# Assessment of Pulmonary Arterial Stiffness in Patients with Systemic Sclerosis Without Overt Pulmonary Hypertension

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# Abstract

Pulmonary hypertension (PH) is a pathophysiological disorder that may involve multiple clinical conditions and complicate most systemic diseases. Systemic Sclerosis (SSc), represents the leading cause of connective tissue disease (CTD) associated with PAH. Although SSc is a rare disease, it is associated with higher morbidity and early mortality than other rheumatological diseases due to developing SSc-associated interstitial pulmonary disease (ILD) and/or pulmonary arterial hypertension (PAH). The impact of the early diagnosis on the prognosis is evident. In this context, in our study, we aimed to investigate the early changes in pulmonary vascular bed by measuring pulmonary arterial stiffness (PAS) in SSc patients without overt PAH. Sixty-two SSc patients and fifty-eight gender and age-matched, healthy subjects enrolled in this cross-sectional observational study. SSc patients were evaluated in terms of disease duration and severity. Modified Rodnan skin score (mRSS) was calculated as disease severity index. Echocardiographic parameters were assessed and compared to the control group. Right Ventricular (RV) diameters, systolic pulmonary artery pressure (sPAP), and right ventricle myocardial performance index (RV-MPI) were significantly higher in the SSc group compared to the control group ($p < 0.05$). Tricuspid annular plane systolic excursion (TAPSE) and right ventricular fractional area change (RV-FAC) were significantly lower in the SSc group compared to the control group ($p < 0.05$). PAS value (25.5 ± 9.2 kHz/ms vs. 18.1 ± 7.4 kHz/ms, $p <0.001$) was significantly higher in the SSc group than in the control group. A statistically significant positive correlation relationship was detected between the PAS value and CRP, ESR, disease duration, mRSS. According to these results, in SSc patients, PAS as an inexpensive and easily applicable echocardiographic method might serve as a marker of early detection of PAH.


# Introduction

Pulmonary hypertension (PH) is a pathophysiological disorder that may involve multiple clinical conditions and complicate most systemic diseases. PH is a common disorder affecting approximately 1% of the global population and about 10% of patients older than 65. Elevation of pulmonary artery pressure (PAP) may result from various underlying causes [1].

Systemic sclerosis (SSc) is a chronic and progressive autoimmune disease. Skin and many other organ involvements can occur [2]. Although SSc is a rare disease, it is associated with higher morbidity and early mortality than other rheumatological diseases as a result of developing SSc-associated interstitial pulmonary disease (ILD) and/or pulmonary arterial hypertension (PAH) [3, 4]. In Western countries, PAH associated with connective tissue disease (CTD) is in second place after idiopathic PAH for etiology of PH. PAH is the leading cause of death in SSc patients [1]. SSc, particularly in its limited variant, represents the leading cause of CTD associated with PAH in Europe and the USA [1].

Precapillary PH was found in 5–12% of SSc patients in large-scale cohort studies [5]. Current guidelines recommend annually screening with biomarkers and respiratory function tests in addition to resting

echocardiography for asymptomatic SSc patients [1]. Because it is well known that; earlier detection of PAH is associated with more favorable clinical outcomes [1, 6].

Transthoracic echocardiography (TTE) has a crucial role in PH diagnostic and screening strategy [7]. Moreover, especially in the early stage of the disease, it is challenging to determine detectable pathological changes in the pulmonary circulation [6]. However, currently, as a determiner of pulmonary vascular bed functions, pulmonary arterial stiffness (PAS) [8] can be easily obtained by dividing the pulmonary flow peak velocity by the pulmonary flow acceleration time (PAT) [9, 10]. A decrease in pulmonary artery compliance in SSc patients can be easily assessed by measuring PAS by echocardiography [11].

SSc-associated PAH can be diagnosed after 10–15 years of initial diagnosis of SSc [12]. The impact of the early diagnosis on the prognosis is evident. In this context, in our study, we aimed to investigate the early changes in pulmonary compliance and whether an early clinical evaluation could be made by PAS in SSc patients without overt PAH.

## Methods

# Study Population

Sixty-two SSc patients who fulfilled the American College of Rheumatology criteria for diagnosis [13] and fifty-eight gender and age-matched, healthy subjects attending the outpatient clinic of cardiology and rheumatology departments enrolled in this cross-sectional observational study.

Exclusion criteria were; congenital heart disease, portal hypertension, HIV infection, coronary artery disease, structural heart disease or heart failure, heart valve disease (more than mild), chronic obstructive pulmonary disease (COPD), obstructive sleep apnea syndrome, other CTD or drugs which are involved in PH etiology, chronic thromboembolic PH (CTePH), hematological disease, chronic renal failure, and inadequate echocardiographic imaging. Patients with a peak tricuspid regurgitation velocity greater than 3.4 m/s on echocardiography were also excluded because of the strong correlation between right heart catheterization and this estimated cutoff level [14].

During the enrollment process, two patients with chronic PAH, three patients with peak tricuspid regurgitation velocity more than 3.4 m/s (newly diagnosed), one patient with end-stage renal disease (ESRD), one patient with left ventricular (LV) systolic dysfunction, and one patient with COPD were excluded according to exclusion criteria. Finally, a total of 54 patients were analyzed (Figure-1).

All participants were informed about the investigation protocol, and all patients signed a written consent form. The local ethics committee approved the study design and methodology with reference number OMUKAEK 2020/384.

# Data Collection

All subjects had a complete history and physical examination. Basic demographic characteristics, including age, gender, body mass index (BMI), systolic and diastolic blood pressure (BP), and heart rate of the whole population, were recorded. TTE was performed on all study participants.

An experienced rheumatologist evaluated the patients with SSc in terms of disease duration and severity, and presence of digital ulcer, Raynaud's phenomenon, and specific visceral involvements such as skin, gastrointestinal, pulmonary, or musculoskeletal.

Clinical data such as routine laboratory tests, immunological markers, and data concerning SSc-related involvements were obtained from recent medical records.

# Echocardiography

Two experienced echocardiographers who were blinded to the study performed TTE systematically on all participants. Vivid E9 (GE Vingmed Ultrasound, Horten, Norway) TTE device and M5S (1.5–4.5 MHz) ultrasound probe was used for the measurements. TTE was performed in the left lateral decubitus position after resting for at least 15 minutes. Left ventricle end-diastolic (LVEDD) and end-systolic diameters (LVESD), and left atrium (LA) anteroposterior diameter was measured from the long-axis view. Ejection fraction (EF) was calculated by the Modified Simpson method using apical 4-chamber and 2-chamber images. Mitral inflow velocities to assess LV filling, including mitral early diastolic inflow velocity (E), atrial late filling peak velocity (A), deceleration time (DT), and E/A ratio, also were measured in apical 4-chamber view. Valvular heart pathologies were detected and graded.

Right ventricular (RV) diameters were measured at RV mid and basal region and the total length from apical four-chamber view. Percentage right ventricular fractional area change (RV-FAC) was calculated by dividing the difference in RV area between the end-diastolic and end-systolic phases by end-diastolic RV area. Tricuspid annular plane systolic excursion (TAPSE) is defined as the distance between end-diastole and end-systole at the lateral corner of the tricuspid annulus. Systolic PAP (sPAP) was calculated as the sum of the right atrial pressure value obtained by Bernoulli's equation from tricuspid valve pressure gradient and caval respiratory index. Calculation of the RV myocardial performance index (RV MPI) was assessed by pulse wave (PW) tissue doppler imaging (TDI). In addition, isovolumic contraction time (IVCT), ejection time (ET), and isovolumic relaxation time (IVRT) was calculated by using PW TDI. RV MPI was measured using the Tei index. All echocardiographic assessments were performed based on recommendations of the American Society of Echocardiography guidelines [15].

# Definitions

# Measurement of Pulmonary Arterial Stiffness

First of all, the pulmonary artery was visualized from the apical short axis. After that, the pulse wave doppler measurement of pulmonary flow was taken 10–15 mm below from the pulmonary valve.

PAS is defined as the ratio between maximum frequency shift (MFS) of the pulmonary flow and pulmonary flow acceleration time (PAT). MFS was measured from the peak velocity of the pulmonary flow, as shown in Figure-2. PAT is defined as the time from the onset of pulmonary flow ejection to the peak moment (Figure-2). Measurements were repeated at least five consecutive beats, and the averages of measurements were calculated.

$$PAS = \frac{MFS(Hertz)}{PAT(ms)}$$

Intra- and inter-observer agreements were 0.97 and 0.93 for PAS measurements, respectively ($P < .001$).

# Rodnan Skin Score

Skin thickening is a characteristic feature of SSc. More extensive skin involvement coincides with more severe internal organ manifestations, poor prognosis, and increased disability in SSc patients. The fully validated, feasible gold standard method for measuring skin involvement is the modified Rodnan skin score (mRSS)[16]. mRSS was calculated for all SSc patients by an experienced rheumatologist.

# Statistical Analysis

All data were analyzed using “SPSS (Statistical Package for Social Sciences) for Windows 21.0 (SPSS Inc, Chicago, IL). Quantitative variables with a normal distribution were specified as means ± standard deviation. Categorical variables were shown as number and percentage values. In order to test normality of distribution Kolmogorov–Smirnov test was used. For comparison of quantitative data, Student-t Test (normally distributed data) and Mann Whitney-U test (non-normally distributed data) were used. Categorical variables were compared with the Chi-square test. Spearman’s correlation coefficient tests were used to assess the strength of the relationship between PAS and CRP, ESR, disease duration, mRSS. The results were evaluated within a 95% confidence interval. A p value $< 0.05$ was considered to indicate statistical significance.

# Results

Demographic, clinical, and laboratory variables of the study population are demonstrated in Table 1. The mean age of the participants was 49.7 ± 14.5 years, and 85.5% were female. There were no significant differences between the two groups regarding baseline variables ($p > 0.05$). ESR (erythrocyte sedimentation rate) and CRP (C-reactive protein) values were significantly higher in the SSc group than the control group ($p < 0.01$). There were no significant differences between the two groups regarding other laboratory findings and blood pressures ($p > 0.05$). The clinical data of SSc patients are displayed in Table 2. Echocardiography findings are presented in Table 3. Heart rate, LV wall diameters, LVEF and LAD, were not significantly different between the two groups ($p > 0.05$). RV diameters, sPAP, and Tissue doppler RV-MPI were significantly higher in the SSc group compared to the control group ($p < 0.05$). TAPSE and RV-FAC were significantly lower in the SSc group compared to the control group ($p < 0.05$). PAS value was

significantly higher in the SSc group than the control group (25.5 ± 9.2 kHz/ms vs. 18.1 ± 7.4 kHz/ms, $p < 0.001$, respectively). The relationships of the PAS with CRP, ESR, disease duration, mRSS was evaluated via Spearman's correlation analyses. The results yielded by Spearman's correlation analysis are presented in Table 4. A statistically significant positive correlation relationship was detected between the PAS value and CRP, ESR, disease duration, mRSS.

Table 1
Baseline characteristics, medical history and laboratory findings of the study population

| Variables | Scleroderma Group (n = 45) | Control Group (n = 45) | p value |
|---|---|---|---|
| **Age, years** | 49.5 ± 14.6 | 50.2 ± 15.1 | 0.093 |
| **Gender, female**, n (%) | 39 (86.7) | 38 (84.4) | 0.853 |
| **Smoking**, n (%) | 7 (15.5) | 8 (17.7) | 0.772 |
| **BMI**, $kg/m^2$ | 23.5 ± 3.1 | 23.1 ± 3.3 | 0.445 |
| **HT**, n (%) | 13 (28.8) | 12 (26.6) | 0.552 |
| **DM**, n (%) | 10 (22.2) | 9 (20) | 0.401 |
| **Hyperlipidemia**, n (%) | 6 (13.3) | 7 (15.5) | 0.369 |
| **SBP**, mmHg | 125 ± 12.6 | 123 ± 11.5 | 0.112 |
| **DBP**, mmHg | 69.9 ± 8.9 | 70.2 ± 9.1 | 0.124 |
| **White blood cell**, $10^3$ uL | 7.9 ± 4.3 | 7.4 ± 4.6 | 0.092 |
| **Hemoglobin**, g/dl | 12.7 ± 1.7 | 13.2 ± 1.6 | 0.126 |
| **Platelet**, $10^3$ uL | 360.5 ± 72.2 | 355 ± 70.2 | 0.086 |
| **Creatinin**, mg/dl | 0.97 ± 0.31 | 0.94 ± 0.41 | 0.157 |
| **ALT**, IU/l | 17.1 ± 1.7 | 16.9 ± 2.6 | 0.102 |
| **AST**, IU/l | 12.2 ± 2.6 | 12.5 ± 2.4 | 0.198 |
| **CRP**, mg/dL | 5.2 ± 4.3 | 3.1 ± 3 | **< 0.001** |
| **ESR**, mm/h | 26.3 ± 11.7 | 11.2 ± 7.6 | **< 0.001** |

Data are given as mean ± SD or n (%). *BMI* Body mass index, *DM* Diabetes mellitus, *HT* Hypertension, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure, *AST* Aspartate aminotransferase, *ALT* Alanine aminotransferase, *CRP* C-reactive protein, *ESR* Erythrocyte sedimentation rate.

Table 2
Clinical data of the systemic sclerosis population

| **Variables** | |
|---|---|
| **Disease duration, years** | 8.1 ± 7.5 |
| **mRSS** | 13.9 ± 6.5 |
| **Raynaud's phenomenon**, n (%) | 38 (84) |
| **Digital ulcer**, n (%) | 15 (33) |
| **Esophageal involvement**, n (%) | 6 (13) |
| **Antinuclear antibodies (positive)**, n (%) | 43 (95) |
| **Anticentromere antibodies (positive)**, n (%) | 4 (8) |
| **Anti-topoisomerase I antibodies (positive)**, n (%) | 22 (48) |
| **Drug treatments** | |
| **Plaquenil**, n(%) | 35 (77) |
| **Methotrexate**, n(%) | 5 (11) |
| **Mycophenolate mofetil**, n (%) | 8 (17) |
| **Prednisolone**, n (%) | 12 (26) |
| **Azathioprine**, n (%) | 7 (8) |
| Calcium channel blockers, n (%) | 14 (31) |
| anti-TNF monoclonal antibody, n (%) | 2 (4) |
| Data are given as mean ± SD or n (%). *mRSS*: Modified Rodnan skin score; *TNF*: Tumor necrosis factor | |

Table 3
Echocardiographic characteristics of study population

| Parameters | Scleroderma Group (n = 45) | Control Group (n = 45) | p value |
|---|---|---|---|
| **Heart beats**, bpm | 70 ± 8 | 71 ± 6 | 0.475 |
| **LVEF**, % | 61.5 ± 1.4 | 61.7 ± 1.2 | 0.254 |
| **LVESD**, mm | 30.1 ± 1.7 | 31.1 ± 1.3 | 0.135 |
| **LVEDD**, mm | 44.2 ± 3.3 | 43.7 ± 3.4 | 0.118 |
| **LVSWT**, mm | 10.2 ± 0.7 | 10 ± 0.6 | 0.302 |
| **PWT**, mm | 9.2 ± 0.5 | 9 ± 0.6 | 0.136 |
| **LAD (a-p), mm** | 31.8 ± 4.7 | 30.8 ± 4.2 | 0.099 |
| **sPAP**, mmHg | 26.4 ± 4.4 | 23.1 ± 5.5 | **< 0.001** |
| **RV mid-diamater**, mm | 27.1 ± 3.1 | 25.9 ± 2.1 | **< 0.001** |
| **RV basal-diamater**, mm | 31.3 ± 3.1 | 30.6 ± 2.9 | **0.045** |
| **RV-FAC**, % | 40.4 ± 4 .4 | 43.4 ± 5.8 | **< 0.001** |
| **Tissue doppler RV-MPI** | 0.50 ± 0.03 | 0.44 ± 0.08 | **< 0.001** |
| **TAPSE**, mm | 22.1 ± 4.4 | 24.4 ± 2.6 | **< 0.001** |
| **PAS**, kHz/ms | 25.5 ± 9.2 | 18.1 ± 7.4 | **< 0.001** |

Data are given as mean ± SD or (%), Bpm: beats per minute; *LVEF* Left ventricular ejection fraction, *LVEDD* Left ventricular end-diastolic diameter, *LVESD* Left ventricular end-systolic diameter, *LVSWT* Left ventricular septal wall thickness, *PWT* Posterior wall thickness, *LAD (a-p)*: Left atrium diamater anterior posterior, *RV*: Right ventricul, *RV-FAC* Right ventricular fractional area change percentage, *RV-MPI* Right ventricular myocardial performance index, *TAPSE* Tricuspid annular plane systolic excursion; *sPAP* Systolic pulmonary arterial pressure, *PAS* Pulmonary arterial stifness.

Table 4
Bivariate correlation analysis

| Variables | PAS, kHz/ms |
|---|---|
| **C - reactive protein** | **rs = 0.558, p < 0.001** |
| **ESR** | **rs = 0.559, p < 0.001** |
| **Disease duration** | **rs = 0.459, p < 0.001** |
| **mRSS** | **rs = 0.485, p < 0.001** |

PAS: Pulmonary arterial stifness. *mRSS*: Modified Rodnan skin score, rs: indicates spearman correlation coefficient

# Discussion

In the present study, a statistically significant increase of PAS was demonstrated in patients with SSc without overt PAH. Our results are important in terms of providing data for early deformation in pulmonary vascular bed in this patient group. As a result of our study, we demonstrate that deformation in the pulmonary vascular bed starts from the early period of the SSc and increases progressively.

To the best of our knowledge, this is the first study using TTE to evaluate the influence of PAS in patients with SSc. SSc, one of the most complicated autoimmune diseases, involves mainly the organ systems. The underlying pathogenetic process includes endothelial damage, inflammation, overexpression of specific adhesion molecules, abnormal neurovascular control, and tissue fibrosis [2]. Several clinical manifestations such as PAH, Raynaud phenomenon, digital ulcers, the hypertensive renal crisis occurs due to these alterations, which are present even in the earliest stages of the disease [17]. An imbalance occurs between the mediators which control vasomotor tone that leads to irreversible remodeling of the pulmonary vessels as a result of vasoconstriction, vascular endothelial cell proliferation, vascular smooth muscle hypertrophy during PAH progression. [3]. Remodeling of the pulmonary vessels causes impairment in pulmonary elasticity [18]. Previous studies demonstrated that changes in elasticity are primarily due to an increase in PAP [19]. In their research, Friesen et al. examined 56 patients with PAH and found that PAS assessed by cardiac magnetic resonance non-invasively is a major contributor to right ventricle dysfunction [10].

SSc patients can be presented with dyspnea, or shortness of breath due to cardiopulmonary involvement especially increased sPAP. However, there is a silent pre-clinical period with an unknown duration in SSc [6, 20]. As the highest prevalence of PAH amongst the various CTD is observed in SSc, patients should be evaluated more carefully, and screening must be planned [17]. Current guidelines suggest at least annually echocardiographic evaluation for all SSc patients [1, 21, 22]. It is clinically hard to diagnose early changes in pulmonary vasculature because most diagnostic tools focus on sPAP. As long as cardiopulmonary involvement, especially PAH, is the most important cause of death in SSc patients, diagnosing the early stages of the disease is crucial [20].

The early microvasculature changes in SSc patients, such as increased pulmonary elasticity, could be examined by PAS [9, 12]. PAS and other abnormal flow hemodynamics in PAH are strongly associated with impaired elevated right ventricular functions and also with disease severity and poor clinical outcomes in patients with PAH [23]. Singh et al., in their research, investigated pulmonary hemodynamics invasively in patients with PAH and found pulmonary vascular distensibility is an early and sensitive hemodynamic marker of pulmonary vascular disease [24]. The gold-standard assessment of PAS, which is a determiner of pulmonary vascular distensibility, is right heart catheterization. Because of its complexity, risks, and widespread inaccessibility, non-invasive methods have been developed of diagnostic techniques [8, 25]. PAS could be determined easily by TTE. The clinical implication of PAS has been validated by several studies. Early detection of impaired pulmonary elasticity and increased PAS evaluated in polycystic ovary syndrome patients by Abacioglu et al. [26], in cirrhosis patients by Oz et al.

[27], in heart failure patients by Yenercag et al.[28], and Yildirim et al. [29], in asthma patients Baysal et al. [30], and in human immunodeficiency virus-infected patients Cerik et al. [31].

Dogan et al., in their study of 25 SSc patients without overt PAH, found that pulmonary pulse transit time was a predictor of the development of PAH [32]. Consistent with this, we revealed that PAS increased in SSc patients compared to healthy volunteers, and we also determined a positive correlation between Scl duration and PAS. In addition, there was also a positive correlation between C - reactive protein, ESR, and mRSS, which are other parameters showing disease severity and PAS [34].

In all these studies, the researchers evaluated the value of PAS for early detection of PAH in risky populations as in our study. It is unclear how the clinical approach should be in these patients in whom a change in the pulmonary vascular bed has been demonstrated, but no overt PAH has occurred. The studies can shed light on the planning of clinical studies on this evidence gap.

### Limitations

The present study has some limitations that need to be addressed:

First of all, the small number of patients and the cross-sectional observational nature of the study are the main limitations. Second, although many clinical studies have proved the validation of clinical efficacy, our data could be confirmed by MRI or RCH. Third, there is no data about the patients' development of overt PAH in clinical follow-up.

## Conclusion

The mortal relationship between SSc and PAH is well known. Signs of pulmonary vascular changes might be helpful in the screening process. We know that the earlier we detect the PAH and start treatment, the more positive clinical outcomes will be reached. In this context, as an inexpensive and easily applicable echocardiographic method, PAS might serve as a marker of early detection of PAH in patients with SSc.

## Declarations

**Conflict of interest:** No financial or other relationship might be perceived as leading to a conflict of interest.

**Informed Consent:** Informed consent was obtained from all participants included in the study.

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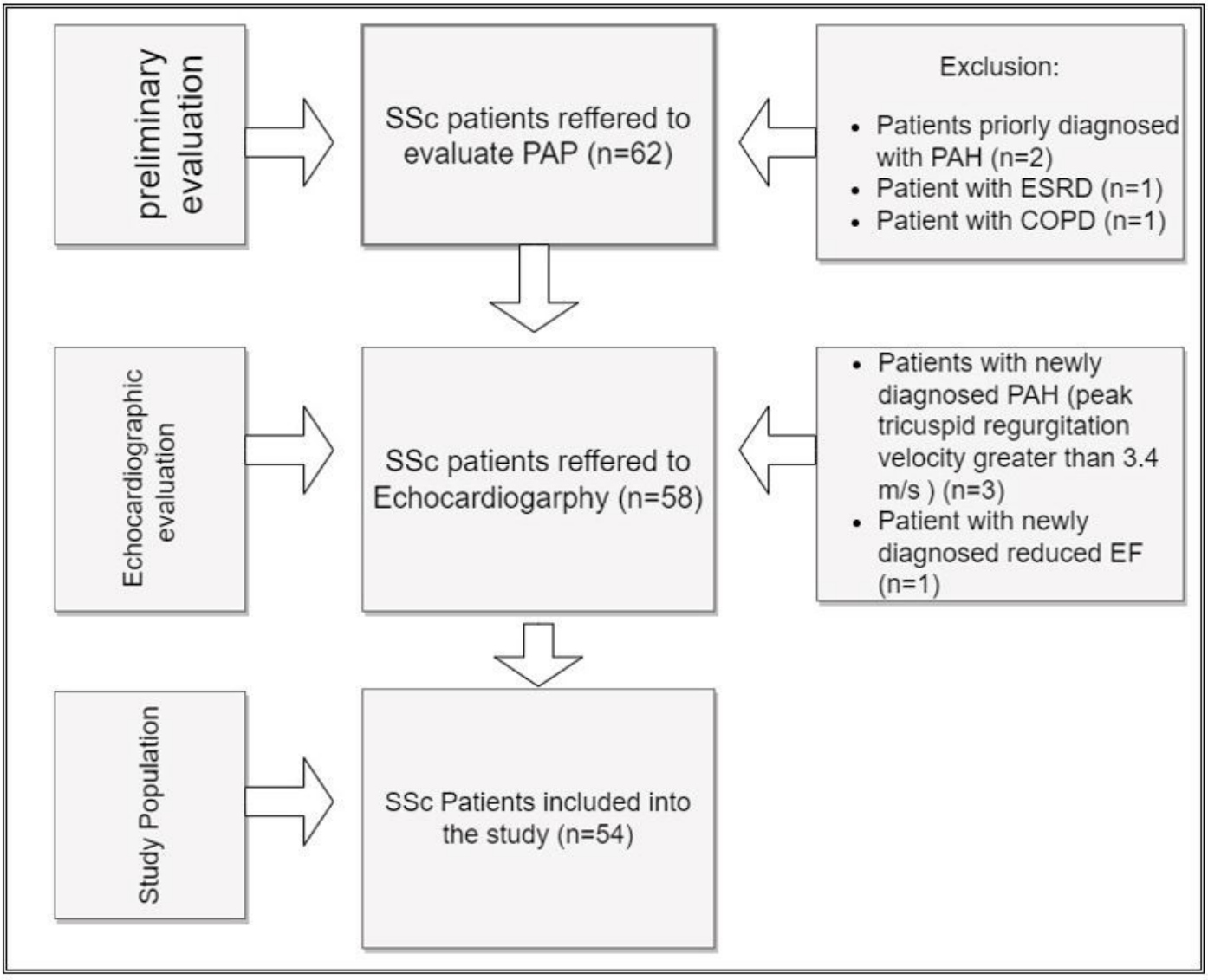
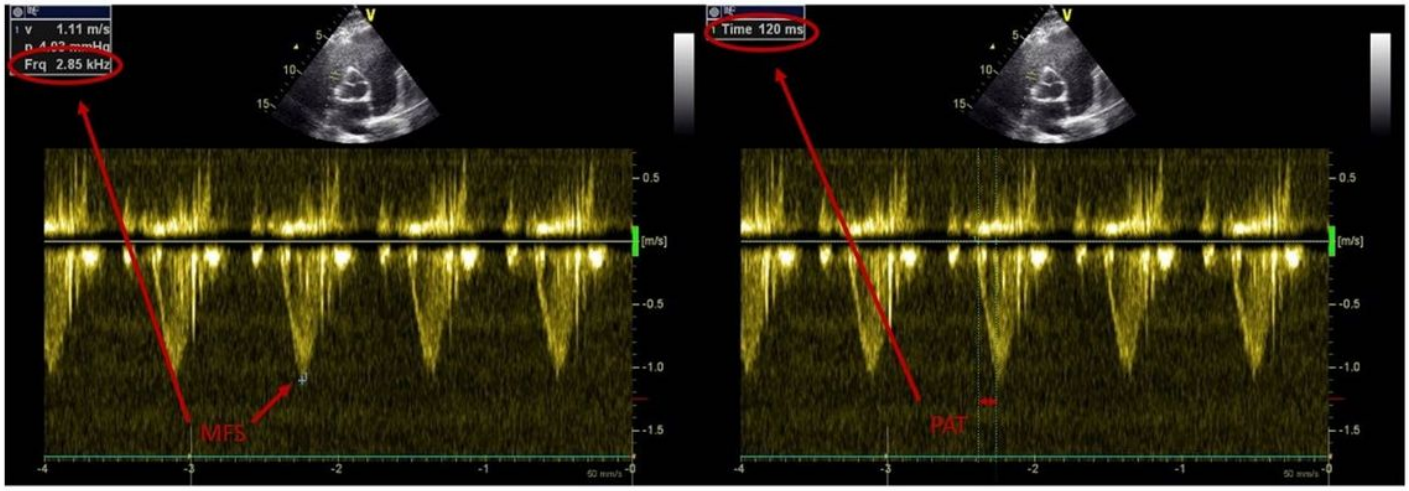
# Figures



## Figure 1

Flowchart of the study population. Abbreviations: SSc: Systemic Sclerosis, PAP: Pulmonary arterial pressure, PAH: Pulmonary arterial hypertension, ESRD: End-stage renal disease, COPD: Chronic obstructive pulmonary disease, sPAP: Systolic pulmonary arterial pressure.




$$\text{Pulmonary arterial stiffness (PAS)} = \frac{\text{Maximum frequency shift (MFS) hertz}}{\text{Pulmonary flow acceleration time (PAT) ms}}$$

## Figure 2

Evaluation of pulmonary arterial stiffness (PAS). PAS = MFS/PAT

MFS maximum frequency shift, PAT pulmonary flow acceleration time