

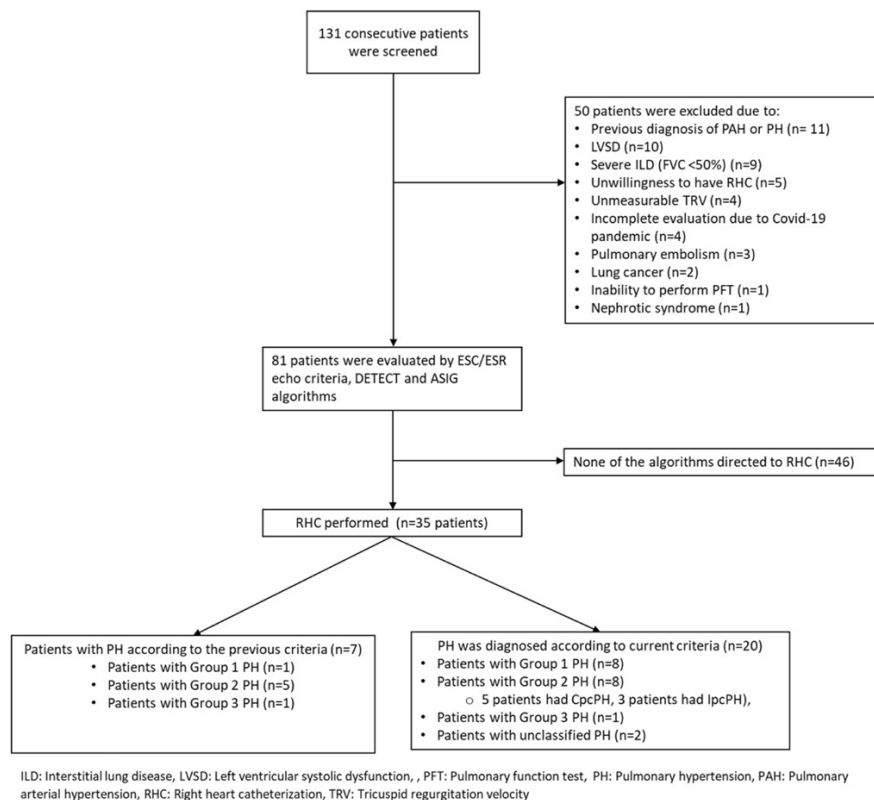
## Supplementary appendix

### Inclusion Criteria

- Age  $\geq 18$  years
- Fulfilling the 2013 ACR/EULAR SSc Classification Criteria

### Exclusion criteria

- Previous pulmonary hypertension (PH)/pulmonary arterial hypertension (PAH) diagnosis
- Patients with left ventricular ejection fraction (LVEF)  $<50\%$
- Severe mitral or aortic valve disease,
- History of myocarditis
- History of myocardial infarction, percutaneous coronary artery intervention or by-pass
- Severe interstitial lung disease (ILD) (FVC of  $<50\%$  of predicted)
- Obstructive lung disease (FEV1/FVC  $<70\%$ )
- Acute or chronic pulmonary artery thromboembolic disease
- Acute or chronic kidney injury
- Chronic severe liver disease
- Pregnancy



**Supplementary Fig. S1.** Screening procedure and summary of the diagnostic evaluation.

### Echocardiography

Comprehensive two-dimensional TTE was performed using a Philips iE33 machine with an S5-1 transducer (Philips Medical Systems, Andover, MA) in the left lateral position, except for inferior vena cava (IVC) diameter measurement, which was performed in the supine position. All parameters were measured by a European Association of Cardiovascular Imaging (EACVI)

certified cardiologist (BKA) following the American Society of Echocardiography and EACVI guidelines (1).

Tricuspid regurgitation velocity (TRV) was measured in the parasternal short-axis view and apical four-chamber view and continuous wave Doppler was used to determine the peak TRV. The highest value was recorded as TRV. sPAP was estimated based on TRV and adding an estimate of right atrial pressure (RAP)

by measuring the size and respiratory collapse of the IVC. The tricuspid annular plane systolic excursion (TAPSE) was calculated as the difference between the end-diastolic and end-systolic distance the of lateral tricuspid annulus to apex. RV fractional area change (RVFAC) was obtained from an apical four-chamber view by tracing the RV endocardial border at end-diastole and end-systole. RVFAC was calculated as  $[(\text{end-diastolic area} - \text{end-systolic area}) / \text{end-diastolic area}] \times 100$ .

Pulsed wave tissue Doppler image examination was performed to obtain lateral tricuspid annulus velocities. The tricuspid annular systolic velocity (Sa), systolic velocity duration (ejection time, ET), the time between the end of systolic velocity and the beginning of early diastolic velocity (isovolumic relaxation time (IVRT)), and the time between the end of the late diastolic velocity and the beginning of the systolic velocity (isovolumic contraction time (IVCT)) were measured at the same cardiac cycle. RV myocardial performance index (RVMPI) was calculated as  $(\text{IVRT} + \text{IVCT}) / \text{ET}$ .

### Pulmonary assessment

Pulmonary function tests (PFTs) were performed according to the ERS/ATS guidelines (2). Diffusing capacity of the lungs for carbon monoxide (DLCO) values were reported as percentages of the predicted values after correction for haemoglobin. Forced vital capacity (FVC) values were reported as percentages predicted for sex, race, and height. High resolution computed tomography (HRCT) of the lungs was performed to assess ILD, if not performed during the previous two years or if there was suspicion for progressive disease (decline in FVC  $>5\%$  compared to the last PFTs, new crackles in the examination, new or worsening dyspnoea) in patients without known severe ILD disease. ILD was staged radiologically as mild ( $<10\%$ ), moderate ( $10\text{--}30\%$ ), and severe ( $>30\%$ ) according to the percentage of involvement (3). Severe ILD was defined as; predicted FVC  $<60\%$  or predicted FVC between  $\geq 60\%$  and severe involvement on HRCT. All patients who required

RHC according to at least one of the screening algorithms were assessed by a ventilation/perfusion (V/Q) scan to exclude thromboembolic disease. If the V/Q scan was suggestive of thromboembolic disease, CT pulmonary angiography was performed to confirm the result.

### Right heart catheterisation

RHC was performed using fluoroscopy and continuous pressure monitoring by 2 experienced cardiologists (BKA, ZO). Venous access was obtained by inserting an introducer into a femoral or jugular vein. Catheterisation was performed using balloon wedge pressure catheters (Arrow) or multi-purpose catheters (Boston Scientific). Pressure transducers were balanced and zeroed at the mid-thoracic level. The RAP (mmHg), systolic, diastolic, and mean pulmonary artery pressures (sPAP, dPAP, mPAP, mmHg), and pulmonary arterial wedge pressure (PAWP, mmHg) were recorded. All pressure readings were done at end-expiration. Cardiac output (CO, L/min) was calculated using the Fick method. PVR(WU) was calculated as  $PVR = (mPAP - PCWP)/CO$ .

PH was defined as an mPAP of  $>20$  mmHg, and PAWP  $>15$  mmHg was used to discriminate post-capillary PH according to guidelines (4). PAH was defined as mPAP  $>20$  mmHg with

PCWP  $\leq 15$  mmHg and PVR  $>2$  WU (4). We additionally performed all analyses according to the previous definition (mPAP  $>25$  mmHg with PAWP  $\leq 15$  mmHg and PVR  $>3$  WU) for PAH (5). For those with PAWP between 12 and 15 mmHg, a fluid challenge test was performed to unmask hidden postcapillary PH by administering 7 ml.kg<sup>-1</sup> saline over 5-10 min during RHC. A positive test was defined as an increase in PAWP to  $>18$  mmHg after saline infusion. No adverse event occurred related to the diagnostic tests during the study.

### Statistical analysis

Statistical analyses were done using the SPSS software v.20. Visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov test) were used to analyse the variables' distribution and select the test method. Descriptive statistics were used for the non-normal distributed variables and presented as median values with interquartile range (IQR). For comparative analyses, independent samples -t-test was used for continuous variables and Chi-square test or Fisher's exact test for the proportions. The prediction performance of an algorithm for RHC was presented as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with a 95% confidence interval (CI). No imputation method was used for mis-

sing values, and analyses were done for each variable's reported number of patients. A *p*-value of less than 0.05 was considered statistically significant.

### References

1. LANG RM, BADANO LP, MOR-AVI V *et al.*: Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; 28(1): 1-39.e14. <https://doi.org/10.1016/j.echo.2014.10.003>
2. GRAHAM BL, STEENBRUGGEN I, MILLER MR *et al.*: Standardization of spirometry 2019 update. An official American thoracic society and European respiratory society technical statement. *Am J Respir Crit Care Med* 2019; 200(8): e70-e88. <https://doi.org/10.1164/rccm.201908-1590st>
3. GOH NS, DESAI SR, VEERARAGHAVAN S *et al.*: Interstitial lung disease in systemic sclerosis: a simple staging system. *Am J Respir Crit Care Med* 2008; 177(11): 1248-54. <https://doi.org/10.1164/rccm.200706-877oc>
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. <https://doi.org/10.1093/eurheartj/ehac237>
5. GALIÈ N, HUMBERT M, VACHERY 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 Respir J* 2015; 46(4): 903-75. <https://doi.org/10.1183/13993003.01032-2015>

Supplementary Table S1.

| ESC /ESR                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                           |                                                                                                                                                                                                                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Echocardiographic probability of pulmonary hypertension in symptomatic patients with a suspicion of pulmonary hypertension*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                           |                                                                                                                                                                                                                  |
| Peak tricuspid regurgitation velocity (m/s)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Presence of other echo PH signs                           | Echocardiographic probability of pulmonary hypertension                                                                                                                                                          |
| ≤2.8 or unmeasurable                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | No                                                        | Low                                                                                                                                                                                                              |
| ≤2.8 or not measurable                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Yes                                                       | Intermediate                                                                                                                                                                                                     |
| 2.9–3.4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | No                                                        | High                                                                                                                                                                                                             |
| 2.9–3.4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Yes                                                       |                                                                                                                                                                                                                  |
| >3.4                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Not required                                              |                                                                                                                                                                                                                  |
| Additional echocardiographic signs suggestive of pulmonary hypertension                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                           |                                                                                                                                                                                                                  |
| A: The ventricles                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | B: Pulmonary artery                                       | C: Inferior vena cava and right atrium                                                                                                                                                                           |
| RV/LV basal diameter/area ratio>1.0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | RVOT AT <105 ms and/or mid-systolic notching              | Inferior cava diameter >21 mm with decreased inspiratory collapse (<50 % with a sniff or <20 % with quiet inspiration)                                                                                           |
| Flattening of the interventricular septum (LVEI >1.1 in systole and/or diastole)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Early diastolic pulmonary regurgitation velocity >2.2 m/s | Right atrial area (end-systole) >18 cm2                                                                                                                                                                          |
| TAPSE/sPAP ratio <0.55 mm/mmHg                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | PA diameter >AR diameter and/or PA diameter >25 mm        |                                                                                                                                                                                                                  |
| Diagnostic management suggested according to echocardiographic probability of pulmonary hypertension in asymptomatic patients with risk factors for pulmonary arterial hypertension                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                           |                                                                                                                                                                                                                  |
| PH probability according to echocardiography                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Risk factors or associated conditions for PAH or CTEPH**  | Recommendations                                                                                                                                                                                                  |
| Low                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | No                                                        | Alternative diagnosis                                                                                                                                                                                            |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Yes                                                       | Echo follow-up                                                                                                                                                                                                   |
| Intermediate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | No                                                        |                                                                                                                                                                                                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Yes                                                       | If associated scleroderma, RHC should be considered                                                                                                                                                              |
| High                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | -                                                         | Further intervention***/ RHC is recommended if indicated****                                                                                                                                                     |
| DETECT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                           |                                                                                                                                                                                                                  |
| STEP 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                           |                                                                                                                                                                                                                  |
| Identify patients who required echocardiography                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                           |                                                                                                                                                                                                                  |
| Non-echocardiographic variables:<br>- FVC % predicted / DLCO % predicted ratio<br>- Presence of current / past telangiectasias<br>- Serum anticentromere antibody<br>- Serum NT-ProBNP level<br>- Serum urate level<br>- Presence of right axis deviation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                           | Total risk point of step 1 is calculated by adding individual risk points of non-echocardiographic variables according to the nomogram.<br><br>↔ Refer to echocardiography if total risk point in step 1 is >300 |
| STEP 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                           |                                                                                                                                                                                                                  |
| Identify patients who required RHC                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                           |                                                                                                                                                                                                                  |
| Echocardiographic variables:<br>Right atrium area<br>Tricuspid regurgitant velocity                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                           | Total risk point in step 2 is calculated by adding risk point of step 1 (converted point according to nomogram) and 2 echocardiographic risk point.<br><br>↔ Refer to RHC if total risk in step 2 is >35         |
| ASIG                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                           |                                                                                                                                                                                                                  |
| Perform RHC if;<br><br>- NT-ProBNP >210 pg/ml and/or<br><br>- DLCO <70% with FVC/DLCO ≥1.8                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                           | Exclude other conditions as indicated such as left hearth disease, ILD, pulmonary artery thromboembolic disease                                                                                                  |
| AR: aortic root; IVC: inferior vena cava; LV: left ventricle; LVEI: left ventricle eccentricity index; PA: pulmonary artery; RA: right atrium; RV: right ventricle; RVOT AT: right ventricular outflow tract acceleration time; sPAP: systolic pulmonary arterial pressure; TAPSE: tricuspid annular plane systolic excursion; TRV: tricuspid regurgitation velocity.<br>*Signs contributing to assessing the probability of PH in addition to TRV. Signs from at least two categories (A/B/C) must be present to alter the level of echocardiographic probability of PH.<br>** Systemic sclerosis is a risk factor for PAH.<br>***Further testing may be necessary (e.g., imaging, CPET).<br>****RHC should be performed if useful information/a therapeutic consequence is anticipated (e.g., suspected PAH or CTEPH), and may not be indicated in patients without risk factors or associated conditions for PAH or CTEPH (e.g., when mild PH and predominant LHD or lung disease are present). |                                                           |                                                                                                                                                                                                                  |