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REVIEW ARTICLE

Pulmonary hypertension in connective tissue diseases: epidemiology, pathogenesis, and treatment

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Abstract

Pulmonary hypertension (PH) is a clinical condition characterized by increased pulmonary arterial pressure arising from a heterogeneous range of diseases that has a deteriorating effect on the quality of life and may cause early mortality if left untreated. Connective tissue disorders (CTD)-associated PH is the second most common cause of pulmonary arterial hypertension (PAH), after the idiopathic form, categorized as group I. Systemic scleroderma (SSc) accounts for 75% of CTD-associated PH cases. Although SSc ranks first place for CTD-associated PH, SSc is followed by systemic lupus erythematosus (SLE) and mixed connective tissue disease (MCTD), having a lesser frequency of PH occurrence, while it occurs as a rare complication in cases with rheumatoid arthritis (RA) and inflammatory myositis. PH may also occur during non-SSc CTDs and even other rheumatic diseases, including Behcet's disease and adult-onset Still's disease, albeit to a lesser extent. The prognosis of CTD-associated PH is worse than the other forms of PH. Although, as in idiopathic pulmonary arterial hypertension (IPAH), the mechanism of CTD-related PH is associated with an increase in vasoconstrictors like endothelin-1 and a decrease in vasodilators like prostacyclin and nitric oxide production, inflammation, and autoimmune mechanisms also play a role in the development and progression of PH. This may lead to the involvement of more than one mechanism in CTD-associated PH. Knowing which mechanism is dominant is very important in determining the treatment option. This review will primarily focus on the epidemiology, risk factors, and prognosis of PH that develops during rheumatic diseases; the pathogenesis and treatment will be briefly mentioned in light of the newly published guidelines.

Key Points

- *Pulmonary arterial hypertension (PAH) associated with connective tissue disease (CTD) in Western countries is the second most common type of PAH after idiopathic PAH (IPAH).*
- *CTD-PH can be seen most often in systemic scleroderma (SSc), less in systemic lupus erythematosus (SLE), mixed CTD (MCTD), and rarely in other CTDs.*
- *While current guidelines recommend annual transthoracic echocardiography as a screening test for asymptomatic SSc patients, screening for PH is not advised in the absence of symptoms suggestive of PH in other CTDs.*
- *CTD-PH treatment can be divided into specific vasodilator PH treatments and immunosuppressive therapy. Current treatment guidelines recommend the same treatment algorithm for patients with CTD-associated PH as for patients with IPAH. Several case series have shown the beneficial effect of immunosuppressive agents in patients with SLE-PH and MCTD-PH.*

Keywords Connective tissue disease · Pulmonary hypertension · Rheumatic disease · Rheumatology

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Introduction

Systemic autoimmune diseases are inflammatory disorders characterized by multi-organ involvement, including heart and lung. In rheumatic diseases, all cardiac structures (valves, transmission system, myocardium, endocardium, pericardium, and coronary arteries) as well as the pulmonary artery might be involved. Pulmonary hypertension (PH) is

characterized by elevated pulmonary arterial pressure, and—as in other cardiovascular diseases—it not only impairs the quality of life but also causes remarkable morbidity and mortality [1].

Description of and classification of pulmonary hypertension

Previously, PH used to be described as the state of mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at rest, measured by right heart catheterization (RHC). It has been argued that decreasing the threshold to 21 mmHg may enable earlier recognition of the patients, which is a major step towards efficient treatment. During the 6th World Symposium on Pulmonary Hypertension (WSPH) in 2018, the Task Force proposes to include pulmonary vascular resistance (PVR) ≥ 3 wood units in the definition of all forms of precapillary PH associated with mPAP > 20 mmHg. [2, 3]. According to the hemodynamic definition revised in 2022, PH can be diagnosed in patients with mPAP > 20 mmHg and PVR > 2 WU. This guideline specifically emphasized that the efficacy of drugs approved for PH has been demonstrated only in patients with mPAP ⩾ 25 mmHg and PVR > 3 WU [4].

The initial classification of PH was published after the first WSPH in 1973. PH is classified based on clinical, hemodynamic, and pathophysiological characteristics. The PH clinical classification is divided into five groups. The 6th WSPH Task Force proposed to simplify the core of the clinical classification of PH. In October 2022, the European Society of Cardiology (ESC)/European Respiratory Society (ERS) published new guidelines for the diagnosis and treatment of PH. The clinical classification has been revised in this guideline; a new algorithm for diagnosis has been proposed; and many areas, such as risk classification, have been revised. The term pulmonary arterial hypertension (PAH) describes the diseases of WHO group 1. Group 2 is PH associated with left heart disease, group 3 is PH associated with lung diseases and/or hypoxia, group 4 is PH associated with pulmonary artery obstructions, and group 5 is PH with unclear and/or multifactorial mechanisms [3, 4].

CTD-PH is the second most common cause of PAH, after the idiopathic form, categorized as group I. Apart from PAH, different types of PH can also be detected in CTDs. Due to the high prevalence of interstitial lung disease (ILD), PH due to this condition (group 3) is quite common, especially in SSc. In some cases, the etiology of PH may also be multifactorial. Nevertheless, the most common type of PH in CTD patients is PAH (group 1) [3]. In addition to clinical classification, PH is also classified by hemodynamics. The hemodynamic classes depending on the pulmonary pressures are isolated precapillary,

Table 1 Hemodynamic definitions of pulmonary hypertension and rheumatic disease examples [2–4, 11, 23]

Definition	Characteristics	Clinical groups (according to WHO)	Examples of rheumatic diseases
Normal hemodynamics	Mean PAP = 14 ± 3.3 mmHg PCWP = 8 ± 2.9 mmHg PVR = 0.93 ± 0.38 WU	-	-
PH	Mean PAP > 20 mmHg		
Precapillary PH	Mean PAP > 20 mmHg PCWP ≤ 15 mmHg PVR > 2 WU	Group 1. Pulmonary arterial hypertension (PAH) Group 3. PH due to lung diseases and/or hypoxia Group 4. PH due to pulmonary artery obstructions Group 5. PH with unclear and/or multifactorial mechanisms	SSc, SLE, MCTD, DM/PM, pSS
Isolated postcapillary PH	Mean PAP > 20 mmHg PCWP > 15 mmHg PVR ⩽ 2 WU	Group 2. PH due to left heart disease Group 5. PH with unclear and/or multifactorial mechanisms	SSc, SLE, MCTD, DM/PM, pSS, Behçet's disease, antiphospholipid syndrome
Combined postcapillary and precapillary PH	Mean PAP > 20 mmHg PCWP > 15 mmHg PVR > 2 WU	Group 2. PH due to left heart disease Group 5. PH with unclear and/or multifactorial mechanisms	RA, SSc
Exercise PH	MeanPAP/CO slope between rest and exercise > 3 mmHg/L/min		

CO, cardiac output; *DM/PM*, dermatomyositis/polymyositis; *MCTD*, mixed connective tissue disease; *PAP*, pulmonary artery pressure; *PCWP*, pulmonary capillary wedge pressure; *PH*, pulmonary hypertension; *pSS*, primary Sjogren's syndrome; *PVR*, pulmonary vascular resistance; *WU*, wood unit; *SLE*, systemic lupus erythematosus; *SSc*, systemic scleroderma; *RA*, rheumatoid arthritis

isolated postcapillary, and combined PH. Hemodynamic classification of PH is given in Table 1 [2].

Search strategy

A comprehensive literature search was performed on the PubMed/MEDLINE and Scopus databases [5]. To this end, we screened these databases using the keywords pulmonary hypertension OR pulmonary arterial hypertension AND rheumatic diseases OR rheumatology OR connective tissue diseases OR systemic scleroderma OR systemic lupus erythematosus OR mixed connective tissue disease OR Sjögren's syndrome OR idiopathic inflammatory myopathy OR Behcet's disease without any restriction as for the start date and captured the results by June 2022. Particularly, we have evaluated the country registries, reviews, and original studies. Case reports and articles in languages other than English were excluded. First of all, general data related to PH and CTD-associated PH and epidemiological data about CTD-associated PH were analyzed. Next, for each rheumatic disease, we analyzed the contribution of the disease to CTD-PH, the prevalence of PH, and predictive factors for and prognosis of PH by subtypes of rheumatic diseases. The pathogenesis, diagnosis and treatment were also briefly evaluated.

Epidemiology of pulmonary hypertension in connective tissue diseases

REVEAL is a multicenter (55 centers) observational PH registry study designed to characterize US PH patient population. The study has evaluated 2525 eligible patients as per the criteria who had been diagnosed with PH upon RHC. The patients were at an average age of 53.0 ± 14.0 years, and 80.3% of them were female. According to the etiological classification, 50.6% of the cases were PAH associated with other conditions (APAH), and 46.2% were IPAH. APAH patients were further classified into collagen vascular disease/connective tissue disease (CVD/CTD) subset, at a proportion of 49.9% [6].

UK PH registry has evaluated 484 CTD-PH patients. In their records, the most common cause is SSc-PH at a rate of 74%, followed by SLE, MCTD, and dermatomyositis/polymyositis (DM/PM) [7]. Chinese and Korean data, on the other hand, reveals that SLE-PH was more frequent than SSc-PH [8, 9]. CTD-PH characteristics by various PH registry data are given in Table 2.

In conclusion, in European countries, the most common type of PH is IPAH, followed by CTD-associated PH. Among the CTDs associated with PH, SSc ranks first place, followed by MCTD, SLE, and other connective tissue diseases, though infrequently. SSc, particularly in

Table 2 Country registry data for connective tissue disease associated pulmonary hypertension

Registry	REVEAL/USA [6]	UK [7]	French [10]	China [8]	Korea [9]
Total number of patients, *n*	2525	-	674	-	-
Number of patients with CTD-PH, *n*	641	484	103	190	321
Gender of patients with CTD-PH, female, %	90.2%	-	79.6%	95.8%	87.5%
Mean age of patients with CTD-PH, age ± SD, and years	57.1 ± 13.7	-	56 ± 15	37.8 ± 10.4	51.9 ± 15.3
Frequency of rheumatic diseases	APAH 50.7% APAH subgroup-CVD/CTD 49.9%	SSc: 74% MCTD: 8% SLE: 8% DM/PM: 4% RA: 3% UCTD: 2% pSS: 1%	SSc: 68% Others: 32%	SLE: 58.4% SSc: 26.3% pSS: 15.3%	SLE: 35.3% SSc: 28.3% RA: 7.8% Overlap: 9% MCTD: 5.9% Myositis: 4.4% pSS: 1.6%
Functional capacities					
I	2.4%	-	NA for CTD	-	40.5%
II	24.1%	-	NA for CTD	-	28%
III	62%	-	NA for CTD	-	26.5%
IV	11.5%	-	NA for CTD	-	5%
III or IV	73.5%	-	73.8%	52.6%	31.8%

APAH, associated pulmonary arterial hypertension; *CTD*, connective tissue disease; DM/PM, dermatomyositis/polymyositis; *IPAH*, idiopathic pulmonary arterial hypertension; *MCTD*, mixed connective tissue disease; *pSS*, primary Sjogren's syndrome; *RA*, rheumatoid arthritis; *SD*, standard deviation; *SLE*, systemic lupus erythematosus; *SSc*, systemic scleroderma; *UCTD*, undifferentiated connective tissue disease

limited form, is the most common cause of CTD-associated PH in Europe and the USA. Across Asia, on the other hand, SLE-associated PH is more common [2, 7, 8].

Recent studies have contributed to the evaluation and management of CTD-associated PH (CTD-PH). The studies on CTD-PH have enabled an updated and advanced understanding of this field. The risk of PH development in CTD patients varies by the type of underlying rheumatic disease. Moreover, any type of CTD-associated PH is prone to a worse prognosis than any other cause of PH. SSc is a leading cause of CTD-PH. SSc is followed by SLE, MCTD, idiopathic inflammatory myositis, RA, and primary Sjögren's syndrome (pSS). Despite all advancements, PH remains to be a major cause of mortality and morbidity encountered along with CTDs, essentially with SSc. While the data about the prevalence of rheumatic diseases could be extracted out of the CTD-PH-related data—basically from the relevant registries—there is no adequate information regarding the prevalence and incidence of PH in patients with rheumatic diseases [6, 7, 10].

Due to the main purpose of our article, we will explain the epidemiology, predictive factors, and prognosis of PH separately by type of rheumatic diseases primarily. For completeness, the pathogenesis of CTD-associated PH, diagnostic and screening methods, and treatment are briefly mentioned.

Pathogenesis of pulmonary hypertension in connective tissue diseases

The pathophysiology of PH is not fully understood. Like IPAH, endothelial dysfunction plays a key role in the pathogenesis of CTD-PH. Impaired production of vasoactive mediators, increased production of vasoconstrictors, and proliferative mediators affect vascular tone, and PH develops as a result of progressive remodeling of the small to the medium pulmonary vasculature. Although the exact mechanisms of this remodeling remain unclear, many factors are thought to play a role [11]. The main pathways responsible for the pathogenesis of CTD-PH are endothelin 1, nitric oxide, and prostacyclin pathways. In addition, it has been suggested that, unlike the idiopathic form, inflammation and autoimmunity may contribute to the initiation and progression of CTD-PH. Infiltrating macrophages and lymphocytes, antinuclear antibodies, rheumatoid factor, and complement were detected in the pulmonary vessels of patients with CTD-PH [12]. Many factors such as vasculitis, thrombosis, and interstitial pulmonary fibrosis are also responsible for the pathogenesis of PH, especially in patients with SLE [13].

Diagnostic methods and screening in connective tissue diseases associated pulmonary hypertension

Screening for PH in patients with CTD, especially SSc, is very important for early diagnosis and treatment. Current screening recommendations for PH in CTDs focus on SSc, as SSc-PH is the most common CTD-PH. The gold standard for diagnosing PH is RHC. With screening tests, it is determined who should undergo RHC. Current screening guidelines for PH in asymptomatic patients with SSc include annual transthoracic echocardiography and pulmonary function tests (PFTs), including diffusing capacity for carbon monoxide (DLCO), N-terminal pro-brain natriuretic peptide (NT-pro-BNP), and/or containing these components are in the form of composite algorithms [14–16, 17]. There are several proposed algorithms for PH screening. The ESC/ERS guidelines, in particular the evidence-based detection of PAH in systemic sclerosis (DETECT) algorithm, and the Australian Scleroderma Interest Group (ASIG) make recommendations for PH screening in SSc, including various combinations of transthoracic echocardiography, PFTs, and biomarkers [2, 4, 18, 19]. DETECT involves the use of transthoracic echocardiography and PFTs to screen for PH in SSc and performs well as a screening tool. There are two steps in this algorithm. In the first step, by combining clinical, physiological, and laboratory data, it is decided who should undergo echocardiography, and in the second step, who should undergo RHC according to the echocardiographic findings [18]. 2022 ESC/ERS guidelines recommend annual echocardiography as a screening test for asymptomatic SSc patients to classify patients into a risk category. The new ESC/ERS guidelines also recommended the use of the DETECT algorithm to determine PH in asymptomatic adult SSc patients with SSc disease duration > 3 years, FVC $\geqslant$ 40%, and DLCO < 60%. The guideline does not recommend screening for PH in the absence of symptoms suggestive of PH in other CTDs but recommends echocardiography in the presence of symptoms. As with other forms of PH, the RHC has been recommended, in all suspected cases of CTD-PH, to confirm the diagnosis, determine its severity, and rule out left heart disease [4]. ASIG, on the other hand, recommends using NT-proBNP and PFTs for scanning in its algorithm. An increased NT-proBNP and/or increased FVC/DLCO ratio is an indication of RHC [19]. All these strategies have well-defined thresholds for when to refer patients to an RHC. The sensitivities, specificities, and positive and negative predictive values of these three scanning algorithms are similar [2, 15, 18, 19].

Few studies have evaluated the prevalence of PH in non-SSc CTDs, and most of these studies in non-SSc CTDs use transthoracic echocardiography instead of the

RHC's gold standard to diagnose PH. However, there are no established recommendations or guidelines for screening for PH in these diseases [2, 14].

Systemic scleroderma and pulmonary hypertension

The best-known CTD-associated PH is SSc-associated PH (SSc-PH). SSc is a rare disease characterized by vascular abnormalities leading to progressive, diffuse fibrosis in the skin and the internal organs. In the general population, the prevalence of SSc ranges between 80 to 240 per million [20, 21].

Although the incidence and prevalence of SSc are lower than that of other CTDs, such as RA or SLE, PH occurs more frequently in SSc compared to other CTDs. Varying figures of PH prevalence have been reported among the SSc patients based on the study and used diagnostic methods. Prospective studies employing RHC revealed PH prevalence in SSc patients was around 7.8–12% [22]. In the DETECT study conducted in high-risk SSc patients using the RHC method, PH prevalence in SSc was 19% [18]. PH is expected in 15% of limited SSc patients and in 7% of diffuse SSc patients, respectively [23].

Various studies have explored the predictive factors for PH development in SSc patients. Accordingly, disease duration longer than 5 years, low DLCO, presence of anti-U3 RNP antibody, presence of anticentromere antibodies, late-onset age, digital ulcers, multiple telangiectasias, and reduced density of nailbed capillaries have been identified as predictive factors for PH development in SSc [12, 24].

Despite the recent advancement in PH treatment, the prognosis of SSc-PH remains poor. PH is one of the leading causes of mortality in SSc patients. Several studies and registries have reported different figures for survival in SSc-associated PH. REVEAL has the largest US cohort comprising RHC-verified PH patients. One-year survival of CTD-associated PH patients as of the date of enrollment, according to the data from REVEAL registries has been analyzed. Compared to the other CTD-associated PH variants, SSc-associated PH patients were attributed with the worst survival rate, which is 82% [6]. UK national registry has investigated 259 cases where 1-year and 3-year survivals were 78 and 47%, respectively [7]. Across 85 patients recorded in the French registry, 1-year and 3-year survival rates are 90 and 56% [25]. In a Chinese study that encompasses CTD-associated PH patients, predominantly composed of SLE-associated PH, 1-, 3, and 5-year survival rates of SSc-PH patients were 72.5%, 63.3%, and 43.9% [8]. In a review, 1, 3-, and 5-year survival rates were 97%, 83%, and 76% [26].

SSc patients may also develop PH associated with interstitial lung disease. In the case of SSc-PH, due to lung involvement following PH-targeted therapy, improvement in WHO functional class was less frequent, and the survival is even worse than that of SSc-PH [27].

Consequently, PH is blamed for 30% of SSc-related mortalities, and thus PH remains to be a leading cause of mortality in SSc patients. The prognosis of SSc-PH is worse than that of IPAH owing to a range of factors, including multisystem involvement of SSc [28].

Systemic lupus erythematosus and pulmonary hypertension

SLE is a systemic disease with a potential effect on the lungs, which may lead to various PH types, including PH associated with interstitial lung disease, PH, and chronic thromboembolic pulmonary hypertension (CTEPH). In the US and European cohort studies, SSc was the most common CTD to cause PH, while cohort studies conducted in Korea and China determined SLE was the most common cause of CTD-PH [6–9, 10]. In the REVEAL study, out of 617 CTD-PH patients, 64.5% had SSc and 2.4% had SLE [6]. Similarly, in UK PH registries covering 429 CTD-PH patients, 8% were found to have SLE [7]. In a large Chinese patient cohort, a total of 190 cases associated with three major CTDs were evaluated. The most common underlying CTD was SLE, at a rate of 58.4%. In this study, the diagnosis of PH was made by RHC. The authors stated that the center where the study was conducted was the referral center. More than half of the patients in this study were referred by other hospitals or cardiologists and were never screened for PH [8]. Among the Korean cohort, SLE was the most common disease to underpin CTD-PH. SLE was followed by SSc, overlap, RA, and MCTD [9]. As a result, the differences in these studies conducted in Asia may be mainly due to the methods used for screening and diagnosis (transthoracic echocardiography and RHC), methodological differences, and ethnical differences.

The results on PH prevalence in SLE are controversial. Substantial differences in PH prevalence in SLE are noted in the cohort studies. As for diagnostic methods, some studies have employed echocardiography, while others used RHC. As a result, older studies had a higher rate of PH prevalence in SLE compared to the estimated prevalence of 0.5 to 17.5% in later studies [13, 29]. In a prospective study that examined 288 SLE patients using echocardiography, PH prevalence was 4.2% [30].

Younger patient age, presence of Raynaud's phenomenon, presence of anti-smooth muscle or anticardiolipin antibodies, and positive history of pericarditis were described as predictive factors of PH in SLE [24].

Expectedly, in SLE patients, the outcomes are worse in those with PH compared to those without PH. Likewise, cohort studies report varying survival rates in SLE patients. European and North American cohorts detected a lower number of deaths from SLE-PH in comparison to Asian cohorts. Results from the UK registry documented a better 3-year survival for SLE-PH (75%), compared to SSc-PH (47%) [7]. In the Chinese cohort, 1-year, 3-year, and 5-year survival rates for SLE-PH were 94.1, 81.3%, and 61.0%, respectively [8].

Mixed connective tissue disease and pulmonary hypertension

Patients with MCTD manifest with clinical features of several CTD, including SSc and SLE. Involvement of lungs and pulmonary vascular is common in MCTD. According to two cohort studies, MCTD prevalence in the CTD-PH group ranges from 5.9 to 8% [7, 9]. There are not numerous studies on the prevalence of PH in MCTD. In one study, out of 201 MCTD patients, 3% were found to have PH, and in a multicenter study, 2% of 147 patients were detected to have PH [31, 32]. The difference may arise from the methodological variances. PH seems to be the most common cause of death among MCTD patients. The 1-year and 3-year survival rates for MCTD-associated PH from a cohort were similar to those for SSc-PH: 89 and 63%, respectively [7]. PH screening is recommended for MCTD patients with SSc characteristics [33].

Rheumatoid arthritis and pulmonary hypertension

RA is another connective tissue disease that involves chronic inflammatory arthritis along with extra-articular organ manifestations such as heart and lungs. PH is a rare complication of RA. According to the UK registry, RA-PH accounts for 3% of CTD-PH records, and RA-PH patients were found to have 1-year and 3-year survival rates of 83 and 66%, respectively [7]. The Korean registry demonstrated differences from European and US cohorts, where 7.8% of 321 CTD-PH patients were RA patients [9]. In another study comparing 18 RA-PH patients with 155 IPAH patients, RA-PH patients had an older age of onset and a lower baseline mPAP measurement. Moreover, survival rates of RA-PH and IPAH patients were comparable [34].

Inflammatory myopathies and pulmonary hypertension

Idiopathic inflammatory myopathies (IIMs) are a group of chronic, autoimmune diseases affecting the proximal muscles. The most common types are DM and PM. Extra-muscular organ involvements such as joints, heart, and lungs may occur. IIMs are relatively infrequent among CTD-PH patients. Based on the UK registry, DM/PM was ranked as 4th most frequent, with a proportion of 4% [7]. Similarly, in the Korea CTD-PH cohort, 4.4% have myositis [9].

PH in the setting of IIMs may arise through various mechanisms. In a study assessing nine IIMs-PH patients, one patient was placed in PH group 2 (left heart disease), five patients in group 3 (lung disease), and three patients in group 1 (PAH) [35]. Development of PH in IIMs in the absence of diffuse interstitial lung disease has been rarely described. In the French PH registry, 34 out of 5223 PH patients had been diagnosed with IIMs, and three IIM patients were detected to have isolated PH (without interstitial lung disease or overlap). In these three patients, only DM was described, and all have developed PH after the onset of myositis. The study, likewise, highlights that IIMs-associated PH is a rare event. In the same study, predictive factors for PH were listed as DM, skin involvement, peripheral microangiopathy, and the presence of anti-SSA antibodies [36].

In terms of survival, 1-year and 3-year survival rates for PM/DM from UK registry data are both 100% [7]. In summary, IIMs are a rare cause of CTD-PH, and PH is an infrequent but still potential complication of IIMs.

Primary Sjögren's syndrome and pulmonary hypertension

pSS is a systemic autoimmune disease that may involve the entire body, including the lungs and extra-glandular organs. The prevalence of PH in pSS or the rank/proportion of pSS within the PH etiology is not well established. In the CTD-PH cohort, pSS holds a relatively smaller portion. There are a few case reports and case series to describe the clinical characteristics and prognosis of pSS-PH patients. A first-of-its-kind study that reported the survival rates of pSS-PH has evaluated 190 CTD-PH patients in a large Chinese PH cohort. A total of 29 all-female pSS-PH patients were at an average age of 40.6 ± 9 years with a CTD duration of 79.1 ± 87.4 months and a time to onset of the PH of 24.7 ± 31.9 months. In their study, the pSS proportion was 15.3%, ranking third place after SLE and SSc in the CTD-PH group. 1-, 3-, and 5-year survival rates for pSS-PH were listed as 78.5%, 72.9%, and 64.8%, respectively. Hence, survival rates of pSS-PH patients lie in between those of SLE-PH and SSc-PH patients [8]. In a Korean study, the share of pSS-PH among CTD-PH patients was 1.6% [9]. In a countrywide, retrospective French study based on the database of national health insurance, 25,666 pSS

patients were included, of whom 0.49% were found to have PH [37].

In another retrospective study to evaluate pSS among IPAH patients, 20% were detected with pSS out of 25 patients [38]. In conclusion, pSS is among the causes of CTD-PH, an increased awareness and meticulous review of pSS, particularly in patients diagnosed with IPAH, may help more patients be diagnosed, and thus an increased proportion of pSS-PH patients.

Other rheumatic diseases and pulmonary hypertension

Behçet's disease and pulmonary hypertension

Although it is not included among the conventional rheumatic diseases that cause PH, a study on cardiac findings detected higher rates of tricuspid regurgitation as well as PH in patients with Behcet's disease compared to the control group. The study paper does not provide details on PH outcomes [39]. PH due to chronic thromboembolism may also develop in Behcet's disease, albeit rarely [40]. Parallel to this data, Yıldızeli et al. reported 9 patients with Behcet's disease who developed chronic thromboembolic pulmonary hypertension. They suggested that pulmonary endarterectomy may be a treatment option in patients who do not respond to anticoagulation and immunosuppressive therapy [41].

Adult-onset Still's disease and pulmonary hypertension

PH is not among the classical involvements or complications of adult-onset Still's disease. On the other hand, in a study

Table 3 Prevalence, predictive factors, and patient survival rates for rheumatic disease/connective tissue disease associated pulmonary hypertension [7–9, 13, 22–24, 31, 32, 42, 43]

Rheumatic diseases	Frequency among patients with CTD-PH	PH prevalence in diseases	Predictive factors for PH	Survival rates
SSc	75%	7.8–12% Limited SSc: 15% Diffuse SSc: 7%	Limited SSc Late onset age Disease duration Raynaud's phenomenon Finger ulcers Multiple telangiectasias Reduction in DLCO Presence of anti U3 RNP Anticentromere antibodies	1- and 3-year survival rates 81 and 52%, respectively, in a meta-analysis
SLE	8–58.4%	2–43% depending on echocardiography-based studies True prevalence: < %1	Female gender Raynaud's phenomenon Serositis Renal disease Anti-U1 RNP Anticardiolipin antibodies	1-, 3-, and 5-year survival rates 94.1%, 81.3%, and 61%, respectively
MCTD	5.9–8%	2–23%	Patients with SSc predominance	1- and 3-year survival rates 89 and 63%, respectively
RA	3–7.8%	Rare	-	1- and 3-year survival rates 83 and 66%, respectively
Inflammatory myopathy	4%	Rare	DM Skin involvement Peripheral microangiopathy Anti-SSA positivity	1- and 3-year survival rates 100 and 100%, respectively
pSS	1–15.3%	0.49%	-	1-, 3-, and 5-year survival rates 78.5%, 72.9%, and 64.8%, respectively
Others				
Behcet's disease	Unknown	Rare	-	-
Adult-onset Still's disease	Unknown	4.8%	Advanced stages of persistent and severe disease	-

CTD, connective tissue disease; *DM*, dermatomyositis; *DLCO*, diffusing capacity of the lung; *MCTD*, mixed connective tissue disease; *PH*, pulmonary hypertension; *pSS*, primary Sjogren's syndrome; *RA*, rheumatoid arthritis; *SLE*, systemic lupus erythematosus; *SSc*, systemic scleroderma

assessing 41 adult-onset Still's disease patients, 4.8% had PH. Both cases with PH were accepted as group 1 PAH [42].

Prevalence, predictive factors, and survival rates of PH in rheumatic diseases are given in Table 3.

Connective tissue diseases associated pulmonary hypertension treatment

In addition to targeted drug therapy, treatment of PH should include general measures such as comprehensive patient management, supplemental oxygen, diuretics, psychosocial support, and standard exercise training. Treatment decisions in patients with IPAH/HPAH/DPAH or CTD-PH should be based on the presence or absence of cardiopulmonary comorbidities and disease severity as determined by risk stratification [4].

CTD-PH treatment can be divided into specific vasodilator PH treatments and immunosuppressive therapy. Endothelin receptor antagonists, including the specific PH agents bosentan, ambrisentan, and macitentan; drugs targeting the nitric oxide pathway, including sildenafil, tadalafil, and riociguat; are classified as prostanoids, including epoprostenol, iloprost, and selexipag. The 2022 ESC/ERS diagnostic and treatment guidelines recommend the same treatment algorithm for patients with CTD-associated PH as for patients with IPAH [4]. Specific vasodilators are the mainstay in the treatment of SSc-PH. Because of the poor prognosis of SSc-PH, initiation of combination therapy of specific vasodilators in patients with SSc should be considered earlier than in other CTD-PH patients [2, 4, 12, 18]. There are no randomized clinical studies on the efficacy of immunosuppressive therapy in patients with CTD-PH. Nevertheless, several case series have shown the effect of immunosuppressive agents in patients with SLE and MCTD [44]. While immunosuppressive therapies are not recommended in SSc-PH, corticosteroids and immunosuppressive agents rapidly combined with vasodilating agents can normalize the hemodynamic profile, particularly in cases of SLE-PH and MCTD-PH diagnosed at a very early stage [11, 12]. Most CTD-PH patients included SSc patients in studies with specific agents used in the treatment of PH. Although there is little evidence base for CTD diseases other than SSc, these specific drugs are commonly used in all their forms. Nevertheless, individualization of treatment is recommended, taking into account the differences in demographic and hemodynamic characteristics between CTD-PH types [11].

Conclusion

CTD-associated PH remains to be a noticeable cause of functional impairment, morbidity, and mortality. Among all causes of PH, CTD-PH stands for a substantial proportion. While the likelihood of PH development during certain rheumatic diseases, particularly SSc, SLE, and MCTD, are well-recognized, it should be kept in mind that PH may also arise in other rheumatic diseases, including pSS, IIMs, Behcet's disease, and adult-onset Still's disease. The most common cause of CTD-associated PH in Europe and the USA is SSc, contrary to Asia, where SLE-associated PH is more common. Rheumatologists have gained experience in PH in an SSc setting that should be applied to other rheumatic diseases. The better the understanding of the PH in CTD/rheumatic diseases gets, the more information will be acquired regarding the PH during these diseases.

Author contribution DUC conceived the study; DUC collected the data; DUC and CK wrote the first draft of the manuscript; DUC and CK revised the manuscript. All authors read and approved the final version before submission.

Data availability Data is available upon a reasonable request.

Materials availability Data is available upon a reasonable request.

Code availability Not applicable.

Declarations

Consent for publication Not applicable.

Disclosures None.

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