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DLco, Kco and FVC/DLco in suspected systemic sclerosis-associated pulmonary hypertension: Insights from the ASPIRE registry

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Abstract

Objectives: There are limited data comparing parameters reflecting gas transfer used to assess the likelihood of pulmonary hypertension (PH) in patients with systemic sclerosis (SSc) and regarding the impact of transitioning to Global Lung Initiative (GLI)-predicted values.

Methods: 632 patients with suspected SSc associated PH were identified from the ASPIRE registry. Spirometry and CT reports were reviewed to identify significant lung disease. ROC curve analysis and correlations of the 3 markers of gas transfer with pulmonary arterial pressure were performed.

Results: Correlations of GLI-derived values with mean pulmonary arterial pressure were: DLco% r=-0.45, Kco% r=-0.42 and FVC%/DLco% r=0.37. Correlations in patients without lung disease were: DLco% r=-0.51, Kco% r=-0.44, FVC%/DLco% r=0.38, compared to patients with lung disease: DLco% r=-0.41, Kco% r=-0.39, FVC%/DLco% r=0.39. Area under the curve for the presence of PH in the overall study cohort was significantly superior for DLco% at 0.84 (optimal threshold 53%), compared with Kco% 0.74 (60%) and FVC%/DLco% was 0.74 (1.91), p both <0.001. Compared with European Coal and Steel Community-derived data, GLI-derived percent-predicted lung volumes were lower, DLco% and Kco% were higher and consequently FVC%/DLco% lower (p all <0.001).

Conclusion: DLco performed as least as strongly as Kco or FVC%/DLco% in terms of correlations with mPAP and diagnostic utility, regardless of the presence or absence of lung disease. Transitioning to GLI equations led to lower predicted spirometric volumes and higher DLco%. This should be considered when interpreting changes in values over time and when using screening algorithms.

Introduction

Pulmonary hypertension (PH) may develop for a number of reasons including the presence of a pulmonary arterial vasculopathy (pulmonary arterial hypertension, PAH), or in association with chronic lung disease (PH-CLD).[1,2] Although PAH is a rare condition in the general population it develops in 6.4-9% of patients with systemic sclerosis (SSc).[3,4] Patients with SSc may also develop PH-CLD given that ≈40% of patients have clinically overt interstitial lung disease (ILD).[5] A number of screening algorithms for the early identification of SSc associated PH have been developed including the DETECT and Australian Scleroderma Interest Group approaches, both of which include a measure of gas transfer.[6,7]

The diffusing capacity for carbon monoxide (DLco) is assessed most commonly via the single breath method.[8] During this, carbon monoxide is removed exponentially from alveolar gas at a rate constant, Kco while alveolar volume, VA, is calculated from dilution of an inert gas, most often helium. The product of Kco and VA is termed DLco. The ratio of FVC percent-predicted (FVC%) to DLco percent-predicted (DLco%), FVC%/DLCo%, has been proposed as a superior measure of gas transfer in patients with SSc, especially those with coexisting ILD.[9] DLco% tends to be lower in patients with SSc-PAH than in patients with idiopathic PAH while a recent study demonstrated an accelerated fall in DLco% and Kco% and accelerated rise in FVC%/DLco% in the ≈6 years prior to diagnosis of PH.[10,11] There are, however, limited published data directly comparing these 3 markers of gas transfer in SSc patients or examining the effect of changing clinical practice from the use of European Coal and Steel Community (ECSC) to Global Lung Function Initiative (GLI) predictive equations in patients with SSc.[12,13,14]

We have therefore interrogated a large database of patients assessed at a specialist referral centre (Assessing the Spectrum of Pulmonary hypertension Identified at a REferral centre, ASPIRE) to test the hypothesis that Kco% or FVC%/DLco% are superior, both in terms of diagnostic utility and correlation with pulmonary arterial pressure, to DLco% in patients with suspected SSc-associated precapillary PH. We also investigated the effect of transitioning from ECSC to GLI reference equations.

Methods

The ASPIRE registry, which consists of consecutive patients reviewed at a UK PH referral centre, was interrogated to identify consecutive patients with SSc who had been investigated during 2000-2020.[15,16] Demographic, haemodynamic and lung function data were collected from clinical data sets.

Haemodynamic diagnostic criteria described in the 2022 European Society of Cardiology/European Respiratory Society (ESC/ERS) PH guidelines were used.[17] Briefly, PH was defined by a mean pulmonary arterial pressure (mPAP) >20 mmHg. Pre-capillary PH (PAH or PH-CLD) was defined by a pulmonary arterial wedge pressure (PAWP) ≤15 mmHg and a pulmonary vascular resistance (PVR) >2 WU, PH due to left heart disease (PH-LHD) by a PAWP >15 mmHg and Unclassified-PH by a PAWP ≤15 mmHg and PVR ≤2WU. Date of diagnosis was the date of the first right heart catheterisation which demonstrated the presence or absence of PH. Ethical approval was gained (REC 22/EE/0011).

Pulmonary function testing was performed according to contemporary ERS guidelines with DLco measured using the single breath technique.[18-23] Prior to 2020, in our service ECSC reference equations were used to produce reference values for individual patients.[13,21] During 2020, reference values began to be calculated using GLI data.[14,24] For the purpose of this study, reference values for spirometry and measures of gas diffusion capacity for carbon monoxide (uncorrected for haemoglobin levels) were derived using both ECSC and GLI Global equations.[25] Patients who had incomplete data to allow calculation of both ECSC and GLI reference values or who had undergone lung function testing >90 days before or after the date of RHC were excluded.

Computed Tomography (CT) clinical reports nearest to the time of diagnosis were retrieved and the extent of any parenchymal lung disease was recorded as being minor, mild, moderate or severe. If no reports were available then descriptions from clinic letters were used. Extensive interstitial lung disease was defined by moderate-severe parenchymal lung disease or by an FVC ≤70% if mild parenchymal disease was noted on CT.[26] Clinically important chronic obstructive pulmonary disease was described by an FEV_1/FVC of <0.7 with an FEV_1 <60% predicted. Patients with any of the above were deemed to have chronic lung disease (CLD). Patients with precapillary PH but without evidence of CLD (including those with minor or mild parenchymal lung disease on CT) were classified into the PAH group. Patients' original haemodynamic and clinical classification was used throughout the study.

Statistical Analysis

Data were analysed using R software (version 4.0.5). Data were presented as mean ±standard deviation or median (25th, 75th centile) as appropriate. ANOVA or Kruskal-Wallis tests with Bonferonni post-hoc correction was used to assess differences in patient characteristics between groups. Correlations were assessed using the Pearson method. Diagnostic thresholds were assessed by ROC curve analysis using pROC (1.18.5) and ggplot2 (version 3.5.0) packages. Long's test was used to assess for significant difference between ROC curves. Steiger's T-test was used to compare correlation coefficients. Paired T-Test was used to compare ECSC and GLI-derived predicted value.

Results

Baseline Characteristics

Out of 912 SSc patients assessed during the study period, 798 patients with adequate RHC data were identified (**Figure 1**). Spirometry and gas transfer measures were available for 697 patients. Fifty-five patients had lung function performed >90 days before or after RHC while in 10 patients ≥85 years, predictive lung function equations could not be used, leaving a total study cohort of 632 patients.

Baseline characteristics are shown in **Table 1**. Seventy-nine patients (13%) had No-PH, 313 (49%) had PAH, 166 (26%) had PH-CLD, 30 (5%) had Unclassified-PH and 44 patients (7%) had PH-LHD. The majority of patients (84%) were female with a mean age of 66.1 ±10 years. Although a higher proportion of patients with PAH and PH-CLD were in WHO FC III & IV, around half of patients with No-PH or Unclassified-PH were also in these higher FC groups. Exercise capacity was worse in patients with pre-capillary PH or PH-LHD than those with No-PH or Unclassified-PH. Patients with PH-CLD and PH-LHD had greater spirometric impairment than patients in the other 3 groups. Whereas values of Kco% in patients with PAH and PH-CLD were similar (and significantly lower than in patients with No-PH, Unclassified-PH and PH-LHD), DLco% was lower in PH-CLD than in PAH but similar to PH-LHD. FVC%/DLco% was similar in patients with PAH and PH-CLD and higher than in the other 3 groups. Patients with Unclassified-PH had a higher PAWP than patients with precapillary PH or No-PH. Compared with ECSC-derived data, GLI-derived percent-predicted lung volumes were lower (FEV_1 81.2 ±20% versus 84.5 ±20% ($p < 0.001$), FVC 87.1 ±22% versus 94.3 ±24% ($p < 0.001$)), DLco% and Kco% were higher (45.5 ±18% versus 40.7 ±15% ($p < 0.001$) and 58.9 ±20% versus 56.8 ±19% ($p < 0.001$)) and consequently FVC%/DLco% lower (2.16 ±0.94 versus 2.61 ±1.2 ($p < 0.001$)). Baseline characteristics of subgroups based on the presence or absence of lung disease are summarised in **Supplementary Table 1.**

Correlations

Correlations between the 3 measures of gas transfer using ECSC and GLI reference values are shown in **Table 2 and Figure 2.** Using GLI reference values, DLco% had the numerically strongest and FVC%/DLco% the weakest correlation with mPAP in the whole cohort and in those patients with or without significant lung disease (**Supplementary Figures 1A and 1B)**. A very similar pattern was observed when using ECSC data.

Diagnostic Utility

ROC curve analysis is summarised in **Table 3 and Figure 3.** As our previous work demonstrated very similar survival of patients with No-PH and Unclassified-PH, for the purposes of ROC analyses the 2 groups were amalgamated.[16] Almost identical results were achieved if the Unclassified-PH patients were excluded from analysis (data not shown). For the overall study cohort, the optimal threshold and area under the curve (AUC) using ECSC data for the prediction of PH for DLco% was 44% (AUC 0.83), for Kco% was 54% (AUC 0.74) and for FVC%/DLco% was 2.19 (AUC 0.73: AUC for DLco% versus Kco% or FVC%/DLco% both $p<0.001$). Using GLI data, the optimal threshold and AUC for the prediction of PH for DLco% was 49% (AUC 0.84), for Kco% was 60% (AUC 0.74) and for FVC%/DLco% was 1.91 (AUC 0.74:

AUC for DLco% versus Kco% or FVC%/DLco% both p<0.001). AUCs for DLco% remained numerically superior in analysis of subgroups of patients with precapillary haemodynamics and the presence or absence of lung disease. ROC analysis using the previous haemodynamic definition of precapillary PH (mPAP ≥25 mmHg and PVR >3 WU) produced almost identical results (data not shown). Only 6 patients with pre-capillary PH had a DLco% (GLI) >80% (sensitivity 99%, specificity 17%) while no patients with pre-capillary PH had a DLco% (ECSC) of >80% (sensitivity 100%, specificity 6%). Conversely, only 3 patients with Unclassified-PH in the absence of lung disease had a DLco% lower than the optimal threshold (47% ECSC and 53% GLI).

Discussion

By interrogating a large registry of SSc patients referred with suspected precapillary PH we have been able to compare the correlation with pulmonary arterial pressure and diagnostic utility of 3 measures of gas transfer (DLco%, Kco% and FVC%/DLco%). We have also compared the effect of changing from the ECSC to GLI predictive equations.

We observed that, in the overall study cohort and in the subgroups with or without significant lung disease, correlations with mPAP were non-inferior (and were indeed numerically strongest) for DLco% and numerically weakest for FVC%/DLco%. We observed correlations between DLco% and mPAP of r=-0.44 (ECSC) or -0.45 (GLI) in the overall cohort and -0.51 (both equations) in patients without significant lung disease, which are stronger than the r=0.30 reported by Mukerjee *et al* in 85 SSc patients without significant fibrosis.[27] Sivova *et al* studied 63 SSc patients and observed correlations between sPAP (derived from echocardiography) and DLco% and FVC%/DLco% of r=-0.67 and r=0.66 respectively.[28] It must be noted that only a minority of their study (n=18) had PH.

We also observed that, within the overall study cohort, the AUC for DLco% was significantly higher than for both Kco% and FVC%/DLco%. In addition, AUC for DLco% was numerically stronger than for Kco% and FVC/DLco% in the subgroup of patients with lung disease. A small number of previous studies have reported a range of AUCs for the presence of PH in patients with SSc (ranging from 0.56 to 0.93 for DLco% and from 0.54 to 0.93 for FVC%/DLco%).[6,12,28,29] The wide range of AUCs likely represents differences in patient characteristics between the studies as well as changes in PH haemodynamic definitions. Of note, Soumagne *et al* studied 572 patients with systemic sclerosis (of whom 336 had no ILD, 226 had ILD and 58 were diagnosed with PH as defined by a mPAP ≥25 mmHg). Similarly to our study, they did not observe any superiority of the diagnostic utility of FVC/DLco% over DLco% alone in patients with or without ILD (no ILD: AUC for DLco% was 0.91 versus 0.87 for FVC%/DLco%, ILD: AUC for DLco% was 0.76 versus 0.73 for FVC%/DLco%).

Although Kco is often described as DLco "adjusted for" VA, DLco is actually the pressure and unit-adjusted product of Kco and VA. It is therefore apparent that conditions differentially affecting Kco and VA may result in the same DLco.[8] SSc may be associated with a reduced Kco as a result of microcirculatory damage with reduced capillary blood volume (Vc) or increased thickness of the alveolar-capillary membrane with reduced membrane diffusing capacity (Dm) or a combination of the two. Interstitial lung disease (ILD) may result in reduced VA, also resulting in lower DLco. It has been hypothesised that the ratio of FVC% and DLco% may be a more powerful marker of pulmonary vascular disease, especially in patients with ILD, as the DLco will fall disproportionately compared with any fall in FVC resulting in an increased ratio.[9] The reason for the lack of a demonstrable superiority *in vivo* of FVC%/DLco% over DLco%, in terms of both correlation with mPAP and of diagnostic utility, is not clear. One could postulate that it relates to the fact that ILD-related reduction in FVC will also reduce VA resulting in correlation between the numerator and denominator.

In 1993 the European Coal and Steel Community (ECSC) reference values for pulmonary function tests were recommended for use by a European Respiratory Society clinical statement.[13,21] These reference values were derived purely from European males working in coal mines and steel works and it is important to note that approximately 80% of patients with SSc are female. The Global Lung Function Initiative (GLI) subsequently published new reference values, based on a sex-balanced and more geographically-diverse patient cohort, for spirometry and DLco in 2012 and 2017, respectively.[14,24] Although GLI data initially included ethnicity-specific equations, the subsequent GLI Global equations used in our study are race-neutral.[30]

In addition to the study of Soumagne *et al* discussed above, Mangseth *et al* subsequently studied 577 non-SSc patients (pulmonary fibrosis, haematology disorders, lung transplant recipients and healthy controls) who had taken part in clinical studies.[12, 31] Both studies observed significantly lower FEV_1% and FVC%, higher DLco% and hence lower FVC%/DLco% predicted values using GLI equations when compared with ECSC. We replicated these findings in an independent large cohort of SSc patients. These observations are clinically important in terms of longitudinal follow-up of patients with historical ECSC data, but also in identifying patients who require further investigations. For example, FVC%/DLco% is one of 6 parameters in step 1 of the DETECT algorithm while DLco <70% predicted and FVC%/DLco% ≥1.8 are criteria for further investigation in the ASIG algorithm.[6,7,32] Both these algorithms were derived before the development of the GLI and so the use of GLI-derived values for a patient raises the risk of a patient with PH not proceeding for further investigation due to a falsely reassuring reading.

Limitations

Lung function data was not always performed at the right heart catheterisation visit. However, we excluded patients with more than 90 days between right heart catheterisation and lung function testing. Although DLco measurements were not corrected for haemoglobin levels, this reflects widespread clinical practice when recent haemoglobin levels are unavailable at the time of lung function testing. Anaemia may reduce DLco and affect correlation and AUC measurements but the impact on either ECSC or GLI predicted values would be similar. Although there were a number of patients without PH at RHC, this study cohort consists of patients in whom PH has been suspected which affects its generalisability of its findings to unselected SSc populations. Nevertheless, our observations are consistent with previous, less selected, studies.

Conclusion

DLco% is at least non-inferior to Kco% or FVC%/DLco% in terms of correlations with mPAP and diagnostic utility in patients with systemic sclerosis and suspected PH. Transitioning to GLI equations leads to lower predicted spirometric volumes, higher

DLco% and hence lower FV%/DLco%. This should be considered when interpreting changes in values over time and when using screening algorithms.

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Conflicts of Interest
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Table 1. Baseline Characteristics

	Whole cohort (n=632)	No-PH (n=79)	PAH (n=313)	PH-CLD (n=166)	Unclassified-PH (n=30)	PH-LHD (n= 44)	P-Value
Female (%)	84	90 [c]	89 [c]	71 [a b]	77	91	<0.001
WHO FC I/II/III/IV (%)	2/16/74/8	8/42/50/0 [b c e]	2/10/80/7 [a c d]	1/8/76/15 [a b d]	3/43/53/0 [b c]		<0.001
WHO FC I/II/III/IV (%)	2/16/74/8	8/42/50/0 [b c e]	2/10/80/7 [a c d]	1/8/76/15 [a b d]	3/43/53/0 [b c]	3/23/73/3 [a]	
Age (years)	66.14 ±10	64.27 ±11	67.14 ±10	66.41 ±10	62.29 ±12	65.05 ±12	0.036
SSc Form: lSSc/dSSc/Not Specified/Overlap (%)	75/8/11/5	59/10/17/14 [a b c d]	85/4/8/4 [a c]	66/17/13/4 [b]	77/7/13/3 b	68/9/18/5	<0.001
ISWD (metres)	160 (80,270)	270 (140,420) [b c d]	140 (70, 270) [a d]	140 (70, 250) [a d]	290 (140, 480) [c e]	140 (80, 260) [a d]	<0.001
mPAP (mmHg)	35.8 ± 14	16.77 ± 2 [b c d e]	40.26 ± 13 [a d]	38.13 ± 13 [a d]	23.9 ± 2 [a b c e]	38.68 ± 14 [a d]	<0.001
PAWP (mmHg)	10.1 ± 3.9	7.7 ± 3 [b c d e]	9.72 ± 3 [a d e]	9.3 ± 3 [a d e]	12.4 ± 2 [a b c e]	17.93 ± 2 [a b c d]	<0.001
PVR (WU)	4.5 (2.7,9.3)	1.8(1.2, 2.4) [b c e]	6.4 (3.6, 11.1) [a d e]	5.4 (3.3, 9.7) [a d e]	1.7 (1.6, 1.9) [b c e]	3.3 (1.7, 6.7) [a b c d]	<0.001
CO (L/min)	4.78 ± 1.6	5.15 ± 2 [b d]	4.47 ± 1 [a d]	4.71 ± 1 [d]	6.83 ± 2 [a b c]	5.33 ± 2 [b d]	<0.001
CI (L/min/m^2)	2.79 ± 0.8	3.06 ± 1 [b c]	2.65 ± 1 [a d]	2.76 ± 1 [a d]	3.5 ± 1 [b c d]	2.95 ± 1 [e]	<0.001
FEV_1/FVC	0.74 ± 0.10	0.76 ± 0.09	0.73 ± 0.08	0.75 ± 0.13	0.76 ± 0.06	0.75 ± 13	0.014
ECSC percent predicted values							
FEV_1%	84.5 ±20	89 ± 20 [c e]	89.91 ± 18 [c e]	73.9 ± 20 [a b d]	88.5 ± 20 [c e]	75.42 ± 20	<0.001

						[a, b ,d]	
FVC%	94.3 ± 24	97.9 ± 22 [c e]	101.84 ± 21 [c e]	82.5 ± 24 [a b d]	96.3 ± 23 [c e]	78.13 ± 25 [a b d]	<0.001
FVC%/DL_{CO}%	2.61 ± 1.15	1.95 ± 0.63 [b c]	2.75 ± 1.04 [a d e]	2.96 ± 1.39 [a d e]	1.72 ± 0.42 [b c]	2.06 ± 1.01 [b c]	<0.001
K_{CO}%	56.8 ±19	68.84 ± 17 [b c]	53.16 ± 17 [a d e]	51.95 ± 19 [a d e]	75.9 ± 13 [b c]	65.58 ± 21 [b c]	<0.001
DL_{CO}%	40.7 ±15	53.4 ± 16 [b c e]	40.29 ± 12 [a c d]	31.57 ± 12 [a b d e]	57.7 ± 15 [b c e]	43.34 ± 16 [a c d]	<0.001
GLI percent predicted values							
FEV_1%	81.2 ± 20	87.7 ± 22 [c e]	85.16 ± 17 [c e]	71.12 ± 19 [a b d]	89.88 ± 24 [c e]	73.27 ± 23 [a b d]	<0.001
FVC%	87.1 ± 22	91.84 ±24 [c e]	92.21 ± 20 [c e]	76.36 ± 21 [a b d]	93.6 ± 25 [c e]	78.39 ± 23 [a b d]	<0.001
Kco%	58.9 ± 21	72.83 ±18 [b c]	54.99 ± 17 [a d e]	53 ± 20 [a d e]	80 ± 16 [b c]	69.18 ± 24 [b c]	<0.001
DLco %	45.5 ± 18	60.9 ±19 [b c e]	44.85 ± 14 [a c d]	34.75 ± 14 [a b d e]	65.98 ± 21 [b c e]	49.08 ± 19 [a c d]	<0.001
FVC%/DLco%	2.16 ± 0.94	1.61 ± 0.54 [b c]	2.24 ± 0.84 [a c d e]	2.5 ± 1.16 [a b d e]	1.49 ± 0.37 [b c]	1.78 ± 0.76 [b c]	<0.001

Abbreviations: CI, cardiac index, CO cardiac output; DLco, diffusion capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity, ISWD, incremental shuttle walk distance; K_{CO}, carbon monoxide transfer coefficient; DL_{CO}, diffusion capacity of the lung for carbon monoxide; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; WHO FC, World Health Organisation functional class; ECSC, European Coal and Steel Community; GLI, Global Lung function Initiative; lSSc, limited cutaneous systemic sclerosis; dSSc, diffuse systemic sclerosis
p-values <0.05: a = versus No PH; b = versus PAH; c = versus PH-CLD, d = versus unclassified-PH, e = versus PH -LHD

Table 2. Correlations of mean pulmonary arterial pressure and percent predicted gas transfer measurements

	Overall Cohort		No Lung Disease		Lung disease	
	r	**P-value**	**r**	**P-value**	**r**	**P-value**
ECSC						
DLco%	-0.44	<0.001	-0.51[a]	<0.001	-0.39	<0.001
Kco%	-0.42	<0.001	-0.44	<0.001	-0.39	<0.001
FVC%/ DLco%	0.37	<0.001	0.37	<0.001	0.38	<0.001
GLI						
DLco%	-0.45	<0.001	-0.51[a]	<0.001	-0.41	<0.001
Kco%	-0.42	<0.001	-0.44	<0.001	-0.39	<0.001
FVC%/ DLco%	0.37	<0.001	0.38	<0.001	0.39	<0.001

Abbreviations: DLco, diffusion capacity of the lung for carbon monoxide; Kco, carbon monoxide transfer coefficient; FVC, forced vital capacity; ECSC, European Coal and Steel Community; GLI, Global Lung Initiative. Significant differences ($p<0.05$) using Steiger's t-test: DLco% vs Kco% = a.

Table 3. Diagnostic utility of percent predicted gas transfer measurements

	DLco%				Kco%				FVC%/DLco%				P-value
	AUC	Threshold (%)	Sens	Spec	AUC	Threshold (%)	Sens	Spec	AUC	Threshold	Sens	Spec	
ECSC													
Pre-capillary PH & PH-LHD versus No/Unclassified-PH	0.83	44	0.81	0.75	0.74	54	0.55	0.86	0.73	2.19	0.61	0.82	a.<0.001 b.<0.001 c.0.62
Pre-capillary PH versus No/Unclassified-PH	0.80	46	0.77	0.72	0.78	54	0.58	0.86	0.79	2.15	0.66	0.81	a. 0.25 b. 0.54 c. 0.54
PAH versus No/Unclassified-PH (No Lung Disease)	0.82	47	0.75	0.80	0.80	68	0.82	0.68	0.80	2.15	0.67	0.80	a. 0.18 b. 0.26 c. 0.97
PH-CLD versus No/Unclassified PH (Lung Disease)	0.77	37	0.72	0.75	0.74	54	0.61	0.86	0.76	2.14	0.69	0.82	a. 0.38 b. 0.86 c. 0.44
GLI													
Pre-capillary PH & PH-LHD versus No/Unclassified-PH	0.84	49	0.81	0.81	0.74	60	0.62	0.80	0.74	1.91	0.60	0.85	a.<0.001 b.<0.001 c. 0.67
Pre-capillary PH versus No/Unclassified-PH	0.81	50	0.75	0.80	0.79	67	0.77	0.69	0.78	1.90	0.59	0.85	a. 0.25 b. 0.54 c. 0.54
PAH versus No/Unclassified-PH	0.83	53	0.75	0.83	0.80	71	0.83	0.67	0.79	1.90	0.59	0.89	a. 0.18

(No Lung Disease)													b. 0.26 c. 0.97
PH-CLD versus No/Unclassified PH (Lung Disease)	0.77	42	0.75	0.75	0.75	58	0.65	0.79	0.74	1.72	0.75	0.71	a. 0.38 b. 0.86 c. 0.44

Abbreviations: DLco, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; Kco, carbon monoxide transfer coefficient; PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; AUC, area under the curve; ECSC, European Coal and Steel Community; GLI, Global Lung Initiative; AUC, area under the curve; Sens, sensitivity, Spec, specificity. P-value: a=DLco% vs Kco%, b=DLco% vs FVC%/DLco%, c=Kco% vs FVC%/DLco%

Supplementary table 1. Baseline characteristics stratified by presence or absence of chronic lung disease

	No-PH, No CLD (n = 57)	No-PH with CLD (n = 22)	Unclassified-PH, No CLD (n = 24)	Unclassified-PH with CLD (n = 6)	PAH (n = 313)	PH-CLD (n = 166)	PH-LHD, No CLD (n = 34)	PH-LHD with CLD(n = 10)	p-Value
Female (%)	91	86	79 [g]	67 [g]	89 [f]	71 [e]	100 [c d]	60	<0.001
WHO FC I/II/III/IV (%)	7/41/52/0 [e f g]	9/45/45/0 [d f g]	4/44/52/0 [e f]	0/33/66/0 [a]	2/10/80/7 [a b c f g]	1/9/75/16 [b c e g]	3/24/60/3 [b e]	0/10/90/0 [a b f]	<0.001
Age (years)	63.5 ± 11	66.13 ± 10	61.12 ± 12	66.97 ± 10	67.1 ± 10	66.41 ± 10	64.16 ± 13	68.04 ± 8	0.053
SSc Form lSSc/dSSc/Not Specified/Overlap (%)	75/8/11/5	59/10/17/14 [e]	85/4/8/4	66/17/13/4	77/7/13/3 [b]	68/9/18/5	71/6/18/6	60/20/20/0	0.694
ISWD (metres)	275 (135, 410) [e f]	265 (180, 435) [e f]	340 (100, 245) [e f]	195 (180, 560)	140 (70, 270) [a b c]	140 (70, 250) [a b c]	140 (80, 250)	220 (40, 270)	<0.001
mPAP (mmHg)	16.9 ± 2 [e f g h]	16.4 ± 3 [e f g h]	23.5 ± 3 [e f g h]	25.3 ± 2 [e g h]	40.3 ± 13 [a b c d]	38.1 ± 12 [a b c]	39.03 ± 15 [a b c]	37.5 ± 13 [a b c]	<0.001
PAWP (mmHg)	7.9 ± 3 [c d e f g h]	7.2 ± 3 [c d e f g h]	12.54 ± 2 [a b e f g h]	12 ± 2 [a b g h]	9.7 ± 3 [a b c g h]	9.3 ± 3 [a b c g h]	17.94 ± 2 [a b c d e f]	17.9 ± 2 [a b c d e f]	<0.001
PVR (WU)	1.8 (1.3, 2.4) [e f g]	1.9 (1.2, 2.4) [e f]	1.7 (1.4, 1.9) [e f]	1.8 (1.8, 1.9) [e f]	6.4 (3.6, 11.1) [a b c d g]	5.4 (3.3, 9.7) [a b c d]	3.5 (1.6, 6.8) [a e f]	2.9 (2, 4.4)	<0.001
CO (L/min)	5.2 ± 2 [c d e]	5 ± 1 [c d]	6.7 ± 1 [a b e f g]	7.23 ± 2 [a b e f]	4.47 ± 1 [a c d g h]	4.7 ± 1 [c d]	5.32 ± 2 [c e]	5.34 ± 2 [e]	<0.001
CI (L/min/m^2)	3.05 ± 1 [e]	3.07 ± 1	3.53 ± 1 [e f]	3.4 ± 1	2.65 ± 1 [a c]	2.76 ± 1 [c]	2.95 ± 1	2.94 ± 1	<0.001
FEV_1/FVC	0.75 ± 0.9 [f]	0.78 ± 0.9	0.76 ± 0.6	0.77 ± 0.6	0.73 ± 0.8	0.75 ± 0.13 [a]	0.75 ± 0.10	0.74 ± 0.20	0.293
ECSC percent predicted values									

FEV_1%	91.9 ± 20 ^{fgh}	81.63 ± 20	91.7 ± 16 ^{f}	75.5 ± 30	89.8 ± 18 ^{gf}	73.9 ± 20 ^{ace}	76.56 ± 20 ^{ae}	71.54 ± 22 ^{a}	<0.001
FVC%	102 ± 21 ^{fg}	87.1 ± 23 ^{e}	100.5 ± 18 ^{fg}	79.14 ± 35	101.9 ± 21 ^{bfg}	82.5 ± 24 ^{ace}	77.56 ± 27 ^{ace}	80.07 ± 21	<0.001
K_{CO}%	70.6 ± 17 ^{ef}	64.2 ± 17 ^{cf}	75.14 ± 14 ^{ef}	78.9 ± 10 ^{ef}	53.2 ± 17 ^{acdg}	52 ± 19 ^{abcdg}	66.11 ± 22 ^{ef}	63.81 ± 15	<0.001
DL_{CO}%	57.8 ± 16 ^{befh}	44.6 ± 15 ^{acfg}	60.4 ± 14 ^{befgh}	46.8 ± 16	40.4 ± 12 ^{acf}	31.6 ± 12 ^{abceg}	44.77 ± 17 ^{bcf}	38.45 ± 13 ^{ac}	<0.001
FVC%/DL_{CO}%	1.91 ± 0.64 ^{ef}	2.06 ± 0.61 ^{f}	1.74 ± 0.46 ^{ef}	1.67 ± 0.20	2.75 ± 1.04 ^{acg}	2.96 ± 1.39 ^{abcg}	1.99 ± 1.02 ^{ef}	2.28 ± 0.99	<0.001
GLI percent predicted values									
FEV_1%	89.78 ± 21 ^{fgh}	82.23 ± 21	93.04 ± 23 ^{fgh}	77.26 ± 27	85.2 ± 17 ^{f}	71.12 ± 19 ^{ace}	74.92 ± 24 ^{ac}	67.69 ± 20 ^{ac}	<0.001
FVC%	94.84 ± 22 ^{fg}	84.09 ± 27	97.42 ± 23 ^{f}	78.31 ± 29	92.3 ± 20 ^{fg}	86.36 ± 21 ^{ace}	80.06 ± 25 ^{ae}	72.71 ± 16	<0.001
Kco%	75.24 ± 18 ^{ef}	65.58 ± 17 ^{ef}	79.08 ± 15.37 ^{ef}	83.65 ± 20 ^{ef}	55.1 ± 17 ^{acdg}	53.01 ± 20.25 ^{abcdg}	70.87 ± 24.78 ^{ef}	63.43 ± 20.79	<0.001
DLco%	64.6 ± 18 ^{befgh}	51.29 ± 18 ^{acf}	69.76 ± 19 ^{befgh}	50.8 ± 21	45 ± 14 ^{acf}	34.8 ± 14 ^{abceg}	51.33 ± 20 ^{acf}	41.44 ± 13 ^{ac}	<0.001
FVC%/DLco%	1.56 ± 0.55 ^{ef}	1.72 ± 0.50 ^{f}	1.45 ± 0.35 ^{ef}	1.64 ± 0.42	2.24 ± 0.84 ^{acf}	2.5 ± 1.16 ^{abceg}	1.75 ± 0.78 ^{f}	1.91 ± 0.72	<0.001

Abbreviations: CI, cardiac index, CO cardiac output; DLco, diffusion capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity, ISWD, incremental shuttle walk distance; K_{CO}, carbon monoxide transfer coefficient; DL_{CO}, diffusion capacity of the lung for carbon monoxide; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PH, pulmonary hypertension,; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; WHO FC, World Health Organisation functional class; ECSC, European Coal and Steel Community; GLI, Global Lung function Initiative.

p-values <0.05: a = versus No PH; b = versus No PH with CLD c = versus Unclassified-PH, d = versus unclassified-PH with CLD, e = versus PAH, f = versus PH-CLD, g = PH-LHD without CLD, h = PH-LHD with CLD.

Figure 1. Study Flow Chart

Abbreviations. SSc, systemic sclerosis; RHC, right heart catheterisation; LHD, left heart disease; DLco, diffusing capacity for carbon monoxide

Figure 2. Correlation between mean pulmonary arterial pressure and gas transfer measure

Vertical dashed lines refer to diagnostic threshold for pulmonary hypertension, horizontal dashed lines refer to optimal threshold identified at ROC curve analysis. Abbreviations: DLco, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; Kco, carbon monoxide transfer coefficient; mPAP, mean pulmonary arterial pressure; ECSC, European Coal and Steel Community; GLI, Global Lung Initiative; PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; CLD, chronic lung disease; LHD, left heart disease

Figure 3. Receiver Operator Characteristic Curve Analysis

A&E: PAH, PH-CLD and PH-LHF versus No PH/Unclassified-PH; B&F: Pre-capillary PH versus No-PH/Unclassified-PH;
C&G: PAH versus No-PH/Unclassified-PH (no lung disease); D&H: PH-CLD versus No-PH/Unclassified-PH (lung disease)
Abbreviations: DLco, diffusion capacity of the lung for carbon monoxide ;FVC, forced vital capacity; K_{CO}, carbon monoxide transfer coefficient; ECSC, European Coal and Steel Community; GLI, Global Lung Initiative; PH, Pulmonary Hypertension; PAH, Pulmonary Hypertension; CLD, chromic lung disease; LHD, left heart disease

Supplementary figure 1A. Correlation between gas transfer measures and mean pulmonary arterial pressure in patients with normal pulmonary arterial wedge pressure, split by presence or absence of lung disease (ECSC)

Vertical dashed lines refer to diagnostic threshold for pulmonary hypertension, horizontal dashed lines refer to optimal threshold identified at ROC curve analysis. Abbreviations: DLco, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; Kco, carbon monoxide transfer coefficient; mPAP, mean pulmonary arterial pressure; ECSC, European Coal and Steel Community; PAH, pulmonary arterial hypertension; PH-CLD, pulmonary hypertension associated with chronic lung disease.

Supplementary figure 1B. Correlation between gas transfer measures and mean pulmonary arterial pressure in patients with normal pulmonary arterial wedge pressure, split by presence or absence of lung disease (GLI)

Vertical dashed lines refer to diagnostic threshold for pulmonary hypertension, horizontal dashed lines refer to optimal threshold identified at ROC curve analysis. Abbreviations: DLco, diffusion capacity of the lung for carbon monoxide; FVC, forced vital capacity; Kco, carbon monoxide transfer coefficient; mPAP, mean pulmonary arterial pressure; GLI, Global Lung function Initiative; PAH, pulmonary arterial hypertension; PH-CLD, pulmonary hypertension associated with chronic lung disease

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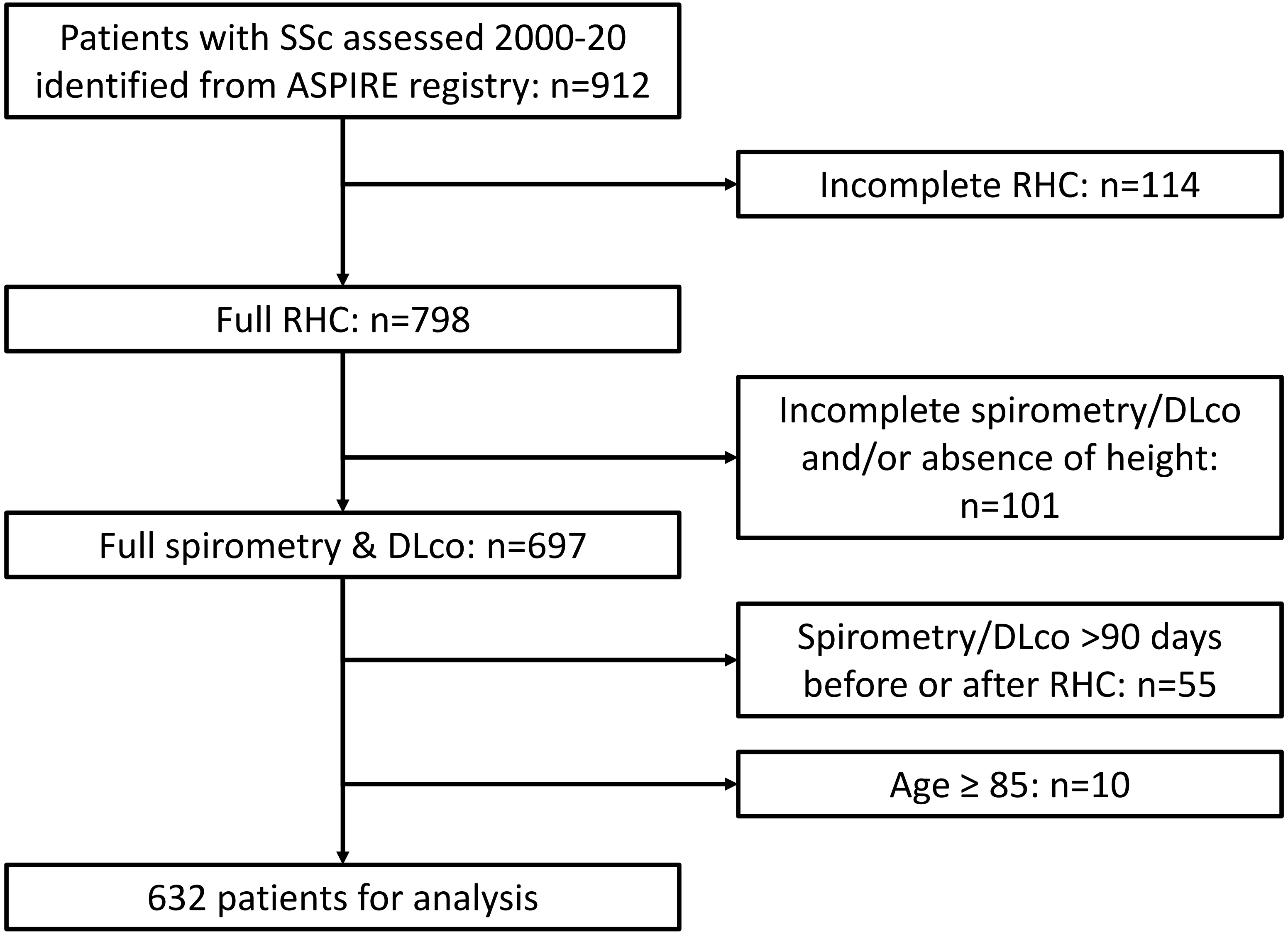
Figure 1. Study Flow Chart



Abbreviations. SSc, systemic sclerosis; RHC, right heart catheterisation; LHD, left heart disease; DLco, diffusing capacity for carbon monoxide

Figure 2. Correlation between mean pulmonary arterial pressure and gas transfer measure

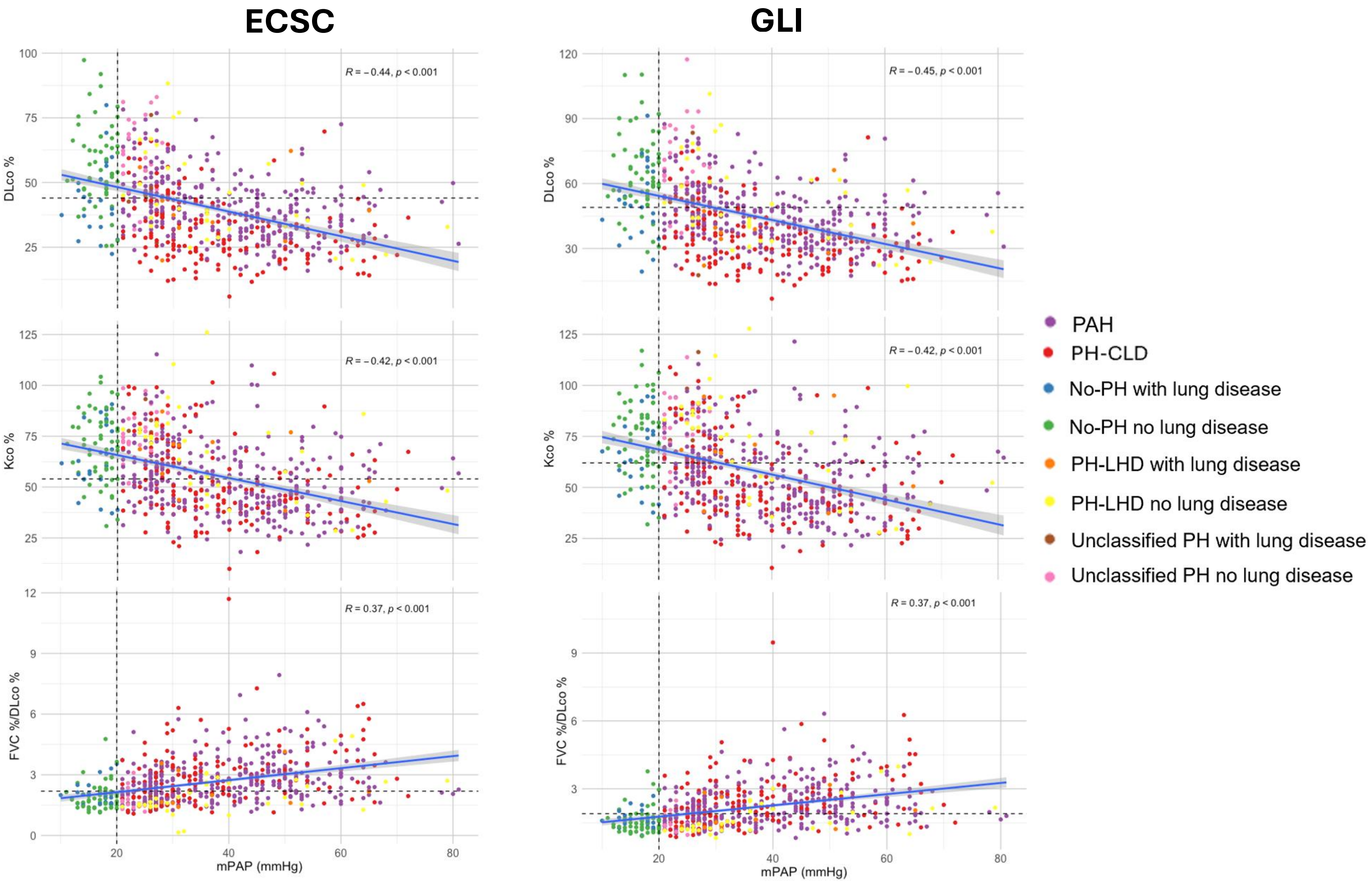


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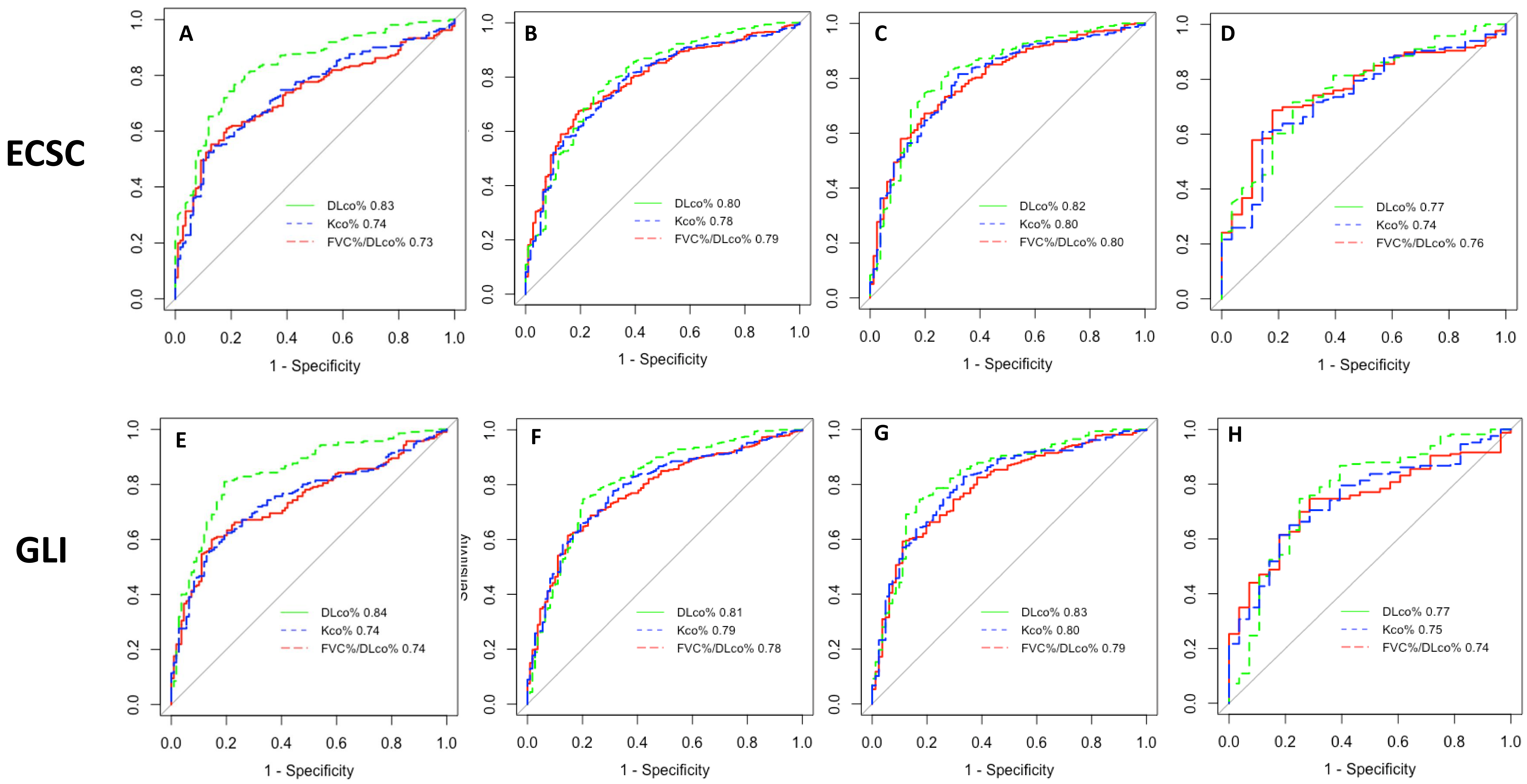
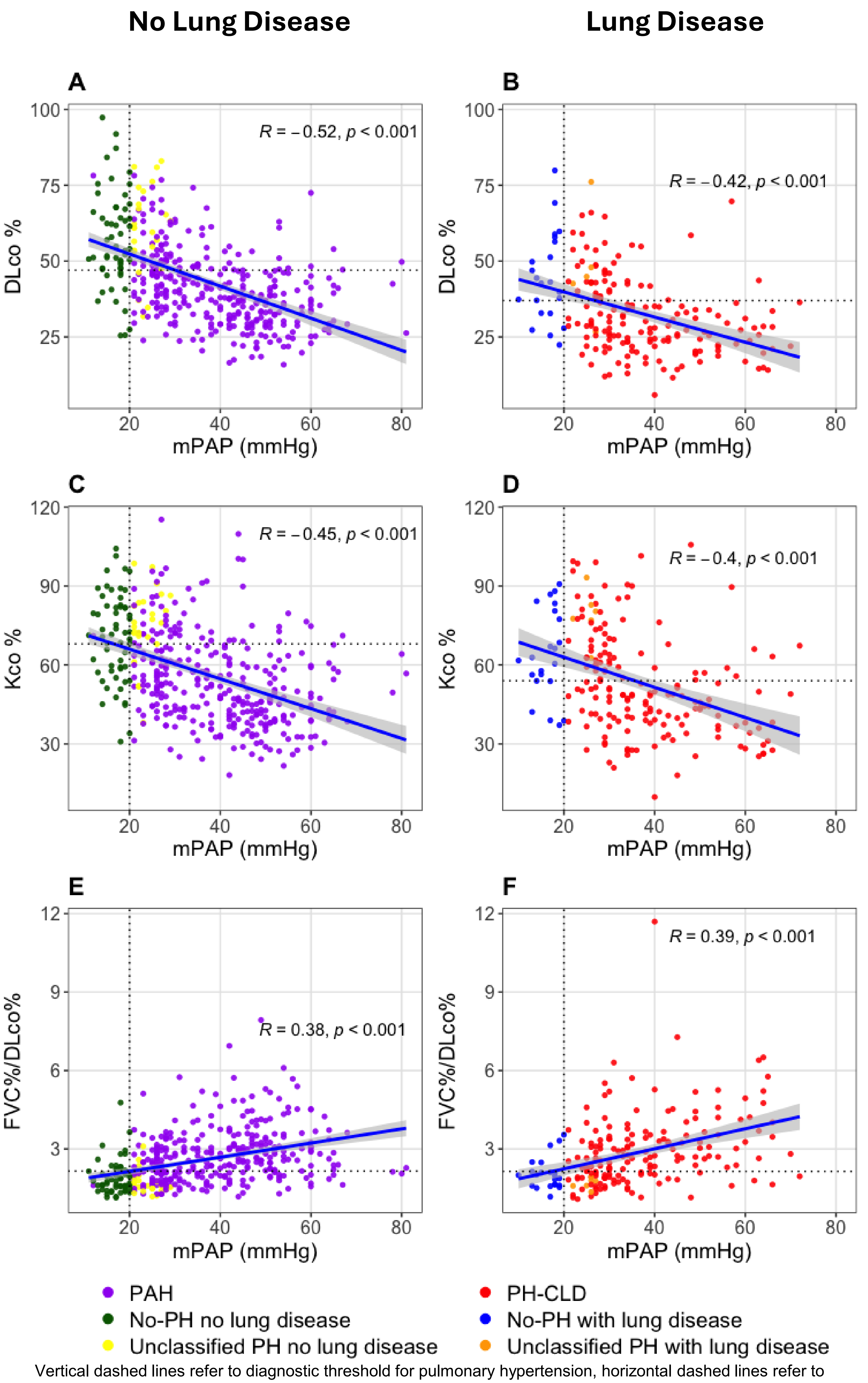
Figure 3. Receiver Operator Characteristic Curve Analysis



A&E: PAH, PH-CLD and PH-LHF versus No PH/Unclassified-PH; B&F: Pre-capillary PH versus No-PH/Unclassified-PH;
C&G: PAH versus No-PH/Unclassified-PH (no lung disease); D&H: PH-CLD versus No-PH/Unclassified-PH (lung disease)
Abbreviations: DLco, diffusion capacity of the lung for carbon monoxide ;FVC, forced vital capacity; K_{CO}, carbon monoxide transfer coefficient; ECSC, European Coal and Steel Community; GLI, Global Lung Initiative; PH, Pulmonary Hypertension; PAH, Pulmonary Hypertension; CLD, chromic lung disease; LHD, left heart disease

Supplementary figure 1A. Correlation between gas transfer measures and mean pulmonary arterial pressure, split by presence or absence of lung disease (ECSC)



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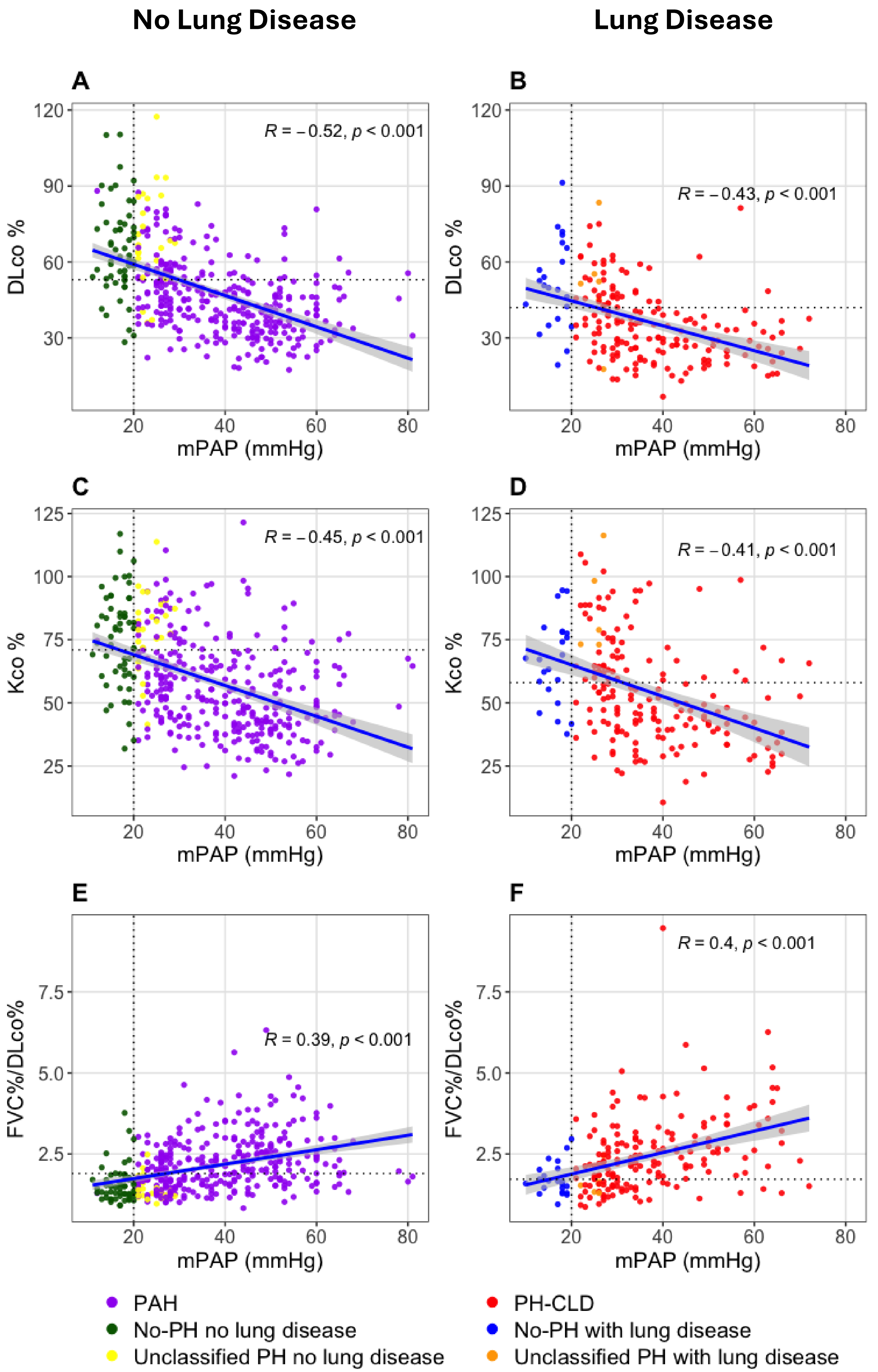
Supplementary figure 1B. Correlation between gas transfer measures and mean pulmonary arterial pressure, split by presence or absence of lung disease (GLI)



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