CHEST Online Supplement

Diffusing Capacity Is an Independent Predictor of Outcomes in Pulmonary Hypertension Associated With COPD

Aparna Balasubramanian, MD; Todd M. Kolb, MD, PhD; Rachel L. Damico, MD, PhD; Paul M. Hassoun, MD; Meredith C. McCormack, MD; and Stephen C. Mathai, MD

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e-Table 1. Clinical characteristics of those missing DLCO data

	DLCO>50% (N=20)	DLCO≤50% (N=40)	Missing DLCO (N=11)
Age at diagnosis	65.4 +/- 8.8	64.9 +/- 8.3	64.6 +/- 10.4
Caucasian, N (%)	16 (80)	26 (65)	7 (64)
% Female, N (%)	14 (70)	27 (68)	8 (73)
BMI (kg/m2)	30.1 +/- 7.9	25.9 +/- 5.5	**32 +/- 5.7**
Ever Smokers, N (%)	17 (85)	38 (95)	11(100)
Current smoker, N (%)	3 (15)	3 (7.5)	1 (9)
Smoking Pack years	36.9 +/- 28.7	47.1 +/- 28	46 +/- 25.6
Oxygen use, N (%)	11 (55)	33 (83)	8 (72)
Nadir Oxygen Saturation %	89.6 +/- 7.5	80.5 +/- 8.4	85 +/- 8
NYHA class, N (%)			
Class I	1 (5.3)	1 (2.6)	0 (0)
Class II	11 (57.9)	12 (30.8)	4 (36)
Class III	6 (31.6)	21 (53.9)	4 (36)
Class IV	1 (5.3)	5 (12.8)	**3 (27)**
6MWD (m)*	314 +/- 128	251 +/- 110	**191 +/- 126**
Borg Dyspnea	2.9 +/- 1.4	5.2 +/- 2.5	**5.4 +/- 2.9**
NT-proBNP, median (IQR) pg/mL	229 (176, 311)	1311 (314, 2176)	771 (526, 1852)
Cr (mg/dL)	1.0 (0.3)	1.1 (0.4)	0.96 (0.2)
eGFR, median (IQR) mL/min/1.73 m2	60 (60, 60)	60 (46, 60)	60 (60, 60)
FEV1 % predicted	56 +/- 21	51 +/- 20	**43 +/- 16**
FVC % predicted	77 +/- 25	73 +/- 20	**58 +/- 11**
FEV1/FVC %	57 +/- 17	57 +/- 12	57 +/- 13
TLC % predicted*	94 +/- 33	91 +/- 19	76 +/- 12**(N=4)
RV % predicted*	119 +/- 48	121 +/- 55	91 +/- 9
DLCO % predicted	67 +/- 15	32 +/- 10	--
DLCO/VA % predicted	81 +/- 27	44 +/- 18	--
PH Medication use, N (%)	13 (65)	28 (70)	7 (64)
Comorbidities, N (%)			
Atrial Fibrillation/Flutter	1 (5)	9 (23)	0(0)
Coronary Artery Disease	4 (20)	12 (30)	2(18)
Cancer	3 (15)	7 (18)	3 (27)
DVT/PE	2 (10)	6 (15)	0 (0)
Congestive Heart Failure	1 (5)	3 (8)	1 (9)
ILD	2 (10)	4 (10)	2 (18)
OSA	5 (25)	4 (10)	5 (45)
RAP (mmHg)	8.3 +/- 4.2	9.4 +/- 5.1	10 +/- 5
mPAP (mmHg)	41.1 +/- 13.7	45.8 +/- 1.8	43 +/- 10
PCWP (mmHg)	14.9 +/- 6.8	12.9 +/- 6.5	17 +/- 7
Cardiac Index (L/min/m2)	2.7 +/- 0.6	2.1 +/- 0.6	2.2 +/- 0.5
PVR (Wood units)	6.2 +/- 5.1	9.7 +/- 5.1	7.9 +/- 4.2
PA Saturation %	69 +/- 9	64 +/- 8	67 +/- 4
Died at 5 years, N(%)	11 (55)	30 (75)	6 (55)

e-Table 2. Unadjusted and Adjusted Transplant-Free Survival including those with DLCO outside 1-year window

	Unadjusted HR	p-value	Model 1	p-value	Model 2	p-value	Model 3	p-value
Age at diagnosis	1.02 (0.98 – 1.06)	0.38	1.04 (0.99 – 1.09)	0.09	1.05 (0.99 – 1.09)	0.06	1.03 (0.98 – 1.08)	0.27
Sex	0.73 (0.36 – 1.48)	0.39	--	--	--	--	--	--
BMI (kg/m2)	0.95 (0.88 – 1.02)	0.16	--	--	--	--	--	--
Smoking Pack years	1.01 (0.99 – 1.02)	0.06	--	--	--	--	--	--
6MWD (m)	0.99 (0.99 – 0.99)*	0.048*	--	--	--	--	--	--
Borg Dyspnea	1.09 (0.93 – 1.28)	0.29	--	--	--	--	--	--
Oxygen Use	2.90 (1.12 – 7.51)*	0.028*	--	--	1.62 (0.57 – 4.59)	0.37	--	--
FEV1 % predicted	1.00 (0.98 – 1.02)	0.65	0.99 (0.98 – 1.02)	0.95	--	--	--	--
FVC % predicted	1.00 (0.99 – 1.02)	0.83	--	--	--	--	--	--
FEV1/FVC %	1.01 (0.99 – 1.04)	0.33	--	--	--	--	--	--
RV % predicted	0.99 (0.99 – 1.00)	0.19	--	--	--	--	--	--
DLCO % predicted	**0.96 (0.94 – 0.98)***	**0.002***	**0.96 (0.93 – 0.98)***	**0.002***	**0.96 (0.94 – 0.99)***	**0.005***	**0.96 (0.94 – 0.99)***	**0.03***
NT-proBNP† (pg/mL)	2.51 (1.32 – 4.79)*	0.005*	--	--	--	--	1.24 (0.57 – 2.67)	0.59
Cr (mg/dL)	1.36 (0.46 – 4.09)	0.58	--	--	--	--	--	--
mPAP (mmHg)	1.02 (1.00 – 1.06)*	0.03*	--	--	--	--	--	--
PVR (Wood units)	1.07 (1.01 – 1.14)*	0.02*	1.04 (0.97 – 1.13)	0.27	1.04 (0.97 – 1.13)	0.26	1.05 (0.96 – 1.14)	0.31
Cardiac Output (L/min)	0.76 (0.58 – 0.99)*	0.045*	--	--	--	--	--	--
PCWP (mmHg)	0.95 (0.89 – 1.02)	0.15	--	--	--	--	--	--
PH Medication Use	1.85 (0.84 – 4.09)	0.13	--	--	--	--	--	--

Model 1 (N=58) included age at diagnosis, FEV1% predicted, DLCO% predicted, and PVR as covariates. Model 2 (N=58) included age at diagnosis, oxygen use, DLCO % predicted, and PVR as covariates. Model 3 (N=44) included age at diagnosis, DLCO % predicted, NT-proBNP, and PVR as covariates.

*Denotes statistical significance $p<0.05$. †NT-proBNP was $\log_{10}$-transformed for normality. Hazard ratios are reported per 1 unit increase in clinical predictor; sex hazard ratio is for females vs males, NT-proBNP is per 10 fold increase in pg/mL. *HR = hazard ratio, BMI = body mass index, 6MWD = six-minute walk distance, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, RV = residual volume, DLCO = diffusing capacity of the lung for carbon monoxide, Cr = creatinine, mPAP = mean pulmonary arterial pressure, PVR = pulmonary vascular resistance, PCWP = pulmonary capillary wedge pressure, PH = pulmonary hypertension*

e-Table 3. Unadjusted and Adjusted Survival excluding "pulmonary vascular phenotype" patients

	Unadjusted HR	p-value	Model 1	p-value	Model 2	p-value	Model 3	p-value
Age at diagnosis	1.01 (0.97 – 1.05)	0.69	0.99 (0.95 – 1.05)	0.93	1.02 (0.96 – 1.07)	0.56	0.99 (0.94 – 1.05)	0.83
Sex	0.62 (0.29 – 1.31)	0.21	--	--	--	--	--	--
BMI (kg/m2)	0.95 (0.87 – 1.03)	0.18	--	--	--	--	--	--
Smoking Pack years	1.01 (1.00 – 1.03)*	0.02*	--	--	--	--	--	--
6MWD (m)	0.99 (0.99 – 0.99)*	0.049*	--	--	--	--	--	--
Borg Dyspnea	1.07 (0.89 – 1.27)	0.47	--	--	--	--	--	--
Oxygen Use	3.66 (1.28 – 10.5)*	0.016*	--	--	1.24 (0.41 – 3.75)	0.71	--	--
FEV1 % predicted	1.00 (0.98 – 1.02)	0.73	1.01 (0.99 – 1.04)	0.21	--	--	--	--
FVC % predicted	1.00 (0.98 – 1.02)	0.89	--	--	--	--	--	--
FEV1/FVC %	1.01 (0.99 – 1.04)	0.35	--	--	--	--	--	--
RV % predicted	0.99 (0.99 – 1.00)	0.34	--	--	--	--	--	--
DLCO % predicted	**0.95 (0.92 – 0.97)***	**<0.001***	**0.95 (0.92 – 0.98)***	**0.002***	**0.96 (0.93 – 0.98)***	**0.005***	**0.96 (0.93 – 0.99)***	**0.008***
NT-proBNP† (pg/mL)	1.39 (1.04 – 1.85)*	0.03*	--	--	--	--	1.02 (0.47 – 2.2)	0.95
Cr (mg/dL)	1.75 (0.51 – 6.07)	0.38						
mPAP (mmHg)	1.04 (1.01 – 1.07)*	0.007*	--	--	--	--	--	--
PVR (Wood units)	1.11 (1.03 – 1.18)*	0.002*	1.06 (0.98 – 1.15)	0.12	1.07 (0.98 – 1.16)	0.09	1.10 (1.00 – 1.21)	0.047*
Cardiac Output (L/min)	0.69 (0.51 – 0.95)*	0.022*	--	--	--	--	--	--
PCWP (mmHg)	0.94 (0.88 – 1.01)	0.11	--	--	--	--	--	--
PH Medication Use	1.94 (0.83 – 4.52)	0.13	--	--	--	--	--	--

Model 1 (N=49) included age at diagnosis, FEV1% predicted, DLCO% predicted, and PVR as covariates. Model 2 (N=49) included age at diagnosis, oxygen use, DLCO % predicted, and PVR as covariates. Model 3 (N=36) included age at diagnosis, DLCO % predicted, NT-proBNP, and PVR as covariates.

*Denotes statistical significance $p<0.05$. †NT-proBNP was $\log_{10}$-transformed for normality. Hazard ratios are reported per 1 unit increase in clinical predictor; sex hazard ratio is for females vs males, NT-proBNP is per 10 fold increase in pg/mL. *HR = hazard ratio, BMI = body mass index, 6MWD = six-minute walk distance, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, RV = residual volume, DLCO = diffusing capacity of the lung for carbon monoxide, Cr = creatinine, mPAP = mean pulmonary arterial pressure, PVR = pulmonary vascular resistance, PCWP = pulmonary capillary wedge pressure, PH = pulmonary hypertension*

e-Table 4. Cause of Death

Cause of Death	N (%)
Respiratory Failure	10 (38%)
Sudden Cardiac Death	5 (19%)
Transplant	3 (11%)
Coronary Artery Disease	3 (11%)
Lung Cancer	2 (8%)
Sepsis	2 (8%)
Gastrointestinal Bleed	1 (4%)

Cause of death was obtained in 23 individuals (68% of those that died), with an additional three undergoing lung transplantation. Percentages listed above are among the 26 with a death or transplant event with known etiology.

e-Table 5. Unadjusted and Adjusted Transplant-free Survival using KCO % predicted

	Unadjusted HR	p-value	Model 1	p-value	Model 2	p-value	Model 3	p-value
Age at diagnosis	1.02 (0.98 – 1.06)	0.38	1.00 (0.95 – 1.05)	0.88	1.01 (0.96 – 1.07)	0.18	0.99 (0.94 – 1.06)	0.91
Sex	0.73 (0.36 – 1.48)	0.39	--	--	--	--	--	--
BMI (kg/m$_2$)	0.95 (0.88 – 1.02)	0.16	--	--	--	--	--	--
Smoking Pack years	1.01 (0.99 – 1.02)	0.06	--	--	--	--	--	--
6MWD (m)	0.99 (0.99 – 0.99)*	0.048*	--	--	--	--	--	--
Borg Dyspnea	1.09 (0.93 – 1.28)	0.29	--	--	--	--	--	--
Oxygen Use	2.90 (1.12 – 7.51)*	0.028*	--	--	2.49 (0.51 – 12.1)	0.26	--	--
FEV1 % predicted	1.00 (0.98 – 1.02)	0.65	0.99 (0.97 – 1.02)	0.52	--	--	--	--
FVC % predicted	1.00 (0.99 – 1.02)	0.83	--	--	--	--	--	--
FEV1/FVC %	1.01 (0.99 – 1.04)	0.33	--	--	--	--	--	--
RV % predicted	0.99 (0.99 – 1.00)	0.19	--	--	--	--	--	--
KCO % predicted	**0.97 (0.96 – 0.99)***	**0.008***	**0.98 (0.96 – 0.99)**	**0.05**	**0.98 (0.96 – 1.00)**	**0.076**	**0.98 (0.96 – 1.00)***	**0.08***
NT-proBNP† (pg/dL)	2.51 (1.32 – 4.79)*	0.005*	--	--	--	--	1.08 (0.75 – 1.56)	0.68
Cr (mg/dL)	1.37 (0.46 – 4.09)	0.58	--	--	--	--	--	--
mPAP (mmHg)	1.02 (1.00 – 1.06)*	0.03*	--	--	--	--	--	--
PVR (Wood units)	1.07 (1.01 – 1.14)*	0.02*	1.04 (0.94 – 1.15)	0.42	1.02 (0.93 – 1.12)	0.69	1.00 (0.88 – 1.15)	0.91
Cardiac Output (L/min)	0.76 (0.58 – 0.99)*	0.045*	--	--	--	--	--	--
PCWP (mmHg)	0.95 (0.89 – 1.02)	0.15	--	--	--	--	--	--
PH Medication Use	1.85 (0.84 – 4.09)	0.13	--	--	--	--	--	--

Model 1 (N=44) included age at diagnosis, FEV1% predicted, KCO% predicted, and PVR as covariates. Model 2 (N=44) included age at diagnosis, oxygen use, KCO% predicted, and PVR. Model 3 (N=32) included age at diagnosis, KCO % predicted, NT-proBNP, and PVR.

*Denotes statistical significance $p<0.05$. †NT-proBNP was $\log_{10}$-transformed for normality. Hazard ratios are reported per 1 unit increase in clinical predictor; sex hazard ratio is for females vs males, NT-proBNP is per 10-fold increase in pg/mL. *HR = hazard ratio, BMI = body mass index, 6MWD = six-minute walk distance, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, RV = residual volume, KCO = gas transfer efficiency, Cr = creatinine, mPAP = mean pulmonary arterial pressure, PVR = pulmonary vascular resistance, PCWP = pulmonary capillary wedge pressure, PH = pulmonary hypertension*

e-Table 6. Adjusted Transplant-free Survival excluding individuals with PCWP>15mmHg

	Model 1	p-value	Model 2	p-value	Model 3	p-value
Age at diagnosis	1.09 (1.03 – 1.17)	0.005*	1.09 (1.02 – 1.16)	0.008*	1.08 (1.01 – 1.15)	0.02*
Oxygen Use	--	--	1.22 (0.35 – 4.19)	0.32	--	--
FEV1 % predicted	0.99 (0.97 – 1.01)	0.42	--	--	--	--
DLCO % predicted	**0.97 (0.94 – 0.99)**	**0.008***	**0.97 (0.94 – 0.99)**	**0.03***	**0.97 (0.94 – 1.00)**	**0.05**
NT-proBNP† (pg/dL)	--	--	--	--	0.93 (0.57 – 1.52)	0.78
PVR (Wood units)	1.03 (0.94 – 1.12)	0.58	1.03 (0.94 – 1.12)	0.59	1.05 (0.94 – 1.16)	0.39

Model 1 (N=40) included age at diagnosis, FEV1% predicted, DLCO% predicted, and PVR as covariates. Model 2 (N=40) included age at diagnosis, oxygen use, DLCO% predicted, and PVR. Model 3 (N=27) included age at diagnosis, DLCO % predicted, NT-proBNP, and PVR.
*Denotes statistical significance $p<0.05$. †NT-proBNP was $\log_{10}$-transformed for normality. Hazard ratios are reported per 1 unit increase in clinical predictor; sex hazard ratio is for females vs males, NT-proBNP is per 10-fold increase in pg/mL. *FEV1 = forced expiratory volume in 1 second, DLCO = diffusing capacity of the lung for carbon monoxide, PVR = pulmonary vascular resistance, PCWP = pulmonary capillary wedge pressure*

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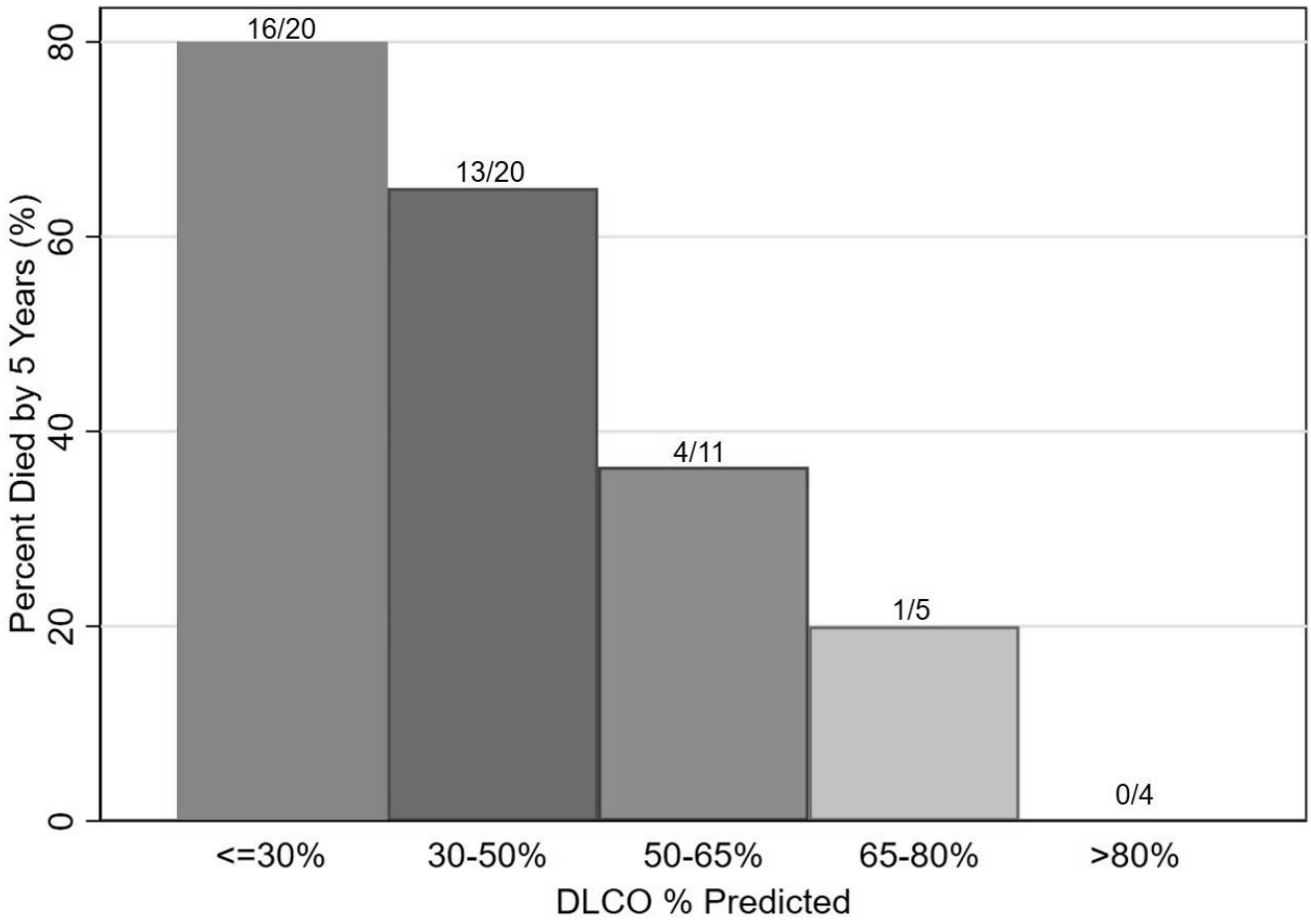
e-Figure 1. Mortality by DLCO Clinical Categories



Percentage of patients in each DLCO group who had died by 5 years. Groups defined as DLCO≤30% (N=20), 30-50% (N=20), 50-65% (N=11), 65-80% predicted (N=5), and >80% predicted (N=4). Numbers above each bar represents absolute number dead/total in each group. Groups were identified by clinically utilized severity classification at Johns Hopkins. *DLCO = diffusing capacity of the lung for carbon monoxide*