Original Article

Prevalence, Classification, and Outcomes of Pulmonary Hypertension in Thai Systemic Sclerosis

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Objective: To determine the prevalence of right heart catheterization (RHC) confirmed pulmonary hypertension (PH) and the potential subtypes of PH and its associations with clinical characteristics and treatment response.

Materials and Methods: A historical cohort study was conducted of Thai SSc patients presenting at Srinagarind Hospital between January 2014 to December 2016. The PH subtypes were categorized using hemodynamic parameters from RHC, pulmonary function tests, and findings on high-resolution computed tomography (HRCT).

Results: 409 SSc patients were enrolled (F: M = 2.17: 1); 75% had diffuse cutaneous SSc. The median age at the time of the study was 57 years (range, 20 to 87). and median disease duration was 4.83 years. The prevalence of PH was 9.5% and the estimated incidence of PH was 1.1 per 100 person-years. Among PH patients 97.4% (38/39) were pre-capillary, of whom 23 (60.5%) had PH due to interstitial lung disease (PH-ILD), 8 (21.1%) combined pulmonary arterial hypertension (PAH) and PH-ILD, 6 (15.8%) isolated PAH, and only 1 (2.6%) pulmonary veno-occlusive disease (PVOD). Pulmonary involvement >20% by HRCT was associated with the presence of PH. The treatment response to PAH-specific drug(s) was better among isolated PAH-SSc compared to subtypes with an interstitial lung component (83 vs. 62%).

Conclusion: The prevalence of PH among Thai patients with SSc was 9.5%; the majority was PH-ILD and combined PAH/PH-ILD. Isolated PAH was identified in 15.8%, which was associated with a better response to treatment. Pulmonary involvement >20% by HRCT was associated with the presence of PH.

Keywords: Systemic sclerosis; Pulmonary hypertension

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Systemic sclerosis (SSc) is a rare multisystem connective tissue disease characterized by extensive fibrosis, vascular abnormalities, and the production of autoantibodies against various cellular antigens. These processes lead to dysfunction and failure of almost all internal organs. The different patterns and severity of internal organ involvement are the most significant determinants of the prognosis[1]. SSc is classified into two subtypes; limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc)[2]. Internal organ involvement is more frequent in dcSSc and becomes a major prognostic determinant[1].

Pulmonary hypertension (PH) is the most serious complication for SSc patients. According to the WHO, PH is classified into 5 groups[3]:

Group 1: Pulmonary arterial hypertension (PAH); Group 2: Pulmonary hypertension due to left heart disease (PH-LHD); Group 3: Pulmonary hypertension due to lung diseases and/or hypoxia (PH-ILD); Group 4: Chronic thromboembolic pulmonary hypertension (CTEPH) and other pulmonary artery obstructions; and Group 5: Pulmonary hypertension with unclear and/or multifactorial mechanisms.

The Mechanisms underlined PH in SSc patients (PH-SSc) can be several, such as primary pulmonary arterial hypertension (PAH), pulmonary veno-occlusive disease (PVOD)[4], left ventricular systolic and diastolic dysfunction[5], interstitial lung disease (ILD)[6], chronic thromboembolic pulmonary hypertension (CTEPH), and possibly multifactorial mechanisms. These may be reflected in worse clinical outcomes after treatment with PAH-specific drugs compared to idiopathic PAH (IPAH)[7], and PAH associated with other connective tissue diseases (PH-CTD)[8].

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The most frequent cause of PH-SSc is PAH, which has become the leading cause of death in this population[9]. The respective estimated 3-year survival rate among SSc patients with PAH compared with those without PAH is 56% and 94%[10]. Currently, a hemodynamic evaluation by right heart catheterization (RHC) is necessary and has become the gold standard for the diagnosis of PAH. The procedure, however, is invasive and inconvenient, so instead, echocardiography (ECHO) is often used for screening and monitoring disease progression and response to treatment[3]. Before the PAH-specific drug era, the reported prevalence of PH-SSc was confused between PH and PAH, ranging from 2.4 to 59.1%[11-15]. The variation depended upon the method and criteria used for diagnosis, also the characteristics of the patients studied. The reported prevalence of PH-SSc defined by ECHO varied between 6 to 32%, while the prevalence of PAH-SSc diagnosed by RHC was lower, between 3.6 to 15%[10,23-27]. In Thai SSc, the accurate prevalence of PAH diagnosed by RHC has never been reported. The prevalence of PH defined by ECHO ranges between 2.4 and 59.1%[11-15].

Treatment of PAH-SSc was adopted from the treatment guideline for IPAH by using PAH-specific drugs[3]. The survival rate was improved, albeit the prognosis of PAH-SSc remained poor compared to IPAH. Based on a US cohort, the 3-year survival rate for PAH-SSc was lower compare to IPAH (60% vs. 77%; $p<0.0001$)[28]. Differences in prognosis and the treatment response are incompletely understood but probably due to the systemic nature of SSc with multiple organs dysfunction. Previous studies demonstrated that the prognosis of PAH-SSc was even worse if concomitant with ILD[29]. Treatment of PAH with specific drugs is not recommended for other causes of PH such as PH-ILD or CTEPH and may cause clinical deterioration in patients with PVOD. PAH-specific drugs may cause drug-induced pulmonary edema in such patients[3]. Thus, identifying the subtype of PH in the SSc patient is a fundamental step for determining the prognosis and response to treatment with PAH-specific drugs.

Objective

To determine the prevalence of right heart catheterization (RHC) confirmed pulmonary hypertension (PH) and the potential subtypes of PH and its associations with clinical characteristics and treatment response.

Materials and Methods

A historical cohort study was performed in all adult SSc patients followed-up between January 2014 and December 2016 at Srinagarind Hospital, Khon Kaen University, Thailand. We excluded any patients who had overlap syndrome, mixed connective tissue disease, and patients who did not have a RHC to confirm the PH diagnosis.

The study was approved by the Human Research Ethics Committee of Khon Kaen University (HE601382).

Operational definitions

Diagnosis of SSc is based on the 1980 American Rheumatism Association classification criteria of SSc[30] or 2013 ACR/EULAR Classification Criteria for Scleroderma[31]. Classification of scleroderma as lcSSc or dcSSc per LeRoy, et al[2]. The onset of SSc is defined as a time of first non-Raynaud SSc symptoms reported by the patient. Disease duration is calculated as the interval between disease onset and time at last data collection. Time to PH is calculated as the interval between disease onset and when the patient had PH determined by RHC.

PH is defined as mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest by RHC[3].

PAH defined by an increase in mPAP ≥25 mmHg at rest and pulmonary arterial wedge pressure (PAWP) ≤15 mmHg and pulmonary vascular resistance (PVR) >3 Wood unit (WU) determined by RHC. PH due to interstitial lung disease (PH-ILD) defined by mPAP 25 to 35 mmHg and forced vital capacity (FVC) <70% or forced expiratory volume 1 (FEV1) <60% predicted or >20% involvement of ILD evaluated by HRCT. Combined PAH and PH-ILD defined by mPAP >35 mmHg or mPAP 25 to 35 mmHg and Cardiac index <2 L/min/m^2[32] and FVC <70% or FEV1 <60% predicted or >20% involvement of ILD evaluated by HRCT. Isolated post-capillary PH or PH due to left heart disease (PH-LHD) defined by mPAP ≥25 mmHg and pulmonary arterial wedge pressure (PAWP) >15 mmHg and diastolic pressure gradient (DPG) <7 mmHg and/or pulmonary vascular resistance (PVR) <3 Wood units (WU). Combined post-capillary and pre-capillary PH defined by mPAP ≥25 mmHg and PAWP >15 mmHg and DPG ≥7 mmHg and/or PVR >3 WU.

The significant restrictive disease is defined as FVC <70%[6]. HRCT chests were review by a radiologist using Goh&Wells method for evaluation[46]. ILD is defined by the presence of an abnormal chest radiograph (CXR) with a restrictive pattern from spirometry, or significant abnormalities (including; ground-glass opacity, fibrosis, bronchiectasis, and honeycombing) evaluated by HRCT of the chest. Patients with >20% HRCT abnormalities are considered to have extensive lung involvement while those with <20% as having limited involvement. If the HRCT evaluation is inconclusive, patients are considered to be affected by extensive lung involvement if FVC <70% predicted and by limited lung involvement if FVC ≥70% predicted. Patients with extensive lung involvement have strikingly higher mortality and faster deterioration of lung function[33].

Pulmonary veno-occlusive disease (PVOD) was defined by the presence of abnormalities evaluated by HRCT. Typical findings suggestive of PVOD are the presence of sub-pleural thickened septal lines, centrilobular ground-glass opacities, and mediastinal lymphadenopathy. The association of these three findings was found to be 100% specific for PVOD in cases of PAH, with 66% sensitivity[3]. This non-invasive approach may avoid the need to perform a hazardous lung biopsy (i.e., the gold standard to confirm

PVOD is a histological diagnosis[3].

Statistical analysis

Data were divided into dichotomous/polytomous or continuous variables. The prevalence of PH was described together with their 95% confidence intervals (CI) and described separately between the lcSSc and dcSSc subsets. The odds ratio (95% CI) and p-value were used to assess the clinical characteristics associated with PH. The continuous data were analyzed using the student t-test or Wilcoxon Ranksum as appropriate. The variables with a p-value <0.20 were entered into a multiple logistic regression. The backward elimination method was applied for model fitting. Variables were tested for significance using the Wald X^2 statistic. All statistical tests were two-tailed. A p-values <0.05 were considered statistically significant. All data analyses were performed using STATA version 11.2 (StataCorp., College Station, TX, USA).

Results

Patients characteristic

A total of 409 cases were included in the study. The female to male ratio was 2.17: 1. The median age at the time of the study was 57 years (range, 20 to 87). The majority (73.5%) had a duration of disease >5 years. Most (75%) had dcSSc with pulmonary involvement.

Characteristic of patients with PH and without PH

A higher proportion of SSc with PH at presentation had (a) poor WHO-FC II-IV, (b) more severe pulmonary function tests (FVC <70%, FEV1 <60%), and (c) >20% pulmonary involvement per HRCT. Abnormal ECG—i.e., right bundle branch block (RBBB) and right ventricular hypertrophy (RVH), and detection of pericardial effusion from echocardiography—were also prominent in patients with PH. As TRV max and RVSP were used as a screening tool for PH in SSc, these tests were inevitably high in all PH patients. There was a trend, however, toward a higher percentage of patients who had anti-RNP and clinical chest discomfort at the first visit developed PH during follow-up. The clinical characteristics of SSc patients with and without PH at the first visit are summarized in Table 1.

The factors associated with PH were analyzed in Table 2. According to the univariate analysis, apart from echocardiographic screening criteria of PH (TRVmax ≥2.9 m/s and RVSP ≥36 mmHg), the factors associated with PH were FC II-IV, chest discomfort, presence of anti-RNP antibody, FVC <70%, FEV1 <60%, RBBB and RVH from EKG, LV D shape, presence of pericardial effusion, and >20% pulmonary involvement by HRCT.

According to the multiple linear regression analysis, only TRVmax ≥2.9 m/s and >20% HRCT pulmonary involvement were significantly correlated with PH.

Prevalence and incidence of PH in SSc patients

The prevalence of PH and PH subtypes are summarized in Figure 1. Overall, the prevalence of RHC-confirmed PH in SSc patients was 9.53% (39/409). The majority (97.4%) of affected persons was precapillary. Figure 1 presents the distribution of PH subtypes in the pre-capillary group (n=38), which represented isolated PAH in 6 patients (15.8%), PH-ILD in 23 (60.5%), combined PAH/PH-ILD in 8 (21.1%), and PVOD in 1 (2.6%). Post-capillary PH due to left-heart disease was demonstrated by RHC in 1 case with a prevalence of 0.24%. None of the patients had combined pre-and post-capillary PH. The estimated incidence of PH among patients with SSc was 1.11 per 100 person-years.

Characteristics of SSc patients determined by subtype of PH

Age at the first non-Raynaud's phenomenon was lower in patients with combined PAH/PH-ILD than isolated PAH and PH-ILD. There was no significant difference in sex, age at diagnosis of PH, disease duration, time to PH, a subtype of SSc, clinical symptoms, and echocardiography parameters. The presence of ACA antibody was found only in the isolated PAH group.

Patients with combined PAH/PH-ILD had a higher mean pulmonary arterial pressure (mPAP), higher pulmonary vascular resistance (PVR), lower cardiac output (CO), and lower cardiac index (CI) than other subtypes.

Treatment of PH by PAH-specific drugs

All patients with isolated PAH were treated with a single PAH-specific drug, while combination therapy was used more often for patients with combined PAH/PH-ILD and PH-ILD subtypes. A single case of SSc-PVOD was treated with combination therapy. Treatment of PH-SSc using PAH-specific drugs is presented in Figure 2.

Response to treatment with PAH-specific agents

The goal of treatment in PH-SSc is to improve FC III-IV to FC II, stabilize at FC II, or improve FC II to FC I. We classified the treatment response into two groups: the poor responder defined as worsening FC or an FC >FC II from the PH diagnosis visit to the last follow-up visit. A good responder was defined by improvement of the FC, to either FC I or stable FC II.

It was noted that 83% of the patients in the isolated PAH subtype had a good response to PAH-specific drugs compared to patients with PH-ILD or combined PAH/PH-ILD who achieved the treatment goal in 67% and 50%, respectively.

Considering the survival curve of time to worsening FC (poor responder), the median time to worsening FC in all PH-SSc was 48 weeks (p=0.81) (Figure 3). By contrast, patients with PH-ILD and combined PAH/PH-ILD had a poorer outcome than the isolated PAH subtype.

Effects of treatment by immunosuppressive drugs

Of the 31 patients with PH-associated ILD (PH-ILD and combined PAH/PH-ILD), 24 (77%) were treated

Table 1. First visit clinical characteristics of SSc patients with and without PH

Data	Overall	PH	No PH	p-value*
Number of patients	409	39	370	-
Female	280 (68.5%)	29 (74.4%)	251 (67.8%)	0.47
Subtype dcSSc	307 (75.1%)	28 (71.8%)	279 (75.4%)	0.69
Age (year), median	57 (20 to 87)	59 (23 to 83)	57 (20-87)	0.43
Age at onset (mean±SD)	48.47±12.11	49.82±11.47	48.34±12.18	0.47
Clinical				
mRSS ≥20	79/353 (22.38%)	6/35 (17.14%)	73/318 (22.96%)	0.53
WHO FC II-IV	131 (60.65%)	30 (76.92%)	101 (57.06%)	0.03**
Raynaud's	316 (77.3%)	29 (74.4%)	287 (77.6%)	0.69
Digital ulcer	103/402 (25.6%)	6/38 (15.8%)	97/364 (26.6%)	0.17
Telangiectasia	51/263 (19.4%)	5/22 (22.7%)	46/241 (19.1%)	0.78
GERD	141/405 (34.8%)	13/39 (33.3%)	128/366 (35%)	0.99
Cough	121/398 (30.4%)	16/37 (43.2%)	105/361 (29.1%)	0.09
Chest discomfort	11/253 (4.3%)	3/22 (13.6%)	8/231 (3.5%)	0.06
Serology				
AntiScl70	223/260 (85.8%)	17/22 (77.3%)	206/238 (86.6%)	0.22
ACA	21/115 (15.3%)	1/11 (9.1%)	20/104 (19.2%)	0.69
AntiRNP	9/119 (7.6%)	3/13 (23.1%)	6/106 (5.7%)	0.06
Pulmonary function test				
FVC <70%	184 (52.42%)	27 (79.41%)	157 (49.53%)	<0.01**
FEV1 <60%	48 (13.87%)	13 (40.63%)	35 (11.15%)	<0.01**
EKG				
QRS duration (median)	88.5 (1 to 150)	89.5 (53 to 130)	88 (1 to 150)	0.22
RBBB	32/322 (9.9%)	8/30 (26.7%)	24/292 (8.2%)	<0.01**
RVH	8/322 (2.5%)	3/30 (10%)	5/292 (1.7%)	0.03**
Echocardiography				
EF	67.66 (31.8 to 96)	68.64 (52.86 to 84.82)	67.13 (31.8 to 96)	0.55
TRVmax	2.46 (0.78 to 33.87)	2.93 (2.14 to 5.38)	2.42 (0.78 to 33.87)	<0.01**
RVSP	32.85 (12.43 to 125.78)	44.11 (28 to 125.78)	32.09 (12.43 to 91)	<0.01**
D-shape left ventricle	6/387 (1.6%)	4/37 (10.8%)	2/350 (0.6%)	<0.01**
Pericardial effusion	40/388 (10.3%)	9/38 (23.7%)	31/350 (8.9%)	<0.01**
HRCT chest				
Pulmonary involvement >20%	64 (18.71%)	21 (55.26%)	43 (14.14%)	<0.01**

* The p-value, compare between patients with PH and without PH; ** statistically significant
dcSSc = diffuse cutaneous systemic sclerosis; SD = standard deviation; mRSS = modified Rodnan skin score; FC = Functional class; GERD = Gastroesophageal reflux; Anti Scl-70 = Anti-topoisomerase I; ACA = Anti centromere antibody; Anti RNP = Anti-RNP antibody; FVC = Forced vital capacity; FEV1 = Forced Expiratory Volume in the first second; RBBB = Right bundle branch block; RVH = right ventricular hypertrophy; EF = Ejection fraction; TRV = tricuspid regurgitant velocity; RVSP = Right ventricular systolic pressure

with immunosuppressive drugs (either cyclophosphamide or mycophenolate mofetil) for active alveolitis. Time to worsening FC seemed to be worse in patients who received immunosuppressive agents albeit not statistically significant (p=0.13) (Figure 4).

At the PH diagnosis visit, there was no difference in mean FVC in either group; 52.5 (±9.85) vs. 51.4 (±9.84) in patients with and without immunosuppressive drugs (p=0.53).

Discussion

Currently, pulmonary hypertension is one of the

Table 2. Factors associated with PH

Patient variable	Univariable analysis		Multivariate analysis	
	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Clinical				
Functional class II-IV	2.51 (1.12, 5.59)	0.03*	2.92 (0.27 to 31.20)	0.38
mRSS ≥20	0.69 (0.27, 1.74)	0.44		
Raynaud's phenomenon	0.84 (0.39, 1.79)	0.65		
Digital ulcer	0.52 (0.21, 1.27)	0.15		
Telangiectasia	1.25 (0.44, 3.55)	0.68		
Gastroesophageal reflux	0.93 (0.46, 1.87)	0.84		
Chest discomfort	4.40 (1.08, 17.98)	0.04*	3.86 (0.35 to 42.06)	0.27
Serology				
AntiRNP****	5.00 (1.08, 23.11)	0.04*	NA	
Pulmonary function test				
FVC <70%**	3.93 (1.66, 9.29)	<0.01*	NA	
FEV1 <60%**	5.45 (2.48, 11.99)	<0.01*	NA	
EKG				
QRS duration	1.01 (0.99, 1.04)	0.28		
RBBB	4.06 (1.63, 10.10)	<0.01*	NA	
RVH	6.38 (1.44, 28.15)	0.01*	NA	
Echocardiography				
EF	1.01 (0.97, 1.05)	0.54		
TRVmax ≥2.9	9.79 (4.24, 22.65)	<0.01*	10.04 (2.55 to 39.51)	<0.01*
RVSP ≥36***	5.6 (2.51, 12.52)	<0.01*	NA	
Diastolic dysfunction	0.89 (0.43, 1.83)	0.75		
LV D shape***	21.09 (3.72, 119.5)	<0.01*	NA	
Pericardial effusion	3.19 (1.39, 7.35)	0.01*	3.33 (0.71 to 15.66)	0.13
HRCT chest				
% Extension >20%	7.50 (3.66, 15.35)	<0.01*	9.74 (2.19 to 43.21)	0.003*

* Statistically significant, ** Not available due to collinearity with HRCT involvement >20%, *** Not available due to collinearity with TRVmax ≥2.9, **** Not available due to small number of patient's records,
NA = not available; mRSS = modified Rodnan skin score; FVC = Forced vital capacity; FEV1 = Forced Expiratory Volume in the first second; RBBB = Right bundle branch block; RVH = right ventricular hypertrophy; EF = Ejection fraction; TRV = tricuspid regurgitant velocity; RVSP = Right ventricular systolic pressure; LV D shape = Left ventricular D shape, % Extension = percentage of pulmonary involvement by HRCT

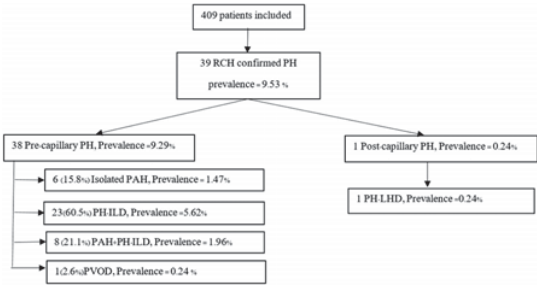
leading causes of death in SSc. Screening protocols for early detection and initiation of PAH-specific drugs are recommended for improving the survival of PAH-SSc[3]. The response to PAH-specific drugs in PAH-SSc was, however, not as good as IPAH; particularly in PAH-SSc with ILD[28,29]. Herein it was interesting to define the real prevalence of RHC confirmed PH in Thai SSc of which majority were dcSSc subtype, high prevalence of ILD, and anti-topoisomerase-I antibody. The subtypes of PH-SSc and their correlation with clinical presentation and treatment response to PAH-specific drugs and immunosuppressive agents were also studied, which may lead to different approaches in diagnostics and treatment of PH-SSc rather than simply adopting them from the IPAH treatment guideline.

Our study included all SSc patients in the Khon Kaen University Scleroderma Cohort Study between 2014 to 2016 which actively followed-up patients. The prevalence of RHC-confirmed PH of 9.53%, which midway between the Australian cohort and the European meta-analysis[24,34].

Considering previous reports of PH in Thai SSc which used echocardiography as a tool for PH diagnosis with a variation of both patients' characteristic (symptomatic

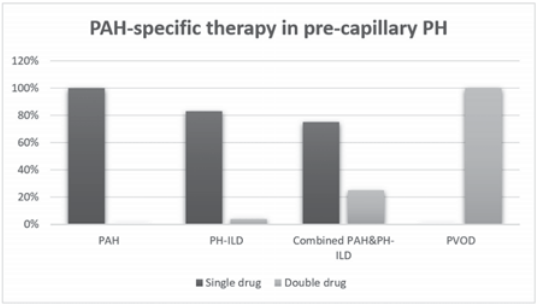
or asymptomatic) and cutoff point of RVSP (36 or 50 mmHg), the prevalence of PH-SSc was inevitably varied ranging between 2.4 to 59.1%[11-15]. It seems that PH diagnosis by echocardiography which was more convenient and non-invasive may yield either underestimate or overestimate results. Thus, performing echocardiography was suitable for identifying SSc patients at risk of PH although subsequent confirmation by RHC is needed for a definite diagnosis of PH.

Subtypes of PH may influence the outcome of treatment with PAH-specific drugs. Among our SSc patients, the majority (97.4%) had pre-capillary PH. Interestingly, only 16% of PH-SSc had isolated PAH and 21% had combined PAH and PH-ILD. Surprisingly, 61% of our PH-SSc patients were categorized as PH-ILD as per the proposed operating definitions. Only 2% of our studied patients had PVOD. Our report contrasts with the studies from Europe and



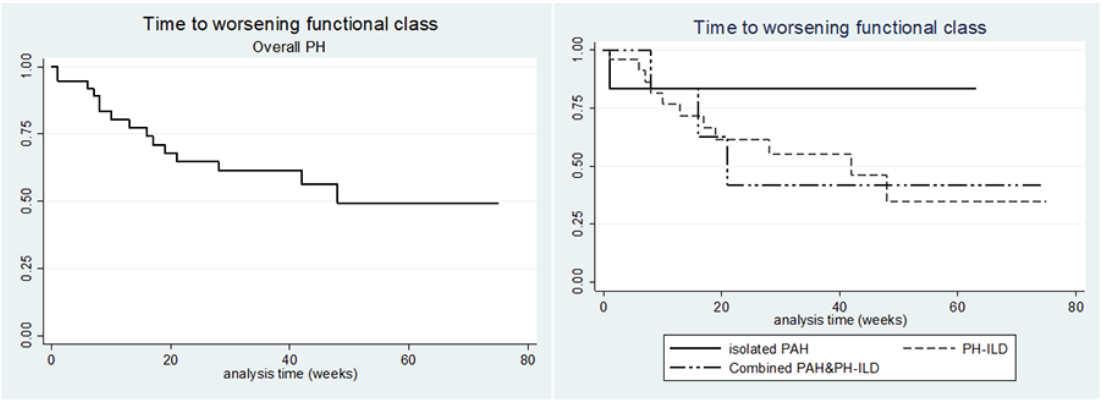
PAH = Pulmonary arterial pressure; PH-ILD = Pulmonary hypertension due to interstitial lung disease; Combined PAH & PH-ILD = Combined Pulmonary arterial hypertension with pulmonary hypertension due to interstitial lung disease; PH-LHD = Pulmonary due to left heart disease; PVOD = Pulmonary veno-occlusive disease

Figure 1. Prevalence of PH and PH subtypes.



PAH = Pulmonary arterial pressure; PH-ILD = Pulmonary hypertension due to interstitial lung disease; Combined PAH & PH-ILD = Combined Pulmonary arterial hypertension with pulmonary hypertension due to interstitial lung disease; PH-LHD = Pulmonary due to left heart disease; PVOD = Pulmonary veno-occlusive disease

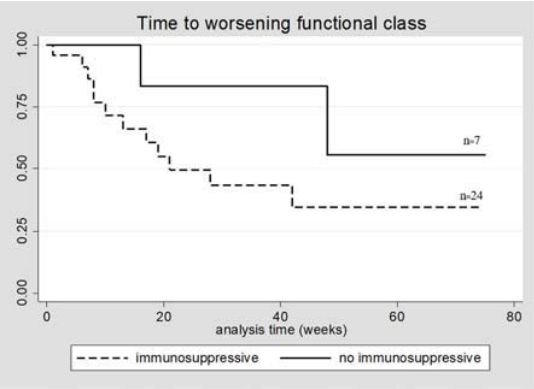
Figure 2. Treatment of pre-capillary Pulmonary hypertension by PAH-specific therapy.



* Median time to worsening FC was 48 weeks in overall PH.
** Median time to worsening FC was 48 and 42 weeks in PH-ILD and combined PAH&PH-ILD subtype, respectively.

PAH = Pulmonary arterial pressure; PH-ILD = Pulmonary hypertension due to interstitial lung disease; Combined PAH&-PH-ILD = Combined Pulmonary arterial hypertension with pulmonary hypertension due to interstitial lung disease; PH-LHD = Pulmonary due to left heart disease; PVOD = Pulmonary veno-occlusive disease

Figure 3. Survival curve of time to worsening FC (weeks) in all PH-SSc and subtypes of PH-SSc.



The median time of worsening of FC in PH-associated ILD with immunosuppressive therapy was 21 weeks

Figure 4. Survival curve of time to worsening FC (weeks) in Pulmonary hypertension due to interstitial lung disease (PH-ILD) and combined pulmonary artery hypertension with pulmonary hypertension due to interstitial lung disease (PAH&PH-ILD) subtypes with and without immunosuppressive agent.

Australia which reported 60 to 80% of pre-capillary PH was isolated PAH, and 26 to 38% PH-ILD. This observation was probably due to the predominant dcSSc subtype, the high prevalence of ILD, and the anti-topoisomerase I antibody in Thai SSc. We also found that our SSc patients were younger at PH diagnosis and experienced a shorter duration of disease to develop to PH than reported in the other studies.

FC II-IV and low FVC were the factors associated with PH as was also reported by Morrisroe, et al, Phung, et al, and Auovac, et al. We found no difference in the cutaneous subtype, clinical characteristics, and the PH and no PH group. ACA antibody was noted only in 1 case of PAH. Even though ACA has been associated with occurring of PH in several reports[35-37], it cannot be concluded that ACA is a good predictor of PH in Thai SSc patients because the prevalence of ACA in the Thai population is quite low (<2%)[38].

Determination subtypes of PH-SSc are necessary for the planning of treatment and predicting response to treatment with PAH-specific drugs. Our study demonstrated that the response to PAH-specific drugs is better in the isolated PAH subtype, but poorer if with the PH-ILD component. This was correlated with the study using PAH-specific therapies in PH-ILD with no significant improvements in functional class, exercise capacity, or hemodynamics[39].

We were interested to identify that in the case with the PH-ILD component, whether treatment with immunosuppressive agents for active alveolitis could affect the treatment outcome. The result from the analysis was disappointing, as there was no significant difference in FC whether the patients received an immunosuppressive agent or not. Moreover, SSc patients who received immunosuppressive agents demonstrated a rapid decline in FC during the first year of treatment; however, after 1 year the FC was not significantly different between the two groups. The patient who had ILD without immunosuppressive treatment also experienced a slow decline in FC.

It seems that ILD in SSc is a progressive disease with a different rate of progression even without evidence of active alveolitis[40]. There is currently an ongoing study on anti-fibrotic drugs for ILD in SSc[41-43]. The new treatment strategy may be proposed in the treatment of PH-SSc with a PH-ILD component.

The limitations of our study were that: (a) it was retrospective (b) it had a small number of SSc-PH and PH subtypes so the conclusions cannot be generalized and (c) it did not study some factors that might be a cause of pulmonary hypertension, for example, obstructive sleep apnea, thalassemia. The strengths were that: (a) this was a single-center study that could enroll a large number of SSc patients (b) diagnosis of PH was confirmed using the RHC gold standard, and (c) the PH subtypes classified using our criteria correlated well with response to the treatment with PAH-specific drugs and had a different survival curve for time to worsening FC.

In summary, our preliminary data indicate the prevalence of RHC-confirmed -PH-SSc, the PH-SSc subtypes, factors associated with PH-SSc, and the response to treatment with PAH-specific drugs among the different subtypes that may influence the treatment strategy of PH-SSc in the future

Conclusion

The prevalence of PH in our study was 9.53%. We classified subtype of PH in SSc as pre-capillary PH (PAH, PH due to ILD, PAH combined PH due to ILD) and post-capillary PH (secondary to left heart disease) according to pathogenesis and WHO classification. And classified subtype of pulmonary hypertension by RHC, PFT, HRCT in SSc predicted the prognosis and clinical outcome after treatment by PAH-specific drug.

What is already known on this topic?

PH is a serious complication in SSc patients. Several mechanisms are predisposing the patients to acquire this condition which will determine the subtype of PH.

What this study adds?

We had identified the prevalence of RHC-confirmed -PH-SSc, the PH-SSc subtypes, factors associated with PH-SSc, and the response to treatment with PAH-specific drugs among the different subtypes.

Authors contributions

Retrospective cohort study: all authors; Manuscript preparation: all authors.

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Potential conflicts of interest

The authors declare no conflict of interest.

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