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RESEARCH

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Mild pulmonary hemodynamic alterations in patients with systemic sclerosis: relevance of the new 2022 ESC/ERS definition of pulmonary hypertension and impact on mortality

Sébastien Puigrenier^{1,2,3†}, Jonathan Giovannelli^{4†}, Nicolas Lamblin^{5,6}, Pascal De Groote^{5,6}, Marie Fertin^{5,6}, Jean-François Bervar⁷, Antoine Lamer⁸, Jean-Louis Edme^{9,10}, Marie-Hélène Balquet¹¹, Vincent Sobanski^{1,2,12,13}, David Launay^{1,2,12,13}, Éric Hachulla^{1,2,12,13} and Sébastien Sanges^{1,2,12,13*}

Abstract

Background and objective: The definition of pre-capillary pulmonary hypertension (PH) has been modified, with lowering of the mean pulmonary arterial pressure (mPAP) threshold from 25 to 20 mmHg and addition of a mandatory criterion of pulmonary vascular resistance (PVR) ≥ 2 Wood units (WU). Our objectives were: 1/ to estimate the proportion of patients reclassified as having pre-capillary PH when using the new 2022 ESC/ERS hemodynamic criteria (i.e. mPAP 21–24 mmHg and PVR ≥ 2 WU), and to describe their clinical characteristics and outcome; and 2/ to study the relationship between PVR and survival in patients with mPAP > 20 mmHg.

Methods: We retrospectively analyzed consecutive SSc patients included in our National Reference Center for a first right-heart catheterization between 2003 and 2018. The association between survival and PVR was studied using smoothing splines.

Results: We included 126 SSc patients with mPAP > 20 mmHg. Among them, 16 (13%) had a baseline mPAP value between 21 and 24 mmHg and PVR ≥ 2 mmHg and were reclassified as pre-capillary PH; 10 of which (62%) raised their mPAP ≥ 25 mmHg during follow-up. In patients with mPAP > 20 mmHg, we observed a linear relation between PVR and mortality for values < 6 WU.

Conclusion: A significant proportion of SSc patients is reclassified as having pre-capillary PH with the new 2022 ESC/ERS hemodynamic definition. Lowering the PVR threshold from 3 to 2 WU captures patients at risk of raising their mPAP > 25 mmHg, with a possibly less severe disease.

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Keywords: Systemic sclerosis, Pulmonary hypertension, Pulmonary arterial hypertension, Pulmonary vascular resistance, Diagnostic criteria, Mortality

Introduction

Pulmonary hypertension (PH) is one of the most severe complications of systemic sclerosis (SSc), affecting more than 10% of patients during the course of the disease [1]. PH in SSc may result from several mechanisms: group 1 due to pulmonary microangiopathy (*i.e.* pulmonary arterial hypertension (PAH)), group 1' due to pulmonary veno-occlusive disease (PVOD), group 2 due to myocardial fibrosis with left heart dysfunction, and/or group 3 due to severe interstitial lung disease (ILD). Its prognosis remains poor despite therapeutic progresses [2, 3].

The diagnosis of PH is based on right-heart catheterization (RHC). A new hemodynamic definition of pre-capillary PH was proposed in the 2022 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines [4]. The mean pulmonary arterial pressure (mPAP) threshold was lowered from 25 to 20 mmHg in combination with pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg; and a mandatory criterion of pulmonary vascular resistance (PVR) ≥ 2 Wood units (WU) was added.

This modified definition of pre-capillary PH is debated in the field of SSc because of several unresolved issues. First, the impact of these revised criteria on the number of patients reclassified as PH has not been extensively studied. Indeed, previous works [5–7] focusing on this issue have used the provisional hemodynamic definition from the 6th World Symposium on PH (WSPH) [8] that set the PVR threshold at 3 WU. Only one study used the current PVR cut-off of 2 WU and suggested a proportion of 9.85% PH-reclassified patients [6]. Second, the optimal PVR cut-off associated with increased mortality is controversial [6].

In order to add data and better decipher the impact of the new definition in SSc, we performed a retrospective monocentric study on our cohort of SSc patients with mPAP > 20 mmHg on their first-ever RHC. Our objectives were: 1/ to estimate the proportion of patients reclassified as having pre-capillary PH when using the new hemodynamic definition (*i.e.* mPAP between 21 and 24 mmHg and PVR ≥ 2 WU), and to describe their clinical characteristics and outcome; and 2/ to study the relationship between PVR and survival in patients with mPAP > 20 mmHg.

Methods

Study population

Consecutive patients were recruited from our National Reference Center for SSc. They were included in the study if they met the following criteria: 1/ a definite

diagnosis of SSc (diffuse cutaneous SSc (dc-SSc) or limited cutaneous SSc (lc-SSc)) according to the 2013 American College of Rheumatology/European League against Rheumatism classification criteria [9] 2/ a first-ever RHC performed between 01/01/2003 and 31/12/2018; 3/ an mPAP value > 20 mmHg; 4/ an age ≥ 18 years old.

Study measurements

Data were retrospectively collected at the baseline visit (which was defined as the visit of the first RHC) and comprised clinical characteristics (including SSc subtype, New York Heart Association (NYHA) functional class, presence of interstitial lung disease (ILD) and 6-min walking distance (6MWD)), echocardiography parameters (tricuspid regurgitation velocity (TRV), right ventricle (RV)/left ventricle (LV) ratio, right atrium (RA) area, pulmonary artery acceleration time (PAAT), tricuspid annular plane systolic excursion (TAPSE), inferior vena cava (IVC) diameter), E/A ratio, left atrium (LA) area and LV ejection fraction (LVEF)), biological results (including brain natriuretic peptide (BNP) levels), electrocardiogram (ECG), pulmonary function tests (PFT) results, RHC parameters and initial treatment strategy. Data were also collected at last follow-up and included last treatment strategy and dead-or-alive status.

RHC were performed by pulmonary hypertension specialist practitioners using a 6-French Swan-Ganz catheter in non-acute clinical conditions. The catheter was placed under fluoroscopic guidance from a right antebraclial vein or a right femoral vein as needed. The correct position of the catheter was confirmed by fluoroscopy and by the presence of characteristic pressure waveforms. The “zero-ing” transducer to atmospheric pressure was at the level of the mid-axillary line. Right atrial pressure (RAP), mPAP and PAWP were determined electronically by the mean of several beats during quiet breathing. mPAP was determined by the mean of the area under pressure curves. Cardiac Output (CO) was measured by the thermodilution technique (mean of 3–6 measures with exclusion of measurements that exceed 10% of the mean); and Cardiac Index (CI) calculated by the ratio of CO to body surface area. Mixed venous oxygen saturation (SvO₂) was measured from blood drawn from the pulmonary artery. PVR were then calculated (PVR = [mPAP-PAWP]/CO). In case of

mPAP > 20 mmHg and a PAWP more than 12 mmHg (13–15 mmHg), suggesting a possible post-capillary pulmonary hypertension, a fluid challenge (500 mL of saline solution over 5 min) was performed as proposed in guidelines [10].

The initial (*i.e.* within the first 4 months of baseline visit) and follow-up treatment strategies were defined according to the number of PAH medications prescribed (endothelin receptor antagonist, phosphodiesterase type 5 inhibitor, and prostacyclin analogue). Patients whose death was not registered were censored at the time of last clinical contact.

Statistical analysis

The characteristics of the population were described by using the mean \pm standard deviation (SD), or median \pm interquartile range (IQR) in case of non-normality, for quantitative variables; numbers (percentage) were used for qualitative variables. PVR were categorized in four groups: <2, 2–3, 3–6 and >6 WU. No imputation was performed for missing data. Characteristics of patients between these groups were compared by using a one-way analysis of variance (ANOVA), or a Kruskal–Wallis test in cases of non-normality for quantitative variables; Fisher exact test was used for qualitative variables, except for the comparison of treatments (Chi-squared test with estimated *p*-values by Monte Carlo simulation).

To discuss the impact of the new PH definition on our patients, we described the clinical characteristics and outcome of patients reclassified as having pre-capillary PH (*i.e.* patients with mPAP between 21 and 24 mmHg, PVR \geq 2 WU and PAWP \leq 15 mmHg) according to the new hemodynamic definition from the 2022 ESC/ERS guidelines.

Survival was right-censored at 5 years and described by using the Kaplan–Meier method, for the whole population and by PVR groups. The relationship between survival and PVR and was assessed by a smoothing spline using a penalized spline basis for predictor, without and with adjustments for age, gender, SSc subtype, date of SSc diagnosis, NYHA class, ILD and follow-up treatment strategy. We also studied the association between survival and PVR groups using Cox proportional hazards models without and with adjustments.

All statistical analyses were performed by using R software, version 3.6.2 (*R Foundation for Statistical Computing*), using “Hmisc” and “survival” packages. The threshold for statistical significance was set to $p < 0.05$.

Results

Characteristics of the whole population according to PVR values

Overall, 126 SSc patients had an mPAP > 20 mmHg on their first-ever RHC and were included in the study (Fig. 1). Patients were classified in 4 groups according to

their PVR values: 12, 18, 50 and 46 patients had PVR < 2 WU, between 2–3 WU, between 3 and 6 WU, and > 6 WU, respectively (Table 1).

We did not observe statistical differences in age, gender, antibody profile and disease duration between groups. In terms of PH characteristics, we did not observe significant differences in ILD occurrence and FVC values, indicating similar proportions of group 3 PH between classes; however, PAWP and LVEF differed significantly according to PVR values, consistent with a higher frequency of post-capillary PH (either isolated or combined with pre-capillary PH) in patients with lower PVR (6, 6, 6 and 4 patients with PAWP > 15 mmHg between in the PVR < 2 WU, PVR [2, 3] WU, PVR [3–6] and PVR > 6 WU groups, respectively). Aside from BNP levels, usual markers of PH severity (NYHA class, 6MWD, DLCO, KCO, TRV, RV/LV ratio, PAAT, RA area) were significantly different among groups, with milder anomalies observed with lower PVR. Therapeutic strategies varied with PVR classes, with patients having higher values being more likely to be treated. Only 3 patients were treated by PAH-specific drugs before PAH diagnosis (bosentan prescribed because of digital ulcers in all cases), all of them from the PVR [3–6] group. Triple therapy was started a median of 2 years [1–3] after PH diagnosis.

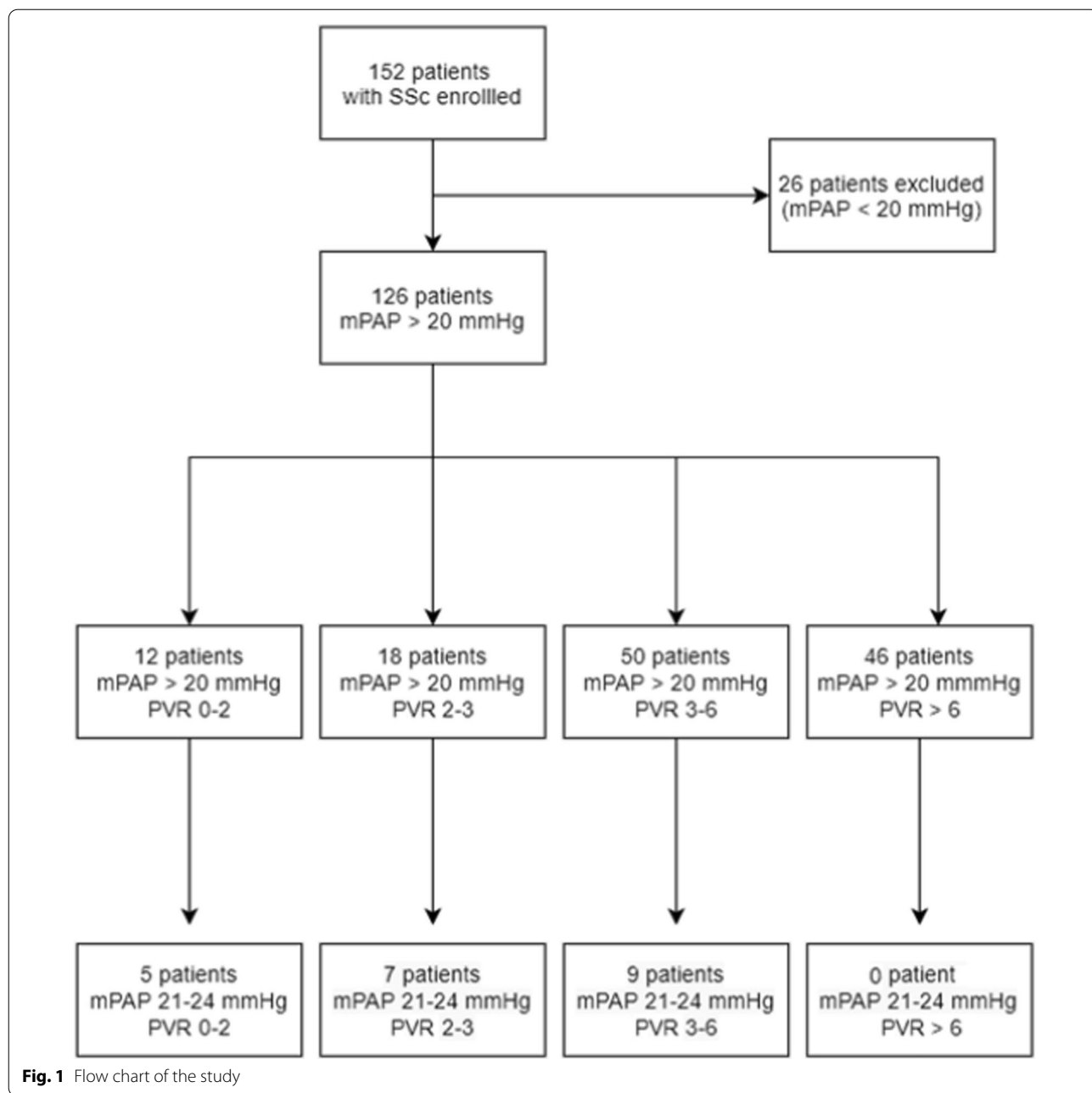
Proportion of pre-capillary PH-reclassified SSc patients and population characteristics

Among the 126 included patients, we identified 16 patients (13%) that had a baseline mPAP value between 21 and 24 mmHg, PVR \geq 2 WU and PAWP \leq 15 mmHg, and who were thus reclassified as having pre-capillary PH according to the 2022 ESC/ERS hemodynamic definition (Table 2).

Most of them were women (14/16, 88%) with a median age of 68 (54–78) years old, a limited cutaneous SSc (13/15, 87%) diagnosed a median of 6.5 (1–6) years before and associated with anti-centromere antibodies (11/15, 73%).

Most patients had CI > 2 L/min/m² (15/16, 94%), RAP < 8 mmHg (14/15, 93%) and SvO₂ > 65% (9/13, 69%). As per definition, PAWP was normal in all cases on resting RHC; but patients #9 and #10 elevated their value above 15 mmHg after fluid challenge, suggesting a possible post-capillary component associated. Two out of 15 patients (13%) had extensive ILD based on chest CT-scan involvement, but all of them had FVC values > 70%. Four out of 9 patients (44%) had signs of PVOD, and none showed evidence of chronic thrombo-embolism on chest CT or VQ-scan (Table 2).

PH screening tests and severity markers were inconsistently informative in these patients: 6/13 (46%) had NYHA class III or IV; 12/13 (92%) had 6MWD < 440 m; 3/13



(23%) had abnormal BNP levels; none had right axis deviation on ECG; 10/14 (71%) had DLCO < 60% and FVC (%)/DLCO(>) > 1.6. Similarly, echocardiographic markers of PH were inconstantly present: 11/15 patients (73%) had TRV > 2.8 m/s; 11/15 (73%) had PAAT < 105 ms; 4/16 (25%) had RA area > 18cm²; 3/15 (20%) had RV/LV ratio > 1.0; and 1/16 (6%) had IVC diameter > 21 mm with decreased inspiratory collapse. All patients had a normal RV function (as estimated by TAPSE and RV S' wave) (Table 2).

Interestingly, 10/16 patients (62%) eventually had an increase of mPAP value above or equal to 25 mmHg on a follow-up RHC performed a median of 34 (20–58) months after their baseline evaluation, thus fulfilling the previous definition of precapillary PH; and 3/16 (19%) died shortly after their initial RHC. The 3 remaining patients (19%) had no PH after a 2-year follow-up (Table 2).

Table 1 Characteristics of the 126 SSc patients with mPAP > 20 mmHg

	N	Whole population (n = 126)	PVR [0—2 WU] (n = 12)	PVR [2—3 WU] (n = 18)	PVR [3—6 WU] (n = 50)	PVR [6—20 WU] (n = 46)	p
SSc characteristics							
Age (yo)	126	66.5 ± 16.6	61.2 ± 8	63.6 ± 18.5	68.8 ± 13.8	67.1 ± 17.1	0.33
Gender (female)	126	104 (82.5)	9 (75)	18 (88.9)	38 (76)	41 (89.1)	0.27
SSc subtype (lcSSc)	116	95 (81.9)	8 (66.7)	16 (100)	31 (70.5)	40 (90.9)	0.005
ACA	107	60 (56.1)	3 (27.3)	12 (70.6)	21 (55.3)	24 (58.5)	0.16
ATA	111	24 (21.6)	5 (41.7)	4 (23.5)	10 (23.8)	5 (12.5)	0.17
Time since SSc diagnosis (y)	120	7 ± 12	9 ± 11.3	6 ± 9.5	7 ± 13	7 ± 12.5	0.67
Time since RP onset (y)	98	14 ± 15.8	9 ± 10	17 ± 12.8	16 ± 18.8	10 ± 17.8	0.26
Time since FEFRRPS onset (y)	98	9.5 ± 12.8	9 ± 9	10.5 ± 7.8	9 ± 14	10 ± 12.5	1
ILD	115	54 (47)	8 (66.7)	5 (31.3)	23 (50)	18 (43.9)	0.3
NYHA	101	41 (40.6)	5 (55.6)	11 (91.7)	19 (47.5)	6 (15)	< 0.001
I—II	101	60 (59.4)	4 (44.4)	1 (8.3)	21 (52.5)	34 (85)	< 0.001
III—IV	87	32.1 ± 173.5	310.5 ± 81.8	388 ± 46.5	348 ± 116.5	240 ± 139	< 0.001
6MWD (m)	75	37 ± 36.5	40 ± 12.5	53.5 ± 30.8	27 ± 27.8	40 ± 35	0.23
BNP (ng/L)							
RHC parameters							
mPAP (mmHg)	126	34.5 ± 16.8	26 ± 8.3	26 ± 5.5	32.5 ± 8.8	47.5 ± 11	< 0.001
PVR (WU)	126	4.9 ± 4.7	1.6 ± 0.2	2.4 ± 0.4	4.4 ± 1.6	9.2 ± 3.4	< 0.001
TPR (WU)	125	7.3 ± 4.9	4.4 ± 3	4.2 ± 1.7	6.5 ± 1.7	11.9 ± 3.3	< 0.001
RAP (mmHg)	121	7 ± 4	8 ± 3.5	6 ± 4	6 ± 4	8 ± 7	0.004
sPAP (mmHg)	124	54 ± 29.3	39 ± 11.5	41 ± 7.5	50 ± 17	75 ± 21	< 0.001
dPAP (mmHg)	124	19 ± 12.3	13 ± 7.3	13 ± 5.8	17 ± 7	28 ± 8	< 0.001
PAWP (mmHg)	126	10 ± 6	15 ± 9.8	12 ± 8	10 ± 5.8	8 ± 4	< 0.001
CO (L/min)	125	4.7 ± 1.6	5.5 ± 1.5	6.1 ± 2.3	4.8 ± 1.4	4.2 ± 1.2	< 0.001
CI (L/min/m ²)	126	2.8 ± 1	3.1 ± 1.1	3.3 ± 0.7	2.8 ± 0.8	2.4 ± 0.7	< 0.001
SvO ₂ (%)	82	68 ± 13.4	70 ± 11.8	74 ± 3	68.5 ± 10.8	59.6 ± 11.5	< 0.001
Hemodynamic classification							
Pre-capillary PH	86	86 (68.3)	0	12 (66.6)	44 (88)	42 (91.3)	< 0.001
Isolated post-capillary PH	12	12 (9.5)	6 (50)	6 (33.3)	0	0	< 0.001
Combined PH	10	10 (7.9)	0	0	6 (12)	4 (8.7)	< 0.001
Pulmonary function tests*							
FVC (% predicted)	95	88 ± 23.5	86.9 ± 27	91.6 ± 19.8	90.2 ± 25.8	84.2 ± 21.4	0.66
FEV1 (% predicted)	95	80.9 ± 22.8	79 ± 23.3	85.6 ± 17.4	85.3 ± 27.2	74.9 ± 18.1	0.21
TLC (% predicted)	92	84.1 ± 18	85.4 ± 25	84.1 ± 15.9	83.1 ± 18.9	84.9 ± 16.3	0.97
DLCO (% predicted)	91	41.8 ± 15.8	59.1 ± 21.1	53.9 ± 14.9	38.5 ± 14.3	38.7 ± 13.2	< 0.001
KCO (% predicted)	80	41.5 ± 12.8	55 ± 13.8	54 ± 10.5	38.9 ± 11.1	36.6 ± 10.5	< 0.001
Echocardiography							
TRV (m/s)	84	3.4 ± 0.8	3 ± 0.6	3 ± 0.5	3.4 ± 0.6	4.1 ± 0.4	< 0.001
RV/LV ratio	69	1 ± 0.4	0.8 ± 0.2	0.8 ± 0.2	0.9 ± 0.2	1.3 ± 0.2	< 0.001
PAAT (m/s)	87	75 ± 28	110 ± 32	86.5 ± 38.3	76 ± 24.5	64 ± 25.5	0.002
RA area (cm ²)	94	18 ± 9.1	16.5 ± 5.6	18 ± 4.5	16.7 ± 8.8	22.6 ± 9	0.014
Expiration IVC diam. (mm)	80	15.2 ± 5.8	17.3 ± 5.4	13.5 ± 3	14.9 ± 4.4	18.8 ± 4.8	< 0.001
TAPSE (mm)	93	20.8 ± 5.9	21 ± 7.2	24 ± 6.6	21.5 ± 4.7	17.7 ± 5.4	< 0.001
LVEF (%)	101	65 ± 5	50 ± 15	65 ± 5	65 ± 10	65 ± 5	0.07
LA area (cm ²)	87	19.5 ± 8.1	21.6 ± 8.9	20.8 ± 5.5	19.6 ± 8.5	17.1 ± 5	0.04
E/A ratio	79	0.8 ± 0.4	0.9 ± 0.5	1 ± 0.4	0.8 ± 0.3	0.7 ± 0.3	0.004
Therapeutic strategy *							
Initial	126	49 (38.9)	10 (83.3)	15 (83.3)	22 (44)	2 (4.4)	0.001
No treatment	126	51 (40.5)	2 (16.7)	3 (16.7)	23 (46)	23 (50)	0.001
Monotherapy		22 (17.5)	0	0	5 (10)	17 (37)	
Dual therapy		4 (3.2)	0	0	0	4 (8.7)	
Triple therapy		36 (28.6)	8 (66.7)	9 (50)	17 (34)	2 (4.4)	
Last follow-up		34 (27)	3 (25)	8 (44.4)	15 (30)	8 (17.4)	
No treatment		34 (27)	0	1 (5.6)	13 (26)	20 (43.5)	
Monotherapy		22 (17.5)	1 (8.3)	0	5 (10)	16 (34.8)	
Dual therapy							
Triple therapy							

6MWD: 6-min walking distance, ACA: anti-centromere antibodies, ATA: anti-topoisomerase antibodies, BNP: brain natriuretic peptide, CI: cardiac index, CO: cardiac output, diam: diameter, DLCO: diffusing capacity of the lung for carbon monoxide, dPAP: diastolic pulmonary arterial pressure, FEFRRPS: first except for RP symptom, FEV1: forced expired volume at 1st minute, FVC: forced vital capacity, ILD: interstitial lung disease, IVC: inferior vena cava, KCO: carbon monoxide transfer coefficient, LA: left atrial, lc-SSc: limited cutaneous systemic sclerosis, LVEF: left ventricular ejection fraction, mPAP: mean pulmonary arterial pressure, NYHA: New York Heart Association, PAAT: pulmonary artery acceleration time, PAWP: pulmonary arterial wedge pressure, PVR: pulmonary vascular resistance, RA: right atrium, RAP: right atrial pressure, RHC: right heart catheterization, RP: Raynaud phenomenon, RV/LV: right ventricle / left ventricle, sPAP: systolic pulmonary arterial pressure, SSc: systemic sclerosis, SvO₂: venous saturation in oxygen, TAPSE: tricuspid annular plane systolic excursion, TLC: total lung capacity, TPR: total pulmonary resistance, TRV: tricuspid regurgitation velocity, y: year, yo: years old

Data were expressed as median ± IQR, except for parameters notified with an asterisk * (mean ± SD)

Table 2 Detailed characteristics of patients with mPAP between 21 and 24 mmHg and PVR ≥ 2 mmHg

Pt #	Patient and SSC characteristics				Clinical characteristics				Lab tests		Chest CT-scan				Pulmonary function tests											
	Sex	Age (yo)	Time since SSC diag/ RP/ FEFRPS (y)	SSc type	Antibody profile	mRSS	Tel	RHF	NYHA class	6MWD (m) (%pred)	Nf-pro-BNP (ng/L)	BNP (ng/L)	Urate (mg/L)	ILD	CTE	PVOD	FVC (% pred)	FEV1 (% pred)	FVC (% pred)	FEV1/FVC (%)	TLC (% pred)	DLCO (% pred)	DLCO (% pred)	KCO (% pred)	CVF/ DLCO	
1	F	81	0/10/0	—	ACA	—	—	Yes	—	—	286	79	No	No	—	—	—	40	57	—	—	—	—	—	—	—
2	F	71	17/17/17	lc	AFA	2	Yes	No	II	—	73	89	No	No	Yes	No	100	83	98	100	92	37	43	—	2.6	
3	F	72	15/-/-	lc	—	—	—	No	III	—	—	87	No	—	—	—	92	109	91	92	79	22	25	—	4.1	
4	F	44	1/-/1	dc	ACA	2	Yes	No	III	—	67	<20	No	—	—	—	65	86	81	65	86	28	27	—	2.9	
5	F	82	1/3/2	lc	No spec	23	No	No	II	—	—	114	Yes	—	—	—	116	110	113	116	81	47	63	—	2.4	
6	F	55	7/25/17	lc	ACA	10	Yes	No	III	—	135	50	(lim)	No	No	No	65	76	93	65	88	44	49	—	2.1	
7	M	60	1/1/1	dc	ATA	26	No	Yes	II	—	—	36	No	—	—	—	94	106	93	94	78	28	31	—	3.3	
8	F	65	2/4/4	lc	ACA	—	—	Yes	III	—	—	—	Yes	—	—	—	84	114	80	84	62	30	40	—	2.7	
9	F	80	1/16/1	lc	ACA	2	Yes	No	III	—	689	74	(ext)	No	No	No	86	100	96	86	88	50	45	—	1.9	
10	F	74	22/23/23	lc	ACA	—	—	Yes	—	—	—	—	Yes	—	—	—	94	96	94	82	—	66	59	—	1.4	
11	F	52	11/17/16	lc	ACA	6	Yes	No	II	—	—	57	(ext)	No	—	—	115	85	115	91	—	53	44	—	2.2	
12	F	77	22/30/22	lc	ATA	—	—	No	III	—	208	—	Yes	—	—	—	87	91	87	91	—	71	70	—	1.2	
13	F	45	30/30/27	lc	ACA	4	Yes	No	II	—	—	—	(lim)	No	—	—	—	—	—	—	—	—	—	—	—	
14	F	65	6/20/20	lc	ACA	2	No	No	II	—	67	54	—	—	—	—	120	105	120	105	—	50	43	—	2.4	
15	M	78	7/-/-	lc	ACA	—	Yes	No	II	—	—	44	59	No	No	No	—	—	—	—	—	—	—	—	—	
16	F	49	2/-/-	lc	ACA	—	Yes	No	II	—	—	36	—	Yes	No	No	—	—	—	—	—	—	—	—	—	

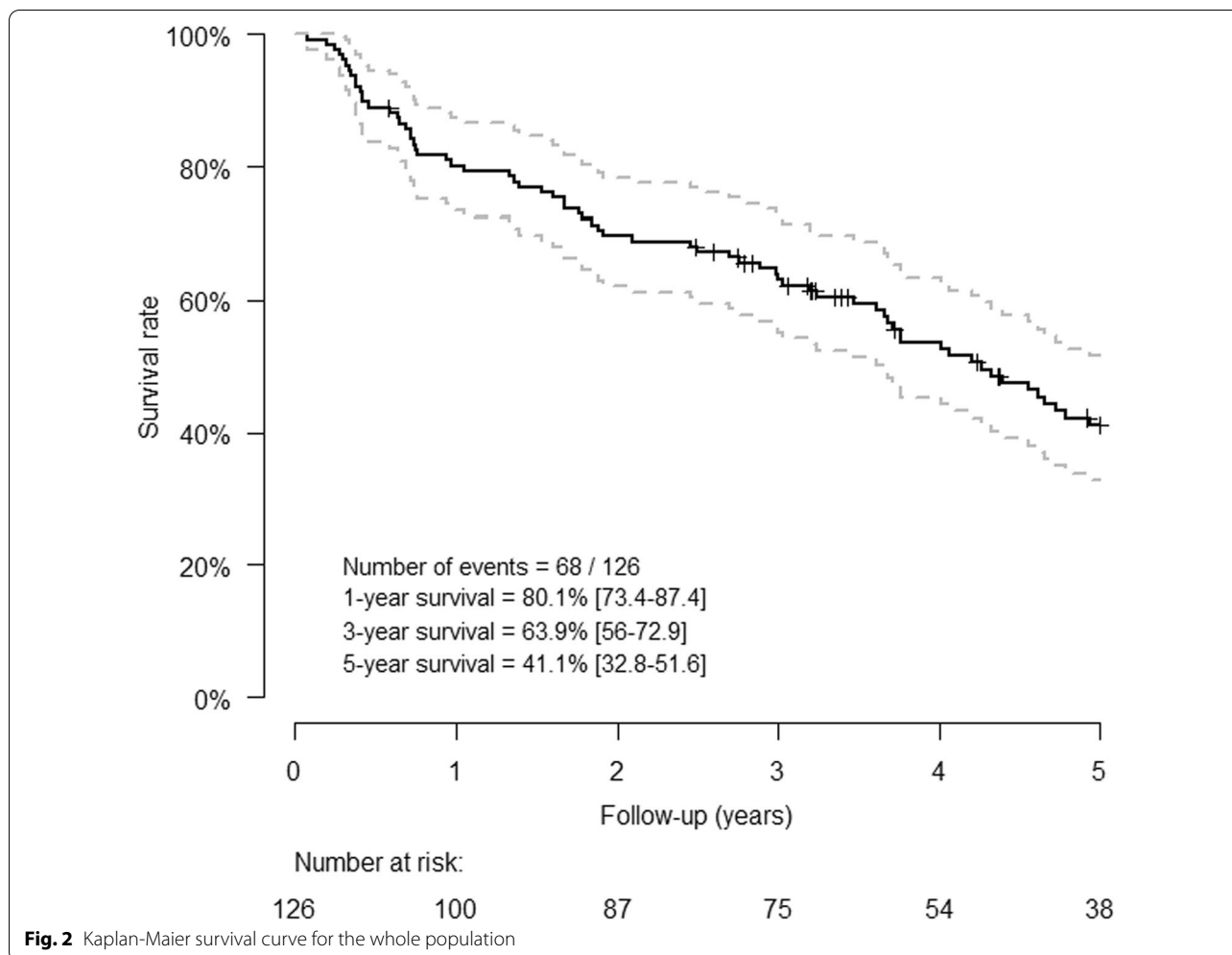
2Pt #	Echocardiography*																							
	ECG	Right-heart catheterization	RAxD	mPAP (mmHg)	PVR (WU)	CO (L/min) (m ²)	CI (L/min/m ²)	PAWP (mmHg)	CI	Fluid ch PAPP (mmHg)	Exercise mPAP (mmHg)	Exercise PAPP (mmHg)	Fluid ch PAPP (mmHg)	RA area RV/LV (cm ²)	PAAT (ms)	IVC diam (mm)	TAPSE (mm)	RV S' wave (cm/s)	LVEF (%)	LA vol. index (mL/m ²)	E/A ratio	E/e' ratio	LVFP	Pericard. effusion
1	No	21	3.1	3.2	2.0	2.0	11	18	55	—	—	—	—	2.13	27	1.2	24	20	—	50	23	0.6	—	No
2	No	24	3.3	4.3	2.6	2.6	10	5	68	—	—	—	—	2.70	11	0.8	7.5	29	—	65	16	0.7	—	No
3	—	21	4.4	3.9	2.8	2.8	6	2	55	No	—	—	—	3.15	12	0.7	17	19	10	45	23	—	—	No
4	No	23	3.9	4.9	2.4	2.4	4	1	68	No	—	28	13	3.37	17	1.0	60	21	10	60	18	0.7	5.0	No
5	No	21	3.5	3.7	2.6	2.6	8	7	—	22	—	—	—	3.2	14	0.9	100	15	24	70	36	1.1	7.9	No
6	No	22	3.3	4.3	2.6	2.6	9	4	71	—	29	—	—	3.3	13	0.7	150	24	11	65	21	1.1	15.2	No
7	No	22	3.4	4.7	2.8	2.8	6	4	74	—	29	6	—	—	16	1.1	43	11	22	60	18	0.7	5.5	No
8	No	23	4.8	3.8	2.3	2.3	5	4	—	38	6	—	—	3.18	12	—	62	15	21	70	18	0.8	6.4	No
9	No	23	3.6	3.1	1.6	1.6	12	5	63	No	—	28	17	2.85	22	0.8	81	10	16	93	60	28	3.7	4.9
10	—	24	2.1	4.2	2.5	2.5	14	—	—	33	19	37	20	3.05	13	0.6	37	19	21	60	21	1.4	14.5	—
11	No	22	2.0	7.2	4.2	4.2	6	6	79	No	—	—	—	3.05	16	0.8	110	12	32	10.6	65	—	—	—
12	No	24	2.3	5.2	3.0	3.0	12	7	73	—	40	13	NA	2.77	20	0.8	104	11	23	—	70	20	0.9	12.2
13	No	22	2.4	3.4	3.3	3.3	7	4	77	—	—	—	—	3.1	14	0.6	114	15	30	12.6	60	—	—	—
14	No	21	2.6	5.0	3.3	3.3	8	5	60	—	37	13	—	3.04	16	0.7	69	16	23	—	50	16	1.0	11.6
15	No	21	2.6	6.1	3.3	3.3	5	2	76	—	—	—	—	3.41	20	1.1	78	10	24	15	65	19	0.8	—
16	No	24	2.6	8.0	4.5	4.5	3	3	79	No	—	—	—	2.0	16	0.8	120	8	29	17.2	65	16.5	0.8	—

Table 2 (continued)

Pt #	Screening strategies		Follow-up			Death		
	DETECT algorithm	ESC/ERS echocardiographic probability of PH	ASIG algorithm	ESC/ERS risk assessment at baseline (worsening or death at 1 year)	Number of PH drugs (at baseline - during follow-up)		Duration of follow-up (y)	Occurrence of mPAP > 25 mmHg during follow-up (delay from 1 st RHC— months)
1	—	—	—	High risk	0–0	0.3	—	Yes
2	RHC recommended	Low	Positive	Intermediate risk	0–0	2.7	No	No
3	—	Intermediate	Positive	High risk	0–0	0.9	—	Yes
4	RHC recommended	Intermediate	Positive	Intermediate risk	1–1	3.4	Yes (11)	No
5	RHC recommended	Intermediate	Positive	Intermediate risk	0–0	3.0	Yes (28)	Yes
6	RHC recommended	Intermediate	Positive	Intermediate risk	0–2	4.9	Yes (24)	No
7	RHC recommended	Intermediate	Positive	High risk	0–0	5.3	Yes (60)	Yes
8	—	Intermediate	Positive	High risk	0–1	1.8	Yes (15)	Yes
9	RHC recommended	Intermediate	Positive	High risk	0–1	3.2	Yes (18)	No
10	—	Intermediate	Positive	Low risk	0–0	4.3	—	Yes
11	—	Intermediate	Positive	Intermediate risk	0–2	8.4	Yes (40)	No
12	—	Low	Negative	Intermediate risk	0–0	3.0	No	Yes
13	—	Intermediate	—	Intermediate risk	0–1	5.4	Yes (60)	No
14	RHC recommended	High	Positive	Intermediate risk	0–0	4.4	Yes (50)	No
15	—	High	—	Intermediate risk	0–0	2.8	No	No
16	—	Low	—	Intermediate risk	0–3	8.0	Yes (64)	No

6MWD: 6-min walking distance, ACA: anti-centromere antibodies, AFA: anti-fibrillar antibodies, ASIG: Australian Scleroderma Interest Group, ATA: anti-topoisomerase antibodies, BNP: brain natriuretic peptide, Ci: cardiac index, CO: cardiac output, CTE: chronic thrombo-embolism, dc: diffuse cutaneous, diag: diagnosis, diam: diameter, DLCO: diffusing capacity for carbon monoxide, ESC/ERS: European Society of Cardiology/European Respiratory Society, ext: extensive, F: female, FEFRPS: first except for RP symptom, FEV1: forced expired volume in 1 min, fluid ch: fluid challenge, FVC: forced vital capacity, HVP: hepatic venous pressure gradient, ILD: interstitial lung disease, IVC: inferior vena cava, KCO: carbon monoxide transfer coefficient, LA: left atrium, Lc: limited cutaneous, lim: limited, LV: left ventricle, LVEF: left ventricular ejection fraction, LVFP: elevated left ventricular filling pressure, M: male, mPAP: mean pulmonary arterial pressure, mRSS: modified Rodnan skin score, N: normal value, NA: not available; no spec: positive antinuclear antibodies without antibody specificity identified, NYHA: New York Heart Association, PAAT: pulmonary artery acceleration time, PAWP: pulmonary arterial wedge pressure, pericard: pericardial, PH: pulmonary hypertension, pred: predicted value, Pt: patient, PVOD: pulmonary veno-occlusive disease, PVR: pulmonary vascular resistance, RA: right atrium, RAP: right atrial pressure, RAXD: right axis deviation, RHC: right heart catheterization, RHF: clinical signs of right heart failure, RP: Raynaud phenomenon, RV: right ventricle, SSC: systemic sclerosis, SvO₂: venous saturation in oxygen, TAPSE: tricuspid annular plane systolic excursion, tel: telangiectasias, TLC: total lung capacity, TRV: tricuspid regurgitation velocity, vol: volume, WU: Wood units, y: years; yo: years old

* Of note, patient #1 had tricuspid valvular disease, making echographic markers of PH unreliable



Survival analysis according to PVR values

Using a lower PVR threshold could increase the proportion of pre-capillary PH-reclassified patients but might not capture additional patients with increased mortality. To test the relevance of this new PVR criterion, we studied the relationship between PVR and survival in SSc patients with mPAP > 20 mmHg.

The 1-, 3- and 5-year survival rate [95% confidence interval] of the whole population was respectively 80.1% [73.4–87.4%], 63.9% [56–72.9%] and 41.1% [32.8–51.6%] (Fig. 2). In univariate analysis, spline analysis suggests a linear relation between mortality and PVR considering PVR between 0 and 6 WU, and a plateau of mortality for PVR values over 6 WU (Fig. 3). After adjusting on age, sex, SSc subtype, disease duration, presence of ILD, NYHA functional class and treatment, the relation appears similar to the univariate analysis (Fig. 4).

Regarding PVR groups, in univariate analysis, the hazard ratio (HR) of death of patients considering their PVR values (reference: PVR < 2WU) were 1.08 [0.2–3.9]

for PVR between 2–3WU, 2.9 [0.9–9.4] for PVR between 3–6WU, and 3.7 [1.1–12] for PVR > 6WU (Fig. 5). In multivariate analysis (Additional file 1: Table S1), after adjusting for age, sex, SSc type, disease duration, presence of ILD, NYHA functional class and treatment, HR of death were respectively 0.49 [0.04–5.56], 2.56 [0.5–11.9] and 5.1 [0.97–27] for PVR between 2–3 WU, 3–6 WU and > 6 WU. Presence of ILD (2.36 [1.22–4.6], $p=0.02$) and triple therapy (0.32 [0.12–0.87], $p=0.03$) were independently associated with survival in our population. After excluding patients treated by triple therapy to limit survival bias, results were similar (data not shown).

Discussion

The results of our study can be summarized as follows: 1/ using the new 2022 ESC/ERS definition of PH, 13% of patients were reclassified as having precapillary PH; 2/ at least 62% of them experienced an increase of mPAP values above 25 mmHg during follow-up and eventually met

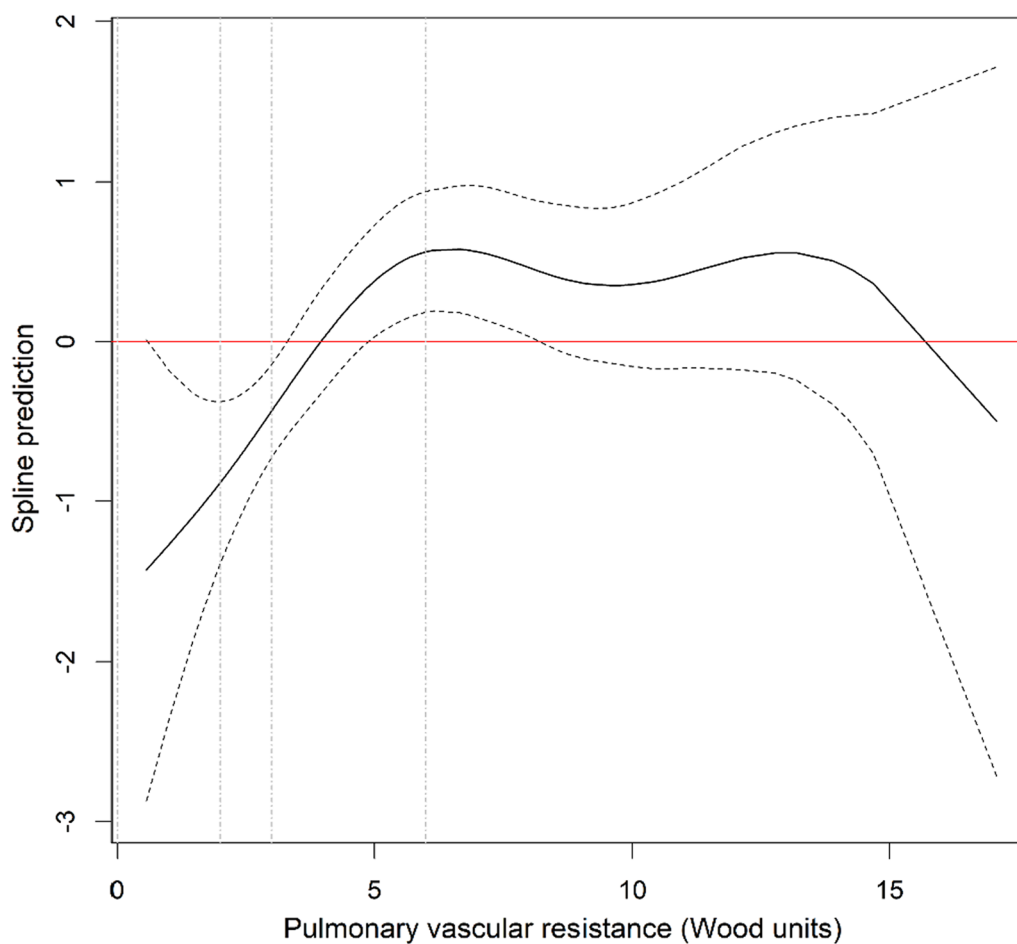


Fig. 3 Spline modelling the relationship between survival and PVR values. Spline modelling the relationship between survival and PVR values. The solid line represents the spline prediction (values > 0 indicates an increased risk of mortality, values < 0 a decreased risk of mortality). The dotted curves represent the 95% confidence interval of the spline prediction. The dotted vertical lines represent the 2-WU, 3-WU and 6-WU cut-offs for PVR (from left to right)

the previous definition of PH; 3/ our spline analysis suggests that mortality increases linearly with PVR values in patients with mPAP > 20 mmHg and PVR < 6 WU.

In our cohort of SSc patients with mPAP > 20 mmHg, 16 (13%) were reclassified as having pre-capillary PH when applying the new criteria. Interestingly, in their work performed in 2 PH centres, Xanthouli et al. identified 28 SSc patients with mPAP 21–24 mmHg and PVR \geq 2 WU, setting the proportion of reclassified patients at 9.85% when considering their total cohort and 20% when considering only patients with mPAP > 20 mmHg. Other studies found lower proportions of reclassification, ranging from 1.4 to 10.8% [5–7], but since they used the provisional 6th WSPH definition with a PVR cut-off at 3 WU, further comparison with our work is challenging. Coghlan et al. analyzed a 3-year follow up of patients with SSc and mPAP < 25 mmHg: 18/71 patients (25%) developed PH during follow-up including 5 with PAH, with an

annual incidence of 6.1% which is higher than incidence described in previous cohorts [11]. Considering all PH causes, association between borderline PH and mortality has already been described (with a mPAP threshold of 19 mmHg) [12]. The treatment of patients with mPAP between 21 et 24 mmHg is also still on evaluation. A recent placebo-controlled trial of ambrisentan in SSc PAH patients with mPAP 21–24 failed to show a statistical difference on the primary endpoint but showed interesting results on secondary endpoints (CI and PVR) [13].

There is an ongoing discussion as to whether these new classification criteria capture more patients with decreased survival. When using PVR as a continuous variable, our spline analysis suggested a linear relationship between PVR and survival for PVR values between 0 and 6 WU, implying that patients with PVR > 2 WU may have increased mortality compared to those with lower PVR values. However, when PVR is used as a

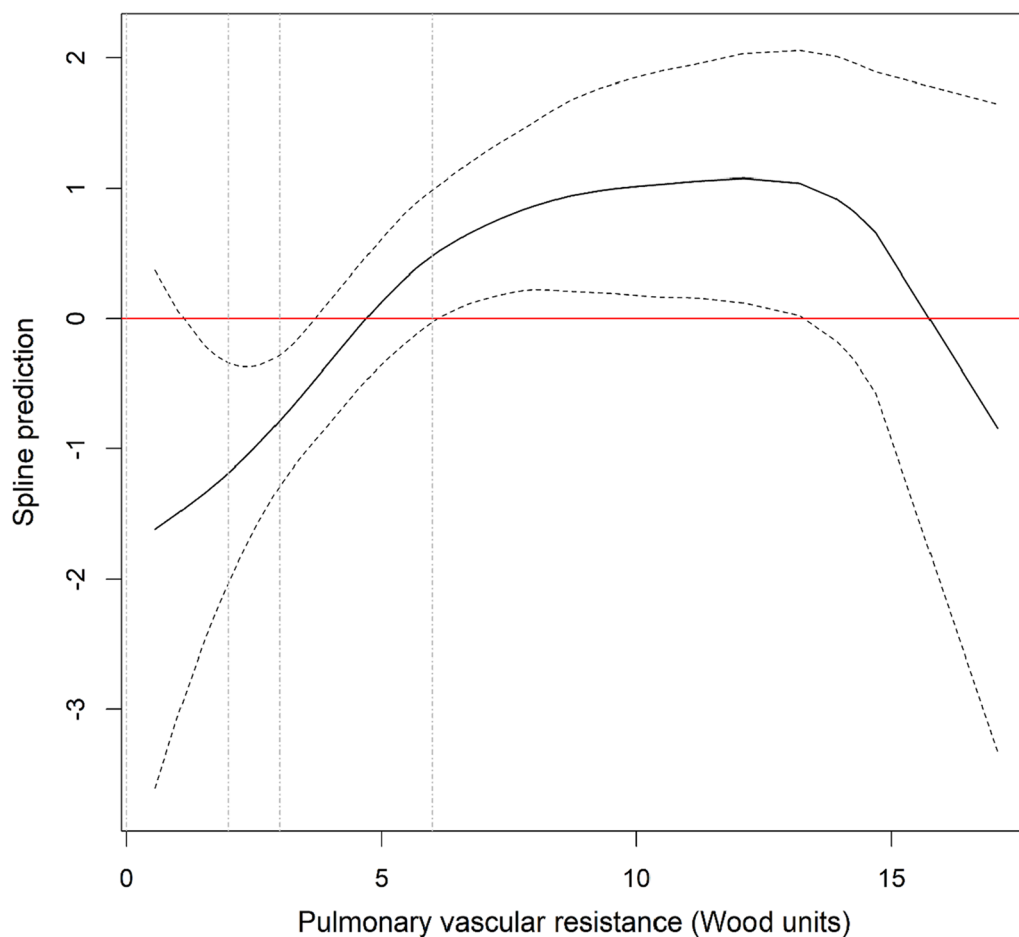
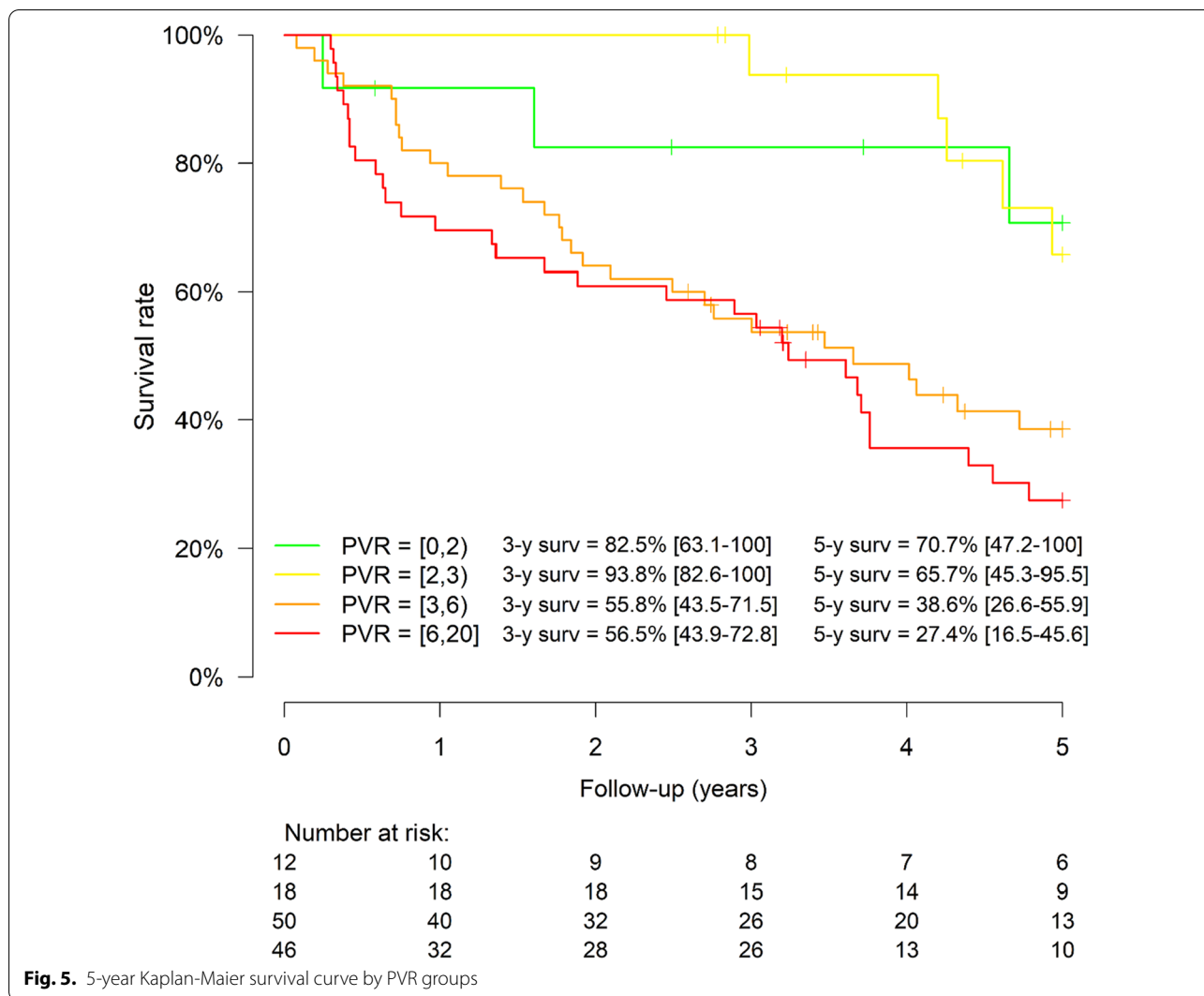


Fig. 4 Spline modelling the relationship between survival and PVR values with adjustments for age, gender, SSc subtype, presence of ILD, NYHA functional class and treatment. Spline modelling the relationship between survival and PVR values. The solid line represents the spline prediction (values >0 indicates an increased risk of mortality, values <0 a decreased risk of mortality). The dotted curves represent the 95% confidence interval of the spline prediction. The dotted vertical lines represent the 2-WU, 3-WU and 6-WU cut-offs for PVR (from left to right)

categorical variable, we did not observe significant differences in survival between PVR 2–3 and PVR 0–2 groups. This discrepancy could be explained by a modest effect size of these low PVR on mortality and by limitations due to our small sample size. In their study performed on 2 large veteran cohorts, Maron et al. [14] suggested that the optimal PVR cut-off identifying increased mortality is set at 2.2 WU. Interestingly, when categorizing PVR into 3 groups (with cut-offs at 2.2 and 3.0 WU), the hazard ratio for mortality (reference: PVR 2.2–3.0) was 0.89 (0.80–1.00) ($p=0.048$) in the PVR <2.2 group, suggesting an only mildly decreased survival for patients with PVR 2.2–3.0. Conversely, Yamamoto et al. [15] did not observe significant differences in the survival of various types of PH patients when comparing PVR <2 WU and PVR 2–3 WU groups, although their analyses are probably limited by small sample sizes as well. Taken together, these

data could suggest an increased mortality at the PVR 2WU cut-off, although it probably remains relatively modest within the 2–3 WU range.

Associations between PVR and mortality have also previously been reported in patients with idiopathic and SSc-associated PH, although with PH defined as $mPAP > 25$ mmHg [6, 16–18], with a minimum PVR threshold of 4.6 WU. PVR appears to be lower compared to patients with idiopathic PAH, but without correlation with mortality although prognosis of idiopathic PAH is better than in SSc [19, 20]. In our cohort, we observed a linear relation between PVR and survival for PVR values <6 WU, although the increase in mortality seems modest between patients with PVR <2 WU and PVR between 2–3 WU. When patients with normal or only mildly elevated PVR were excluded, we did not observe a difference in relationship between PVR and CI in patients with SSc-PAH suggesting that increased stiffness of the



pulmonary arterial bed is unlikely to be responsible for differences in outcomes. The patients with PVR between 2 and 3 also appear to be at risk of progression to PH [21], which seems to be also observed in our cohort.

Our study has several limitations. RHC was only performed in patients with a suspicion of PH, leading to selection bias with patients with milder hemodynamic alterations which may have been underdiagnosed; and RHC indications have changed during the inclusion period. Our study is also limited by its retrospective single-center design and its small sample sizes, although it includes a rather large cohort of SSc patients with hemodynamic evaluation. Our population may be heterogeneous as it mixed patients with different mechanisms of PH (groups 1 and/or 2 and/or 3) and thus possibly different prognosis; however, this remains relevant as all patients with $mPAP \geq 20$ mmHg and $PVR \geq 2$ WU are considered to have at least

pre-capillary PH (with or without an associated post-capillary PH, depending on their PAWP value) and some degree of pulmonary microangiopathy. Moreover, in SSc patients with ILD and PH, it is often difficult to determine whether PH is exclusively due to the chronic lung disease (group 3 only) or also caused by an underlying microangiopathy (group 1 + 3). Finally, multivariate analysis must be taken with caution as the adjustment is limited by the small effectives and by missing data for several predetermined variables.

Conclusion

A significant proportion of SSc patients is reclassified as having pre-capillary PH with the new 2022 ESC/ERS hemodynamic definition. Lowering the PVR threshold from 3 to 2 WU captures patients at risk of raising their $mPAP > 25$ mmHg, with a possibly less severe disease.

Prospective studies on larger cohorts are warranted to draw firm conclusions on the impact of this new definition.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12931-022-02205-4>.

Additional file 1: Multivariate analysis after adjusting for age, sex, SSC type, disease duration, presence of ILD, NYHA functional class and treatment.

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Author contributions

All individuals listed as authors met the ICMJE guidelines for determining authorship. SP, JG, EH and SS conceived and designed the study. SP and SS screened patients and collected clinical data. NL, PDG and MF extracted RHC and TTE data. JLE extracted PFT data. AL constituted and managed the database. JG performed statistical analyses and created the figures. SP wrote the first draft of the manuscript. SS made major revisions to the manuscript. JG provided his methodological expertise. NL, PDG and MF provided their cardiologic expertise. JLE, JFB and MHB provided his pneumologic expertise. VS, DL and EH provided their SSC and CTD-related PH expertise. All authors read and approved the final manuscript.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request from any qualified researcher.

Declarations

Ethics approval and consent to participate

The study complied with the recommendations of the Helsinki declaration. French legislation on noninterventional studies does not require ethics committee approval for the use of de-identified data collected during patient care. The data were de-identified and complied with the requirements of the "Commission Nationale de l'Informatique et des Libertés" (CNIL), the organization responsible for ensuring the ethical use of data collected for scientific purposes in France. The CNIL approved the methods used to collect and analyze data from our patient database (approval #DEC18-445). French legislation on noninterventional studies requires collecting the non-opposition of patients but does not require written consent. As such, non-opposition was obtained from each patient included in the study for the use of their de-identified medical record data.

Consent for publication

Not applicable.

Competing interests

SS reports travel grants from Shire, Sanofi-Genzyme, SOBI and Novartis; consulting fees from Novartis. DL reports research support from Actelion, GSK, and Pfizer; Octapharma, Takeda, Biocryst, CSL Behring. NL reported personal fees from Actelion (Janssen), Akcea, Alnylam, Amicus therapeutics, Bayer, Novartis, MSD, Pfizer, Sanofi-Aventis, and travel grants from Amgen and Bristol-Myers Squibb. PDG reports fees from Novartis, Servier, Astra-Zeneca, Abbott, Vifor, Janssen, Boehringer Ingelheim, Bayer, MSD. JFB reports travel grants from Pfizer, MSD, Janssen, AstraZeneca, Novartis Pharma France, and Chiesi; and board participation fees from Novartis Pharma France. EH reports consulting fees from Actelion, Boehringer Ingelheim, GSK, Roche-Chugai,

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