Pulmonary hypertension in systemic sclerosis: prevalence, incidence and predictive factors in a large multicentric Italian cohort

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Received on September 6, 2012; accepted in revised form on December 6, 2012.

Clin Exp Rheumatol 2013; 31 (Suppl. 76): S31-S36.

Key words: pulmonary hypertension, systemic sclerosis, epidemiology

Competing interests: none declared.

ABSTRACT

Objectives. *This paper aims to investigate the prevalence, the incidence of pulmonary hypertension (PH) and its subtypes in Italian patients with systemic sclerosis (SSc) and to characterise features associated with and predictive of development of PH.*

Methods. *Eight-hundred and sixty-seven consecutive SSc patients recruited at 4 Italian centres were enrolled. At admission, all patients underwent a careful history, physical examination, EKG, lung high resolution computed tomography (HRCT), pulmonary function tests, B-mode echocardiography and right heart catheterisation (RHC), if indicated. Patients were then visited every 6–12 months. A RHC was performed in those patients in whom PH was suspected for the presence of prespecified criteria.*

Results. *Among the 212 patients in whom it was suspected, PH was confirmed by RHC in 69 patients. On 31st December 2010, the point prevalence of P-arterial-H(PAH) and PH associated with interstitial lung disease (PH-ILD) was 3.7% and 1.4%, respectively; that of postcapillary PH was 1.3%. The estimated incidence rates of PH and PAH were respectively 1.85/100 patient-years and 1.02/100 patient-years. Multivariate analysis indicated that diffusing lung capacity for CO (DLCO) ≤55% (HR 4.45, 95%CI 2.24–8.83; p<0.001) and sPAP >40 mmHg (HR 18.03, 95%CI 9.01–36.06; p<0.001) were associated with an increased risk to develop PAH. SystolicPAP >40 mmHg resulted the only predictor of PH-ILD (HR 5.17, 95%CI 1.37–19.5; p=0.018) and post-capillary PH (HR 7.91, 95%CI 1.88–33.1; p=0.005) development.*

Conclusion. *Our study confirms a lower prevalence of PH in Italy compared to Anglo-Saxon cohorts. We also identified patients at high risk, who should be carefully monitored.*

Introduction

Systemic sclerosis (SSc) is a multisystemic connective tissue disease (CTD) characterised by distinct autoimmune abnormalities, microvascular obliterative and small artery proliferative disease and accumulation of collagen and other matrix constituents in the skin and target internal organs (1).

Genetic and environmental factors are believed to contribute to individual susceptibility (2, 3). Actually, SSc has been found to present differences in both the prevalence of the disease and that of distinct organ manifestations among different countries (4-6).

Considering the former aspect, a greater prevalence and incidence of SSc has been detected in the USA, compared to European, Asiatic and Australian populations (7-13). Moreover, scleroderma renal crisis (SRC) as well as anti-RNA polymerase I-III antibodies are known to be more frequent in North American with respect to both French and Italian patients (14).

Interstitial lung disease (ILD) and pulmonary hypertension (PH) represent challenging complications of the disease (15) and presently constitute the main related causes of death (16). In SSc, both pre- and post-capillary PH, resulting from a primitive pulmonary vessels involvement (PAH) or secondary to lung or left heart disease can be detected. PAH represents the most frequent form, complicating the course of SSc. Aside from early reports including patients with echocardiographically diagnosed PH, recent studies based on right heart catheterisation (RHC) demonstration of PAH have pointed

out its different prevalence in distinct countries, ranging from 3.3% to 12% (17-21).

In 2000, an inception cohort study was established in 4 Italian tertiary centres. Here, we analyse our results in order to: a) investigate both the prevalence and the incidence of PH and its subtypes in a large Italian SSc sample; 2) characterise clinical, serological and laboratory features associated with each subtype of PH; and 3) identify predictors of PH development.

Materials and methods

From 1st November 2000 to 31st December 2010, 867 new SSc patients, fulfilling the ACR criteria (22), or LeRoy criteria for early SSc (23), consecutively admitted to the outpatient clinics of 4 Italian tertiary centres, were enrolled in an inception cohort study after giving their informed written consent. All patients were investigated, at admission, for core set variables considered in the EUSTAR clinical chart (24) (Table I). In particular, patients underwent a careful clinical history, a complete physical examination, EKG, HRCT of lungs, pulmonary functional tests, B-mode echocardiography by techniques already described (25) and RHC, if indicated. Patients were then visited every 6–12 months in order to assess the course of the disease. In addition, 237 out of the 867 patients were investigated for NT-proBNP at admission, the role of which as a tool useful to assess cardiac alterations in SSc patients has been established (26, 27)

A RHC was performed in those patients in whom PH was suspected for the presence of at least one of the following criteria (at admission or during follow-up): a) electrocardiographic findings suggesting PH (right ventricle hypertrophy, right atrial dilatation, right axis deviation); b) an estimated echocardiographic systolic pulmonary arterial pressure (sPAP) >40 mmHg (28); c) presence of both diffusion capacity for carbon monoxide (DLCO) < 55% of the predicted value and forced vital capacity (FVC) >70% of the predicted value (29), either associated or not with an impaired six-minute walking test (30). The third condition was considered when a concurrent ILD was ruled out by lung HRCT and bronchoalveolar lavage (BAL) analysis.

The study was approved by the Ethics Committees of the Universitary Centres involved in the study.

NT-proBNP

In 237 patients, NT-proBNP levels were analysed on venous blood obtained at admission, using a Luminex 100 system (Luminex, Austin, TX, USA) and a multi-analyte profiling bead-based assay kit (Millipore, Billerica, MA, USA) according to the manufacturers' recommendations. Assay sensitivities (minimum detectable concentations, pg/ml) was 11.50 pg/ml.

Right heart catheterisation

Pulmonary arterial, right atrial, and pulmonary capillary wedge pressures and systemic pressures were recorded at the end of a quiet respiratory cycle. Cardiac output was measured by thermodilution or by the indirect Fick method using an average of at least three measurements Pulmonary and systemic vascular resistance indices were calculated using the standard formula.

Pre-capillary PH was defined as a mean resting pulmonary artery pressure (mPAP) ≥25 mmHg and pulmonary capillary wedge pressure (PWP) ≤15 mmHg upon RHC (31). Pre-capillary PH was considered pulmonary arterial hypertension (PAH) in the absence of other causes of pre-capillary PH such as PH due to lung disease or chronic thromboembolic PH (31). It was considered secondary to ILD (ILD-PH) when FVC was <70% of the predicted value in addition to significant change on chest high-resolution CT (HRCT), as assessed in recent studies (32, 33). Pulmonary veno-occlusive disease was defined as the occurrence of PH associated with radiographic evidence of pulmonary oedema and a normal pulmonary artery occlusion pressure (34). A ventilation/perfusion lung scan was performed in patients with pre-capillary PH in whom a thromboembolic PH was suspected, *i.e.* deep vein thrombosis and/or high levels of D-dimers.

Statistical analysis

GraphPad Prism 5.0 and MedCalc 11.3 for Windows software were used for statistical analyses. Data were presented as mean±SD for continuous variables and absolute values and percentages for categorical variables. Continuous data were expressed as mean±SD and median with range, and were compared by Student's *t*-test or Mann-Whitney U-test as appropriate. Categorical data were analysed by either the chi-square test or Fisher's exact test. The prevalence of the different forms of PH was calculated as the ratio of patients over the eligible population. The incidence rate of PH was calculated as the ratio between the number of patients with a diagnosis of PH during the follow-up period and the cumulative duration of follow-up, and was expressed as the number of patients-years. A stepwise Cox proportional hazard analysis was performed to identify the variables assessed at admission associated with increased risk to develop PAH. A p-value <0.05 was considered statistically significant.

Results

PH prevalence and incidence

Table I shows the main epidemiological and clinical characteristics of each SSc cohort and combined samples. Patients from Naples resulted to be younger than patients from each of three other cohorts (p<0.002), whereas the observed proportion of dcSSc patients was significantly higher in Rome cohort (p<0.01) and that of anti-Scl 70 positivity was significantly lower in Pavia cohort (p<0.01). In our opinion this variability does not reflect differences in the SSc spectrum of patients from distinct Italian regions. Indeed, it is likely to depend on the relationships between each centre and the respective General Practitioners. In Pavia, where the University Hospital is actually the city hospital, a stronger link with the GP does exist, with the consequent enrolment of a greater number of patients with limited disease and a shorter disease duration.

As shown in Figure 1, PH was suspected in 95 patients at admission (Table II) and in further 117 patients

Table I. Characteristics of patients from Naples, Pavia Modena and Rome separately and combined.

Characteristics of patients	Na n=289	Pv n=247	Mo n=236	Rm n=95	Combined n=867	*p*-value
Age, yrs (median; range)	49 (12–85)	59 (20–83)	60 (19–89)	63 (22–78)	59 (12–89)	<0.001
Age at onset of RP, yrs, mean (SD)	41 (15)	50 (15)	48 (16)	47 (15)	46 (16)	<0.001
mRss, (median; range)	4 (0–36)	4 (0–34)	4 (0–39)	7 (3–39)	4 (0–39)	NS
Disease duration, yrs (median; range)	5 (0.4–55)	3 (0.4–40)	6 (0.2–36)	4 (0.2–41)	4 (0.2–55)	<0.001
Women/men	260/29	214/33	210/26	89/6	773/94	NS
lcSSc, n (%)	232 (79)	200 (80)	178 (75.4)	66 (69.4)	676 (78)	<0.001
dcSSc, n (%)	57 (20)	47 (20)	58 (24.5)	29 (30.5)	191 (22.0)	<0.001
Anticentromere antibodies, n (%)	116 (39)	104 (42)	98 (41.5)	40 (42)	358 (41.2)	NS
Antitopoisomerase I antibodies, n (%)	105 (37)	54 (21)	81 (34.3)	34 (35.7)	274 (31.6)	<0.001
Nucleolar pattern, n (%)	21 (7)	23 (10)	28 (11.8)	11 (11.5)	83 (9.5)	NS
ESR, mean (SD)	16 (15)	18 (12)	25 (18)	22 (17)	20 (16)	NS
CK elevation, %	3.8	3.0	2.5	5.7	4.5	NS
Proteinuria, %	1.5	2.4	3.4	1.2	2.6	NS
Hypocomplementemia, %	6	8	8	12	6	NS
Dyspnoea, %	39	39	44	49	41	NS
DLCO (% predicted) mean (SD)	73 (21)	75 (21)	71 (24)	62 (18)	71 (21)	<0.001
FVC, (% predicted) mean (SD)	95 (20)	102 (24)	102 (25)	94 (19)	97 (22)	<0.001
ESSG-AI ≥3, n (%)	42 (17)	6 (24)	32 (34)	31 (33)	74 (23)	<0.001
Esophageal symptoms, %	63	34	74	77	59	<0.001
SRC, %	1	1	0	1	<1	NS
Arterial hypertension, %	22	31	22	46	26	<0.001

Na: Naples; Pv: Pavia; Mo: Modena; Rm: Rome.
NS: Not significant; yrs: years; RP: Raynaud's phenomenon; mRss: modified Rodnan skin score; lcSSc: limited cutaneous systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis; ESR: erythrocyte sedimentation rate; CK: creatin kinase; DLCO: diffusion capacity for carbon monoxide; FVC: forced vital capacity; ESSG-AI: European Scleroderma Study Group - Activity Index; SRC: scleroderma renal crisis.

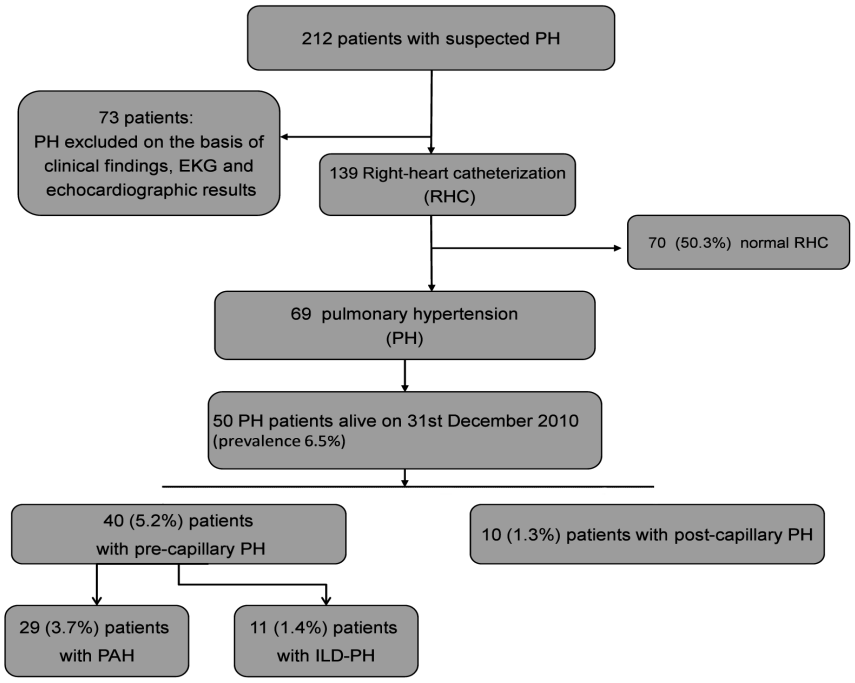

Fig. 1. The distribution of patients with suspected pulmonary hypertension (PH) according to the non-invasive screening process and results of right-heart catheterisation (RHC). PAH: pulmonary arterial hypertension; ILD: interstitial lung disease.

during follow-up (Table II). PH was ruled out on the basis of clinical and instrumental findings in 73 patients. RHC was planned in the remaining 139 patients. All patients who were asked to undergo RHC accepted the procedure. RHC ruled out any significant increase in pulmonary artery pressure in 70 patients, and in 69 patients PH was detected (Fig. 1).

On 31st December 2010, 51 patients were dead (5.8%) and 50 were lost to follow-up (5.8%). Out of the remaining 766 patients, 29 resulted to have PAH (10 diagnosed at admission), 11 ILD-PH (1 at admission) and 10 post-capillary PH (3 at admission).

The point prevalence of precapillary PH was 5.2 % (40/766 patients). Among these, 29 patients (3.7%) and 11 patients (1.4%) were found to have PAH and ILD-PH, respectively. The prevalence of postcapillary PH secondary to left-heart disease was 1.3 % (10 patients). In no patient a diagnosis of PH secondary to pulmonary venocclusive disease or chronic thromboembolic PH was made (Fig. 1).

The patients were followed up for 51.7±34.3 months (median 48 months). The estimated incidence rates of PH and PAH were 1.85/100 patient-years and 1.02/100 patient-years, respectively.

Precapillary PH: patients features and predictors of development

Overall, 36 out of 676 lcSSc (5.3%) and 4 out of 191 dcSSc patients (2.1%) (p=0.06) developed PAH. Table III shows the haemodynamic data of these patients. PAH diagnosis occurred after 13.5±11.15 years from Raynaud's onset in patients with lcSSc, and after 9.0±1.7 years in patients with dcSSc (p=0.874). At PAH diagnosis, patients affected by lcSSc were older than those affected by dcSSc (65.5±8.7 *vs*. 51.75±13.6 years; p=0.004). By univariate analysis, limited cutaneous subset (HR 3.70, 95%CI 1.13–12.02; p=0.029), anticentromere antibodies (HR 1.88, 95%CI 1.00–3.53; p=0.049), DLCO ≤70% if FVC> 70% of predicted value (HR 3.04, 95%CI 1.51–6.13; p>0.001), DLCO ≤60% if FVC >70% of predicted value (HR 4.69, 95%CI 2.38–9.24; p<0.001), DLCO ≤55% if FVC >70% of predict-

Table II. Numbers of patients with suspected pulmonary hypertension at admission and during follow-up.

Items inducing suspicion	At admission	During follow-up
Pulmonary arterial systolic pressure >40 mmHg on echocardiography, n	31 pts	35 pts
DLCO <55% of the predicted value and FVC >70% of the predicted value, n	38 pts	66 pts
Pulmonary arterial systolic pressure >40 mmHg on echocardiography + DLCO <55% of the predicted value, n	26 pts	16 pts
Electrocardiographic findings suggesting PH (right ventricle hypertrophy, right atrial dilatation, right axis deviation), n	0 pts	0 pts

DLCO: diffusion capacity for carbon monoxide; FVC: forced vital capacity

Table III. Haemodynamic data of patients with PAH.

Right heart catheterisation parameters*	Results
Mean PAP, mmHg	37.91 (10.27)
Cardiac index, L/min/m^2	2.51 (0.84)
mPAWP, mmHg	10 (3.59)
Right atrial pressure, mmHg	9.53 (3.68)

*Data are presented as mean±SD; mPAWP: mean pulmonary arterial wedge pressure.

Table IV. Epidemiological, clinical and serological features of the 29 patients affected by SSc-PAH, 11 patients affected by ILD-PH and 10 affected by post-capillary PH.

Patients features, n	PAH-SSc, 29	ILD-PH, 11	Post capillary-PH, 10	P1	P2	P3
Women (n, %)	26 (89.6)	9 (81.8)	9 (90)	0.503	0.973	0.592
Age at PH diagnosis						
Mean±SD	63.2±10.78	57±12.67	71.1±4.35	0.198	0.014	0.010
Median (range)	65 (30–77)	59 (38–72)	70.5 (65–78)			
Disease duration at PH diagnosis						
Mean±SD	15.44±11.90	8.90±4.82	14.3±7.74	0.282	0.987	0.098
Median (range)	13 (2–42)	9 (3–20)	14.5 (3–26)			
Clinical subset lcSSc (n, %)	27 (93.1)	6 (54.5)	9 (90)	0.010	0.587	0.08
Clinical subset dcSSc (n, %)	2 (6.9)	5 (18.2)	1 (10)	0.010	0.587	0.08
Anticentromere antibodies (n, %)	19 (65.5)	1 (9)	6 (60)	0.001	0.519	0.019
Antitopoisomerase antibodies (n, %)	5 (17.2)	4 (36.4)	2 (20)	0.190	0.589	0.358
Nucleolar pattern (n, %)	3 (15.7)	3 (27.3)	0 (0)	0.195	0.399	0.124
Other autoantibodies	2 (10.5)	3 (27.3)	2 (20)	0.116	0.264	0.802

P1. PAH-SSc *vs*. ILD-PH; P2. PAH-SSc *vs*. post-capillary PH; P3. ILD-SSc *vs*. post-capillary PH.

ed value (HR 4.90, 95%CI 2.58–9.32; $p<0.001$) and sPAP >40 mmHg (HR 19.77, 95%CI 10.18–38.39; $p<0.001$) assessed at admission, were independent factors associated with development of PAH (Table V).

Multivariate stepwise Cox proportional hazard analysis indicated that DLCO ≤55% if FVC >70% of predicted value (HR 4.45, 95%CI 2.24–8.83; $p<0.001$) and sPAP >40 mmHG at admission (HR 18.03, 95%CI 9.01–36.06; $p<0.001$), but not the other tested variables, were associated with an increased risk to develop PAH.

Table IV summarises the epidemiological, clinical and serological features of the patients affected by ILD-PH. In the 11 patients presenting with PH secondary to ILD, the percentage of ACA positivity was significantly lower than that recorded in PAH- ($p=0.001$) and post-capillary PH ($p=0.019$) patients, and they were more likely to have a diffuse subset of disease.

At multivariate analysis, sPAP >40 mmHg at admission has resulted the only predictor of PH-ILD (HR 5.17, 95%CI 1.37–19.5; $p=0.018$) development.

Post-capillary PH: patients' features and predictors of development

Table IV summarises the epidemiological, clinical and serological features of the patients affected by post-capillary PH. These patients were significantly older than those of each of the two other groups ($p<0.014$). At multivariate analysis, sPAP >40 mmHg at admission has resulted the only predictor of post-capillary PH (HR 7.91, 95%CI 1.88–33.1; $p=0.005$) development. It is noteworthy that an E/A <1 indicating an impaired left ventricular filling was not found to be associated with post-capillary PH.

NT-proBNP serum levels

NT-proBNP serum levels were measured in 237 patients at admission. There were no significant differences in age, sex, disease duration, subset and autoantibody positivity among these patients and those in which the measurement was not done. Basal NT-proBNP resulted higher than the normal value in 35 out of 221 of SSc-patients not developing PAH (15.8%) and in 7 out of 16 patients in whom a diagnosis of PAH was made (43.7%) ($p=0.002$). Univariate and multivariate stepwise Cox proportional hazard analysis were performed in this group of patients. Increased serum levels on NT-proBNP at admission resulted to be predictive of development of PAH in univariate (HR 9.26, 95%CI 3.28–26.01; $p<0.001$), but not in multivariate analysis.

Discussion

Pulmonary hypertension (PH) is a severe complication of SSc and represents one of the leading causes of death (16). Assessing its prevalence and identifying subjects at risk can be very useful for the clinicians to make an earlier diagnosis and treatment of this life-threatening complication. In

Table V. Predictive factors of PAH development as assessed at baseline.

Disease phenotype associations	Univariate analysis HR (95%CI)	*p*-value*	Multivariate analysis HR (95%CI)	*p*-value*
Sex (female)	1.87 (0.36–3.86)	0.775	–	–
Disease duration at admission >10 yrs	1.02 (0.98–1.06)	0.249	–	–
Age >49 yrs	2.01 (0.97–4.15)	0.057	–	–
Limited cutaneous subset	3.70 (1.13–12.02)	0.029	–	–
Anticentromere antibodies	1.88 (1.00–3.53)	0.049	–	–
Antitopoisomerase antibodies	0.51 (0.23–1.12)	0.094	–	–
Nucleolar pattern	1.07 (0.98–1.45)	0.123	–	–
DLCO ≤70% + FVC >70% of predicted value	3.04 (1.51–6.13)	<0.001	–	–
DLCO ≤60% + FVC >70% of predicted value	4.69 (2.38–9.24)	<0.001	–	–
DLCO ≤55% + FVC >70% of predicted value	4.90 (2.58–9.32)	<0.001	4.45 (2.24–8.83)	<0.001
sPAP >40 mmHg	19.77 (10.18–38.39)	<0.001	18.03 (9.01–36.06)	<0.001

*Significant when $p<0.05$. yrs: years; DLCO: diffusion capacity for carbon monoxide; FVC: forced vital capacity; sPAP: pulmonary arterial systolic pressure

previous reports, PH prevalence rates in SSc were found to be quite different (5–50%) (35). These results can be explained by differences in PH definition criteria (excluding or including the presence of pulmonary fibrosis, left-heart disease, or both) and method of diagnosis (echocardiography, RHC). A recent metanalysis, including 4 European studies (1 from France; 1 from France and Italy; 1 from the Netherlands; 1 from UK) and 1 Australian study (all studies used RHC for diagnosis of PH), revealed a 9% point prevalence of precapillary PH in SSc patients. Only in 2 studies a distinction between PH due to ILD and primitive PAH prevalence was made (21).

In our study enrolling 867 SSc patients from 4 University tertiary centres from different Italian regions, we found a 6.5% point prevalence of PH diagnosed by RHC. Among these patients, the majority had PAH (3.7 %), 1.4% had ILD-PH and 1.3 % had post-capillary PH. As regards the prevalence of PAH, our findings are surprisingly similar to those described by Avouac *et al*. in a French-Italian survey (21) and highlight a trend towards a lower prevalence of RHC diagnosed PAH in Mediterranean countries with respect to Anglo-Saxon populations (9.9%–12%) (19, 20). We also found a similar prevalence of ILD-PH (1.4% *vs*. 1.6%) and of post-capillary PH (1.3% *vs*. 2%) as compared to Avouac *et al*. figures (21).

We assessed the incidence rate of PAH in our cohorts, which resulted to be of 1.02 patients-100 years-follow-up, slightly higher than that recorded in the ItinérAIR Study by Hachulla *et al*. (36). To date, there are no available data on the incidence of PAH in Italy.

Patients with lcSSc have been historically considered to be at greater risk of PAH than patients with dcSSc (37). However, more recent papers showed that PAH may be similarly prevalent in the two subsets of the disease (19, 36, 38). Our data seem to be in line with these reports. In fact, we did not find a significant difference in the development of PAH in the two subsets, even if the majority of PAH patients had lcSSc. Moreover, at multivariate analysis neither lcSSc subset nor anticentromere autoantibodies predicted the development of PAH. As recently observed (38), lcSSc patients who developed PAH from our cohort were older than patients with dcSSc. Finally, baseline sPAP >40 mmHg and DLCO<55% of the predicted value, in absence of interstitial lung disease, represent useful tools to identify patients at higher risk to develop PAH, as already described in other surveys (29, 39).

We also investigated the features of patients with PH secondary to ILD who, as expected, were more likely to be affected by diffuse disease and showed a lower prevalence of anti-centromere autoantibodies. On the other hand, post-capillary PH has been found to affect mainly older patients (mean±SD 71.1±4.35 years) in both disease subsets. We did not find baseline factors predicting the development of ILD- and post-capillary-PH, except for sPAP >40 mmHg.

One limitation of the present study could be that all the patients were recruited by tertiary centres. This aspect would induce to predict an even lower prevalence of PH in SSc patients from our country, since patients referred to tertiary centres are commonly more severe than those observed in the general population.

In conclusion, our study confirms a lower prevalence of PH in Italy with respect to Anglo-Saxon cohorts and for the first time gives the opportunity to assess the incidence rate of one of the leading causes of death in SSc in a large cohort of Italian patients. These data underline the need to explore genetic and environmental factors possibly involved in these variations.

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