

The NHLBI LAM Registry

Prognostic Physiologic and Radiologic Biomarkers Emerge From a 15-Year Prospective Longitudinal Analysis

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e-Table 1: Scoring sheet to calculate radiologic disease severity

Lung Zone	Extent of LAM burden on right lung (0 – 3)	Extent of LAM burden on left lung (0 – 3)	Total Score Right	Total Score Left	Total CT score
Upper					
Middle					
Lower					

Definitions:

Upper lung zone = Apex to carina

Middle lung zone = Carina to inferior pulmonary vein

Lower lung zone: Inferior pulmonary vein to diaphragm

Disease extent scoring criteria:

0 = No abnormality

1 = <30% abnormality

2 = 31-60% abnormality

3 = >61% abnormality

Total disease severity score was calculated by adding up the scores for each lung zone. The total score could range from 0 – 18. For each patient, the CT score was calculated independently by two different thoracic radiologists. The final score was computed as an average of the two independent CT scores.

e-Table 2: Association between various disease-related parameters and the risk of death or lung transplantation. All disease-related parameters in this analysis were adjusted for age at diagnosis, except the one marked with asterisk.

Characteristics	N, Mean (standard deviation) or N (%)		Hazard ratio (95% confidence interval)	p-value	
	Lung transplantation or death	Censored on December 31, 2014			
Age at diagnosis*	68, 40.0 (9.3)	148, 41.5 (10.2)	0.99 (0.96, 1.01)	0.26	
FEV1 % predicted	69, 51.3 (20.1)	146, 78.0 (21.0)	0.96 (0.95, 0.97)	<0.0001	
FEV1 slope (ml/year)	69, -108 (53.5)	146, -80 (51.1)	0.992 (0.988, 0.995)	<0.0001	
FVC % predicted	69, 80.0 (15.1)	146, 89.0 (17.0)	0.98 (0.97, 0.99)	0.005	
FVC slope in the follow-up (ml per year)	69, -84 (61.3)	146, -65.3 (55)	0.994 (0.990, 0.998)	0.006	
DLCO % predicted	68, 44.2 (15.8)	146, 71.8 (22.1)	0.95 (0.94, 0.96)	<0.0001	
DLCO Slope (ml/mmHg/min/year)	68, -0.73 (0.14)	146, -0.85 (0.22)	8.28 (2.3, 29.67)	0.001	
CT score	54, 14.0 (4.4)	111, 9.6 (4.1)	1.18 (1.11, 1.26)	<0.0001	
Log ₂ (VEGF-D)	47, 10.3 (1.3)	112, 9.8 (1.4)	1.22 (0.99, 1.50)	0.06	
Log ₂ (VEGF-D) Slope	47, 0.18 (0.28)	112, 0.07 (0.3)	2.53 (0.99, 6.49)	0.05	
Serum VEGF-D >600pg/ml	No	11 (21)	42 (79)	Ref	0.10
	Yes	36 (34)	70 (66)	1.76 (0.89, 3.48)	
Bronchodilator response	No	46 (28)	120 (72)	Ref	0.004
	Yes	23 (48)	25 (52)	2.15 (1.28, 3.59)	
Angiomyolipomas	No	43 (33)	86 (67)	Ref	0.43
	Yes	26 (30)	62 (70)	0.82 (0.50, 1.35)	
Menopausal status	No	26 (37)	44 (63)	Ref	0.06
	Yes	38 (28)	97 (72)	0.56 (0.30, 1.03)	
H/o pneumothorax	No	27 (28)	69 (72)	Ref	0.72
	Yes	41 (34)	79 (66)	1.10 (0.64, 1.90)	
Supplemental oxygen use	No	27 (18)	120 (82)	Ref	<0.0001
	Yes	42 (60)	28 (40)	4.09 (2.48, 6.72)	
Number of pneumothoraces per patient		2.8 (4.5)	2.2 (5.3)	1.00 (0.96, 1.04)	0.96
Sporadic LAM		59 (33)	121 (67)	Ref	0.59
TSC LAM		9 (25)	27 (75)	0.83 (0.41, 1.67)	

Abbreviations: DLCO = Diffusion capacity of the lung for carbon monoxide, FEV1 = Forced expiratory volume in one-second, FVC = Forced vital capacity, LAM = Lymphangiomyomatosis, TSC = Tuberosus sclerosis complex, VEGF-D = Vascular endothelial growth factor-D.

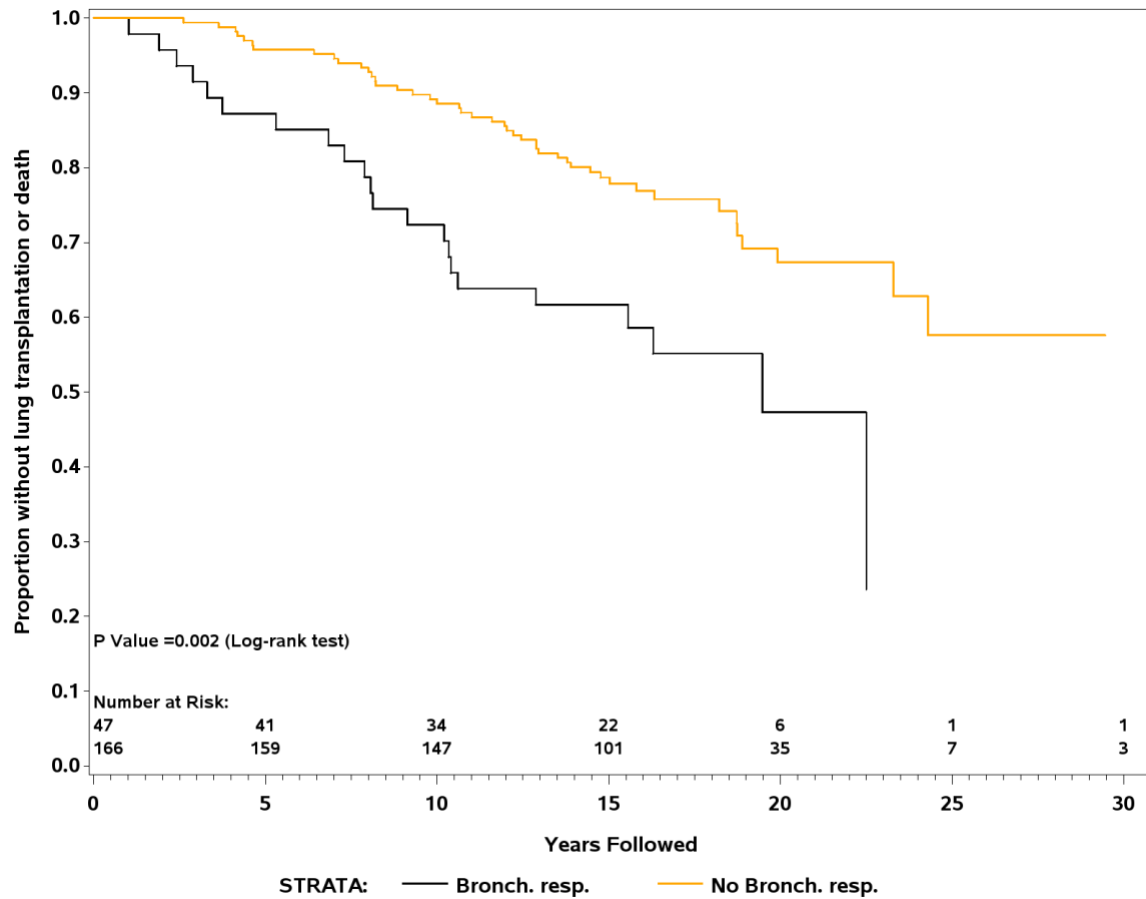
e-Table 3: Difference in baseline FEV1 and rate of decline of FEV1 in our cohort when divided into patients with and without bronchodilator responsiveness on spirometry. Patients with a positive bronchodilator response on spirometry had worse FEV1 at the time of registry enrollment as compared to the patients without bronchodilator responsiveness ($p=0.0007$), and had a trend towards a faster rate of decline of FEV1 ($p=0.09$).

Bronchodilator responsiveness	Number of patients	Mean baseline FEV1 (Liters)	Standard deviation (liters)	Mean baseline FEV1 (%predicted)	Rate of decline of FEV1 (ml/year)
No	166	2.17	0.76	73%	82.8
Yes	48	1.72	0.81	57%	113.2

Abbreviations: Same as e-Table 2.

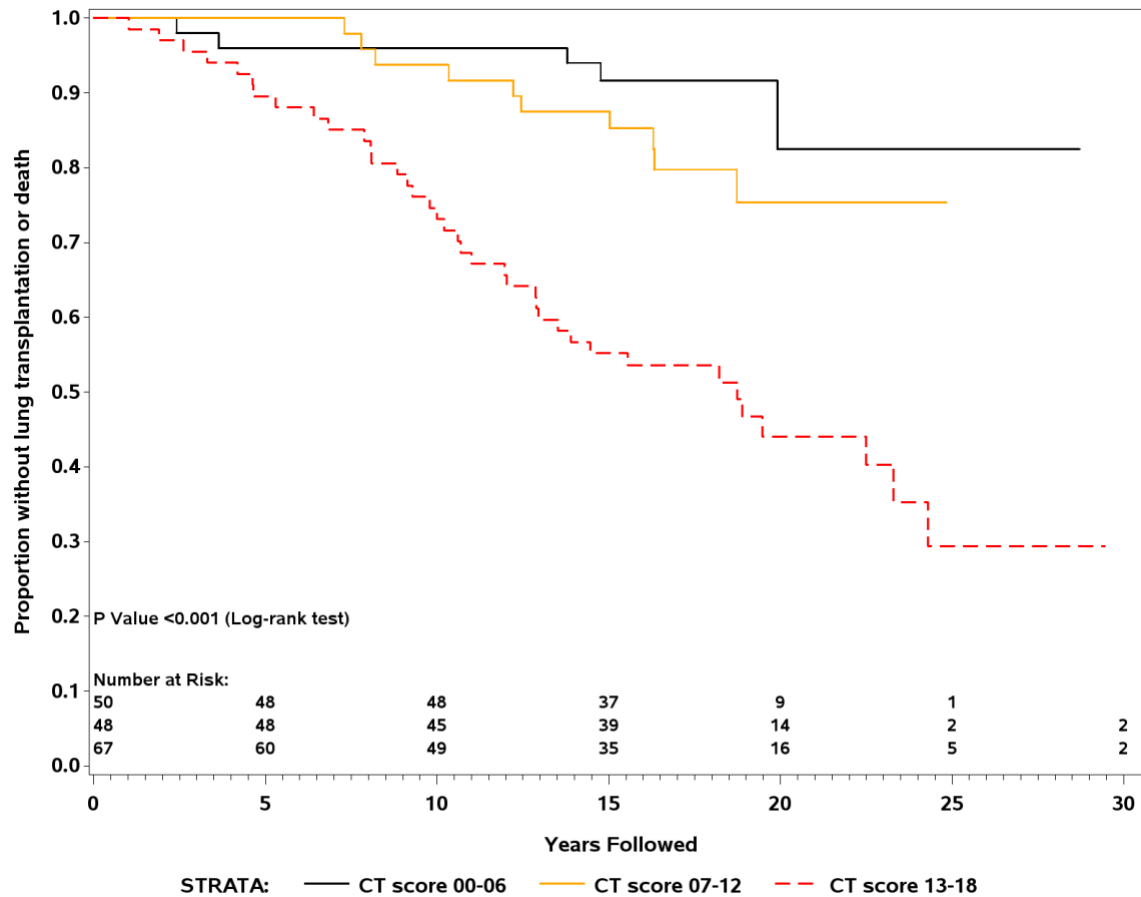
e-Figure 1: Kaplan-Meier curve demonstrating the difference in survival (based on the composite end point of death or lung transplant) in patients with or without bronchodilator responsiveness.

BR=bronchodilator responsiveness



e-Figure 2: Kaplan-Meier curve demonstrating the difference in survival (based on the composite end point of death or lung transplant) in patients segregated based on the initial radiologic disease severity as measured by the CT score.

CT = Computed tomography



e-Figure 3: Kaplan-Meier curve demonstrating the difference in survival (based on the composite end point of death or lung transplant) in patients segregated based on the initial serum VEGF-D (elevated to a value greater than 800pg/ml, or serum VEGF-D less than 800 pg/ml).
 VEGF-D = Vascular Endothelial Growth Factor-D

