Acta Cardiol Sin 2023;39:213–241
Consensus
doi: 10.6515/ACS.202303_39(2).20230117A

2023 Taiwan Society of Cardiology (TSOC) and Taiwan College of Rheumatology (TCR) Joint Consensus on Connective Tissue Disease-Associated Pulmonary Arterial Hypertension

Wei-Chun Huang,[1,2,3] Song-Chou Hsieh,[4]* Yen-Wen Wu,[2,5,6]* Tsu-Yi Hsieh,[7,8,9] Yih-Jer Wu,[10,11] Ko-Jen Li,[12,13] Min-Ji Charng,[2,14] Wei-Sheng Chen,[2,15] Shih-Hsien Sung,[16,17] Yen-Po Tsao,[15,18] Wan-Jing Ho,[19,20] Chien-Chih Lai,[2,15] Chin-Chang Cheng,[21] Hung-Cheng Tsai,[2,15] Chih-Hsin Hsu,[22] Cheng-Hsun Lu,[4,23] Yu-Wei Chiu,[24,25] Chieh-Yu Shen,[4,13,23] Chun-Hsien Wu,[26] Feng-Cheng Liu,[27,28,29] Yen-Hung Lin,[30,31] Fu-Chiang Yeh,[27] Wei-Shin Liu,[32] Hui-Ting Lee,[33,34] Shu-Hao Wu,[10,34] Chi-Ching Chang,[35,36] Chun-Yuan Chu,[37,38,39] Charles Jia-Yin Hou[10,40#] and Chang-Youh Tsai[41#]*

Background: Pulmonary arterial hypertension (PAH), defined as the presence of a mean pulmonary artery pressure > 20 mmHg, pulmonary artery wedge pressure ≤ 15 mmHg, and pulmonary vascular resistance (PVR) > 2 Wood units based on expert consensus, is characterized by a progressive and sustained increase in PVR, which may lead to right heart failure and death. PAH is a well-known complication of connective tissue diseases (CTDs), such as systemic sclerosis, systemic lupus erythematosus, Sjogren's syndrome, and other autoimmune conditions. In the past few years, tremendous progress in the understanding of PAH pathogenesis has been made, with various novel diagnostic and screening methods for the early detection of PAH proposed worldwide.

Received: December 21, 2022 Accepted: January 17, 2023
[1]Department of Critical Care Medicine, Kaohsiung Veterans General Hospital, Kaohsiung; [2]School of Medicine, National Yang-Ming Chiao-Tung University, Taipei; [3]Department of Physical Therapy, Fooyin University, Kaohsiung; [4]Division of Allergy, Immunology, and Rheumatology, Department of Internal Medicine, National Taiwan University Hospital, Taipei; [5]Division of Cardiology, Cardiovascular Medical Center, Far Eastern Memorial Hospital, New Taipei City; [6]Graduate Institute of Medicine, Yuan Ze University, Taoyuan; [7]Attending Physician of Division of Allergy-Immunology-Rheumatology, Department of Internal Medicine; [8]Director of Division of Clinical Training, Department of Medical Education, Taichung Veterans General Hospital; [9]Program of Business, College of Business, Feng Chia University, Taichung; [10]Cardiovascular Center, Department of Internal Medicine, MacKay Memorial Hospital, Taipei; [11]Department of Medicine, MacKay Medical College, New Taipei City; [12]Department of Internal Medicine, National Taiwan University Hospital; [13]National Taiwan University, College of Medicine; [14]Division of Cardiology; [15]Division of Allergy, Immunology and Rheumatology; [16]Department of Medicine, Taipei Veterans General Hospital; [17]Institute of Emergency and Critical Care Medicine; [18]Institutes of Clinical Medicine, National Yang Ming Chiao Tung University, Taipei; [19]Department of Cardiology, Chang Gung Memorial Hospital; [20]College of Medicine, Chang Gung University, Taoyuan; [21]Department of Internal Medicine, Pingtung Veteran General Hospital, Pingtung; [22]Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan; [23]Graduate Institute of Clinical Medicine, College of Medicine, National Taiwan University, Taipei; [24]Division of Cardiology, Cardiovascular Medical Center, Far Eastern Memorial Hospital, New Taipei City; [25]Department of Computer Science and Engineering, Yuan Ze University, Taoyuan; [26]Division of Cardiology, Department of Internal Medicine; [27]Division of Rheumatology/ Immunology and Allergy, Department of Medicine; [28]Department of General Medicine, Tri-Service General Hospital, National Defense Medical Center; [29]Graduate Institute of Medical Sciences, National Defense Medical Center; [30]Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine; [31]Cardiovascular Center, National Taiwan University Hospital, Taipei; [32]Division of Cardiology, Tzu-Chi General Hospital, Hualien; [33]Division of Allergy, Immunology and Rheumatology, Department of Internal Medicine, MacKay Memorial Hospital, Taipei; [34]Department of Medicine, MacKay Medical College, New Taipei City; [35]Division of Allergy, Immunology & Rheumatology, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University; [36]Division of Rheumatology, Immunology, and Allergy, Department of Internal Medicine, Taipei Medical University Hospital, Taipei; [37]Division of Cardiology, Department of Internal Medicine, Kaohsiung Medical University Hospital; [38]Faculty of Medicine; [39]Graduate Institute of Clinical Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung; [40]MacKay Medical College; [41]Division of Immunology & Rheumatology, Fu Jen Catholic University Hospital, New Taipei City, Taiwan.
Corresponding author: Dr. Charles Jia-Yin Hou, Cardiovascular Center, MacKay Memorial Hospital, No. 92, Sec. 2, Zhongshan N. Rd., Taipei 10449, Taiwan. Tel: 886-2-2543-3535; Fax: 886-2-2523-2448; E-mail: jiayinhou@gmail.com
* These authors contributed equally to this work.
# Charles Jia-Yin Hou and Chang-Youh Tsai (cytsai1240@gmail.com) supervised this work jointly and contributed equally as corresponding authors.

Objectives: This study aimed to obtain a comprehensive understanding and provide recommendations for the management of CTD-PAH in Taiwan, focusing on its clinical importance, prognosis, risk stratification, diagnostic and screening algorithm, and pharmacological treatment.

Methods: The members of the Taiwan Society of Cardiology (TSOC) and Taiwan College of Rheumatology (TCR) reviewed the related literature thoroughly and integrated clinical trial evidence and real-world clinical experience for the development of this consensus.

Conclusions: Early detection by regularly screening at-risk patients with incorporations of relevant autoantibodies and biomarkers may lead to better outcomes of CTD-PAH. This consensus proposed specific screening flowcharts for different types of CTDs, the risk assessment tools applicable to the clinical scenario in Taiwan, and a recommendation of medications in the management of CTD-PAH.

Key Words: Connective tissue diseases • Pulmonary arterial hypertension • Sjogren's syndrome • Systemic lupus erythematosus • Systemic sclerosis

Abbreviations

ACR	American College of Rheumatology
AMBITION	Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension
ANA	Antinuclear antibody
APL	Antiphospholipid
APS	antiphospholipid syndrome
ASIG	Australian Scleroderma Interest Group
BNP	Brain natriuretic peptide
cGMP	Cyclic guanosine monophosphate
CI	Confidence interval
COMPERA	Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension
COPD	Chronic obstructive pulmonary disease
CTD	Connective tissue disease
CYP	Cytochrome p450
dcSSc	Diffuse cutaneous SSc
DLCO	Diffusion capacity of carbon monoxide
DMARDs	Disease-modifying antirheumatic drugs
EKG	Electrocardiography
ERAs	Endothelin receptor antagonists
ERS	European Respiratory Society
ESC	European Society of Cardiology
ET-1	Endothelial 1
ETA	Endothelin-A
ETB	Endothelin-B
EULAR	European Alliance Association for Rheumatology
FC	Functional Class
FDA	Food and Drug Administration
lcSSc	Limited cutaneous SSc
ILD	Interstitial lung disease
IVC	Inferior vena cava
MCTD	Mixed connective tissue disease
NO	Nitric oxide
NT-proBNP	N-terminal pro-brain natriuretic peptide
OATP1B1	Organic anion transporting polypeptide 1B1
PACES-1	Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil
PAH	Pulmonary arterial hypertension
PAWP	Pulmonary arterial wedge pressure
PDE-5	Phosphodiesterase type 5
PH	Pulmonary hypertension
PHIRST	Pulmonary Arterial Hypertension and Response to Tadalafil
RA	Rheumatoid arthritis
RAD	Right axis deviation
REVEAL	Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management
RHC	Right heart catheterization
RNP	Ribonuclear protein
RV	Right ventricle
sGC	Soluble guanylate cyclase
SLE	Systemic lupus erythematous
SPAHR	Swedish PAH Registry
SSA	Sjogren's syndrome related antigen A
SSB	Sjogren's syndrome related antigen B
SSc	Systemic sclerosis
sSSc	Scleroderma spectrum disease
SUPER	Sildenafil Use in Pulmonary Arterial Hypertension
tid	Three times daily
TRV	Tricuspid regurgitation velocity
TSOC	Taiwan Society of Cardiology
TTE	Transthoracic echocardiography
WHO	World Health Organization
6MWD	6-minute walk distance

TABLE OF CONTENTS

1. THE IMPORTANCE OF CONNECTIVE TISSUE DISEASES IN PULMONARY ARTERIAL HYPERTENSION

1.1. Systemic lupus erythematosus

Introduction

Systemic lupus erythematous (SLE) is an autoimmune disease with a variety of clinical manifestations such as fever, arthritis, dermatitis, nephritis and pulmonary arterial hypertension (PAH). Among patients with connective tissue disease (CTD)-associated PAH (CTD-PAH) in Western countries, SLE is the second most prevalent CTD after systemic sclerosis (SSc).[1] In contrast, SLE is more prevalent than SSc among patients with CTD-PAH in China, Korea, or Japan.[2-4] Similar to the distribution of autoimmune causes of CTD-PAH in East Asian countries, SLE accounts for 57% and SSc accounts for 30% of CTD-PAH cases in Taiwan.[5]

Tremendous progress has been made in understanding the pathogenesis of and developing therapeutic approaches for PAH in the past few years. The proposed mechanisms for the pathogenesis of PAH include endothelial dysfunction, genetic aberrations, refractory vasoconstriction, and excess proliferation accompanied by impaired apoptosis of vascular cells, all of which can become targets of future therapeutic designs.

According to the World Symposium on Pulmonary Hypertension (WSPH) classification,[6] there are 5 groups of pulmonary hypertension (PH): (1) PAH, (2) PH due to left heart diseases, (3) PH due to lung diseases and/or hypoxia, (4) PH due to pulmonary artery obstructions, and (5) PH with unclear and/or multifactorial mechanisms. SLE-PAH is classified as group I PH.[7] According to the experts' consensus, PAH is defined as the presence of a mean pulmonary artery pressure (mPAP) > 20 mmHg, pulmonary artery wedge pressure $\leq$ 15 mmHg, and pulmonary vascular resistance (PVR) > 2 Wood units.[7]

Risk factors and screening recommendations for SLE-PAH

Various diagnostic and screening recommendations have been proposed for the early detection of PAH.[7-9] On the other hand, numerous important independent predictors for SLE-PAH have been identified, and these predictors include the presence of Raynaud's phenomenon, pleuritis, lupus nephritis and its disease activity, thrombocytopenia, acute/chronic cutaneous lupus, systemic hypertension, and mild interstitial lung disease (ILD).[1,10-12] Immunological variables such as anti-U1-ribonuclear protein (RNP), anti-Sjogren's syndrome related antigen A (SSA), anti-Sjogren's syndrome related antigen B (SSB) and anti-cardiolipin antibodies are also associated with an increased risk of SLE-PAH.[1,11-13] However, early detection of SLE-PAH continues to be difficult.

Outcome and prognosis of SLE-PAH

Although advances in therapies for PAH have been made in recent decades, delays in diagnosis remain common. Therefore, early detection of SLE-PAH is of great importance. The mean duration between symptom onset and diagnosis was shown to be 2.8 years,[14] and delays in diagnosis have been associated with poor outcomes.[15] CTD-PAH has a worse prognosis than idiopathic PAH (IPAH), with SSc-PAH having the worst prognosis among all CTD-PAH.[3] Various prognostic factors, including a low diffusion capacity of carbon monoxide (DLCO), pleural effusion, diabetes mellitus, a high mPAP, a high PVR, elevated brain natriuretic peptide (BNP), and a low 6-minute walk distance (6MWD), were shown to be related to poor survival.[16,17] In contrast, anti-U1-RNP antibody was demonstrated to be a protective factor.[16] Although anti-U1-RNP antibody-positive patients were found to be more prone to PAH development than anti-U1-RNP antibody-negative patients, antibody-positive patients were found to be functionally less impaired; thus, the presence of anti-U1-RNP antibody was negatively associated with mortality.

Recommendations

1. Early screening for PAH with different modalities should be considered for SLE patients who present with Raynaud's phenomenon, pleuritis, high disease activity, thrombocytopenia, acute/chronic cutaneous lupus, systemic hypertension, and ILD, as well as for those with anti-U1-RNP, anti-SSA, anti-SSB, and anti-cardiolipin antibodies.
2. Early referral to specialty PAH centers should be considered for SLE-PAH patients with poor prognostic factors, i.e., anti-U1-RNP antibody negativity and anti-SSA, anti-SSB or anti-cardiolipin antibody positivity.

1.2. Systemic sclerosis

Rationale for screening in SSc patients

SSc is an autoimmune disease characterized by widespread vasculopathy and fibrosis. Of specific note, PAH is a major cause of morbidity and mortality in patients with SSc. The prevalence of PAH in patients with SSc is approximately 10%, with a range of 7% to 19%.[18] The estimated incidence of SSc-PAH was noted to be 0.61 per 100 patient-years in a French study after a 3-year follow-up,[19] while the incidence was higher (1.6 per 100 person-years) in a Taiwanese national cohort study.[5] The cumulative incidence of PAH rises with longer SSc disease duration, resulting in 18% of patients with diffuse cutaneous SSc (dcSSc) and 24% of patients with limited cutaneous SSc (lcSSc) developing PAH over a period of 15 years.[18] However, half of patients with either lcSSc or dcSSc have early-onset PAH, arising within the first five years after disease onset.[20] Various risk factors for PAH in patients with SSc have been described, including chronic persistent disease, older age, late onset of disease, postmenopausal status, severe Raynaud's phenomenon, severe digital ischemia, cutaneous telangiectasias, isolated DLCO < 50%, DLCO/alveolar volume < 70%, forced vital capacity/DLCO < 1.6 and an increase in right ventricular systolic pressure > 2 mmHg/year.[21] Therefore, patients with SSc are a high PAH risk group in whom screening can be justified.

Early detection of PAH should be of paramount importance since this condition accounts for approximately 30% of deaths among SSc patients.[22] At PAH diagnosis, most patients present with advanced symptoms and right heart dysfunction, which predicts a worse survival.[23] A study from the French PH registry reported transplant-free survival rates of 87%, 55%, and 35% at 1, 3, and 5 years, respectively, in SSc-PAH patients.[24] These results were similar to the results of the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) study in the USA, where the 3-year survival was 51.2% among newly diagnosed and 61.4% among previously diagnosed SSc-PAH patients.[25] The 1-, 3-, and 5-year survival rates for patients with SSc-PAH in a Taiwanese national cohort study were 88.3%, 72.1% and 61.9%, respectively.[5] The prospective PHAROS study reported better SSc-PAH survival rates of 95%, 75% and 63% at the 1-, 3-, and 5-year follow-ups, respectively, which may have been attributable to more widespread screening resulting in earlier detection and less severe symptoms at diagnosis.[26] The long-term survival of patients with SSc-PAH was also significantly better in the early detection cohort than in those in the routine practice cohort, whose 8-year survival rates were 64% and 17%, respectively.[27] This finding suggests that earlier diagnosis and treatment could lead to better long-term outcomes.

Recommendations

SSc-PAH is a rare but life-threatening disease for which early detection with systematic and regular screening for PAH in all patients can lead to earlier diagnoses and better subsequent outcomes in at-risk patients with SSc.

1.3. Sjogren's syndrome

Introduction

Primary Sjogren's syndrome (pSS) is characterized by the lymphocytic infiltration of exocrine glands and extraglandular tissues and the presence of autoantibodies directed against the Ro/SSA and La/SSB antigens.[28] Nevertheless, Sjogren's syndrome (SS) can present as a primary disease or in association with other CTDs, such as rheumatoid arthritis (RA) or SLE, and predominantly affects women.

Systemic autoimmune diseases in general can affect any organ system, and PH associated with systemic autoimmune diseases can be in any of the five World Health Organization (WHO) PH classification groups.[29] Extraglandular involvement of the lungs is common in pSS, typically manifesting as ILD and including lymphocytic interstitial pneumonia, nonspecific interstitial pneumonitis, usual interstitial pneumonitis, and organizing pneumonia.[30] Therefore, patients with pSS frequently present with PAH (group 1 PH) and/or PH secondary to lung diseases (group 3 PH).[29-32] However, PH resulting from chronic thromboembolism (group 4 PH) has also been reported in pSS.[33] Therefore, a systematic evaluation of PH associated with pSS should be performed to achieve the correct diagnosis. A histological examination case report demonstrated the presence of immune complex deposition in the pulmonary vessel walls, implicating an immunological etiology in the pathogenesis of pSS-PAH.[34]

As described previously, although SSc-PAH accounts for the most commonly observed CTD-PAH in Western countries,[35] SLE is the most prevalent autoimmune condition in CTD-PAH in Asian countries.[2,4,36-38] pSS-PAH has been reported to be the second most common CTD-PAH in Chinese individuals.[37,38] In a national cohort study in Taiwan, pSS-PAH was the third most common type of CTD-PAH among affected patients.[5] Therefore, the clinical significance of pSS-PAH cannot be ignored in Taiwan.

Risk factors and prognosis

PAH is a severe complication of pSS, although its exact prevalence is unknown.[35] In a Turkish study, the presence of PAH, according to echocardiographic evidence, was reported to be up to 22% among pSS patients.[39] Compared with pSS patients without PAH, patients with pSS-PAH are more frequently found to exhibit Raynaud's phenomenon, the presence of anti-Ro/SSA and anti-nuclear ribonucleoprotein (anti-RNP) autoantibodies, the presence of rheumatoid factor, hypergammaglobulinemia, cutaneous vasculitis, and ILD.[40,41] In a case-control study, a younger onset of pSS and the presence of anti-SSB or anti-U1-RNP antibodies were associated with the occurrence of PAH.[38]

The 1-, 3-, and 5-year survival rates of patients with pSS-PAH have been reported to be 73.0-94.0%, 66.0-88.8% and 64.8-80.6%, respectively.[5,7,38,42] Elevated PVR, high serological alkaline phosphatase levels, a low cardiac index, and an increased SS disease damage index were identified as potential predictors of poorer outcomes in patients with pSS-PAH.[37,38]

The main symptom of pSS-PAH is exertional dyspnea, which usually requires differentiation from ILD.[40] Right heart catheterization (RHC) remains the gold standard for diagnosis.[7] One study showed that patients with pSS-PAH had worse hemodynamic profiles on diagnostic RHC than patients with SLE-PAH and patients with SSc-PAH at the time of PAH diagnosis, probably because the diagnoses were performed in a more advanced stage of the illness in pSS-PAH patients.[35,41] Therefore, clinicians must be keenly aware of the possibility of PAH in patients with pSS.

Recommendations

1. PAH should be evaluated as one of the etiologies for patient-reported dyspnea in pSS patients.
2. Routine screening for PAH may be necessary for pSS patients, especially for those with a younger disease onset, Raynaud's phenomenon, anti-SSA or anti-SSB autoantibodies, anti-U1-RNP autoantibodies, rheumatoid factor, hypergammaglobulinemia, cutaneous vasculitis, and ILD.

1.4. Other autoimmune conditions with a high risk of pulmonary arterial hypertension

In addition to progressive pSS, SLE, and SS, patients

with other autoimmune diseases, including RA, mixed connective tissue disease (MCTD), and antiphospholipid syndrome (APS), may also have a propensity for developing PAH. RA involves progressive erosion of multiple small joints, pain, and joint motion limitations. In comparison with ankylosing spondyloarthritis, RA tends to affect peripheral joints, especially those of the hands, leading to a profound decline in quality of life and a large disease burden, as indicated in a recent census.[43] According to a recent registry study in Taiwan, approximately 3% of RA patients suffer from PAH.[5] RA-PAH tends to be diagnosed at an older age than other autoimmune diseases.[2] The demographics and severity of RA with or without PAH do not differ greatly, nor do the corresponding treatments.[44] MCTD is characterized by the presentations of increased digital thickness, Raynaud's phenomenon, joint inflammation with hand swelling, and myositis, and the diagnosis should be confirmed by testing for the presence of anti-U1-RNP antibody. It should be noted that anti-U1-RNP antibody positivity may also be an independent protective factor against PAH in pSS patients.[45] APS, which often accompanies SLE and RA, may lead to thrombosis and frequent premature pregnancy loss. In patients with SLE, the presence of autoantibodies associated with APS is a risk factor for PAH, which can be found in 46.6% of SLE patients.[46] Although the incidence of PAH in RA, MTCD, and APS may not be as high as that in pSS, clinicians should pay more attention to this comorbidity to prevent severe complications.

For PAH screening for suspected autoimmune diseases, some noninvasive modalities have been suggested in systematic reviews published previously. Transthoracic echocardiography (TTE) plays an important role in the detection of PAH and has a sensitivity and specificity of over 90%.[47] TTE can be performed when patients suffer from symptoms of PAH, such as walking dyspnea, constant cough, or chest tightness. Together with TTE, serum N-terminal pro-BNP (NT-proBNP) level measurements have been shown to further enhance the specificity and sensitivity of detecting PAH.[48] A multidisciplinary care team, including cardiologists, could consider performing examinations to measure the DLCO and 6MWD in addition to serological marker assays or TTE to diagnose PAH in patients in whom it is suspected.[49]

Recommendations

1. Patients with autoimmune diseases, including RA, MCTD, and APS, may also suffer from PAH, and a careful evaluation for PAH is suggested for these patients.
2. A multidisciplinary care team, including cardiologists, could perform noninvasive evaluations, including TTE, NT-proBNP level measurements, and pulmonary function tests (DLCO and 6MWD), to facilitate the diagnosis of PAH among patients with autoimmune diseases in whom it is suspected.

2. SCREENING AND DIAGNOSTIC ALGORITHM FOR CONNECTIVE TISSUE DISEASE-ASSOCIATED PULMONARY ARTERIAL HYPERTENSION

2.1. Interpretation of serum markers for connective tissue disease-associated pulmonary arterial hypertension

In Western countries, SSc is the most common underlying CTD in patients with CTD-PAH, where 62.3-74% of patients have SSc.[50,51] SLE is the most common underlying disease of CTD-PAH and can be found in 29-49% of patients with CTD-PAH in Asia.[3,37] Other CTDs, including pSS, MCTD, RA, and myositis, may also be associated with PAH, although less frequently.[37,52] According to an epidemiological study based on the Taiwan National Health Insurance Research Database, the most common CTD among all CTD-PAH patients was SLE (57%), followed by SSc (30%), pSS (9%), RA (3%), and myositis (1%).[5]

SLE is a clinical diagnosis supported by immunological findings including the presence of antinuclear antibodies (ANAs) (1:80 and above), anti-double stranded DNA (dsDNA), anti-Smith antigen (Sm), and antiphospholipid (APL) antibodies in addition to hypocomplementemia. Newer classification criteria have been developed to enable the earlier diagnosis of SLE. Among them, the European Alliance Association for Rheumatology (EULAR)/American College of Rheumatology (ACR) 2019 guideline lists ANA positivity as the diagnostic criterion with the best sensitivity and specificity for detecting SLE.[53] Predictive biomarkers of PAH in SLE, such as anti-U1-RNP, anti-Ro, and APL antibodies, have been recognized.[1]

The ACR-EULAR criteria for the classification of SSc include the presence of specific serum autoantibodies

such as anti-topoisomerase I, anti-centromere, and anti-RNA polymerase III.[54] In particular, anti-centromere autoantibodies are more specifically associated with PAH and have been emphasized in the DETECT algorithm. In addition, SSc-PAH patients have higher BNP/NT-proBNP levels than patients with SSc without PAH.[55,56]

pSS typically presents with chronic dry eyes and dry mouth. In addition to evidence of lacrimal and salivary gland dysfunction, either histopathological evidence of focal sialadenitis with lymphocytic infiltrates in minor salivary gland biopsy samples or positive serological findings of anti-Ro/La antibodies is required for the diagnosis of pSS.[57,58] A multicenter cohort study involving pSS patients in China showed that the presence of anti-La and anti-U1-RNP antibodies and the age of disease onset were independent risk factors for PAH.[38]

MCTD is a syndrome with phenotypes that overlap with those of SSc, SLE, RA, and inflammatory myositis associated with anti-U1-RNP antibody. Clinical features include Raynaud's phenomenon, sclerodactyly, arthritis, polymyositis and ILD.[59] Although rarely seen in the population of patients with CTD-PAH in Taiwan, MCTD-associated PAH was reported to represent 43% and 9% of CTD-PAH cases in Japan and China, respectively.[3,37] A high prevalence of PH was reported in MTCD patients, with 20-30% of the patients presenting the condition; thus, screening for PAH in patients with MCTD is warranted.[60]

Recommendations

1. Patients with PAH may need to be screened for SLE, SSc, pSS, and MTCD, as these immunological conditions are common in the CTD-PAH population in Asia. Screening methods may include blood tests for ANA, anti-dsDNA, anti-Sm/U1-RNP, APL, anti-topoisomerase I (SCL-70), anti-RNA polymerase III, anti-Ro/La antibodies, and C3/C4/CH50 (Table 1).
2. Baseline and sequential BNP/NT-proBNP levels could be measured as predictors of clinical outcomes in patients with PAH secondary to SSc and other CTDs.

2.2. Connective tissue disease-pulmonary arterial hypertension high-risk population screening and diagnostic flowchart

Systematic screening for patients with different CTDs, even asymptomatic patients, plays an important part in the detection and subsequent early management of PAH to achieve better long-term outcomes.[61] Due to the presence of an underlying CTD, CTD-PAH patients may have better chances of PAH detection in the early stages than patients with IPAH. Existing evidence demonstrates a survival benefit attributable to a structured screening protocol rather than the protocol routinely utilized in clinical practice.[62]

Although some screening and diagnostic modalities have been successful in Europe and North America, a timely diagnosis of CTD-PAH remains challenging in Taiwan for a number of reasons. The most important reason is the type of underlying CTD in Taiwanese patients with CTD-PAH. Quite different from Western countries, investigations revealed that SLE, rather than scleroderma, was the leading underlying CTD in Taiwan and most East Asian countries.[5,63] The prevalent CTD will greatly affect the accuracy of screening.[61] However, there

Table 1. Recommended screening blood tests for CTD-PAH

Underlying CTD	CTD diagnostic markers	PAH risk markers
SLE	ANA (> 1:80), anti-dsDNA, anti-Sm, antiphospholipid antibodies, and C3/C4/CH50	Anti-U1-RNP, anti-Ro, and anti-phospholipid antibodies
SSc	Anti-topoisomerase I (SCL-70), anti-centromere and anti-RNA polymerase III antibodies	Anti-centromere antibodies
pSS	Anti-Ro/La antibodies	Anti-La and anti-U1-RNP antibodies
MCTD	Anti-U1-RNP antibody	

Anti-phospholipid antibodies include lupus anticoagulants, anticardiolipin IgG/M, and anti-beta-2-glycoprotein I IgG/M.

ANA, antinuclear antibody; CTD, connective tissue disease; Ig, immunoglobulin; MCTD, mixed connective tissue disease; PAH, pulmonary arterial hypertension; pSS, primary Sjögren's syndrome; RNP, ribonuclear protein; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

is no universally accepted protocol for PAH screening in lupus patients that has a good balance of cost, benefit and screening capacity.

For these reasons, we decided to propose specific screening protocols for different types of CTDs. SSc or scleroderma spectrum diseases (sSScs) include MCTD and other CTDs with prominent scleroderma features (e.g., sclerodactyly, nail fold capillary abnormalities and SSc-specific autoantibodies). We recommend following the international recommendations[56,64-67] with some minor modifications that are more applicable to the Taiwanese setting.

For SSc and sSSc patients in Taiwan, we suggest regular routine screening for all SSc and sSSc patients. Yearly screening should be suitable for most SSc and sSSc patients, as recommended by the 2009 American College of Cardiology (ACC)/American Heart Association (AHA)[6] and 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines.[64] However, it is difficult to apply the current screening protocols, particularly when patients are unable to undergo pulmonary function tests or their access to such tests is limited, such as during the coronavirus disease 2019 (COVID-19) pandemic. Therefore, we suggest modifications of indications for screening. Patients who met at least two of the three indications were deemed suitable for SSc-PAH screening. The indications have three components: the pulmonary function, imaging, and serological components (Figure 1). This modification justified further evaluation for high-risk patients even when pulmonary function testing was unavailable.

A patient is considered positive for component A, the pulmonary function component, if their uncorrected DLCO is < 80% of the predicted value.[56,64] A patient is considered positive for component B, the imaging component, if at least one of the following three imaging findings is identified: 1) the presence of any sign suggesting PH in an advanced image evaluation, such as magnetic resonance imaging (MRI) or computer tomography (CT);[64,68] 2) the presence of a decreased capillary density or active/late scleroderma pattern on nailfold capillaromicroscopy;[69,70] and 3) the presence of right axis deviation (RAD) or sign(s) of right ventricle (RV) strain on electrocardiography (EKG).[56] A patient is considered positive for component C, the serological component, if they have > 1 of the following findings: an unexplained NT-proBNP elevation ≥ 300 pg/mL[56] or the presence of anti-centromere antibodies, anti-U3 RNP antibodies, anti-Th/To antibodies or APL antibody (Figure 1).[71,72]

For SSc or sSSc patients with indications for screening, we suggested the DETECT algorithm (evidence-based

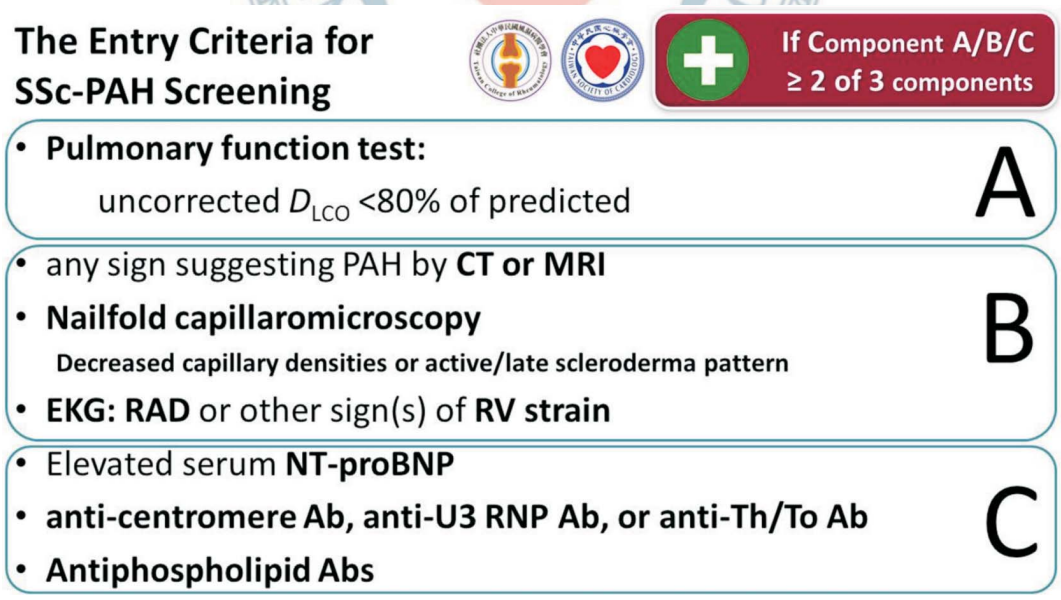


Figure 1. *The entry criteria for SSc-PAH screening. CT, computer tomography; EKG, electrocardiography; MRI, magnetic resonance imaging; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; RAD, right axis deviation; RNP, ribonuclear protein; RV, right ventricle; SSc, systemic sclerosis.*

detection of PAH in SSc, Figure 2) as the second step of SSc-PAH screening.[56] This suggestion is based on the fact that the DETECT algorithm has been widely validated in different SSc cohorts[73,74] and is generally recommended in almost all guidelines.[64,65,67]

In contrast, an easier approach proposed by the Australian Scleroderma Interest Group (ASIG) could be recommended as an alternative screening protocol for SSc and sSSc patients, as it has an accuracy that is similar to that of the DETECT algorithm.[66] The ASIG screening algorithm has two components: pulmonary function (component A) and serum NT-proBNP (component B) (Figure 3).[66]

Patients with SSc and sSSc disease with positive re-

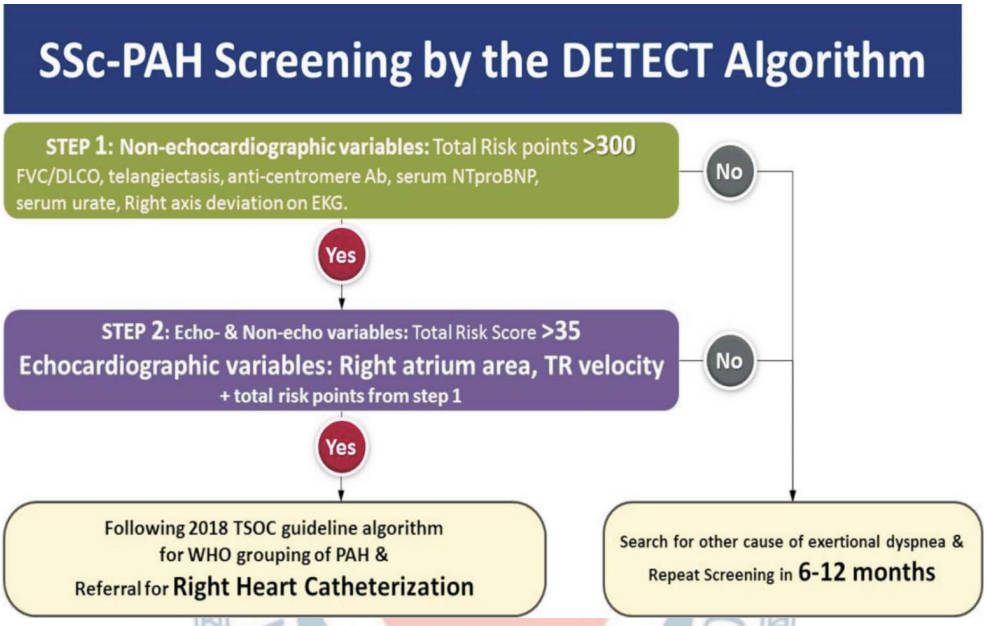


Figure 2. *SSc-PAH screening by the DETECT algorithm. DLCO, diffusion capacity of carbon monoxide; EKG, electrocardiography; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; SSc, systemic sclerosis; TSOC, Taiwan Society of Cardiology; WHO, World Health Organization.*

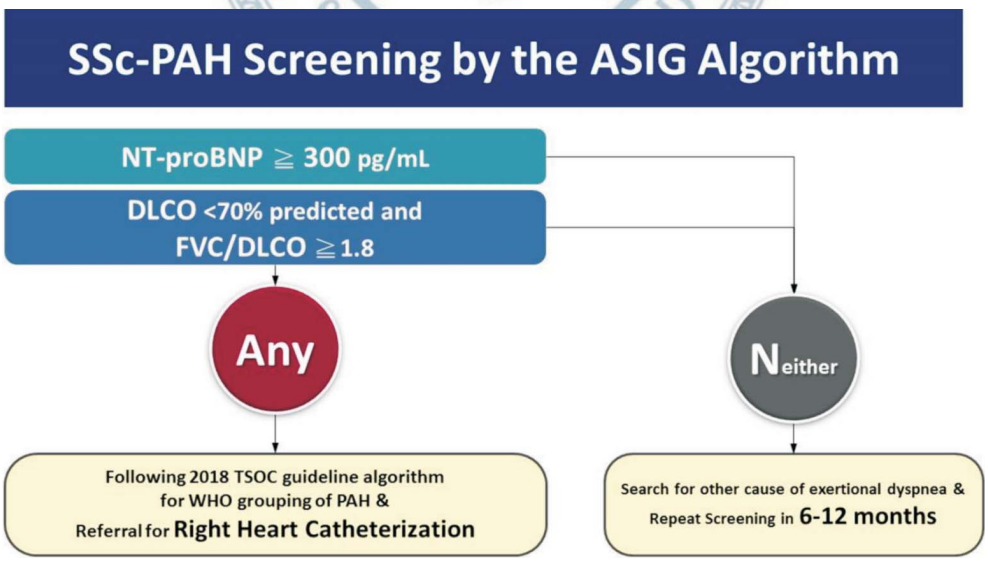


Figure 3. *SSc-PAH screening by the ASIG algorithm. ASIG, Australian Scleroderma Interest Group; DLCO, diffusion capacity of carbon monoxide; FVC, forced vital capacity; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; SSc, systemic sclerosis; TSOC, Taiwan Society of Cardiology; WHO, World Health Organization.*

sults in the DETECT or ASIG algorithm should be considered high-risk patients for SSc-PAH. As CTD-PAH patients might have multiple pathogenic modalities, the 2018 Taiwan Society of Cardiology (TSOC) guideline algorithm for WHO grouping of PAH should be followed for the best management.[9] Despite this, RHC remains the gold standard for the confirmation of SSc-PAH.[9,65,67]

For nonscleroderma CTDs, especially SLE, which is the most common autoimmune disease among CTD-PAH patients in Taiwan, we propose a 2-step screening that is based on the capacities of key screening instruments (e.g., echocardiography, ventilation/perfusion lung scan, etc.).

Based on prior research on independent predictors of PAH in lupus patients, we divided the screening protocol into two parts. The first step is the evaluation of at-risk patients,[1] which includes three components (Figure 4), while the second step is the evaluation of PAH (Figure 5).

Component A is the clinical component. CTD patients with a history of active Raynaud's phenomenon (confirmed by a physician by direct observation or the medical record), active arthritis, or serositis (including pericarditis or pleuritis disease) are considered to be positive for component A.[1,13] Component B is the general laboratory component. CTD patients with NT-proBNP/BNP levels more than 2-fold above normal limits, RAD or sign(s) of RV strain on EKG[64,75] not due to an alternative cause are considered to be positive for component B. Component C is the autoantibody component. Some CTD patients have a history of a confirmed presence of anti-RNP antibody or APL antibodies.[76] The presence of APL antibodies should meet the classification criteria for definite APS in the updated international consensus statement.[76,77]

Non-SSc CTD patients positive for at least two of three components (components A, B and C) in the first screening step should be considered for further evaluation in the next step. The second part of screening (Figure 5) was inspired by the ItinérAIR-Sclérodermie Study,[78] which used Doppler echocardiography and serum NT-proBNP/BNP level analysis to evaluate the necessity of invasive heart catheterization.

The other challenge of screening implementation is that CTD might lead to PAH by several mechanisms, including thromboembolism, left heart disease, and ILD, or by a combination of mechanisms. Therefore, different optimal management strategies should be employed. In summary, we propose that the 2018 TSOC guideline algorithm (Figure 6) should be followed in identifying PH in patients with intermediate to high probability of PH for potentially coexisting left heart disease, thromboembolism and ILD.[9] The significance of the results in directing further management should be addressed by discussion among the members of a multidisciplinary care team. Patient management, aiming to achieve optimal

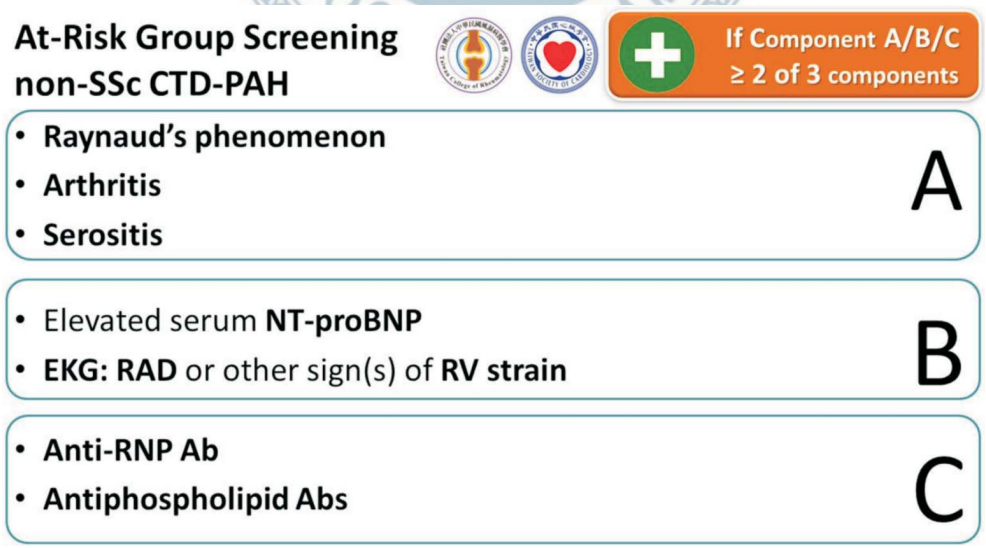


Figure 4. *At-risk group screening for non-SSc CTD-PAH. CTD, connective tissue disease; EKG, electrocardiography; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; RAD, right axis deviation; RNP, ribonuclear protein; RV, right ventricle; SSc, systemic sclerosis.*

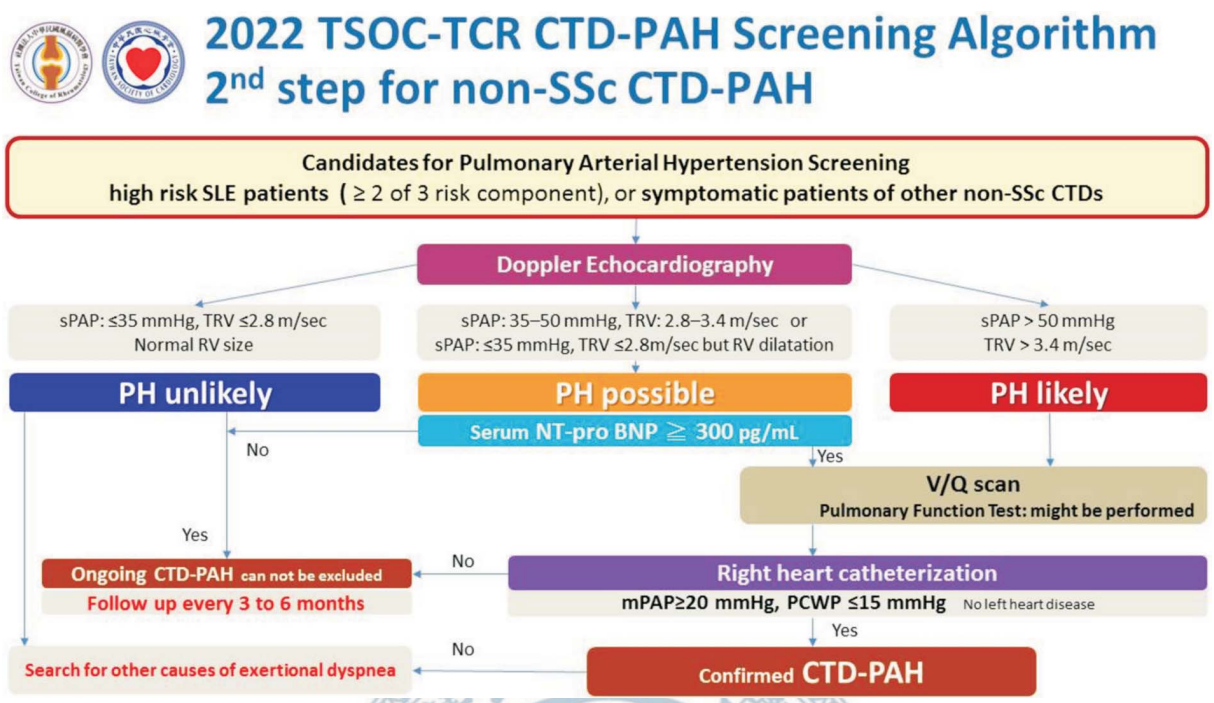


Figure 5. *2nd step of screening for non-SSc CTD-PAH. CTD, connective tissue disease; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; RV, right ventricle; SLE, systemic lupus erythematous; sPAP, systolic artery pressure; SSc, systemic sclerosis; TCR, Taiwan College of Rheumatology; TRV, tricuspid regurgitation velocity; TSOC, Taiwan Society of Cardiology; V/Q, ventilation/perfusion.*

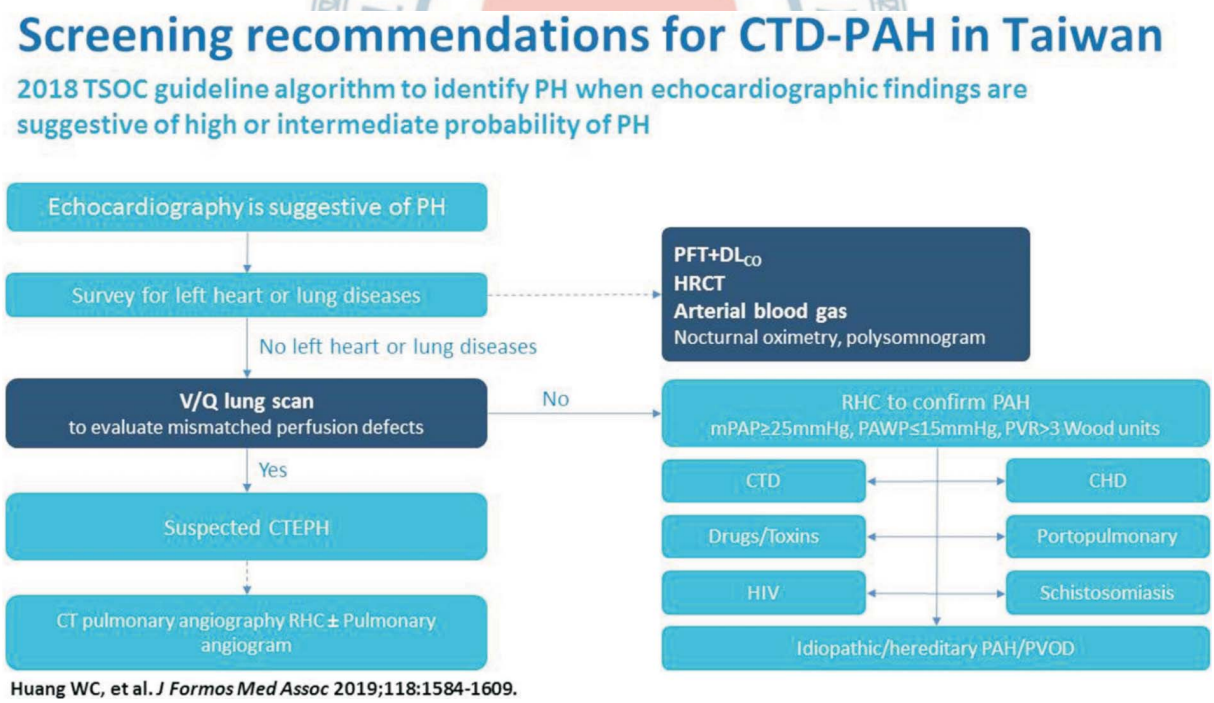


Figure 6. *Screening recommendations for CTD-PAH in Taiwan. CHD, congenital heart disease; CT, computed tomography; CTD, connective tissue disease; CTEPH, chronic thromboembolic pulmonary hypertension; DLCO, diffusing capacity of carbon monoxide; HIV, human immunodeficiency virus; HRCT, high-resolution computed tomography; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PFT, pulmonary function test; PH, pulmonary hypertension; RHC, right heart catheterization; PVOD, pulmonary veno-occlusive disease; TSOC, Taiwan Society of Cardiology; V/Q, ventilation/perfusion.*

long-term outcomes, should also be monitored by a multidisciplinary care team.

2.3. Screening for connective tissue disease-associated pulmonary arterial hypertension by echocardiography

TTE is a noninvasive examination that can be used to estimate PAP and the effects of PH on the right heart. The estimation of systolic PAP is based on the tricuspid regurgitation pressure gradient and right atrium (RA) pressure. The RA pressure is estimated by echocardiography according to the diameter and respiratory variation of the inferior vena cava (IVC): an IVC diameter < 2.1 cm with suggestions of > 50% collapse suggest a normal RA pressure of 3 mmHg (range 0-5 mmHg), whereas an IVC diameter ≥ 2.1 cm with suggestions of ≤ 50% collapse or < 20% collapse on quiet inspiration suggest a high RA pressure of 15 mmHg (range 10-20 mmHg). In the scenario that the IVC diameter and collapse do not fit this paradigm, an intermediate value of 8 mmHg (range 5-10 mmHg) may be presumed.[7,9]

In addition, echocardiographic examination can be used to indicate the probability of PH. Doppler-derived pressure estimation may be inaccurate under specific circumstances, such as a significantly underestimated or overestimated tricuspid regurgitation velocity (TRV) in some patients or conditions.[79] The ESC Guideline suggests grading the probability of PH as high, intermediate or low according to the TRV at rest and the presence of prespecified echocardiographic variables suggestive of PH, and these variables include the right ventricle (RV size, signs of pressure overload, the pattern of blood flow velocity at the RV outflow tract, the diameter of the pulmonary artery and the estimated RA pressure (Table 2).[80,81] In summary, an unevaluable TRV or a peak TRV ≤ 2.8 m/second indicates a low probability of PH in the absence of echocardiographic PH signs or an intermediate probability of PH in the presence of echocardiographic PH signs. A peak TRV of 2.9 to 3.4 m/second indicates an intermediate probability of PH in the absence of echocardiographic PH signs or a high probability of PH in the presence of echocardiographic PH signs. Finally, a peak TRV of > 3.4 m/second indicates a high probability of PH regardless of the presence or absence of echocardiographic PH signs (Table 3).[7]

PAH is a serious complication of CTD. Patients with CTD-PAH have shorter survival times than those with IPAH. In the REVEAL, the 1-year survival was worse in CTD-PAH patients than in IPAH patients. Of note, SSc was independently associated with the worst prognosis among the subtypes of CTD-PAH, and limited sclerosis is the most common CTD associated with PAH in Europe and the USA.[82] Early diagnosis and management are important in this group of patients. Annual echocardiography is recommended as a screening test for asymptomatic SSc patients.[83] Compared to symptom-based

Table 3. Echocardiographic probability of PH in symptomatic patients with a suspicion of PH

Peak tricuspid regurgitation velocity (m/s)	Presence of other echo 'PH signs'	
2.8 or not measurable	No	Low
2.8 or not measurable	Yes	Intermediate
2.9-3.4	No	
2.9-3.4	Yes	High
> 3.4	No	

PH, pulmonary hypertension.

Table 2. Echocardiographic signs suggestive of PH and used to assess the probability of PH

A: The ventricles*	B: Pulmonary artery*	C: Inferior vena cava and right atrium*
Right ventricles/left ventricle basal diameter ratio > 1.0	Right ventricular outflow Doppler acceleration time < 105 msec and/or mid-systolic notching	Inferior cava diameter > 21 mm with decreased inspiratory collapse (< 50% with a sniff or < 20% with quiet inspiration)
Flattening of the interventricular septum (left ventricular eccentricity index > 1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity > 2.2 m/sec	Right atrial area (end-systole) > 18 cm^2
	PA diameter > 25 mm	

* Echocardiographic signs of at least two different categories (A/B/C) should be present to grade the probability of PH.
PA, pulmonary artery; PH, pulmonary hypertension.

detection, the cost-effectiveness of echocardiography as a screening tool has not been investigated extensively. Echocardiography is also recommended in patients with CTDs other than SSc who show symptoms of PAH.

Recommendations

1. Echocardiography is recommended as a screening test for asymptomatic SSc patients and should be repeated annually.
2. Echocardiography is recommended for patients with symptoms PAH who have CTDs other than SSc.
3. The aim of echocardiography in these patients is to determine the grade of the probability of PH. The grading of the probability of PH should be based on the TRV and the presence of prespecified echocardiographic signs suggestive of PH.

2.4. Screening for connective tissue disease-associated pulmonary arterial hypertension by right heart catheterization

RHC plays a central role in the diagnosis and management of PAH, where the test is used to evaluate hemodynamics, stratify risk, measure vasoreactivity, and unmask intracardiac shunts. Despite widespread acceptance, significant interhospital or interphysician discrepancies remain in the practice of performing RHC. Therefore, RHC procedures should be standardized to ensure the accuracy of the hemodynamic parameters obtained from the test.

Pulmonary arterial wedge pressure

To measure the pulmonary arterial wedge pressure (PAWP), it is recommended to inflate a balloon in the RA and advance a catheter until it reaches the wedge position. The accuracy of PAWP measurements is susceptible to over- or underwedging, which can lead to false results. Moreover, repeated inflations and deflations in the wedge position should be avoided to prevent pulmonary artery rupture. The measurement of PAWP should be conducted at the end-expiratory phase, when the intra- and extrathoracic pressures are equal. Averaging PAWP over several respiratory cycles is an acceptable compromise to compensate for respiratory fluctuation.

Cardiac output

In addition to the measurement of pulmonary pressures, RHC enables the measurement of cardiac output using the widely acknowledged thermodilution method, which is a preferred method for cardiac output monitoring even among patients with very low cardiac output and/or severe tricuspid regurgitation. The indirect Fick technique that estimates the amount of oxygen uptake is less reliable than the other techniques. The cardiac index should be calculated thereafter.

Vasoreactivity test

The vasoreactivity test is recommended only for patients with IPAH or hereditary or drug-related PAH, since more than half of these patients may experience truly clinical responses to calcium channel blockers (CCBs) when the result of the vasoreactivity test is positive.[65]

Detection of intracardiac shunts

A high pulmonary arterial O_2 saturation of $\geq$ 75% may indicate a cardiac left to right shunt.[9] In the event of an intracardiac shunt, measurements of O_2 saturation in the superior vena cava, IV, RA and pulmonary artery should be obtained to identify the severity of the condition.

Recommendations

Given that RHC is essential for the diagnosis of PAH, as well as its disease severity evaluation and clinical intervention selection, we make the following recommendations regarding RHC:

1. RHC should be performed at the diagnosis of PAH.
2. RHC might be considered annually in PAH patients whose condition is stable.
3. RHC could be conducted in PAH patients whose conditions are deteriorating have indications for therapy escalations or even lung transplantation.
4. The vasoreactivity test is not recommended during RHC for CTD-PAH patients.

2.5. Risk stratification in patients with connective tissue disease-associated pulmonary arterial hypertension

Risk assessment is a crucial step after diagnosis confirmation or treatment initiation. Several published guidelines recommend the tailoring of treatment after risk assessment,[9,65] which, together with the various treatment strategies available, has resulted in better survival among

patients with IPAH in the modern era.[84] Different risk assessment tools have been proposed and reviewed thoroughly.[85] In this section, we aim to provide a focused update on the risk assessment tools applicable to patients with CTD-PAH.

Derived from the traffic light risk table recommended in the ESC/ERS guidelines,[7,65] three major simplified risk assessment scores have been studied in CTD-PAH. Patients with either SSc-associated PAH or other CTD-PAH were evaluated in the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA)[62,86] and the Swedish PAH Registry (SPAHR).[87,88] Initially, the COMPERA risk score categorized risk into low, intermediate, or high based on the variable cutoffs proposed by the ESC/ERS,[65] but this 3-strata model was less effective in differentiating CTD-PAH patients with an intermediate risk from those with a low risk.[86] The COMPERA 2.0 system comprises three parameters, namely, the WHO Functional Class (FC), BNP/NT-proBNP level, and 6MWD, and classifies the risks into low, intermediate-low, intermediate-high, or high based on the grades in t 4-strata model (Table 4). The 4-strata version significantly differentiates the survival among groups and sensitively reflects the treatment response according to validation in the French PH registry.[86,89] The 3-strata SPAHR equation showed limited efficacy in accurately identifying the intermediate-risk group in patients with CTD-PAH;[87,88] therefore, the 4-strata SPAHR equation was proposed to categorize the risk in a different way (Table 5). With the same risk definition for each variable as the 3-strata SPAHR equation, the intermediate-risk group was further divided into those with intermediate-low and intermediate-high risk in the 4-strata SPAHR equation. A significantly higher risk was reported in the intermediate-high risk group than in the intermediate-low risk group.[90] On the other hand, the initial French criteria, including the WHO FC, 6MWD, right atrial pressure, cardiac index, and BNP/NT-proBNP level, were developed without data from CTD-PAH patients[91] but were later validated in patients with SSc-PAH.[24,92] In addition, the newer 4-strata COMPERA model comprising the same variables as the French criteria showed better survival discrimination.[89] In their 2022 guidelines, the ESC/ERS[93] suggested using a 3-strata model at the time of diagnosis and emphasized the importance of hemodynamics in patients with PAH, including CTD-PAH. Better discriminability was demonstrated by the abovementioned 4-strata risk assessment tools, and hemodynamics in follow-up but not at baseline showed a significant correlation with transplant-free SSc-PAH.[24] Thus, the 4-strata risk assessment tools may be considered either at baseline or in follow-up.

In addition to the ESC/ERS guideline-based risk assessment tools, another risk score developed according to the REVEAL has provided a good risk discriminative ability in the registry's CTD-PAH subgroup.[94] Although fair prognostic discrimination was validated in SSc-PAH and SLE-PAH patients,[95,96] the accuracy of the predicted

Table 4. The 4-strata COMPERA risk assessment

Grade	1	2	3	4
WHO FC	I or II	-	III	IV
6MWD (m)	> 440	440-320	319-165	< 165
NT-proBNP (ng/l)	< 300	300-649	650-1100	> 1100
BNP (ng/l)	< 50	50-199	200-800	> 800
Average grades	Low risk: < 1.5; intermediate-low risk: 1.5-2.49; intermediate-high risk: 2.5-3.49; high risk: ≥ 3.5			

BNP, brain natriuretic peptide; COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; NT-proBNP, N-terminal pro-brain natriuretic peptide; WHO FC, World Health Organization functional class; 6MWD, 6-minute walking distance.

Table 5. The 4-strata SPAHR-equation

Grade	1	2	3
WHO FC	I or II	III	IV
6MWD (m)	> 440	165-440	< 165
NT-proBNP (ng/l)	< 300	300-1400	> 1400
BNP (ng/l)	< 50	50-300	> 300
RA area (cm^2)	< 18	18-26	> 26
Pericardial effusion	No	Minimal	Yes
RAP (mmHg)	< 8	8-14	> 14
CI ($L/min/m^2$)	≥ 2.5	2.0-2.4	< 2.0
S_vO_2 (%)	> 65	60-65	< 60
Average grades	Low risk: < 1.5; intermediate-low risk: 1.5-1.99; intermediate-high risk: 2.0-2.4; high risk: ≥ 2.5		

BNP, brain natriuretic peptide; CI, cardiac index; NT-proBNP, N-terminal pro-brain natriuretic peptide; RA, right atrium; RAP, right atrial pressure; SPAHR, Swedish PAH Registry; S_vO_2, mixed venous oxygen saturation; WHO FC, World Health Organization functional class; 6MWD, 6-minute walking distance.

survival was questionable in the high- or very high-risk groups of these patients. Renal insufficiency and WHO FC III may have a greater impact on the survival of CTD-PAH patients, while heart rate, the BNP/NT-proBNP level, and the 6MWD may have less impact in CTD-PAH patients.[95,96] With few external validations for the more recently developed REVEAL 2.0 risk score and REVEAL Lite 2,[97] REVEAL-based risk assessment tools should be utilized with caution in CTD-PAH patients.

The intermediate-high risk group has a significantly higher risk than the intermediate-low risk group; hence, a more aggressive treatment strategy is suggested for the intermediate-high risk group. Furthermore, risk status demonstrated a better correlation with survival during follow-up than at baseline. Thus, a risk-directed approach throughout clinical management is recommended (Figure 7).

Recommendations

1. The ESC/ERS guideline-based 4-strata risk assessment tools are recommended for risk evaluation in CTD-PAH patients at baseline and during follow-up.
2. When applying REVEAL-based risk assessment tools for CTD-PAH patients, the accuracy of the predictions should be further confirmed for the high- or very high-risk group.
3. A risk-directed approach throughout clinical management is recommended.

3. PHARMACOLOGICAL TREATMENTS IN CONNECTIVE TISSUE DISEASE-ASSOCIATED PULMONARY ARTERIAL HYPERTENSION

3.1. Pulmonary arterial hypertension medications targeting the nitric oxide pathway

Impaired nitric oxide (NO) synthesis and signaling through the NO-soluble guanylate cyclase (sGC)–cyclic guanosine monophosphate (cGMP) pathway are involved in the pathogenesis of endothelial dysfunction and PAH.[96] Treatments targeting the NO pathway include phosphodiesterase type 5 (PDE-5) inhibitors and sGC stimulators, which can increase the level of cGMP and in turn facilitate antiproliferation, anticoagulation and vasodilatation.[96]

In the current ESC and TSOC guidelines, PDE-5 inhibitors, including sildenafil and tadalafil, and the sGC stimulator riociguat are class I recommended medications

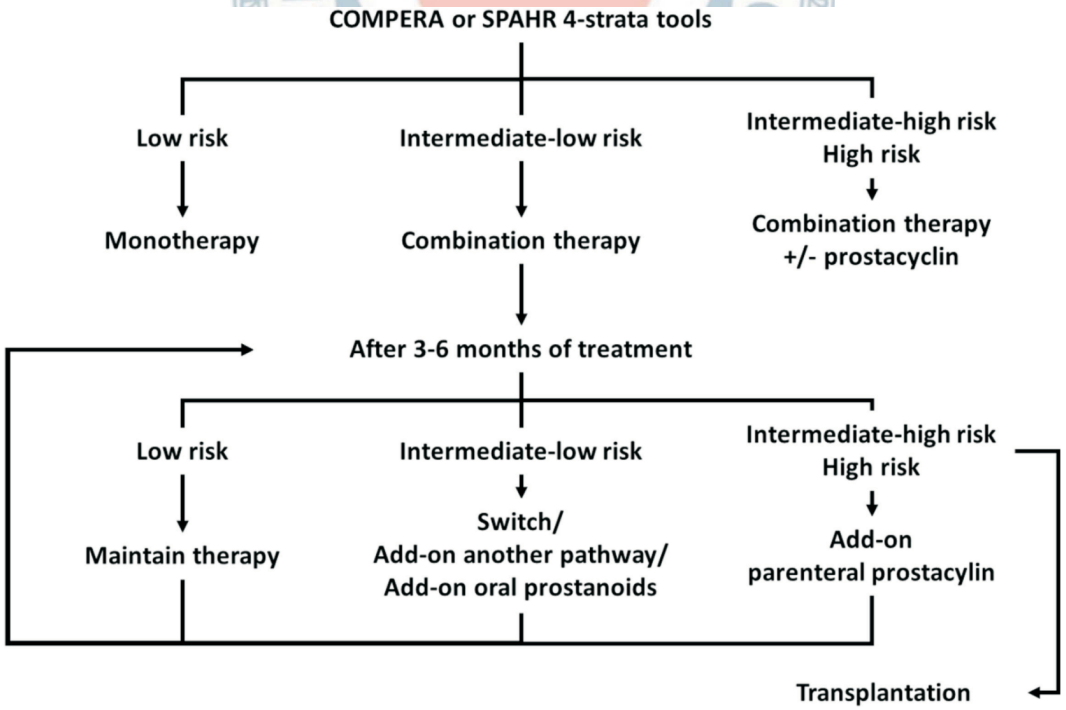


Figure 7. *Risk stratification tools for CTD-PAH. COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; CTD, connective tissue disease; PAH, pulmonary arterial hypertension SPAHR, Swedish PAH Registry.*

for PAH patients with WHO FC II-III and class IIb recommended medications for PAH patients with WHO FC IV.[9,65] In this section, the clinical trials investigating these medications in the management of CTD-PAH are summarized.

Sildenafil

Sildenafil is an orally active, potent, and selective PDE-5 inhibitor. The results of the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) 1 trial, a large double-blind, randomized controlled trial, were reported in 2005, with 278 symptomatic PAH patients enrolled and allocated to receive either placebo or sildenafil (20, 40, 80 mg).[97] The patients who received sildenafil demonstrated an improved exercise capacity and WHO FC along with favorable hemodynamic parameters. Hemodynamic data, including the mPAP, cardiac index, and PVR index, appeared to improve in a dose-dependent manner under sildenafil treatment, while patients treated with sildenafil 20 mg three times daily (tid) reached a maximum 6MWD at the plateau of the dose-response curve.[97] A further open-label uncontrolled extension study (SUPER 2) confirmed the long-term tolerability and WHO FC maintenance or improvement with sildenafil treatment.[98] Patients with a diagnosis of CTD-PAH accounted for approximately 30% of the SUPER-1 study population, with scleroderma (45%) as the most common diagnosis, followed by SLE (23%). In a post hoc analysis of 84 CTD-PAH patients in the SUPER-1 trial, patients receiving sildenafil 20 mg tid exhibited a better exercise capacity, WHO FC and hemodynamic measurements than patients receiving placebo after 12 weeks of treatment.[99]

The Pulmonary Arterial Hypertension Combination Study of Epoprostenol and Sildenafil (PACES-1) trial is a randomized, double-blind, placebo-controlled study in which the efficacy of add-on oral sildenafil was evaluated in PAH patients under stable epoprostenol therapy.[100] In the PACES-1 trial, patients with CTD-PAH accounted for approximately 20% of the total PAH cohort (n = 276), where scleroderma (n = 31) and SLE (n = 14) were the most common CTDs. The dose of sildenafil was titrated from 20 mg tid during the first 4 weeks to 40 mg tid at week 4 and then to 80 mg tid at week 8 when tolerated. Patients receiving add-on sildenafil showed improved 6MWD, hemodynamic parameters, and WHO FC and delayed time to clinical worsening compared to patients receiving placebo. The open-label extension (PACES-2) trial also confirmed the long-term 3-year safety and efficacy of sildenafil as an add-on to the background intravenous epoprostenol therapy.[101]

Tadalafil

Tadalafil is a selective PDE-5 inhibitor that is dispensed once daily. The efficacy of tadalafil was evaluated in the Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) study.[102] For this study, a total of 405 PAH patients who were treatment naive or under background bosentan therapy were enrolled and randomized to receive either placebo or tadalafil (2.5, 10, 20, or 40 mg orally once daily). After the 16-week treatment, patients receiving tadalafil 40 mg once daily demonstrated improved exercise capacity (6MWD), with statistical significance, as well as delayed clinical worsening, reduced incidence of clinical worsening and better quality of life. However, the WHO FC of these patients was not improved significantly in this trial. The subgroup analysis of CTD-PAH patients, accounting for 23% of the study population, also showed an increased 6MWD when treated with 20 mg and 40 mg tadalafil once daily. The long-term safety and efficacy durability (up to 52 additional weeks) of tadalafil were confirmed in the PHIRST-2 trial.[103] In a separate post hoc analysis of the PHRIST-2 trial, both the CTD-PAH and IPAH/heritable PAH groups showed a maintained improvement in the 6MWD, while the CTD-PAH group showed worse outcomes in either safety or efficacy durability than the IPAH/heritable PAH group.[104]

The Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) trial was designed to determine the benefit of initial therapy with a combination of ambrisentan and tadalafil in treatment-naive PAH patients.[105] A total of 500 PAH patients were enrolled and assigned to the combination therapy, ambrisentan monotherapy or tadalafil monotherapy groups in a 2:1:1 ratio. The combination therapy group showed a significantly lower risk of clinical failure events than the two monotherapy groups. The etiology of PAH in approximately 37% of patients in the AMBITION trial was attributed to CTD-PAH. Two post hoc analyses of the AMBITION trial confirmed the benefit of combination therapy over monotherapy in PAH-CTD patients.[106,107]

Riociguat

Riociguat is an oral sGC stimulator approved for the treatment of PAH and chronic thromboembolic PH. The Pulmonary Arterial Hypertension Soluble Guanylate Cyclase–Stimulator Trial 1 (PATENT-1) study was the landmark trial to demonstrate the efficacy of riociguat.[108] A total of 443 PAH patients were assigned to receive placebo, riociguat 1.5 mg tid (1.5 mg-maximum group for exploratory purposes), or riociguat 2.5 mg tid (2.5 mg-maximum group). After 12 weeks of treatment, patients receiving riociguat showed improved exercise capacity and other secondary efficacy endpoints, including PVR, NT-proBNP levels, WHO FC, time to clinical worsening, Borg dyspnea scale score, and quality-of-life variables, compared to those receiving placebo. In the subgroup analysis of 111 CTD-PAH patients, who represented 25% of the study population, a positive trend in the 6MWD was still observed. The PATENT-2 trial further demonstrated sustained improvements in exercise and functional capacity for up to 1 year in PAH patients receiving riociguat, the dosage of which was adjusted up to 2.5 mg tid.[109] Another post hoc analysis of CTD-PAH patients from the PATENT-1 and PATENT-2 trials also revealed a greater PVR and cardiac index improvement in patients receiving riociguat than in those receiving placebo at up to 1 year and a sustained positive trend in the 6MWD and WHO FC at 2 years.[110]

The Riociguat Replacing PDE5i Therapy Evaluated Against Continued PDE5i Therapy (REPLACE) trial is a recently completed randomized controlled trial that assessed the effect of switching to riociguat compared to maintenance on stable PDE-5 inhibitors with or without an endothelin receptor antagonist in PAH patients with intermediate risk.[111] Two hundred ninety-three PAH patients were enrolled, and clinical improvement, which was defined as an absence of clinical worsening and prespecified improvements in at least two of three variables (i.e., 6MWD, WHO FC, and NT-proBNP), was evaluated at 24 weeks. The results showed that the proportion of patients who achieved the primary endpoint was significantly greater in the riociguat group than in the PDE-5 inhibitor group. In the subgroup analysis of CTD-PAH patients in the REPLACE trial, the trend in patients achieving the primary endpoint remained positive.

Recommendations

1. PDE-5 inhibitors such as sildenafil and tadalafil are recommended as monotherapies or components of combined therapy for CTD-PAH patients.
2. An oral sGC stimulator (riociguat) is recommended as a monotherapy or a component of a combined therapy for CTD-PAH patients.

3.2. Pulmonary arterial hypertension medications targeting the endothelial pathway

The overexpression of endothelial 1 (ET-1), a vasoconstrictive peptide, as a result of endothelial cell dysfunction plays a prominent role in the pathogenesis of PAH.[112] Serum plasma concentrations of ET-1 correlate with markers of SSc disease severity, and the expression of ET-1 inversely correlates with survival in patients with PAH.[113] ET-1 exerts its vascular effects by binding to two distinct receptor isoforms in pulmonary vascular smooth muscle cells, endothelin-A (ETA) and endothelin-B (ETB) receptors. Dual ETA and ETB antagonists and selective endothelin receptor antagonists (ERAs) have been developed for the treatment of PAH.[114-116] Three Food and Drug Administration (FDA)-approved ERAs are currently available: bosentan, ambrisentan, and macitentan.

Bosentan

Bosentan is an orally active dual ETA/ETB ERA that received FDA approval in 2001. In the 351 and BREATHE-1 studies,[114,117] the efficacy of bosentan versus placebo was evaluated with a primary endpoint of a change in exercise capacity (6MWD) from baseline to week 16. The subanalysis performed in patients with CTD-PAH (n = 66) showed that at the end of the study, the exercise capacity of the 44 patients treated with bosentan (125 mg twice daily) increased by an average of 19.5 [95% confidence interval (CI): -3.2 to 42.2] meters, whereas that of patients treated with placebo deteriorated by 2.6 (95% CI: -54.0 to 48.7) meters.[118] In contrast to the overall study population, the difference was not significant in the CTD-PAH subgroup. The lack of improvement in 6MWD with bosentan in the specific patient group may be attributable to the intrinsic 6MWD impairment caused by musculoskeletal involvement and deconditioning, as observed in CTD. Sixty-four of these patients were followed up in the open-label extension trial with a mean follow-up duration of 1.8 years. In marked contrast to previously published studies, the 1-year and 2-year survival rates were 86% and 73%, respectively.[119]

Ambrisentan

Ambrisentan is a selective ETA ERA that received FDA approval in 2007 for patients with PAH with a New York Heart Association (NYHA) FC of II-III.

Two large randomized controlled trials (ARIES 1 and 2) assessed the efficacy and safety of ambrisentan (2.5, 5, and 10 mg daily) in PAH. Ambrisentan was well tolerated and induced a significant improvement in the 6MWD and time to clinical worsening relative to placebo.[120] Fischer et al. performed a subanalysis in patients with CTD-PAH (n = 124) based on a pooled analysis of the ARIES 1 and 2 trials (ARIES-C) and their open-label extensions (ARIES-E).[121] At 1, 2, and 3 years, 62.6%, 57.3%, and 58.2% of CTD-PAH patients treated with ambrisentan exhibited an increase in the 6MWD. At three years, 64% of patients were free from clinical worsening, and 76% of patients were still alive.

The AMBITION trial was the first study to evaluate the effect of an initial combination therapy on long-term outcomes in patients with PAH.[105] Five hundred PAH patients were randomized to receive placebo, an upfront combination of ambrisentan and tadalafil (10 mg and 40 mg daily, respectively), or monotherapy with either ambrisentan or tadalafil. In the CTD-PAH subgroup, upfront combination therapy was able to reduce the risk of clinical failure events, including death, hospitalization, and PAH progression [hazard ratio: 0.43 (95% CI: 0.24 to 0.77)], compared to either monotherapy.[106]

Macitentan

Macitentan is the newest dual ERA and was approved by the FDA in 2013 for PAH patients with FC II and III symptoms. Macitentan has been evaluated in a long-term, event-driven randomized controlled trial (SERAPHIN).[116] Macitentan administered once daily decreased the risk of the morbidity/mortality endpoint by 45% versus placebo. Moreover, improvements in functional status and cardiac hemodynamics were observed. Importantly, the effect of macitentan was also maintained in patients on background-specific therapy (mainly sildenafil). The subgroup analysis showed likely clinical benefits in patients with CTD-PAH (n = 224). The SERAPHIN study revealed no liver toxicity, although anemia was observed in approximately 13% of patients taking the 10 mg dose, probably due to fluid retention and hemodilution.

Recommendations

1. ERAs, including bosentan, ambrisentan, and macitentan, are recommended as monotherapy or a part of a combined therapy for CTD-PAH.
2. An ERA in addition to PDE5 inhibitors is recommended as a drug combination therapy for patients with WHO FC II and III CTD-PAH.

3.3. Pulmonary arterial hypertension medications targeting the prostacyclin pathway

Prostacyclin analogs bind to the prostacyclin receptor, leading to an increase in cyclic adenosine monophosphate and corresponding vasodilative, antiproliferative, and antithrombotic effects. Medications that work through the prostacyclin pathway include synthetic prostacyclin (epoprostenol), prostacyclin analogs (treprostinil and iloprost), and selective prostacyclin IP receptor agonists (selexipag). At present, epoprostenol (intravenous), treprostinil (intravenous, subcutaneous, inhaled, and oral), iloprost (inhaled), and selexipag (oral) have been approved by the FDA and European Medicines Agency for the treatment of PAH.[50] Current treatment recommendations for patients with PAH, including CTD-PAH, depend on the results of risk assessment. Epoprostenol monotherapy was the first for which a decrease in mortality was observed in an IPAH clinical trial and improved exercise capacity and cardiopulmonary hemodynamics was observed in patients with PAH-associated scleroderma spectrum disease.[51] Guidelines recommend the use of epoprostenol in high-risk PAH patients. However, analyses of American and European registries have demonstrated an underuse of this drug in clinical practice.[50] A fear of common side effects and the administration route could be related to this finding.[51] Continuous subcutaneous infusion of treprostinil in CTD-PAH patients is associated with improved exercise capacity, PAH symptoms, and hemodynamics according to the results of a randomized controlled trial subgroup analysis. Clinical trials with subcutaneous treprostinil, inhaled iloprost, and treprostinil versus placebo in a wide variety of patients have been conducted, but these trials failed to demonstrate a difference in survival in contrast to epoprostenol under similar conditions.[51] Compared to the overall GRIPHON study population, the CTD-PAH subgroup was slightly older and had more female patients and a shorter time since diagnosis.[122] Selexipag

reduced the risk of the composite morbidity/mortality endpoint in CTD-PAH patients by 41%, and the efficacy was consistent irrespective of baseline PAH therapy and CTD-PAH subtype.[37] Selexipag treatment was well tolerated and delayed the progression of PAH, and the use of multiple PAH therapies could yield benefits in patients with CTD-PAH.

The main drawbacks of epoprostenol are the administration route and associated side effects. However, catheter-associated infections or thromboses that require intravenous line removal are uncommon. Jaw pain, headache, nausea, or diarrhea are more frequent, although they rarely cause drug discontinuation. These symptoms can be easily treated with common analgesic, antiemetic or antidiarrheal agents. New drugs that act on the prostacyclin pathway have been developed to overcome such problems, but the results have been suboptimal. Infusion-site pain with subcutaneous treprostinil may be the reason for premature treatment discontinuation. The gastrointestinal side effects of selexipag are similar to those of epoprostenol.

Recommendations

1. Epoprostenol is still the best treatment option for high-risk PAH patients. The safety and efficacy of epoprostenol, both as a monotherapy and as part of a combination therapy, are supported by clinical trial results and experience. Epoprostenol should be considered a destination treatment in high-risk patients and not only as a bridge to lung transplantation.
2. Continuous subcutaneous infusion of treprostinil in CTD-PAH patients is associated with improved exercise capacity, symptoms of PAH, and hemodynamics.
3. Selexipag reduced the risk of composite morbidity/mortality events and delayed disease progression in CTD-PAH patients.

3.4. Other pulmonary arterial hypertension medications

Oral anticoagulants

The potential benefit of oral anticoagulants in CTD-PH patients is unclear; thus, the routine use of oral anticoagulants is not recommended. In patients with higher thromboembolic risk, such as continuous intravenous prostaglandin users or APS patients, oral anticoagulants may be considered after a careful evaluation of their bleeding risks.

Diuretics

CTD-PH patents may encounter right ventricular failure with fluid overload, as in other PAH patients. Without evidence from randomized controlled trials but based on clinical experiences, diuretics are widely used to relieve symptoms. The monitoring of renal function and electrolytes is important, especially in patients who use a higher diuretic dose or multiple diuretics.

Digoxin

An early report showed that in patients with IPAH and RV failure, acute intravenous digoxin administration improved carbon monoxide levels. However, the efficacy of chronic digoxin use is unknown. Digoxin may be administered to slow the ventricular rate in CTD-PAH patients with atrial arrhythmia.

CCBs

CCBs were widely used to treat PAH before the application of PAH-directed therapy.[123,124] However, CCBs are now recommended only for patients with IPAH, hereditary PAH, or drug-induced PAH with positive vasoreactivity test results. CCBs should be considered only for patients with conditions other than PH (e.g., Raynaud's phenomenon, systemic hypertension, etc.).

Recommendations

1. Oral anticoagulants can be considered in patients with higher thromboembolic risks, such as those with APS or intravenous prostaglandin users.
2. Diuretics may be helpful in relieving right heart failure and fluid overload.
3. Acute use of digoxin may increase cardiac output.
4. CCBs should be considered only in patients with conditions other than PH, such as Raynaud's phenomenon.

3.5. Medical treatments for autoimmune diseases

PAH can be associated with CTDs, especially in patients with SLE, pSS, SSc, and MCTD. The specific pulmonary vasodilator therapy in the setting of CTDs has been discussed above. This section focuses on medical treatments for underlying CTDs in the context of PAH.

Immunosuppressants and conventional disease-modifying antirheumatic drugs

1. Cyclophosphamide

Numerous observational studies have reported that cyclophosphamide, especially combined with glucocorticoids, significantly improved the NYHA functional status and 6MWD in CTD-PAH patients,[123,124] including those with SLE,[46,125-129] MCTD,[126,127,129] pSS,[40,41,129,130] and SSc.[127]

The recommended dose of cyclophosphamide for Asian people is 200 to 500 mg/m^2. The dosing frequency may follow either one of the following protocols:

A. The National Institutes of Health protocol, which indicates 6 monthly doses and then maintenance doses every 3 months until 1 year after remission.[131] The cyclophosphamide dose suggested in the original guidelines is 500 to 750 mg/m^2, but for Asian people, we suggest 200 to 500 mg/m^2. The usual dose used in Taiwan is approximately 10 mg/kg.
B. The Euro-lupus protocol is a high-dose protocol, which indicates 6 monthly doses, followed by a dose 1.5 times the previous dose (according to the leukocyte count), with 2 more doses every 3 months.[131] The suggestion from the original article is 500 mg/m^2 monthly for 6 months (the usual dose used in Taiwan is 500 mg), with the addition of a dose of 250 mg or more cyclophosphamide (according to the leukocyte count, maximal 1500 mg) for 2 more courses every 3 months.

2. Other disease-modifying antirheumatic drugs

Several retrospective cohort studies investigated disease-modifying antirheumatic drugs (DMARDs) and immunosuppressants other than cyclophosphamide. A number of case reports have shown that mycophenolate mofetil effectively improves outcomes in SLE patients with PH.[132,133] Other retrospective cohort studies have shown hydroxychloroquine and chloroquine,[40,41,134-137] methotrexate,[41,130] leflunomide,[130] and tacrolimus[130,138] to be effective in CTD-PAH patients.

3. Early initiation of combination immunosuppressant therapy has also been highly suggested in several studies.[46,126,127]

Glucocorticoids

Glucocorticoids are usually prescribed in combination with immunosuppressants and DMARDs.[35,41,46,129,139] Glucocorticoid therapy, by itself or in conjunction with standard vasodilators, has been shown to be effective in small studies of CTD-PAH patients,[139-141] with doses ranging from 1 mg/kg prednisolone to pulse therapy. At present, there is no consensus on the dosage and duration of glucocorticoids in treating CTD-PAH, and physicians should weigh the efficacy and side effects of glucocorticoids and patients' tolerance in their decision-making.

Biological DMARDs

The role of emerging biological therapies has been evaluated in recent studies. A randomized controlled double-blind trial in patients with SSc-PAH showed that two infusions of rituximab at 1,000 mg administered 2 weeks apart improved the estimated change in 6MWD compared to placebo through 48 weeks.[142] B-cell depletion therapy is a potentially effective and safe adjuvant treatment for SSc-PAH.

In an open-label phase II study of intravenous tocilizumab (8 mg/kg) over 6 months in Group 1 PAH patients, both intention-to-treat and modified intention-to-treat analyses demonstrated no change in the mPVR.[143,144] There were no deaths, and the adverse events were consistent with the known safety profile of tocilizumab.

Future studies are required to confirm disease responsiveness to emerging biological therapies.

Drug-drug interactions

In addition to the medications mentioned above, a literature search on other DMARDs, such as azathioprine and cyclosporin, that are often used in the treatment of autoimmune diseases was performed, but limited evidence was found in the context of PH treatment.

No definitive report on drug-drug interactions between PH medications and cyclophosphamide, rituximab, mycophenolate mofetil, hydroxychloroquine or chloroquine, methotrexate, glucocorticoids, or azathioprine was found. However, some reports on drug-drug interactions among bosentan, leflunomide, and tacrolimus have been published.

Bosentan is a substrate of organic anion transporting polypeptide 1B1 (OATP1B1) and 1B3 transporters. Teriflunomide, the active metabolite of leflunomide, inhibits the activity of OATP1B1/1B3. The concurrent use of leflunomide and OATP1B1/1B3 substrates may result in increased exposure to OATP1B1/1B3 substrates, and a bosentan dose reduction is suggested when bosentan is

used in conjunction with leflunomide.[142]

Bosentan is a cytochrome p450 (CYP) 3A4 and 2C9 inducer. Concurrent use of tacrolimus or cyclosporin with CYP3A inducers may result in decreased tacrolimus trough concentrations and an increased risk of organ rejection.[143,144]

Recommendations

1. Immunosuppressant therapy should be administered to CTD-PAH patients.
2. Early initiation of immunosuppressant therapy is suggested.
3. Immunosuppressant agents such as cyclophosphamide should benefit CTD-PAH patients.
4. Other immunosuppressants/DMARDs/biological agents, including rituximab, mycophenolate mofetil, methotrexate, leflunomide, antimalarial agents, and tacrolimus, may be helpful to CTD-PAH patients, especially those who cannot tolerate or are unresponsive to cyclophosphamide.
5. A combination therapy of cyclophosphamide and glucocorticoids may be useful, and emerging biological therapies may be considered in patients with severe or refractory disease.
6. Patients receiving bosentan and leflunomide or bosentan and tacrolimus and/or cyclosporin should be carefully monitored for drug-drug interactions.

3.6. Pulmonary artery hypertension-specific treatment for connective tissue disease-associated pulmonary artery hypertension patients with comorbidities

The presence of comorbidities in patients with CTD-PAH negatively affects the clinical outcomes. Nearly 75% of PAH patients have at least one comorbidity, and comorbidities increase the complexity of PAH management.[145,146] The presence of comorbidities may lead to difficulties in distinguishing between Group 1 (PAH) and Groups 2-5 (PH due to left heart diseases, lung diseases and/or hypoxia, pulmonary artery obstructions, and unclear and/or multifactorial mechanisms). In the REVEAL study, the most common comorbidities upon PH diagnosis were hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), thyroid disease, and heart failure.[147] During the treatment for CTD-PAH, chronic kidney disease or chronic liver disease may develop and require multiple pharmacological management. The dose of PAH-specific medications should be adjusted according to patients' renal and liver function. Monitoring CTD-PAH patients for drug-drug interactions is also an important issue, as multiple medications for CTD and PAH may be used concomitantly. For example, serum levels of bosentan, a CYP3A4 substrate, may be increased 4-fold in the presence of cyclosporine, and their combined use is contraindicated. Bosentan is also a CYP2C9 inducer, which may increase warfarin metabolism, and the dose of warfarin should be adjusted when it is used concomitantly with bosentan. Clinicians are advised to check the potential drug-drug interactions and to select an appropriate dosage according to the patient's renal and liver function when prescribing PAH-specific medications.

Hypertension is a common comorbidity in CTD-PAH patients, especially in the elderly population. The risk of hypotension should be assessed when antihypertensive and PAH-specific medications are used concomitantly. Beta-blockers benefit patients with hypertension and ischemic heart disease but are not suggested as a first-line antihypertensive drug for PAH patients due to the possibility of right heart failure worsening.[7] The prevalence of left heart disease or ILD is high in CTD patients; thus, it is important to distinguish which of the conditions of Group 1-3 PH is the primary condition. Although some clinical trials showed that PAH-specific medications benefitted Group 3 patients with severe PH (mPAP $\geq$ 35 mmHg), PAH-specific therapies are not currently recommended in patients with Group 2 or 3 PH. If CTD-PAH is the primary condition, PAH-specific medications could be used for patients with COPD or heart failure (combined pre- and postcapillary PH).[148,149] In the presence of these coexisting conditions, physicians should be aware of the possible treatment side effects, especially hypoxia, hypotension, and a worsening of heart failure. An incorrect diagnosis could result in inappropriate treatment choices and a deterioration of a patient's disease status.

In the current ESC/ERS PAH guidelines, it is suggested that patients with low or intermediate risk upon diagnosis should be treated with dual oral combination therapy if possible, and parenteral prostanoids should be included for high-risk patients. Monotherapies are less considered as a first-line therapy. However, for el-

derly patients and patients with multiple comorbidities, the treatment strategy of initial monotherapy with individualized sequential combination therapy is preferred because of potential drug-drug interactions and adverse events associated with polypharmacy (Figure 8).[150] The current evidence for PAH therapy in pediatric patients is limited, and the specific treatment recommendations are mainly applicable to adult patients. A number of randomized controlled studies involving pediatric PAH patients are currently underway. Sildenafil and bosentan were approved for the treatment of pediatric PAH in Europe, and the doses of both should be adjusted according to body weight and low upon initiation. Higher doses may be associated with increased mortality and thus should be avoided. The treatment of pediatric PAH was suggested to be offered by expert centers only.

In summary, comorbidities could mask the symptoms, delay the diagnosis, and worsen the outcomes of PAH. The diagnosis of PAH in CTD patients should be carefully conducted, distinguishing Group 1 from other PH groups, and PAH-specific medication should be prescribed only to CTD-PAH patients. In the management of patients with PAH and comorbidities, drug interactions, compliance, adverse events, and evidence-based strategies should be considered. Initial PAH-specific oral monoagent therapy is favored for elderly patients or patients with multiple comorbidities.

Recommendations

1. Clinicians are advised to check the potential drug-drug interactions and to select an appropriate dosage according to the patient's renal and liver function when prescribing PAH-specific medication(s).
2. Clinicians should monitor patients for hypotension when antihypertensive and PAH-specific medications are used concomitantly. Beta-blockers are not suggested to be used in first-line antihypertensive therapy for PAH patients, and hemodynamics and heart failure symptoms should be monitored during treatment.

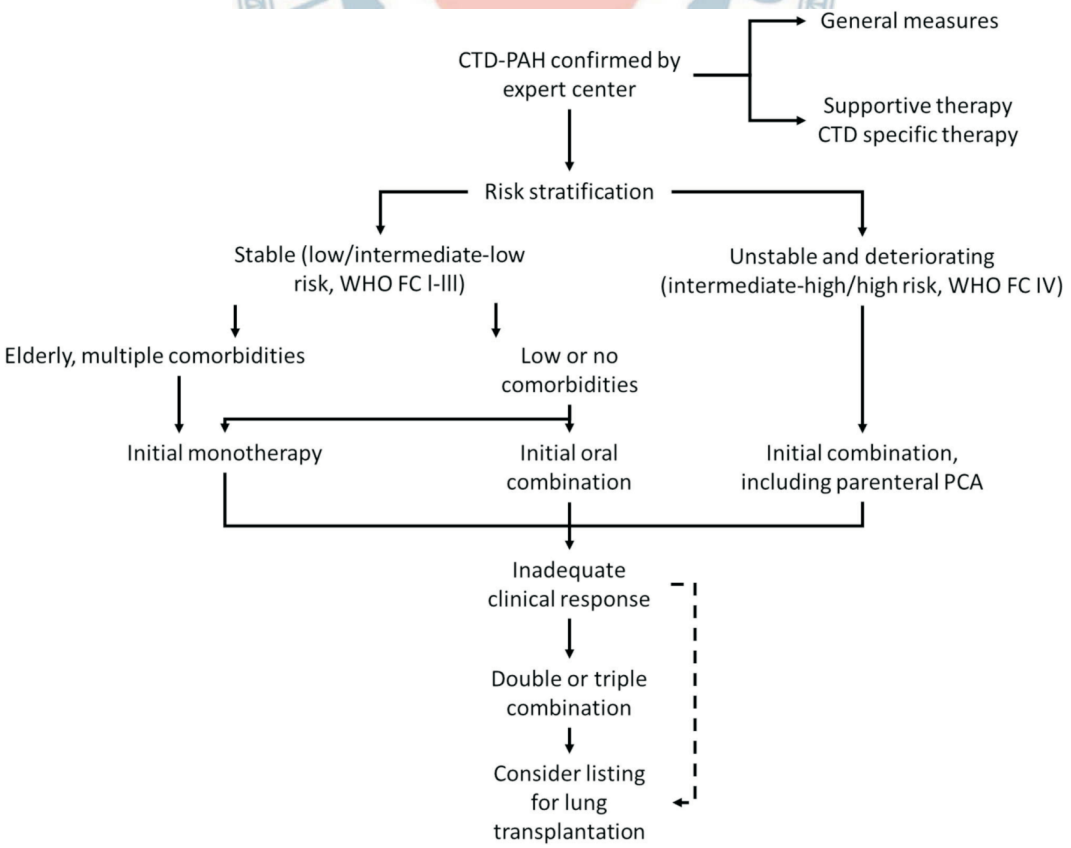


Figure 8. *Treatment strategy according to CTD-PAH risk stratification. CTD, connective tissue disease; PAH, pulmonary arterial hypertension; PCA, prostacyclin analogues; WHO FC, World Health Organization Functional Class.*

3. It is important to distinguish the type of PH (i.e., Group 1, 2, or 3) in CTD patients. PAH-specific therapies are not recommended for patients with Group 2 or 3 PH but can be used for Group 1 patients with concomitant COPD or heart failure.
4. For elderly PAH patients and PAH patients with multiple comorbidities, initial monotherapy with individualized sequential combination therapy is suggested.

4. CONCLUSIONS

PAH is a severe complication of CTDs, especially SSc, SLE, pSS and MCTD. Patients with CTD-PAH have a worse prognosis than patients with IPAH, and for at-risk patients early detection of PAH through regular screening incorporating testing for several relevant autoantibodies and biomarkers may lead to better subsequent outcomes. In the present Taiwan Consensus on CTD-PAH, developed through the collaboration of the TSOC and TCR, specific screening flowcharts for different types of CTDs as well as risk assessment tools applicable to the clinical scenarios in Taiwan were proposed. Furthermore, a broad spectrum of medications targeting different pathways used in the management of CTD-PAH were reviewed comprehensively to form the recommendations. This consensus is not mandatory. Individualized treatment strategies based on clinicians' judgment are still needed in daily practice.

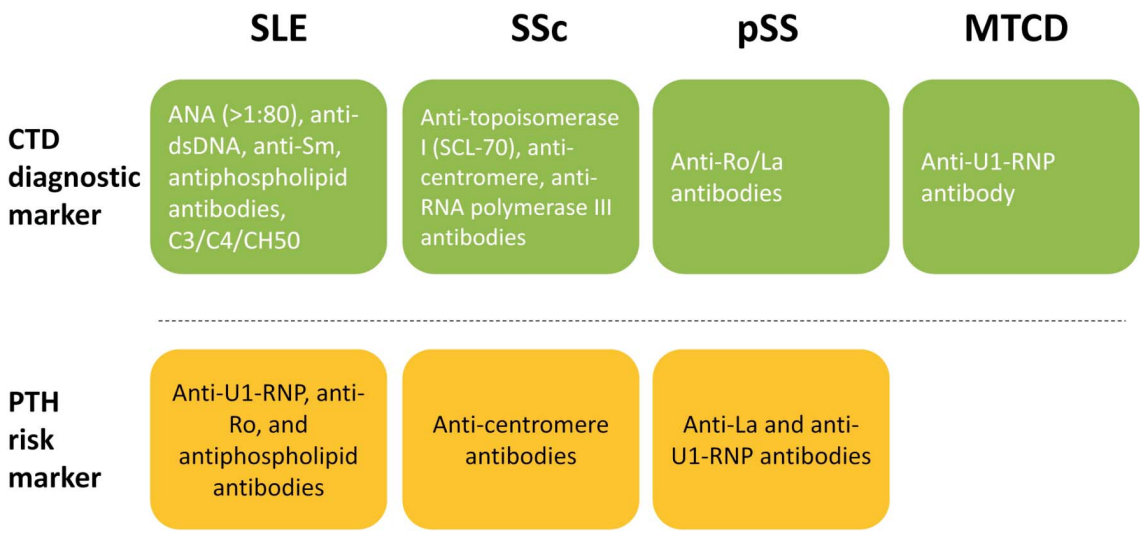
5. NEW KNOWLEDGE GAINED

CTDs needs to be screened in suspected PAH patients as these immunological conditions are common in CTD-PAH population in Asia. Screening methods may include blood tests for ANA, anti-dsDNA, anti-Sm/U1-RNP, APL, anti-topoisomerase I (SCL-70), anti-RNA polymerase III, anti-Ro/La antibodies, and C3/C4/CH50. Echocardiography is recommended for the screen of asymptomatic SSc patients annually and of other subtypes of CTDs with symptoms. The ESC/ERS guideline-based 4-strata risk assessment tools are recommended for the risk evaluation in CTD-PAH patients at baseline and follow-up (Central Illustration).

ACKNOWLEDGMENTS

The authors thank all of the consensus committee members and the Taiwan Society of Cardiology and Taiwan College of Rheumatology for their full support.

Recommended screening blood tests for CTD-PAH



Central Illustration. *Recommended screening blood tests for CTD-PAH. CTD, connective tissue disease; MCTD, Mixed connective tissue disease; PAH, pulmonary arterial hypertension; pSS, primary Sjogren's syndrome; RNP, ribonuclear protein; SLE, systemic lupus erythematous; SSc, systemic sclerosis.*

Pharmedia Medical Integrated Marketing Co. Ltd. provided medical editorial support for the preparation of this manuscript. All authors met the authorship criteria as recommended by the International Committee of Medical Journal Editors (ICMJE) and retained full control of the manuscript content.

DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

REFERENCES

1. Tselios K, Gladman DD, Urowitz MB. Systemic lupus erythematosus and pulmonary arterial hypertension: links, risks, and management strategies. *Open Access Rheumatol* 2017;9:1-9.
2. Jeon CH, Chai JY, Seo YI, et al. Pulmonary hypertension associated with rheumatic diseases: baseline characteristics from the Korean registry. *Int J Rheum Dis* 2012;15:e80-9.
3. Shirai Y, Yasuoka H, Okano Y, et al. Clinical characteristics and survival of Japanese patients with connective tissue disease and pulmonary arterial hypertension: a single-centre cohort. *Rheumatology (Oxford)* 2012;51:1846-54.
4. Wu CH, Lin CY, Hsu CH, et al. Connective tissue disease-associated pulmonary arterial hypertension in southern Taiwan: a single center 10-year longitudinal observation cohort. *Healthcare (Basel)* 2021;9:615.
5. Lin CY, Ko CH, Hsu CY, et al. Epidemiology and mortality of connective tissue disease-associated pulmonary arterial hypertension: a national cohort study in Taiwan. *Semin Arthritis Rheum* 2020;50:957-62.
6. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009;54:S43-54.
7. Humbert M, Kovacs G, Hoeper MM, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J* 2022;43:3618-731.
8. Galie N, McLaughlin VV, Rubin LJ, Simonneau G. An overview of the 6th World Symposium on Pulmonary Hypertension. *Eur Respir J* 2019;53:1802148.
9. Huang WC, Hsu CH, Sung SH, et al. 2018 TSOC guideline focused update on diagnosis and treatment of pulmonary arterial hypertension. *J Formos Med Assoc* 2019;118:1584-609.
10. Chen HA, Hsu TC, Yang SC, et al. Incidence and survival impact of pulmonary arterial hypertension among patients with systemic lupus erythematosus: a nationwide cohort study. *Arthritis Res Ther* 2019;21:82.
11. Li M, Wang Q, Zhao J, et al. Chinese SLE Treatment and Research Group (CSTAR) registry: II. prevalence and risk factors of pulmonary arterial hypertension in Chinese patients with systemic lupus erythematosus. *Lupus* 2014;23:1085-91.
12. Qu J, Li M, Wang Y, et al. Predicting the risk of pulmonary arterial hypertension in systemic lupus erythematosus: a Chinese Systemic Lupus Erythematosus Treatment and Research Group Cohort Study. *Arthritis Rheumatol* 2021;73:1847-55.
13. Huang C, Li M, Liu Y, et al. Baseline characteristics and risk factors of pulmonary arterial hypertension in systemic lupus erythematosus patients. *Medicine (Baltimore)* 2016;95:e2761.
14. Badesch DB, Raskob GE, Elliott CG, et al. Pulmonary arterial hypertension: baseline characteristics from the REVEAL Registry. *Chest* 2010;137:376-87.
15. Khou V, Anderson JJ, Strange G, et al. Diagnostic delay in pulmonary arterial hypertension: insights from the Australian and New Zealand pulmonary hypertension registry. *Respirology* 2020;25:863-71.
16. Kang KY, Jeon CH, Choi SJ, et al. Survival and prognostic factors in patients with connective tissue disease-associated pulmonary hypertension diagnosed by echocardiography: results from a Korean nationwide registry. *Int J Rheum Dis* 2017;20:1227-36.
17. Qian J, Wang Y, Huang C, et al. Survival and prognostic factors of systemic lupus erythematosus-associated pulmonary arterial hypertension: a PRISMA-compliant systematic review and meta-analysis. *Autoimmun Rev* 2016;15:250-7.
18. Nihtyanova SI, Schreiber BE, Ong VH, et al. Prediction of pulmonary complications and long-term survival in systemic sclerosis. *Arthritis Rheumatol* 2014;66:1625-35.
19. Hachulla E, de Groote P, Gressin V, et al. The three-year incidence of pulmonary arterial hypertension associated with systemic sclerosis in a multicenter nationwide longitudinal study in France. *Arthritis Rheum* 2009;60:1831-9.
20. Hachulla E, Launay D, Mouthon L, et al. Is pulmonary arterial hypertension really a late complication of systemic sclerosis? *Chest* 2009;136:1211-9.
21. Yaqub A, Chung L. Epidemiology and risk factors for pulmonary hypertension in systemic sclerosis. *Curr Rheumatol Rep* 2013;15:302.
22. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. *Ann Rheum Dis* 2007;66:940-4.
23. Launay D, Sitbon O, Hachulla E, et al. Survival in systemic sclerosis-associated pulmonary arterial hypertension in the modern management era. *Ann Rheum Dis* 2013;72:1940-6.
24. Weatherald J, Boucly A, Launay D, et al. Haemodynamics and serial risk assessment in systemic sclerosis associated pulmonary arterial hypertension. *Eur Respir J* 2018;52:1800678.
25. Chung L, Farber HW, Benza R, et al. Unique predictors of mortality in patients with pulmonary arterial hypertension associated with systemic sclerosis in the REVEAL registry. *Chest* 2014;146:1494-504.
26. Kolstad KD, Li S, Steen V, et al. Long-term outcomes in systemic sclerosis-associated pulmonary arterial hypertension from the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma Registry (PHAROS). *Chest* 2018;154:

862-71.
27. Humbert M, Yaici A, de Groote P, et al. Screening for pulmonary arterial hypertension in patients with systemic sclerosis: clinical characteristics at diagnosis and long-term survival. *Arthritis Rheum* 2011;63:3522-30.
28. Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjogren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. *Ann Rheum Dis* 2017;76:9-16.
29. Mathai SC. Pulmonary hypertension associated with connective tissue disease. *Cardiol Clin* 2022;40:29-43.
30. Hatron PY, Tillie-Leblond I, Launay D, et al. Pulmonary manifestations of Sjogren's syndrome. *Presse Med* 2011;40:e49-64.
31. Chen HH, Lin CH, Hsieh TY, et al. Factors associated with incident severe pulmonary arterial hypertension in systemic autoimmune rheumatic diseases: a nationwide study. *Rheumatology (Oxford)* 2021;60:5351-61.
32. Flament T, Bigot A, Chaigne B, et al. Pulmonary manifestations of Sjogren's syndrome. *Eur Respir Rev* 2016;25:110-23.
33. Lee AS, Scofield RH, Hammitt KM, et al. Consensus guidelines for evaluation and management of pulmonary disease in Sjogren's. *Chest* 2021;159:683-98.
34. Nakagawa N, Osanai S, Ide H, et al. Severe pulmonary hypertension associated with primary Sjogren's syndrome. *Intern Med* 2003;42:1248-52.
35. Depascale R, Del Frate G, Gasparotto M, et al. Diagnosis and management of lung involvement in systemic lupus erythematosus and Sjogren's syndrome: a literature review. *Ther Adv Musculoskelet Dis* 2021;13:1759720X211040696.
36. Chen CH, Chen HA, Wang HP, et al. Pulmonary arterial hypertension in autoimmune diseases: an analysis of 19 cases from a medical center in northern Taiwan. *J Microbiol Immunol Infect* 2006;39:162-8.
37. Hao YJ, Jiang X, Zhou W, et al. Connective tissue disease-associated pulmonary arterial hypertension in Chinese patients. *Eur Respir J* 2014;44:963-72.
38. Wang J, Li M, Wang Q, et al. Pulmonary arterial hypertension associated with primary Sjogren's syndrome: a multicentre cohort study from China. *Eur Respir J* 2020;56:1902157.
39. Kobak S, Kalkan S, Kirilmaz B, et al. Pulmonary arterial hypertension in patients with primary Sjogren's syndrome. *Autoimmune Dis* 2014;2014:710401.
40. Launay D, Hachulla E, Hatron PY, et al. Pulmonary arterial hypertension: a rare complication of primary Sjogren syndrome: report of 9 new cases and review of the literature. *Medicine (Baltimore)* 2007;86:299-315.
41. Yan S, Li M, Wang H, et al. Characteristics and risk factors of pulmonary arterial hypertension in patients with primary Sjogren's syndrome. *Int J Rheum Dis* 2018;21:1068-75.
42. Zhao J, Wang Q, Liu Y, et al. Clinical characteristics and survival of pulmonary arterial hypertension associated with three major connective tissue diseases: a cohort study in China. *Int J Cardiol* 2017;236:432-7.
43. Safiri S, Kolahi AA, Hoy D, et al. Global, regional and national burden of rheumatoid arthritis 1990-2017: a systematic analysis of the Global Burden of Disease study 2017. *Ann Rheum Dis* 2019;78:1463-71.
44. Montani D, Henry J, O'Connell C, et al. Association between rheumatoid arthritis and pulmonary hypertension: data from the French Pulmonary Hypertension Registry. *Respiration* 2018;95:244-50.
45. Sobanski V, Giovannelli J, Lynch BM, et al. Characteristics and survival of anti-U1 RNP antibody-positive patients with connective tissue disease-associated pulmonary arterial hypertension. *Arthritis Rheumatol* 2016;68:484-93.
46. Xia YK, Tu SH, Hu YH, et al. Pulmonary hypertension in systemic lupus erythematosus: a systematic review and analysis of 642 cases in Chinese population. *Rheumatol Int* 2013;33:1211-7.
47. Rajaram S, Swift AJ, Capener D, et al. Comparison of the diagnostic utility of cardiac magnetic resonance imaging, computed tomography, and echocardiography in assessment of suspected pulmonary arterial hypertension in patients with connective tissue disease. *J Rheumatol* 2012;39:1265-74.
48. Escribano-Subias P, Lopez R, Almenar L, et al. Changes in REVEAL risk score in patients with pulmonary arterial hypertension treated with macitentan in clinical practice: results from the PRACMA study. *BMC Pulm Med* 2020;20:154.
49. Young A, Nagaraja V, Basilious M, et al. Update of screening and diagnostic modalities for connective tissue disease-associated pulmonary arterial hypertension. *Semin Arthritis Rheum* 2019;48:1059-67.
50. Chung L, Liu J, Parsons L, et al. Characterization of connective tissue disease-associated pulmonary arterial hypertension from REVEAL: identifying systemic sclerosis as a unique phenotype. *Chest* 2010;138:1383-94.
51. Condliffe R, Kiely DG, Peacock AJ, et al. Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. *Am J Respir Crit Care Med* 2009;179:151-7.
52. Chung WJ, Park YB, Jeon CH, et al. Baseline characteristics of the Korean registry of pulmonary arterial hypertension. *J Korean Med Sci* 2015;30:1429-38.
53. Fanouriakis A, Tziolos N, Bertsias G, et al. Update omicronn the diagnosis and management of systemic lupus erythematosus. *Ann Rheum Dis* 2021;80:14-25.
54. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Arthritis Rheum* 2013;65:2737-47.
55. Cavagna L, Caporali R, Klersy C, et al. Comparison of brain natriuretic peptide (BNP) and NT-proBNP in screening for pulmonary arterial hypertension in patients with systemic sclerosis. *J Rheumatol* 2010;37:2064-70.
56. Coghlan JG, Denton CP, Grunig E, et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. *Ann Rheum Dis* 2014;73:1340-9.

57. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002;61:554-8.
58. Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjogren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. *Arthritis Rheumatol* 2017;69:35-45.
59. Venables PJ. Mixed connective tissue disease. *Lupus* 2006;15: 132-7.
60. Burdt MA, Hoffman RW, Deutscher SL, et al. Long-term outcome in mixed connective tissue disease: longitudinal clinical and serologic findings. *Arthritis Rheum* 1999;42:899-909.
61. Humbert M, Gerry Coghlan J, Khanna D. Early detection and management of pulmonary arterial hypertension. *Eur Respir Rev* 2012;21:306-12.
62. Hoeper MM, Pausch C, Olsson KM, et al. COMPERA 2.0: a refined four-stratum risk assessment model for pulmonary arterial hypertension. *Eur Respir J* 2022;60:2102311.
63. Sung YK, Chung L. Connective tissue disease-associated pulmonary arterial hypertension. *Rheum Dis Clin North Am* 2015; 41:295-313.
64. Frost A, Badesch D, Gibbs JSR, et al. Diagnosis of pulmonary hypertension. *Eur Respir J* 2019;53:1801904.
65. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016;37:67-119.
66. Hao Y, Thakkar V, Stevens W, et al. A comparison of the predictive accuracy of three screening models for pulmonary arterial hypertension in systemic sclerosis. *Arthritis Res Ther* 2015;17: 7.
67. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol* 2009;53:1573-619.
68. Freed BH, Collins JD, Francois CJ, et al. MR and CT imaging for the evaluation of pulmonary hypertension. *JACC Cardiovasc Imaging* 2016;9:715-32.
69. Minopoulou I, Theodorakopoulou M, Boutou A, et al. Nailfold capillaroscopy in systemic sclerosis patients with and without pulmonary arterial hypertension: a systematic review and meta-analysis. *J Clin Med* 2021;10:1528.
70. Smith V, Vanhaecke A, Vandecasteele E, et al. Nailfold videocapillaroscopy in systemic sclerosis-related pulmonary arterial hypertension: a systematic literature review. *J Rheumatol* 2020; 47:888-95.
71. Jiang Y, Turk MA, Pope JE. Factors associated with pulmonary arterial hypertension (PAH) in systemic sclerosis (SSc). *Autoimmun Rev* 2020;19:102602.
72. Nunes JPL, Cunha AC, Meirinhos T, et al. Prevalence of autoantibodies associated to pulmonary arterial hypertension in scleroderma - a review. *Autoimmun Rev* 2018;17:1186-201.
73. Guillen-Del Castillo A, Callejas-Moraga EL, Garcia G, et al. High sensitivity and negative predictive value of the DETECT algorithm for an early diagnosis of pulmonary arterial hypertension in systemic sclerosis: application in a single center. *Arthritis Res Ther* 2017;19:135.
74. Soukup T, Pudil R, Kubinova K, et al. Application of the DETECT algorithm for detection of risk of pulmonary arterial hypertension in systemic sclerosis: data from a Czech tertiary centre. *Rheumatology (Oxford)* 2016;55:109-14.
75. Kopec G, Tyrka A, Miszalski-Jamka T, et al. Electrocardiogram for the diagnosis of right ventricular hypertrophy and dilation in idiopathic pulmonary arterial hypertension. *Circ J* 2012;76: 1744-9.
76. Schreiber K, Sciascia S, de Groot PG, et al. Antiphospholipid syndrome. *Nat Rev Dis Primers* 2018;4:18005.
77. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006;4: 295-306.
78. Hachulla E, Gressin V, Guillevin L, et al. Pulmonary arterial hypertension in systemic sclerosis: definition of a screening algorithm for early detection (the ItinerAIR-Sclerodermie Study). *Rev Med Interne* 2004;25:340-7.
79. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2015;16:233-70.
80. Foale R, Nihoyannopoulos P, McKenna W, et al. Echocardiographic measurement of the normal adult right ventricle. *Br Heart J* 1986;56:33-44.
81. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010; 23:685-713; quiz 86-8.
82. Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). *Circulation* 2010; 122:164-72.
83. Khanna D, Gladue H, Channick R, et al. Recommendations for

screening and detection of connective tissue disease-associated pulmonary arterial hypertension. *Arthritis Rheum* 2013;65:3194-201.
84. Boucly A, Savale L, Jais X, et al. Association between initial treatment strategy and long-term survival in pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2021;204:842-54.
85. Hoeper MM, Kramer T, Pan Z, et al. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. *Eur Respir J* 2017;50:1700740.
86. Hjalmarsson C, Kjellstrom B, Jansson K, et al. Early risk prediction in idiopathic versus connective tissue disease-associated pulmonary arterial hypertension: call for a refined assessment. *ERJ Open Res* 2021;7:00854-2020.
87. Kylhammar D, Kjellstrom B, Hjalmarsson C, et al. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. *Eur Heart J* 2018;39:4175-81.
88. Boucly A, Weatherald J, Savale L, et al. External validation of a refined four-stratum risk assessment score from the French pulmonary hypertension registry. *Eur Respir J* 2022;59:2102419.
89. Kylhammar D, Hjalmarsson C, Hesselstrand R, et al. Predicting mortality during long-term follow-up in pulmonary arterial hypertension. *ERJ Open Res* 2021;7:00837-2020.
90. Mercurio V, Diab N, Peloquin G, et al. Risk assessment in scleroderma patients with newly diagnosed pulmonary arterial hypertension: application of the ESC/ERS risk prediction model. *Eur Respir J* 2018;52:1800497.
91. Boucly A, Weatherald J, Savale L, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. *Eur Respir J* 2017;50:1700889.
92. Benza RL, Gomberg-Maitland M, Miller DP, et al. The REVEAL Registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension. *Chest* 2012;141:354-62.
93. Qu J, Li M, Zeng X, et al. Validation of the REVEAL prognostic models in systemic lupus erythematosus-associated pulmonary arterial hypertension. *Front Med (Lausanne)* 2021;8:618486.
94. Mullin CJ, Khair RM, Damico RL, et al. Validation of the REVEAL prognostic equation and risk score calculator in incident systemic sclerosis-associated pulmonary arterial hypertension. *Arthritis Rheumatol* 2019;71:1691-700.
95. Benza RL, Kanwar MK, Raina A, et al. Development and validation of an abridged version of the REVEAL 2.0 risk score calculator, REVEAL Lite 2, for use in patients with pulmonary arterial hypertension. *Chest* 2021;159:337-46.
96. Klinger JR, Kadowitz PJ. The nitric oxide pathway in pulmonary vascular disease. *Am J Cardiol* 2017;120:S71-9.
97. Galie N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005;353:2148-57.
98. Rubin LJ, Badesch DB, Fleming TR, et al. Long-term treatment with sildenafil citrate in pulmonary arterial hypertension: the SUPER-2 study. *Chest* 2011;140:1274-83.
99. Badesch DB, Hill NS, Burgess G, et al. Sildenafil for pulmonary arterial hypertension associated with connective tissue disease. *J Rheumatol* 2007;34:2417-22.
100. Simonneau G, Rubin LJ, Galie N, et al. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension: a randomized trial. *Ann Intern Med* 2008;149:521-30.
101. Simonneau G, Rubin LJ, Galie N, et al. Long-term sildenafil added to intravenous epoprostenol in patients with pulmonary arterial hypertension. *J Heart Lung Transplant* 2014;33:689-97.
102. Galie N, Brundage BH, Ghofrani HA, et al. Tadalafil therapy for pulmonary arterial hypertension. *Circulation* 2009;119:2894-903.
103. Oudiz RJ, Brundage BH, Galie N, et al. Tadalafil for the treatment of pulmonary arterial hypertension: a double-blind 52-week uncontrolled extension study. *J Am Coll Cardiol* 2012;60:768-74.
104. Galie N, Denton CP, Dardi F, et al. Tadalafil in idiopathic or heritable pulmonary arterial hypertension (PAH) compared to PAH associated with connective tissue disease. *Int J Cardiol* 2017;235:67-72.
105. Galie N, Barbera JA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med* 2015;373:834-44.
106. Coghlan JG, Galie N, Barbera JA, et al. Initial combination therapy with ambrisentan and tadalafil in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH): subgroup analysis from the AMBITION trial. *Ann Rheum Dis* 2017;76:1219-27.
107. Kuwana M, Blair C, Takahashi T, et al. Initial combination therapy of ambrisentan and tadalafil in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) in the modified intention-to-treat population of the AMBITION study: post hoc analysis. *Ann Rheum Dis* 2020;79:626-34.
108. Ghofrani HA, Galie N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension. *N Engl J Med* 2013;369:330-40.
109. Rubin LJ, Galie N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension: a long-term extension study (PATENT-2). *Eur Respir J* 2015;45:1303-13.
110. Humbert M, Coghlan JG, Ghofrani HA, et al. Riociguat for the treatment of pulmonary arterial hypertension associated with connective tissue disease: results from PATENT-1 and PATENT-2. *Ann Rheum Dis* 2017;76:422-6.
111. Hoeper MM, Al-Hiti H, Benza RL, et al. Switching to riociguat versus maintenance therapy with phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension (REPLACE): a multicentre, open-label, randomised controlled trial. *Lancet Respir Med* 2021;9:573-84.
112. Galie N, Manes A, Branzi A. The endothelin system in pulmonary arterial hypertension. *Cardiovasc Res* 2004;61:227-37.
113. Shetty N, Derk CT. Endothelin receptor antagonists as disease

modifiers in systemic sclerosis. *Inflamm Allergy Drug Targets* 2011;10:19-26.
114. Channick RN, Simonneau G, Sitbon O, et al. Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 2001;358:1119-23.
115. Galie N, Badesch D, Oudiz R, et al. Ambrisentan therapy for pulmonary arterial hypertension. *J Am Coll Cardiol* 2005;46:529-35.
116. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med* 2013;369:809-18.
117. Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;346:896-903.
118. Denton CP, Humbert M, Rubin L, et al. Bosentan treatment for pulmonary arterial hypertension related to connective tissue disease: a subgroup analysis of the pivotal clinical trials and their open-label extensions. *Ann Rheum Dis* 2006;65:1336-40.
119. McLaughlin VV, Presberg KW, Doyle RL, et al. Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004;126:78S-92S.
120. Galie N, Olschewski H, Oudiz RJ, et al. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. *Circulation* 2008;117:3010-9.
121. Fischer A, Denton CP, Matucci-Cerinic M, et al. Ambrisentan response in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) - a subgroup analysis of the ARIES-E clinical trial. *Respir Med* 2016;117:254-63.
122. Gaine S, Chin K, Coghlan G, et al. Selexipag for the treatment of connective tissue disease-associated pulmonary arterial hypertension. *Eur Respir J* 2017;50:1602493.
123. Ando T, Yamasaki Y, Takakuwa Y, et al. Concurrent onset of acute lupus myocarditis, pulmonary arterial hypertension and digital gangrene in a lupus patient: a possible role of vasculitis to the rare disorders. *Mod Rheumatol Case Rep* 2020;4:21-7.
124. Sanges S, Savale L, Lamblin N, et al. Efficacy of immunosuppressants with bridge vasodilator therapy in severe lupus erythematosus-associated pulmonary arterial hypertension. *ESC Heart Fail* 2019;6:1322-5.
125. Dhala A. Pulmonary arterial hypertension in systemic lupus erythematosus: current status and future direction. *Clin Dev Immunol* 2012;2012:854941.
126. Jais X, Launay D, Yaici A, et al. Immunosuppressive therapy in lupus- and mixed connective tissue disease-associated pulmonary arterial hypertension: a retrospective analysis of twenty-three cases. *Arthritis Rheum* 2008;58:521-31.
127. Sanchez O, Sitbon O, Jais X, et al. Immunosuppressive therapy in connective tissue diseases-associated pulmonary arterial hypertension. *Chest* 2006;130:182-9.
128. Tanaka E, Harigai M, Tanaka M, et al. Pulmonary hypertension in systemic lupus erythematosus: evaluation of clinical characteristics and response to immunosuppressive treatment. *J Rheumatol* 2002;29:282-7.
129. Yasuoka H, Shirai Y, Tamura Y, et al. Predictors of favorable responses to immunosuppressive treatment in pulmonary arterial hypertension associated with connective tissue disease. *Circ J* 2018;82:546-54.
130. Liu Z, Yang X, Tian Z, et al. The prognosis of pulmonary arterial hypertension associated with primary Sjogren's syndrome: a cohort study. *Lupus* 2018;27:1072-80.
131. Jacob M. Immunosuppressive drugs. In: G.S. Firestein, et al., Ed. *Firestein & Kelley's Textbook of Rheumatology.* Philadelphia: Elsevier, 2020:1031-45.
132. Machireddy K, Myint Z, Dein E, et al. Mycophenolate mofetil in a lupus patient with pulmonary hypertension. *Cureus* 2018;10:e2121.
133. Nawata M, Nagayasu A, Fujita Y, et al. Severe pulmonary arterial hypertension and interstitial pneumonia related to systemic lupus erythematosus successfully treated with mycophenolate mofetil: a novel case report. *Lupus* 2020;29:1955-60.
134. Kaymak E, Akin AT, Tufan E, et al. The effect of chloroquine on the TRPC1, TRPC6, and CaSR in the pulmonary artery smooth muscle cells in hypoxia-induced experimental pulmonary artery hypertension. *J Biochem Mol Toxicol* 2021;35:e22636.
135. Long L, Yang X, Southwood M, et al. Chloroquine prevents progression of experimental pulmonary hypertension via inhibition of autophagy and lysosomal bone morphogenetic protein type II receptor degradation. *Circ Res* 2013;112:1159-70.
136. Ryan JJ. Chloroquine in pulmonary arterial hypertension: a new role for an old drug? *Circ Cardiovasc Genet* 2013;6:310-1.
137. Wu K, Zhang Q, Wu X, et al. Chloroquine is a potent pulmonary vasodilator that attenuates hypoxia-induced pulmonary hypertension. *Br J Pharmacol* 2017;174:4155-72.
138. Boehm M, Tian X, Ali MK, et al. Improving right ventricular function by increasing BMP signaling with FK506. *Am J Respir Cell Mol Biol* 2021;65:272-87.
139. Kato M, Kataoka H, Odani T, et al. The short-term role of corticosteroid therapy for pulmonary arterial hypertension associated with connective tissue diseases: report of five cases and a literature review. *Lupus* 2011;20:1047-56.
140. Kamata Y, Nara H, Sato H, et al. Effect of steroid pulse therapy on mixed connective tissue disease with pulmonary arterial hypertension. *Ann Rheum Dis* 2005;64:1236-7.
141. Shimomura Y, Hara M, Mizote I, et al. Sildenafil and steroid therapy effectively improved POEMS syndrome-associated pulmonary arterial hypertension. *Int J Hematol* 2010;92:774-6.
142. Zamanian RT, Badesch D, Chung L, et al. Safety and efficacy of B-cell depletion with rituximab for the treatment of systemic sclerosis-associated pulmonary arterial hypertension: a Multicenter, Double-Blind, Randomized, Placebo-controlled Trial. *Am J Respir Crit Care Med* 2021;204:209-21.
143. Niemi M, Backman JT, Kajosaari LI, et al. Polymorphic organic anion transporting polypeptide 1B1 is a major determinant of repaglinide pharmacokinetics. *Clin Pharmacol Ther* 2005;77:

468-78.
144. Niemi M, Pasanen MK, Neuvonen PJ. Organic anion transporting polypeptide 1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake. *Pharmacol Rev* 2011;63:157-81.
145. Hjalmarsson C, Radegran G, Kylhammar D, et al. Impact of age and comorbidity on risk stratification in idiopathic pulmonary arterial hypertension. *Eur Respir J* 2018;51.
146. Lang IM, Palazzini M. The burden of comorbidities in pulmonary arterial hypertension. *Eur Heart J Suppl* 2019;21:K21-8.
147. Poms AD, Turner M, Farber HW, et al. Comorbid conditions and outcomes in patients with pulmonary arterial hypertension: a REVEAL registry analysis. *Chest* 2013;144:169-76.
148. Nathan SD, Barbera JA, Gaine SP, et al. Pulmonary hypertension in chronic lung disease and hypoxia. *Eur Respir J* 2019;53: 1801914.
149. Vachiery JL, Tedford RJ, Rosenkranz S, et al. Pulmonary hypertension due to left heart disease. *Eur Respir J* 2019;53:1801897.
150. Hoeper MM, Apitz C, Grunig E, et al. Targeted therapy of pulmonary arterial hypertension: updated recommendations from the Cologne Consensus Conference 2018. *Int J Cardiol* 2018; 272S:37-45.