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The role of TAPSE/sPAP ratio in predicting pulmonary hypertension and mortality in the systemic sclerosis EUSTAR cohort

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ABSTRACT

Objectives: The study aim was to evaluate the predictive role of the echocardiography-derived tricuspid annular plane systolic excursion/systolic pulmonary artery pressure (TAPSE/sPAP) ratio for pulmonary hypertension (PH) diagnosis and mortality in the European Scleroderma Trials and Research (EUSTAR) cohort.

Methods: Eligible patients were systemic sclerosis (SSc) patients registered in the EUSTAR database with at least one visit recording TAPSE and sPAP data. Individual centres were required to provide TAPSE and sPAP data at 12 ± 3 months before right heart catheterization (RHC). Logistic regression analysis was applied to analyse the predictive ability of TAPSE/sPAP ratio for PH diagnosis. Cox regression analysis was performed to evaluate TAPSE/sPAP ratio as a predictive factor for all-cause mortality.

Results: 2555 SSc patients met the inclusion criteria for this study with 355 SSc patients having available RHC data at baseline. PH was confirmed by RHC in 195 SSc patients (54.9%). TAPSE/sPAP ratio < 0.55 mm/mmHg [OR 0.251 (95% CI 0.084–0.753), $p < 0.05$] and FVC/DL_{CO} [OR 2.568 (95% CI 1.227–5.375), $p < 0.05$] were significantly associated with PH diagnosis. In logistic regression analysis with echocardiographic parameters at 12 ± 3 months before RHC, TAPSE/sPAP ratio < 0.55 mm/mmHg [OR 0.265 (95% CI 0.102–0.685), $p < 0.01$] and FVC/DL_{CO} [OR 2.529 (95% CI 1.358–4.711), $p < 0.01$] were associated with PH diagnosis. In multivariate Cox regression analysis, TAPSE/sPAP ratio ≤ 0.32 mm/mmHg [HR 0.310 (0.164–0.585), $p < 0.001$] was the most significant predictive factor for death.

Conclusions: TAPSE/sPAP ratio < 0.55 mm/mmHg is a predictive risk factor for PH. TAPSE/sPAP ratio ≤ 0.32 mm/mmHg is a predictive risk marker for all-cause mortality.

Abbreviations: TAPSE/sPAP, tricuspid annular plane systolic excursion/systolic pulmonary artery pressure.

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1. Introduction

Pulmonary arterial hypertension (PAH) is a major cause of morbidity and mortality in systemic sclerosis (SSc), affecting approximately 6–12% of SSc patients [1–4]. Despite therapeutic advances, long-term survival is still disappointing [5,6]. Early diagnosis and treatment are crucial to significantly improve patient outcomes [7]. The echocardiography-estimated systolic pulmonary artery pressure (sPAP) has a key role in PAH annual screening. However, the diagnostic accuracy of echocardiography or other tests alone in detecting PAH is suboptimal. The new 2022 pulmonary hypertension (PH) guidelines recommend the use of composite measures for PAH screening in SSc patients [8]. In particular, the DETECT algorithm, combining clinical features, echocardiography, pulmonary function tests (PFTs) and N-terminal pro-brain natriuretic peptide (NT-proBNP), improves diagnostic accuracy and patient selection for right heart catheterization (RHC) referral to confirm PAH diagnosis [8–10].

The right ventricular - pulmonary arterial (RV-PA) coupling describes the RV adaptation to its afterload. In PAH the progressive pulmonary vascular remodelling leads to an increasing pulmonary vascular resistance and pulmonary artery pressure, an additional load on the contracting RV and an altered RV-PA coupling [11,12]. Tricuspid annular plane systolic excursion/systolic pulmonary artery pressure (TAPSE/sPAP) ratio is the validated non-invasive estimation of RV-PA coupling easily obtained during a standard Doppler echocardiography [13].

A previous study on 51 SSc patients, comparing the positive predictive value (PPV) between a TAPSE/sPAP ratio of $\leq$0.60 mm/mmHg and the DETECT algorithm, suggested the potential utility of TAPSE/sPAP ratio in addition to the DETECT algorithm in selecting patients requiring RHC to confirm PAH diagnosis [14]. In the new 2022 pulmonary hypertension (PH) guidelines, the TAPSE/sPAP ratio has been included among the additional echocardiographic signs suggestive of PH [8]. However, to date, the role of TAPSE/sPAP ratio as a screening tool for PH in SSc patients is underinvestigated.

A previous European Scleroderma Trials and Research (EUSTAR) study showed that a sPAP >36 mmHg was significantly and independently associated with reduced survival in SSc patients [15]. The role of TAPSE/sPAP ratio in risk stratification and predicting mortality has already been described in several conditions, including heart failure and PH [16–22]. In patients with PH, a TAPSE/sPAP ratio < 0.31 mm/mmHg has been identified as the cut-off value discriminating RV-PA uncoupling and has been associated with a significantly worse prognosis [13]. Besides, TAPSE/sPAP ratio was independently associated with overall mortality in 290 patients with PAH and the worst overall survival was reported for a TAPSE/sPAP ratio < 0.19 mm/mmHg [21]. In the new 2022 PH guidelines, the TAPSE/sPAP ratio has been included among the echocardiographic parameters for 1-year mortality risk assessment [8]. To date, only a few studies with small sample size specifically investigated the prognostic role of TAPSE/sPAP ratio in SSc patients [23,24].

The primary aim of the study was to evaluate the RV-PA coupling by the echocardiography-derived TAPSE/sPAP ratio and to assess the predictive role of TAPSE/sPAP ratio in the diagnosis of PH in the SSc EUSTAR cohort. The secondary aim of the study was to evaluate the prognostic role of TAPSE/sPAP ratio in predicting mortality in the SSc EUSTAR cohort.

2. Materials and methods

2.1. Study design and inclusion criteria

The prospective cohort study was a post hoc analysis of data from the multinational EUSTAR database. The structure of the online database, the collected data set and definitions of clinical variables have been described in detail previously [1,25].

Patients registered since 2010 in the EUSTAR database (start of the online version), aged ≥18 years, who fulfilled the 2013 American College of Rheumatology/European League Against Rheumatism SSc classification criteria [26] and with available TAPSE and sPAP measurements on echocardiography at baseline were included. The first visit with available TAPSE and sPAP data was considered as the study baseline. TAPSE/sPAP ratio is not present in the EUSTAR database and was calculated for all SSc patients with recorded TAPSE and sPAP data. All-cause mortality was assessed in all SSc patients with available TAPSE and sPAP values at baseline. The time interval (months) between the date of study baseline and the date of death was calculated.

The presence of PH, reported in the EUSTAR database as PH "yes", "no" or "unknown", independently of RHC confirmation, was also evaluated in these patients.

The outcomes evaluated in this population were:

a. The predictive value of sPAP and TAPSE/sPAP ratio for all-cause mortality;
b. The association between sPAP and TAPSE/sPAP ratio and PH.

2.2. Patients with available RHC data

All SSc patients with available RHC data (mean PAP) at baseline were selected among enrolled patients. PH was defined by a mPAP >20 mmHg [8]. In all SSc patients with available RHC at baseline, TAPSE and sPAP values at 12 ± 3 months before RHC were also evaluated. TAPSE and sPAP measurements at 12 ± 3 months before RHC were not reported in the EUSTAR database. Principal investigators of individual centres were required to provide missing data. All-cause mortality was assessed in all SSc patients with available RHC data. The time interval (months) between the date of RHC and the date of death was calculated.

The outcomes evaluated in this population were:

a. The association between sPAP and TAPSE/sPAP ratio and PH diagnosis confirmed by RHC;
b. The predictive value of sPAP and TAPSE/sPAP ratio at 12 ± 3 months before RHC for PH diagnosis confirmed by RHC;
c. The predictive value of sPAP and TAPSE/sPAP ratio for all-cause mortality.

2.3. Echocardiographic data

sPAP was reported in mmHg and a value of >36 mmHg was considered increased [8,15,27]. TAPSE/sPAP ratio was expressed in mm/mmHg and a cut-off of <0.55 mm/mmHg for PH diagnosis was selected according to the new 2022 PH guidelines [8]. As for mortality risk assessment, a cut-off of TAPSE/sPAP ratio ≤ 0.32 mm/mmHg for intermediate-high risk of mortality and a cut-off of <0.19 for high risk of mortality were selected according to the new 2022 PH guidelines [8].

2.4. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 26. Data were reported as mean and standard deviation (SD); categorical data were represented as frequencies and proportions. Student's test was used to evaluate the difference between numerical variables. Chi-square test or Fisher's exact test were used to compare categorical variables. Receiver Operating Characteristic (ROC) curves were used to evaluate the diagnostic performance of sPAP and TAPSE/sPAP ratio. Univariate and multivariate logistic regression analyses with odds ratio (OR) and 95% confidence interval (CI) were applied to analyse the association between variables and PH at baseline and the predictive ability of variables for PH at 12 ± 3 months before RHC. The variables included in logistic regression analysis were: categorical variables [increased sPAP (yes or no), reduced TAPSE/sPAP ratio (yes or no)] and numerical variables [NT-proBNP (pg/mL), forced vital capacity/diffusing capacity

of the lungs for carbon monoxide (FVC/DL_{CO}) and age (years)]. Overall survival (OS) data were represented by Kaplan-Meier curves and the log-rank test was used for statistical comparisons. Univariate Cox regression analysis was applied to evaluate the significant variables for overall survival. Multivariate Cox regression analysis was performed on the significant variables in univariate Cox regression analysis. Hazard Ratio (HR) and 95% CI were reported. A significance level of 0.05 was used for all tests.

3. Results

From the EUSTAR database, 2555 SSc patients met the inclusion criteria for this study. Demographic and clinical characteristics of all included 2555 SSc patients are reported in Table 1. sPAP and TAPSE/sPAP ratio mean values were 30 ± 14 mmHg and 0.83 ± 0.30 mm/mmHg, respectively. With a cut-off of >36 mmHg for sPAP, 513 (20.1%) SSc patients had an increased sPAP value. 460 (18%) SSc patients had a reduced TAPSE/sPAP ratio with a cut-off of <0.55 mm/mmHg; 152 (5.9%) and 39 (1.5%) SSc patients had a reduced TAPSE/sPAP ratio with a cut-off of ≤0.32 mm/mmHg and < 0.19 mm/mmHg, respectively.

3.1. Overall survival in all EUSTAR cohort

After excluding 107 (4.2%) SSc patients lost at follow-up, all-cause mortality was analyzed in 2448 (95.8%) SSc patients. Of these, 116 (4.7%) SSc patients died after a follow-up of 24.6 ± 21.5 months. The ROC curve analysis showed an AUC of 0.759 (0.709–0.809, $p < 0.001$) for sPAP and 0.765 (0.716–0.813, $p < 0.001$) for TAPSE/sPAP ratio.

Overall survival was evaluated with a cut-off of >36 mmHg for sPAP and a cut-off of ≤0.32 mm/mmHg for TAPSE/sPAP ratio. Kaplan Meier curves showed a higher mortality in SSc patients with increased sPAP (Log Rank χ^2 124.1, $p < 0.001$) and in SSc patients with reduced TAPSE/sPAP ratio (Log Rank χ^2 105, $p < 0.001$). In univariate Cox regression analysis, increased sPAP [HR 0.147 (0.099–0.217), $p < 0.001$], reduced TAPSE/sPAP ratio [HR 0.160 (0.107–0.240), $p < 0.001$] and age [HR 1.052 (1.035–1.069), $p < 0.001$)] were predictive factors for death; while male sex was not [HR 0.816 (0.512–1.301), $p = 0.394$]. In multivariate Cox regression analysis, increased sPAP [HR 0.252 (0.159–0.399), $p < 0.001$], reduced TAPSE/sPAP ratio [HR 0.460 (0.293–0.723), $p < 0.01$] and age [HR 1.030 (1.013–1.048), $p < 0.01$] were predictive factors for all-cause mortality.

Overall survival was also assessed with a cut-off of >36 mmHg for sPAP and a cut-off of <0.19 mm/mmHg for TAPSE/sPAP ratio. Kaplan Meier curves showed a higher mortality in SSc patients with increased sPAP (Log Rank χ^2 124.1, $p < 0.001$) and in SSc patients with reduced TAPSE/sPAP ratio (Log Rank $\chi 2$ 81.7, $p < 0.001$). In univariate Cox regression analysis, increased sPAP [HR 0.147 (0.099–0.217), $p < 0.001$], reduced TAPSE/sPAP ratio [HR 0.111 (0.063–0.199), $p < 0.001$] and age [HR 1.052 (1.035–1.069), $p < 0.001$)] were predictive factors for death; while sex was not [HR 0.816 (0.512–1.301), $p = 0.394$]. In multivariate Cox regression analysis, increased sPAP [HR 0.215 (0.140–0.329), $p < 0.001$], reduced TAPSE/sPAP ratio [HR 0.330 (0.181–0.600), $p < 0.001$] and age [HR 1.029 (1.012–1.047), $p < 0.01$] were predictive factors for all-cause mortality.

3.2. Echocardiographic parameters in SSc patients with available PH data

TAPSE, sPAP and PH (yes or no) data were available in 664 (26%) SSc patients at baseline. In this group of patients, PH was reported as present in 307 (46.2%) SSc patients. Demographic and clinical characteristics of 664 SSc patients with available PH data are reported in Table 1.

The mean values of sPAP and TAPSE/sPAP ratio were 41 ± 19 mmHg and 0.61 ± 0.28 mm/mmHg, respectively. Analyzing PH data, a cut-off of >36 mmHg for sPAP and a cut-off of <0.55 mm/mmHg for TAPSE/sPAP ratio were selected. In this group of SSc patients, 322

Table 1
Demographic and clinical characteristics of systemic sclerosis (SSc) patients.

	TAPSE and sPAP data available at baseline ($n = 2555$)		PH data (yes or no) available at baseline ($n = 664$)		RHC data available at baseline ($n = 355$)		
	Results	*N*	*Results*	*N*	*T0*	*T(−1)*	*N*
Age, years, mean ± SD	62 ± 14	2555	67 ± 12	664	69 ± 11	68 ± 11	355
Male, n (%)	414 (16.2)	2555	125 (18.8)	664	59 (16.6)	N.A.	355
Disease duration, years, mean ± SD	14 ± 10	2215	17 ± 10	592	16 ± 11	N.A.	302
Limited cutaneous SSc, n (%)	1479 (70.5)	2097	349 (64.7)	539	196 (70.5)	N.A.	278
Diffuse cutaneous SSc, n (%)	618 (29.5)	2097	190 (35.3)	539	82 (29.5)	N.A.	278
ACA, n (%)	815 (43.9)	1857	206 (41.3)	499	123 (48.2)	N.A.	255
Scl-70, n (%)	628 (33.5)	1876	166 (33.2)	500	70 (27)	N.A.	259
RNA Pol III, n (%)	138 (9.5)	1448	23 (6.2)	373	13 (6.2)	N.A.	210
mRSS, mean ± SD	6 ± 8	1916	8 ± 8	462	8 ± 8	N.A.	206
Digital ulcers history, n (%)	1075 (45.5)	2364	301 (52.3)	575	154 (50.8)	N.A.	303
Tendon friction rubs, n (%)	87 (3.6)	2394	33 (5.6)	591	16 (5.4)	N.A.	296
Telangiectasias, n (%)	1493 (63.5)	2352	430 (72.6)	592	229 (75.1)	N.A.	205
NT-proBNP, pg/mL, mean ± SD	643 ± 3508	1514	1035 ± 2487	315	1172 ± 2961	N.A.	157
FVC, % predicted, mean ± SD	92 ± 22	2200	87 ± 23	585	88 ± 24	92 ± 22	308
DL_{CO}, % predicted, mean ± SD	66 ± 22	2087	51 ± 20	531	51 ± 19	56 ± 18	265
FVC/DL_{CO}, mean ± SD	1.58 ± 0.63	2047	1.97 ± 0.80	526	2 ± 0.78	1.79 ± 0.64	263
LVEF, %, mean ± SD	60.9 ± 6.5	2322	60.4 ± 7	589	60.7 ± 7.3	N.A.	297
Diastolic dysfunction, n (%)	625 (28.9)	2160	239 (41.8)	572	121 (42.3)	N.A.	286
TAPSE, mm, mean ± SD	21.8 ± 4.2	2555	20.7 ± 4.8	664	20.4 ± 5	21.2 ± 4.6	355
sPAP, mmHg, mean ± SD	30 ± 14	2555	41 ± 19	664	46 ± 19	39.7 ± 17.2	355
TAPSE/sPAP, mm/mmHg, mean ± SD	0.83 ± 0.30	2555	0.61 ± 0.28	664	0.52 ± 0.24	0.64 ± 0.29	355
sPAP >36 mmHg, n (%)	513 (20.1)	2555	322 (48.5)	664	224 (63.1)	169 (47.6)	355
TAPSE/sPAP <0.55 mm/mmHg, n (%)	460 (18)	2555	288 (43.4)	664	199 (56.1)	154 (43.4)	355
TAPSE/sPAP ≤0.32 mm/mmHg, n (%)	152 (5.9)	2555	113 (17)	664	76 (21.4)	49 (13.8)	355
TAPSE/sPAP <0.19 mm/mmHg, n (%)	39 (1.5)	2555	33 (5)	664	25 (7)	10 (2.8)	355

Percentages are calculated on the number of available data. *TAPSE*: tricuspid annular plane systolic excursion; *sPAP*: systolic pulmonary arterial pressure; *PH*: pulmonary hypertension; *RHC*: right heart catheterization; *N*: number of patients with available data; *T0*: baseline; *T(−1)*: 12 ± 3 months before RHC; *N.A.*: not applicable; *ACA*: anticentromere antibodies; *Scl-70*: antitopoisomerase I antibodies; *RNA Pol III*: RNA polymerase III antibodies; *mRSS*: modified Rodnan skin score; *NT-proBNP*: N-terminal pro-B-type natriuretic peptide; *FVC*: forced vital capacity; *DLco*: diffusing capacity of the lungs for carbon monoxide; *LVEF*: left ventricular ejection fraction.

(48.5%) had an increased sPAP value and 288 (43.4%) had a reduced TAPSE/sPAP ratio. The ROC curve analysis showed an AUC of 0.833 (0.802–0.864, $p < 0.001$) for sPAP and 0.845 (0.815–0.874, $p < 0.001$) for TAPSE/sPAP ratio. The OR for PH was 9.8 (95% CI 6.9–14) for sPAP and 11.1 (95% CI 7.7–16) for TAPSE/sPAP ratio. The logistic regression analysis showed that increased sPAP [OR 0.395 (95% CI 0.182–0.854), $p < 0.05$], reduced TAPSE/sPAP ratio [OR 0.268 (95% CI 0.124–0.579), $p < 0.01$] and FVC/DL_{CO} [OR 1.707 (95% CI 1.125–2.592), $p < 0.05$] were significantly associated with PH (Table 2).

3.3. Echocardiographic parameters in SSc patients with available RHC data at baseline

RHC data at baseline were available in 355 SSc patients. No patient had a previously reported diagnosis of PH at the study baseline in the EUSTAR database. Demographic and clinical characteristics of 355 SSc patients with available RHC data are reported in Table 1.

mPAP mean value was 27 ± 11 mmHg. sPAP and TAPSE/sPAP ratio mean values were 46 ± 19 mmHg and 0.52 ± 0.24 mm/mmHg, respectively. With a cut-off of >36 mmHg for sPAP and a cut-off of <0.55 mm/mmHg for TAPSE/sPAP ratio, 224 (63.1%) SSc patients had an increased sPAP value and 199 (56.1%) had a reduced TAPSE/sPAP ratio. In this group of SSc patients, the prevalence of PH, confirmed by RHC, was 54.9% ($n = 195$). As for PH diagnosis by RHC, the ROC curve analysis showed an AUC of 0.815 (0.771–0.858, $p < 0.001$) for sPAP and 0.832 (0.790–0.874, $p < 0.001$) for TAPSE/sPAP ratio (Fig. 1, A and B). The OR for PH was 7.8 (95% CI 4.7–12.7) for sPAP and 9 (95% CI 5.6–14.6) for TAPSE/sPAP ratio. The logistic regression analysis showed that only reduced TAPSE/sPAP ratio [OR 0.251 (95% CI 0.084–0.753), $p < 0.05$] and FVC/DL_{CO} [OR 2.568 (95% CI 1.227–5.375), $p < 0.05$] were significantly associated with PH diagnosis (Table 2).

3.4. Echocardiographic parameters at 12 ± 3 months before RHC

In this group of 355 SSc patients, the mean values of sPAP and TAPSE/sPAP ratio at 12 ± 3 months before RHC were 39.7 ± 17.2 mmHg and 0.64 ± 0.29 mm/mmHg, respectively. With a cut-off of >36 mmHg for sPAP and a cut-off of <0.55 mm/mmHg for TAPSE/sPAP ratio, 160 (47.6%) had an increased sPAP value and 154 (43.4%) had a reduced TAPSE/sPAP ratio. As for PH diagnosis by RHC, the ROC curve analysis showed an AUC of 0.775 (0.728–0.822, $p < 0.001$) for sPAP and 0.783 (0.736–0.830, $p < 0.001$) for TAPSE/sPAP ratio (Fig. 1, C and D). The OR for PH was 4.7 (95% CI 3–7.4) for sPAP and 5.6 (95% CI 3.5–9) for TAPSE/sPAP ratio. The logistic regression analysis showed that only TAPSE/sPAP ratio [OR 0.265 (95% CI 0.102–0.685), $p < 0.01$] and FVC/DL_{CO} [OR 2.529 (95% CI 1.358–4.711), $p < 0.01$] at 12 ± 3 months before RHC were significantly associated with PH diagnosis (Table 2).

Table 2
Logistic regression analysis in different groups of systemic sclerosis (SSc) patients.

PH in 664 SSc patients		
	OR (95% CI)	*p*
sPAP >36 mmHg	0.395 (0.182–0.854)	<0.05
TAPSE/sPAP <0.55 mm/mmHg	0.268 (0.124–0.579)	<0.01
NT-proBNP, pg/mL	1.000 (1.000–1.000)	0.118
FVC/DL_{CO}	1.707 (1.125–2.592)	<0.05
Age, years	1.009 (0.982–1.037)	0.519
PH in 355 SSc patients at T0		
	OR (95% CI)	*p*
sPAP >36 mmHg	0.785 (0.282–2.188)	0.643
TAPSE/sPAP <0.55 mm/mmHg	0.251 (0.084–0.753)	<0.05
NT-proBNP, pg/mL	1.000 (1.000–1.001)	0.242
FVC/DL_{CO}	2.568 (1.227–5.375)	<0.05
Age, years	0.974 (0.934–1.015)	0.205
PH in 355 SSc patients at T(−1)		
	OR (95% CI)	*P*
sPAP >36 mmHg	0.521 (0.226–1.201)	0.126
TAPSE/sPAP <0.55 mm/mmHg	0.265 (0.102–0.685)	<0.01
FVC/DL_{CO}	2.529 (1.358–4.711)	<0.01
Age, years	1.021 (0.991–1.053)	0.176

OR: odds ratio; *PH*: pulmonary hypertension; *TAPSE*: tricuspid annular plane systolic excursion; *sPAP*: systolic pulmonary arterial pressure; *NT-proBNP*: N-terminal pro-B-type natriuretic peptide; *FVC*: forced vital capacity; *DLco*: diffusing capacity of the lungs for carbon monoxide; *T0*: baseline; *T(−1)*: 12 ± 3 months before right heart catheterization.

3.5. Mortality in SSc patients with available RHC data

In this group of 355 SSc patients, the predictive value of sPAP and TAPSE/sPAP ratio for all-cause mortality was also analyzed. 41 of 355 (11.5%) SSc patients died after a follow-up of 38.8 ± 25.1 months. The ROC curve analysis showed an AUC of 0.735 (0.666–0.805, $p < 0.001$) for sPAP and 0.773 (0.703–0.843, $p < 0.001$) for TAPSE/sPAP ratio.

Overall survival was evaluated with a cut-off of >36 mmHg for sPAP and a cut-off of ≤0.32 mm/mmHg for TAPSE/sPAP ratio. Kaplan Meier curves showed a higher mortality in SSc patients with increased sPAP (Log Rank $\chi 2$ 24.6, $p < 0.001$) and in SSc patients with reduced TAPSE/sPAP ratio (Log Rank χ^2 41.1, $p < 0.001$) (Fig. 2, A and B). In univariate Cox regression analysis, increased sPAP [HR 0.066 (0.016–0.276), $p < 0.001$], reduced TAPSE/sPAP ratio [HR 0.167 (0.089–0.310), $p < 0.001$] and age [HR 1.047 (1.014–1.080), $p < 0.01$)] were predictive factors for death. In multivariate Cox regression analysis, reduced TAPSE/sPAP ratio [HR 0.310 (0.164–0.585), $p < 0.001$] was the most significant predictive factor for all-cause mortality (Table 3).

Overall survival was also assessed with a cut-off of >36 mmHg for sPAP and a cut-off of <0.19 mm/mmHg for TAPSE/sPAP ratio. Kaplan Meier curves showed a higher mortality in SSc patients with increased sPAP (Log Rank χ^2 24.6, $p < 0.001$) and in SSc patients with reduced TAPSE/sPAP ratio (Log Rank χ^2 29.3, $p < 0.001$) (Fig. 2, A and C). In univariate Cox regression analysis, increased sPAP [HR 0.066 (0.016–0.276), $p < 0.001$], reduced TAPSE/sPAP ratio [HR 0.173 (0.084–0.356), $p < 0.001$] and age [HR 1.047 (1.014–1.080), $p < 0.01$)] were predictive factors for death. In multivariate Cox regression analysis, increased sPAP [HR 0.092 (0.022–0.388), $p < 0.01$] and reduced TAPSE/sPAP ratio [HR 0.317 (0.154–0.656), $p < 0.01$] were predictive factors for all-cause mortality (Table 3).

4. Discussion

This is the first study to show the association between a reduced TAPSE/sPAP ratio and PH diagnosis and, even more important, its predictive ability 12 months before PH diagnosis in a large cohort of SSc patients. Moreover, this is the largest study to demonstrate the predictive role of a reduced TAPSE/sPAP ratio for all-cause mortality in SSc patients.

According to the new 2022 PH guidelines, we assessed all-cause mortality selecting two different cut-off values for TAPSE/sPAP ratio. For both cut-off values, a reduced TAPSE/sPAP ratio was a predictive risk factor for all-cause mortality and SSc patients with a reduced TAPSE/sPAP ratio had worse survival than patients with higher values. Previous studies described the prognostic role of different TAPSE/sPAP cut-off values in several conditions, including heart failure [16–18], valvular heart disease [28–30], pulmonary embolism [31], chronic lung disease [32] and PH [19–22]. Only two small sample size studies specifically evaluated the prognostic role of TAPSE/sPAP ratio in SSc patients. Lai et al. reported the association between a TAPSE/sPAP ratio ≤ 0.194 mm/mmHg and the composite endpoint of all-cause death and clinical worsening in 60 SSc patients with PAH [23]. Instead, Xanthouli et al. identified a TAPSE/sPAP ratio ≤ 0.6 mm/mmHg as an independent predictor of survival in 225 SSc patients [24]. Furthermore, a previous

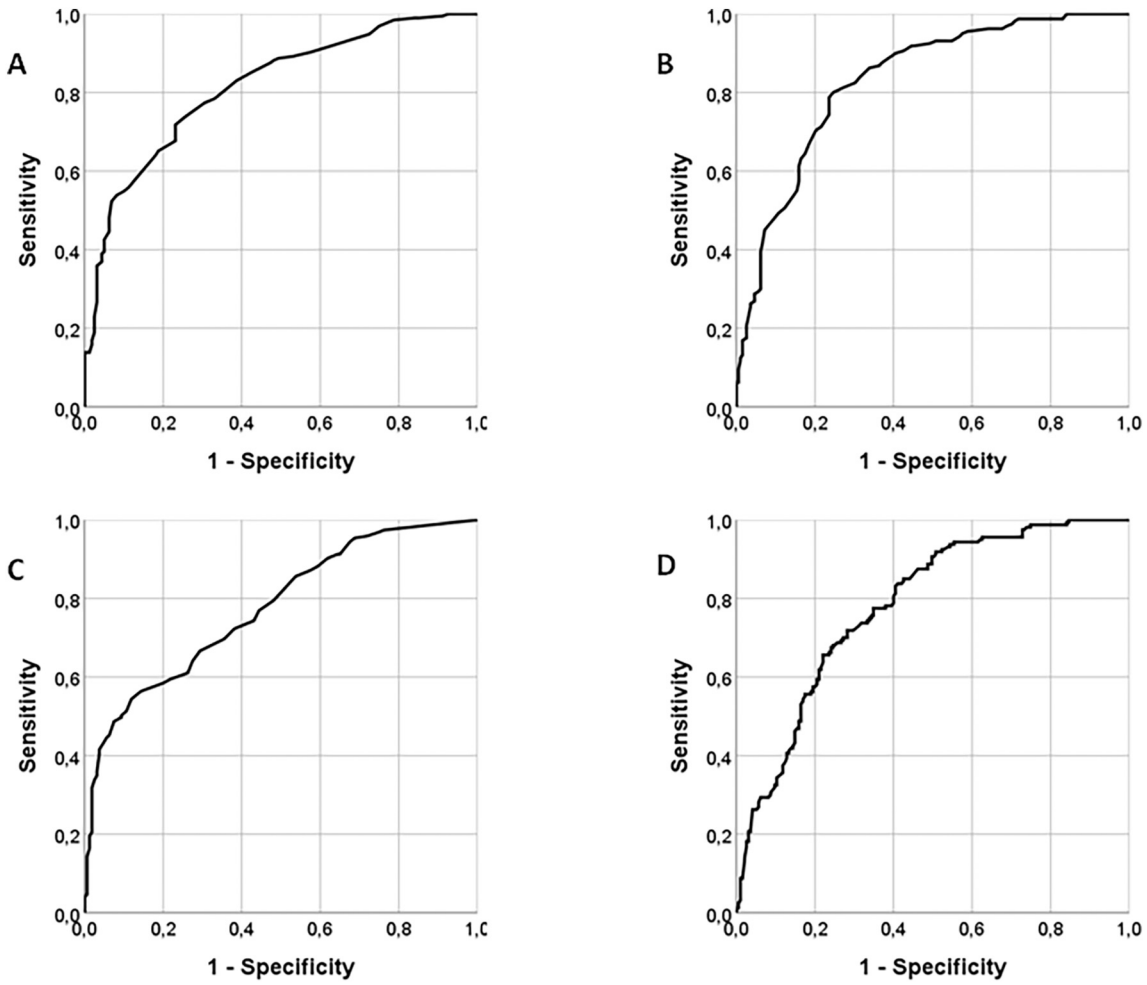

Fig. 1. Receiver Operating Characteristic (ROC) curves for the echocardiographic parameters for the prediction of pulmonary hypertension in 355 systemic sclerosis patients. **A:** ROC curve for systolic pulmonary artery pressure (sPAP) at baseline; **B:** ROC curve for tricuspid annular plane systolic excursion (TAPSE)/sPAP ratio at baseline; **C:** ROC curve for sPAP at 12 ± 3 months before right heart catheterization (RHC); **D:** ROC curve for TAPSE/sPAP ratio at 12 ± 3 months before RHC.

EUSTAR study showed that a sPAP >36 mmHg was associated with reduced survival in SSc patients [15]. In our study, a TAPSE/sPAP ratio ≤ 0.32 mm/mmHg emerged as a stronger predictor of all-cause mortality than a sPAP >36 mmHg in a large cohort of SSc patients undergoing RHC, independently of PH diagnosis and PH group. The TAPSE/sPAP ratio, the ratio between an index of RV function (TAPSE) and an index of RV afterload (sPAP), is the validated non-invasive measure of RV-PA coupling. A TAPSE/sPAP ratio < 0.36 mm/mmHg and a TAPSE/sPAP ratio < 0.31 mm/mmHg have been identified as the cut-off values discriminating RV-PA uncoupling in heart failure and PH, respectively [13,18]. RV-PA uncoupling occurs when RV contractility is unable to match RV afterload. Prompt detection of RV-PA uncoupling, before RV failure occur, is therefore crucial to identify patients at higher risk of clinical deterioration and mortality and to optimise treatment strategies. Vicenzi et al. reported that including TAPSE/sPAP ratio in two different risk scores improved risk stratification in 102 patients with PAH [20]. Our results confirm that TAPSE/sPAP ratio should be included in the prognostic assessment of SSc patients.

In the present study, a TAPSE/sPAP ratio < 0.55 mm/mmHg was significantly and independently associated with the presence of PH in a large cohort of SSc patients. Besides, we evaluated the association between TAPSE/sPAP ratio measured 12 months before RHC and PH diagnosis. We demonstrated for the first time that a TAPSE/sPAP ratio < 0.55 mm/mmHg 12 months before RHC was a risk factor for PH confirmed by RHC. In healthy subjects of all ages, a median (5th–95th percentiles) normative value of 1.25 (0.81–1.78) mm/mmHg has been reported for TAPSE/sPAP ratio [33]. Early PH detection, before RV-PA uncoupling and RV dysfunction occur, is crucial to promptly start treatment and significantly improve patients exercise capacity, quality of life and survival. According to 2022 PH guidelines, our findings suggest that a cut-off of <0.55 mm/mmHg for TAPSE/sPAP ratio is the optimal cut-off value identifying SSc patients who are more likely to have PH. Our results are in line with a previous study that investigated the role of TAPSE/sPAP ratio as a potential screening tool for PAH in 51 SSc patients comparing the PPV between TAPSE/sPAP ratio and DETECT algorithm. The PPV of TAPSE/sPAP ratio was higher than the PPV of DETECT algorithm, suggesting potential utility for TAPSE/sPAP ratio in SSc patients with a DETECT algorithm step 2 total score > 35 to select patients requiring RHC to confirm PAH diagnosis [14]. According to PH guidelines, echocardiography has a central role in PH screening and a TRV >2.8 m/s, corresponding to an estimated sPAP >36 mmHg, is the cut-off value discriminating patients with intermediate-high probability of PH [8]. In our study, a TAPSE/sPAP ratio < 0.55 mm/mmHg emerged as a stronger risk factor for PH than a sPAP >36 mmHg in a large cohort of SSc patients. To date, there is an unmet need for screening tools able to improve the selection of patients requiring further diagnostic testing to exclude or confirm PH. Our results confirm that TAPSE/sPAP ratio should be included in the PH screening algorithm of SSc patients.

Strengths of the study are the large sample size and the applicability of results to clinical practice due to the use of representative real-world data. Nevertheless, this study has several limitations. This is a

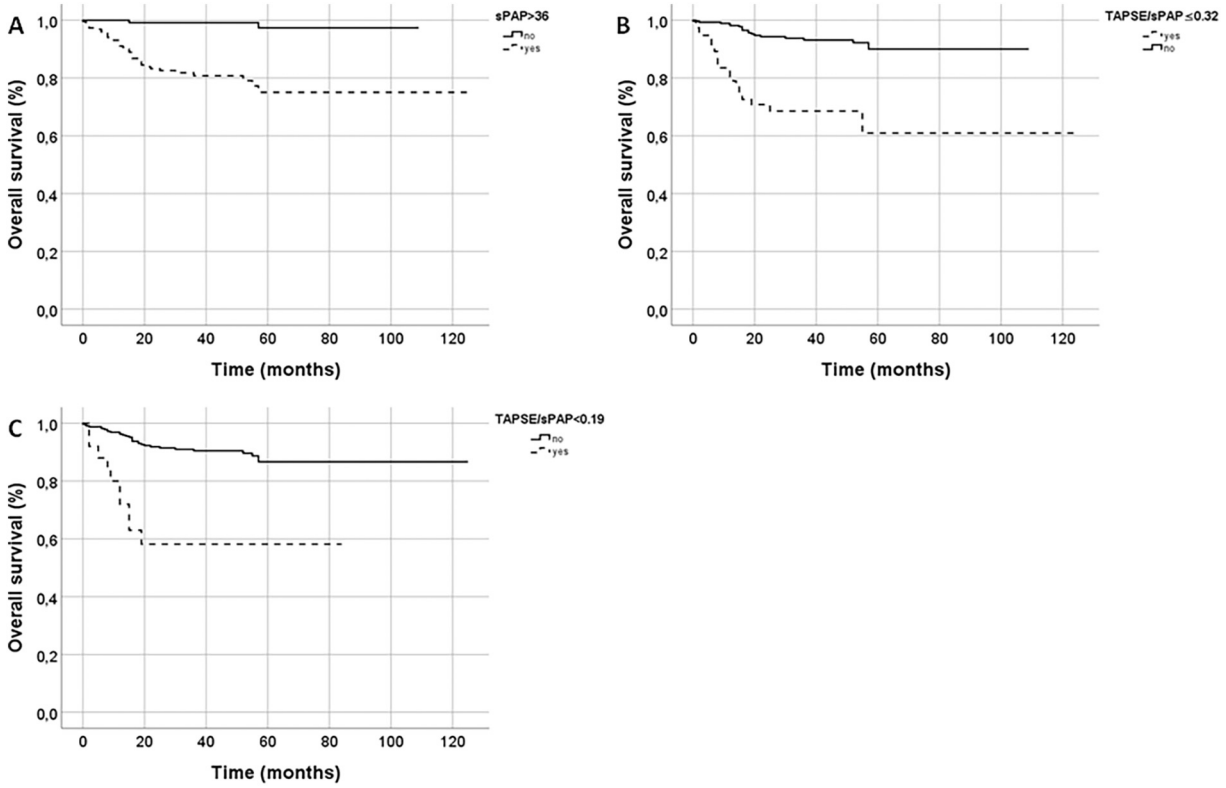

Fig. 2. Overall survival in 355 systemic sclerosis (SSc) patients. **A:** overall survival in SSc patients with systolic pulmonary artery pressure (sPAP) >36 mmHg (dotted line) and sPAP <36 mmHg (continuous line); **B:** overall survival in SSc patients with tricuspid annular plane systolic excursion (TAPSE)/sPAP ratio ≤ 0.32 mm/mmHg (dotted line) and TAPSE/sPAP ratio > 0.32 mm/mmHg (continuous line); **C:** overall survival in SSc patients with TAPSE/sPAP ratio < 0.19 mm/mmHg (dotted line) and TAPSE/sPAP ratio > 0.19 mm/mmHg (continuous line).

Table 3
Univariate and multivariate Cox regression analysis for overall survival using standardized cut-off values of TAPSE/sPAP ratio in 355 systemic sclerosis patients with available right heart catheterization data.

Intermediate-high risk TAPSE/sPAP ratio				
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*	*HR (95% CI)*	*p*
sPAP >36 mmHg	0.066 (0.016–0.276)	<0.001	0.124 (0.029–0.543)	<0.01
TAPSE/sPAP ≤0.32 mm/mmHg	0.167 (0.089–0.310)	<0.001	0.310 (0.164–0.585)	<0.001
Age, years	1.047 (1.014–1.080)	<0.01	1.032 (0.998–1.067)	0.062
Male sex	0.881 (0.407–1.909)	0.749	–	–
High risk TAPSE/sPAP ratio				
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*	*HR (95% CI)*	*p*
sPAP >36 mmHg	0.066 (0.016–0.276)	<0.001	0.092 (0.022–0.388)	<0.01
TAPSE/sPAP <0.19 mm/mmHg	0.173 (0.084–0.356)	<0.001	0.317 (0.154–0.656)	<0.01
Age, years	1.047 (1.014–1.080)	<0.01	1.029 (0.995–1.064)	0.101
Male sex	0.881 (0.407–1.909)	0.749	–	–

HR: hazard ratio; *TAPSE*: tricuspid annular plane systolic excursion; *sPAP*: systolic pulmonary arterial pressure.

retrospective study in which patients were selected on available TAPSE and sPAP data. Patients with available RHC data did not have serial TAPSE and sPAP measurements and therefore a longitudinal analysis was not possible. Many RHC parameters data were missing (e.g. wedge pressure was not recorded in 84/355 SSc patients with RHC) and could not be used for the analysis. Many data were missing for parameters included in the DETECT algorithm (e.g. TRV was documented only in 67/355 patients and right atrium area only in 62/355 patients), so that comparing the PPV of TAPSE/sPAP ratio and DETECT algorithm was not possible. The cause of death for SSc was missing in many patients. PH-specific mortality was not provided by the EUSTAR database.

Routine echocardiography is crucial for early PH diagnosis, for the prognostic assessment of patients with PH and for their follow-up under therapy. TAPSE/sPAP ratio is a non-invasive, low cost, easy repeatable measure of RV performance related to pulmonary hemodynamics that integrates seamlessly into the existing diagnostic work-up and risk assessment strategies.

In conclusion, in SSc patients a TAPSE/sPAP ratio < 0.55 mm/mmHg is significantly and independently associated with PH and is a potential predictive risk factor for PH. A TAPSE/sPAP ratio ≤ 0.32 mm/mmHg is a predictive risk factor for all-cause mortality.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Ivan Castellvi' reports a relationship with Janssen-Cilag SAS that

includes: consulting or advisory and funding grants. Ivan Castellvi' reports a relationship with Boehringer Ingelheim Ltd. that includes: consulting or advisory and funding grants. Ivan Castellvi' reports a relationship with Genentech that includes: consulting or advisory and funding grants. Ivan Castellvi' reports a relationship with Kern Pharma SL that includes: funding grants. Paolo Airo' reports a relationship with Bristol Myers Squibb Co that includes: consulting or advisory and travel reimbursement. Paolo Airo' reports a relationship with Boehringer Ingelheim Ltd. that includes: consulting or advisory. Paolo Airo' reports a relationship with Novartis that includes: consulting or advisory. Paolo Airo' reports a relationship with CSL Behring LLC that includes: travel reimbursement. Paolo Airo' reports a relationship with Janssen Pharmaceuticals Inc. that includes: travel reimbursement. Paolo Airo' reports a relationship with Roche that includes: travel reimbursement.

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Data availability

The data that has been used is confidential.

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References

[1] Elhai M, Meune C, Boubaya M, Avouac J, Hachulla E, Balbir-Gurman A, et al. Mapping and predicting mortality from systemic sclerosis. Ann Rheum Dis 2017; 76:1897–905. https://doi.org/10.1136/annrheumdis-2017-211448.

[2] Rubio-Rivas M, Homs NA, Cuartero D, Corbella X. The prevalence and incidence rate of pulmonary arterial hypertension in systemic sclerosis: systematic review and meta-analysis. Autoimmun Rev 2021;20:102713. https://doi.org/10.1016/j.autrev.2020.102713.

[3] Avouac J, Airò P, Meune C, Beretta L, Dieude P, Caramaschi P, et al. Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies. J Rheumatol 2010;37:2290–8. https://doi.org/10.3899/jrheum.100245.

[4] Hoffmann-Vold AM, Fretheim H, Midtvedt Ø, Kilian K, Angelshaug M, Chaudhary A, et al. Frequencies of borderline pulmonary hypertension before and after the DETECT algorithm: results from a prospective systemic sclerosis cohort. Rheumatology (Oxford) 2018;57:480–7. https://doi.org/10.1093/rheumatology/kex435.

[5] Kolstad KD, Li S, Steen V, Chung L, PHAROS Investigators. Long-term outcomes in systemic sclerosis-associated pulmonary arterial hypertension from the pulmonary hypertension assessment and recognition of outcomes in scleroderma registry (PHAROS). Chest 2018;154:862–71. https://doi.org/10.1016/j.chest.2018.05.002.

[6] Morrisroe K, Stevens W, Huq M, Prior D, Sahhar J, Ngian GS, et al. Survival and quality of life in incident systemic sclerosis–related pulmonary arterial hypertension. Arthritis Res Ther 2017;19:122. https://doi.org/10.1186/s13075-017-1341-x.

[7] Brown Z, Proudman S, Morrisroe K, Stevens W, Hansen D, Nikpour M. Screening for the early detection of pulmonary arterial hypertension in patients with systemic sclerosis: a systematic review and meta-analysis of long-term outcomes. Semin Arthritis Rheum 2021;51:495–512. https://doi.org/10.1016/j.semarthrit.2021.03.011.

[8] Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 2022;43:3618–731. https://doi.org/10.1093/eurheartj/ehac237.

[9] Coghlan JG, Denton CP, Grünig E, Bonderman D, Distler O, Khanna D, et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Ann Rheum Dis 2014;73:1340–9. https://doi.org/10.1136/annrheumdis-2013-203301.

[10] Young A, Moles VM, Jaafar S, Visovatti S, Huang S, Vummidi D, et al. Performance of the DETECT algorithm for pulmonary hypertension screening in a systemic sclerosis cohort. Arthritis Rheum 2021;73:1731–7. https://doi.org/10.1002/art.41732.

[11] Vonk Noordegraaf A, Westerhof BE, Westerhof N. The relationship between the right ventricle and its load in pulmonary hypertension. J Am Coll Cardiol 2017;69:236–43. https://doi.org/10.1016/j.jacc.2016.10.047.

[12] Naeije R, Richter MJ, Rubin LJ. The physiological basis of pulmonary arterial hypertension. Eur Respir J 2022;59:2102334. https://doi.org/10.1183/13993003.02334-2021.

[13] Tello K, Wan J, Dalmer A, Vanderpool R, Ghofrani HA, Naeije R, et al. Validation of the tricuspid annular plane systolic excursion/systolic pulmonary artery pressure ratio for the assessment of right ventricular–arterial coupling in severe pulmonary hypertension. Circ Cardiovasc Imag 2019;12:e009047. https://doi.org/10.1161/CIRCIMAGING.119.009047.

[14] Colalillo A, Grimaldi MC, Vaiarello V, Pellicano C, Leodori G, Gigante A, 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;61:2450–6. https://doi.org/10.1093/rheumatology/keab748.

[15] Hachulla E, Clerson P, Airò P, Cuomo G, Allanore Y, Caramaschi P, et al. Value of systolic pulmonary arterial pressure as a prognostic factor of death in the systemic sclerosis EUSTAR population. Rheumatology (Oxford) 2015;54:1262–9. https://doi.org/10.1093/rheumatology/keu450.

[16] Ghio S, Guazzi M, Scardovi AB, Klersy C, Clemenza F, Carluccio E, et al. Different correlates but similar prognostic implications for right ventricular dysfunction in heart failure patients with reduced or preserved ejection fraction. Eur J Heart Fail 2017;19:873–9. https://doi.org/10.1002/ejhf.664.

[17] Legris V, Thibault B, Dupuis J, White M, Asgar AW, Fortier A, et al. Right ventricular function and its coupling to pulmonary circulation predicts exercise tolerance in systolic heart failure. ESC Heart Fail 2022;9:450–64. https://doi.org/10.1002/ehf2.13726.
[18] Guazzi M, Dixon D, Labate V, Beussink-Nelson L, Bandera F, Cuttica MJ, et al. RV contractile function and its coupling to pulmonary circulation in heart failure with preserved ejection fraction: stratification of clinical phenotypes and outcomes. JACC Cardiovasc Imaging 2017;10:1211–21. https://doi.org/10.1016/j.jcmg.2016.12.024.
[19] Kazimierczyk R, Kazimierczyk E, Knapp M, Sobkowicz B, Malek LA, Blaszczak P, et al. Echocardiographic assessment of right ventricular-arterial coupling in predicting prognosis of pulmonary arterial hypertension patients. J Clin Med 2021;10:2995. https://doi.org/10.3390/jcm10132995.
[20] Vicenzi M, Caravita S, Rota I, Casella R, Deboeck G, Beretta L, et al. The added value of right ventricular function normalized for afterload to improve risk stratification of patients with pulmonary arterial hypertension. PLoS One 2022;17:e0265059. https://doi.org/10.1371/journal.pone.0265059.
[21] Tello K, Axmann J, Ghofrani HA, Naeije R, Narcin N, Rieth A, et al. Relevance of the TAPSE/SPAP ratio in pulmonary arterial hypertension. Int J Cardiol 2018;266:229–35. https://doi.org/10.1016/j.ijcard.2018.01.053.
[22] Guo X, Lai J, Wang H, Tian Z, Wang Q, Zhao J, et al. Predictive value of non-invasive right ventricle to pulmonary circulation coupling in systemic lupus erythematosus patients with pulmonary arterial hypertension. Eur Heart J Cardiovasc Imaging 2021;22:111–8. https://doi.org/10.1093/ehjci/jez311.
[23] Lai J, Zhao J, Li K, Qin X, Wang H, Tian Z, et al. Right ventricle to pulmonary artery coupling predicts the risk stratification in patients with systemic sclerosis-associated pulmonary arterial hypertension. Front Cardiovasc Med 2022;9:872795. https://doi.org/10.3389/fcvm.2022.872795.
[24] Xanthouli P, Miazgowski J, Benjamin N, Gordjani O, Egenlauf B, Harutyunova S, et al. Prognostic meaning of right ventricular function and output reserve in patients with systemic sclerosis. Arthritis Res Ther 2022;24:173. https://doi.org/10.1186/s13075-022-02863-1.
[25] Meier FM, Frommer KW, Dinser R, Walker UA, Czirjak L, Denton CP, 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;71:1355–60. https://doi.org/10.1136/annrheumdis-2011-200742.
[26] van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European league against rheumatism collaborative initiative. Arthritis Rheum 2013;65:2737–47. https://doi.org/10.1002/art.38098.
[27] Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685–788. https://doi.org/10.1016/j.echo.2010.05.010.
[28] Trejo-Velasco B, Estevez-Loureiro R, Carrasco-Chinchilla F, Fernández-Vázquez F, Arzamendi D, Pan M, et al. Prognostic role of TAPSE to SPAP ratio in patients undergoing MitraClip procedure. J Clin Med 2021;10:1006. https://doi.org/10.3390/jcm10051006.
[29] Fortuni F, Butcher SC, Dietz MF, van der Bijl P, Prihadi EA, De Ferrari GM, et al. Right ventricular-pulmonary arterial coupling in secondary tricuspid regurgitation. Am J Cardiol 2021;148:138–45. https://doi.org/10.1016/j.amjcard.2021.02.037.
[30] Sultan I, Cardounel A, Abdelkarim I, Kilic A, Althouse AD, Sharbaugh MS, et al. Right ventricle to pulmonary artery coupling in patients undergoing transcatheter aortic valve implantation. Heart 2019;105:117–21. https://doi.org/10.1136/heartjnl-2018-313385.
[31] Lyhne MD, Kabrhel C, Giordano N, Andersen A, Nielsen-Kudsk JE, Zheng H, et al. The echocardiographic ratio tricuspid annular plane systolic excursion/pulmonary arterial systolic pressure predicts short-term adverse outcomes in acute pulmonary embolism. Eur Heart J Cardiovasc Imaging 2021;22:285–94. https://doi.org/10.1093/ehjci/jeaa243.
[32] Tello K, Ghofrani HA, Heinze C, Krueger K, Naeije R, Raubach C, et al. A simple echocardiographic estimate of right ventricular-arterial coupling to assess severity and outcome in pulmonary hypertension on chronic lung disease. Eur Respir J 2019;54:1802435. https://doi.org/10.1183/13993003.02435-2018.
[33] Wolsk E, Bakkestrøm R, Kristensen CB, Aagaard Myhr K, Thomsen JH, Balling L, et al. Right ventricular and pulmonary vascular function are influenced by age and volume expansion in healthy humans. J Card Fail 2019;25:51–9. https://doi.org/10.1016/j.cardfail.2018.11.013.