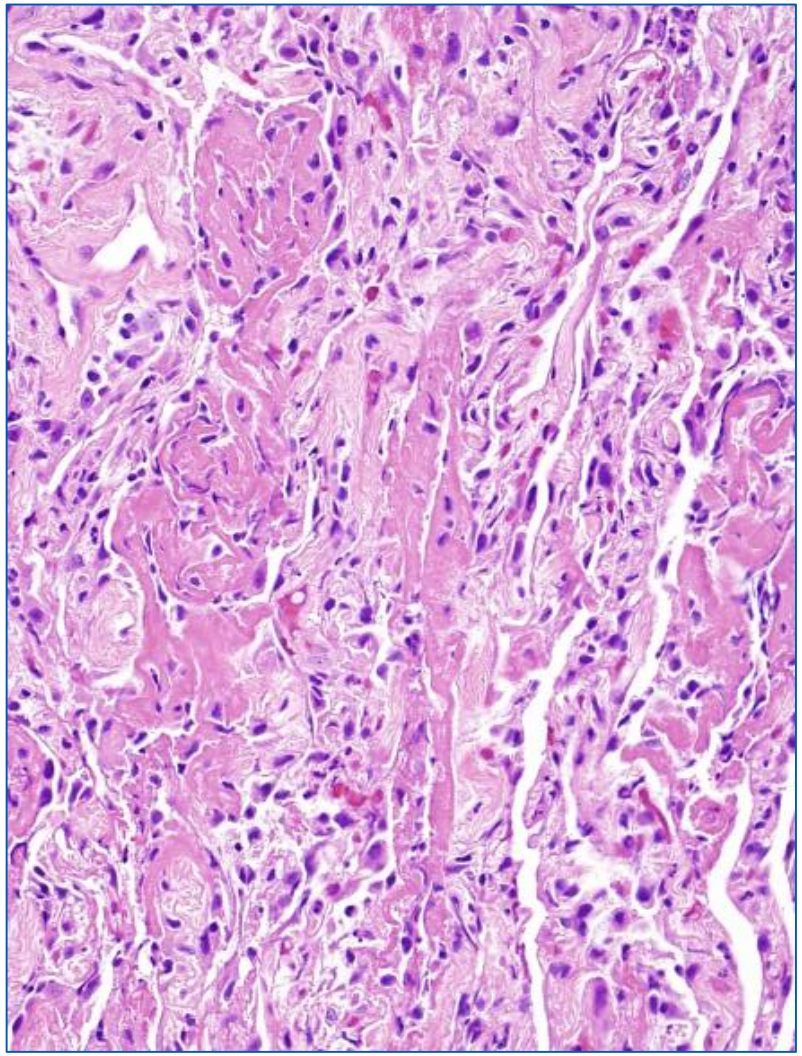
Interstitial fibrosis (can resemble NSIP)

©2021 Mayo Foundation for Medical Education and Research

BOTTOM LINE DIAGNOSIS?

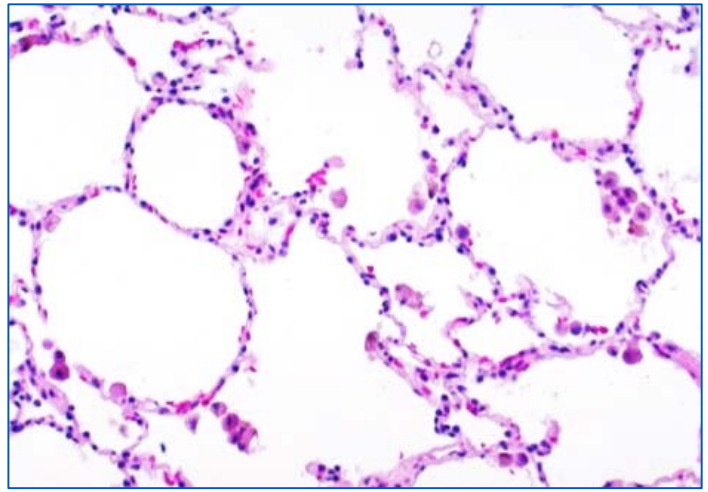


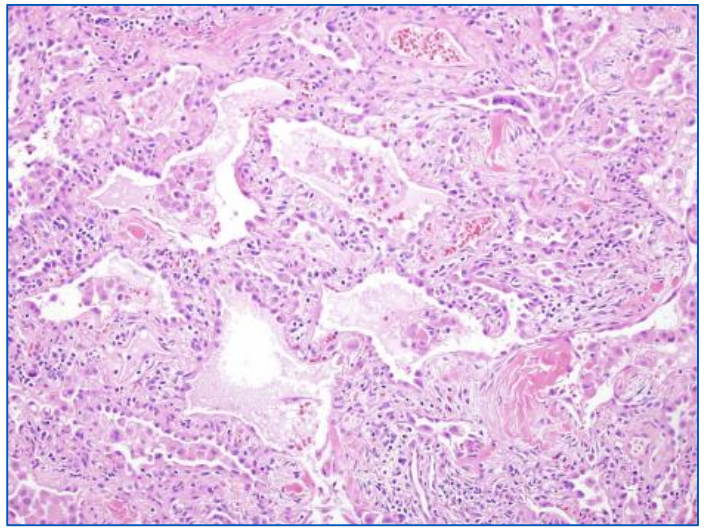
Diffuse alveolar damage



Acute and organizing diffuse alveolar damage

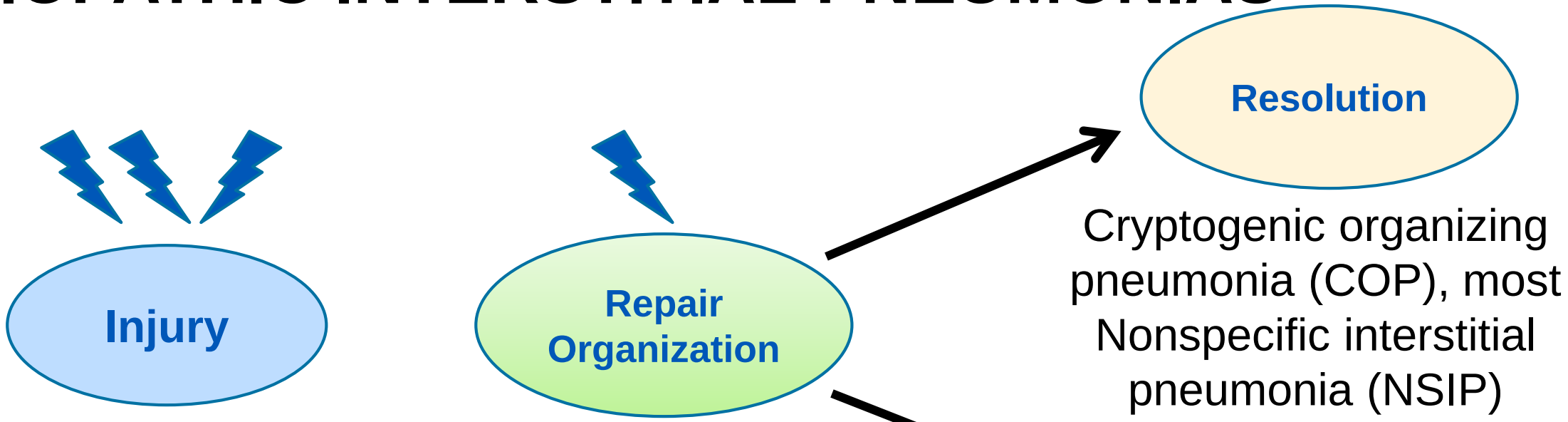
Normal lung





Fibrotic NSIP?
Unclassifiable int fib c/w late DAD

IDIOPATHIC INTERSTITIAL PNEUMONIAS



Acute interstitial pneumonia (AIP)

Acute fibrinous and organizing pneumonia

Cryptogenic organizing pneumonia (COP)
Nonspecific interstitial pneumonia (NSIP)
Usual interstitial pneumonia (UIP)

Cryptogenic organizing pneumonia (COP), most
Nonspecific interstitial pneumonia (NSIP)

(UIP/IPF)
NSIP- some
Hyalinizing COP

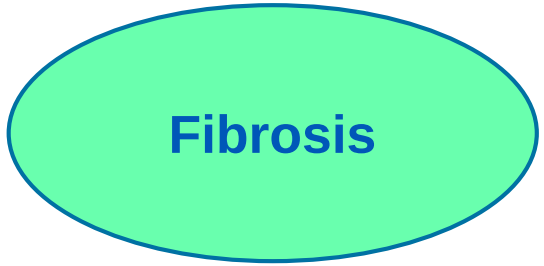
©2021 Mayo Foundation for Medical Education and Research

These are potentially reversible



Eosinophilic pneumonia
Cryptogenic organizing pneumonia
Diffuse alveolar damage
Hypersensitivity pneumonitis
NSIP- some cases

These are irreversible

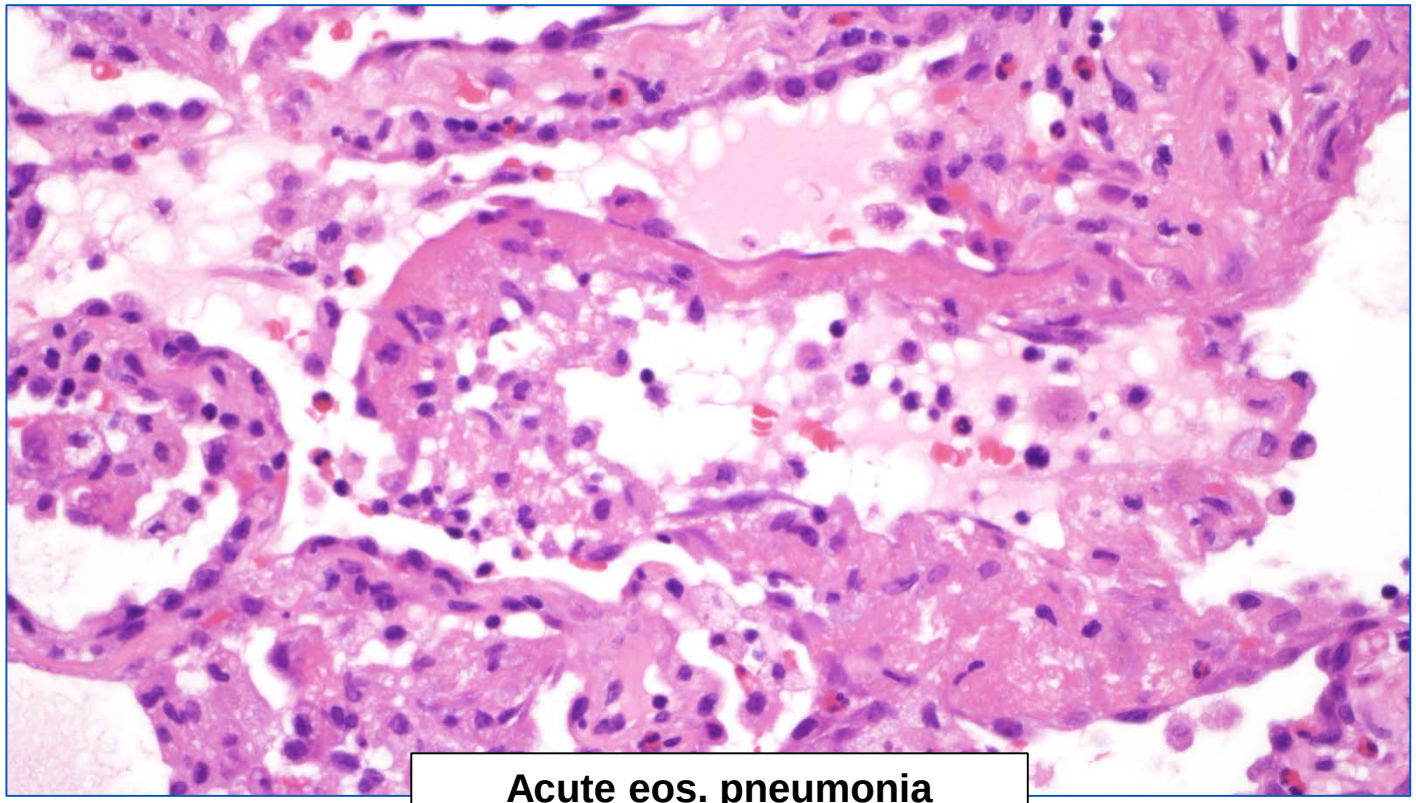


Idiopathic pulmonary fibrosis
Other causes of UIP pattern
NSIP- some cases
Hypersensitivity pneumonitis
Langerhan's cell histiocytosis
Pleuroparenchymal fibroelastosis
Sarcoidosis

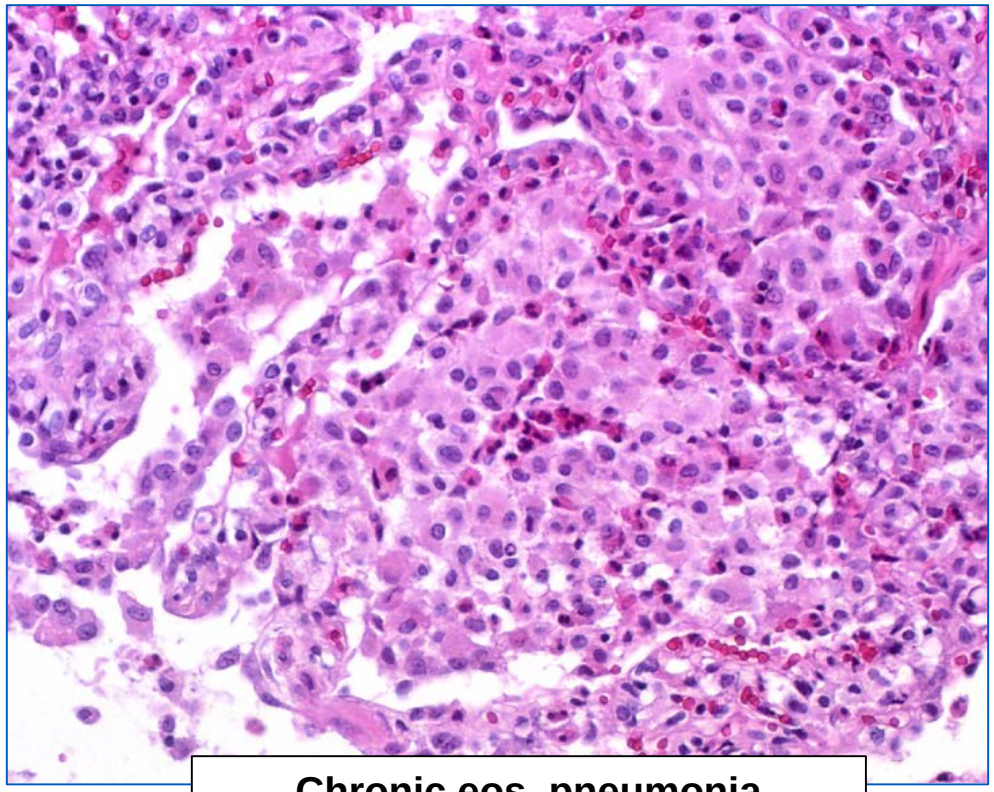
©2021 Mayo Foundation for Medical Education and Research

EOSINOPHILIC PNEUMONIA

- Steroids
  - Acute: generally complete rapid resolution
  - Chronic: long term steroids, challenging to treat

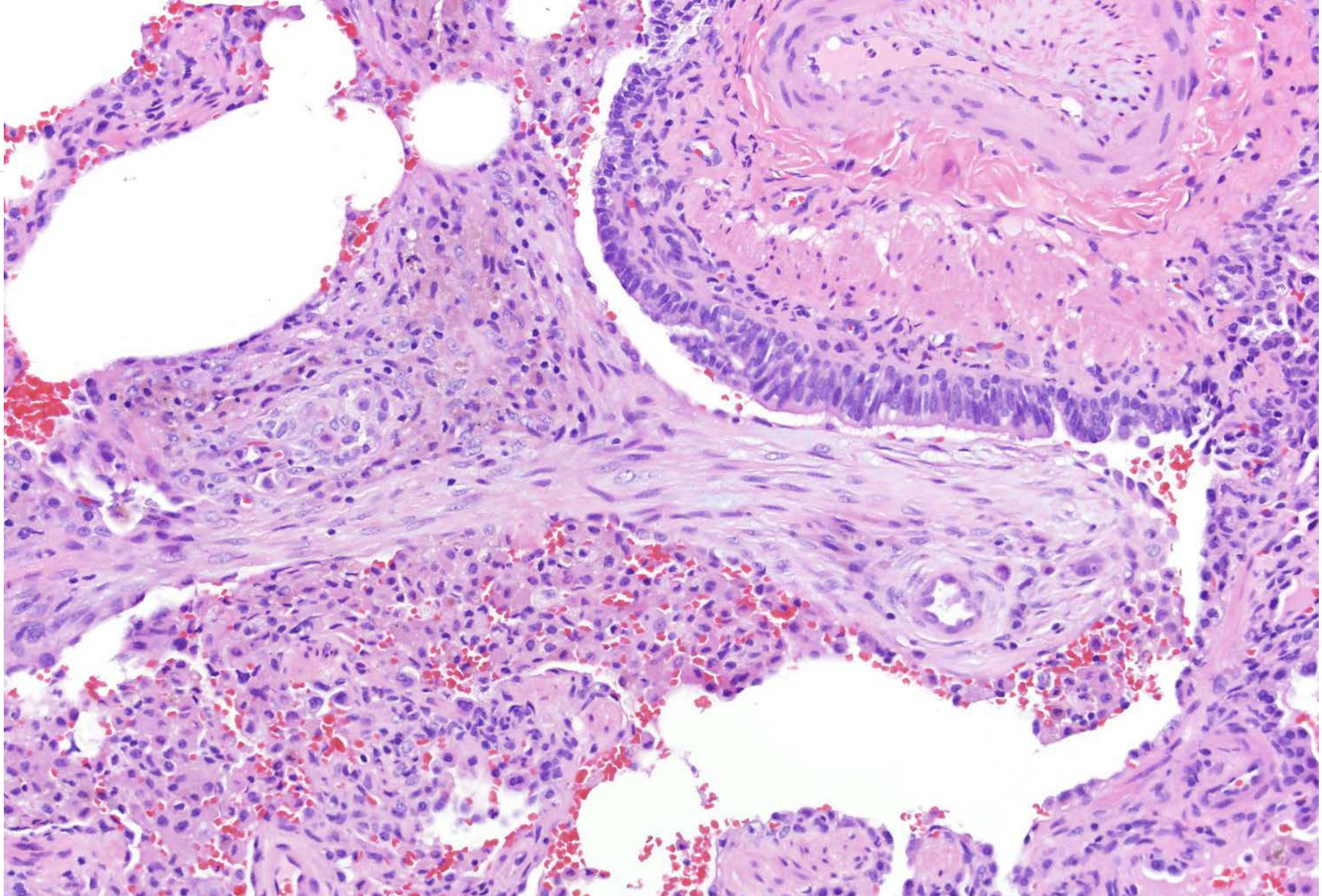


Acute eos. pneumonia



Chronic eos. pneumonia

©2021 Mayo Foundation for Medical Education and Research

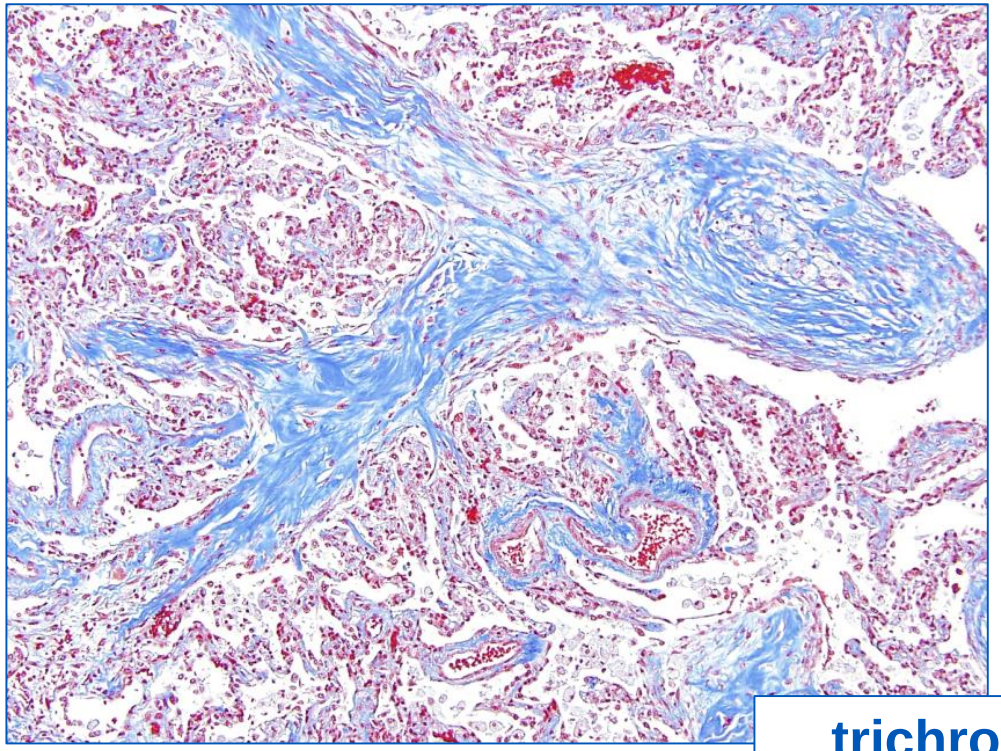


CRYPTOGENIC ORGANIZING PNEUMONIA

- Steroids
  - 2/3 resolve completely
  - 1/3 persistent/recurrent disease



Cicatricial/hyalinized/collagenized/ fibrosing OP



trichrome

©2021 Mayo Four

CICATRICIAL ORGANIZING PNEUMONIA

- 12 patients with COP
- 55% had progressive or persistent infiltrates
- 25% had osseous metaplasia
- ? Contribution of pre-existing non fibrotic lung disease e.g. emphysema, which impairs healing
- Suggested the pattern might be associated with poor response to steroids

Yousem SA Hum Pathol 2017;64:76-82

©2021 Mayo Foundation for Medical Education and Research

CICATRICIAL ORGANIZING PNEUMONIA

- 10 pts identified by pattern, not disease
- 20% had radiographic ossification
- Mimic of fibrotic NSIP
- Non-progressive disease
- Ehlers Danlos-1 patient

Churg et al Histopathol 2018;72:846-854

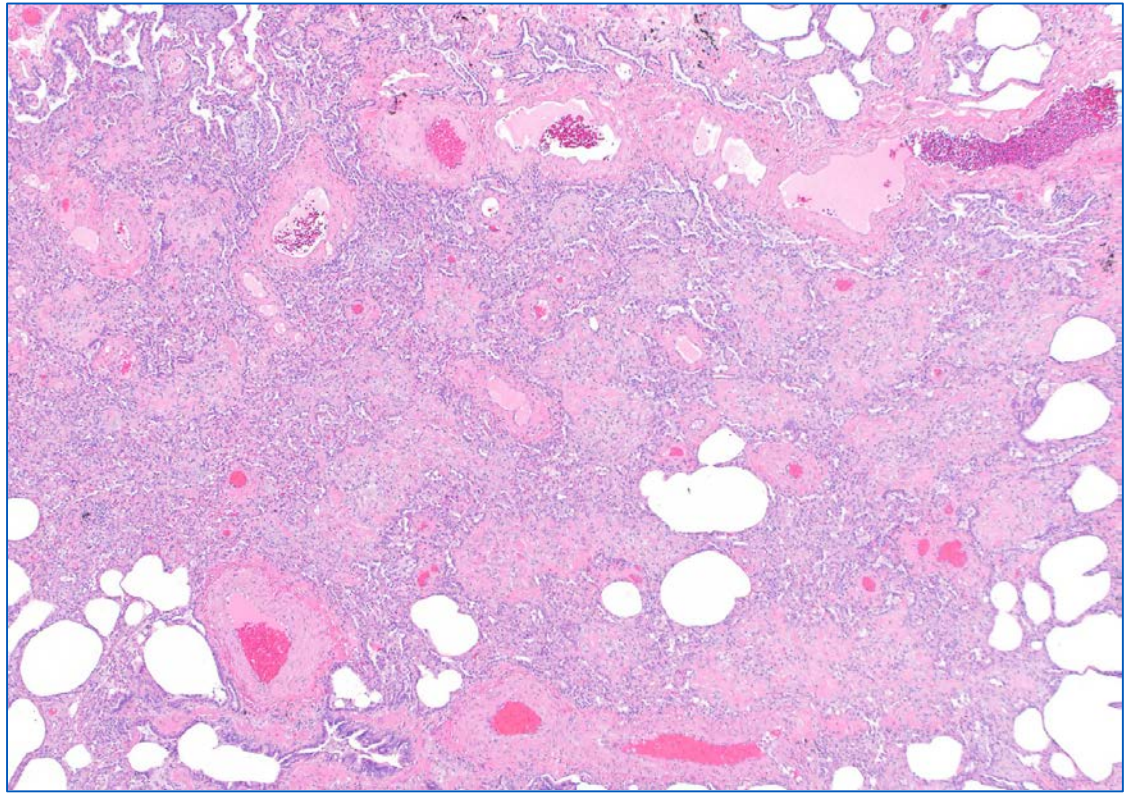
©2021 Mayo Foundation for Medical Education and Research

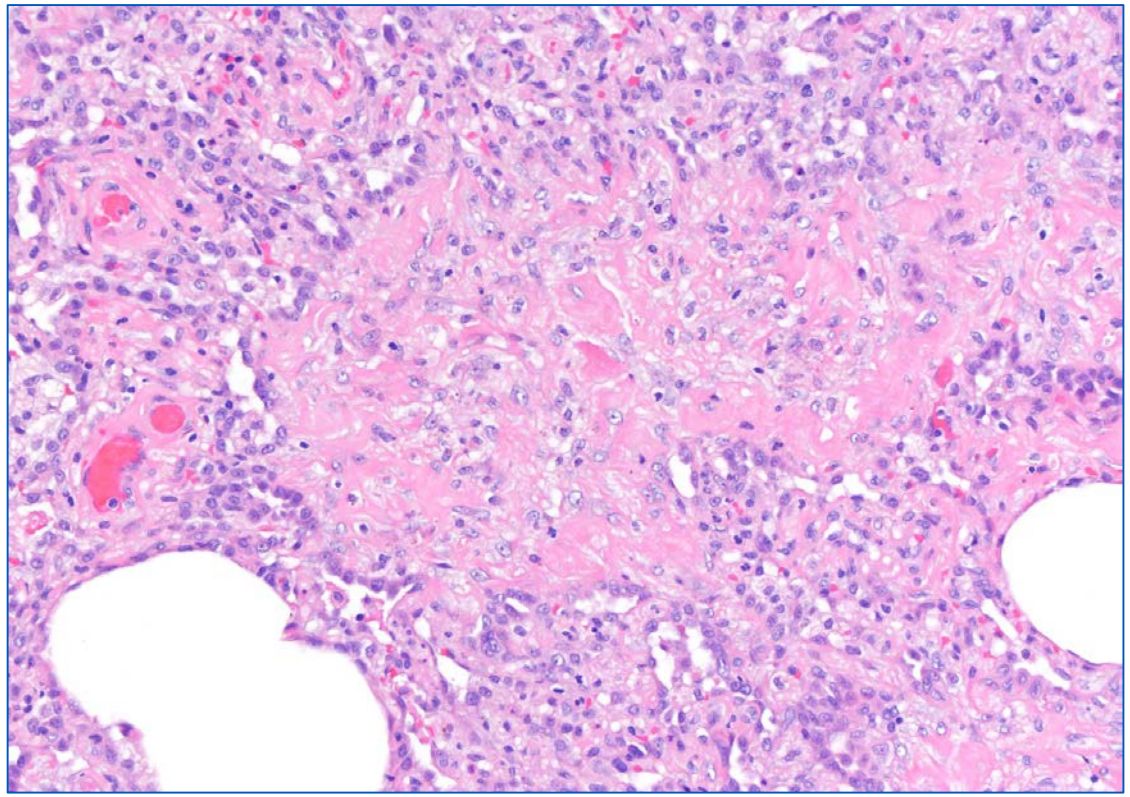
CICATRICIAL ORGANIZING PNEUMONIA

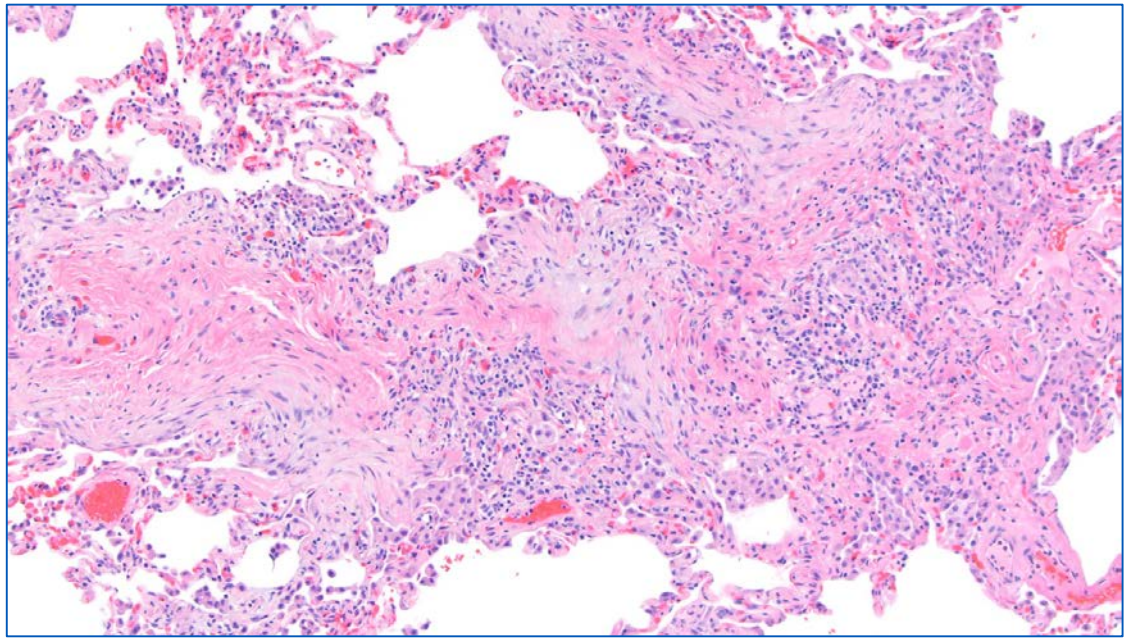
- Single institution
- 56 total cases with ≥ 10% cicatricial foci
  - 9/56 (16%) ≥ 50%, 5 with ossification, all with fibrous linear bands (Mimic of fibrotic NSIP)
- COP, 7; RA, 1; aspiration, 1
- No adverse outcome-indolent course

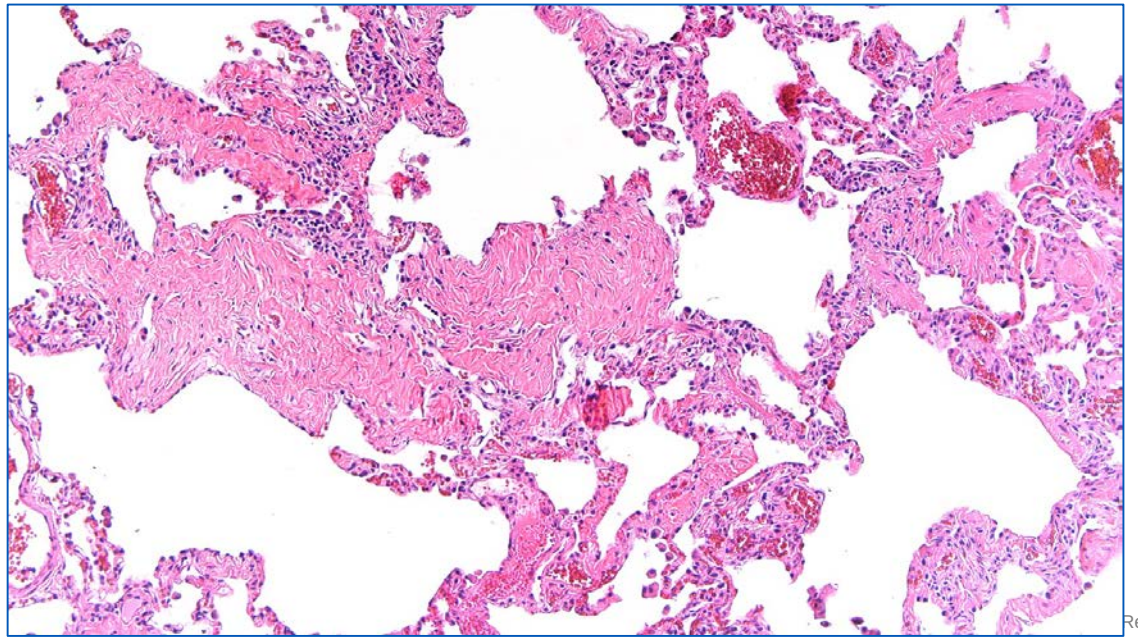
Woge MJ et al Hum Pathol 2020;101:58-63;

©2021 Mayo Foundation for Medical Education and Research









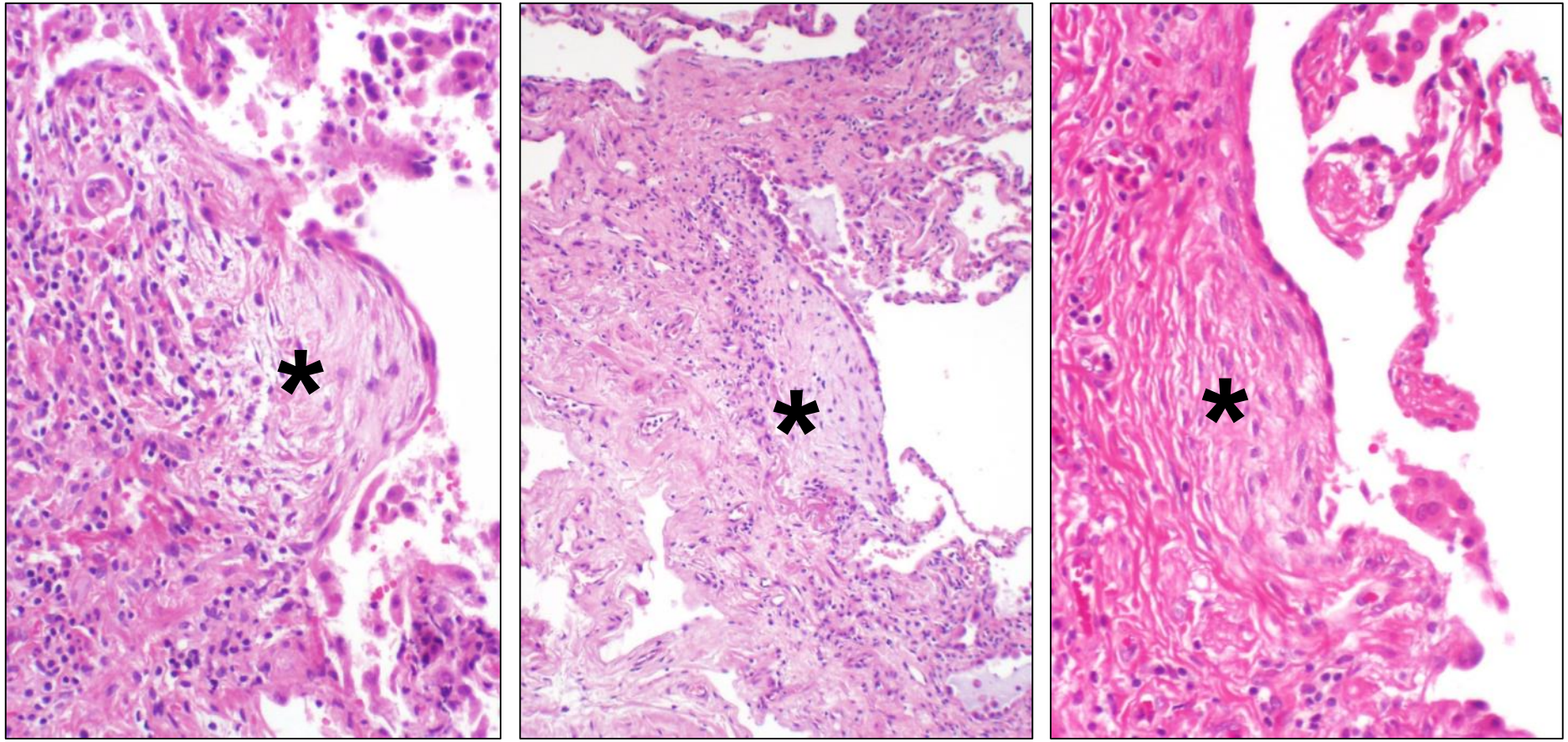
CICATRICIAL ORGANIZING PNEUMONIA

- Probably not associated with worse outcome
- Differential diagnosis
  - Cryptogenic disease
  - Ehlers Danlos syndrome
  - CTD
  - Aspiration
- Can be a trap for pathologists

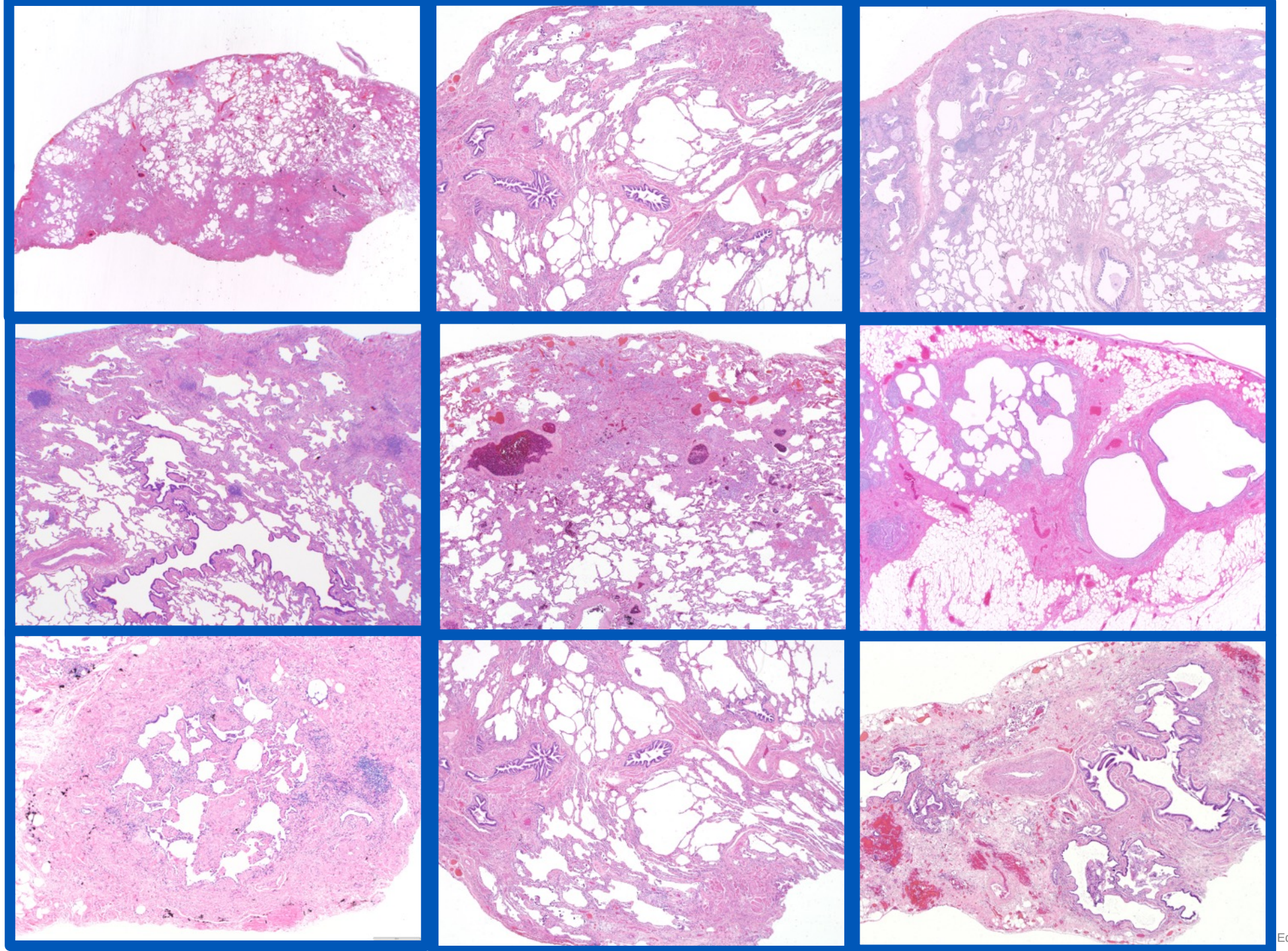
©2021 Mayo Foundation for Medical Education and Research

FIBROSIS IN USUAL INTERSTITIAL PNEUMONIA/IPF

- Prevailing hypothesis is that fibroblast foci (recent organization) becomes dense collagen/fibrotic



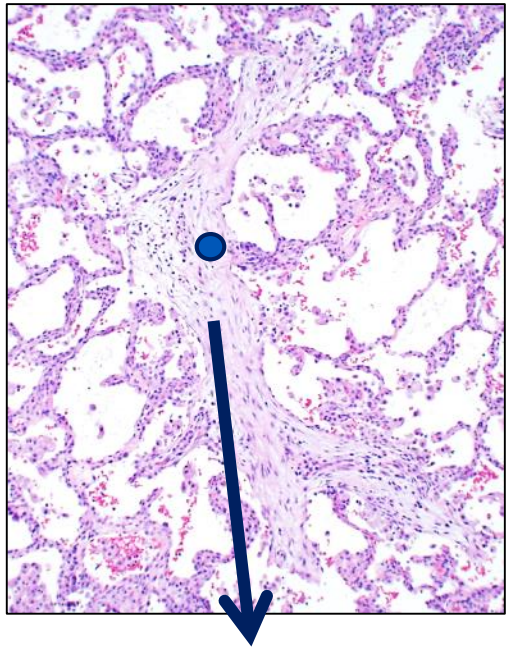
©2021 Mayo Foundation for Medical Education and Research



FIBROSIS IN USUAL INTERSTITIAL PNEUMONIA/IPF

- Fibroblast foci look like microfoci of organizing pneumonia

Organizing pneumonia



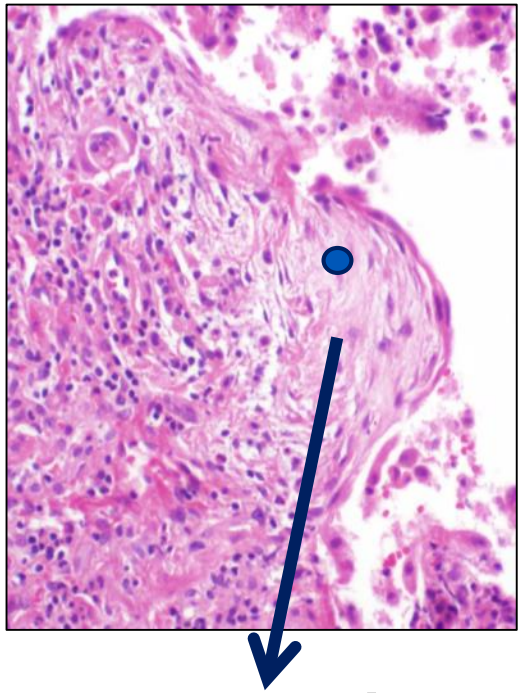
Most cases reversible

Both composed of fibroblastic tissue

OP is seen in architecturally normal lung

Fibroblastic foci are at the edge of scarring

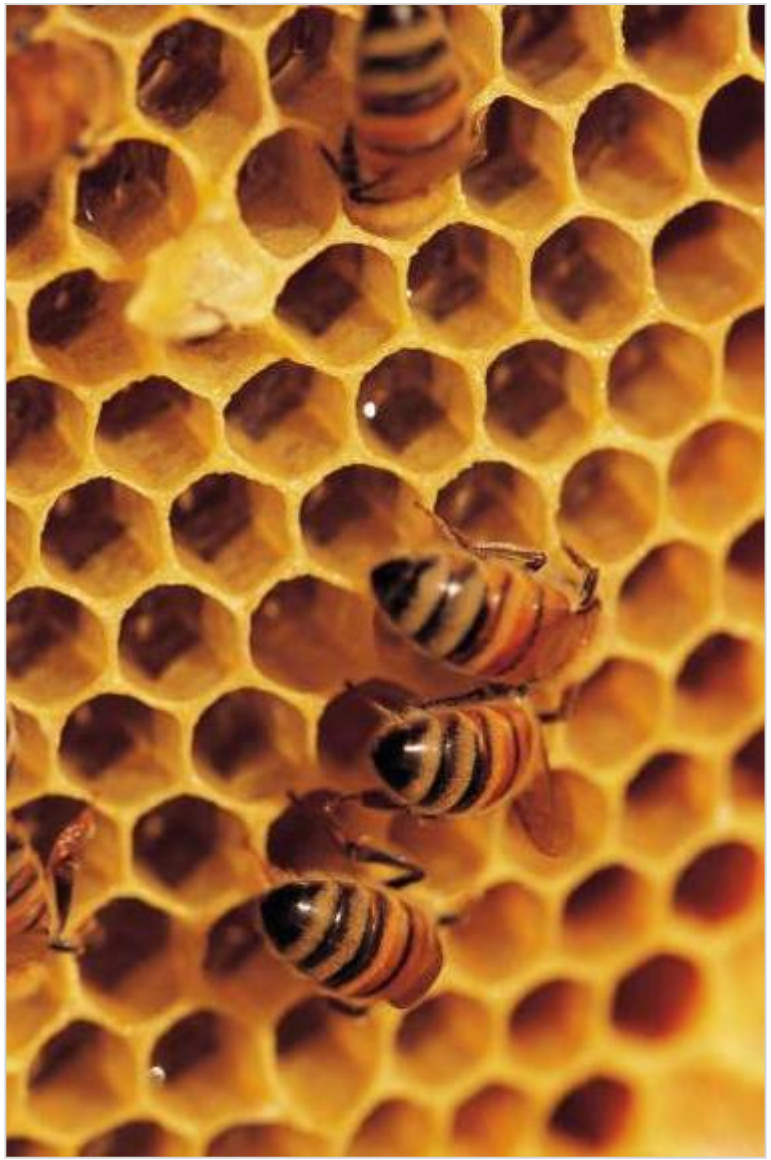
Fibroblast focus



Progressive fibrosis

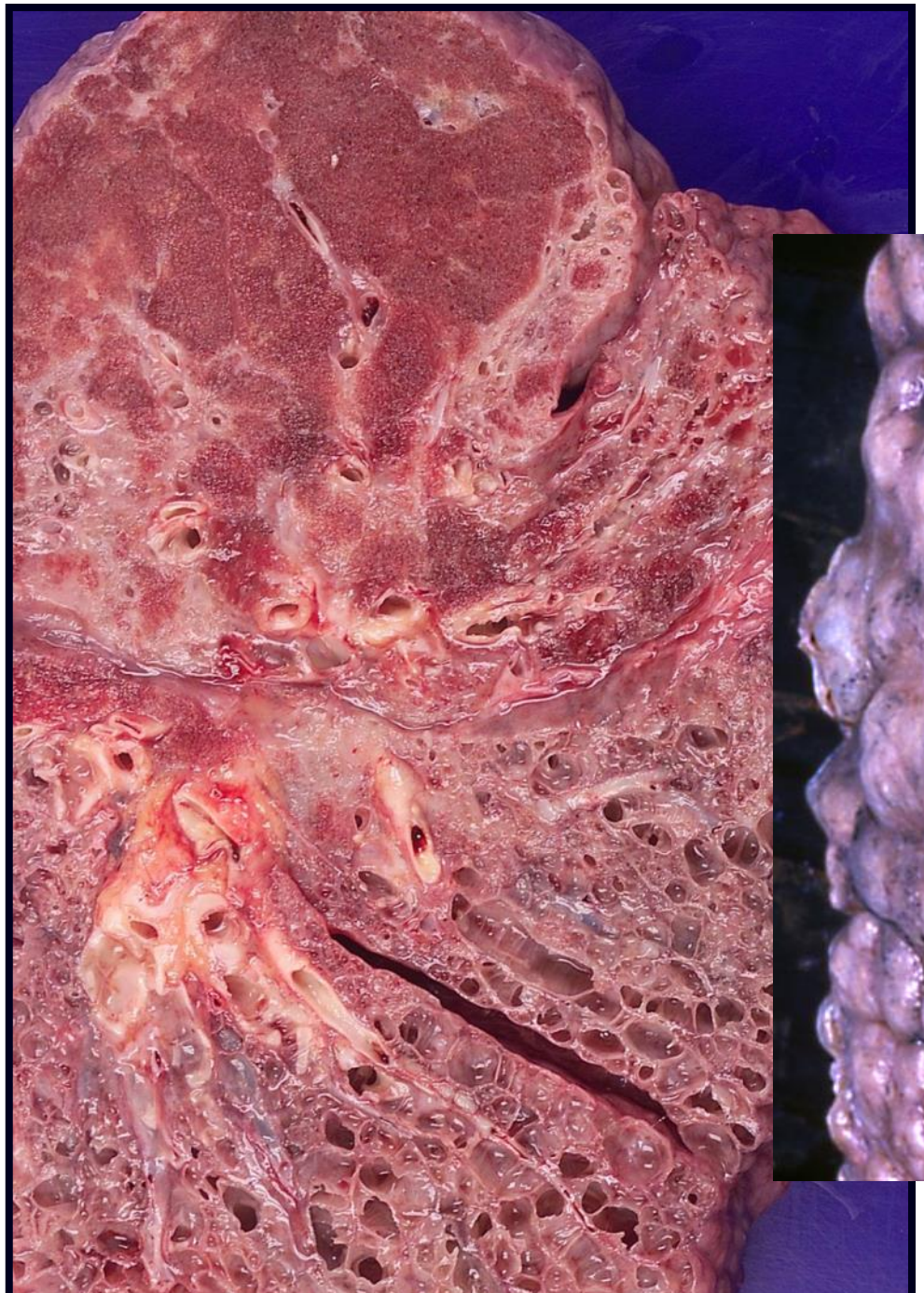
©2021 Mayo Foundation for Medical Education and Research

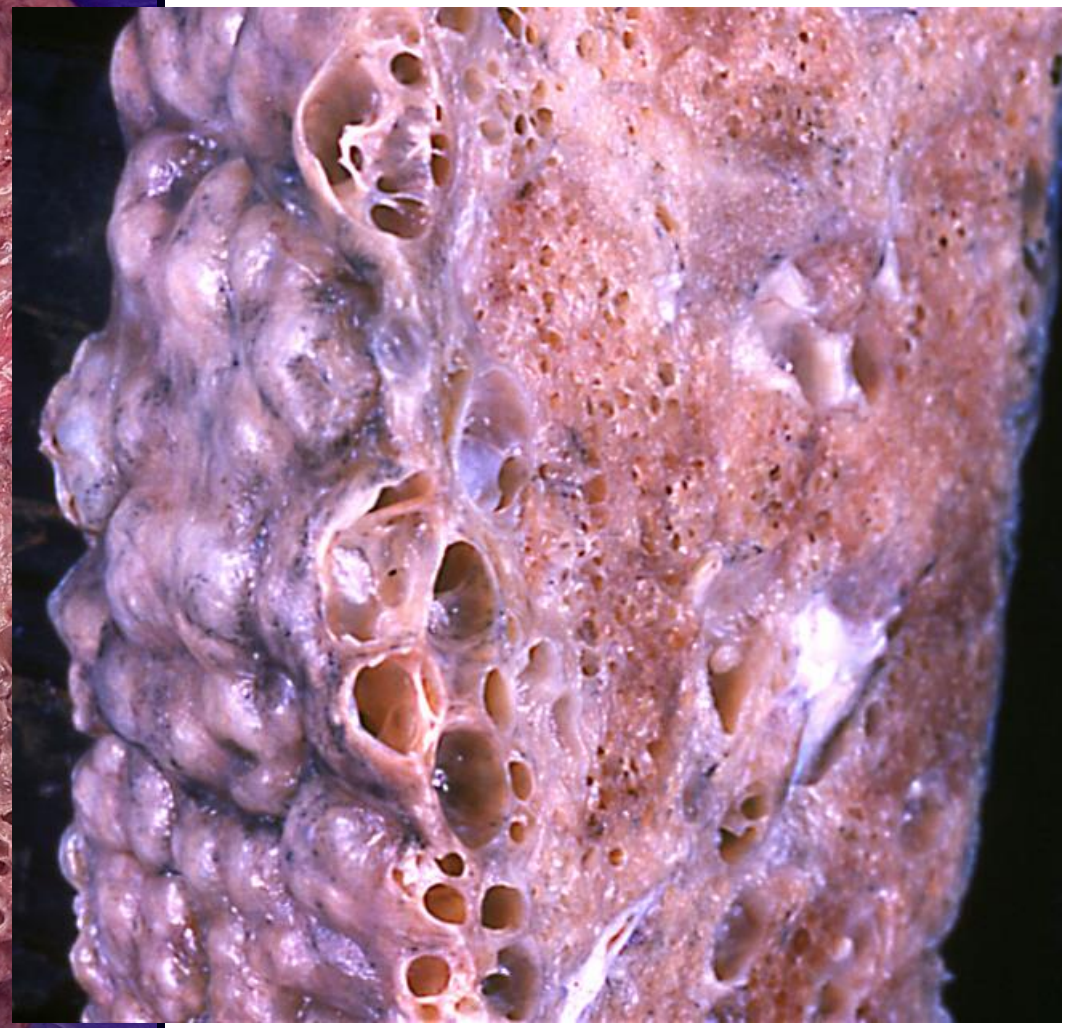




©2021 Mayo Foundation for Medical Education and Research

Honeycombing

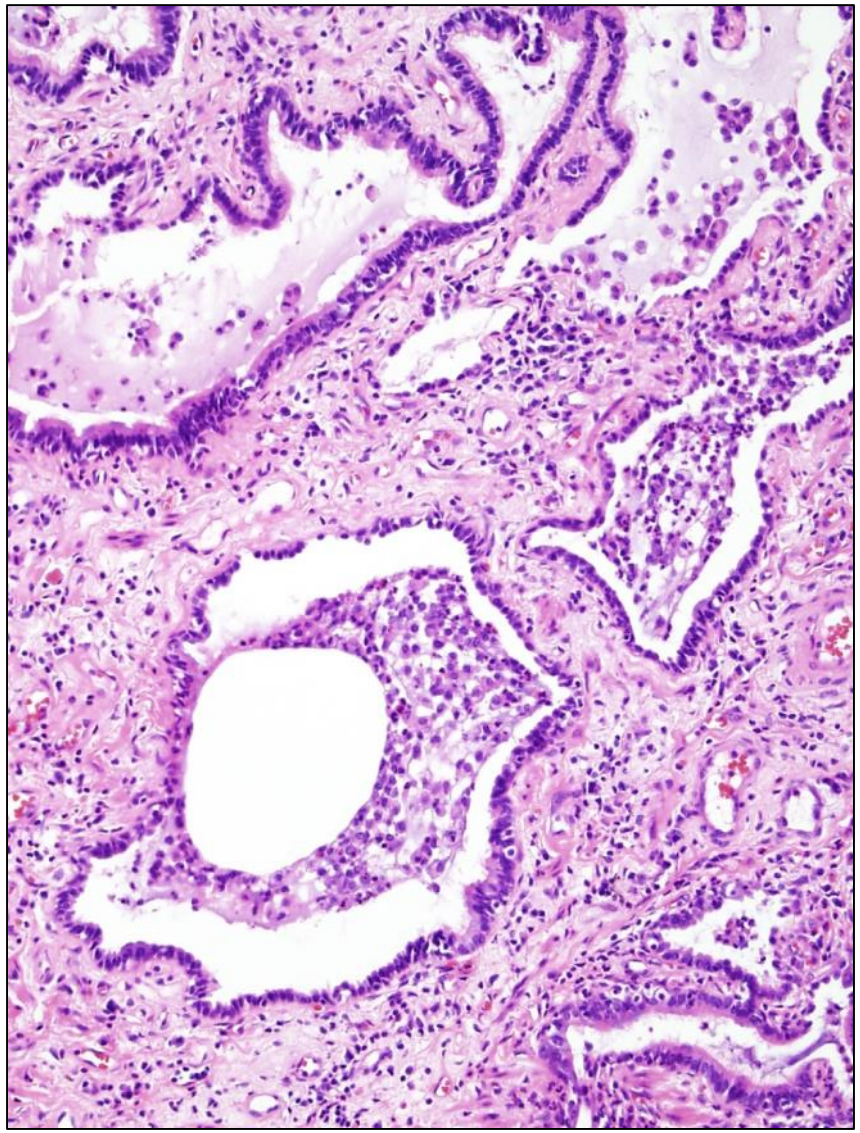




©2021 Mayo Foundation for Medical Education and Research

HONEYCOMB LUNG

Enlarged, restructured airspaces with thick fibrotic walls.…lined by…cuboidal or ciliated columnar cells ...squamous metaplasia occasionally …mucus… macrophages or neutrophils often fill the spaces… hyperplasia of smooth muscle is… common…”

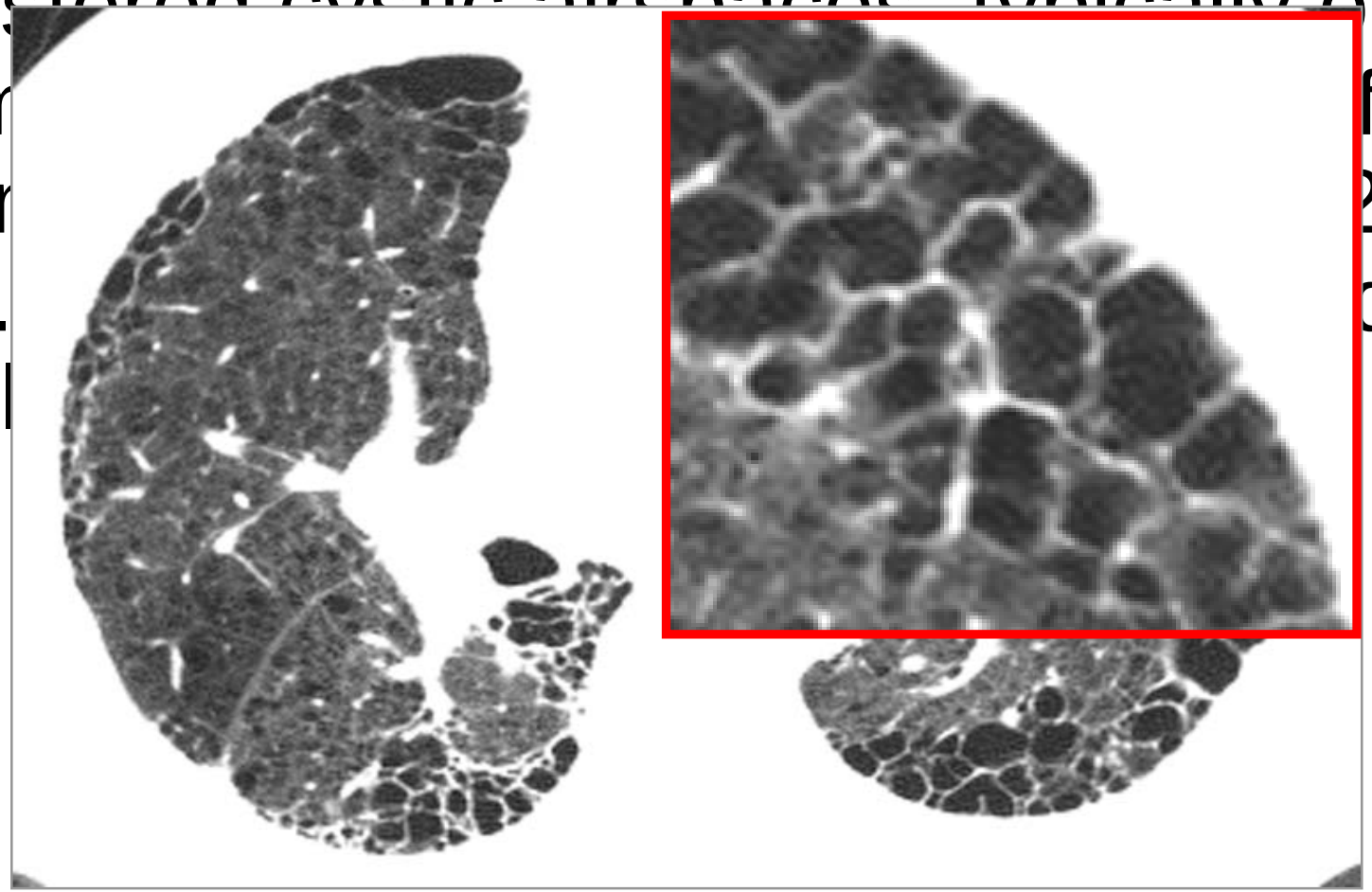


Katzenstein & Askin’s Surgical Pathology of Non-neoplastic Lung Disease, 3rd Edition

©2021 Mayo Foundation for Medical Education and Research

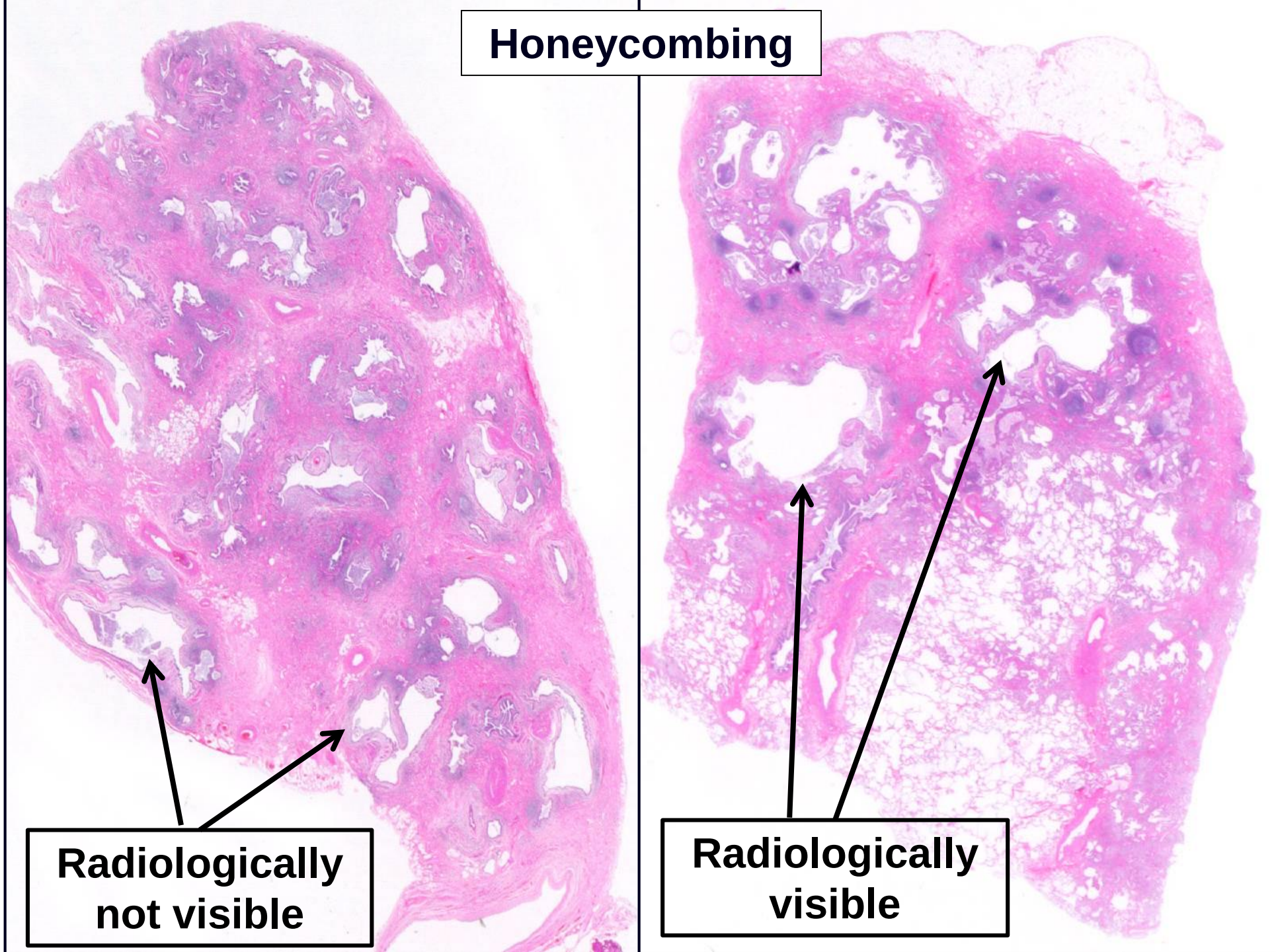
CT DEFINITION OF HONEYCOMB LUNG

Clustered cystic airspaces, typically of
com f 3-
10 r 2.5
cm. d
wall



©2021 Mayo Foundation for Medical Education and Research

Honeycombing



HONEYCOMB LUNG

- Be aware of the implications of the term and the context in which it is used
- Not synonymous with UIP/IPF
- Always irreversible

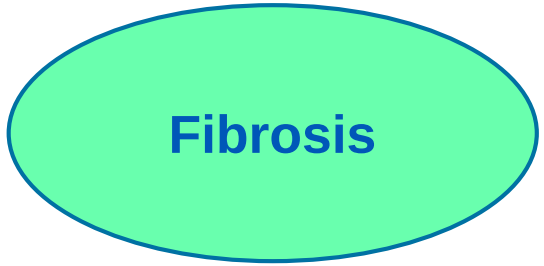
©2021 Mayo Foundation for Medical Education and Research

These are potentially reversible



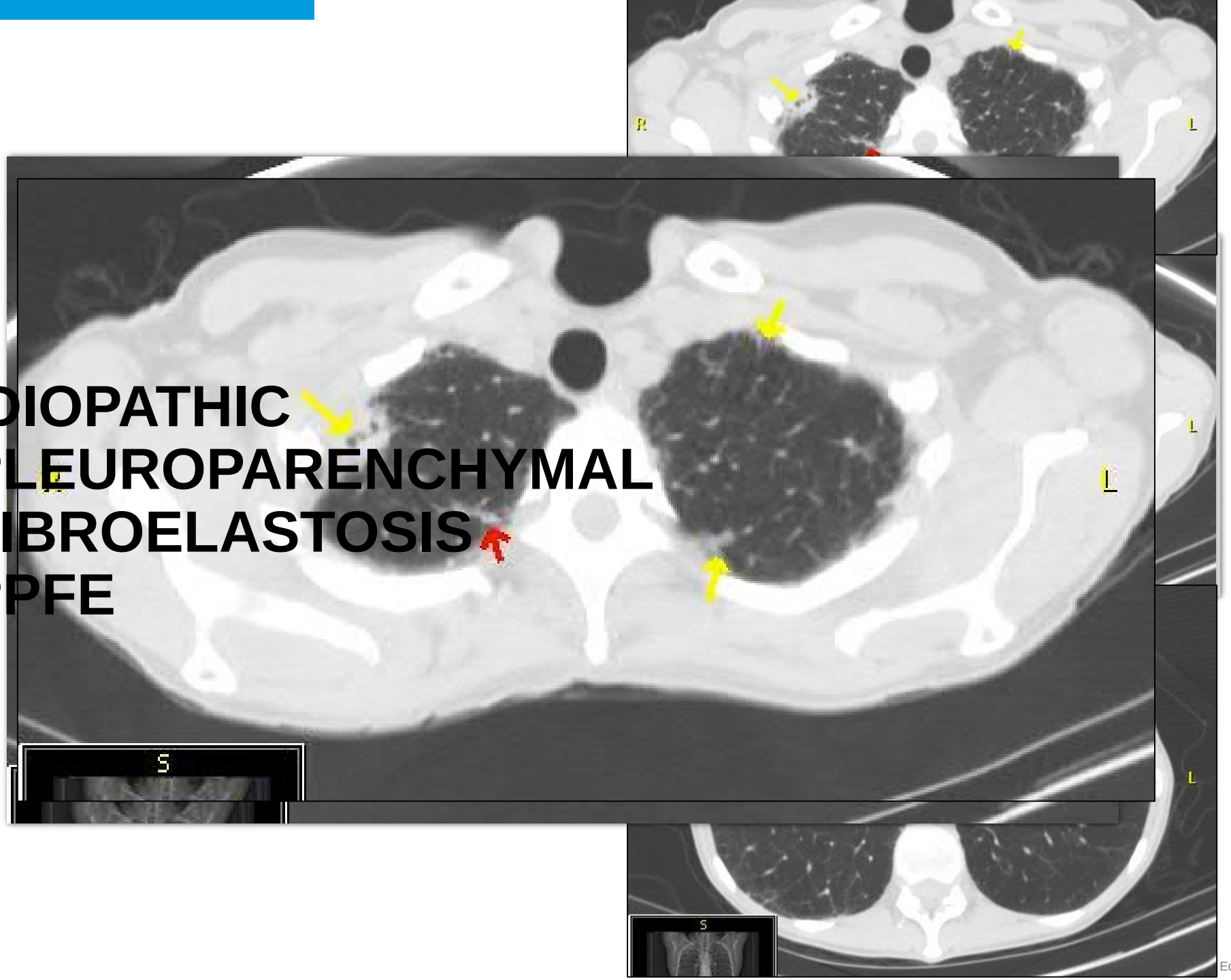
Eosinophilic pneumonia
Cryptogenic organizing pneumonia
Diffuse alveolar damage
Hypersensitivity pneumonitis
NSIP- some cases

These are irreversible

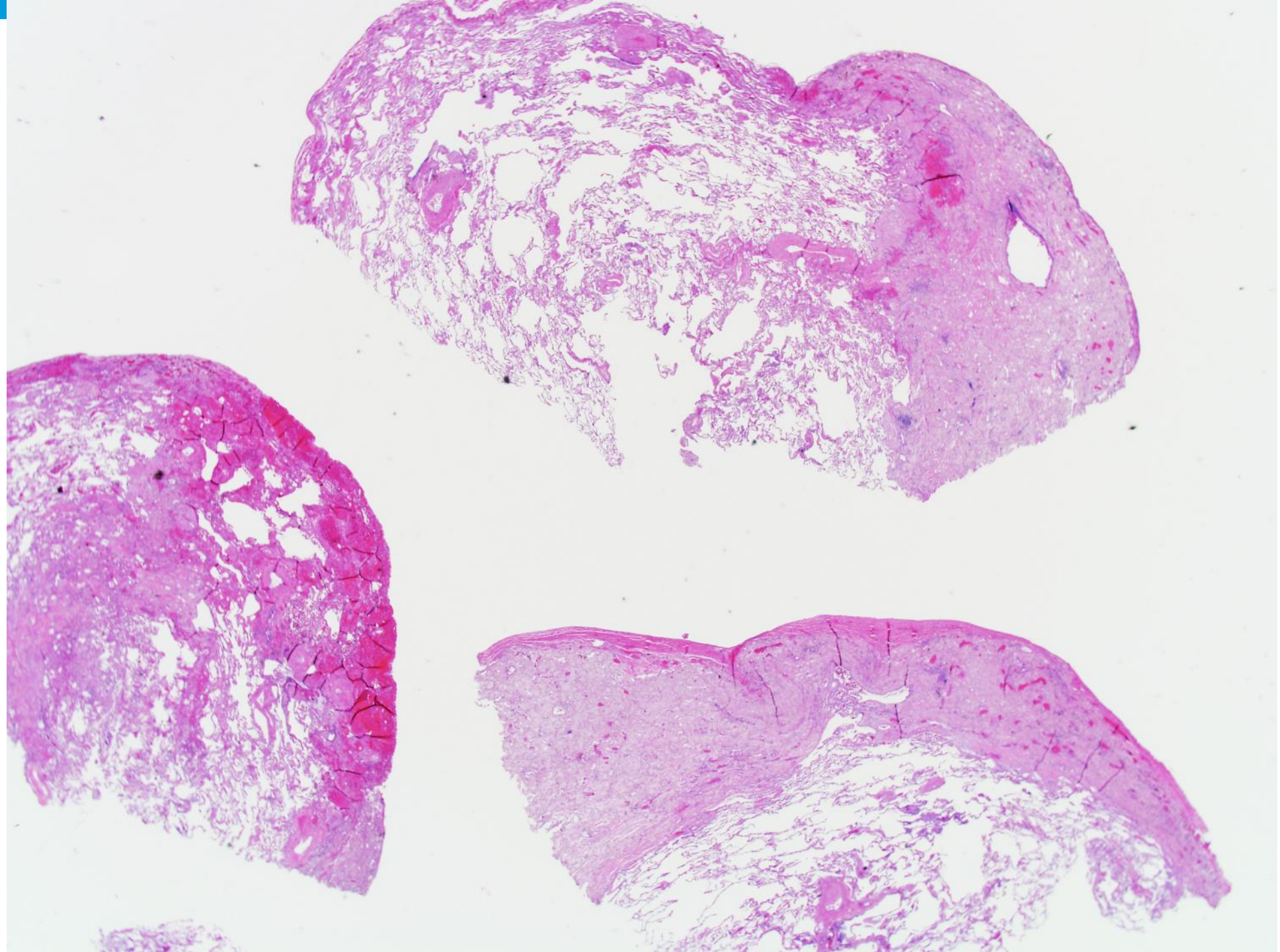


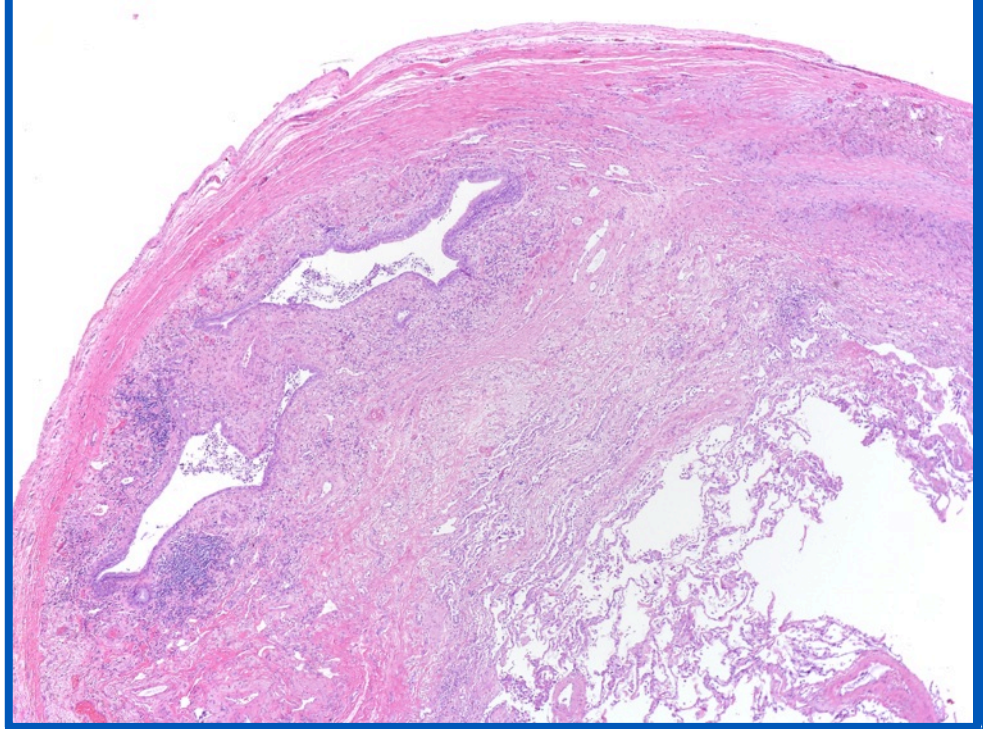
Idiopathic pulmonary fibrosis
Other causes of UIP pattern
NSIP- some cases
Hypersensitivity pneumonitis
Langerhan's cell histiocytosis
Pleuroparenchymal fibroelastosis
Sarcoidosis

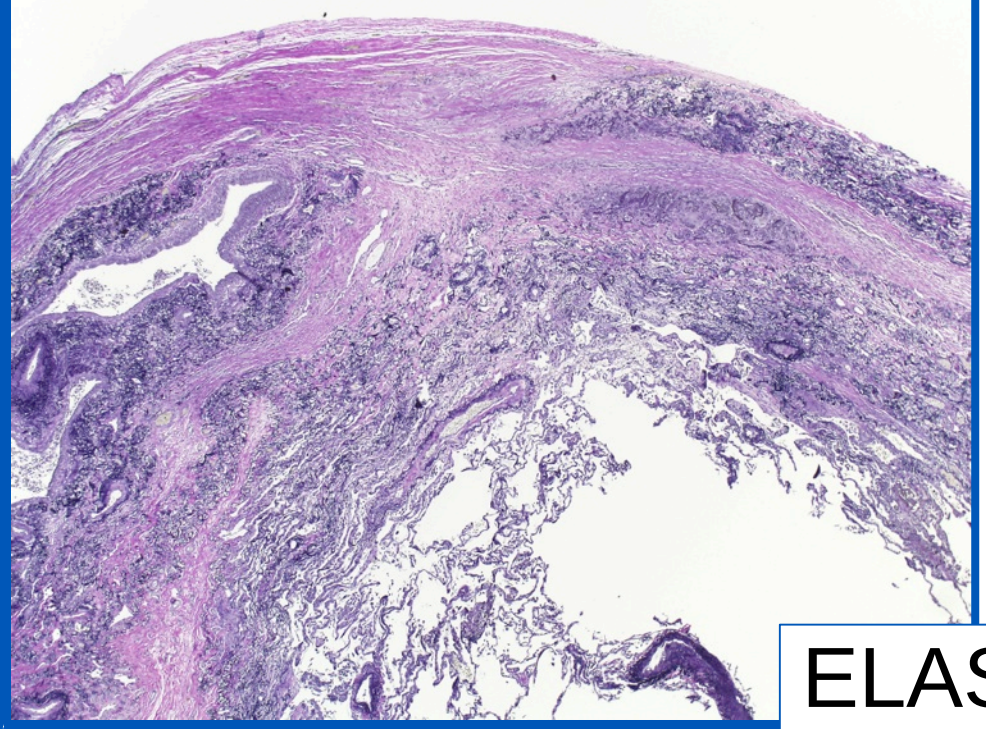
©2021 Mayo Foundation for Medical Education and Research



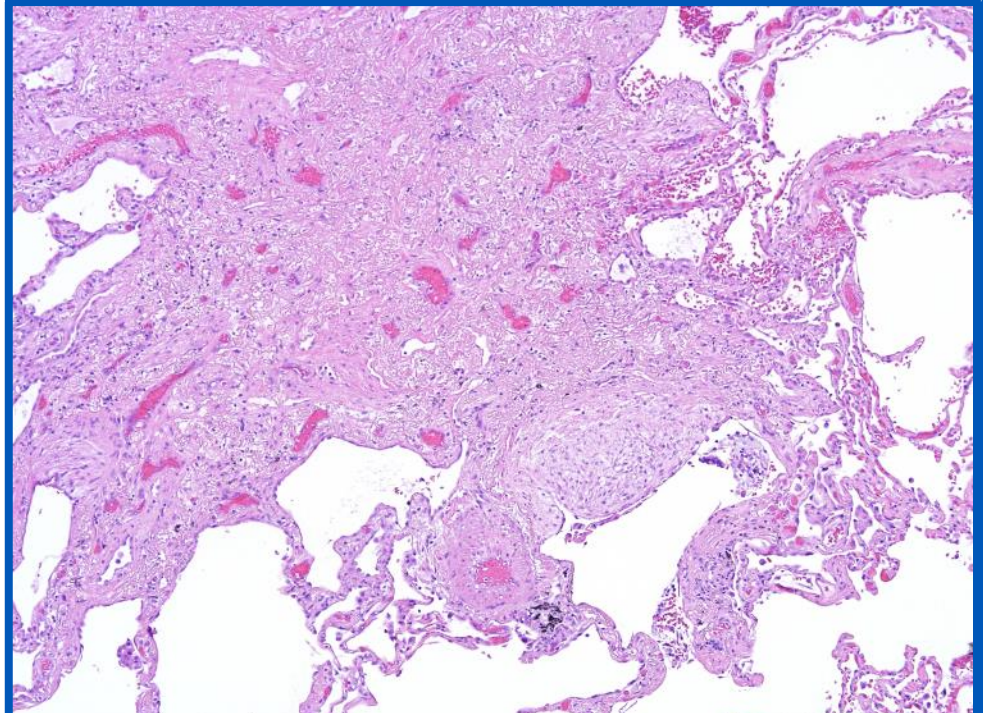
IDIOPATHIC PLEUROPARENCHYMAL FIBROELASTOSIS PPFE

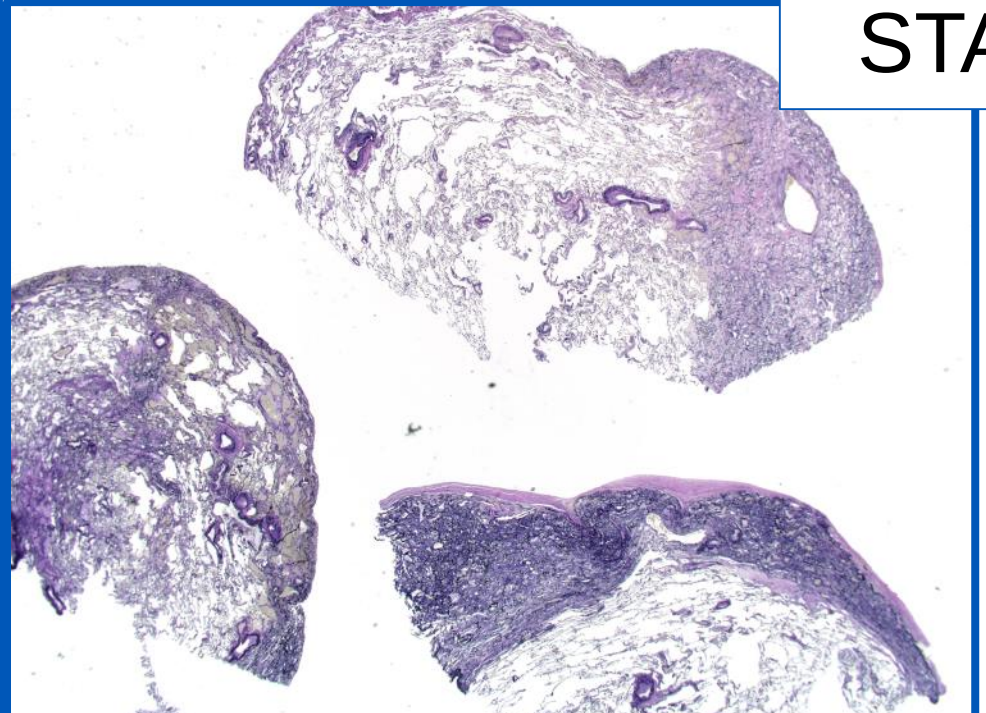






ELASTIC STAIN





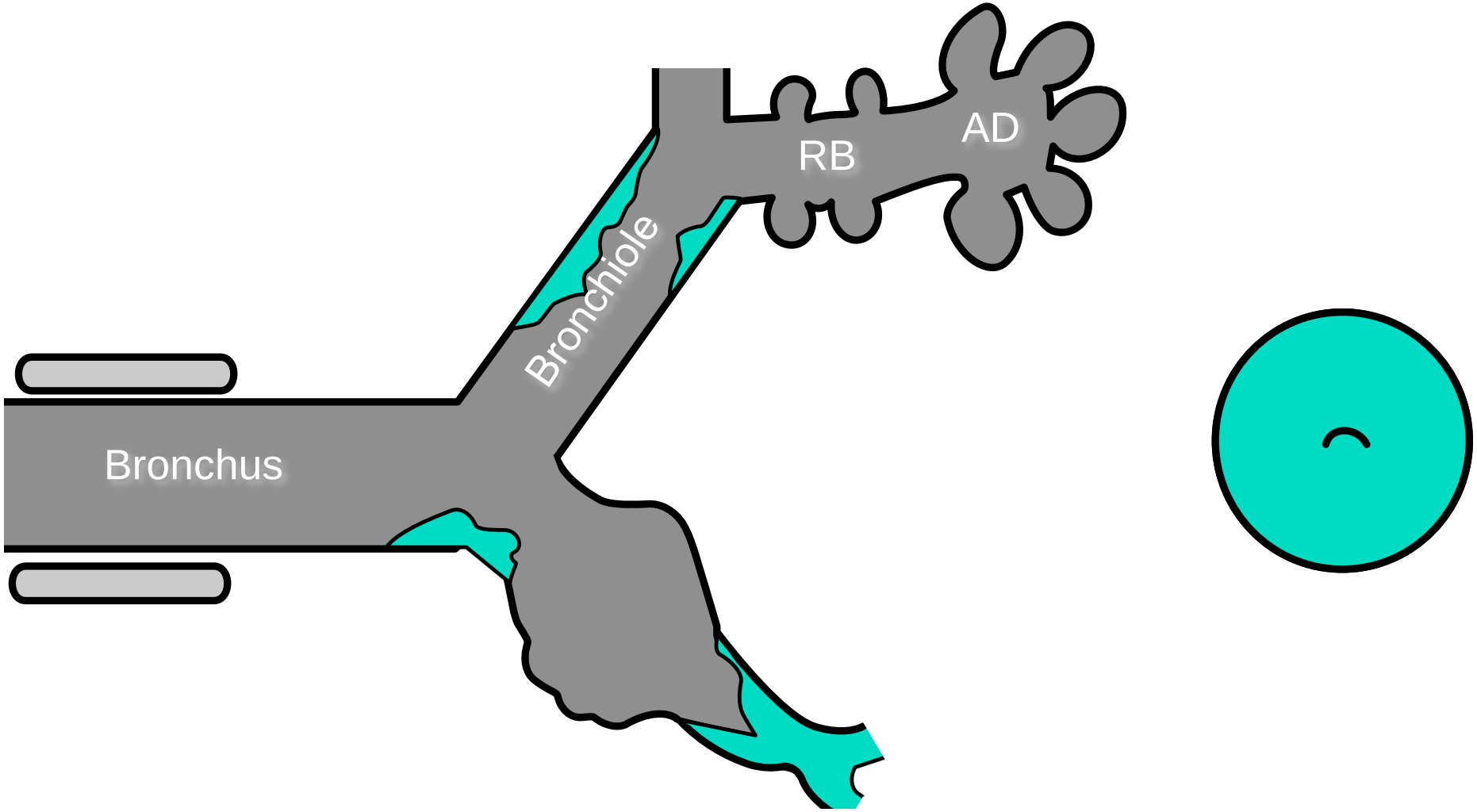
AIRWAY CENTERED “FIBROSIS"

- Organizing pneumonia/COP
- Obliterative/constrictive bronchiolitis
- Airway centered interstitial fibrosis
- Peribronchiolar metaplasia

} NOT reversible

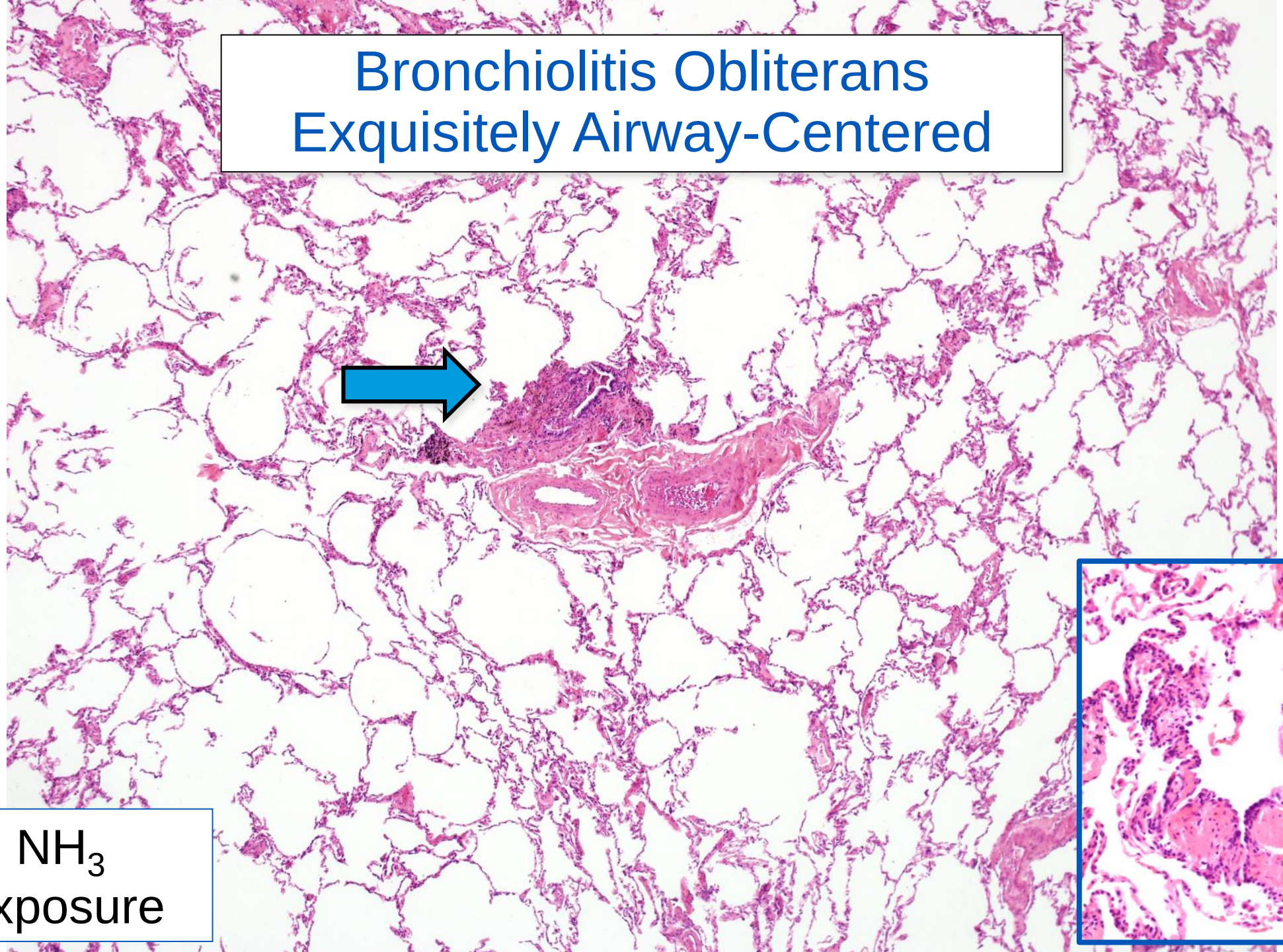
©2021 Mayo Foundation for Medical Education and Research

OBLITERATIVE BRONCHIOLITIS



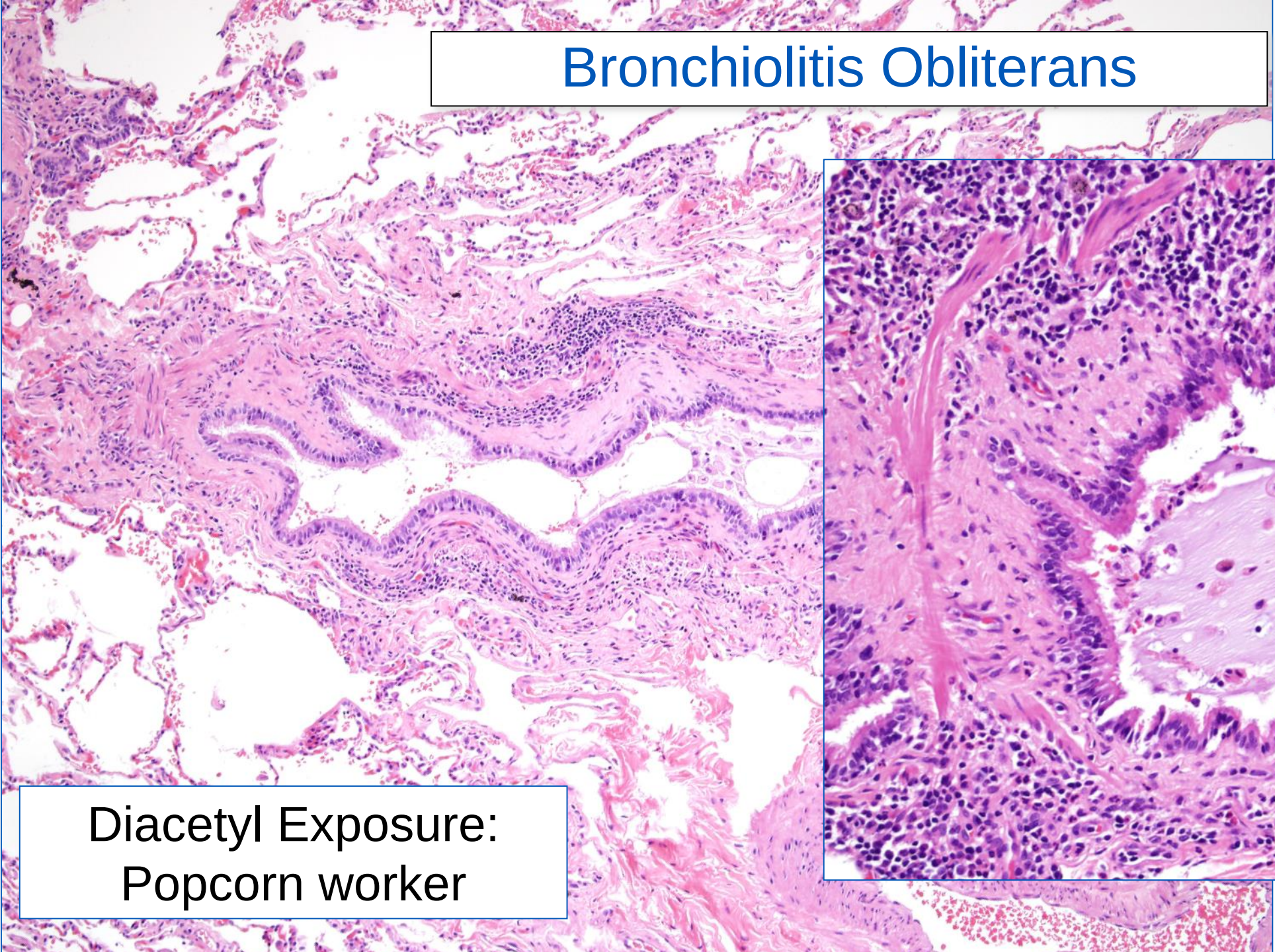
Some radiologists and pathologists use constrictive bronchiolitis to describe this entity, as well as reversible non fibrotic disease

Bronchiolitis Obliterans
Exquisitely Airway-Centered



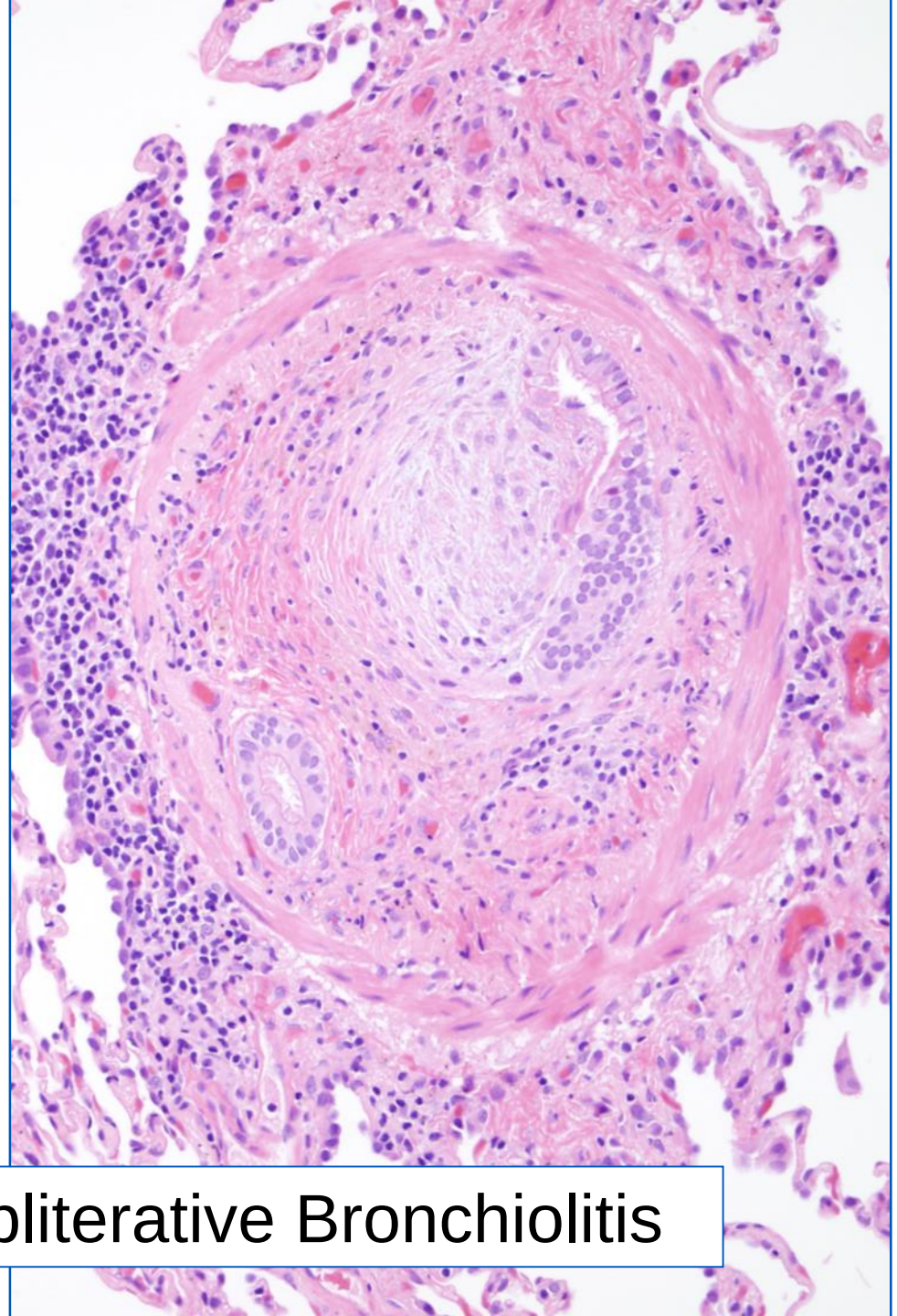
NH_3
Exposure

Bronchiolitis Obliterans

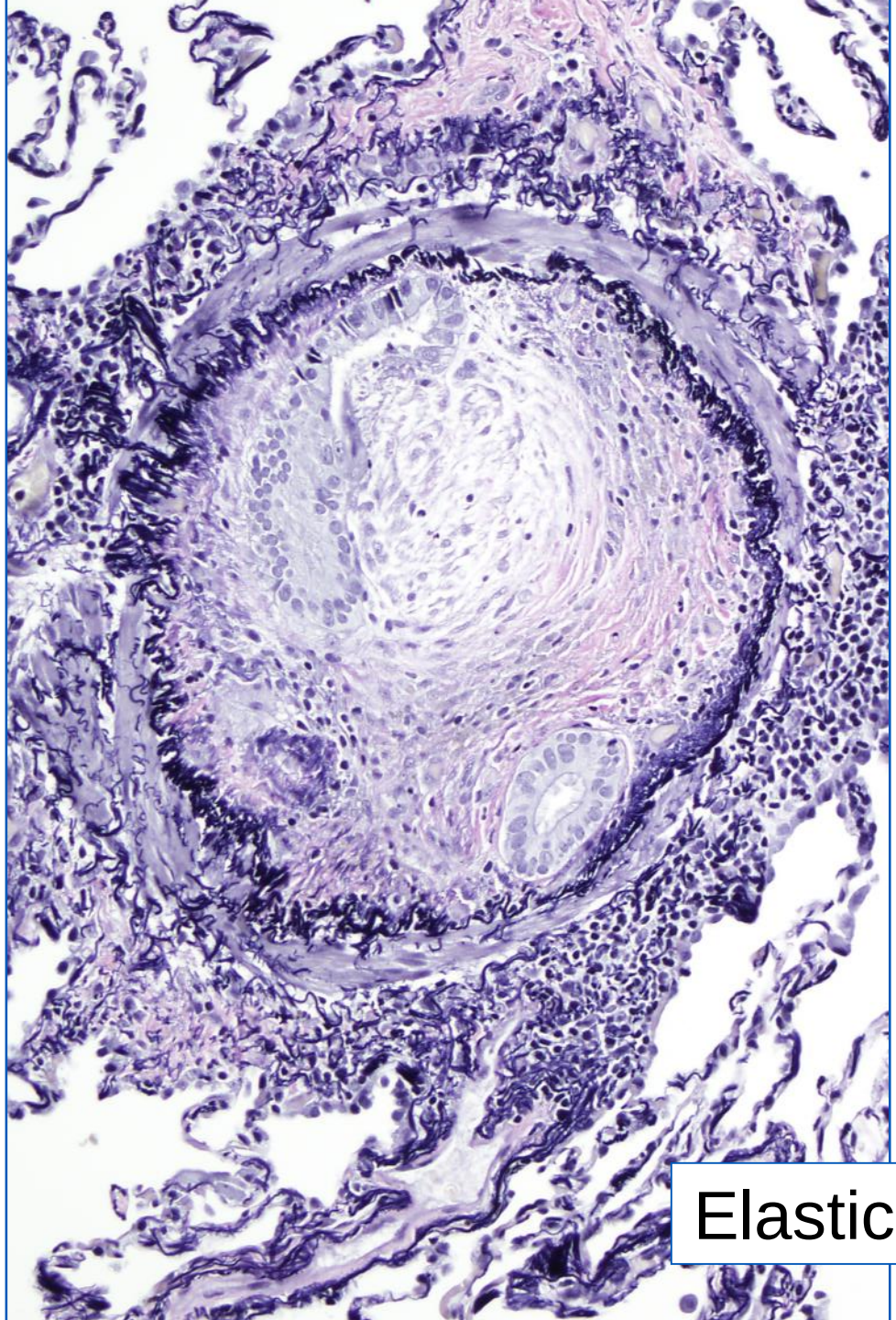


Diacetyl Exposure:
Popcorn worker

©2021 Mayo Foundation for Medical Education and Research



Obliterative Bronchiolitis



Elastic Stain

AIRWAY CENTERED INTERSTITIAL FIBROSIS

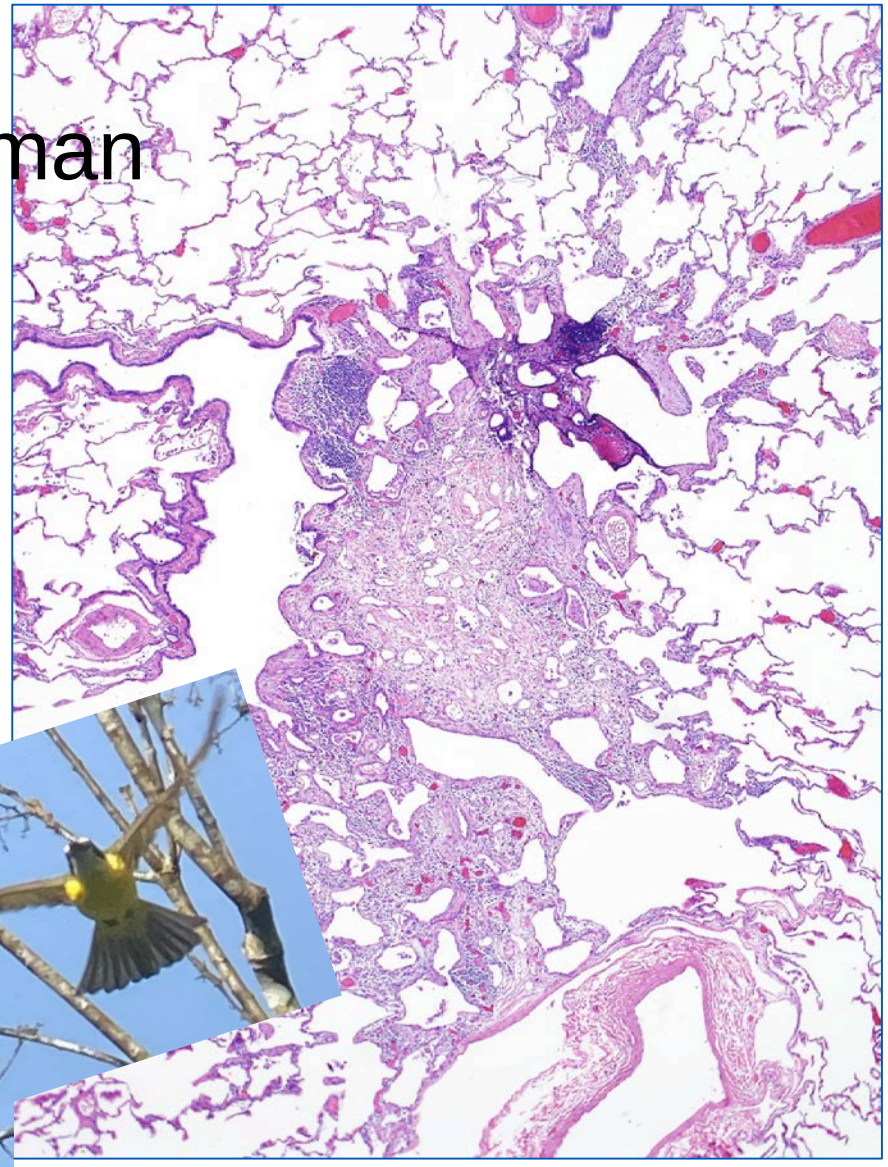
- Women > men (2:1), mean 54 years (23-69)
- Chronic dry cough, dyspnea > 1 year
- Mild restriction and hypoxemia
- Some likely end stage HP, or secondary to chronic microaspiration
- 30-40% mortality

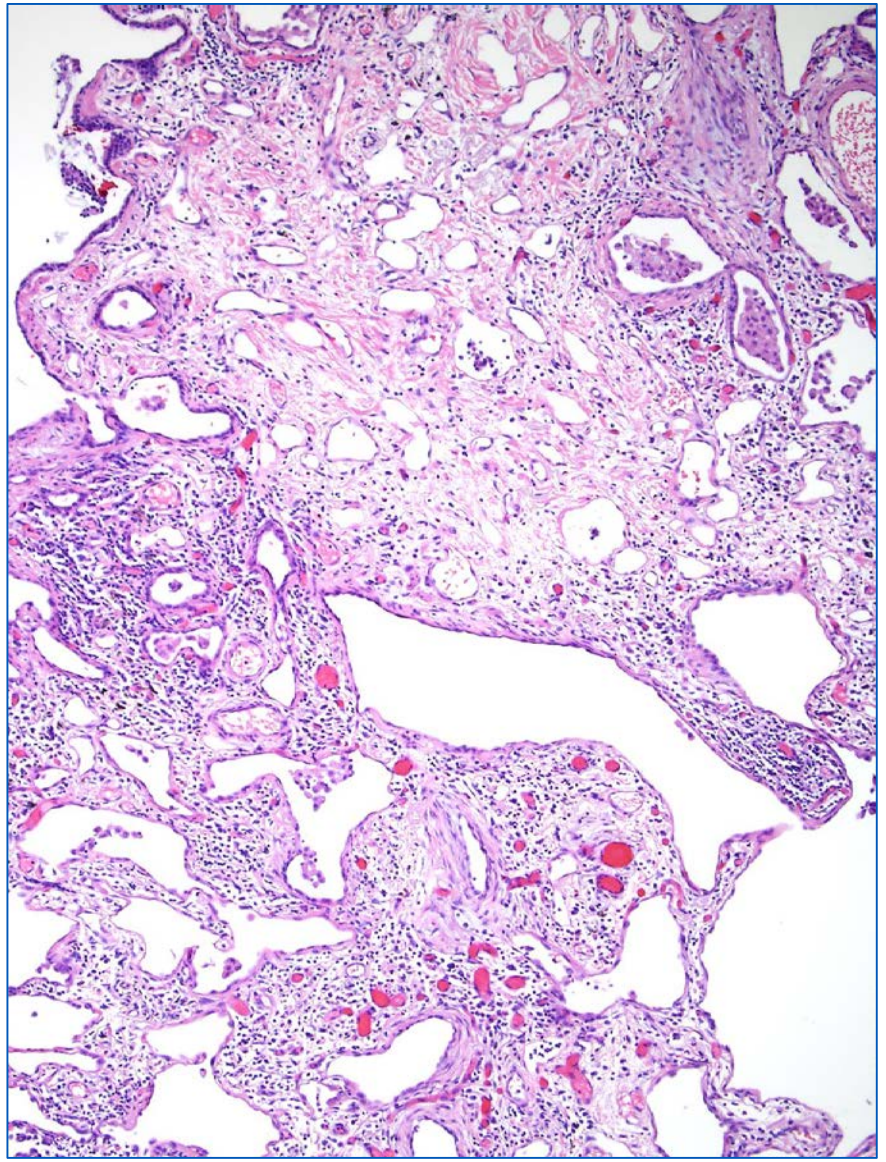
©2021 Mayo Foundation for Medical Education and Research

- 47-year-old man

300 birds in his house!







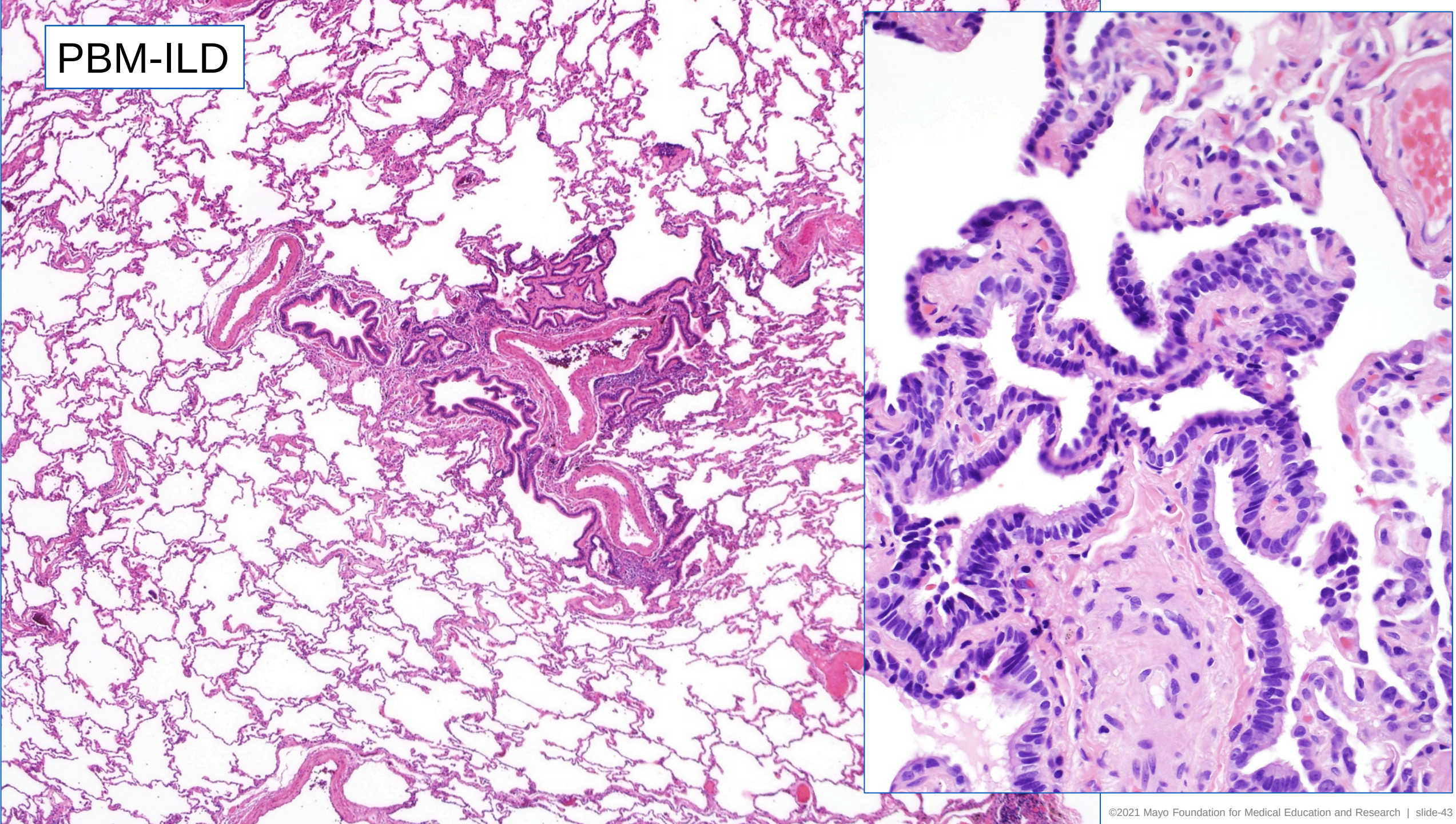
©2021 Mayo Foundation for Medical Education and Research

PERIBRONCHIOLAR METAPLASIA (PB)

- Proliferation of bronchiolar epithelium along thickened peribronchiolar alveolar walls
- Bronchiole occasionally completely replaced
- May be the only finding in surgical lung biopsy
- Differential diagnosis
  - Idiopathic (PB-ILD)
  - Connective tissue disease
  - Chronic HP
  - Exposures-smoke, welding

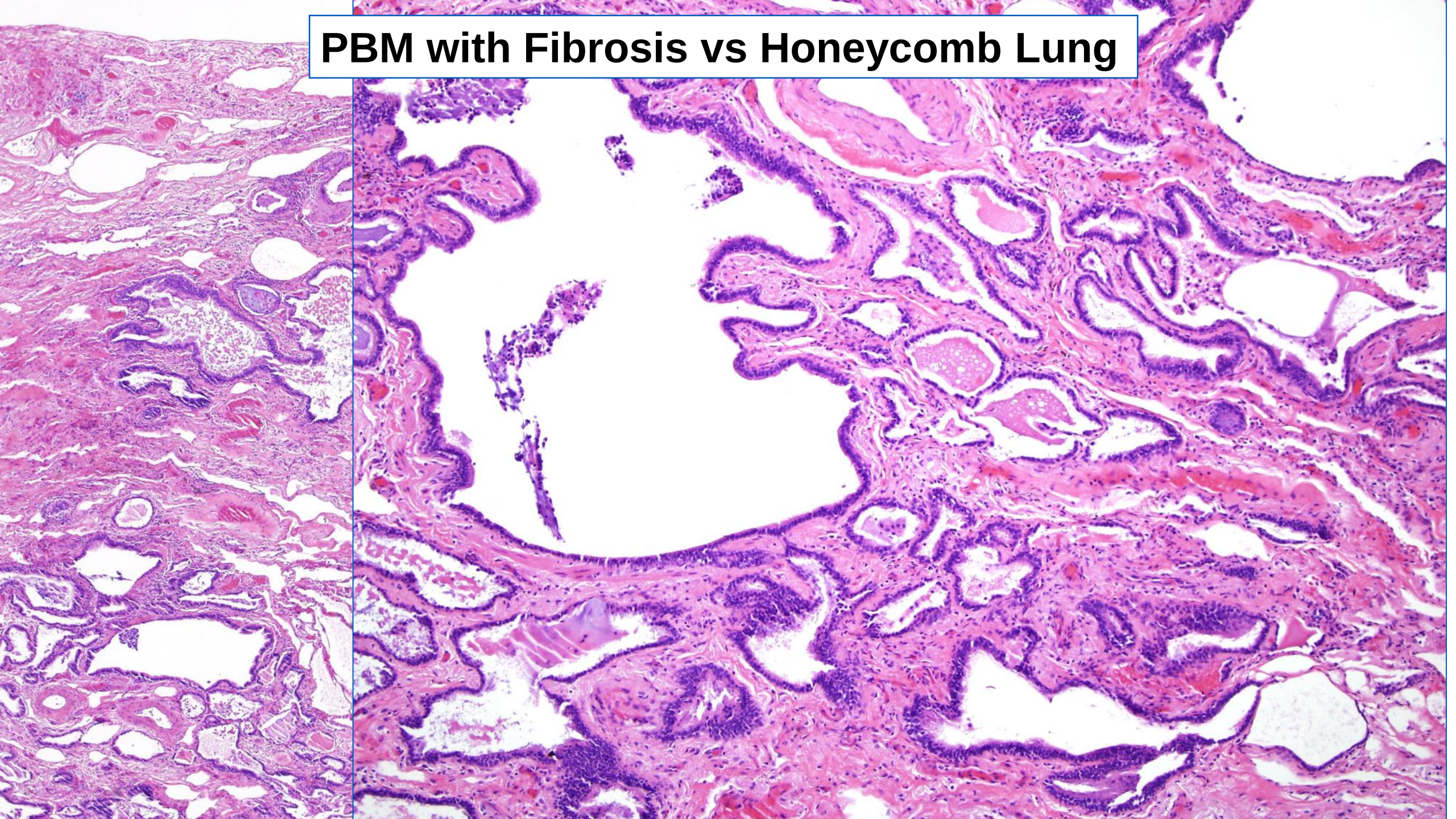
©2021 Mayo Foundation for Medical Education and Research

PBM-ILD



©2021 Mayo Foundation for Medical Education and Research

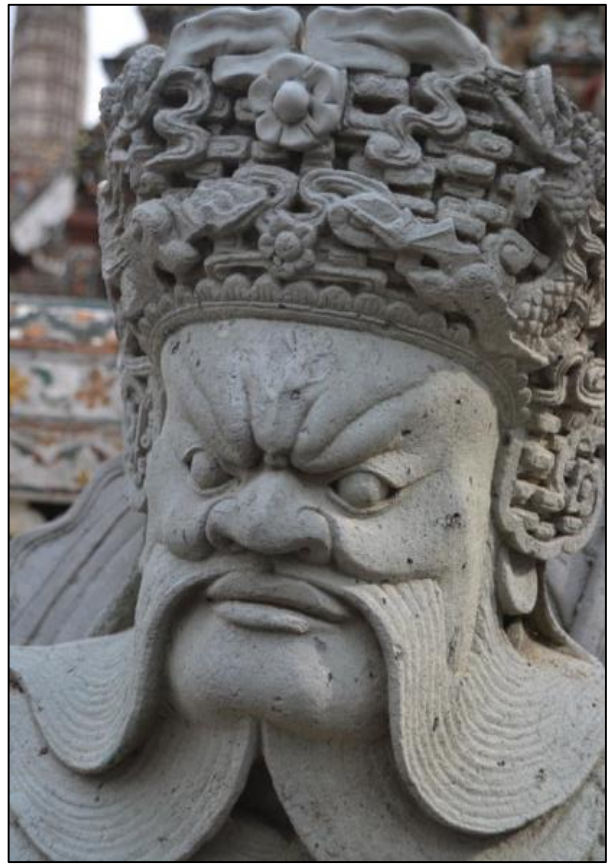
PBM with Fibrosis vs Honeycomb Lung



TAKE HOME POINT

- Not all “fibrosis” in the lung has the same clinical and prognostic implication, even though it may superficially look the same





©2021 Mayo Foundation for Medical Education and Research

COVID-19 LUNG PATHOLOGY

ACUTE CHANGES

- Diffuse alveolar damage/acute fibrinous and organizing pneumonia
- Organizing pneumonia
- Large and small thrombi
  - Infarction/hemorrhage
- Perivascular and peribronchiolar chronic inflammation

©2021 Mayo Foundation for Medical Education and Research

LATE PULMONARY COMPLICATIONS

- Define the CT findings, histopathology and presence of SARS-CoV-2 in tissue by PCR in patients with infection ≥ 28 days
- Consultation and Mayo Clinic files
  - May 20- Apr 21
- 43 pts, 44 specimens
  - Most large samples: VATS- 52%, Autopsy- 27%, explant, 5%

Roden AJ et al Arch Pathol Lab Med 2022 146:791-804

©2021 Mayo Foundation for Medical Education and Research

LATE PULMONARY COMPLICATIONS
RESULTS

- Mean age 59 yrs (31-89); 60% male
- Days between onset of symptoms or first positive SARS-CoV-2 test: 97 days (30-359)
- Lung disease prior to COVID-19: 28 %
- Connective tissue disease: 11 %

Roden A et al. submittedTo ss

©2021 Mayo Foundation for Medical Education and Research

COVID 19 PATHOLOGY ≥ 28 DAYS

Pattern	% (n=44)
Acute lung injury	88
Acute DAD	34
Acute and organizing DAD	61
OP	66
Acute fibrinous pneumonia +/- organization	58
Fibrotic diffuse alveolar damage areas	50
Fibrotic NSIP-like regions	50
Cicatricial OP-areas	27
Cysts	9
Thrombi	Recent 27
	Recanalized 9

©2021 Mayo Foundation for Medical Education and Research

COVID 19 PATHOLOGY ≥ 28 DAYS

Pattern	%
Acute bronchopneumonia	30
Aspiration pneumonia	7
Non-necrotizing granulomas	14
Necrotizing granulomas	5
Lymphocytic infiltrates	30

©2021 Mayo Foundation for Medical Education and Research

COVID 19 PATHOLOGY ≥ 28 DAYS

Pattern	Days from symptom onset to biopsy, median days (range) P=0.009
Diffuse ALI	62 (30-279)
Focal ALI	140 (30-298)
No ALI	130 (101-359)

©2021 Mayo Foundation for Medical Education and Research

LATE PULMONARY COMPLICATIONS
RESULTS: DROPLET DIGITAL PCR

- n = 20 (of 44 samples)
- 80% positive, all with acute lung injury (were unable to test in patients with no ALI)
- 30 – 174 days after symptom onset or positive COVID test
- Slight negative correlation with ddPCR copy number (-0.281) and time from diagnosis
  - Nonetheless, copy numbers >10,000 identified at 83 and 97 days

Roden A et al. submittedTo ss

©2021 Mayo Foundation for Medical Education and Research

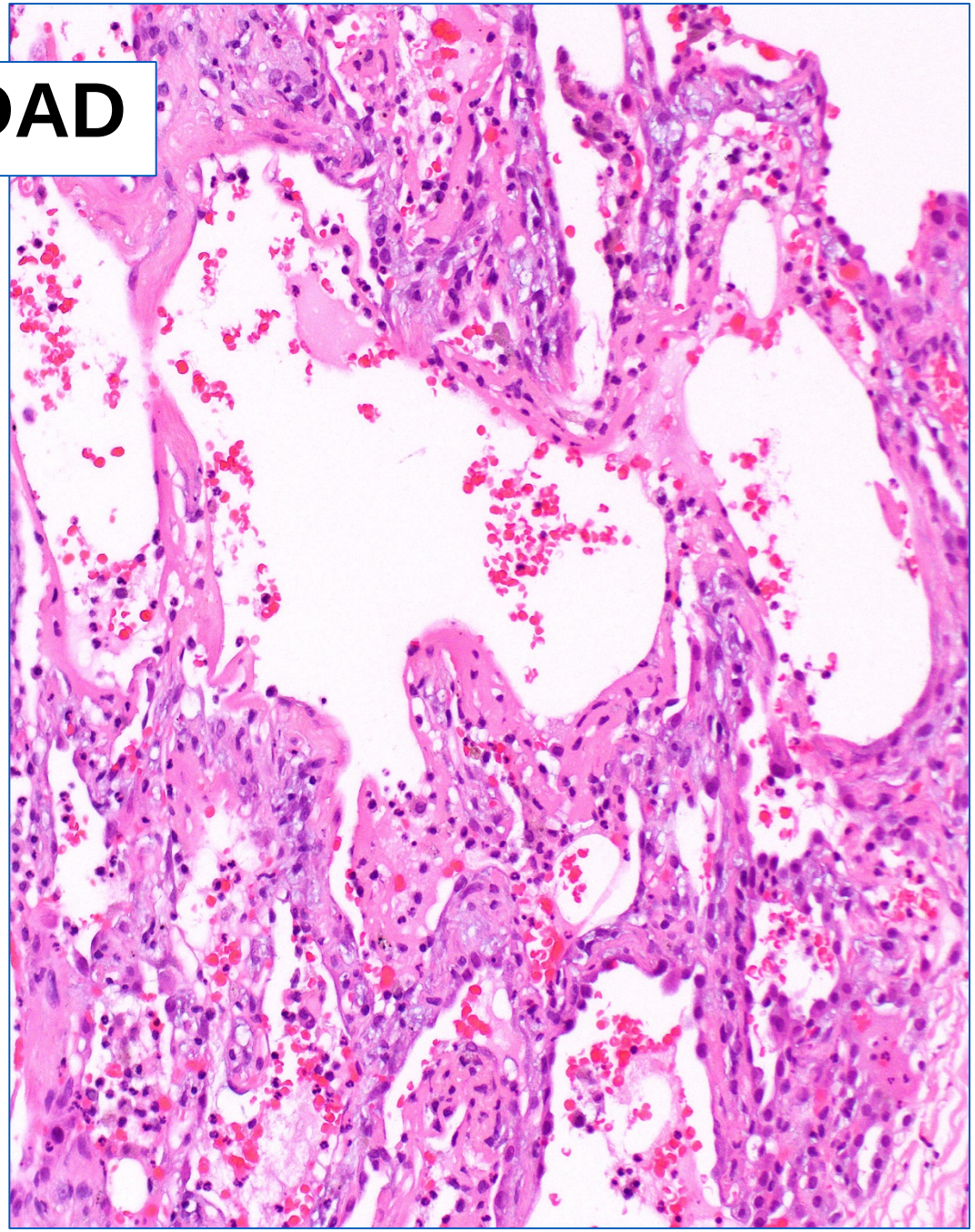
DAY 106



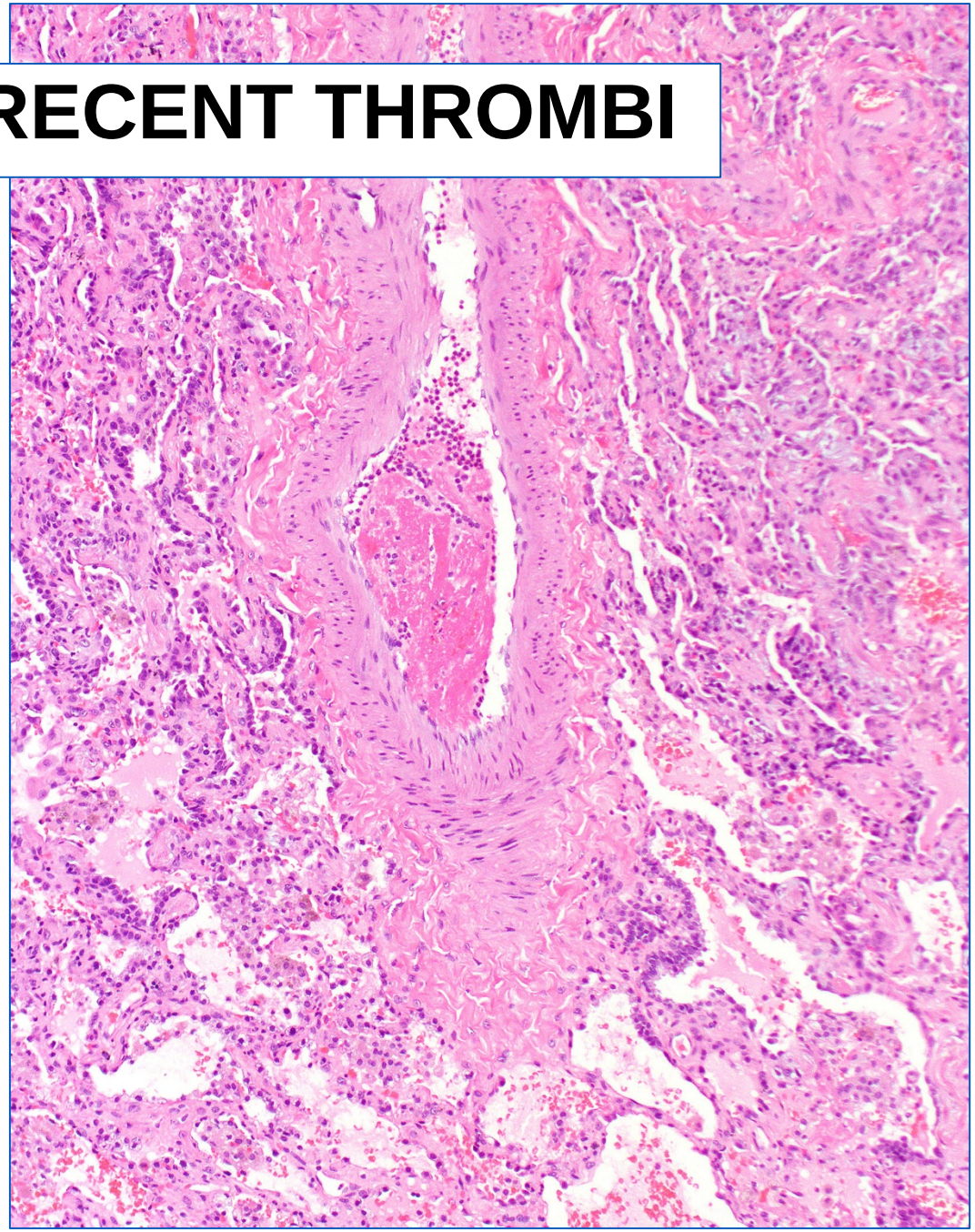


©2021 Mayo Foundation for Medical Education and Research

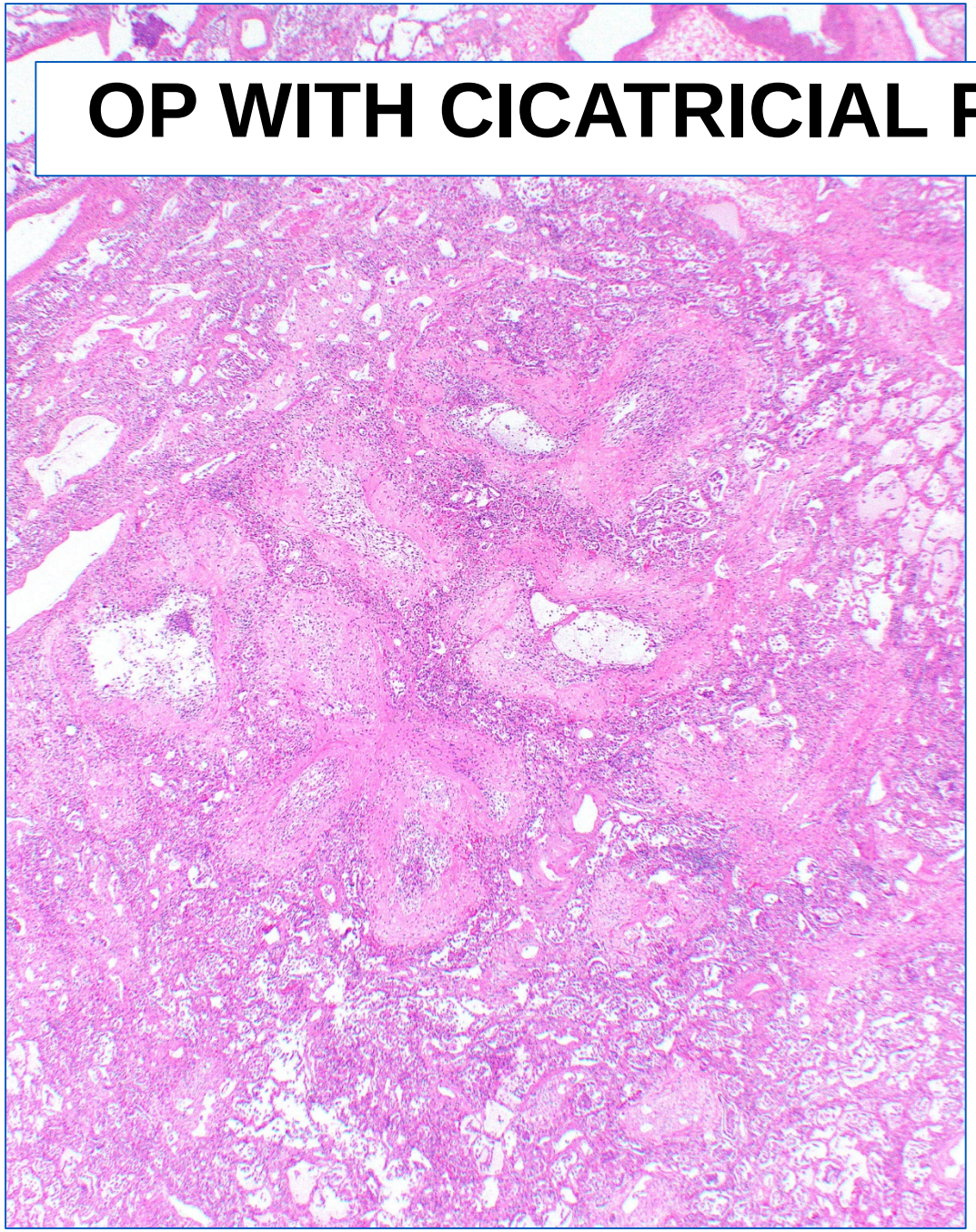
DAD

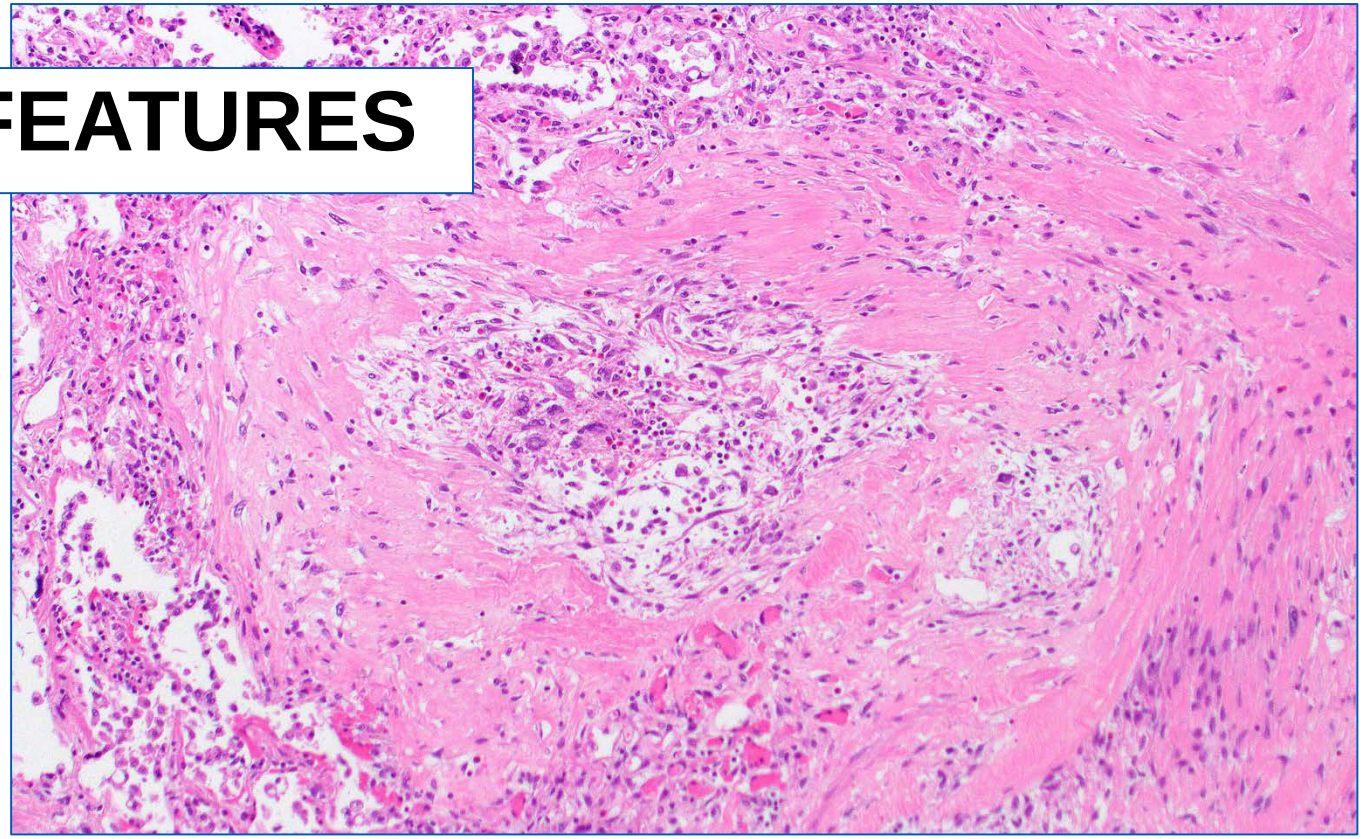


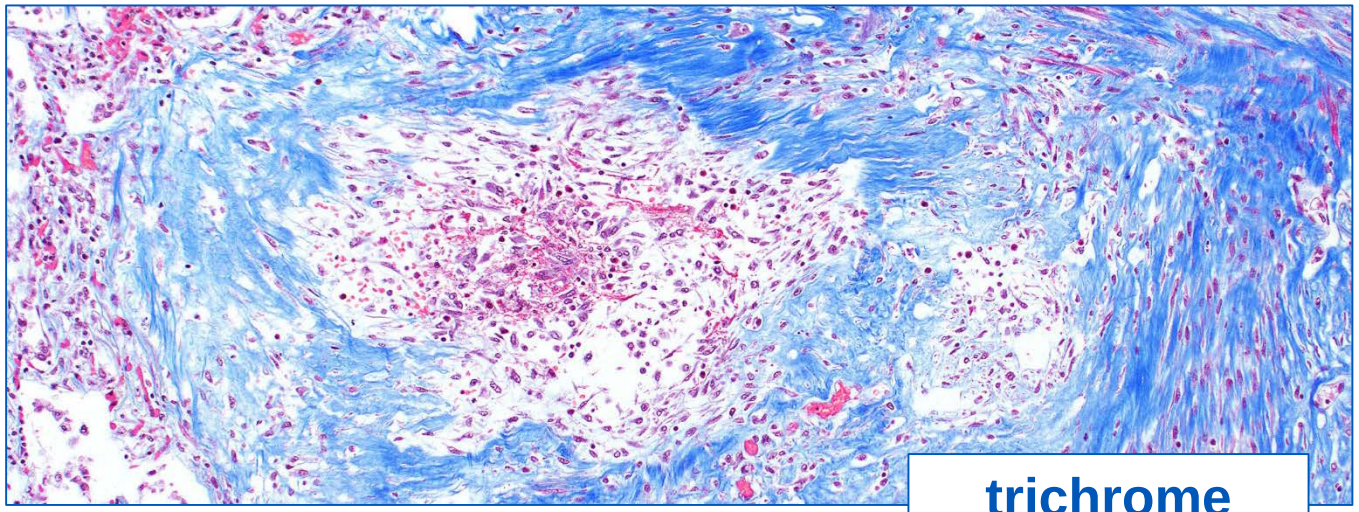
RECENT THROMBI



OP WITH CICATRICIAL FEATURES

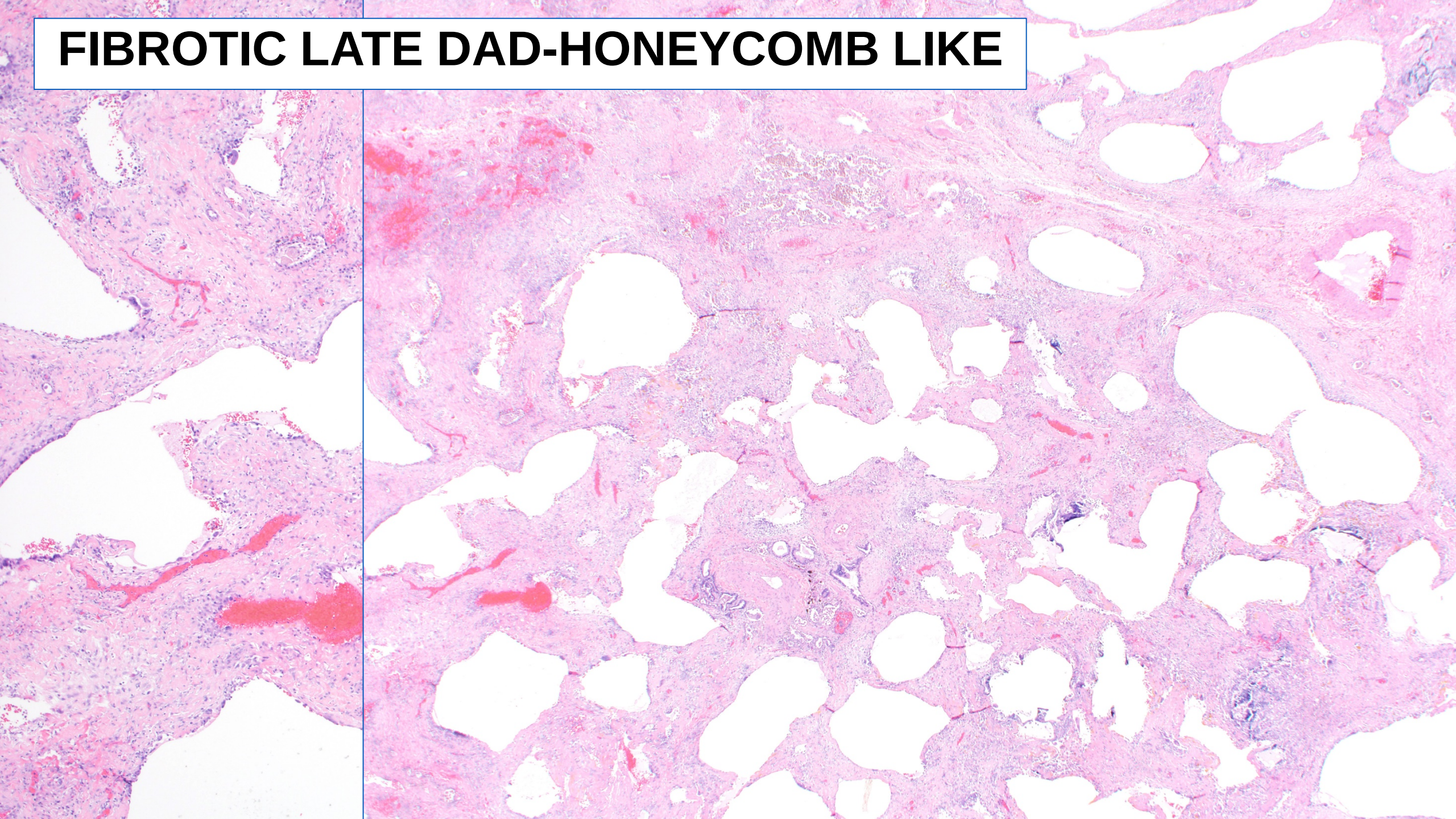




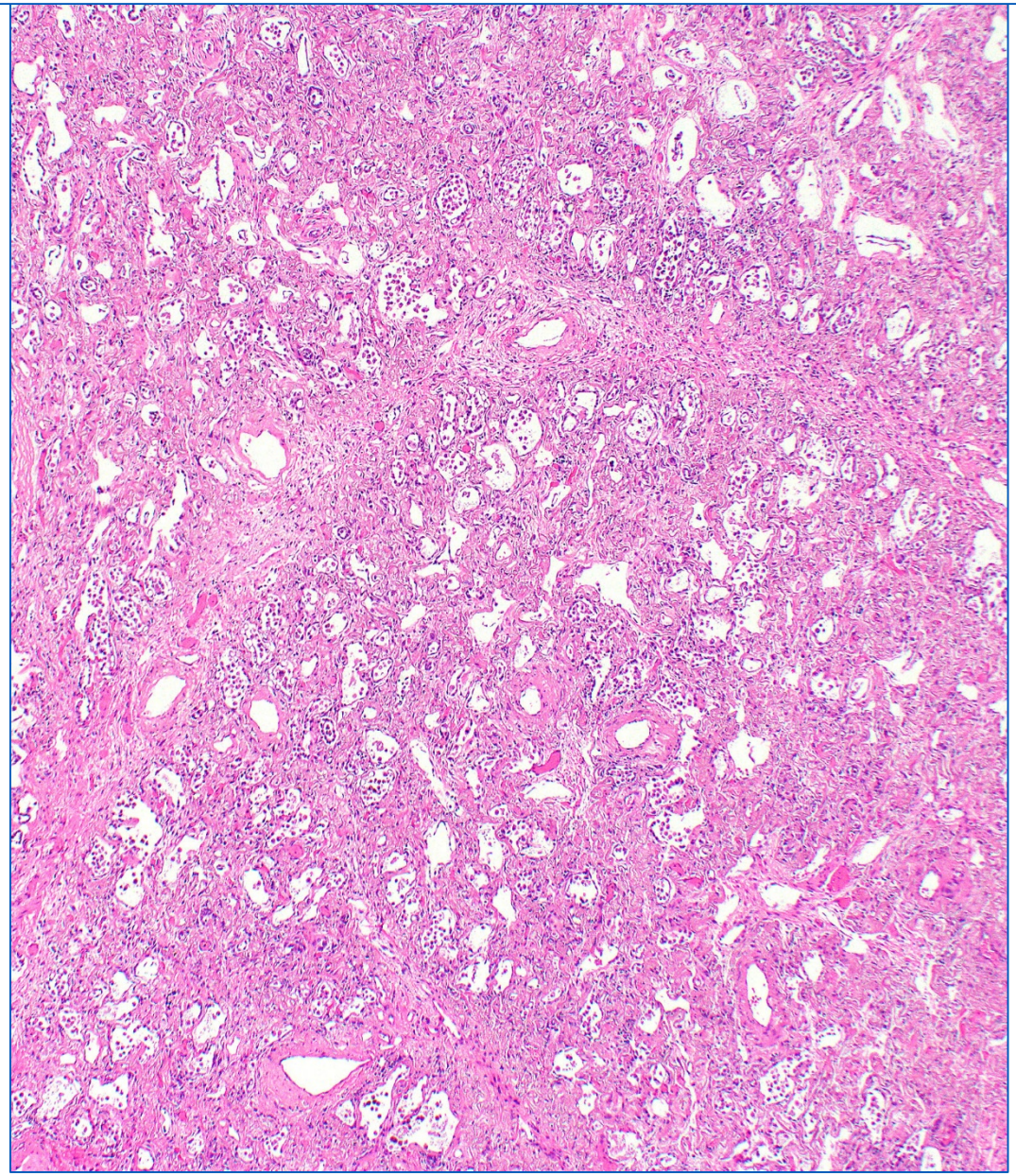


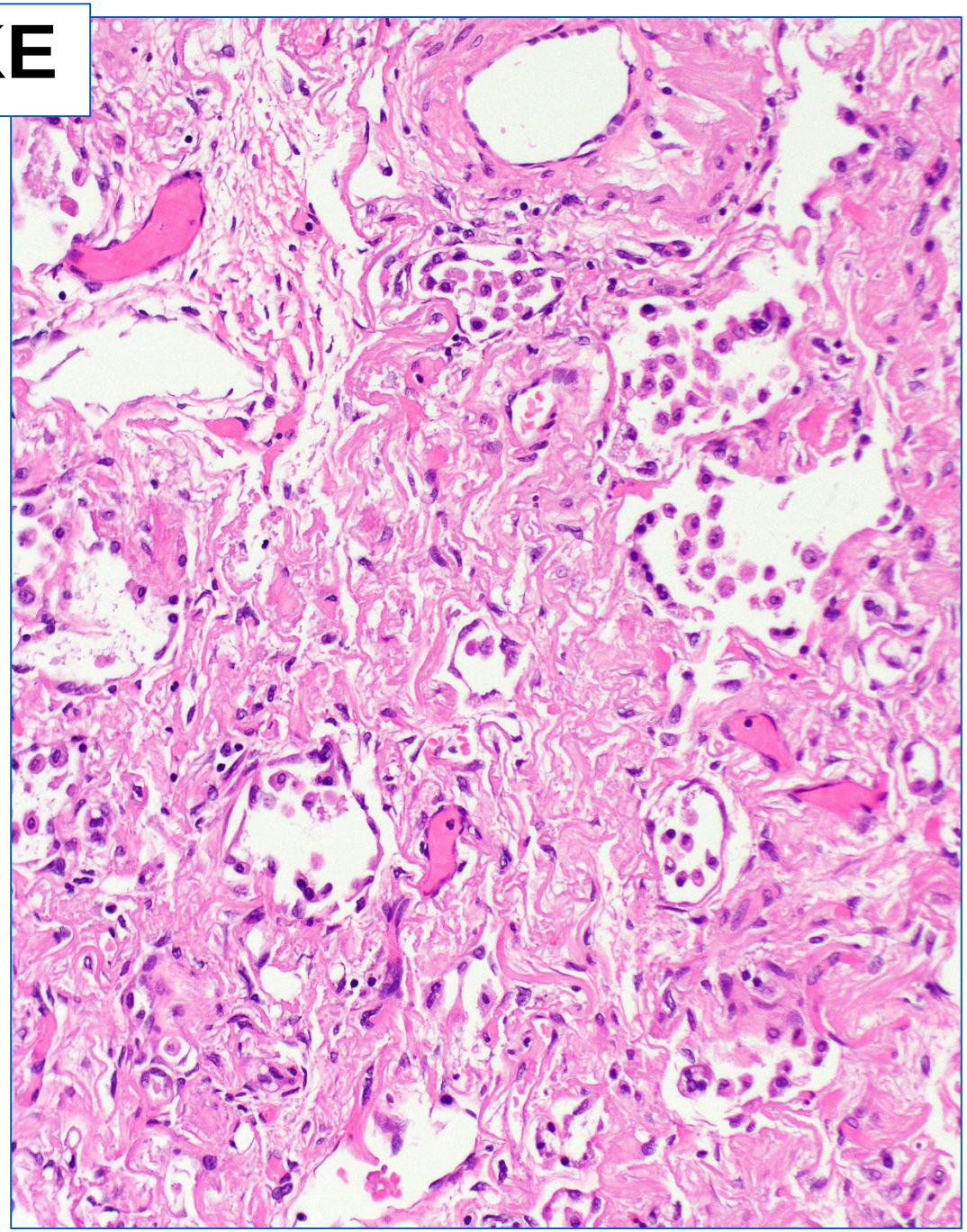
trichrome

FIBROTIC LATE DAD-HONEYCOMB LIKE

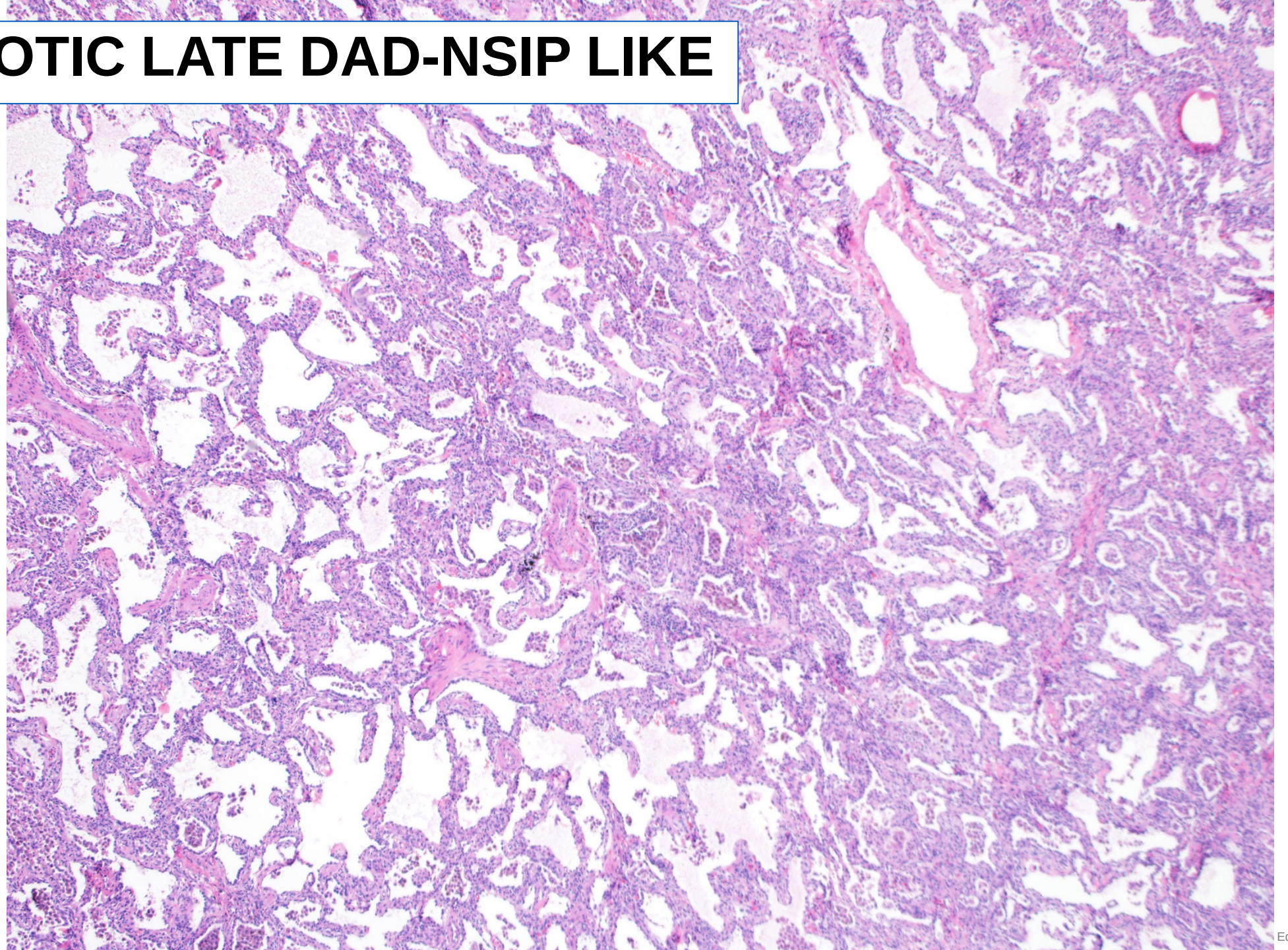


FIBROTIC LATE DAD-NSIP LIKE

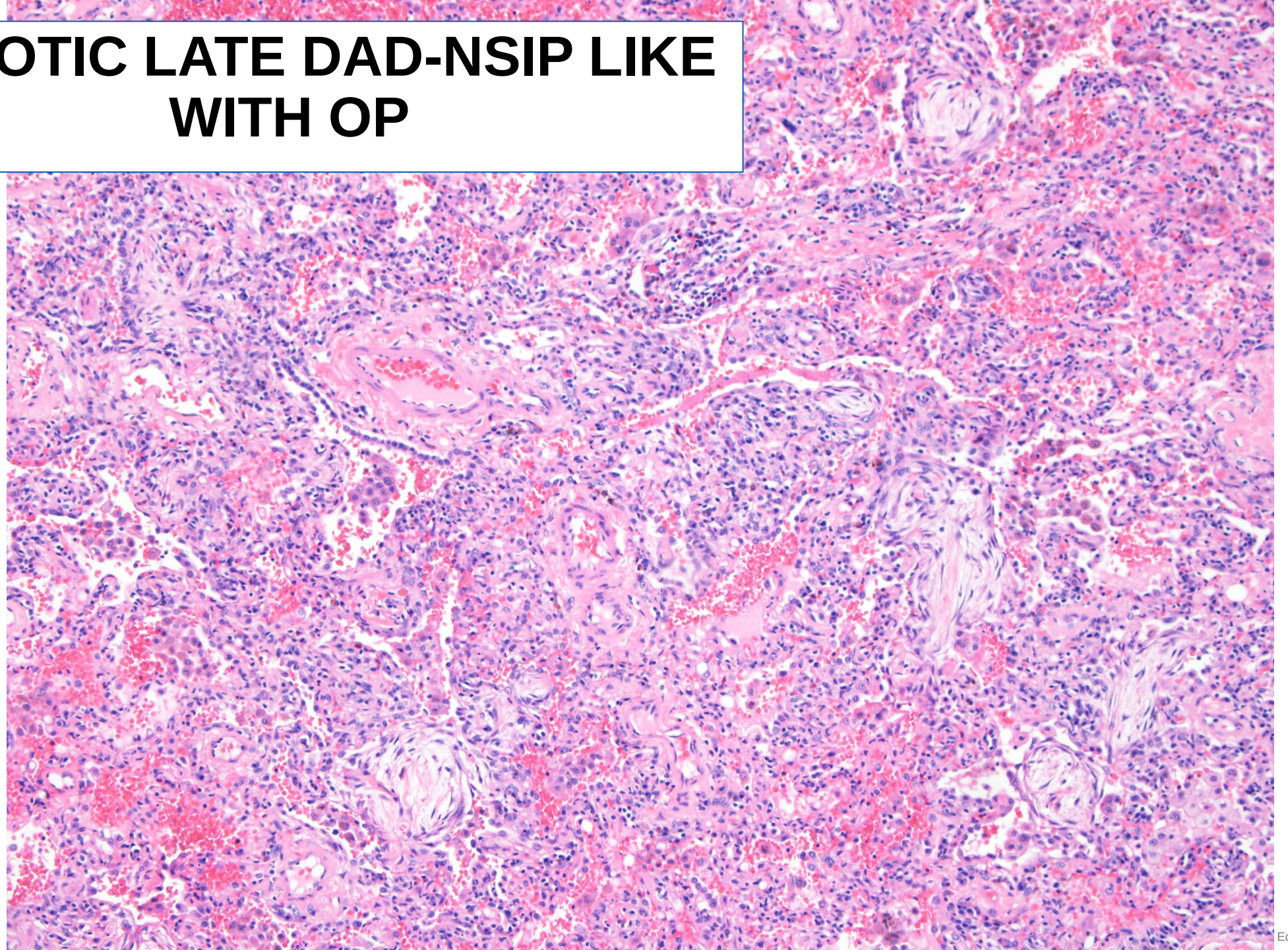




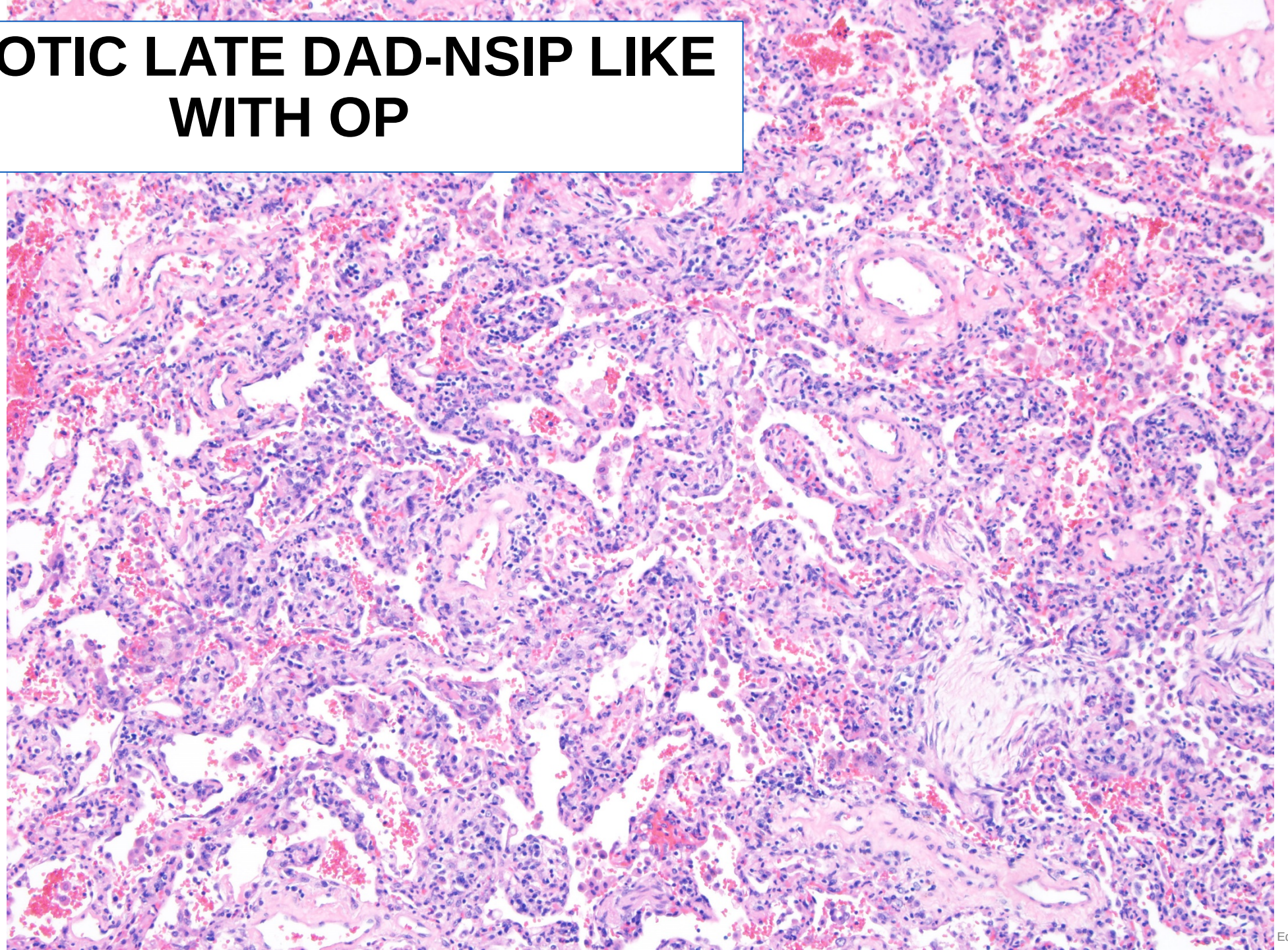
FIBROTIC LATE DAD-NSIP LIKE



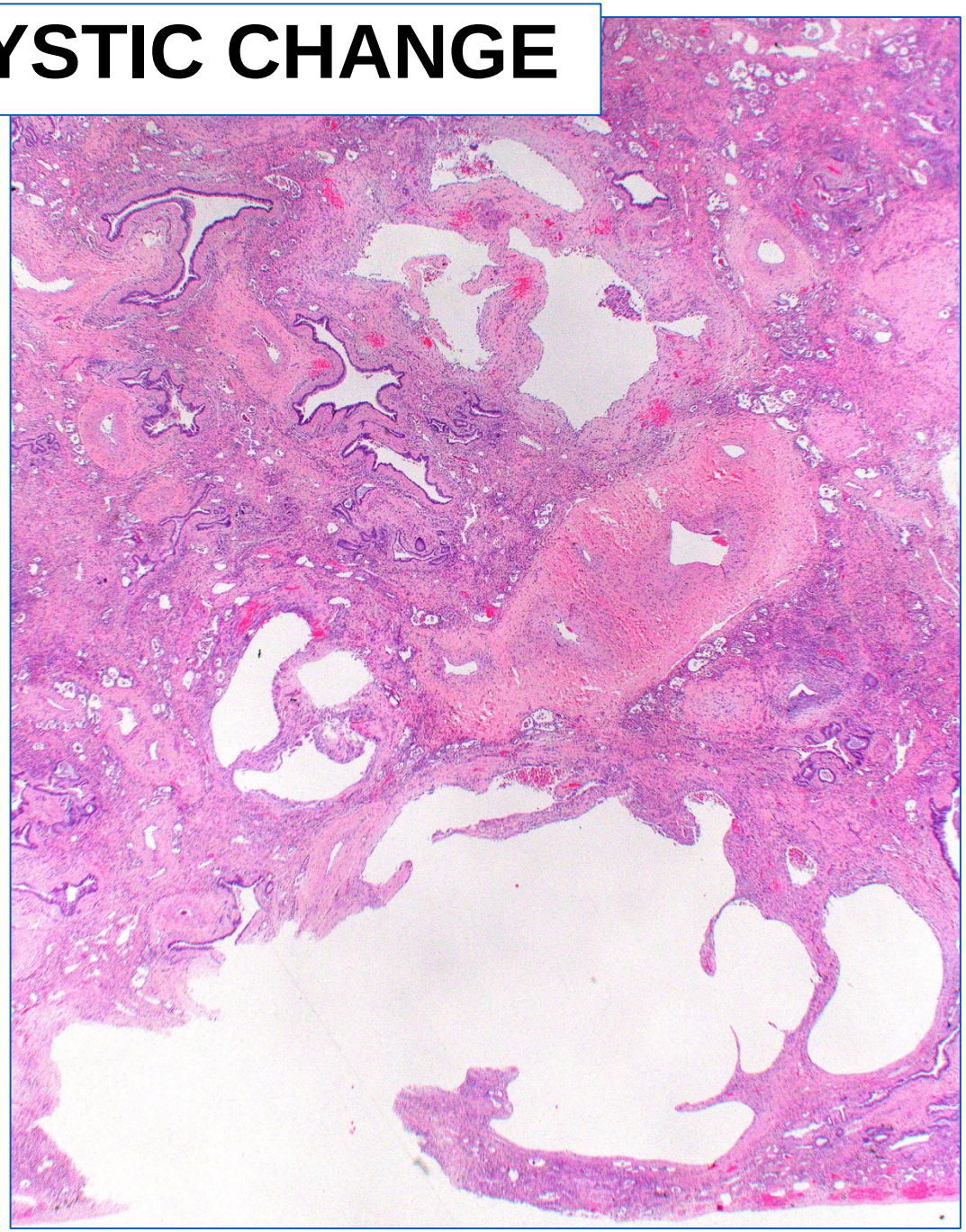
FIBROTIC LATE DAD-NSIP LIKE WITH OP

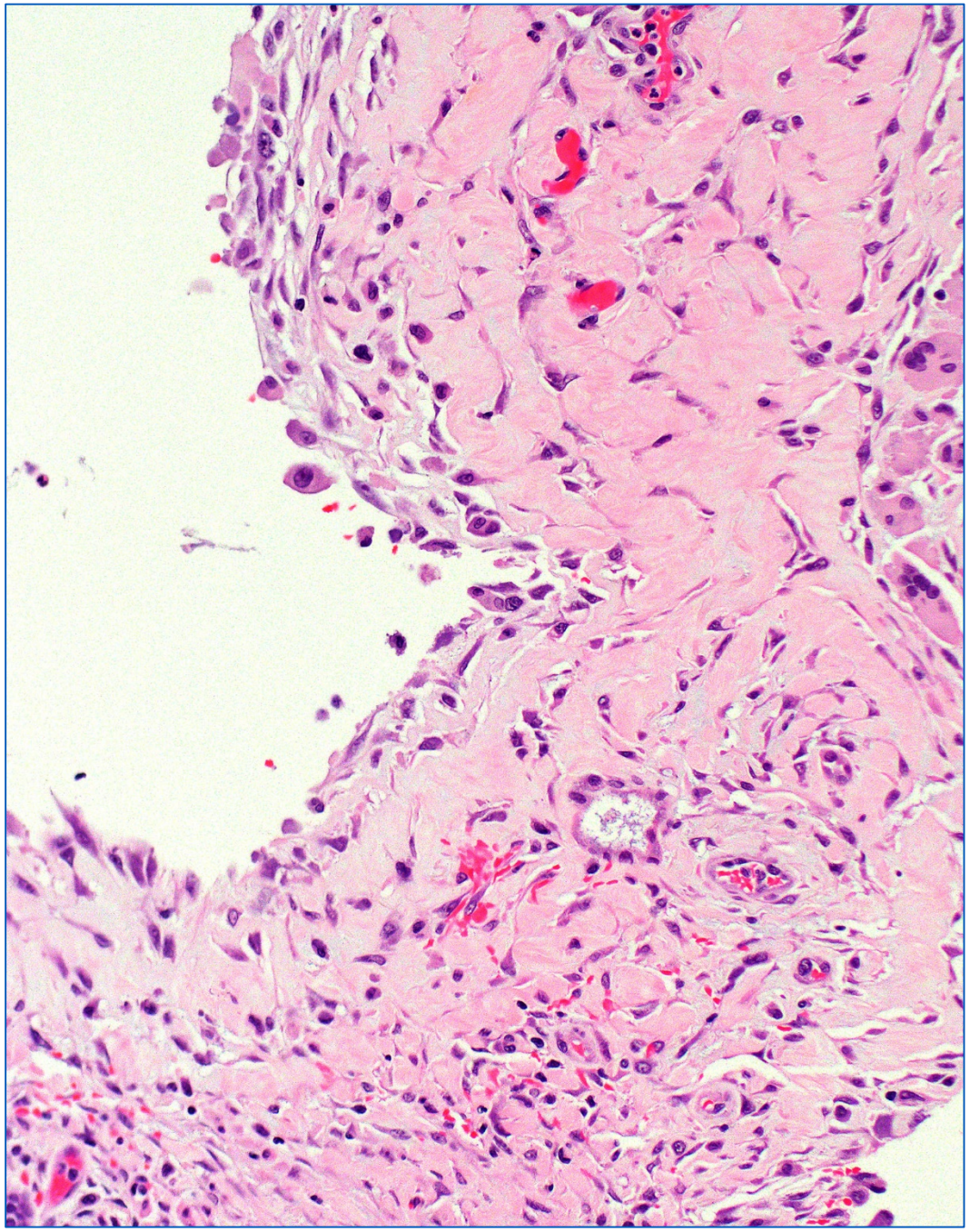


FIBROTIC LATE DAD-NSIP LIKE WITH OP



CYSTIC CHANGE





UIP IN POST COVID LUNG BIOPSIES

- 18 surgical lung bx 30 - 365 days (mean145, Jan 20-Apr 21))
- Persistent ILD post acute COVID-19

Pattern	%
UIP def, probable; (with ALI)	8 (2)
UIP indeterminate	1
DAD, acute or with fibrosis	3
Chronic bronchiolitis with OP	2
DIP, Bronchopneumonia, non-specific abnormalities	4

- Conclusion: UIP unmasked by COVID-19

Konopka KE et al EClinicalMedicine 2021: 42:101209

CONCLUSIONS

- COVID related pathology very similar to other forms of lung injury
- ALI can be seen up to 10 months post infection
- PCR may be positive for extended periods of time, suggesting virus may be active for extended time
- Some ALI could be secondary to treatment e.g. remdesivir, ECMO

©2021 Mayo Foundation for Medical Education and Research

CONCLUSIONS

- “Fibrosis” encompasses a variety of entities
- Some are reversible, some are not
- Patterns of fibrosis provide clues to reversibility and possibly etiology
- Long term COVID pathology shows nonreversible patterns

©2021 Mayo Foundation for Medical Education and Research

Questions and Answers



LUNG TRANSPLANTATION FOR CYSTIC FIBROSIS: A COMPLEX AND CHANGING LANDSCAPE

Sofya Tokman, MD

- Associate Professor of Medicine, Creighton School of Medicine
- Director of Eller Lung Transplant Clinic
- Director of LAM Clinic
- Norton Thoracic Institute, Dignity Health, St. Joseph Hospital and Medical Center, Phoenix, AZ

Disclosures

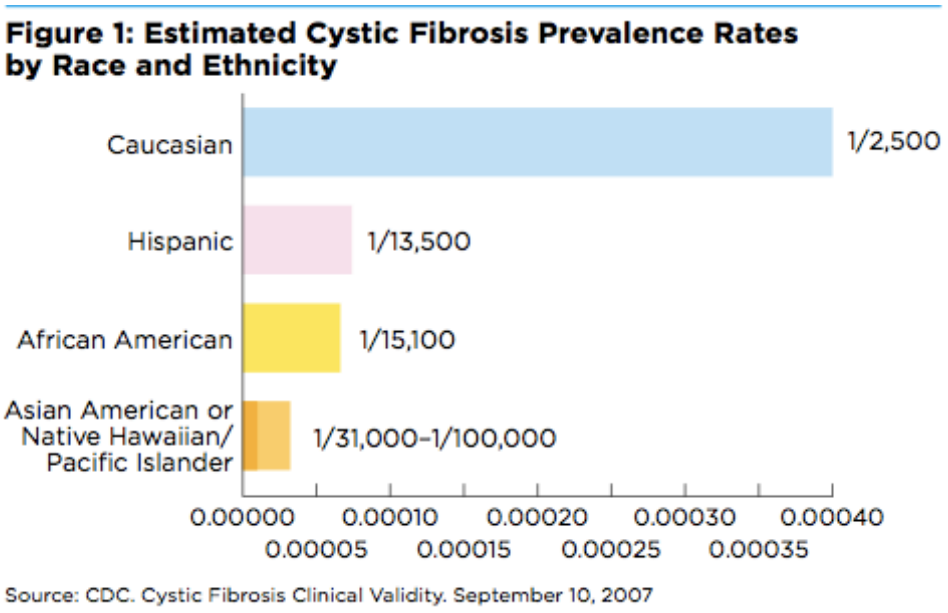
- None

Outline

- Epidemiology of CF
- Timing of LTx referral and listing
- Role of CFTR modulators
- Challenging respiratory infections
- Extra-pulmonary considerations

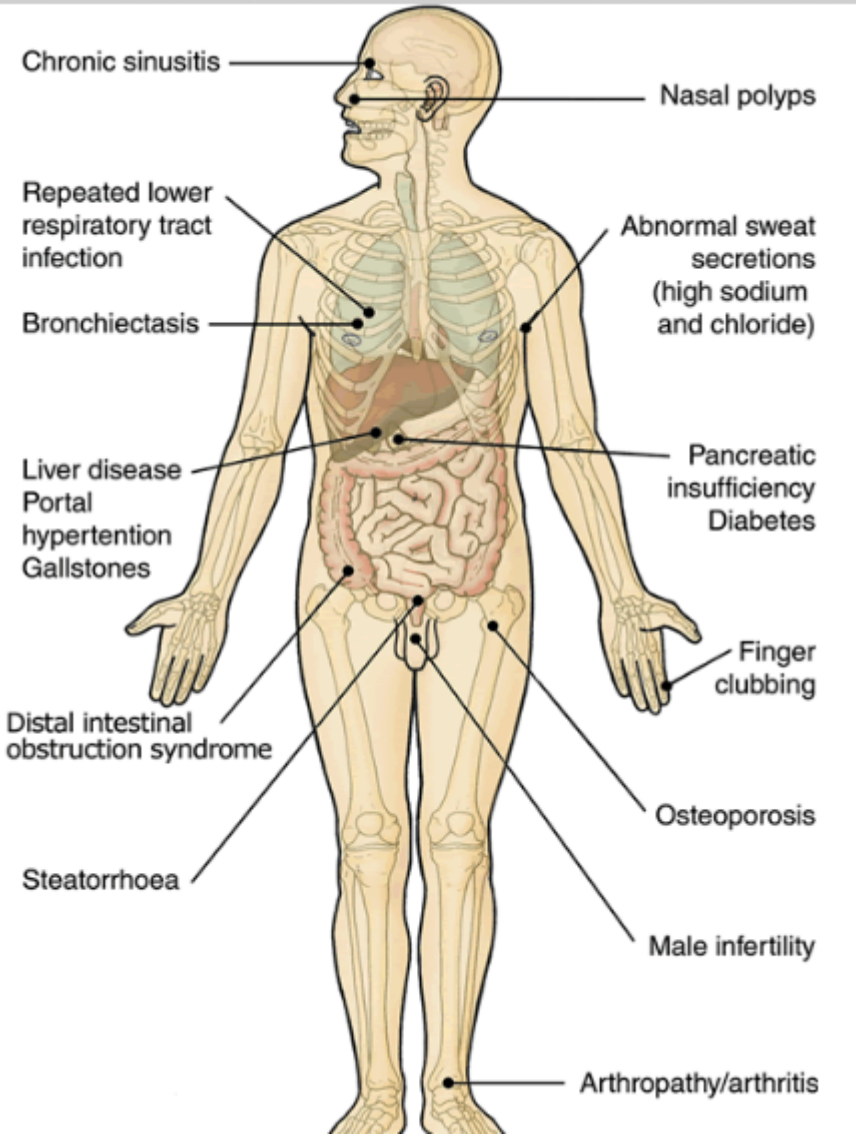
Epidemiology of CF

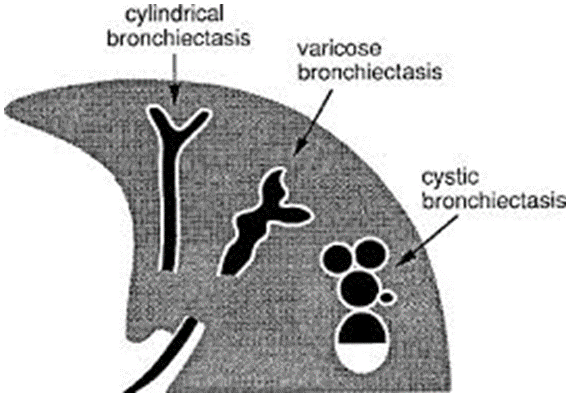
- The most common life-shortening, inherited disorder among Caucasians in the US.
- Results from dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein.
- ~30,000 Americans have CF, and there are ~1,000 new cases diagnosed each year.

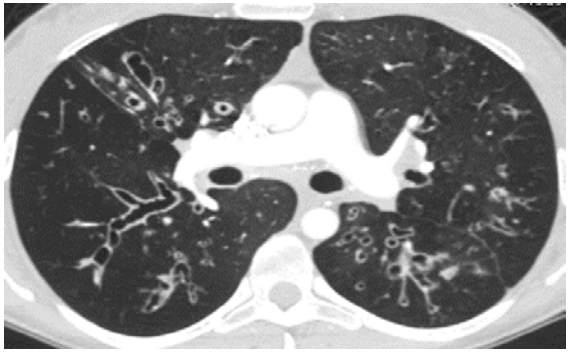


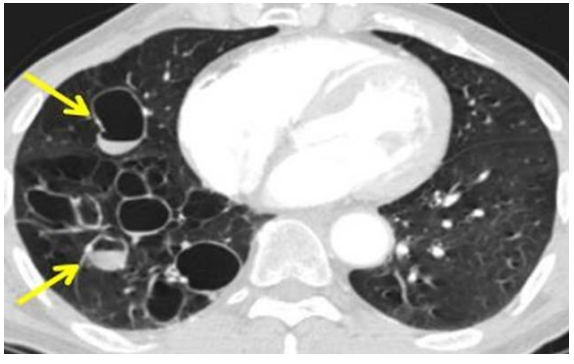
Centers for Disease Control and Prevention. Newborn Screening for Cystic Fibrosis. Morbidity and Mortality Weekly Report.October 15, 2004; 53(RR13):1-36

CFTR Dysfunction = Systemic Complications









Timing of Lung Transplant Referral

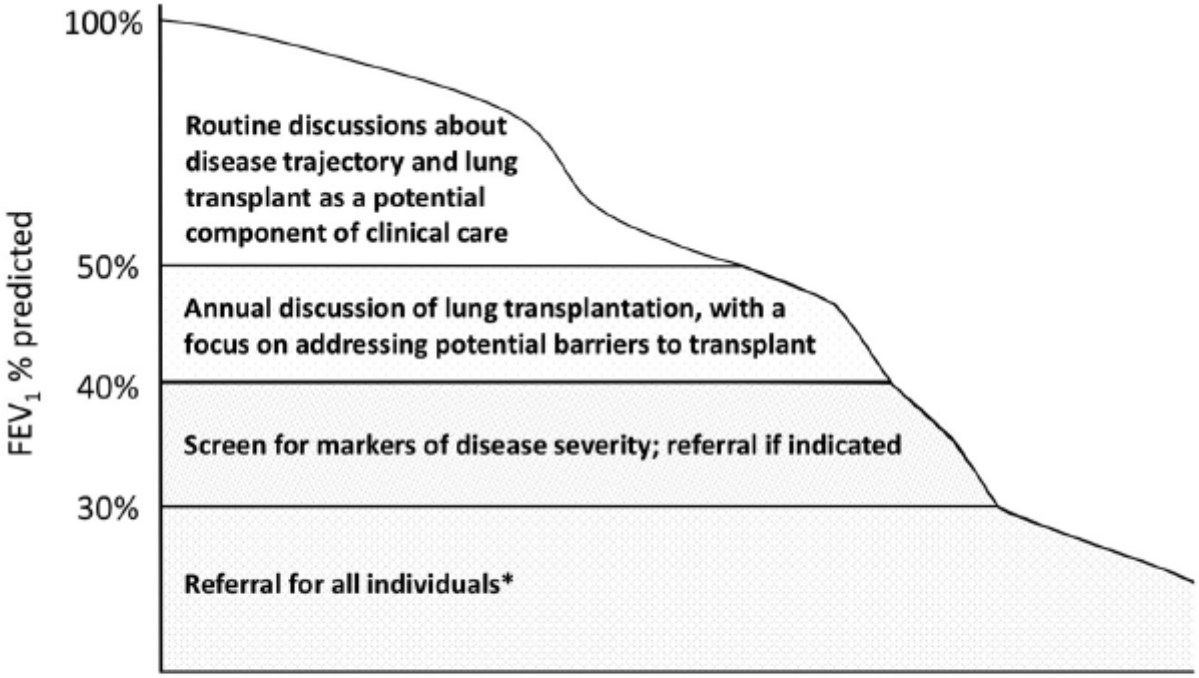


Fig. 1. Lung function thresholds for discussion of lung transplantation and timing of lung transplant referral.

Timing of Lung Transplant Referral: CF Foundation Recommendations

Age	Lung Function	Markers of Shortened Survival
≥18 years	• FEV1 <50% and rapidly declining (>20% in 12mo) • FEV1 <40% with markers of shortened survival • FEV1 <30%	• 6MWD < 400 m • Hypoxemia • Hypercarbia (>50 mmHg) • Pulmonary hypertension (PASP>50 mmHg on TTE or evidence of RV dysfunction) • BMI <18 • >2 exacerbations/year requiring IV abx or 1 exacerbation requiring PPV • Massive hemoptysis requiring ICU admission or bronchial artery embolization • Pneumothorax
<18 years	• FEV1 <50% and rapidly declining (>20% in 12mo) • FEV1 <50% with markers of shortened survival • FEV1 <40%	

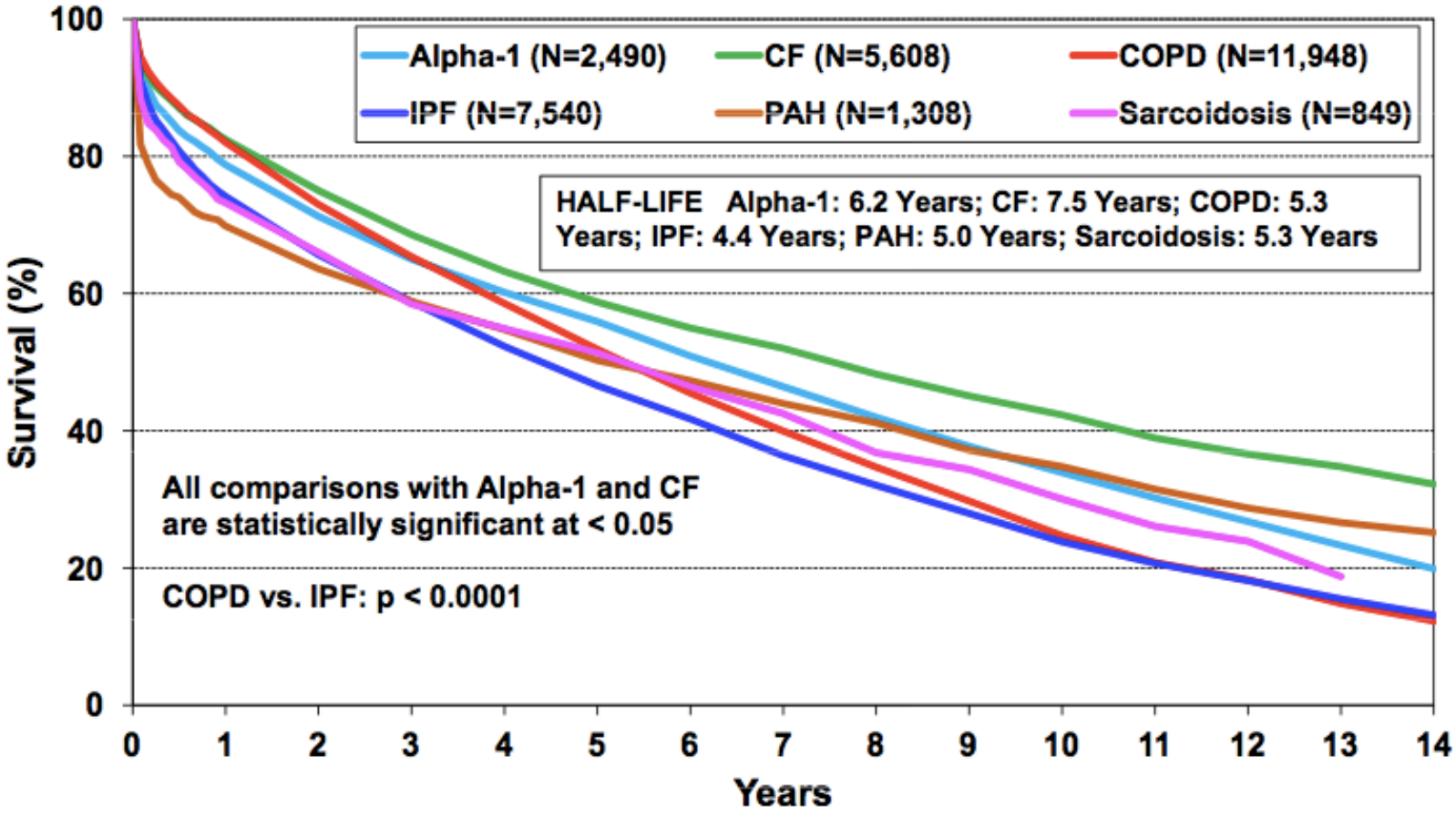
Pneumothorax in CF

- 3-5% of patients with CF have at least 1 pneumothorax.
  - Results from sub-pleural alveolar hyperinflation due to air-trapping.
- More common in patients with advanced lung disease.
- If pneumothorax life threatening or recurrent: pleurodesis
  - Anecdotaly, Talc pleurodesis leads to more dense adhesions and scarring with increased risk of intraoperative bleeding, phrenic nerve injury, and chest wall restriction.
    - Starting Feb 2023, transplant programs will have to report whether the recipient's prior pleurodesis was talc, doxy, or mechanical.

Timing of Lung Transplant Listing

- FEV1 < 25%
- Rapid decline in lung function or progressive symptoms (>30% decline in FEV1 over 12 months)
- Frequent hospitalization (esp if hospitalized > 28 days in the preceding year)
- Any exacerbation requiring mechanical ventilation
- Chronic respiratory failure with hypoxemia or hypercapnia (esp with increasing oxygen requirements or needing long-term NIPPV)
- Pulmonary hypertension (PASP> 50 mmHg on TTE or RV dysfunction)
- Worsening nutritional status (esp if BMI < 18 despite nutritional interventions)
- Recurrent massive hemoptysis despite bronchial artery embolization
- WHO functional class IV

Survival Among Lung Transplant Recipients with CF



Christie JD, et al. International Society of H, Lung T. The Registry of the International Society for Heart and Lung Transplantation: 29th adult lung and heart-lung transplant report-2012. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation* 2012; 31: 1073-1086.

CFTR Function

- Mainly a chloride channel
- Sweat glands: CFTR reabsorbs chloride
  - In CF: impaired chloride absorption → elevated sweat chloride
- Epithelial cells lining the airways: CFTR secretes chloride, which, in combination with sodium, draws moisture into the airway (airway surface liquid)
  - In CF: reduced airway surface liquid → thick dehydrated mucous, impaired ciliary function, and reduced mucociliary clearance

Classification of Gene Mutations Causing CF

Class 1	CFTR protein synthesis is defective or absent	CFTR is not produced	G542X
Class 2	CFTR misfolded	Misfolded CFTR is degraded and doesn't reach cell surface	F508del
Class 3 "Gating Mutations"	CFTR activation by ATP or cAMP is impaired	CFTR reaches cell surface, but gating is impaired (open time reduced)	G551D
Class 4	CFTR function is impaired	CFTR reaches cell surface, but chloride transport is impaired	R334W
Class 5	CFTR synthesis reduced	Reduced # of CFTR channels on cell surface	R117H
Class 6	CFTR turnover accelerated	Reduced # of CFTR channels on cell surface	118+1.6kb A>G

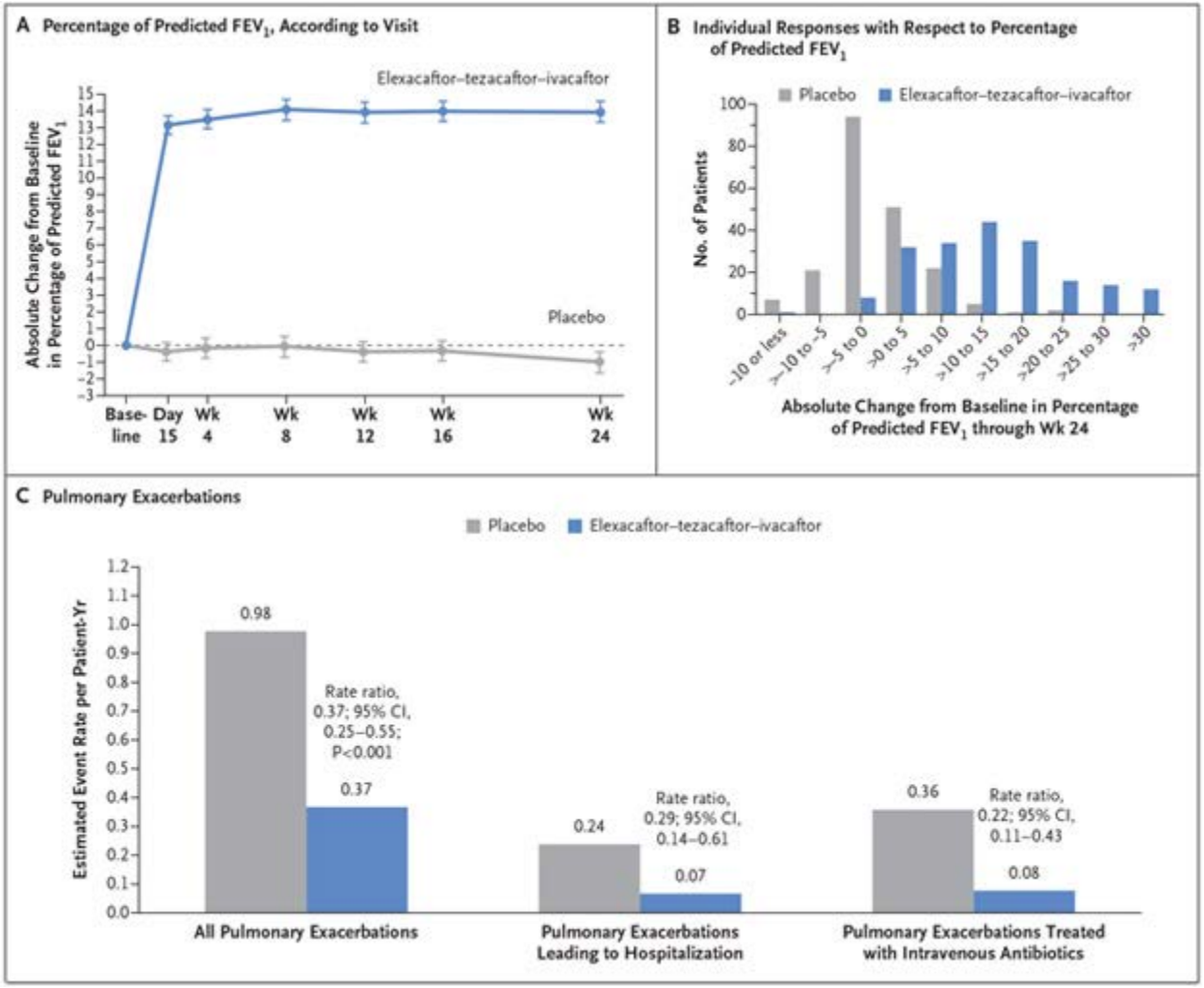
CFTR Modulators as Therapy for CF

Potentiator	Binds to CFTR on cell surface and opens the chloride channel	ivacaftor
Corrector	Helps the CFTR protein fold, traffic to the cell surface, and stay there longer.	Lumacaftor Tezacaftor Elexacaftor

CFTR Modulators as Therapy for CF

ivacaftor (Kalydeco®)	>6 mo old with gating mutations
lumacaftor/ivacaftor (Orkambi®)	>2 years old, f508del homozygous
tezacaftor/ivacaftor (Symdeko®)	>6 years old, f508del homozygous >6 years old, f508 del heterozygous + 1 of 26 specified mutations
elexacaftor/tezacaftor/ivacaftor (Trikafta™)	>6 years old with at least 1 f508del

Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele



Efficacy and safety of the elexacaftor/tezacaftor/ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial

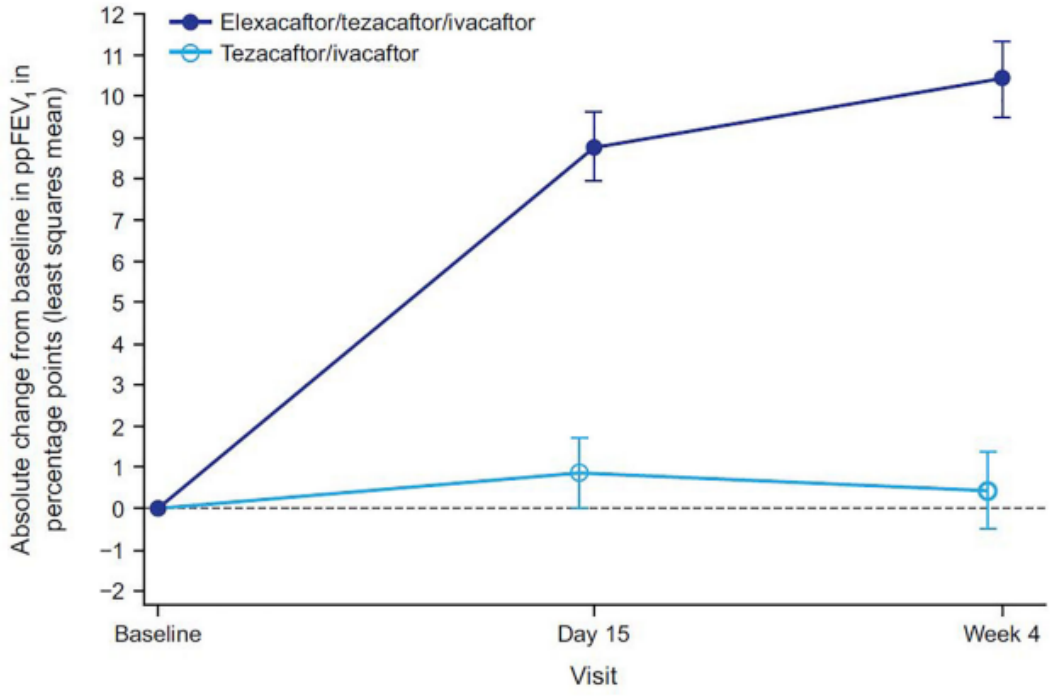
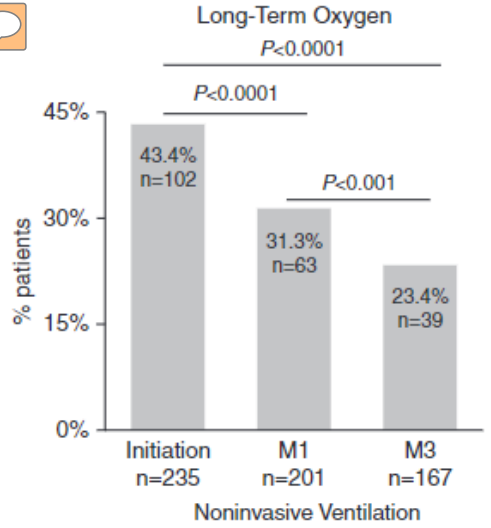
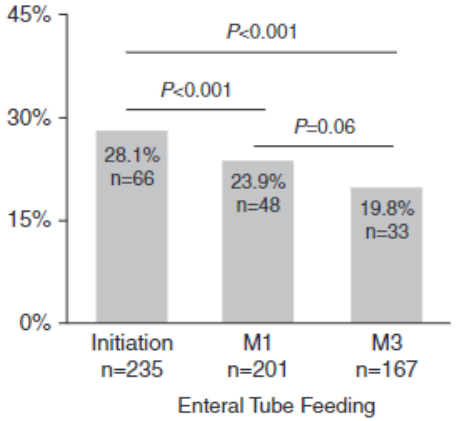


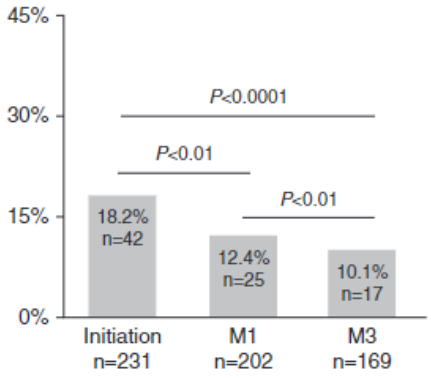
Figure 2. Absolute Change Over Time in Percent Predicted Forced Expiratory Volume in 1 Second ($ppFEV_1$) From Baseline.
Data are least squares means based on a mixed-effects model for repeated measures, and error bars indicate standard errors; the dashed line indicates no change from baseline (measured at the end of the tezacaftor/ivacaftor run-in).

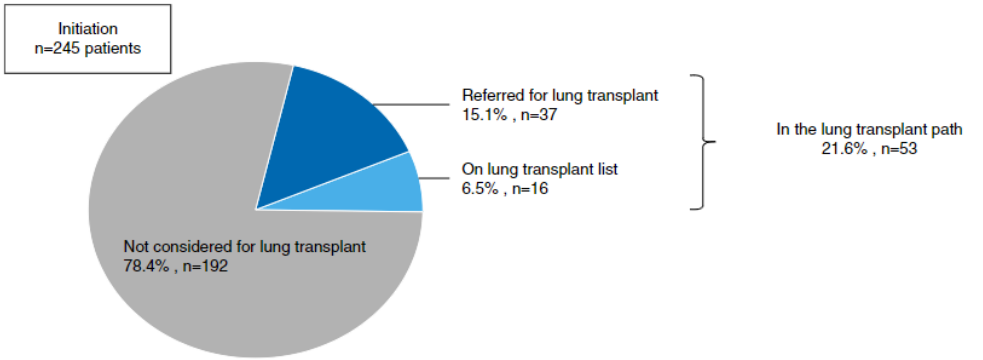
Rapid Improvement after Starting Elexacaftor/Tezacaftor/Ivacaftor in Patients with CF and Advanced Pulmonary Disease

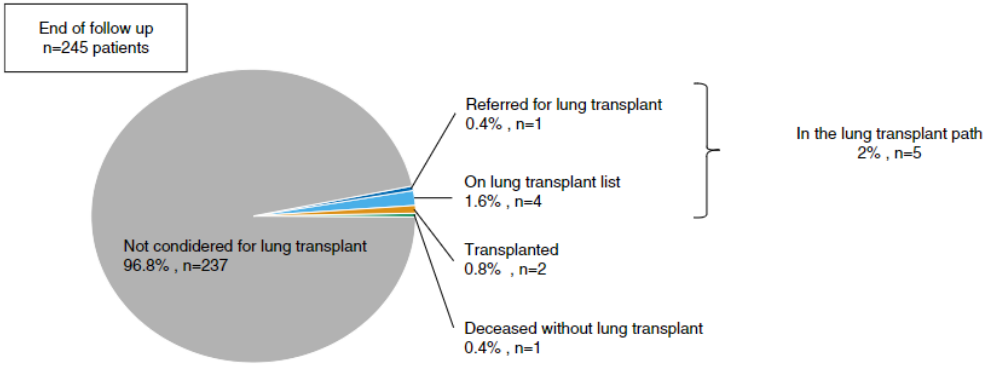
- A prospective observational study: >12 years old, FEV1<40% who initiated elexacaftor/tezacaftor/ivacaftor b/w December 2019 and August 2020 in France





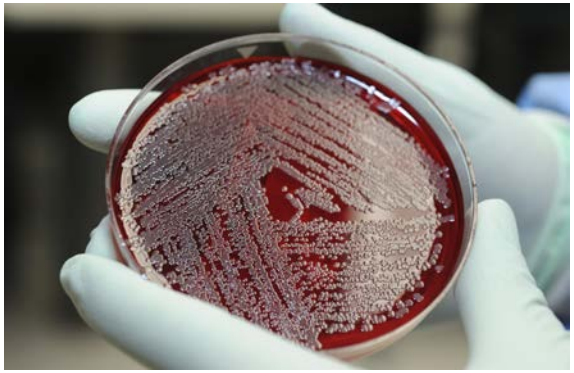


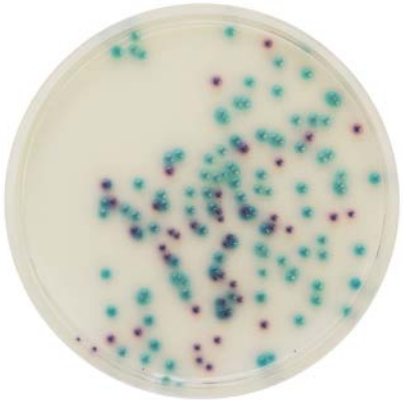




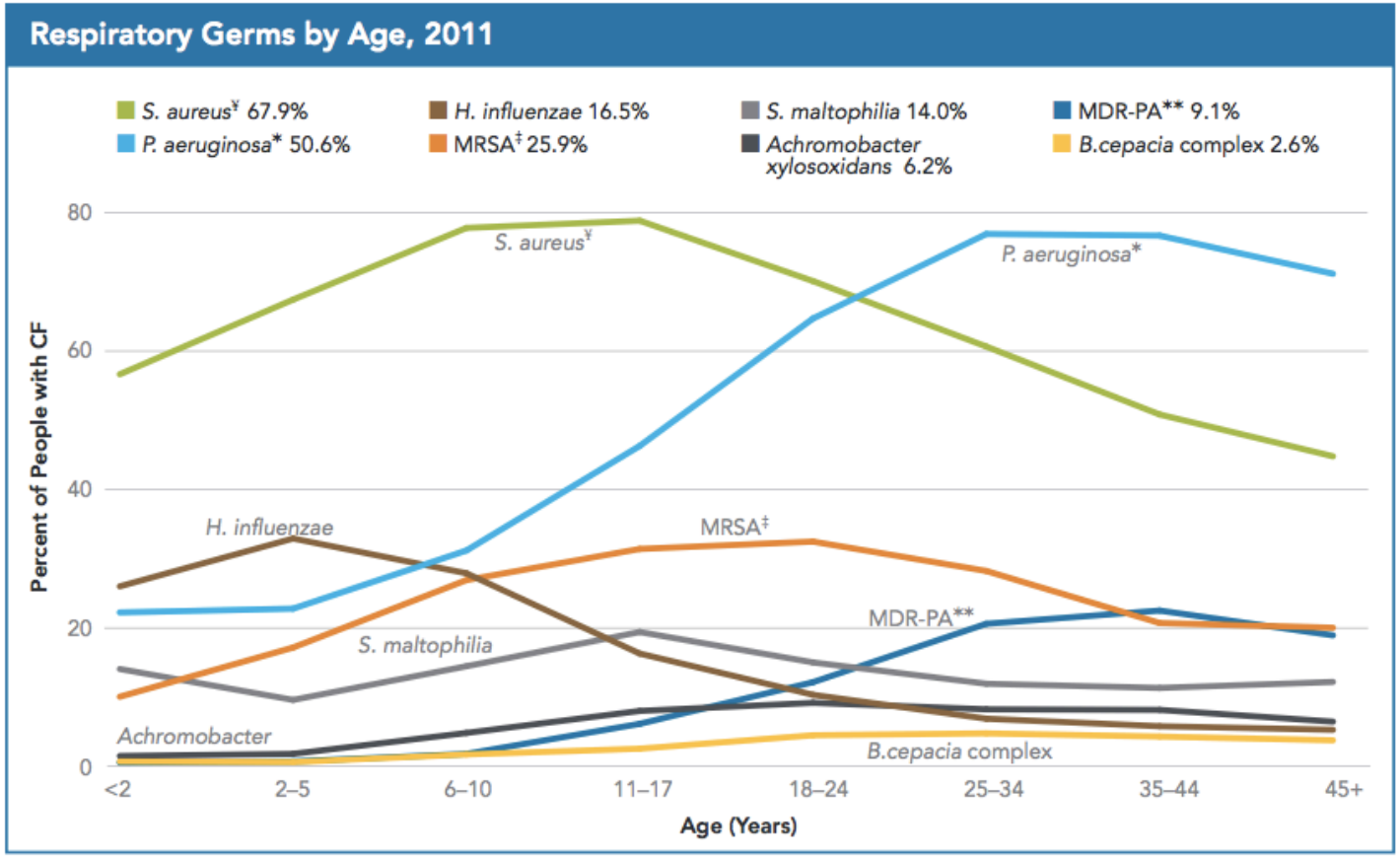
Difficult to Treat Infections







Respiratory pathogens in CF



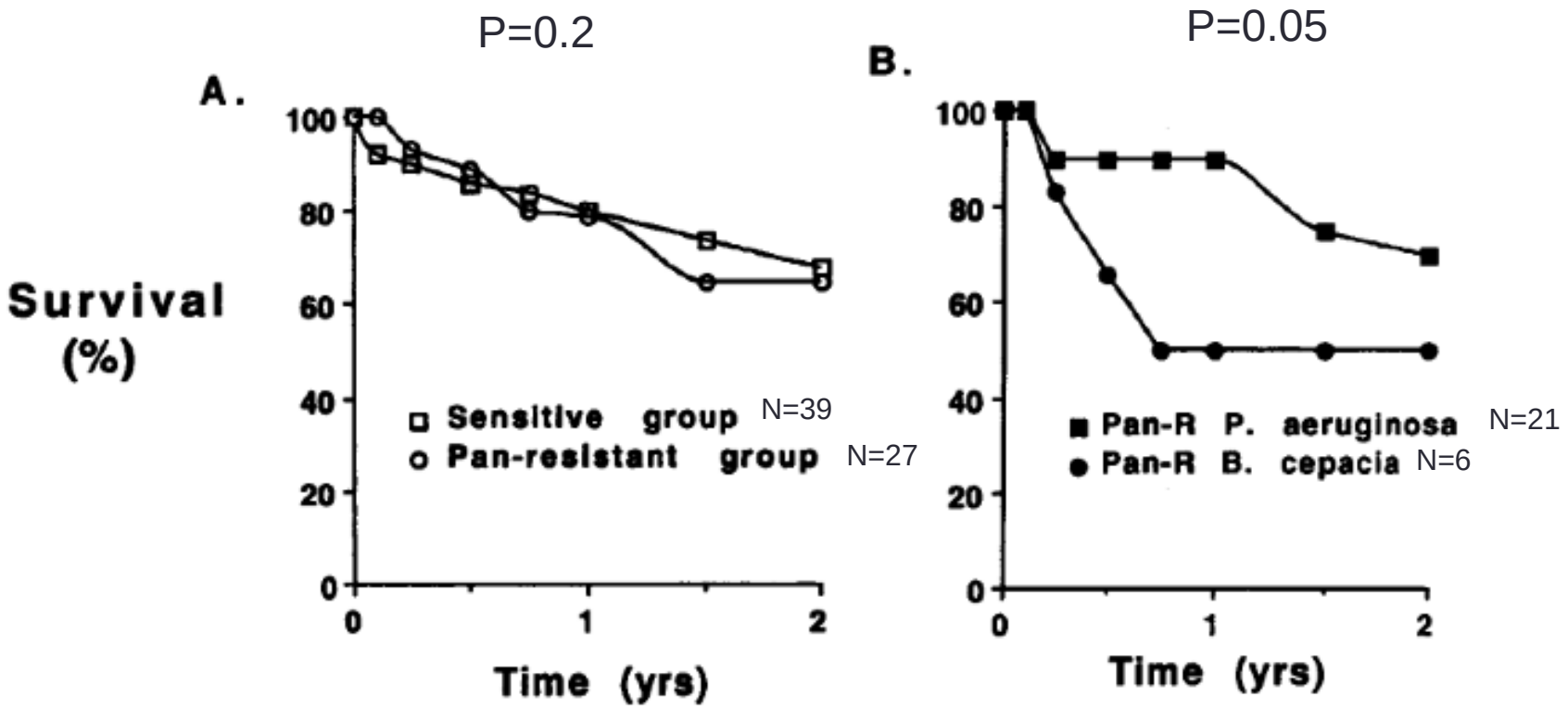
*P. aeruginosa *includes people with MDR-PA.*

***MDR-PA is multi-drug resistant* Pseudomonas aeruginosa (P. aeruginosa).**

¥S. aureus *includes people with MRSA.*

‡*MRSA is methicillin-resistant* Staphylococcus aureus (S. aureus).

Non-BCC Pan-resistant Microbes are NOT Associated with Worse Lung Transplant Outcomes



Aris RM, et al. The effects of panresistant bacteria in cystic fibrosis patients on lung transplant outcome. *American journal of respiratory and critical care medicine* 1997; 155: 1699-1704.

Burkholderia cepacia complex infection in CF

- Glucose non-fermenting GNR
- Found in soil, water, on plant surfaces, and in home environment (vegetable drawer!)
- Transmitted from person to person
- Resistant to antibiotics even before antibiotic exposure
- Most common species in CF:
  - *B. cepacia*
  - ** B. cenocepacia*
  - *B. multivorans*
  - *B. vietnamiensis*
  - *B. dolosa*
  - B. *stabilis*

* Multiple strains of B*. cenocepacia:* ET12, PHDC, Midwest clone. ET12 (most common in Ontario Canada and the UK) is most virulent.

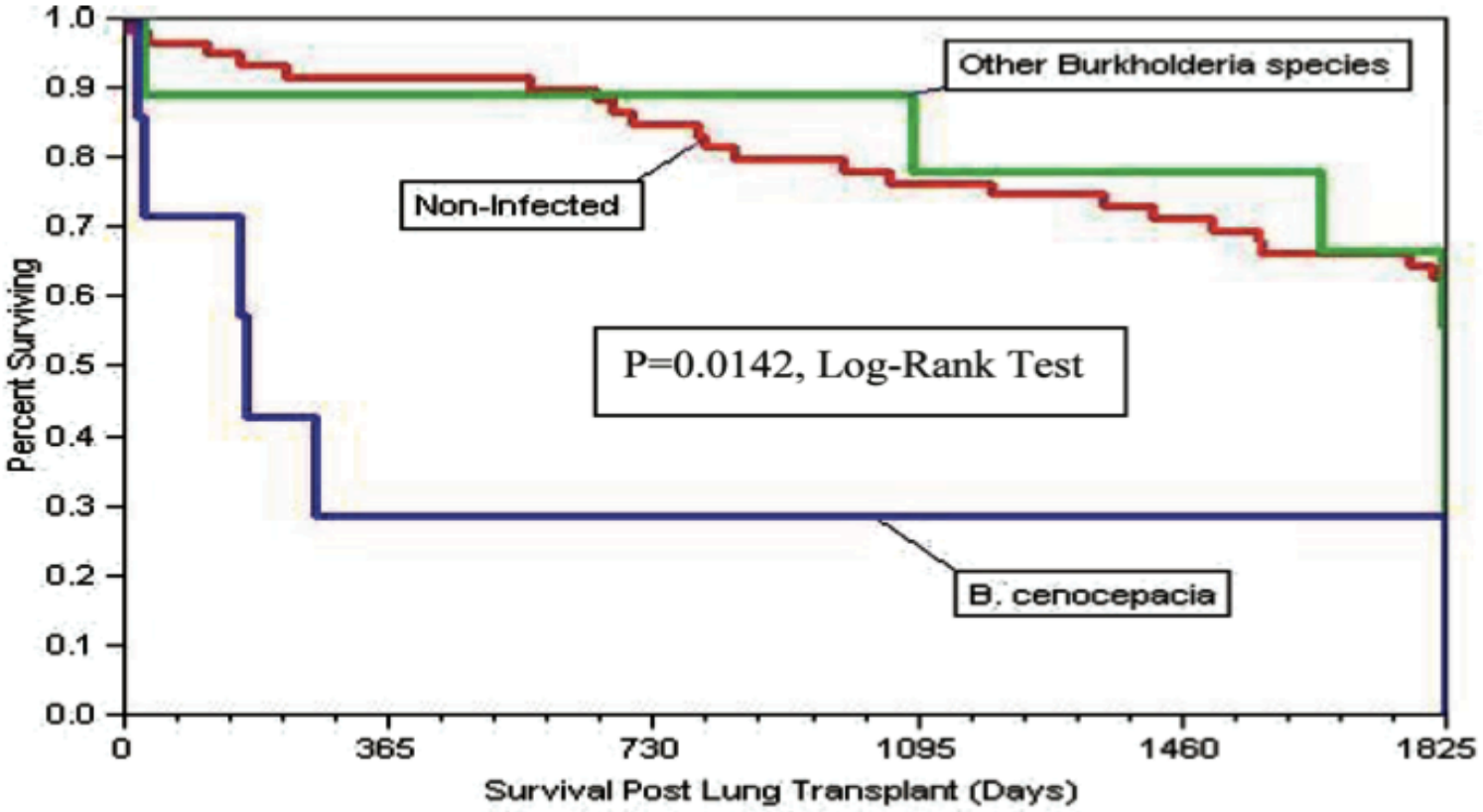
Mahenthiralingam E, Urban TA, Goldberg JB. The multifarious, multireplicon Burkholderia cepacia complex. *Nature reviews Microbiology* 2005; 3: 144-156.

Burkholderia cepacia complex: "Cepacia syndrome"

- High Fevers
- Bacteremia
- Necrotizing pneumonia: cavities, empyema
- Most commonly caused by *B. cenocepacia*, but also seen with *B. multivorans,* and *B. dolosa*
- *B. cenocepacia* has been associated with post-transplant infections and increased mortality especially within the first 6-12 months.



Survival After Lung Transplantation Varies Between Different Species of *BCC*



Nontuberculous Mycobacteria in CF

Nontuberculous mycobacteria

M. *avium* complex

(M. avium, M. intracellulare)

- Slow grower (>7 days to grow in culture)
- Patients tend to be older with better lung function

M. *abscessus* complex

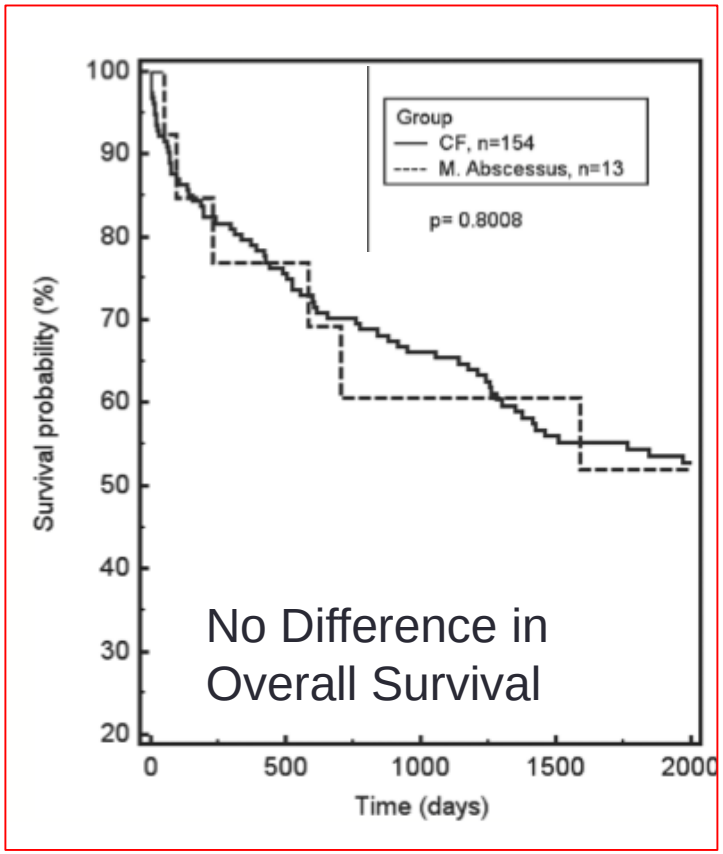
(M. abscessus, M. bolletii, M. massiliense)

- Rapid grower (<7 days to grow in culture)
- Erm gene: macrolide resistance
- More common in children
- Leads to lung function decline
- Associated with higher mortality
- Mostly acquired from environmental exposure
  - patient-to-patient and fomite-related transmission

Slide courtesy of Dr. Valerie Waters

M. *Abscessus* Infection in Lung Transplant Recipients with CF

- 13 patients with CF and pre-transplant M. *abscessus* infection
- 11 treated with antibiotics prior to LTx
  - 8 did not clear their infection prior to LTx
- 3 developed M. *abscessus* related complications:
    - Mediastinal abscess
    - Sternal osteomyelitis
    - Empyema
- None of the deaths were related to NTM infection.



CF Foundation's Recommendation for Lung Transplantation in Patients with CF and M. *Abscessus* Infection

- Recommendation 46: Patients with current or past NTM infection can still be considered for transplant.
- Recommendation 47: Treatment of NTM should commence treatment prior to transplant listing.
- Recommendation 50: The presence of persistent M. abscessus complex infection despite optimal therapy is not an absolute contraindication to lung transplant referral.

Bilton et al. Cystic Fibrosis Foundation and European Cystic Fibrosis Society Guidelines for the Management of Nontuberculous Mycobacteria in Individuals with Cystic Fibrosis. 2014

Fungal Infection/Colonization in CF

- **Aspergillus:**
  - *Aspergillus spp :* 20-50% of sputum cultures among CF patients awaiting LTx.
  - Pre-LTx colonization with *Aspergillus* increases risk of *Aspergillus* tracheobronchitis and anastomotic infections after LTx.

- **Scedosporium:** *Scedosporium apiospermum & Lomentospora prolificans*
  - Less common than *Aspergillus* species
  - S. apiospermum: resistant to amphotericin
  - L. prolificans may be associated with worse outcomes after LTx.
    - intrinsic resistance to most of the available antifungal agents
    - Synergy between voriconazole and terbenifine

Pre-LTx Colonization with *Scedosporium/Lomentospora spp*

- 9 patients with *Scedosporium spp* colonization before LTx:
  - 8 *apiospermum* ,1 *L. prolificans*
- All of the patients colonized by *S. apiospermum* before LTx became free of *Scedosporium* colonization with antifungal prophylaxis pre and post-LTx
  - None of the patients colonized by *S. apiospermum* before transplantation developed scedosporial disease.
- The patient colonized by *L. prolificans* developed a scedosporial invasive disease

Pre-LTx Colonization with *Scedosporium/Lomentospora spp*

- *Scedosporium apiospermum* or *Lomentospora prolificans* may lead to severe disseminated infections after LTx.
- For *S. apiospermum*, acceptable results have been observed, while *L. prolificans* still seems to incur a substantially higher risk due to its resistance patterns.

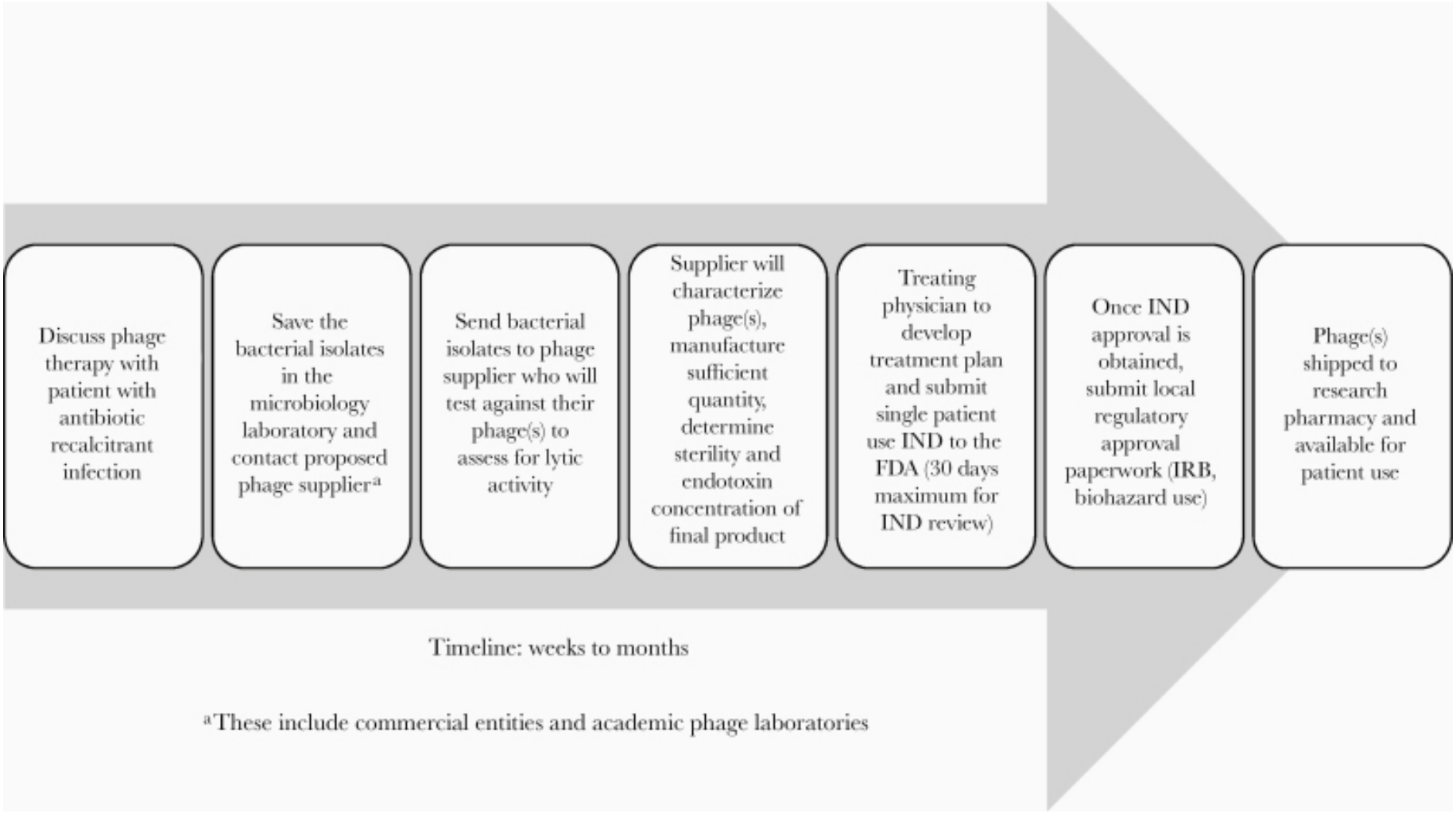
Bacteriophage Therapy

- Bacteriophages
  - Viruses that infect specific bacterial hosts
  - Commandeer reproductive machinery of bacteria to divide
  - Destroy the bacteria, split it open, and release new viral particles that infect more bacteria
- Phage therapy fell out of favor in the U.S. and most of Europe with the advent of antibiotics
  - Continued in regions where antibiotics were not as easily accessed — Russia, Poland and the Republic of Georgia
- Advantages over antibiotics:
  - Bacteria specific (allows for preservation of microbiome)
  - If bacterial resistance develops, can chose a different phage
- Risks:
  - Septic shock as bacteria release endotoxin at the time of lysis

Bacteriophage Therapy

- 2016: UC San Diego School of Medicine used IV phage therapy to treat and cure colleague Tom Patterson, PhD, from a MDR bacterial infection.
- Center for Innovative Phage Applications and Therapeutics (IPATH) at UC San Diego was created
- 2020: IPATH published data from 10 cases of IV bacteriophage therapy to treat MDR bacterial infections.
  - Successful outcome In 7 of 10 cases
- Patients treated with a combination of phage and systemic antibiotics
- Phages administered IV, nebulized, intra-articular, percutaneously into abdominal drains

Bacteriophage Therapy



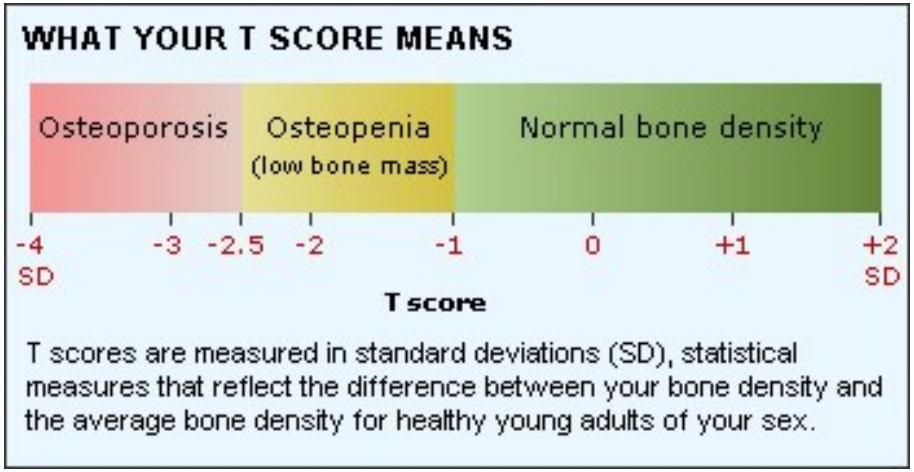
Bacteriophage Therapy

Patient	Infection	Organism	Phage Therapy	Time from Request to Phage therapy	Outcome
68 yo M	Pancreatic pseudocyst + abdominal abscesses	Acinetobacter baumanii	IV + PC (into drains) x 18 weeks	21 days	Success
67 yo M	Pneumonia in LTxR	Pseudomonas aeruginosa	IV and nebulized x 16 weeks	22 days	Success
77 yo M	Sub + epidural empyema + cranial osteo	Acinetobacter baumanii	IV x 8 days	12 days	? (hospice)
26 yo F	Pneumonia in CF	Pseudomonas aeruginosa	IV x 8 weeks	23 days	Success
60 yo M	VAD infection	Pseudomonas aeruginosa	IV x 6 weeks	37 days	Failure
65 yo M	VAD infection	Staph aureus	IV x 4 weeks	28 days	Success
61 yo F	Prosthetic joint	Staph aureus	IV and intra-articular x 8 weeks	28 days	Success
82 yo M***	VAD infection	Pseudomonas aeruginosa	IV and 1 time intra-op x 13 weeks	58 days	Failure
56 yo M	Recurrent UTI in liver transplant	E Coli.	IV x 2 weeks	355 days	Success
64 yo M	Aortic graft infection	Pseudomonas aeruginosa	IV x 6 weeks	374 days	Success

***Phage related adverse outcomes: (1/10 patients) fever and wheezing, resolved by lowering phage concentration

Systemic Complications of CF

Osteoporosis in CF



T-score = Bone mineral density compared to normal 30 year old of the same sex. Score is assigned based upon # of standard deviations the patients bone density is above or below the control.

Z-score = Bone mineral density compared person of the same age, sex, weight, and ethnic or racial origin. Score is assigned based upon # of standard deviations the patient's bone density is above or below the control.

Normal bone density: T-score > -1
Osteopenia: T-score b/w -1.0 and -2.5
Osteoporosis: T-score ≤ -2.5

Osteoporosis in CF: Epidemiology and Risk Factors

- Epidemiology:
  - Rates of osteopenia and osteoporosis may be as high as 69% and 57%
  - Incidence of bone disease increases with age and severity of lung disease.
  - Adults with CF have higher fracture rates than the general population.

- Risk factors:
  - Delayed puberty/hypogonadism
  - Malabsorption of vitamin D
  - Poor nutritional status
  - Physical inactivity
  - Corticosteroid therapy
  - Chronic inflammation

Treatment of Osteoporosis

Treatment for DXA T/Z score ≥ -1.0

Recommendations	Evaluation of the Evidence
2. Improve nutritional status: a. Optimize vitamin D[2] calcium[3] and vitamin K supplementation[3] b. Achieve a target body mass index > 25th c. Encourage outdoor weight-bearing exer	
Repeat DXA every five years	

Treatment for D

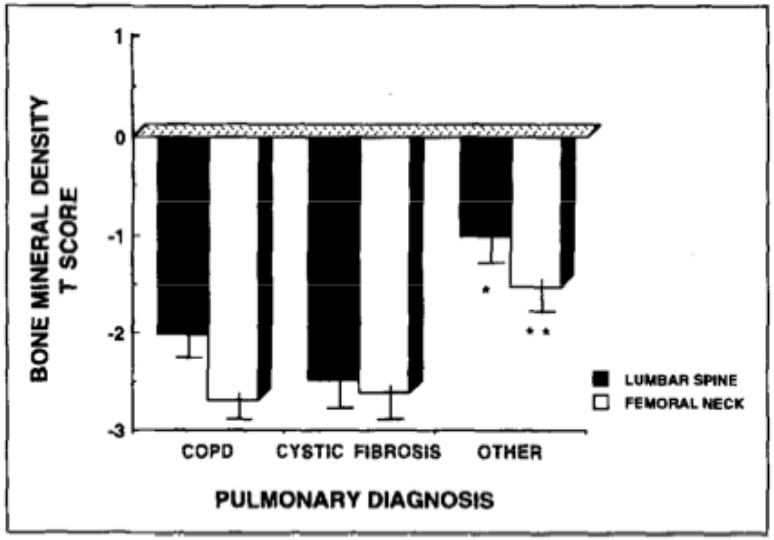
Recommendations
4. Improve nutritional status as above
5. Address potential pulmonary and endoc a. Aggressive pulmonary infection treatme b. Minimize steroid dosing c. Treat CF-related diabetes[4], delayed pub d. Endocrine referral e. If fragility fractures have occurred, patie or BMD loss is > 3-5 percent per year, st
6. Repeat DXA two to four years

Treatment for T/Z score ≤ -2.0

Recommendations	Evaluation of the Evidence
7. Improve nutritional status as above	
8. Address potential pulmonary and endocrine pathology as above	
9. Consider bisphosphonates[6] a. Oral: Alendronate 70 mg weekly (or 10 mg daily) i. Risendronate 35 mg weekly (or 5 mg daily) b. IV: Pamidronate 30 mg in 500 ml saline infused over three hours every three months c. Zoledronic acid 4-5 mg infused over 15-20 minutes yearly d. Zoledronic acid 2 mg every three months for two years	Grade: I Grade: I Grade: I Grade: III Grade: I
Annual DXA	

Osteoporosis In Lung Transplant Candidates with CF

- Trombetti et al:
  - 42 patients, 17 with COPD, 8 with CF
  - Patients with COPD or CF had lower bone mineral density as compared with other diseases
- Shane et al:
  - 70 patients, 28 with COPD, 11 with CF
  - Transplant candidates with COPD and CF had lower bone mineral density than “Other” patients.
  - Prevalence rate of vertebral fracture was 29%in COPD and 25% in CF.



Malignancy in CF

CF is Associated with Increased Risk of Digestive Tract Cancers

Cancer Risk in Cystic Fibrosis: A 20-Year Nationwide Study From the United States

Patrick Maisonneuve, Bruce C. Marshall, Emily A. Knapp, Albert B. Lowenfels

Table 4. Observed and expected post-transplant cancers and standardized incidence ratios (SIRs) among cystic fibrosis patients after transplantation in the United States during the periods from 1990 to 1999 and from 2000 to 2009*

Site (ICD-9 code)	Ol c
All but skin (140–208, excl. 173)	
Digestive organs (150–159)	
Esophago-gastric (150, 151)	
Esophagus (150)	
Small intestine (152)	
Colon (153)	
Rectum (154)	
Liver (155)	
Gallbladder, extrahepatic bile ducts (156)	
Other digestive organs (158, 159)	
Female reproductive organs (179–184)	
Prostate (185)	
Kidney (189)	
Thyroid gland (193)	

Table 5. Observed and expected post-transplant cancers and standardized incidence ratios (SIRs) among cystic fibrosis patients after transplantation in the United States during the combined period (1990–2009)*

Site (ICD-9 code)	Observed cancers	Expected cancers	SIR (95% CI)	AER/100 000 person-years	Time between transplant and cancer, years
All but skin (140–208, excl. 173)	26	9.6	2.7 (1.8 to 3.9)	199.5	
Digestive organs (150–159)	19	1.1	17.3 (10.7 to 26.5)	217.4	
Esophago-gastric (150, 151)	2	0.2	13.2 (2.2 to 43.8)	22.5	3,10
Esophagus (150)	2	0.06	35.8 (6.0 to 118.0)	23.6	3,10
Small intestine (152)	2	0.04	52.5 (8.8 to 175.0)	23.8	5,5
Colon (153)	11	0.4	30.1 (15.8 to 52.2)	129.1	1,1,1,4,4,5,7,7,8,8,9
Rectum (154)	1	0.3	3.5 (0.2 to 17.3)	8.7	1
Liver (155)	1	0.09	11.3 (0.6 to 55.4)	11.1	3
Gallbladder, extrahepatic bile ducts (156)	1	0.03	31.9 (1.6 to 159.0)	11.8	0
Other digestive organs (158, 159)	1	0.03	32.8 (1.6 to 159.0)	11.8	14
Female reproductive organs (179–184)	2	0.7	3.0 (0.5 to 9.8)	16.1	1,5
Prostate (185)	1	0.6	1.8 (0.1 to 8.7)	5.3	12
Kidney (189)	1	0.3	3.6 (0.2 to 17.8)	8.8	13
Thyroid gland (193)	3	0.8	4.0 (1.0 to 10.9)	27.3	1,1,10

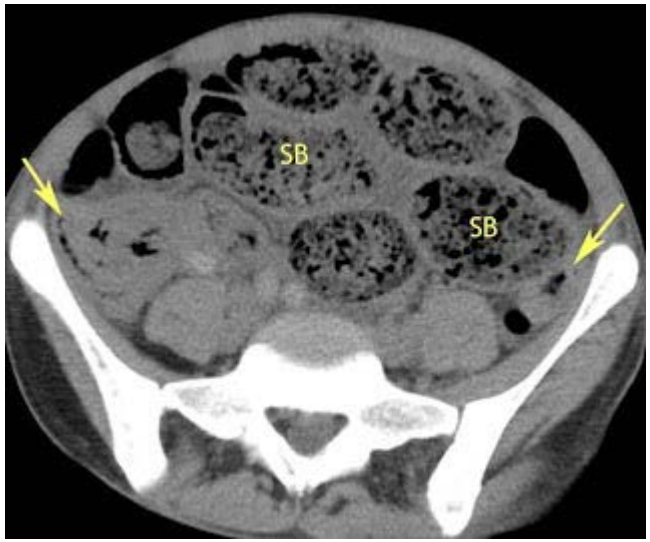
* The table is restricted to sites for which at least one cancer was observed during the study period. AER = absolute excess risk; CI = confidence interval; ICD-9 = *International Classification of Diseases, Ninth Revision.*

Colon Cancer Screening in Lung Transplant Recipients with CF

Table 1. Recommendation Statements

	Consensus Recommendation Statement	Votes	% Agreement
1	The CF Foundation recommends that all decisions on colorectal cancer screening and surveillance in individuals with CF be based on shared decisions between the provider and individual with CF about: treatment, comorbidities, safety, and quality of life.	18/18	100
2	The CF Foundation recommends that all colorectal cancer screening and surveillance for individuals with CF are jointly managed by CF health care professionals and an endoscopist.	18/18	100
3	The CF Foundation recommends colonoscopy as the screening examination for CRC in individuals with CF.	18/18	100
4	The CF Foundation concludes that the evidence is insufficient to recommend the use of computed tomography colonography, stool-based tests, or flexible sigmoidoscopy in individuals with CF for the purpose of CRC screening.	17/18	94
5	The CF Foundation recommends that CRC screening begin at age 40 y in individuals with CF with continued rescreening every 5 y.	18/18	100
6	The CF Foundation recommends that individuals with CF who have undergone a colonoscopy that had any adenomatous polyps have surveillance colonoscopy in 3 y, unless a shorter interval is indicated by individual findings, with subsequent intervals based on the most recent endoscopic examination.	18/18	100
7	The CF Foundation recommends that individuals with CF who are 30 years of age and older and have adequately recovered after receiving a solid organ transplantation begin CRC screening within 2 years of transplantation, except when they have had a negative colonoscopy within the past 5 y.	17/18	94
8	The CF Foundation recommends continued CRC rescreening every 5 y in individuals with CF who have received a solid organ transplant.	18/18	100
9	The CF Foundation recommends that individuals with CF who have undergone a solid organ transplantation and had colonoscopy that had any adenomatous polyps have surveillance colonoscopy in 3 years, unless a shorter interval is indicated by individual findings, with subsequent intervals based on the most recent endoscopic examination.	18/18	100
10	The CF Foundation recommends that adults with CF undergoing a colonoscopy receive intensive regimens for bowel preparation to allow for optimal examination. The intensive regimen should include: 3–4 washes (minimum of 1 L purgative per wash) with the last wash occurring within 4–6 h before the examination.	18/18	100

Distal Intestinal Obstruction Syndrome



‘Fecalization' of small bowel, and collapsed descending colon



Distal Intestinal Obstruction Syndrome (DIOS)

- Occurs in ~22% of CF patients
- Incidence increases with age (~ 80% presents in adults)
- Accumulation of viscous mucus and fecal material in the terminal ileum, caecum and ascending colon which form obstructing muco-feculant impactions
- Recurrence rate is ~50%

Risk factors for DIOS

- Severe genotype
- Pancreatic insufficiency
- Dehydration
- Poorly controlled fat malabsorption
- History of meconium ileus
- History of DIOS
- Post organ transplantation
- CF related diabetes

DIOS in the Lung Transplant Recipient

- Incidence as high as 10–20% after lung transplant.
- If not managed aggressively laparotomy may be required in the early postoperative period.
- Risk factors after transplantation
  - Postoperative ileus
  - Delayed use of pancreatic enzymes
  - Opiate use
  - Hypoperfusion in the acute postoperative phase.

Prevention of DIOS After Lung Transplant

:

- Early enteral feeding
- Immediate introduction pancreatic enzymes (unless elemental formula is being used)
- If the patient has been unable to eat within 24 h, electrolytes GI lavage solution (50-100 mL/h) via NG tube

Treatment of DIOS

- **Incomplete DIOS:**
- Oral rehydration
- Osmotic laxative containing polyethylene glycol (PEG) such as Klean-Prep®, Golytely®, Movicol®.
  - Or
- Gastrographin via NG tube

Complete DIOS:

- IV rehydration and NG aspiration
- Gastrografin enema (Gastrografin may cause fluid shifts causing shock, perforation and necrotizing enterocolitis)
- Surgical consult:
  - Laparotomy with washout via enterostomy
  - Extreme cases: resection of the ileocaecum

Other Considerations

- Anatomic problems:
  - Vascular anomalies from prior manipulation (PICC lines, ports, etc)
  - Pleural adhesions leading to intra-operative/post-operative hemorrhage.
- CF related diabetes
- Challenges with drug absorption/metabolism
- Psychosocial/behavioral challenges

Summary

- LTx can be life saving for patients with CF.
- CFTR modulator therapy improves lung function and may stave off lung transplant, even among patients with advanced lung disease.
- Lung transplantation remains necessary for patients unresponsive to modulator therapy, however, CF specific considerations are important to bear in mind.
  - Antimicrobial-resistant infections
  - Increased risk of GI malignancy
  - Extra-pulmonary CF manifestations: osteoporosis, DIOS, etc

Thank you!

References

- Flume et al. CHEST / 128 / 2 / AUGUST, 2005
- Flume et al. Am J Respir Crit Care Med Vol 182. pp 298–306, 2010
- UpToDate. *"Lung transplantation: General guidelines for recipient selection"*
- Ramos KJ et al. Lung transplant referral for individuals with cystic fibrosis: Cystic Fibrosis Foundation consensus guidelines. J Cyst Fibros. 2019 May. CF Lung Transplant Referral Guidelines Committee
- Parize P et al. Clinical outcome of cystic fibrosis patients colonized by Scedosporium species following lung transplantation: A single-center 15-year experience. Transpl Infect Dis. 2017;19(5)
- Middleton PG. Elexacaftor–Tezacaftor–Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. N Engl J Med. 2019 November 07; 381(19): 1809–1819
- Heijerman HGM et al. Efficacy and safety of the elexacaftor/tezacaftor/ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 Trial. Lancet. 2019 November 23; 394(10212)
- Burgel et al. Rapid Improvement after Starting Elexacaftor–Tezacaftor–Ivacaftor inPatients with Cystic Fibrosis and Advanced Pulmonary Disease. Am J Respir Crit Care Med Vol 204, Iss 1, pp 64–73, Jul 1, 2021
- Aslam et al. Lessons Learned From the First 10 Consecutive Cases of Intravenous Bacteriophage Therapy to Treat MultidrugResistant Bacterial Infections at a Single Center in the United States. Open Forum Infectious Diseases. 21 August 2020
- Hecker TM, Aris RM. Management of osteoporosis in adults with cystic fibrosis. *Drugs* 2004; 64: 133-147.
- Cystic Fibrosis CRC Screening Consensus Recommendations. Feb 2018
- Maisonneuve, P et al. Cancer Risk in Cystic Fibrosis: A 20-Year Nationwide Study From the United States. JNCI Vol. 105, Issue 2 | January 16, 2013
- Hirche et al. Practical Guidelines: Lung Transplantation in Patients with Cystic Fibrosis. Pulmonary Medicine. Volume 2014
- Nash EF, Thomas A, Whitmill R, Rashid R, Barker B, Rayner RJ, Whitehouse JL, Honeybourne D. "Cepacia syndrome" associated with Burkholderia cepacia (genomovar I) infection in an adolescent with cystic fibrosis. *Pediatric pulmonology* 2010.
- Courtney JM, Dunbar KE, McDowell A, Moore JE, Warke TJ, Stevenson M, Elborn JS. Clinical outcome of Burkholderia cepacia complex infection in cystic fibrosis adults. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society* 2004; 3: 93-98.
- Alexander BD et al. Survival after lung transplantation of cystic fibrosis patients infected with Burkholderia cepacia complex. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons 2008; 8: 1025-1030.
- Lobo LJ, Chang LC, Esther CR, Jr., Gilligan PH, Tulu Z, Noone PG. Lung transplant outcomes in cystic fibrosis patients with pre-operative Mycobacterium abscessus respiratory infections. *Clinical transplantation* 2013; 27: 523-529.
- Shane et al. Osteoporosis in lung transplantation candidates with end-stage pulmonary disease. *The American journal of medicine* 1996; 101: 262-269.
- Trombetti A et al. Bone mineral density in lung-transplant recipients before and after graft: prevention of lumbar spine post-transplantation-accelerated bone loss by pamidronate. *The Journal of heart and lung transplantation : the official publication of the International Society for Heart Transplantation* 2000; 19: 736-743.
- Cystic Fibrosis CRC Screening Consensus Recommendations. Feb 2018
- Gilljam M, Chaparro C, Tullis E, Chan C, Keshavjee S, Hutcheon M. GI complications after lung transplantation in patients with cystic fibrosis. *Chest* 2003; 123: 37-41.
- Colombo C, Ellemunter H, Houwen R, Munck A, Taylor C, Wilschanski M, Ecfs. Guidelines for the diagnosis and management of distal intestinal obstruction syndrome in cystic fibrosis patients. *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society* 2011;

End of LAS Era: Changes to US Transplant System and Potential Impact on Patients and Programs

Maryam Valapour, MD, MPP
Respiratory Institute

Cleveland Clinic



I have no financial relationships with commercial interests to disclose.

AND

My presentation does not include discussion of off-label or investigational use.

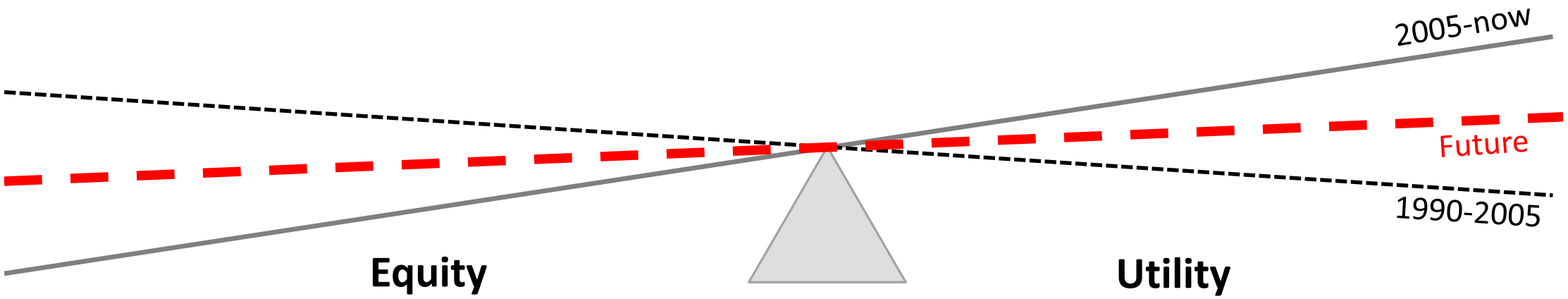
Objectives

1. Discuss the attributes of the continuous distribution allocation system for lung transplantation in the United States

2. Describe the key empiric analyses that supported the adoption of the Lung Composite Allocation Score (CAS)

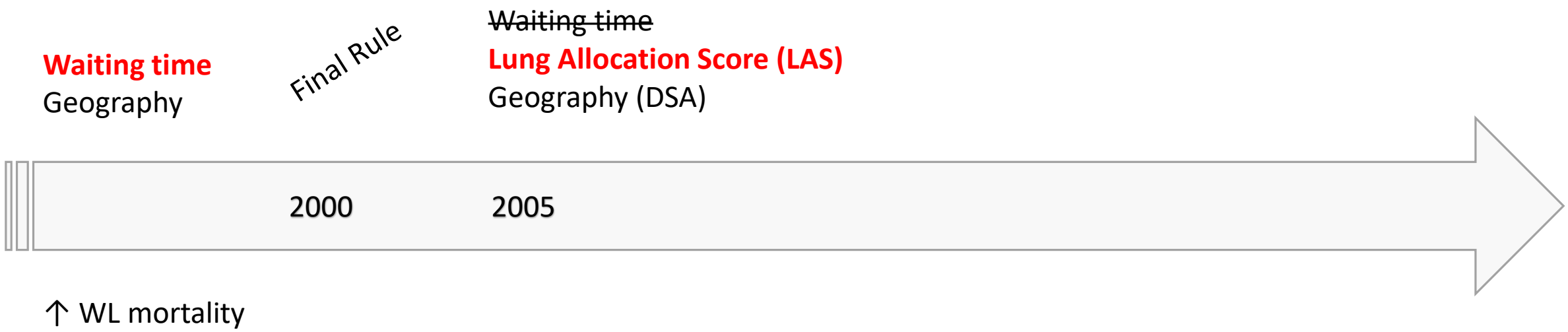
3. Demonstrate key CAS pre-implementation data.

Understanding of goals of the lung allocation system has evolved



Evolution of Donor Lung Allocation Policies and Impact

Policy



Impact

Calculation of Lung Allocation Score (LAS)

Waitlist urgency measure =
Expected # of days lived without transplant during the next year

Posttransplant survival measure =
Expected # of days lived during 1st year after transplant

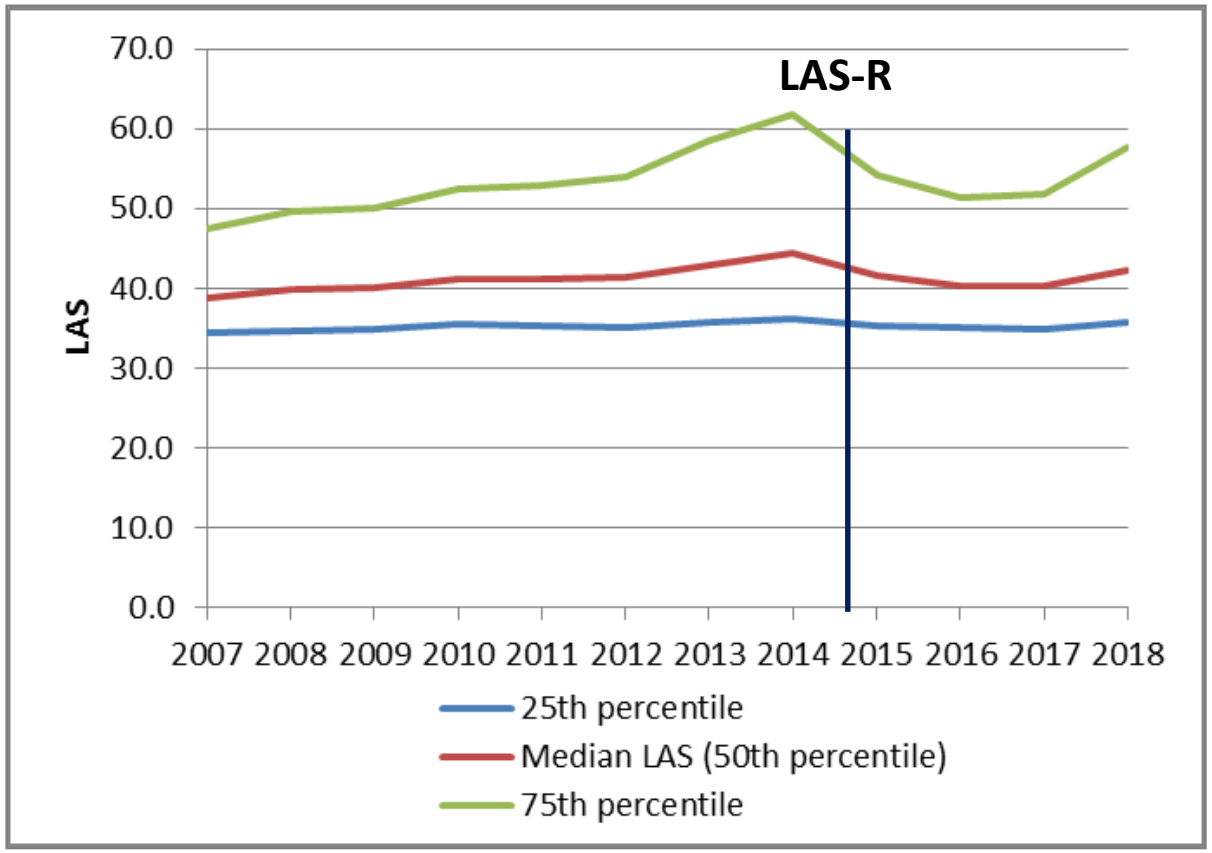
Raw allocation score =
Posttransplant survival measure – 2x (waitlist urgency measure)

Normalized LAS =
100x (raw score + 2 x 365)/3 x 365

Am J Transplant. 2006; 6(2): 1212-1227

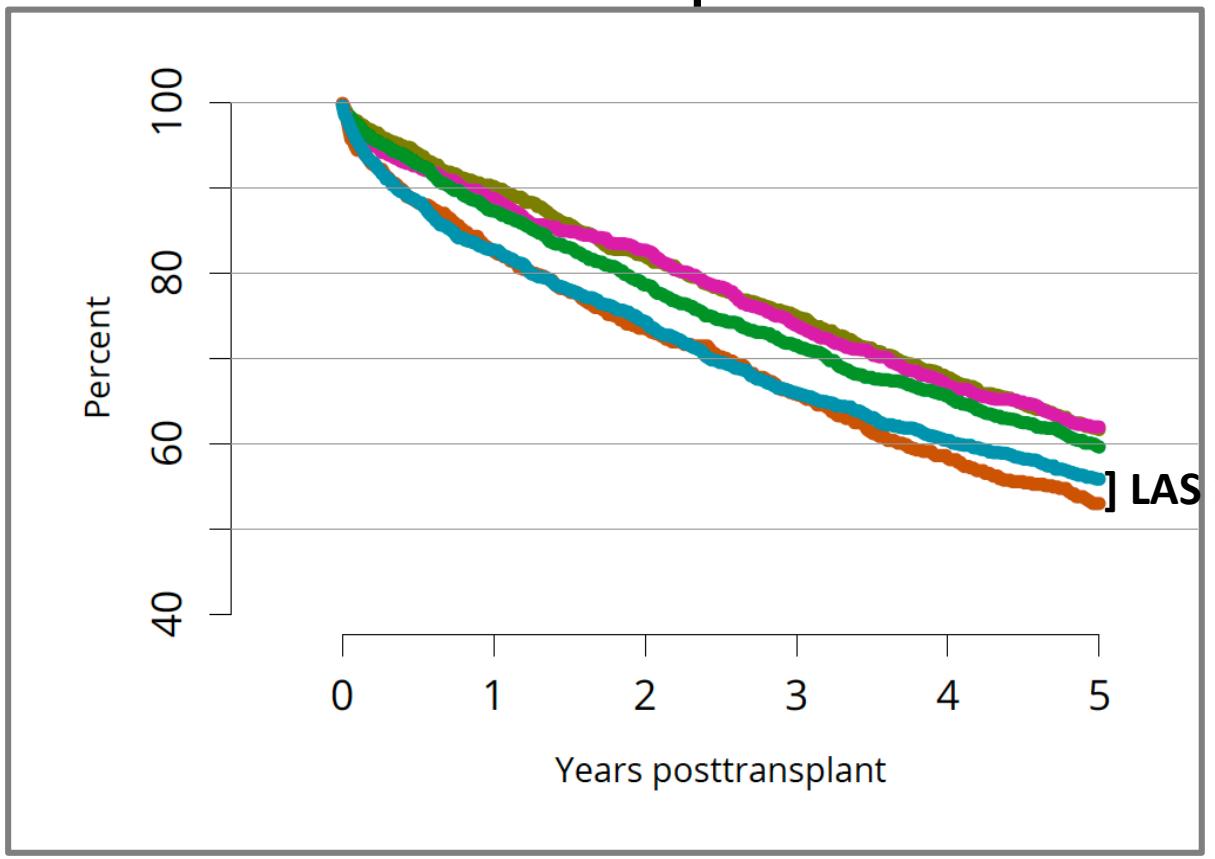
LAS: Recipients are sicker, and they have shorter survival

Median LAS at Transplant



Am J Transplant. 2020; Jan; 20(S1): 427-508

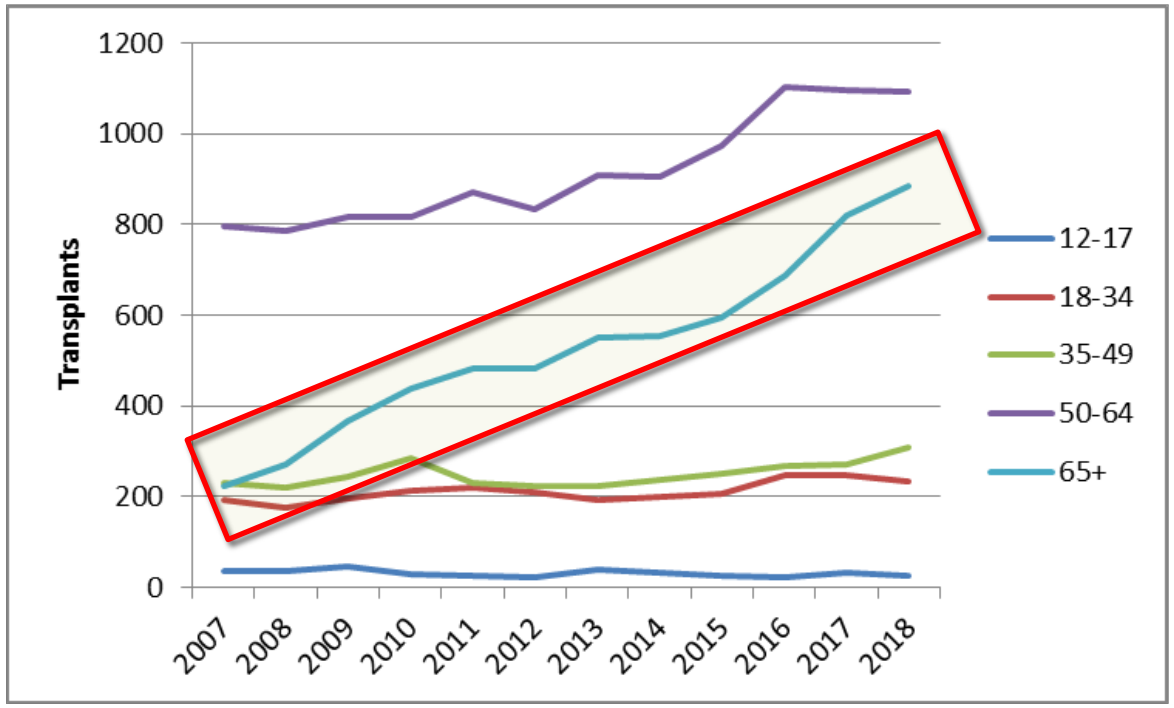
LAS at Transplant



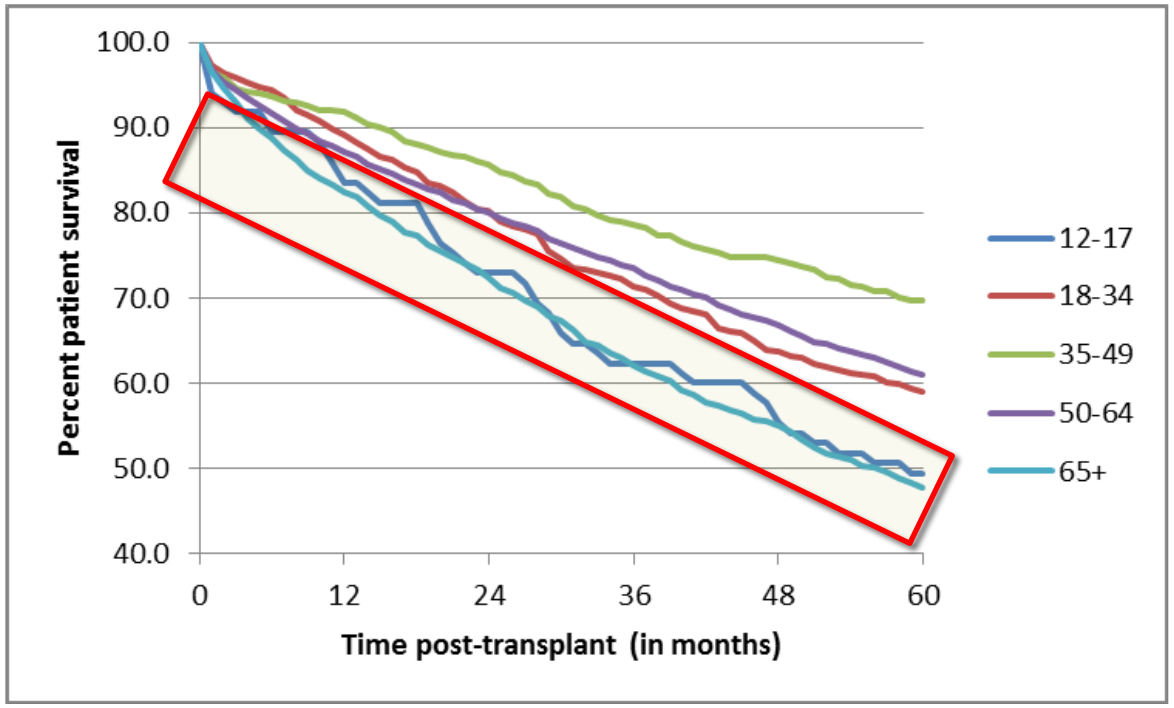
Am J Transplant. 2021; Feb; 21(S2): 441-520

LAS: Recipients are older, and they have shorter survival

Lung Transplants per Year by Age

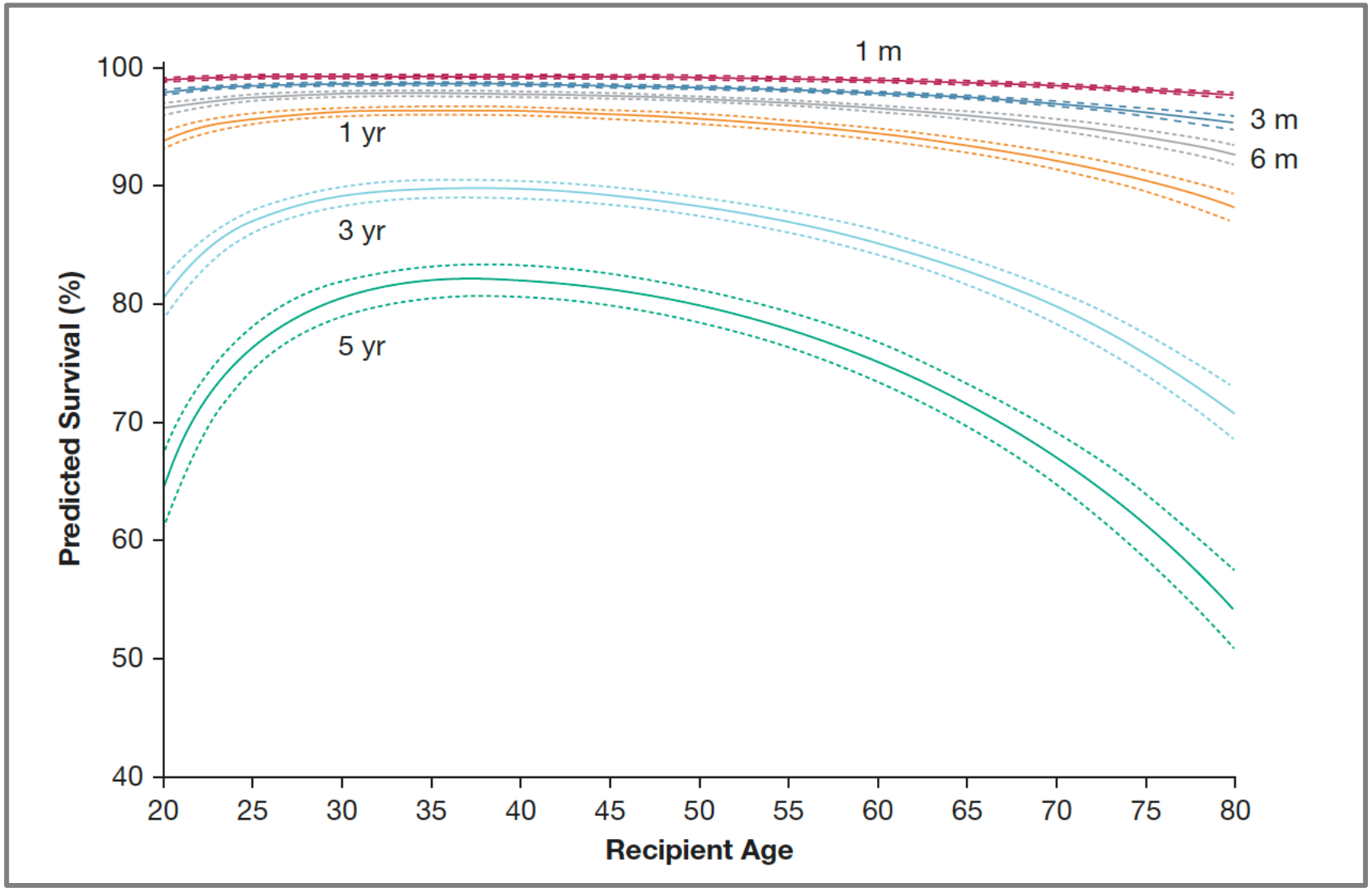


Survival by Age among Lung Recipients 2011-2013



Am J Transplant. 2020; 20(S1): 427-508

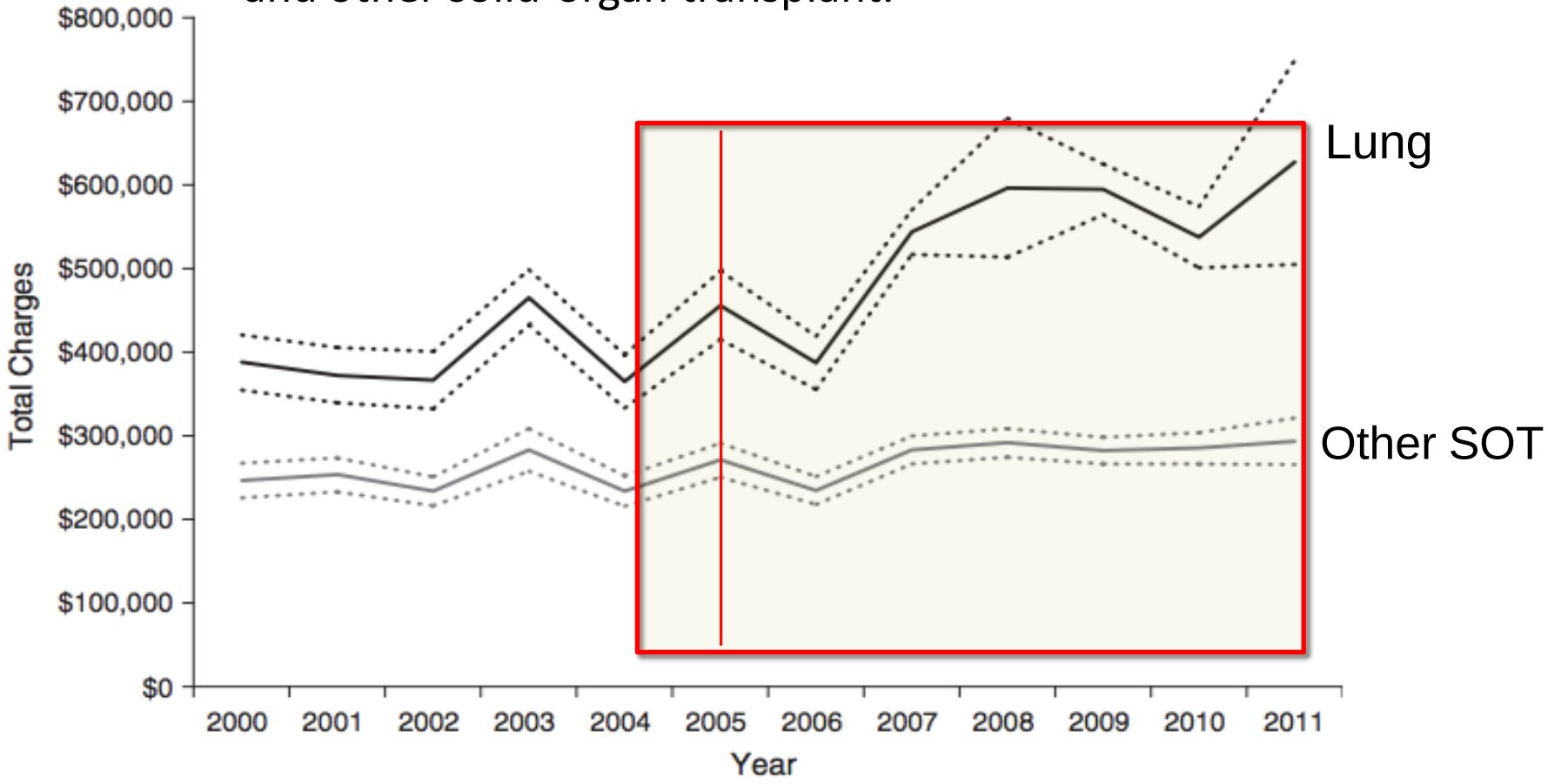
Shorter survival remains after risk adjustments



Chest. 2020 Apr; 157 (4): 907-915

LAS: Patient care costs are increasing

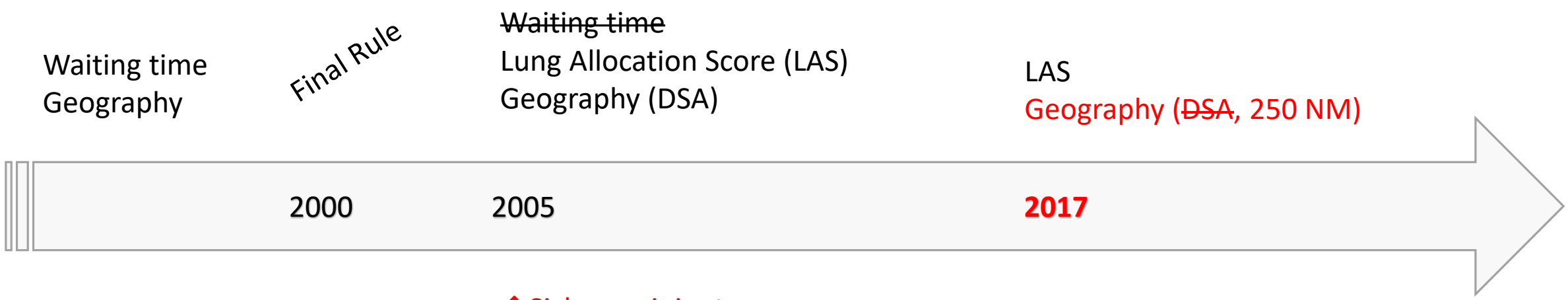
Hospital charges per admission for patients undergoing lung transplant and other solid-organ transplant.



Am J Respir Crit Care Med. 2015; 191(3): 302-308

Evolution of Donor Lung Allocation Policies and Impact

Policy

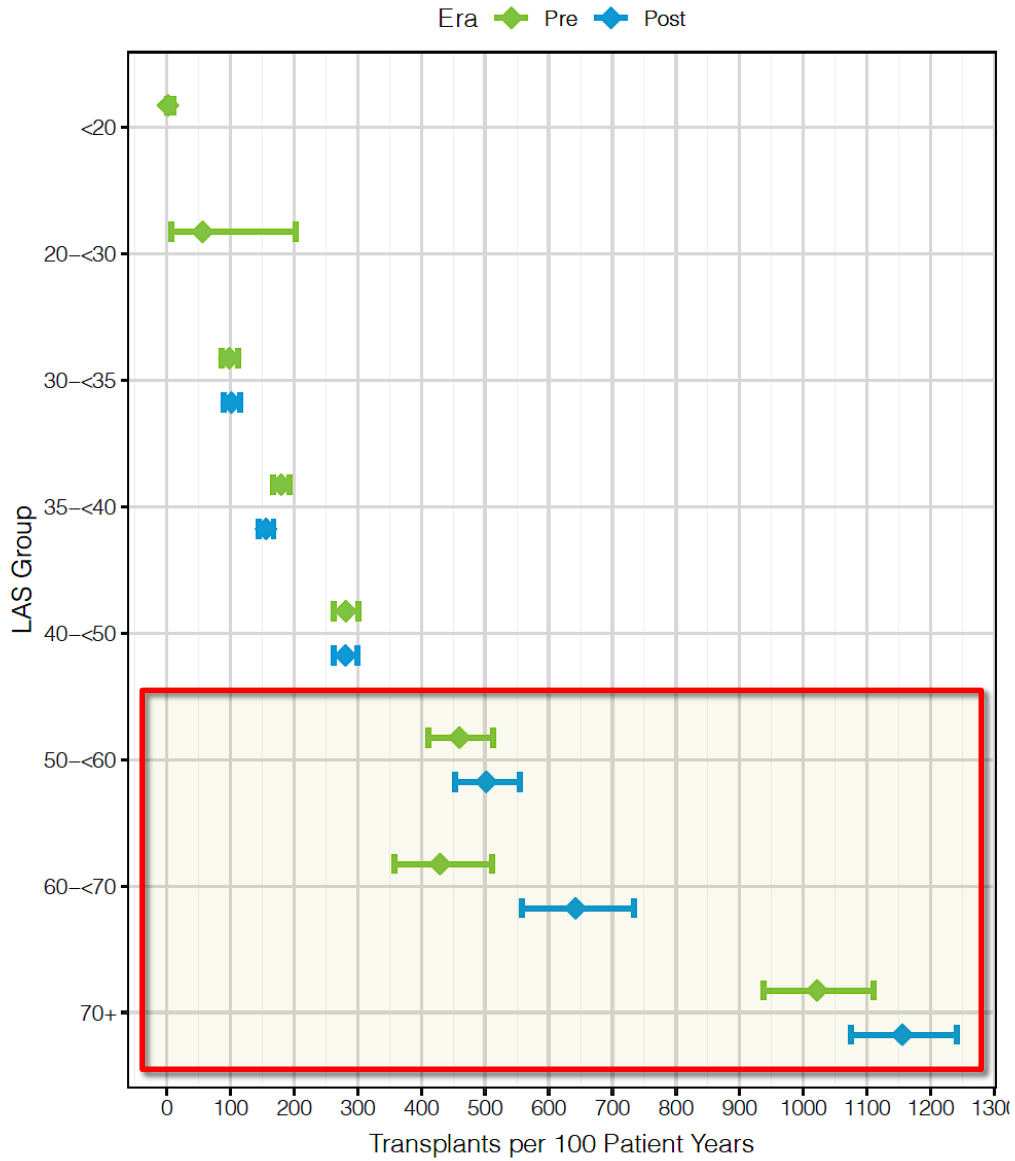


Impact

↑ WL mortality

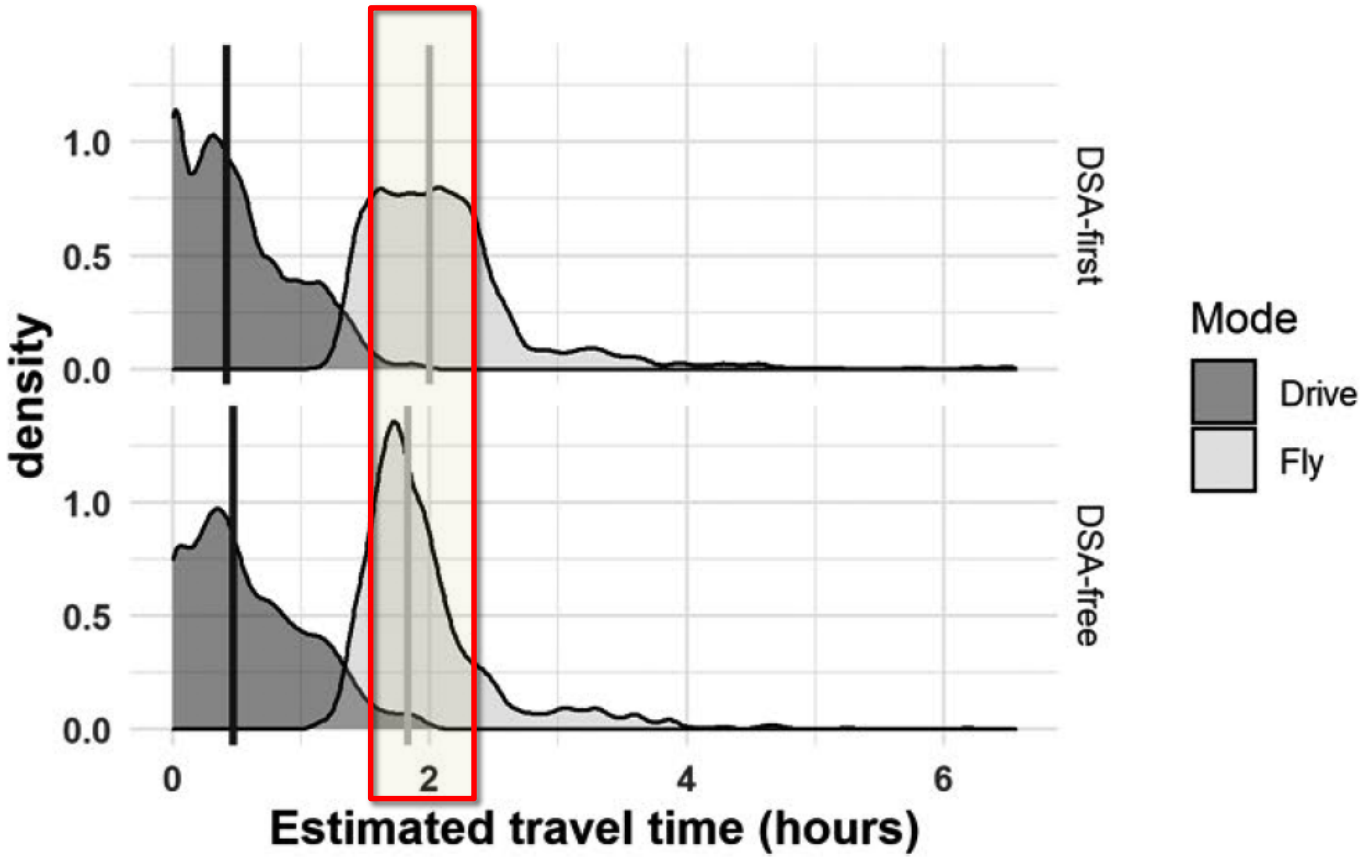
↑Sicker recipients
↑Older recipients
↑Patient-care costs
↑Innovations
Plateaued long-term survival

~~DSA~~ → 250 NM: Recipients are even sicker



Monitoring of OPTN Lung Allocation Change, 2-yr Report; Feb 12, 2020

~~DSA~~ → 250 NM: Procurement is less efficient, and more costly



Cost increases by $14,000 when travel mode is changed from driving to flying

Am J Transplant. 2021; Dec; 21(12): 4012-4022

Evolution of Donor Lung Allocation Policies and Impact

Policy

Waiting time
Geography

Final Rule

~~Waiting time~~
Lung Allocation Score (LAS)
Geography (DSA)

LAS
Geography ~~(DSA)~~



Impact

↑ WL mortality

↑Sicker recipients
↑Older recipients
↑Patient-care costs
↑ Innovation
Plateaued long-term survival

↑↑Sicker recipients
↑Inefficiencies in procurement

Continuous Distribution Framework: Path towards removing geographic boundaries

PERSONAL VIEWPOINT

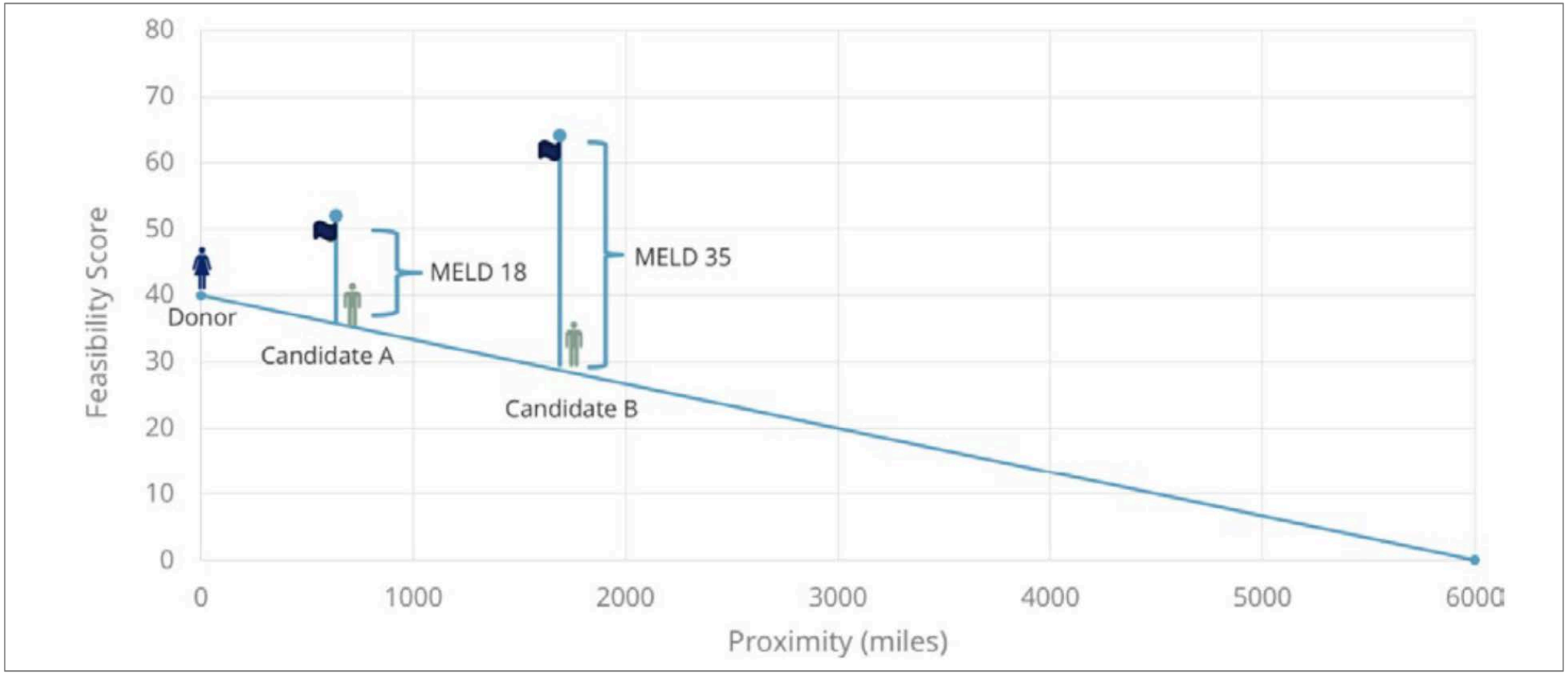
AJT

Organ distribution without geographic boundaries: A possible framework for organ allocation

Jon J. Snyder[1,2] | Nicholas Salkowski[1] | Andrew Wey[1] | Joshua Pyke[1] | Ajay K. Israni[1,2,3,4] | Bertram L. Kasiske[1,2,3,4]

Am J Transplant. 2018; 18:2635-2640

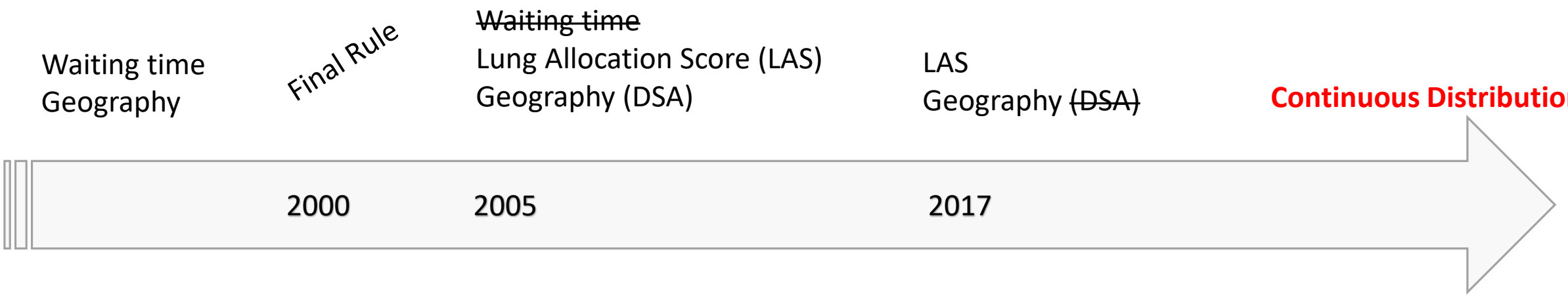
Continuous Distribution:
Compromise between geographic feasibility and medical priority



Am J Transplant. 2021; 15(2):541-6

Evolution of Donor Lung Allocation Policies and Impact

Policy



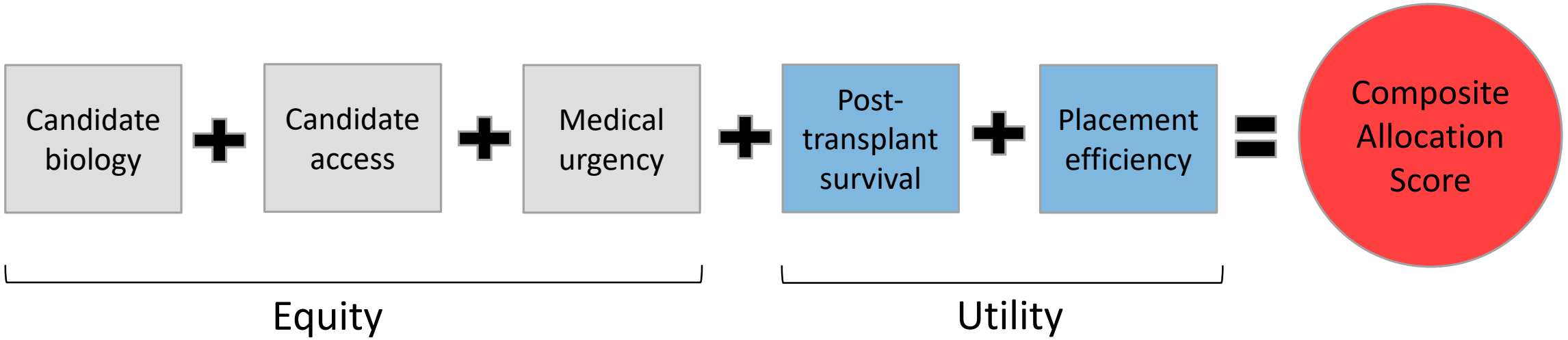
Impact

↑ WL mortality

↑Sicker recipients
↑Older recipients
↑Patient-care costs
↑ Innovation
Plateaued long-term survival

↑↑Sicker recipients
↑Inefficiencies in procurement

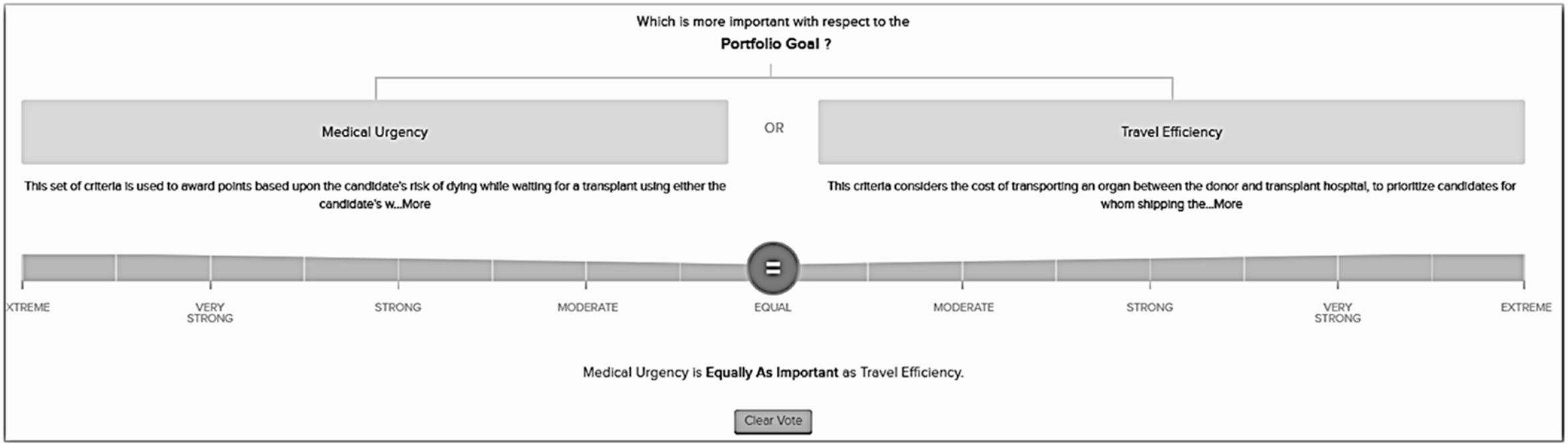
Components of the Lung Composite Allocation Score (CAS)



Continuous Distribution – Lung. optn.transplant.hrsa.gov/policies-bylaws

CAS: Ranking relative importance of factors

Sample pairwise comparisons



BMC Med Inform Decis Mak. 2021 Jan 6; 21(1): 8

1-yr and 5-yr posttransplant models are equally predictive, but 5-yr model better identifies long-term survivors in CAS

	1-year models			5-year models		
Year	Cox PH (current)	Cox PH (updated)	PEM (no-TV)	Cox PH (updated)	PEM (no-TV)	PEM (yes-TV)
1-year	60.2%	60.8%	60.7%	58.9%	58.8%	59.0%
5-year	–	–	–	59.2%	59.2%	59.4%

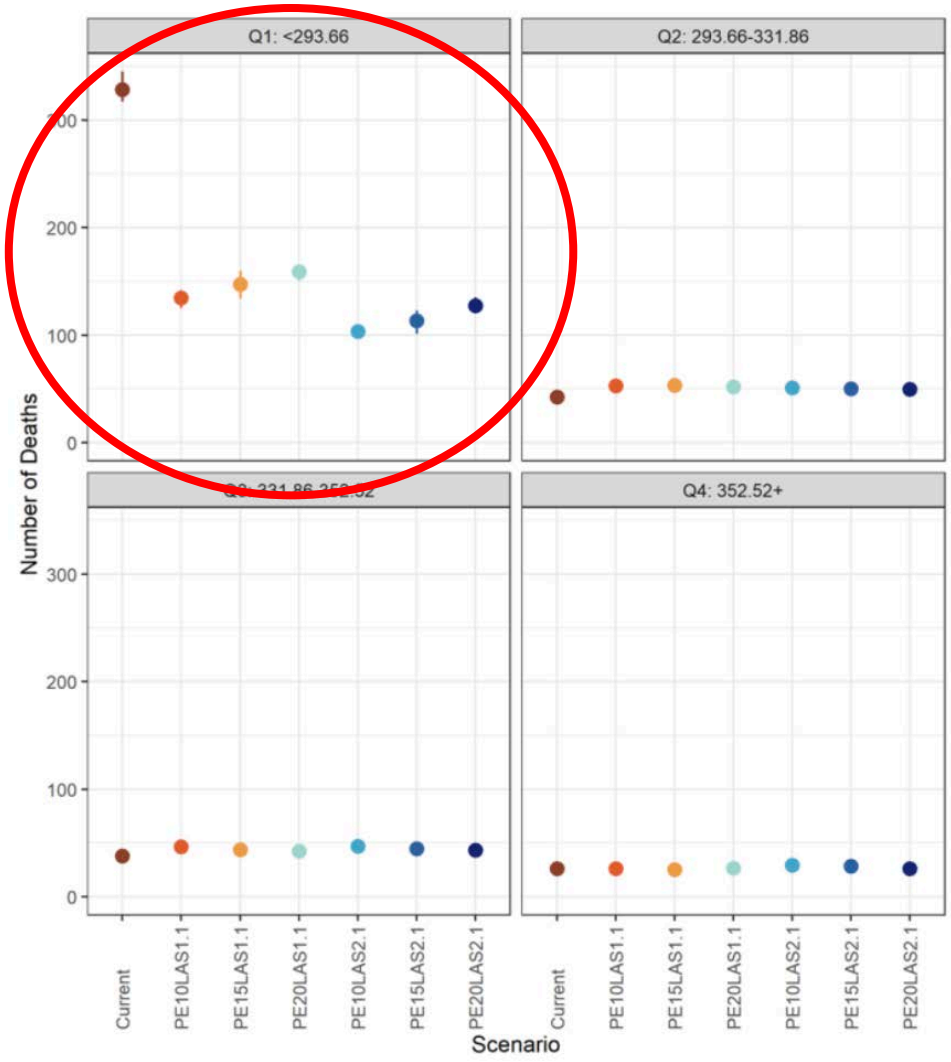
J Heart Lung Transplant. 2022 Jul; 41(7): 866-873

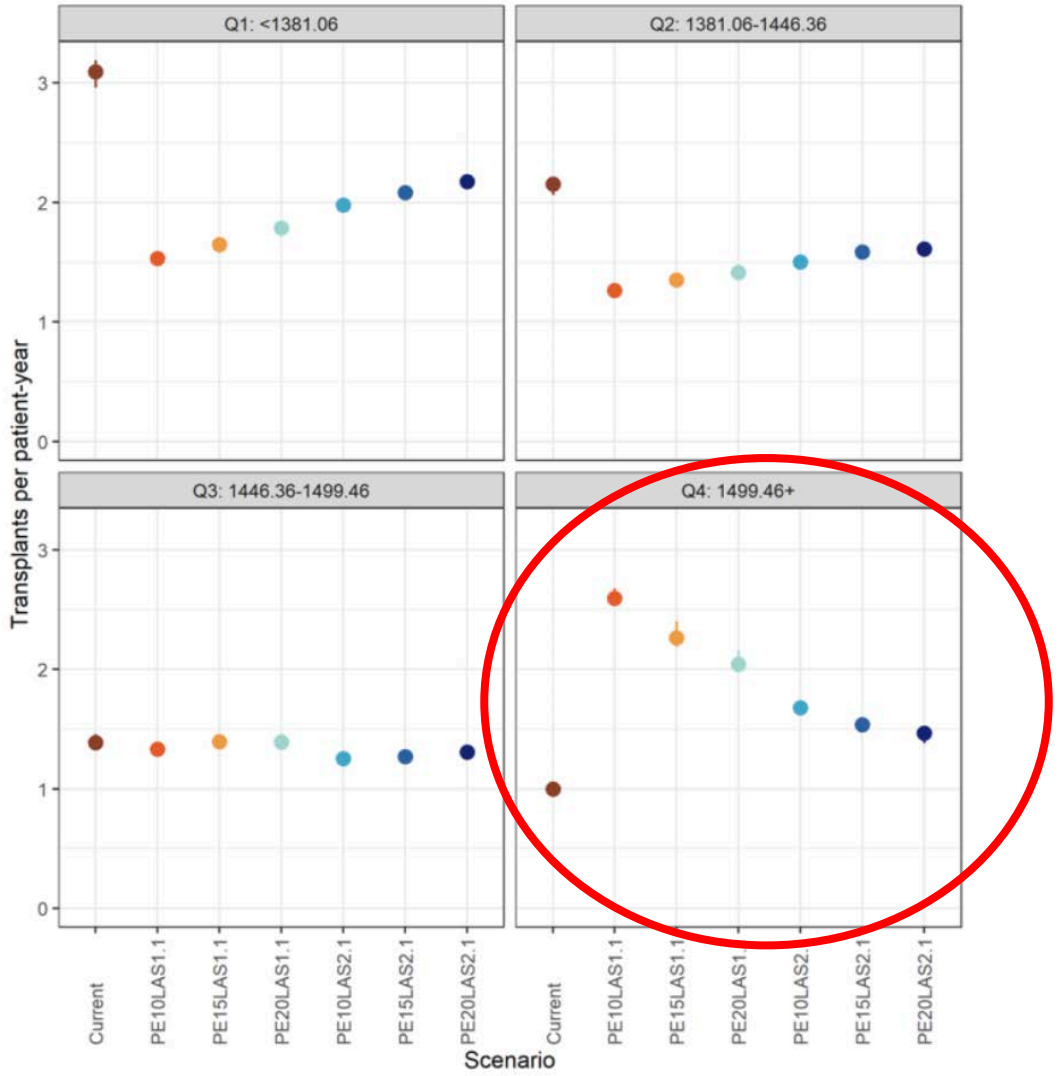
Lung Composite Allocation Score (CAS) Components and Weights

Component	Weights per component (%)					
	1:1 WLAUC:PTAUC			2:1 WLAUC:PTAUC		
	10% PE	15% PE	20% PE	10% PE	15% PE	20% PE
Waitlist survival	**25**	**22.5**	**20**	**33.33**	**30**	**26.67**
Posttransplant survival	**25**	**22.5**	**20**	**16.67**	**15**	**13.33**
Candidate biology	15	15	15	15	15	15
Pediatric	20	20	20	20	20	20
Prior living donor	5	5	5	5	5	5
Proximity efficiency	**10**	**15**	**20**	**10**	**15**	**20**

SRTR Data Request ID: LU2021_01 (addendum)

CAS: Considered tradeoffs in survival





SRTR Data Request ID: LU2021_01 (addendum)

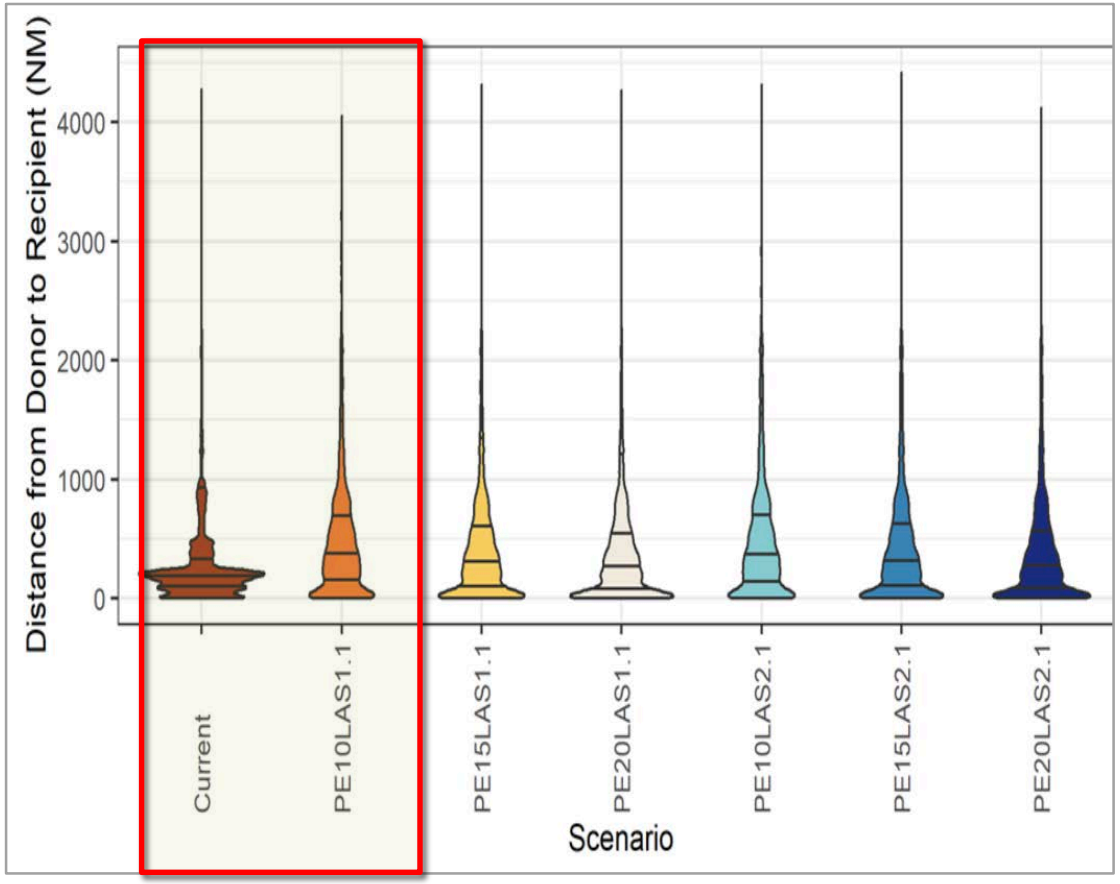
Lung Composite Allocation Score Components and Weights

Component	Weights per component (%)					
	1:1 WLAUC:PTAUC			2:1 WLAUC:PTAUC		
	10% PE	15% PE	20% PE	10% PE	15% PE	20% PE
Waitlist survival	**25**	**22.5**	**20**	**33.33**	**30**	**26.67**
Posttransplant survival	**25**	**22.5**	**20**	**16.67**	**15**	**13.33**
Candidate biology	15	15	15	15	15	15
Pediatric	20	20	20	20	20	20
Prior living donor	5	5	5	5	5	5
Proximity efficiency	**10**	**15**	**20**	**10**	**15**	**20**

SRTR Data Request ID: LU2021_01 (addendum)

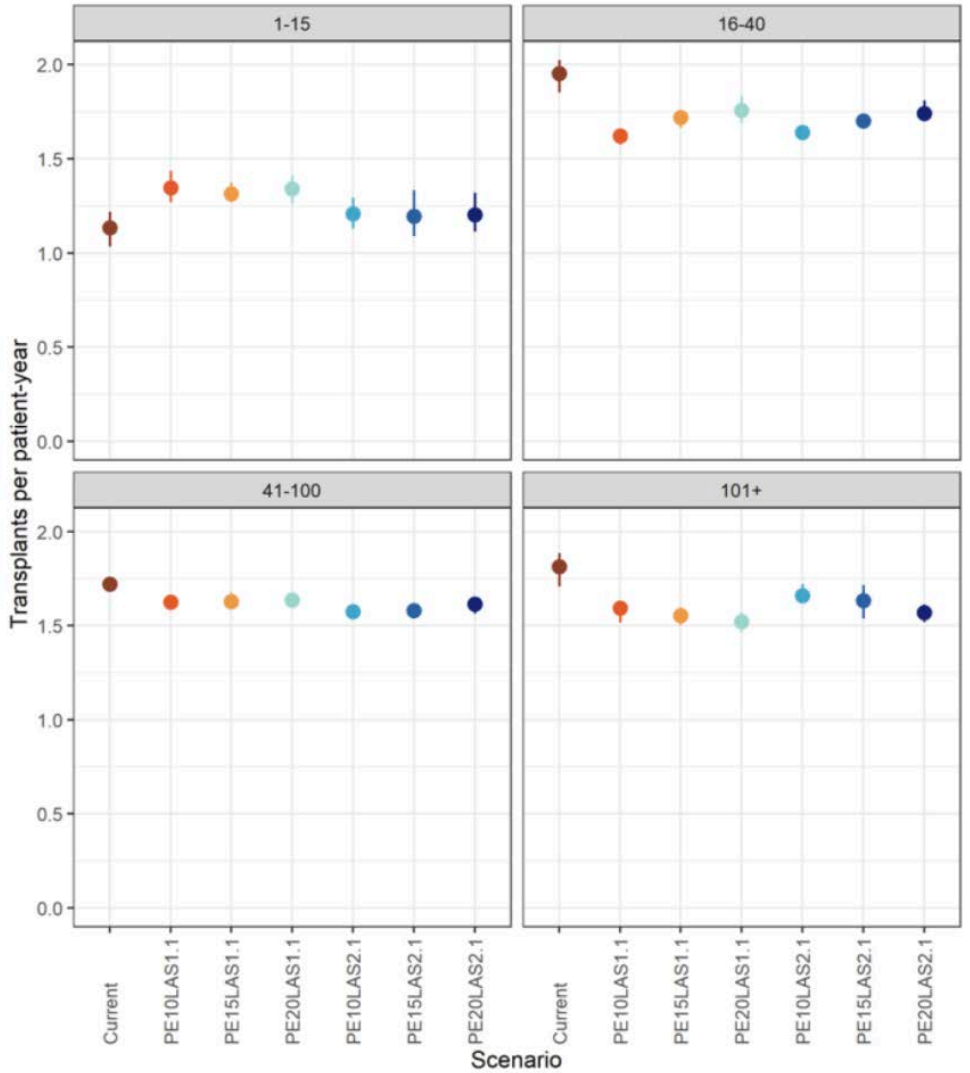
CAS: Anticipated impact on travel distance

Distance (NM)	Current	PE10 LAS1:1	PE15 LAS1:1	PE20 LAS1:1	PE10 LAS2:1	PE15 LAS2:1	PE20 LAS2:1
0-<50	713	882	1144	1305	919	1125	1245
50-<100	598	345	402	443	355	402	446
100-<250	**2229**	757	813	854	768	820	884
250-<500	826	1202	1166	1140	1182	1141	1123
500-<1000	503	1318	1107	984	1270	1118	992
1000+	187	559	449	359	591	491	412



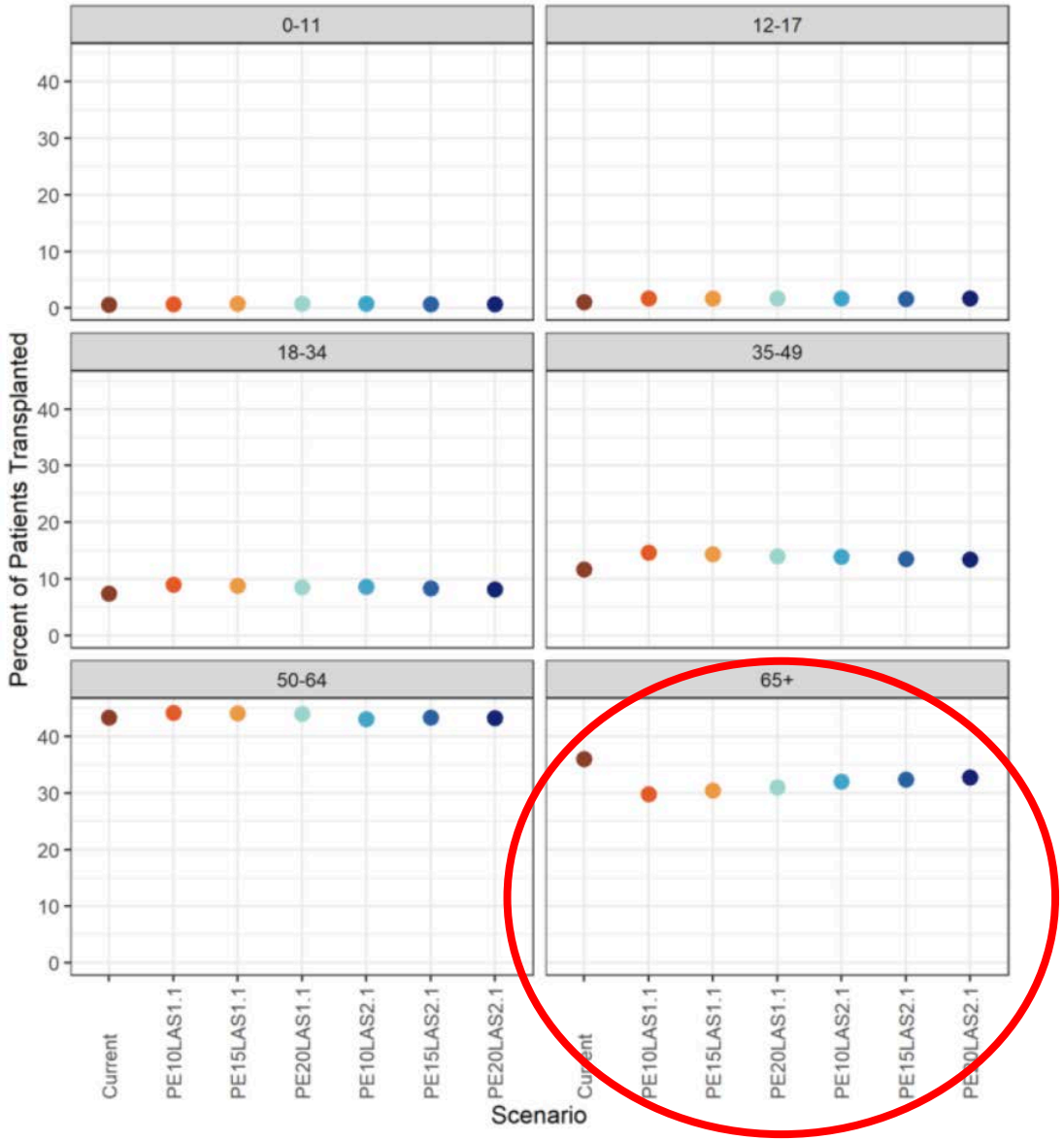
Am J Transplant. 2022. Online ahead of print.

CAS: Anticipated impact on centers



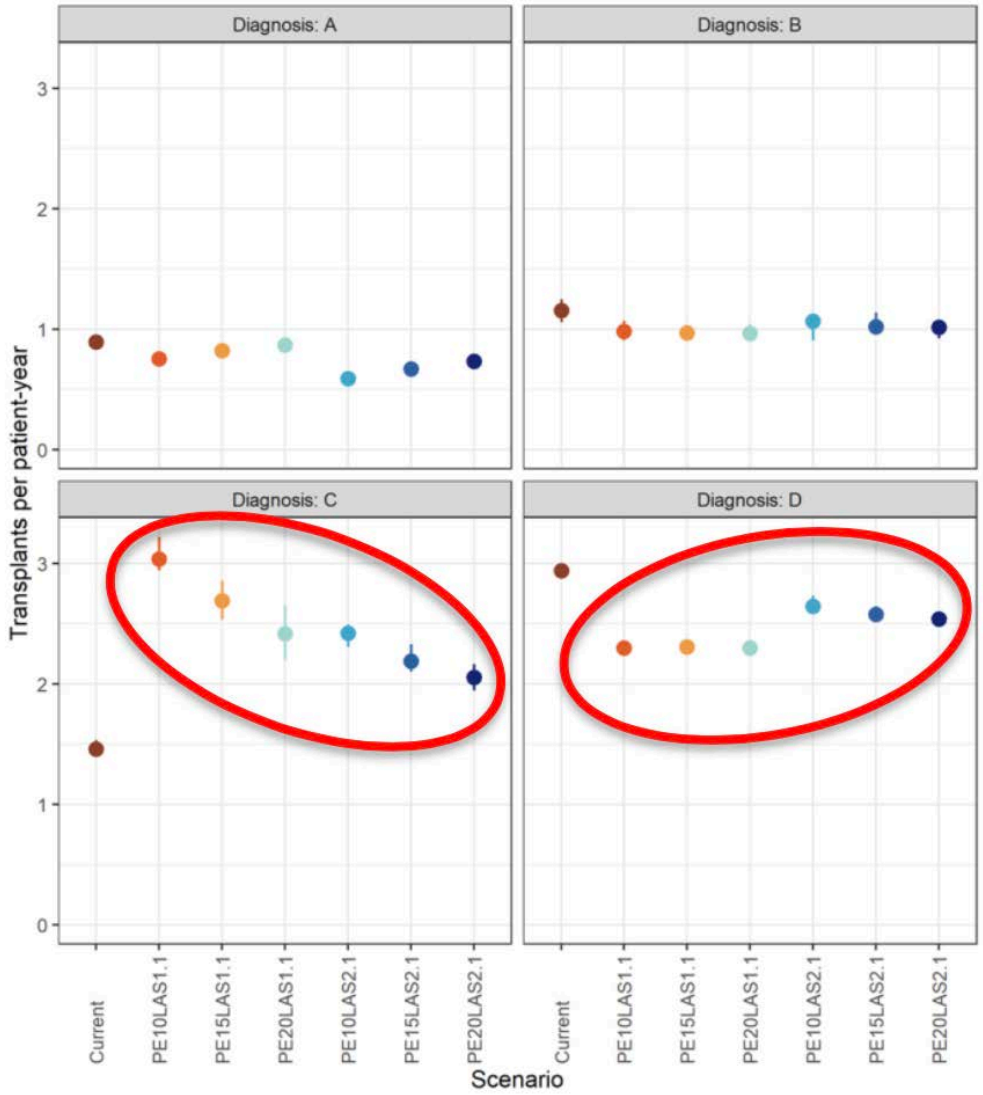
Am J Transplant. 2022. Online ahead of print.

CAS: Anticipated impact on transplants for candidates by age



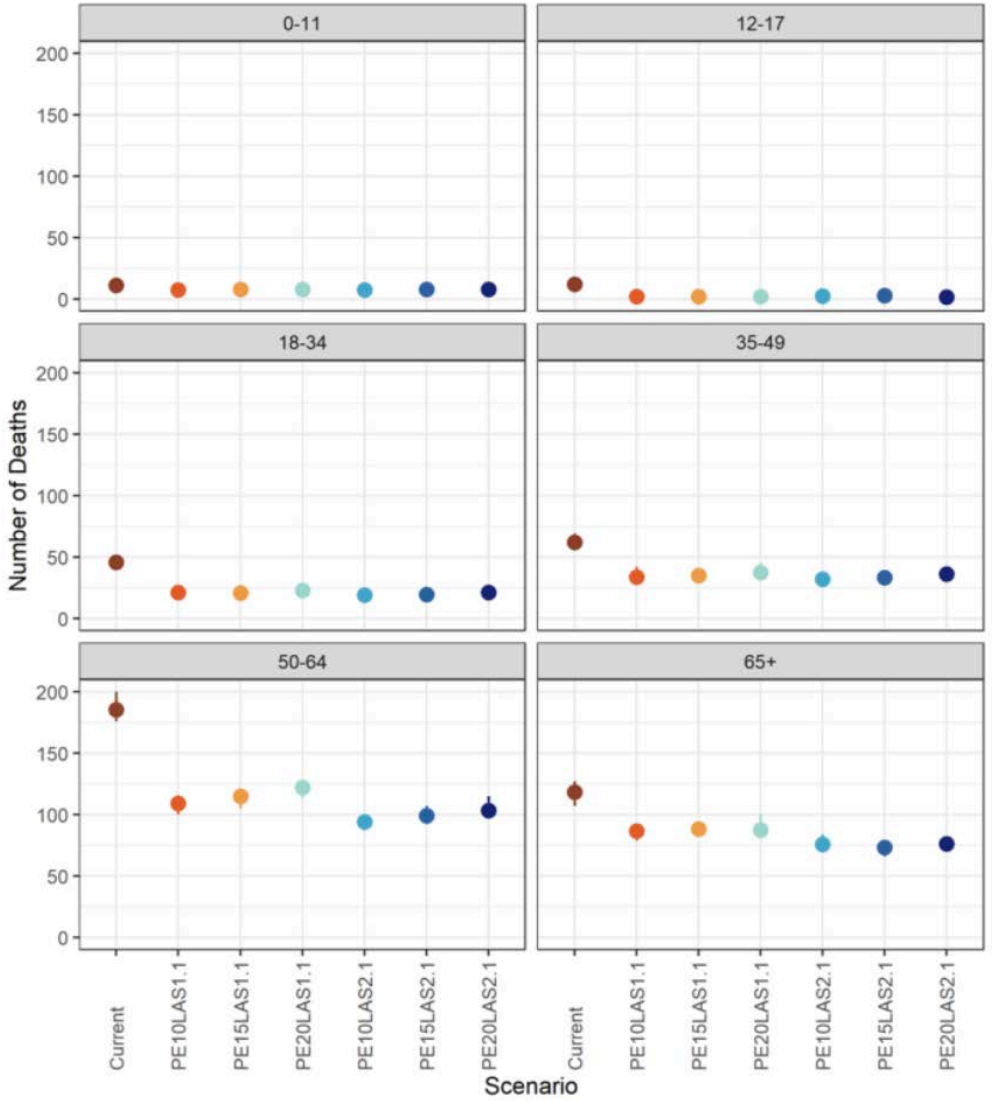
Am J Transplant.
2022. Online ahead of print.

CAS: Anticipated impact on diagnosis groups



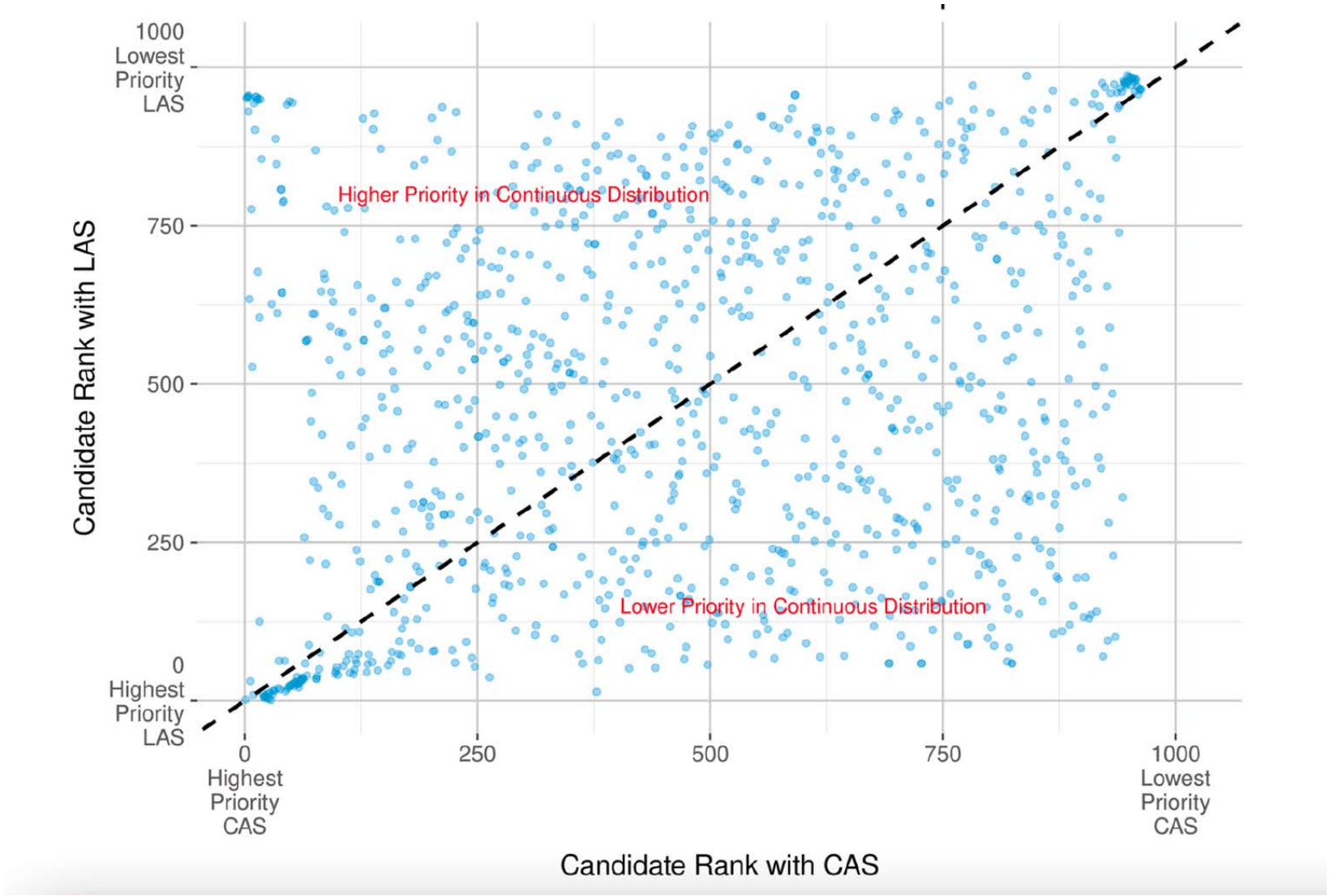
Am J Transplant. 2022 Online ahead of print.

CAS: Anticipated impact on mortality for candidates by age



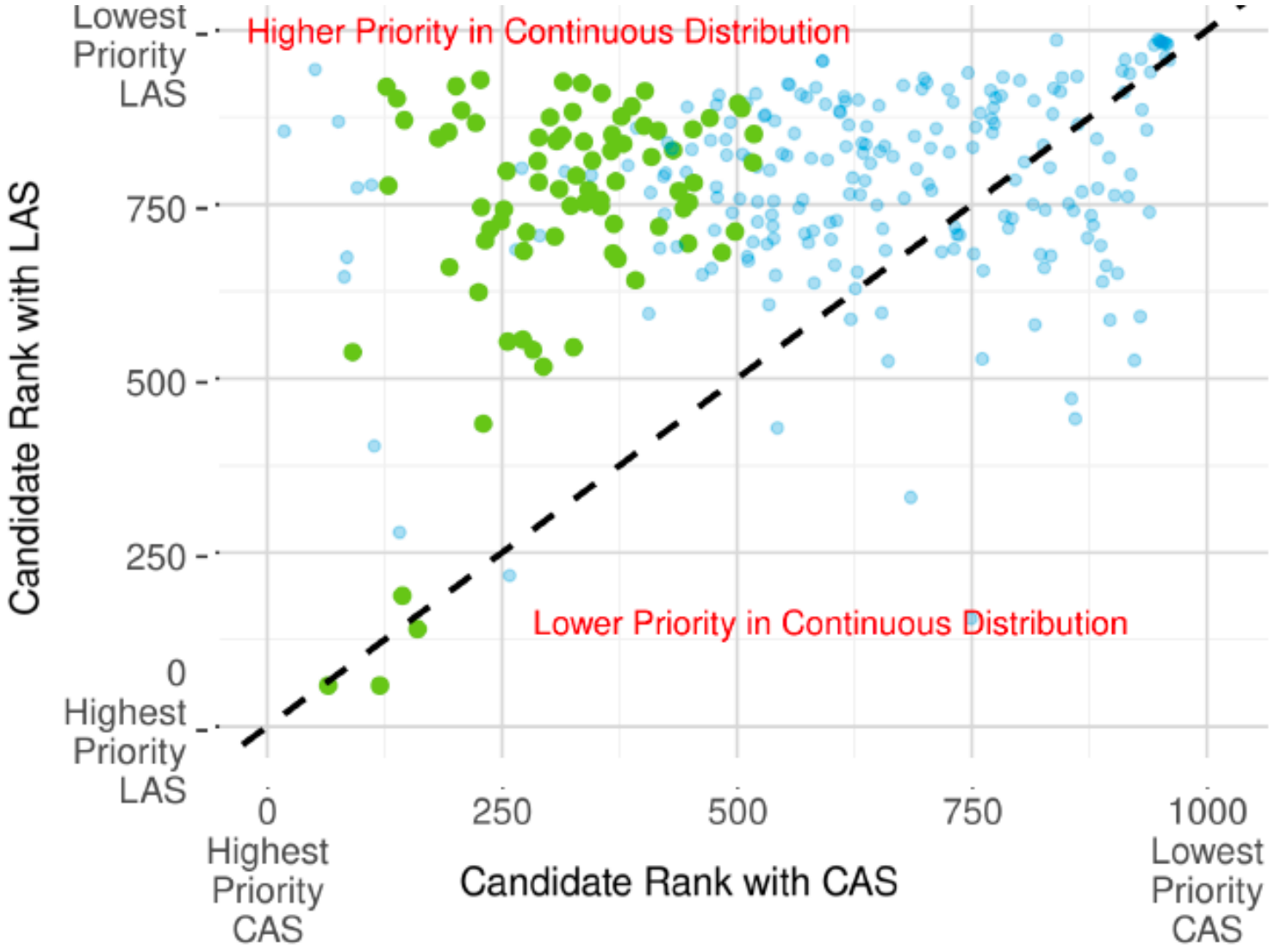
Am J Transplant. 2022. Online ahead of print.

Candidate LAS and CAS Rank Change Comparison



UNOS presentation to Lung Transplant Committee, November 23, 2022.

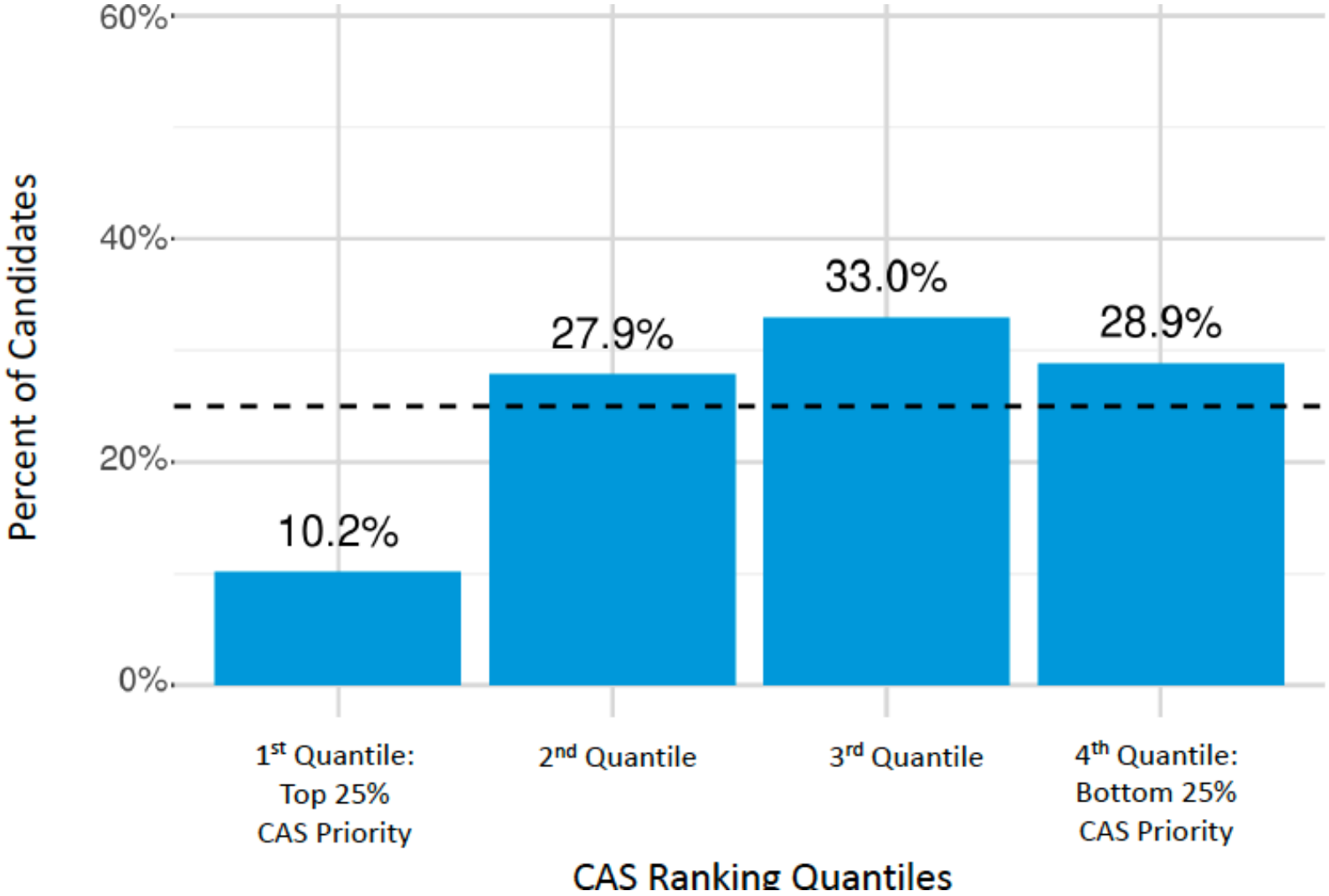
Group A: Posttransplant (PT) survival and rank change



- Top 25% PT Survival
- Bottom 75% PT Survival

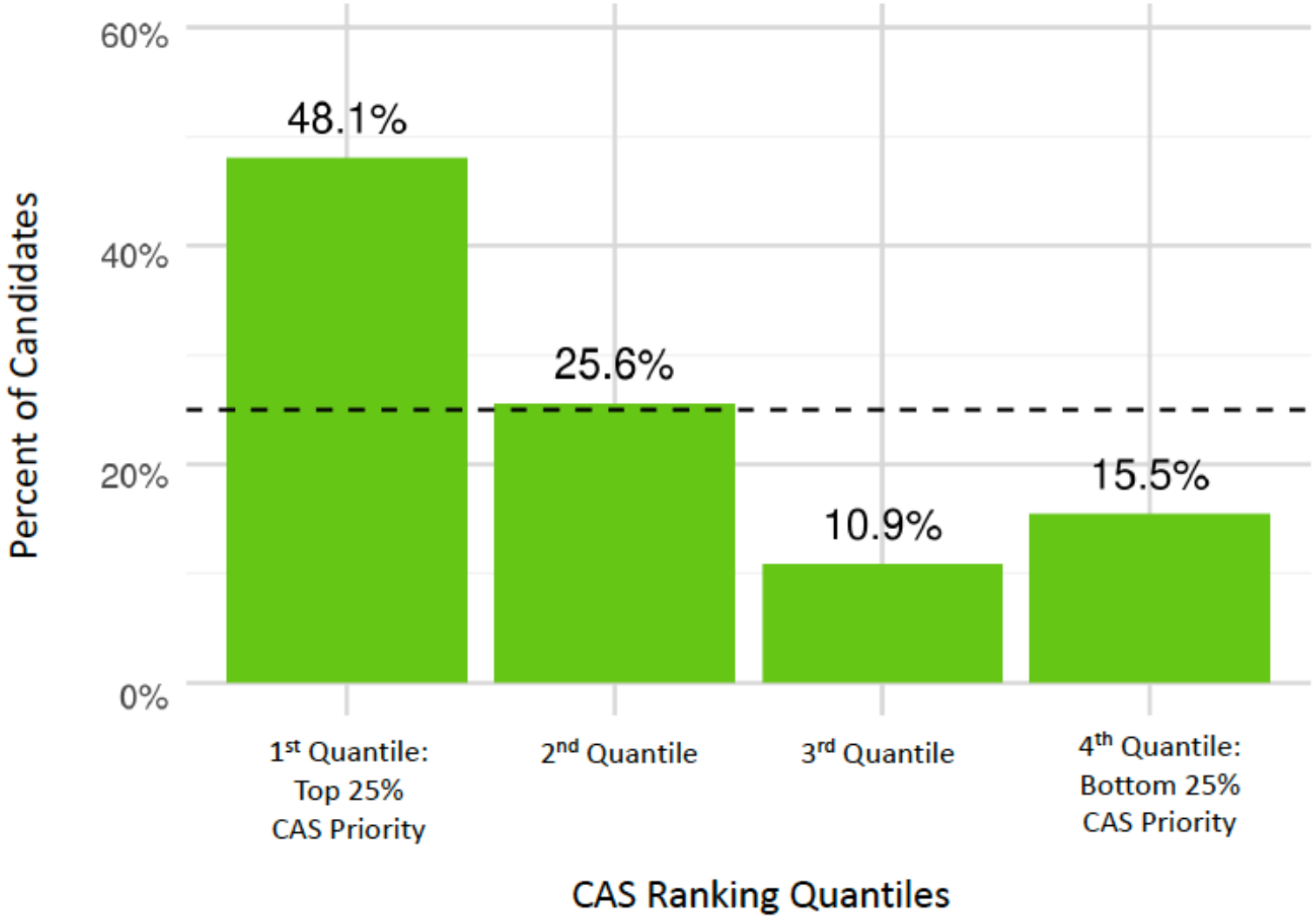
UNOS presentation to Lung Transplant Committee, November 23, 2022.

Group A: Percent of candidates in CAS rank quantile



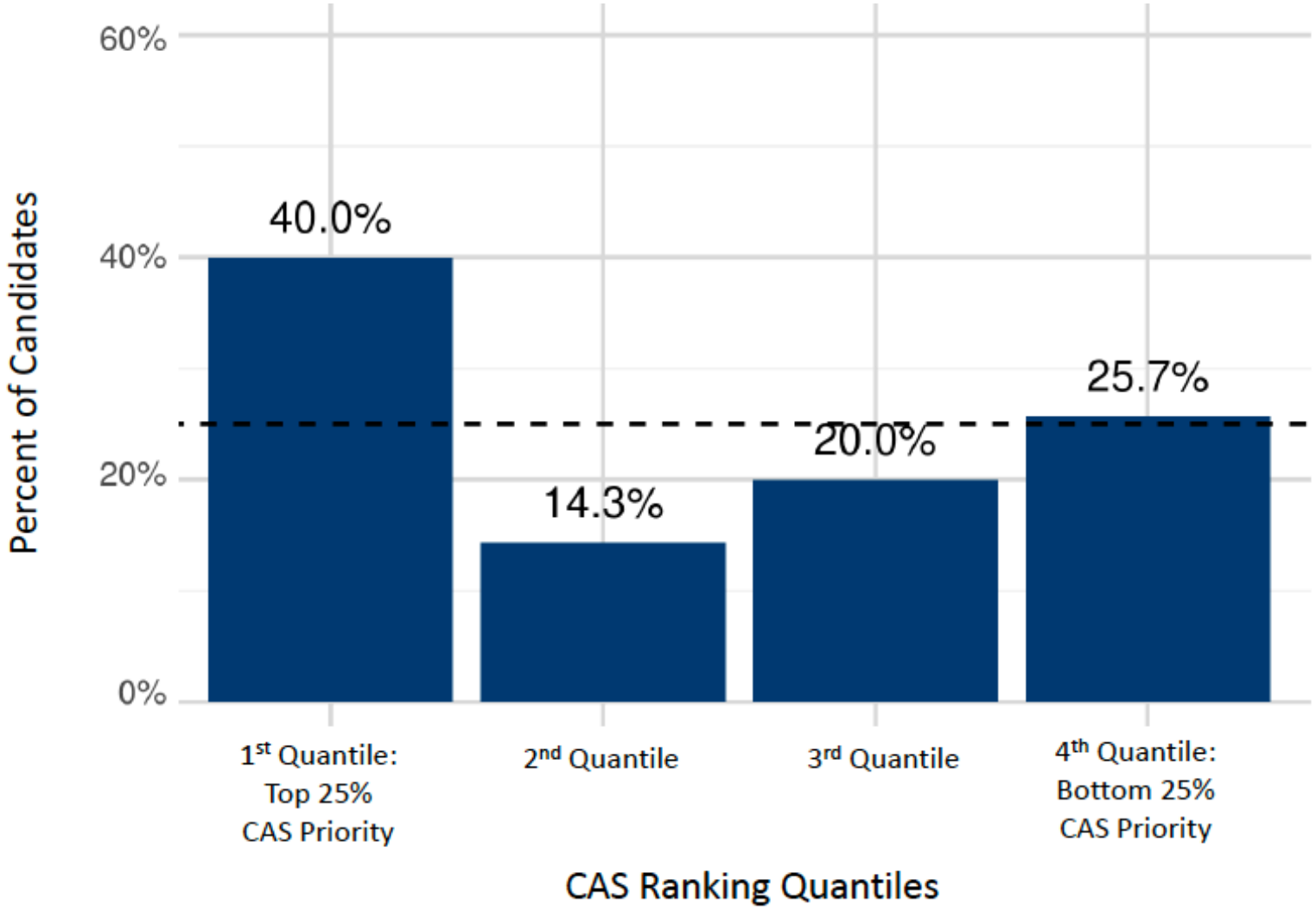
UNOS presentation to Lung Transplant Committee, November 23, 2022.

Group B: Percent of candidates in CAS rank quantile



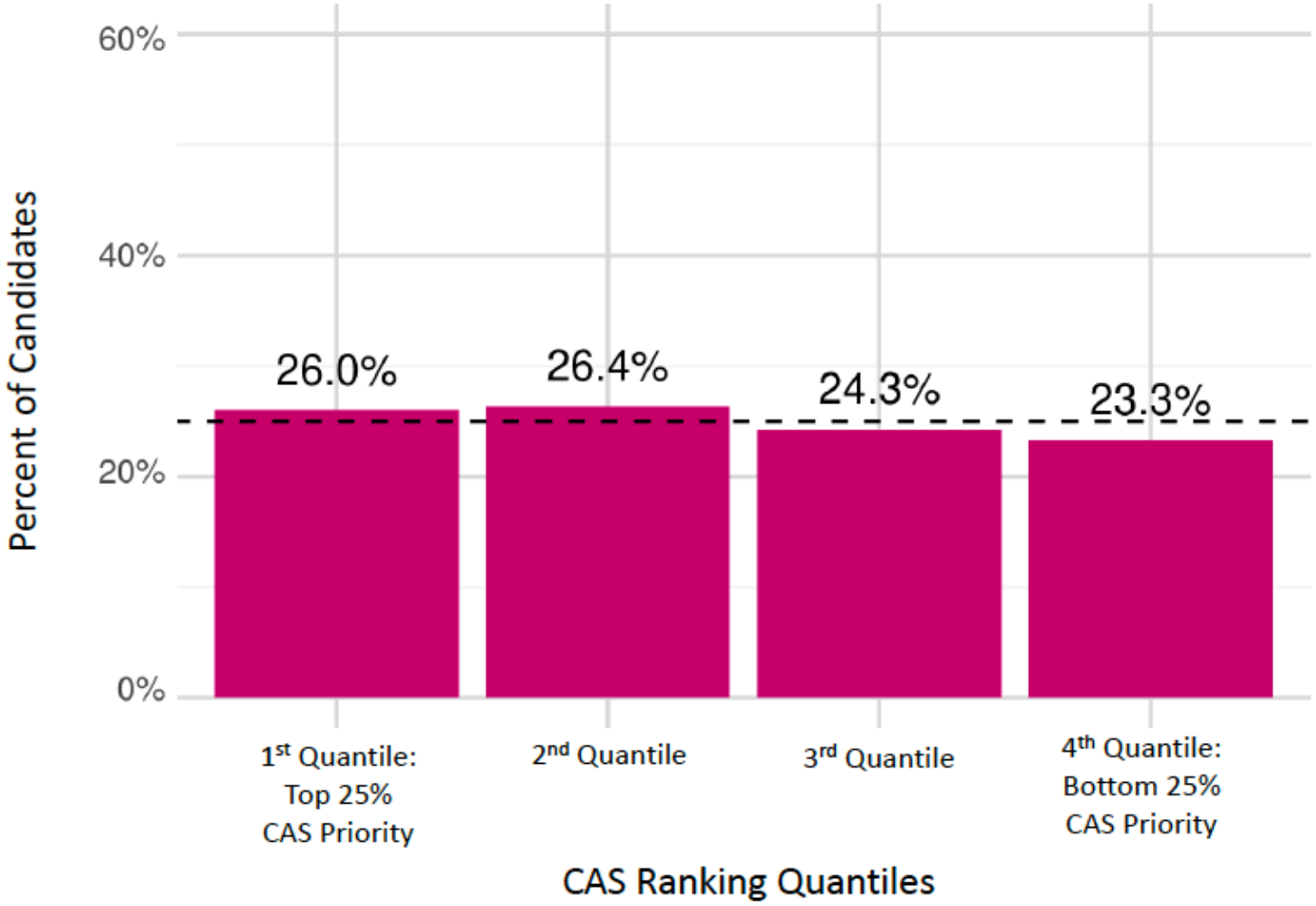
UNOS presentation to Lung Transplant Committee, November 23, 2022.

Group C: Percent of candidates in CAS rank quantile



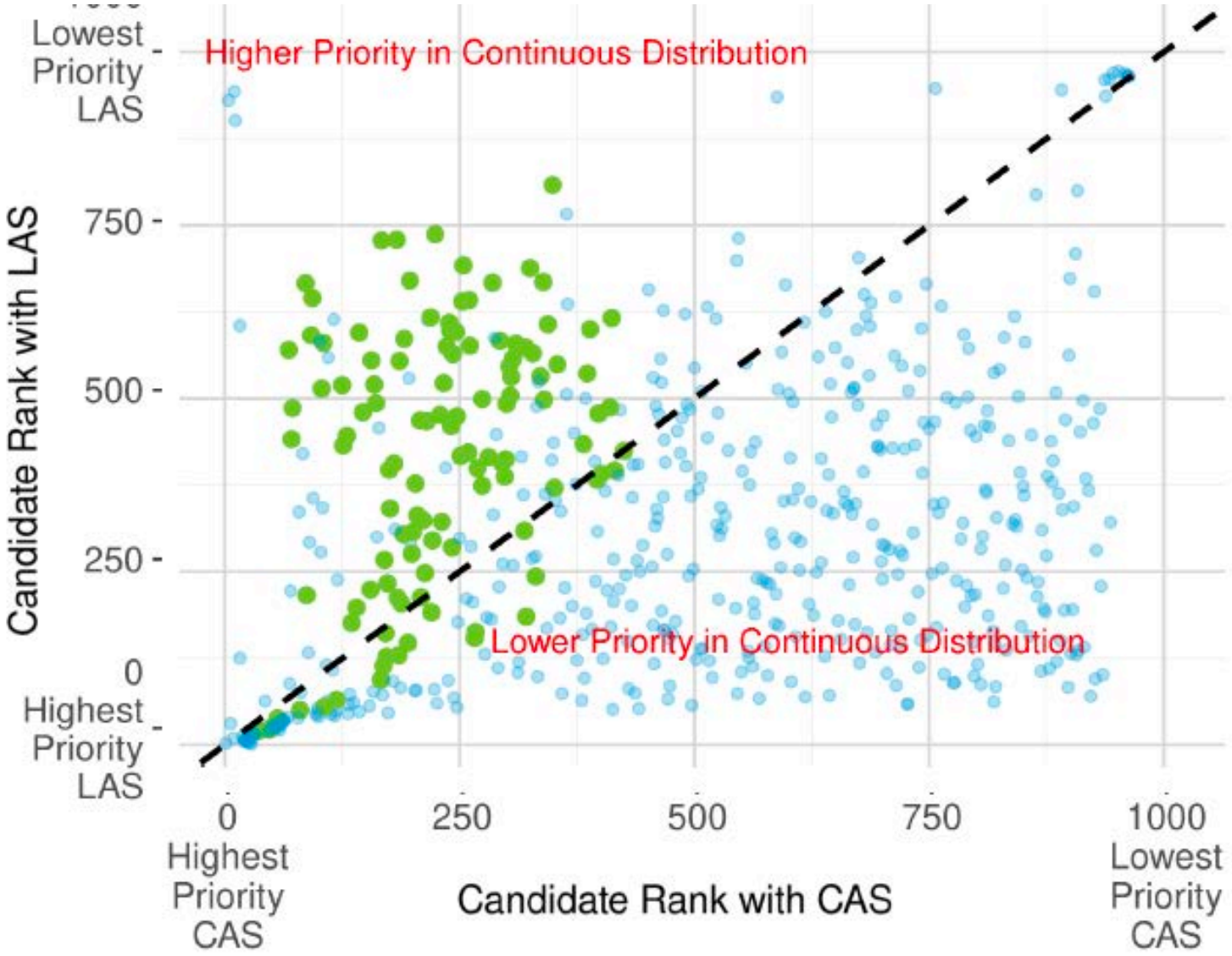
UNOS presentation to Lung Transplant Committee, November 23, 2022.

Group D: Percent of candidates in CAS rank quantile



UNOS presentation to Lung Transplant Committee, November 23, 2022.

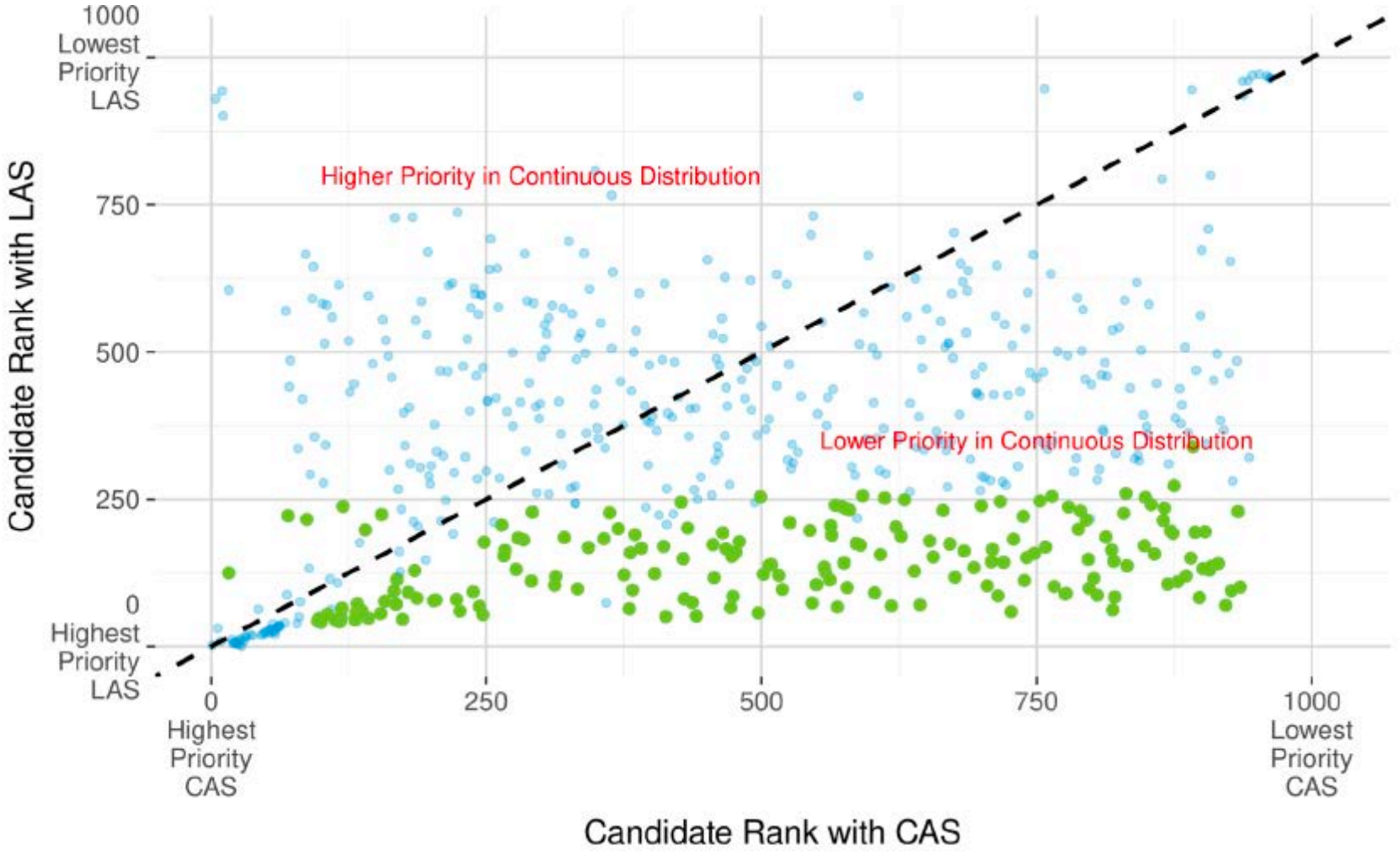
Group D: Posttransplant (PT) survival and rank change



- Top 25% PT Survival
- Bottom 75% PT Survival

UNOS presentation to Lung Transplant Committee, November 23, 2022.

Group D: Medical Urgency and Rank Change

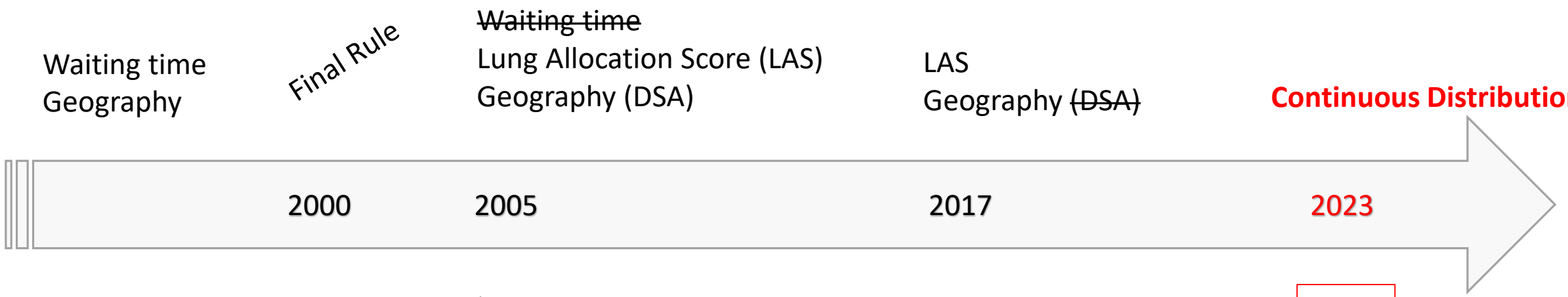


- Top 25% medical urgency under LAS and rank change of at least 50
- All other candidates

UNOS presentation to Lung Transplant Committee, November 23, 2022.

Evolution of Donor Lung Allocation Policies and Impact

Policy



Impact

↑ WL mortality

↑Sicker recipients
↑Older recipients
↑Patient-care costs
↑ Innovation
Plateaued long-term survival

↑↑Sicker recipients
↑Inefficiencies in procurement

TBD

Acknowledgments

Cleveland Clinic (NIH)
Jarrod Dalton, PhD
Carli Lehr, MD, MS, PhD
Johnie Rose, MD, PhD
Tim Chan, MD, PhD
Ivan Juric, PhD
Jodi Bell, MA
Lyla Mourany, MS
Paul Gunsalus, MS
Kate Lowe, MS, MDc
Mark Swiler, BS

Scientific Registry of Transplant Recipients (HRSA)
Andy Wey, PhD
Melissa Skeans, MS
David Schladt, MS

OPTN/UNOS Lung Committee (HRSA)



Cleveland Clinic

Every life deserves world class care.