Non-invasive methods for screening pulmonary arterial hypertension in patients with systemic sclerosis

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ABSTRACT

Background. Pulmonary arterial hypertension (PAH) is a very severe consequence that may arise in individuals diagnosed with Systemic Scleroderma (SSc). Transthoracic echocardiography (TTE) is an important screening method for PAH. A new useful echocardiographic marker has been noted: the ratio between the tricuspid annular plane systolic excursion and the systolic pulmonary arterial pressure (TAPSE/sPAP). This ratio correlates with invasive measurements.

Objectives. In the present study, we aim to evaluate the new echocardiographic marker and correlate it with other echocardiographic markers specific to assessing PAH, with age, with form of disease, and with high risk of PAH according to the DETECT algorithm.

Material and methods. An observational study that included 27 patients diagnosed with SSc according to the ACR/EULAR 2013 criteria was conducted between November 2022 and June 2023. The patients were clinically and paraclinically evaluated in the first Rheumatology Clinic, Iasi. TTE evaluation was performed in the third Internal Medicine Clinic, Iasi. The threshold value of TAPSE/CPAP was <0.6mm/mmHg. High-risk PAH was determined using the DETECT algorithm, employing the online calculator at https://www.detectionofpah.com. The statistical analysis was conducted using the PSPP 2.0.0 program. P-values of <0.05 were considered significant.

Outcomes. A total of 9 patients (33.34%) presented the TAPSE/sPAP ratio value <0.6 mm/mmHg. All these patients had tricuspid regurgitation peak gradient (TRPG) >30 mmHg, and 8 of them had a value >2.8 m/s in tricuspid regurgitation velocity assessment. According to DETECT algorithm, seven patients were identified as having a high risk of PAH. They all had a TAPSE/sPAP ratio <0.6 mm/mmHg.

Conclusion. The TAPSE/sPAP ratio is an effective method for assessing right ventricular coupling in patients with SSc-PAH. Given the invasive nature and difficulty associated with right heart catheterization (RHC), this echocardiographic marker can be used in screening. TTE remains an important screening tool, and a correlation between different echocardiographic variables can be an advantage in screening.

Keywords: systemic sclerosis, pulmonary arterial hypertension, TAPSE/sPAP ratio, DETECT algorithm

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a highly severe complication that may manifest in individuals diagnosed with systemic sclerosis (SSc). It is induced by pulmonary circulation remodeling [1]. The diagnosis is established through right heart catheterization (RHC) when the mean pulmonary arterial pressure (mPAP) values are > 20 mmHg [2]. Among the five forms of pulmonary hypertension (PH), patients with scleroderma most often belong to group 1, PAH with

an incidence of approximately 12% [3,4]. Given the poor long-term prognosis, with a median survival of 4 years, screening methods are essential [5].

Due to nonspecific symptoms, patients are often diagnosed in advanced stages of the disease [6]. Reducing the time between disease onset and diagnosis through screening methods is an important objective, as it allows for the early initiation of treatment [4,7].

Transthoracic echocardiography (TTE) is an important screening method for PAH [8]. In addition to classic parameters for evaluating right heart hemodynamics, a new helpful marker in assessment has been noted in recent years: the ratio between tricuspid annular plane systolic excursion and systolic pulmonary arterial pressure (TAPSE/sPAP). Colalillo et al. concluded that a value <0.6 mm/mmHg is associated with the presence of PAH [9]. This ratio is the only echocardiographic index that correlates with invasive measurements of pulmonary pressures [10].

Although TTE provides essential information about right heart hemodynamics, the obtained data must be sufficient for adequate screening. The DETECT algorithm is a high-sensitivity screening algorithm, as demonstrated in multiple studies [11].

In addition to echocardiographic evaluation, non-echocardiographic data such as Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO), NT-proBNP, uric acid, right axis deviation on electrocardiogram (ECG), presence of telangiectasias, and detection of anti-centromere antibodies (ACAs) are included in patient assessment. After inputting the data, patients at high risk of PAH are identified, with the RHC recommendation for diagnosis. The DETECT algorithm is included in the 2022 ESC and ERS Pulmonary Hypertension Guidelines [8].

This study aims to evaluate the new echocardiographic marker and correlate it with other specific echocardiographic markers for PAH assessment, considering age, disease form, and high-risk indication according to the DETECT algorithm.

MATERIALS AND METHODS

An observational study was conducted between November 2022 and June 2023, involving 27 patients diagnosed with SSc according to the ACR/EULAR 2013 criteria, aged 18 and above. Exclusion criteria were the inability to perform echocardiographic measurements and patient refusal. Patients were clinically and paraclinically evaluated at the first Rheumatology Clinic in Iasi. Parameters such as age, gender, disease form (limited cutaneous, diffuse cutaneous), telangiectasias, symptoms, and the presence of ACAs were assessed.

TTE evaluation took place on the third Internal Medicine Clinic utilizing a GE Health Care Vivid T8

v204 ultrasound machine. A single, experienced examiner performed Two-dimensional and Doppler measurements. The following parameters were evaluated: tricuspid regurgitation peak gradient (TRPG), tricuspid regurgitation velocity (TRV), right ventricular area, right atrial area, tricuspid valve regurgitation degree, systolic pulmonary arterial pressure (sPAP) and the TAPSE/PAPs ratio. The criteria used for identifying patients with pulmonary arterial hypertension (PAH) using echocardiography are as follows: a TRV more than 2.8 m/s [8], a sPAP higher than 36 mmHg [9], a TRPG over 30 mmHg (13), and the presence of tricuspid regurgitation grade II/III.

High-risk PAH was determined using the DETECT algorithm, employing the online calculator available at https://www.detectionofpah.com. The statistical analysis was conducted using the PSPP 2.0.0 program. P-values of <0.05 were considered significant.

OUTCOMES

A group of 27 patients were included in the study; patients' demographic, clinical, and paraclinical characteristics are presented in Table 1. The female gender predominated, with a female-to-male ratio of 9:1. The average age was 56.34 years. Limited cutaneous form was present in 37.07% (n=10) of patients, and ACA were present in 8 patients (29.62%). Symptomatology expressed through dyspnea was placed in most patients (77.78%, n=21), with no other symptoms commonly associated with PAH. By using the DETECT screening algorithm, seven patients were identified as having a high risk of PAH, with a recommendation for RHC.

TABLE 1. Demographic, clinical and immunological characteristics of patients

Characteristics	N (%)	n
Mean age	56.34	27
Gender – female	24 (88.8%)	27
Gender – male	3 (12.2%)	27
Diffuse cutaneous	17 (62.96%)	27
Limited cutaneous	10 (37.07%)	27
Telangiectasias	18 (66.67%)	27
Dyspnea	21 (77.78%)	27
Anti-centromer antibodies (ACAs)	8 (29.62%)	27
High risk of PAH - DETECT	7 (25.92%)	27

The results of the echocardiographic evaluation are presented in Table 2. The average TRV was 2.52 m/s, and the average TRPG was 28.5 mmHg. The TAPSE/sPAP ratio was assessed in all patients, with an average ratio of 0.73 mm/mmHg.

Considering the previously mentioned threshold values, a total of 10 patients presented values of TRPG, TRV, and sPAP above the threshold. The TAPSE/

TABLE 2. Echocardiographic parameters

Echocardiographic parameters	Min-max; mean	n
Tricuspid regurgitation peak gradient (TRPG)- mmHg	9.5-50; 28.5	27
Peak tricuspid regurgitation velocity (TRV) – m/s	1.33-3.5; 2.52	27
Systolic pulmonary arterial pressure (sPAP) - mmHg	55-20; 33.1	27
Tricuspid annular plane systolic excursion (TAPSE) - mm	12-28; 22.5	27
TAPSE/sPAP - mm/mmHg	0.2-1.6; 0.73	27
Right atrium area – cm²	9.5-18.4; 13.2	27

sPAP ratio < 0.6 mm/mmHg was found in 33.34% (n=9) of patients – Table 3.

TABLE 3. Echocardiographic parameters with their thresholds

Characteristic echocardiographic values for PAH	N (%)	n
TRPG > 30 mmHg	10 (37.03%)	27
TRV > 2.8 m/s	10 (37.03%)	27
sPAP > 36 mmHg	10 (37.03%)	27
TAPSE/sPAP < 0.6 mm/mmHg	9 (33.34%)	27

Regarding patients with a TAPSE/sPAP index <0.6 mm/mmHg, Table 4 shows their characteristics compared to the rest. A correlation of this index with other indices used in echocardiographic screening for PAH was observed. All these patients had TRPG >30 mmHg, and 8 had a value >2.8 m/s in TRV assessment. Tricuspid regurgitation of grade II was revealed in 4 of these patients, while in patients with TAPSE/sPAP >0.6 mm/mmHg, no tricuspid regurgitation with a grade more significant than one was identified. All seven patients identified as having a high risk of PAH according to the DETECT algorithm belong to this category (TAPSE/sPAP < 0.6 mm/mmHg). No correlations were found between TAPSE/sPAP and age or disease form.

DISCUSSION

In patients with PAH, right ventricular (RV) function is affected by increased afterload, leading to the onset of symptoms [14]. Cardiac involvement in PAH can result in right heart failure, causing a two- to threefold increase in the risk of cardiac death [15]. The gold standard for determining pressures is RHC. Considering the invasiveness and difficulty of this procedure, various echocardiographic parameters have been explored over time as prognostic and screening factors in PAH: sPAP, TRV, TRPG [16]. The 2022 ESC and ESR Pulmonary Hypertension Guidelines recommend using TRV to suggest PH more accurately than sPAP [8]. Considering these recommendations, correlations were made in this study between the TAPSE/sPAP index and TRV, confirming the utility of this ratio in the echocardiographic evaluation of PAH. However, for a correct assessment, other variables characterizing RV function are needed [17]. In this study, a correlation of echocardiographic parameters assessing right heart function was observed, confirming their utility.

The DETECT algorithm is a screening tool designed by Coghlan et al. that helps reduce the number of missed RHCs and streamlines the screening of patients with SSc-PAH. Although the negative predictive value (NPV) of DETECT is around 98%, the positive predictive value (PPV) is low (35%) [12]. In these conditions, there is a need to explore new screening tools to optimize RHC indications.

In 2022, Colalillo et al. conducted a study in which 51 patients were screened for PAH through TTE and DETECT. The PPV of the TAPSE/sPAP ratio (62.5%) was higher than that of the DETECT algorithm (31.3%). Considering these data, TAPSE/sPAP evaluation can optimize RHC recommendations through DETECT.

In our study, the percentage of patients recommended for RHC according to DETECT was 25.72% (n=7), a similar value to that identified in the study's patient group (31.4%). SSc-PAH is more common in patients with limited cutaneous disease, confirmed by multiple studies in the literature [9,18]. In our study, no predominance of limited cutaneous disease was identified among patients with echocardiographic markers indicating the presence of PAH.

In a 2021 study by Vriz et al., age-specific changes in right ventricular function and right ventricle-pulmonary artery

TABLE 4. Patients characteristics based on the TAPSE/sPAP ratio

	TAPSE/sPAP<0.6 mm/mmHg (n=9) N (%)	TAPSE/sPAP>0.6 mm/mmHg (n=18) N, (%)	p value
Mean age (age range)	57.77 (47-70)	55.67 (40-73)	0.536
Dispnea	6 (66.67%)	14 (77.78%)	0.752
Limited cutaneos	3 (33,34%)	7 (38,89%)	1.00
TRPG > 30mmHg	9 (90%)	1 (10%)	<0.001
TRV > 2.8m/s	8 (88.89%)	1 (5.56%)	<0.001
Tricuspide regurgitation – grade II	4 (44.45%)	0	<0.001
High risk of HTAP - DETECT	7 (77.78%)	0	0.001

(RV-PA) coupling were analyzed in a cohort of 1899 apparently healthy patients. RV-PA coupling was assessed by the TAPSE/sPAP ratio. Results revealed a negative association between TAPSE/sPAP and age [19]. A correlation of the TAPSE/sPAP ratio with age was also found in the study by Colalillo et al. [9]. However, there are also studies where the value of the TAPSE/sPAP ratio did not correlate with age [10,20]. In our study, no associations were identified between TAPSE/sPAP and the age of patients, with the average age being approximately equal in the two groups (57.77 vs. 55.67).

The prognostic significance of the TAPSE/sPAP ratio has been established in a multitude of medical conditions, including chronic lung diseases [24], pulmonary embolism [21,22], and heart failure [21, 22]. A recent study from 2023, including 2555 patients from the European Scleroderma Trials and Research (EUSTAR) diagnosed with SSc-PAH through RHC, investigated the correlation between TAPSE/sPAP and mortality. The result was that a value <0.32 mm/mmHg is essential for all-cause mortality. Only one

patient with TAPSE/sPAP <0.32 mm/mmHg was identified in our patient cohort. Prior research has also shown that this proportion serves as a prognostic indicator for death in patients with SSc-PAH, although with smaller groups of patients [25,26].

A limited number of patients and the incapacity to execute right cardiac catheterization (RHC) constitute the study's limitations. In addition, the patient's current medication regimen was not considered.

CONCLUSION

The TAPSE/sPAP ratio is an effective method for assessing RV coupling in patients with SSc-PAH. Given the invasive nature and difficulty associated with RHC, this echocardiographic marker can be used in screening. TTE remains an important screening tool, and a correlation between variables can be advantageous. Although not included in screening strategies, TAPSE/sPAP is a marker that provides essential information regarding cardiac impairment in PAH.

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