Diffusing Capacity of the Lungs for Carbon Monoxide and Echocardiographic Parameters in Identifying Mild Pulmonary Hypertension in the EUSTAR Cohort of Patients With Systemic Sclerosis

Amalia Colalillo, Eric Hachulla, Chiara Pellicano, Vanessa Smith, Christina Bergmann, Gabriela Riemekasten, Elisabetta Zanatta, Jörg Henes, David Launay, Antonella Marcoccia, et al.

[Pulmonary and Cardiovascular Original Research]

CHEST

Diffusing Capacity of the Lungs for Carbon Monoxide and Echocardiographic Parameters in Identifying Mild Pulmonary Hypertension in the EUSTAR Cohort of Patients With Systemic Sclerosis

*Amalia Colalillo, MD; Eric Hachulla, MD, PhD; Chiara Pellicano, MD; Vanessa Smith, MD, PhD; Christina Bergmann, MD; Gabriela Riemekasten, MD, PhD; Elisabetta Zanatta, MD, PhD; Jörg Henes, MD, PhD; David Launay, MD, PhD; Antonella Marcoccia, MD; Ana Maria Gheorghiu, MD, PhD; Marie-Elise Truchetet, MD, PhD; Florenzo Iannone, MD, PhD; Carmen Pilar Simeón Aznar, MD, PhD; Susana Oliveira, MD; Madelon Vonk, MD, PhD; Francesco Del Galdo, MD, PhD; and Edoardo Rosato, MD, PhD; for the EUSTAR Collaborators**

BACKGROUND: The 2022 European Society of Cardiology/European Respiratory Society guidelines define pulmonary hypertension (PH) as a resting mean pulmonary artery pressure (mPAP) > 20 mm Hg at right heart catheterization (RHC). Previously, patients with an mPAP between 21 and 24 mm Hg were classified in a "gray zone" of unclear clinical significance.

RESEARCH QUESTION: What is the diagnostic performance of the main parameters used for PH screening in detecting patients with systemic sclerosis (SSc) with an mPAP of 21 to 24 mm Hg at RHC?

STUDY DESIGN AND METHODS: Patients with SSc from the European Scleroderma Trials and Research (EUSTAR) database with available tricuspid annular plane systolic excursion (TAPSE), systolic PAP (sPAP), and mPAP data were included. Patients with mPAP 21 to 24 mm Hg and patients with mPAP ≤ 20 mm Hg were considered for the analysis. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated.

RESULTS: TAPSE/sPAP was lower in the group of patients with SSc with mPAP 21 to 24 mm Hg than in the non-PH group (0.58 [0.46-0.72] vs 0.69 [0.57-0.81] mm/mm Hg, respectively; $P < .01$). No difference was found in other parameters between the two groups. Diffusing capacity of the lungs for carbon monoxide (D_{LCO}) < 80% of the predicted value had the highest sensitivity (88.9%) and NPV (80%), but the lowest specificity (18.2%) and PPV (30.8%) in detecting patients with SSc with mPAP 21 to 24 mm Hg. TAPSE/sPAP < 0.55 mm/mm Hg had the highest specificity (78.9%), PPV (50%), and accuracy (68.1%); its NPV was 75.4%, and its sensitivity was 45.1%.

INTERPRETATION: D_{LCO} < 80% of the predicted value is the parameter with the highest sensitivity and NPV in detecting patients with SSc with mPAP 21 to 24 mm Hg. TAPSE/sPAP < 0.55 mm/mm Hg has the highest specificity, PPV, and accuracy and, therefore, can be a useful additional parameter to decrease the number of unnecessary RHCs.

CHEST 2024; ■(■):■-■

KEY WORDS: diffusing capacity of the lungs for carbon monoxide; pulmonary hypertension; screening; systemic sclerosis; tricuspid annular plane systolic excursion/systolic pulmonary arterial pressure

FLA 5.6.0 DTD ■ CHEST6228_proof ■ 20 July 2024 ■ 5:31 pm ■ EO: CHEST-D-24-00353

Take-home Points

Study Question: What is the diagnostic performance of the main parameters used for PH screening in detecting patients with systemic sclerosis (SSc) with a mean pulmonary arterial pressure (mPAP) of 21 to 24 mm Hg at right heart catheterization?

Results: Diffusing capacity of the lungs for carbon monoxide (DLCO) < 80% of the predicted value is the parameter with the highest sensitivity and negative predictive value in detecting patients with SSc with mPAP 21 to 24 mm Hg, whereas a TAPSE/sPAP (tricuspid annular plane systolic excursion/systolic PAP) ratio < 0.55 mm/mm Hg has the highest specificity, positive predictive value, and accuracy.

Interpretation: DLCO < 80% of the predicted value identifies most patients with SSc with mPAP 21 to 24 mm Hg, whereas TAPSE/sPAP ratio < 0.55 mm/mm Hg can be a useful additional parameter to decrease the number of unnecessary right heart catheterizations.

For many years pulmonary hypertension (PH) has been defined as a mean pulmonary arterial pressure (mPAP) ≥ 25 mm Hg at rest measured invasively by right heart catheterization (RHC).[1] Normal mPAP at rest is 14 ± 3 mm Hg with an upper limit of 20 mm Hg. Thus, patients with an mPAP between 21 and 24 mm Hg were classified in a "gray zone" of unclear clinical significance.[1] Subsequent studies have shown a significant increase in mortality and hospitalization risk with mPAP > 20 mm Hg.[2,3] The 2022 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines define PH as a resting mPAP > 20 mm Hg at RHC.[4] PH in patients with systemic sclerosis (SSc) may also be caused by left heart diseases (group 2) and lung diseases (group 3).[4]

Several screening tools are available to guide patient selection for RHC referral to confirm PH diagnosis in patients with SSc. Resting echocardiography remains the most common screening tool used for early detection of PH, both as a single measure or as part of a composite measure.[5] Tricuspid regurgitation velocity (TRV) or estimated systolic pulmonary artery pressure (sPAP) are the key variables for assigning the echocardiographic probability of PH.[4] In the current PH guidelines, the tricuspid annular plane systolic excursion (TAPSE)/sPAP ratio has been included for the first time among the additional echocardiographic signs suggestive of PH.[4] Moreover, it has recently been shown that a reduced TAPSE/sPAP ratio is a predictive risk factor for PH in patients with SSc.[6] An isolated reduced diffusing capacity of the lungs for carbon monoxide (DLCO) and in particular an isolated reduced DLCO with a relatively preserved FVC is associated with SSc-PH.[7-10] Increased N-terminal pro-B-type natriuretic peptide (NT-proBNP)[9-11] and serum urate levels[9] have also been associated with a higher risk of PH in patients with SSc.

However, to date, and to the best of our knowledge, there are no studies specifically investigating the performance of the existing PH screening tools in detecting patients with SSc with an mPAP of 21 to 24 mm Hg.

ABBREVIATIONS: DLCO = diffusing capacity of the lungs for carbon monoxide; ERS = European Respiratory Society; ESC = European Society of Cardiology; EUSTAR = European Scleroderma Trials and Research Group; IQR = interquartile range; mPAP = mean pulmonary rterial pressure; NPV = negative predictive value; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PFT = pulmonary function test; PH = pulmonary hypertension; PPV = positive predictive value; RHC = right heart catheterization; sPAP = systolic pulmonary arterial pressure; SSc = systemic sclerosis; TAPSE = tricuspid annular plane systolic excursion; TRV = tricuspid regurgitation velocity

AFFILIATIONS: From the Department of Translational and Precision Medicine (A. C., C. P., and E. R.), Sapienza University of Rome, Rome, Italy; the University of Lille (E. H. and D. L.), INSERM, CHU Lille, Department of Internal Medicine and Clinical Immunology, Hôpital Claude Huriez, CERAINOM, U1286-INFINITE-Institute for Translational Research in Inflammation, Lille, France; the Department of Internal Medicine and Department of Rheumatology (V. S.), Ghent University Hospital, and the Unit for Molecular Immunology and Inflammation (V. S.), VIB Inflammation Research Center (IRC), Ghent, Belgium; the Department of Internal Medicine (C. B.), University Hospital Erlangen, Erlangen, Germany; the Department of Rheumatology and Clinical Immunology (G. R.), University of Lübeck, Lübeck, Germany; the Rheumatology Unit (E. Z.), Padova University Hospital, Padua, Italy; the Center for Interdisciplinary Rheumatology, Auto-inflammatory Diseases and Internal Medicine (J. H.), University Hospital Tübingen, Tübingen, Germany; the Centro di Riferimento Interdisciplinare (A. M.), Interdipartimentale per la Diagnosi Precoce della Sclerodermia (CRIIS), Sandro Pertini Hospital, Rome, Italy; the Carol Davila University on Medicine and Pharmacy, Internal Medicine and Rheumatology Department (A. M. G.), Cantacuzino Hospital, Bucharest, Romania; the Department of Rheumatology (M.-E. T.), CHU de Bordeaux, Bordeaux, France; the Rheumatology Unit (F. I.), University of Bari, Bari, Italy; the Unit of Autoimmune Diseases, Department of Internal Medicine (C. P. S. A.), Hospital Universitario Vall d'Hebron, Barcelona, Spain; the Systemic Immunomediated Diseases Unit, Department of Medicine (S. O.), Amadora, Portugal; the Department of Rheumatology (M. V.), Radboud University Medical Center, Nijmegen, The Netherlands; and the Leeds Raynaud's and Scleroderma Program (F. D. G.), NIHR Biomedical Research Centre Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, England.
*Collaborators from EUSTAR are listed in the Acknowledgment.

CORRESPONDENCE TO: Edoardo Rosato, MD, PhD; email: edoardo.rosato@uniroma1.it

DOI: https://doi.org/10.1016/j.chest.2024.05.010

The aim of this study was to compare the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of the main echocardiographic, pulmonary function test (PFT), and laboratory parameters for PH screening in the European Scleroderma Trials and Research Group (EUSTAR) cohort of patients with SSc with mPAP 21 to 24 mm Hg.

Study Design and Methods

Study Design and Inclusion Criteria

This was an observational cross-sectional study of data collected from the multinational EUSTAR database. The structure of the online database, the collected data set, and definitions of clinical variables have been previously reported in detail.[12,13]

Inclusion criteria were as follows: (1) registration in the EUSTAR database since 2010 (start of the online version), (2) age ≥ 18 years, (3) fulfillment of the 2013 American College of Rheumatology/European League Against Rheumatism SSc classification criteria,[14] (4) availability of TAPSE and sPAP measurements on echocardiography, and (5) availability of RHC data (mPAP). The TAPSE/sPAP ratio was calculated for all patients with SSc included. PH was defined as mPAP > 20 mm Hg.[4] Among patients included were identified three groups based on RHC data: (1) patients with mPAP ≤ 20 mm Hg (PH diagnosis excluded), (2) patients with mPAP 21 to 24 mm Hg, and (3) patients with mPAP ≥ 25 mm Hg. Only group 1 and group 2 were considered for the analysis.

Statistical Analysis

Statistical analysis was performed with SPSS Statistics version 26 (IBM). In this study, our objective was to ascertain the diagnostic sensitivity, with an anticipated threshold of 0.9. Given a prevalence of PH of 0.15 and aiming for a precision of 0.1 within the 95% CI, we calculated the optimal sample size to be 231 participants. Taking into account a dropout rate of 5% to 10%, we adjusted the anticipated sample size, resulting in a final cohort of 250 participants. The Shapiro-Wilk test was used to evaluate the normal distribution of data.

Categorical data are represented as frequencies and proportions. Continuous variables are reported as median and interquartile range (IQR). Nonparametric tests were used to evaluate statistical differences because data for some variables (sPAP, DLCO, NT-proBNP, FVC/DLCO, serum urate) are not normally distributed. TAPSE/sPAP, FVC, and TAPSE are normally distributed. The Mann-Whitney test was used to assess differences between continuous variables. The Fisher exact test was used to evaluate the difference between categorical variables. Sensitivity, specificity, PPV, and NPV, and accuracy of echocardiographic, PFT, and laboratory parameters were calculated to assess the diagnostic performance of these items in identifying patients with SSc with mPAP 21 to 24 mm Hg. Parameters included in the analysis were as follows: sPAP > 36 mm Hg,[4,14] TAPSE/sPAP < 0.55 mm/mm Hg,[4,5] DLCO < 80% of the predicted value, DLCO < 60% of the predicted value, FVC/DLCO ≥ 1.82,[9] NT-proBNP ≥ 125 pg/mL,[15] NT-proBNP ≥ 210 pg/mL,[9] serum urate ≥ 6 mg/dL. Sensitivity was calculated as the number of true positives/(number of true positives + number of false negatives); specificity was calculated as the number of true negatives/(number of true negatives + number of false positives); PPV was calculated as the number of true positives/(number of true positives + number of false positives); NPV was calculated as the number of true negatives/(number of true negatives + number of false negatives). Accuracy was calculated as (number of true positives + number of true negatives)/(number of true positives + number of true negatives + number of false positives + number of false negatives). Listwise deletion was done to handle missing data. Moreover, the multivariate imputation by chained equations was used to handle missing data (we used the function mice of the R package mice). Receiver operating characteristic curves were used to evaluate the diagnostic performance of sPAP, TAPSE/sPAP ratio, DLCO, FVC/DLCO, NT-proBNP, and serum urate. A significance level of .05 was used for all tests.

Results

From the EUSTAR database, 355 patients with SSc met the inclusion criteria for this study. Of these, 109 patients with SSc had mPAP ≤ 20 mm Hg, 51 patients with SSc had mPAP 21 to 24 mm Hg, and 195 patients with SSc had mPAP ≥ 25 mm Hg.

Demographic and clinical characteristics of the 51 patients with SSc with mPAP 21 to 24 mm Hg and of the 109 patients with mPAP ≤ 20 mm Hg are shown in Table 1. None of the patients were treated with colchicine or xanthine oxidase inhibitors. RHC parameters and PH group classification of the 51

FLA 5.6.0 DTD ■ CHEST6228_proof ■ 20 July 2024 ■ 5:31 pm ■ EO: CHEST-D-24-00353

TABLE 1] Demographic and Clinical Characteristics of Patients With SSc With PH Confirmed by Right Heart Catheterization (mPAP, 21-24 mm Hg) and Patients With SSc With PH Not Confirmed by Right Heart Catheterization (mPAP, ≤ 20 mm Hg)

Characteristic	Patients with mPAP 21-24 mm Hg (n = 51)		Patients with mPAP ≤ 20 mm Hg (n = 109)		*P* Value
	Results	No.	Results	No.	
Age, median (IQR), y	69 (63-75)	51	67 (61-75)	109	.218
Male, No. (%)	9 (17.6)	51	24 (22)	109	.676
Disease duration, median (IQR), y	12 (8-22)	39	12 (9-18)	92	.559
lcSSc, No. (%)	27 (73)	37	48 (58.5)	82	.154
ACA, No. (%)	19 (46.3)	41	32 (41.6)	77	.839
ATA, No. (%)	14 (32.6)	43	30 (38)	79	.543
ARA, No. (%)	3 (9.4)	32	0 (0)	58	< .05
mRSS, median (IQR)	3 (0-10)	33	7 (2-13)	73	< .05
Digital ulcer history, No. (%)	18 (43.9)	41	49 (50.5)	97	.585
Telangiectasia, No. (%)	29 (61.7)	47	72 (74.2)	97	.079
NYHA class, No. (%)					
I	12 (25.5)	47	27 (27.6)	98	.846
II	23 (48.9)	47	45 (45.9)	98	
III	10 (21.3)	47	24 (24.5)	98	
IV	2 (4.3)	47	2 (2)	98	
NT-proBNP, median (IQR), pg/mL	286 (97-805)	27	247 (111-532)	48	.691
NT-proBNP ≥ 125 pg/mL, No. (%)	16 (59.3)	27	34 (71)	48	.321
NT-proBNP ≥ 210 pg/mL, No. (%)	14 (51.9)	27	27 (56.2)	48	.810
Serum urate, median (IQR), mg/dL	5.5 (4.1-6.4)	27	4.9 (4.3-6.2)	47	.649
Serum urate ≥ 6 mg/dL, No. (%)	9 (33.3)	27	13 (27.7)	47	.599
FVC, % predicted, median (IQR)	88 (74-109)	44	95 (76-110)	94	.281
D_{LCO}, % predicted, median (IQR)	48 (43-66)	40	61 (45-76)	88	.150
D_{LCO} < 80% predicted, No. (%)	32 (80)	40	72 (81.8)	88	.426
D_{LCO} < 60% predicted, No. (%)	22 (55)	40	43 (48.9)	88	.240
FVC/D_{LCO}, median (IQR)	1.69 (1.35-2.09)	40	1.54 (1.32-2)	87	.358
FVC/D_{LCO} ≥ 1.82, No. (%)	13 (32.5)	40	26 (29.9)	87	.528
LVEF, %, median (IQR)	61 (55-66)	43	60 (57-65)	94	.993
Right atrium area, median (IQR), cm^2	16.4 (14.9-17.1)	10	15.8 (13-17)	18	.408
TAPSE, median (IQR), mm	20 (18-24)	51	23 (20-25)	109	< .01
sPAP, median (IQR), mm Hg	35 (30-45)	51	31 (28-40)	109	.070
sPAP > 36 mm Hg, No. (%)	21 (41.2)	51	41 (37.6)	109	.729
TAPSE/sPAP, median (IQR), mm/mm Hg	0.58 (0.46-0.72)	51	0.69 (0.57-0.81)	109	< .01
TAPSE/sPAP < 0.55 mm/mm Hg, No. (%)	23 (45.1)	51	23 (21.1)	109	< .01
Serum creatinine, mg/dL	0.78 (0.71-0.90)	51	0.80 (0.80-0.90)	109	> .05

Percentages are calculated on the number of available data (n = number of patients with available data). ACA = anti-centromere antibodies; ARA = anti-RNA polymerase III antibodies; ATA = anti-topoisomerase I antibodies; D_{LCO} = diffusing capacity of the lungs for carbon monoxide; IQR = interquartile range; lcSSc = limited cutaneous SSc; LVEF = left ventricular ejection fraction; mPAP = mean pulmonary artery pressure; mRSS = modified Rodnan skin score; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PH = pulmonary hypertension; sPAP = systolic pulmonary arterial pressure; SSc = systemic sclerosis; TAPSE = tricuspid annular plane systolic excursion.

patients with SSc with mPAP 21 to 24 mm Hg are reported in Table 2.

The TAPSE/sPAP ratio was significantly lower in patients with SSc with mPAP 21 to 24 mm Hg than in patients with SSc with mPAP ≤ 20 mm Hg (0.58 [0.46-0.72] vs 0.69 [0.57-0.81] mm/mm Hg; $P < .01$). No difference was found in sPAP, right atrium area, D_{LCO}, FVC/D_{LCO}, NT-proBNP, and serum urate between

FLA 5.6.0 DTD ■ CHEST6228_proof ■ 20 July 2024 ■ 5:31 pm ■ EO: CHEST-D-24-00353

TABLE 2] Right Heart Catheterization Parameters of 51 Patients With Systemic Sclerosis With mPAP 21 to 24 mm Hg

Parameter	Results	No.
mPAP, mm Hg	22 (21-23)	51
PAWP, mm Hg	11 (8-12)	43
PVR, WU	2.8 (1.9-3.6)	28
CO, L/min	5.3 (4.3-6.2)	29
CI, L/min/m^2	3.3 (2.6-3.8)	41
Group 1 or 3 PH	17 (65.4)	26
Group 2 PH	0	26
Unclassified PH[a]	9 (34.6)	26

Values are expressed as median and interquartile range (IQR) or as number and percentage (%). Percentages are calculated on the number of available data (No. = number of patients with available data). CI = cardiac index; CO = cardiac output; mPAP = mean pulmonary artery pressure; PAWP = pulmonary arterial wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; WU = Wood units.
[a]Patients with elevated mPAP (> 20 mm Hg) but low PVR (≤ 2 WU) and PAWP (≤ 15 mm Hg).

patients with SSc with mPAP 21 to 24 mm Hg and the non-PH group.

The receiver operating characteristic curve analysis showed an area under the curve of 0.653 (0.562-0.745; $P < .01$) for the TAPSE/sPAP ratio, 0.589 (0.492-0.686; $P > .05$) for sPAP, 0.583 (0.475-0.690; $P > .05$) for DLCO, 0.447 (0.337-0.557; $P > .05$) for FVC/DLCO, 0.528 (0.384-0.672; $P > .05$) for NT-proBNP, and 0.532 (0.391-0.674; $P > .05$) for serum urate.

TAPSE/sPAP ratio < 0.55 mm/mm Hg was the parameter with the highest specificity (78.9%) and PPV (50%) in detecting patients with SSc with mPAP 21 to 24 mm Hg. TAPSE/sPAP ratio < 0.55 mm/mm Hg NPV was 75.4%. TAPSE/sPAP ratio < 0.55 mm/mm Hg had higher sensitivity, specificity, PPV, and NPV compared with sPAP > 36 mm Hg. DLCO < 80% of the predicted value was the parameter with the highest sensitivity (88.9%) and NPV (80%), but with the lowest specificity (18.2%) and PPV (30.8%). FVC/DLCO ≥ 1.82 had a specificity of 70.1% and an NPV of 72.6%, but low sensitivity (36.1%) and PPV (33.3%). NT-proBNP ≥ 210 pg/mL had a sensitivity, specificity, PPV, and NPV of 51.9%, 43.8%, 34.1%, 61.8%, respectively. Serum urate ≥ 6 mg/dL had a sensitivity, specificity, PPV, and NPV of 34.6.%, 72.3.%, 40.9%, and 66.7%, respectively. TAPSE/sPAP ratio < 0.55 mm/mm Hg was the parameter with the highest accuracy (68.1%). Sensitivity, specificity, PPV, and NPV, and accuracy of echocardiographic, PFT, and laboratory parameters for PH screening in patients with SSc, are shown in Table 3.

Discussion

In this study, a DLCO < 80% of the predicted value showed the highest sensitivity and NPV in identifying patients with mPAP 21 to 24 mm Hg, whereas the parameter with the highest specificity and PPV was a TAPSE/sPAP ratio < 0.55 mm/mm Hg. Moreover, a TAPSE/sPAP ratio < 0.55 showed the highest accuracy among the considered parameters.

Previous guidelines defined PH as a resting mPAP ≥ 25 mm Hg measured by RHC and included patients with mPAP 21 to 24 mm Hg in a so-called "gray zone" of unclear clinical significance. Patients presenting with an mPAP in this range needed to be carefully monitored when they were at risk for developing PH, for example, patients with connective tissue disease.[1] The 2022 ESC/ERS guidelines removed this gray area and defined PH as a resting mPAP > 20 mm Hg, supporting the prognostic relevance of identifying patients with PH earlier in the preclinical disease course.[4] Available PH screening tools in patients with SSc have been widely validated on the previous definition of PH. To date, there are no studies on the diagnostic performance of the existing PH screening parameters in detecting patients with SSc with mPAP 21 to 24 mm Hg.

Our results show that most of the patients with SSc with mPAP 21 to 24 mm Hg had a DLCO < 80% of the predicted value, less than one-half had an increased sPAP, and none of them had an increased right atrial area (RAA) > 18 cm^2. Despite the missing data, the RAA does not seem to be a reliable measure in identifying patients with SSc with mPAP 21 to 24 mm Hg. RAA is the echocardiographic parameter included in the DETECT algorithm in association with TRV to select patients for RHC referral.[9] TAPSE/sPAP ratio was the only parameter showing a significant difference between patients with SSc with mPAP 21 to 24 mm Hg and patients with SSc without PH.

In this study, the probability of a DLCO < 80% of the predicted value identifying patients with SSc with mPAP 21 to 24 mm Hg was 88.9%. However, the probability of a DLCO > 80% predicted correctly identifying non-PH participants was only 18.1%. A high sensitivity is usually desired in a screening test, because when sensitivity increases the number of patients with preclinical disease not diagnosed by the test decreases. Therefore, sensitivity is usually increased at the expense of specificity when the disease is serious and curable in its preclinical phase. However, a test with an extremely low specificity produces a high percentage of erroneously

FLA 5.6.0 DTD ■ CHEST6228_proof ■ 20 July 2024 ■ 5:31 pm ■ EO: CHEST-D-24-00353

TABLE 3 Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Accuracy of Echocardiographic, Pulmonary Function Tests and Laboratory Parameters for Pulmonary Hypertension Screening of Patients with Systemic Sclerosis With mPAP 21 to 24 mm Hg With Listwise Deletion and Multiple Imputation

Parameter	Listwise Deletion					Multivariate Imputation				
	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
sPAP > 36 mm Hg	41.2	62.4	33.9	69.4	55.6	NA	NA	NA	NA	NA
TAPSE/sPAP < 0.55 mm/mm Hg	45.1	**78.9**	**50**	**75.4**	**68.1**	NA	NA	NA	NA	NA
D_{LCO} < 80% predicted	**88.9**	18.2	30.8	**80**	38.7	89.8	18.3	34	42.1	41.1
D_{LCO} < 60% predicted	61.1	51.1	33.8	76.3	54	61.6	49.9	36.5	42.2	53.6
FVC/D_{LCO} ≥ 1.82	36.1	70.1	33.3	72.6	60.2	35.3	69.4	35	40.5	58.5
NT-proBNP ≥ 125 pg/mL	59.3	29.2	32	56	40	65.1	33.4	31.4	37.5	43.5
NT-proBNP ≥ 210 pg/mL	51.9	43.8	34.1	61.8	46.7	58	45	33.1	39	49.1
Serum urate ≥ 6 mg/dL	34.6	72.3	40.9	66.7	58.9	35.7	71.2	37.1	42.2	59.9

D_{LCO} = diffusing capacity of the lungs for carbon monoxide; mPAP = mean pulmonary artery pressure; NA = XXX; NPV = negative predictive value; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PPV = positive predictive value; sPAP = systolic pulmonary arterial pressure; TAPSE = tricuspid annular plane systolic excursion.

positive results, increasing the number of patients to be referred for an invasive diagnostic procedure and, consequently, increasing the costs and associated risks.

TAPSE/sPAP ratio < 0.55 mm/mm Hg showed better diagnostic performance than sPAP > 36 mm Hg. Moreover, TAPSE/sPAP ratio was the parameter with the highest specificity. The probability of a TAPSE/sPAP ratio ≥ 0.55 mm/mm Hg correctly identifying non-PH patients with SSc was 78.9%. The higher specificity decreases the number of false positives, reducing unnecessary RHC. This high specificity was at the expense of a quite low sensitivity. Moreover, the TAPSE/sPAP ratio PPV was significantly higher than the PPV of all the other considered parameters. Among patients with SSc who had a TAPSE/sPAP ratio < 0.55 mm/mm Hg, the probability of PH was 50%. The DETECT study reported a PPV of 35% with the DETECT algorithm.[9] In a previous study, we compared the TAPSE/sPAP ratio PPV and the DETECT algorithm PPV in 51 patients with SSc: the PPV of the TAPSE/sPAP ratio was higher than the PPV of the DETECT algorithm (62.5% vs 31.3%).[17] Hao and colleagues[18] compared the predictive accuracy of three screening models in 73 patients with SSc (DETECT vs Australian Scleroderma Interest Group [ASIG] vs 2009 ESC/ERS). The reported PPV for the three algorithms was between 55% and 60%. With PH prevalence set at 10%, the PPV was less than 20%. All the aforementioned studies defined PH as an mPAP ≥ 25 mm Hg. Ciurzyński and colleagues[19] demonstrated that sPAP has the highest area under the curve between resting and exercise echo Doppler parameters. Doppler resting and exercise echocardiography may provide a reliable, noninvasive method for determining resting and exercise sPAP, mPAP, and PVR in patients with SSc. In our study, TAPSE/sPAP ratio was also the parameter with the highest accuracy among the considered parameters. The overall probability of TAPSE/sPAP ratio < 0.55 mm Hg correctly identifying patients with SSc with mPAP 21 to 24 mm Hg (true positives) and patients with mPAP < 20 mm Hg (true negatives) was 68.1%.

Therefore, we can assume that a D_{LCO} < 80% of the predicted value is the most reliable parameter to minimize the number of missed PH diagnoses in patients with SSc with mPAP 21 to 24 mm Hg, and that the TAPSE/sPAP ratio can be a useful additional parameter in association with the D_{LCO} for identifying patients who should be referred to RHC and reducing

the number of unnecessary invasive diagnostic procedures.

This is, to our knowledge, the first study that attempts to redefine the screening approach in the specific subsets of patients with SSc with mild PH. Echocardiography combined with other tests (BNP/NT-proBNP, PFTs, serum urate) is recommended as a screening test in asymptomatic patients with SSc, followed by annual assessments.[4]

However, the study has some limitations. Patients were selected on the basis of available TAPSE, sPAP, and mPAP data. Many data were missing for parameters included in the DETECT algorithm, in particular TRV and RAA, so that comparing the diagnostic performance of TAPSE/sPAP ratio and the DETECT algorithm was not possible. Some RHC data were missing (pulmonary arterial wedge pressure and pulmonary vascular resistance), so that defining the PH group was not possible for all patients included. Although patient selection was based on available data and many RHC data were missing in the EUSTAR database, the results are generalizable and applicable to the general population because they are based on cutoffs of parameters established by the ESC/ERS guidelines. In addition, the imputation confirms the data present in the EUSTAR register.

Interpretation

In conclusion, $D_{LCO} < 80\%$ of the predicted value is the parameter with the highest sensitivity and NPV in detecting patients with SSc with mPAP 21 to 24 mm Hg. TAPSE/sPAP < 0.55 mm/mm Hg has the highest specificity, PPV, and accuracy and, therefore, can be a useful additional parameter to decrease the number of unnecessary RHCs.

Funding/Support

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Financial/Nonfinancial Disclosures

The authors have reported to *CHEST* the following: V. S. is senior clinical investigator of the Research Foundation—Flanders (Belgium): (FWO) (1.8.029.20N). This funding source had no role in the literature review and the synthesis and interpretation of the data; in the writing of the report; or in the decision to submit the paper for publication. C. B. received grants from Boehringer-Ingelheim, consulting fees from Janssen, honoraria for lectures from Novartis, and travel grants from Kyverna, which were not related to this project; E. Z. received speaking and lecture fees from Janssen and consulting fees from Janssen and GSK; F. I. received honoraria and speaking fees from AbbVie, Eli Lilly, Galapagos, Janssen, Novartis, Pfizer, and UCB outside this work; C. P. S. A. received consulting fees and support for attending meetings from Janssen-Cilag SAS, Boehringer Ingelheim Ltd and MSD. None declared (A. C., E. H., C. P., G. R., J. H., D. L., A. M., A. M. G., M.-E. T., S. O., M. V., F. D. G., E. R.).

Acknowledgments

Author contributions:

*__EUSTAR Collaborators:__ Oliver Distler (Zurich, Switzerland), Mike Becker (Zurich, Switzerland); Melissa De Decker (Ghent, Belgium); Danilo Alunni Fegatelli (Rome, Italy); Elise Siegert (Berlin, Germany); Ivan Castellví (Barcelona, Spain); Alberto Cauli (Monserrato, Italy); Kamal Solanki (Hamilton, New Zealand); Lorenzo Dagna (Milan, Italy); Mickaël Martin (Poitiers, France); Gianluca Moroncini (Ancona, Italy); Hadi Poormoghim (Tehran, Iran); Masataka Kuwana (Tokyo, Japan); Patricia E. Carreira (Madrid, Spain); Paolo Airò (Brescia, Italy); Christina Bergmann (Erlangen, Germany); Julia Spierings (Utrecht, The Netherlands); Yoshiya Tanaka (Kitakyushu, Japan); Enrico Selvi (Siena, Italy); Tomas Soukup (Hradec Kralove, Czech Republic).

References

1. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS); endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37(1):67-119.
2. Assad TR, Maron BA, Robbins IM, et al. Prognostic effect and longitudinal hemodynamic assessment of borderline pulmonary hypertension. *JAMA Cardiol*. 2017;2(12):1361-1368.
3. Maron BA, Hess E, Maddox TM, et al. Association of borderline pulmonary hypertension with mortality and hospitalization in a large patient cohort: insights from the Veterans Affairs Clinical Assessment, Reporting, and Tracking Program. *Circulation*. 2016;133(13):1240-1248.
4. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43(38):3618-3731 [published correction appears in *Eur Heart J*. 2023;44(15):1312].
5. Bruni C, De Luca G, Lazzaroni MG, et al. Screening for pulmonary arterial hypertension in systemic sclerosis: a systematic literature review. *Eur J Intern Med*. 2020;78:17-25.
6. Colalillo A, Hoffmann-Vold AM, Pellicano C, et al. The role of TAPSE/sPAP ratio in predicting pulmonary hypertension and mortality in the

systemic sclerosis EUSTAR cohort. *Autoimmun Rev*. 2023;22(4):103290.

7. Steen V, Medsger TA Jr. Predictors of isolated pulmonary hypertension in patients with systemic sclerosis and limited cutaneous involvement. *Arthritis Rheum*. 2003;48(2):516-522.
8. Allanore Y, Borderie D, Avouac J, et al. High N-terminal pro-brain natriuretic peptide levels and low diffusing capacity for carbon monoxide as independent predictors of the occurrence of precapillary pulmonary arterial hypertension in patients with systemic sclerosis. *Arthritis Rheum*. 2008;58(1):284-291.
9. Coghlan JG, Denton CP, Grünig E, et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. *Ann Rheum Dis*. 2014;73(7):1340-1349.
10. Thakkar V, Stevens WM, Prior D, et al. N-terminal pro-brain natriuretic peptide in a novel screening algorithm for pulmonary arterial hypertension in systemic sclerosis: a case-control study. *Arthritis Res Ther*. 2012;14(3):R143.
11. Williams MH, Handler CE, Akram R, et al. Role of N-terminal brain natriuretic peptide (N-TproBNP) in scleroderma-associated pulmonary arterial hypertension. *Eur Heart J*. 2006;27(12):1485-1494.
12. Elhai M, Meune C, Boubaya M, et al. Mapping and predicting mortality from systemic sclerosis. *Ann Rheum Dis*. 2017;76(11):1897-1905.
13. Meier FM, Frommer KW, Dinser R, et al. Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research group database. *Ann Rheum Dis*. 2012;71(8):1355-1360.
14. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum*. 2013;65(11):2737-2747.
15. Hachulla E, Clerson P, Airò P, et al. Value of systolic pulmonary arterial pressure as a prognostic factor of death in the systemic sclerosis EUSTAR population. *Rheumatology (Oxford)*. 2015;54(7):1262-1269.
16. McDonagh TA, Metra M, Adamo M, et al; ESC Scientific Document Group. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599-3726.
17. Colalillo A, Grimaldi MC, Vaiarello V, et al. In systemic sclerosis, the TAPSE/sPAP ratio can be used in addition to the DETECT algorithm for pulmonary arterial hypertension diagnosis. *Rheumatology (Oxford)*. 2022;61(6):2450-2456.
18. Hao Y, Thakkar V, Stevens W, et al. A comparison of the predictive accuracy of three screening models for pulmonary arterial hypertension in systemic sclerosis. *Arthritis Res Ther*. 2015;17(1):7.
19. Ciurzyński M, Bienias P, Ciesielska K, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary circulation in patients with systemic sclerosis. *Adv Med Sci*. 2019;64(2):309-314.

FLA 5.6.0 DTD ■ CHEST6228_proof ■ 20 July 2024 ■ 5:31 pm ■ EO: CHEST-D-24-00353