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2020 Chinese expert-based consensus on the diagnosis and treatment of connective tissue disease associated pulmonary arterial hypertension

Jiuliang Zhao[1], Qian Wang[1], Qiang Wang[2], Yongfeng Zhang[3], Na Zhang[4], Rong Zhang[5], Yanjie Hao[6], Junfeng Jia[7], Mengtao Li[1,*], Xiaofeng Zeng[1,*] ; Group of Pulmonary Vascular and Interstitial Lung Diseases Associated with Rheumatic Diseases; Chinese Association of Rheumatology and Immunology Physicians, Chinese Medical Doctors Association; Chinese Rheumatic Disease Data Center (CRDC); National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID)

[1]*Department of Rheumatology, Peking Union Medical College Hospital (PUMCH), Chinese Academy of Medical Sciences, National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID), Key Laboratory of Rheumatology and Clinical Immunology, Ministry of Education, Chinese Rheumatism Data Center (CRDC), Chinese SLE Treatment and Research Group (CSTAR), Beijing, China*
[2]*Department of Rheumatology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu Province, China*
[3]*Department of Rheumatology, Beijing Chaoyang Hospital, Capital Medical University, Beijing, China*
[4]*Department of Rheumatology, Tianjin Medical University General Hospital, Tianjin, China*
[5]*Department of Rheumatology, The First Affiliated Hospital of China Medical University, Shenyang, Liaoning Province, China*
[6]*Department of Rheumatology and Clinical Immunology, Peking University First Hospital, Beijing, China*
[7]*Department of Clinical Immunology, PLA Specialised Research Institute of Rheumatology and Immunology, Xijing Hospital, Fourth Military Medical University, Xi'an, Shaanxi Province, China*

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Abstract

Pulmonary arterial hypertension (PAH) is a severe complication of connective tissue disease (CTD) and is one of the leading causes of morbidity and mortality among patients with this condition. To establish an expert-based consensus on the diagnosis and treatment of CTD-associated PAH, a multidisciplinary consensus development panel was established. The consensus panel is composed of 45 experts in rheumatology, cardiology, pulmonology, and radiology, most of whom are members of the Group of Pulmonary Vascular and Interstitial Lung Diseases (ILD) Associated with Rheumatic Diseases. The consensus development panel compiled 9 recommendations for the diagnosis and treatment of CTD-associated PAH. It covers screening, diagnosis, disease evaluation, risk assessment, the use of immunosuppressive agents, and PAH-specific therapy with a treat-to-target approach. The consensus is intended to facilitate decision-making and standardize the care of CTD-associated PAH in China.

Keywords

consensus • connective tissue disease • early screening • pulmonary arterial hypertension • risk assessment • treat to target

INTRODUCTION

Pulmonary hypertension (PH) is a severe complication of connective tissue disease (CTD). Group 1 PH-pulmonary arterial hypertension (PAH) is a common form of PH and is characterized by latent onset, lack of specific clinical manifestations, difficulty in early diagnosis, and poor therapeutic efficacy. As PAH remains one of the leading causes of mortality among patients with CTD, although treatment has been greatly improved, it received more attention from both the rheumatology and immunology communities. The common CTDs that tend to be the underlying causes of PAH include systemic

Address for correspondence:
*Li Mengtao/Zeng Xiaofeng, Department of Rheumatology, Peking Union Medical College Hospital (PUMCH), Chinese Academy of Medical Sciences, National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID), Key Laboratory of Rheumatology and Clinical Immunology, Ministry of Education, Chinese Rheumatism Data Center (CRDC), Chinese SLE Treatment and Research Group (CSTAR), Beijing, China.
E-mail: mengtao.li@cstar.org.cn/zengxfpumc@163.com

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lupus erythematosus (SLE), systemic sclerosis (SSc), mixed connective tissue disease (MCTD), and Sjögren's syndrome (SS). Early diagnosis and standardized treatment of CTD-associated PAH remain major challenges to clinicians.

In recent years, several academic communities from China and abroad, including the European Society of Cardiology (ESC), European Respiratory Society (ERS), American College of Chest Physicians (ACCP), Working Group on Pulmonary Vascular Diseases of Chinese Society of Cardiology, and Working Group on Pulmonary Embolism and Pulmonary Vascular Disease of Chinese Society of Respiratory Diseases, updated their Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension.[1–3] The Group of Pulmonary Vascular and Interstitial Lung Diseases (ILD) Associated with Rheumatic Diseases, Chinese Association of Rheumatology and Immunology Physicians, Chinese Medical Doctors Association, and Chinese Rheumatism Data Center also released the Chinese Expert-based Consensus on the Diagnosis and Treatment of SLE-associated PAH in Adults in 2015.[4] However, since international guidelines rarely include epidemiological and clinical evidence from the Chinese population, the above guidelines/consensuses still face many challenges in guiding the practical diagnosis and treatment of CTD-associated PAH in China. Given this circumstance, the Group of Pulmonary Vascular and Interstitial Lung Diseases Associated with Rheumatic Diseases, along with Chinese Rheumatism Data Center, converged Chinese experts in rheumatology, immunology, cardiology, pulmonology, and ultrasound imaging to develop this consensus based on the latest evidence from China and abroad, combined with clinicians' experience, to seek a balance between the pros and cons of intervention measures. The consensus was made to improve clinicians' understanding of CTD-associated PAH and standardize the clinical diagnosis and treatment of CTD-associated PAH in China. This consensus emphasizes on screening, early diagnosis, and early intervention, and it also highly values the importance of patient follow-up and management to improve the outcome and quality of life of patients with CTD-associated PAH.

The causes of PAH secondary to CTD are complicated. The consensus focuses on Group 1 PH based on the clinical classification of PH recommended by the World Health Organization (WHO), that is, isolated PAH with normal left atrial and pulmonary venous pressure. This type of PH is caused by increased pulmonary vascular resistance (PVR) mainly due to pulmonary arteriolar lesions, without chronic respiratory disorders, chronic thromboembolism, or other known factors.

As the management of CTD-associated PAH remains challenging, a multidisciplinary team led by rheumatologists and composed of specialists in cardiology, pulmonology, intensive care, ultrasound imaging, radiology, and rehabilitation was formed to make the consensus, focusing on the diagnosis, assessment, treatment, and follow-up of patients. Overall, the most appropriate treatment and follow-up plan should be jointly developed by clinicians and patients. The treatment of CTD-associated PAH should consider the available medical resources and take health economics into account.

The members of the consensus panel rated each item on a scale of 0 (strongly disagree) to 10 (strongly agree). The score was calculated as the recommendation level for each item. A total of 45 experts from the consensus panel participated in the scoring (Table 1).

Clinical Scenario 1: How to Diagnose CTD-associated PAH?

Recommendation 1: Clinicians should increase awareness of CTD-associated PAH. CTD patients with suspected PAH should be asked about PAH-associated symptoms in detail and receive a comprehensive physical examination. Transthoracic echocardiogram (TTE), electrocardiogram (ECG) and chest X-ray are recommended as the first-line assessment, and then right heart catheterization (RHC), pulmonary function test, radionuclide pulmonary ventilation/perfusion imaging, CT pulmonary angiogram (CTPA), and other examinations should be completed as early as possible for accurate diagnosis and classification.

The lack of specific clinical manifestations at the early stage of PAH results in a significant delay in the diagnosis of most patients. There was a 2-year delay from the onset of disease to the final diagnosis in more than 20% of patients.[5] Some PAH patients may present only with the symptoms of the underlying diseases in the early stage and then develop right heart failure when the pulmonary arterial pressure is significantly increased. PAH manifests mainly as exertional dyspnea, fatigue, dizziness, chest pain, chest tightness, palpitation, amaurosis, and syncope. PAH complicated by severe right ventricular dysfunction may manifest as lower extremity edema, abdominal distension, poor appetite, diarrhea, and right abdominal pain. Some patients have mechanical compression symptoms due to pulmonary artery dilatation (such as hoarse voice caused by compression of the left recurrent laryngeal nerve, dry cough caused by compression of the airway, angina caused by compression of the left main coronary artery, etc.), and hemoptysis due to the rupture of malformed pulmonary arteriovenous shunt or compensatory dilated bronchial arteries (Figure 1).

Patients with CTD-associated PAH may present precordial bulge caused by right atrial enlargement, accentuation of second heart sound at the pulmonary valve area caused by increased pulmonary arterial pressure, and a holosystolic

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Table 1: Chinese expert-based consensus on the diagnosis and treatment of CTD-associated PAH

	Recommendations	Recommendation level (points, $x \pm SD$)
1	Clinicians should increase awareness of CTD-associated PAH. CTD patients with suspected PAH should be asked about PAH-associated symptoms in detail and receive a comprehensive physical examination. Transthoracic echocardiogram (TTE), ECG and chest X-ray are recommended as the first-line assessment, and then RHC, pulmonary function test, radionuclide pulmonary ventilation/perfusion imaging, CTPA, and other examinations should be completed as early as possible for accurate diagnosis and classification.	9.62 ± 0.66
2	CTD-associated PH is not limited to PAH, and thus, attention should be paid to the potential causes or concurrent causes of PH, including left heart diseases, respiratory disorders and/or hypoxia, pulmonary artery obstructive diseases, and other related conditions.	9.88 ± 0.33
3	For CTD patients at risk of PAH, they should be advised to receive PAH screening, inquired about PAH-associated symptoms every 3–6 months, and screened for TTE every 6–12 months. For patients with confirmed PAH, they should be referred to rheumatologists to clarify the diagnosis of specific CTD such as SLE, SSc, SS, etc.	9.71 ± 0.64
4	Patients with confirmed CTD-associated PAH should be recommended to receive a comprehensive assessment. For CTD, disease activity and degree of damage should be assessed according to the primary diseases. On the other hand, for PAH, the WHO functional class, exercise tolerance, TTE, serum biochemical markers, and hemodynamic parameters should be assessed. Additionally, risk assessment should be performed to adjust the treatment regimen during the follow-up period.	9.86 ± 0.42
5	The treatment of CTD-associated PAH should follow the principle of early individualized treatment, which can delay disease progression, reduce organ damage, prolong survival, and improve the quality of life and prognosis to the maximum extent. The treatment goals for both CTD and PAH should be achieved.	9.74 ± 0.66
6	Intensive immunosuppressive therapy contributes to the improvement of CTD-associated PAH. An individualized immunosuppressive regimen should be developed based on the types of CTD, disease activity, disease duration, organs involved, and disease severity.	9.60 ± 0.77
7	Special attention should be paid to the general and basic treatment for PAH in the management of CTD-associated PAH, including strict contraception measures, rehabilitation exercise, infection prevention, psychological support, diuresis, oxygen inhalation, cardiotonic and anticoagulant therapy, etc.	9.69 ± 0.77
8	It is recommended to initiate PAH-targeted therapy or combination therapy based on risk assessment, and the regimen should be adjusted based on risk assessment during regular follow-up, and finally reach a "low-risk state."	9.88 ± 0.33
9	Regular follow-up is helpful for disease control and prognosis improvement of CTD-associated PAH. It is recommended that patients with CTD-associated PAH should be transferred to the CTD-associated PAH diagnosis and treatment center for management and follow-up.	9.48 ± 0.74

CTD, connective tissue disease; CTPA, CT pulmonary angiogram; ECG, echocardiogram; PH, pulmonary hypertension; PAH, pulmonary arterial hypertension; RHC, right heart catheterization; SS, Sjögren's syndrome; SLE, systemic lupus erythematosus; SSc, systemic sclerosis; WHO, World Health Organization.

murmur of tricuspid regurgitation. Signs such as jugular vein engorgement or distention, hepatomegaly, lower extremity edema, polyserositis, icterus, and cyanosis may be found in patients with severe right ventricular dysfunction. Right ventricular hypertrophy can lead to subxyphoid heaving impulses, third heart sounds indicating elevated right ventricular diastolic filling pressure as well as right ventricular dysfunction, and a gallop rhythm (fourth heart sounds) of the right ventricle, which can be heard in approximately 38% of patients.

At present, resting TTE is recommended as the initial screening method for PAH. The possibility of PH can be assessed according to the tricuspid regurgitation peak velocity and other indicators measured by TTE. The necessity for RHC is determined by the clinical presentations and the possibility of PAH detected by TTE.

RHC examination is not only the "gold standard" to confirm the diagnosis of PAH but also an essential way for differential diagnosis, disease assessment, and therapeutic selection. For RHC examination, right atrial pressure (RAP), pulmonary arterial pressure (systolic, diastolic, mean), pulmonary artery wedge pressure (PAWP), cardiac output (CO), mixed venous oxygen saturation (SvO_2), and PVR must be measured. In experienced centers of pulmonary vascular diseases, the incidence of RHC complications was reported as only 1.1%[6]; Liu et al.[6] from Peking Union Medical College Hospital (PUMCH) reported that PAH patients who received RHC had no pneumothorax, hemothorax, death, prolonged hospital stay, or other serious complications. PAH was defined according to the 2015 ESC/ERS Guidelines as the mean pulmonary arterial pressure (mPAP) $\geq$ 25 mmHg, PAWP $\leq$ 15 mmHg, and PVR $>$ 3 Wood Units (WU) as measured by RHC at sea level in a resting state.[1] In 2018, the 6th World Symposium on Pulmonary Hypertension (WSPH) proposed new definitions for PAH, i.e., precapillary PH was defined as mPAP $>$ 20 mmHg, PAWP $\leq$ 15 mmHg, and PVR $\geq$ 3 WU. Based on the RHC data from a large sample of healthy people, the mPAP at rest was 14.0 ± 3.3 mmHg. Taking this mPAP of 14 mmHg as the mean, mean plus 2 standard deviations, that is mPAP $>$20 mmHg, suggests that mPAP is above the normal upper limit (i.e., >97.5th percentile). Thus, the mPAP cutoff value of PH was determined as 20 mmHg.[7] For patients with CTD-associated PAH, a reduced mPAP cutoff value in the definitions of PAH may facilitate early screening

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and early intervention. It is recommended to increase the frequency of screening and monitor disease progression closely, if necessary. However, the issue of whether patients with mPAP between 21 mmHg and 24 mmHg can benefit from PAH-targeted treatment needs to be studied.

Acute vascular challenging test (AVC) is effective in identifying reversible factors such as pulmonary vasospasm. Although a few patients with CTD-associated PAH meet the positive criteria for AVC, they seldom benefit from calcium channel blocker therapy alone. Therefore, AVC is not recommended as a routine test for patients with CTD-associated PAH.

ECG and chest X-ray can provide important clues for diagnosis, differential diagnosis, and prognosis of PAH, but they cannot be used to confirm or exclude the diagnosis PAH. The ECG of PAH patients typically manifests as pulmonary P waves, right deviation of the QRS axis, right ventricular hypertrophy, right bundle branch block, and prolonged QTc interval. Supraventricular arrhythmias, particularly atrial flutter and atrial fibrillation, may be seen in the late stage of PAH. The chest X-ray of PAH patients usually manifests as bulging pulmonary artery segment and central pulmonary artery dilatation, accompanied by sparse peripheral pulmonary vessels (increased transmittance of the lung field) and right atrial/ventricular enlargement.

In addition, pulmonary function tests (PFTs) are valuable tools in PAH screening and etiological diagnosis, and thus is included in integrated screenings. If the diffusing capacity of the lung for carbon monoxide (DLCO% predicted) shows a trend of decreasing and the ratio of forced vital capacity (FVC% predicted)/DLCO% predicted is increased (especially the ratio of FVC% predicted/DLCO% predicted $>$ 1.6), the possibility of PAH should be considered, and a further screening with TTE is needed.[8, 9] Studies reported that FVC% predicted/DLCO% predicted $>$ 1.8 may predict the occurrence and development of SSc-associated PAH. Radionuclide pulmonary ventilation/perfusion imaging is an important examination to determine whether PAH patients are complicated with pulmonary artery stenosis or chronic thromboembolic pulmonary hypertension (CTEPH). If the presence of segmental perfusion defect does not match the ventilation imaging, the possibility of pulmonary artery stenosis/occlusion needs to be considered. Compared with CTPA, radionuclide pulmonary ventilation/perfusion imaging is more sensitive but prone to false positives, especially in the presence of severe cardiopulmonary diseases, which needs to be differentiated by combining with other examinations. Chest CT, which provides detailed information on cardiac, vascular, pulmonary parenchymal, and mediastinal lesions, is useful for etiological screening of CTD-associated PAH, as well as for imaging assessment of pulmonary vascular interventions.

Clinical Scenario 2: How to Make the Differential Diagnosis of CTD-associated PAH?

Recommendation 2: CTD-associated PH is not limited to PAH, and thus, attention should be paid to the potential causes or concurrent causes of PH, including left heart diseases, respiratory disorders and/or hypoxia, pulmonary artery obstructive diseases, and other related conditions.

CTD-associated PH has its unique complexity. Not all cases of CTD-associated PH are PAH. CTD-associated PH may also include PH due to left heart diseases, ILD-associated PH, CTEPH, and pulmonary veno-occlusive diseases (PVOD). Attention should also be paid to potential or concurrent conditions in CTD patients with confirmed PAH.

(1) Studies have shown that 12% of patients with SSc-associated PH are secondary to left heart diseases, and all of them have postcapillary PH (i.e., PAWP $>$ 15 mmHg) confirmed by RHC. The potential causes include left ventricular dysfunction caused by myocardial fibrosis.[10]
(2) A small number of CTD patients are complicated with PH due to valvular lesions, such as noninfective endocarditis and massive mitral or aortic regurgitation, which can be clearly indicated by TTE or transesophageal echocardiogram.[11]
(3) ILD, especially in patients with SSc and inflammatory myopathy, is a common complication of CTD.[12] Severe pulmonary interstitial fibrosis on chest imaging and lung function tests in some CTD patients reveal severe restrictive ventilatory dysfunction, resulting in pulmonary capillary bed damage and hypoxia-induced capillary remodeling, thus leading to ILD-associated PH.[13] Ventilatory dysfunction found with PFTs during the screening of PAH suggests this type of PH, which is more likely confirmed further by high-resolution chest CT. It should be noted that PAWP $\leq$ 15 mmHg as measured by RHC does not differentiate this type of PH from PAH.
(4) CTD patients are at high risk of venous thromboembolism, especially those with positive antiphospholipid antibodies.[14, 15] As positive antiphospholipid antibody is one of the important risk factors for the transformation of acute pulmonary embolism into CTEPH,[16, 17] radionuclide pulmonary ventilation/perfusion image examination is recommended for the screening of patients with CTD-associated PH. If the result is negative, CTEPH can be excluded, while negative CTPA cannot exclude CTEPH. If radionuclide pulmonary ventilation/perfusion imaging suggests CTEPH, pulmonary arteriogram should be considered for the diagnosis or exclusion of CTEPH.[18]
(5) Others: CTD can also be complicated with pulmonary artery stenosis,[19] PVOD,[20] and other special conditions; however, these diseases are rare in clinical practice.

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In addition, it should be noted that CTD patients may have PAH that is in coexistence with other types of PH, such as congenital heart diseases and other structural abnormalities. Multidisciplinary cooperation is required for a definite diagnosis.

Clinical Scenario 3: How to Diagnose CTD-associated PAH at an Early Stage?

Recommendation 3: For CTD patients at risk of PAH, they should be advised to receive PAH screening, inquired about PAH-associated symptoms every 3–6 months, and screened for TTE every 6–12 months. For patients with confirmed PAH, they should be referred to rheumatologists to clarify the diagnosis of specific CTD such as SLE, SSc, SS, etc.

Patients with CTD-associated PAH are usually lack of specific clinical symptoms at the early stage, while CTD may also have similar manifestations of PAH; thus, PAH is further masked. French PAH cohort studies and PHAROS cohort studies found that 40.5–73.0% of patients with SSc-associated PAH had of WHO functional class (Fc) III-IV at the time of diagnosis.[21] Cohort studies of the Chinese Systemic Lupus Erythematosus Treatment and Research Group (CSTAR) found that approximately 55.1% of patients with SLE-associated PAH,[22, 23] 44.8% of patients with SS-associated PAH,[24] and 52% of patients with SSc-associated PAH[25] had WHO Fc III-IV at the time of diagnosis. DETECT study[26] developed and validated a strategy for early screening of SSc-associated PAH from an international multicenter SSc cohort. The strategy is effective in the early screening of PAH patients and is included in the ERS/ESC Guidelines in 2015. However, a real-world study in Australia in 2017 found that less than half of SSc patients took the initiative to be screened for PAH according to international guidelines.[27] Therefore, it will remain a particularly important task in the field of CTD-associated PAH to increase the awareness of early screening and early interventions.

Rheumatologists should actively screen patients at high risk of CTD-associated PAH to diagnose potential PAH at a subclinical stage when the patient is asymptomatic. Due to the relatively low incidence of PAH in CTD patients, extensive PAH screening for all CTD patients may result in a significant waste of medical resources, and thus there is an urgent need to develop specific screening strategies for different CTDs and for patients with different level of risk factors.

Unlike western countries, SLE is the most common underlying disease in Chinese patients with CTD-associated PAH. Based on the CSTAR multicenter prospective cohort study, it is proposed that active SLE (especially in the presence of pericarditis and pleuritis) and positive anti-RNP antibody (with/without Raynaud's phenomenon) are high-risk factors for PAH in SLE patients. Therefore, for SLE patients with the above high-risk factors, attention should be given to early screening for PAH. It is recommended to perform routine echocardiographic screening every 6–12 months.[6, 28, 29] For patients with suspected PAH by TTE, RHC should be performed as soon as possible to confirm the diagnosis.

For patients with SSc, based on the DETECT study, the guidelines for CTD-associated PAH published by the National Institutes of Health (NIH) in 2013, the PH guidelines by ESC/ERS in 2015, and the WSPH symposium report in 2018, recommend that patients with clinically asymptomatic SSc spectrum diseases (SSc, MCTD, etc.) should receive routine echocardiographic screening, DLCO adjusted by hemoglobin from PFTs, and serological markers testing for PAH each year. A single-center study from PUMCH found that telangiectasia and gastroesophageal reflux disease were also risk factors for SSc-associated PAH. Positive anti-U1RNP antibody, elevated serum IgA level, and an elevated FVC% predictive/DLCO% predictive value were significantly related to SSc-associated PAH.[30]

SS is a common underlying disease of CTD-associated PAH in Chinese population[7, 31]; however, there are few international studies in this field, indicting a lack of evidence-based information for this specific disease. The results of a prospective cohort study of SS-associated PAH in China suggested that PAH screening should be conducted for SS patients with pericardial effusion, liver involvement, Raynaud's phenomenon, and high-titer rheumatoid factor.[24, 32] If the screening does not indicate PAH but the primary disease activity persists in a high level or deteriorates, the screening should be repeated within 3–6 months. If the screening does not indicate PAH and the disease activity remains at a low level or the patient does not show new symptoms, the screening should be repeated once a year.

CTD is one of the most common factors associated with PAH. According to the REVEAL study in the U.S., CTD-associated PAH accounted for 25.3% of all PAH patients.[33] A survey conducted by PUMCH showed that CTD-associated PAH accounted for 31.1% of all hospitalized PH patients. As mentioned above, the most common CTDs that cause PAH include SSc, MCTD, SLE, and SS. Other CTDs, including rheumatoid arthritis, inflammatory myopathy, systemic vasculitis, and adult-onset Still's disease, can also result in PAH but with a much lower frequency. Therefore, all patients diagnosed with PAH should be routinely screened for CTD, including a detailed history with a checking list for joint swelling and pain, Raynaud's phenomenon, purpuric rash, oral ulcer, alopecia, photosensitivity, dry mouth and eyes, enlargement of parotid gland, tooth loss, etc.; careful physical examination including puffy fingers, fingertip ulcer, butterfly erythema, caries, mirror-like tongue, etc.; and laboratory tests for antinuclear antibody, anti-dsDNA antibody, anti-ENA antibody, and antiphospholipid antibodies. The clinical features, treatment

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strategies, and prognosis of PAH varies among different underlying CTDs. Rheumatologists should be involved in the differential diagnosis to identify underlying CTDs and develop a better treatment strategy.

Clinical Scenario 4: How to Comprehensively Assess CTD-associated PAH?

Recommendation 4: Patients with confirmed CTD-associated PAH should be recommended to receive a comprehensive assessment. For CTD, disease activity and damage should be assessed according to the primary diseases. On the other hand, for PAH, the WHO functional class, exercise tolerance, TTE, serum biochemical markers, and hemodynamic parameters should be assessed. Additionally, risk assessment should be performed to adjust the treatment regimen during the follow-up period.

The assessment of CTD-associated PAH aims to assess the disease status of CTD and the severity of PAH after a definite diagnosis of PAH has been made. The comprehensive assessment of the severity and reversibility of the patient's status is critical to the treatment strategy. Additionally, CTD-associated PAH should be continuously assessed during follow-up visits to judge the risk stratification and to adjust the treatment.

Assessment of CTDs

For assessing of the primary CTDs, the most important is to determine whether the primary disease is active or not and whether organ involvement is reversible or not, and then a comprehensive assessment should be performed according to different CTDs. The assessment of disease activity is primarily based on the accepted global activity assessment tools for different CTDs, such as the modified Rodnan skin score for SSc, Systemic Lupus Erythematosus Disease Activity Index (SLEDAI),[34] British Isles Lupus Assessment Group (BILAG) [35] for SLE, and EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) for SS. The physician's global assessment (PGA) is often the final judgment of rheumatologists, with a PGA < 1 indicating relative clinical remission of CTD, while an increase of 0.3 in PGA score indicates worsening disease.

Assessment of PAH

As there is no single indicator can accurately indicate the severity and prognosis of PAH, multiple clinical indicators are needed for comprehensive assessment. Functional assessment, imaging, serological markers, hemodynamic assessments, and assessments of quality of life should be performed for PAH.

1. Functional assessment is important and easy-to-use in clinical practice. It includes the following measures:
   (1) WHO Fc: This is an important tool to assess the severity of disease and predict the survival of PAH patients. The change in Fc after treatment is also a main indicator of efficacy. The WHO function can be classified into classes I–IV, with a similar classification principle to that of the New York Heart Association classification but with an additional description of syncope. The survival rate of patients with class I/II is significantly higher than patients with class III/IV. Deterioration in Fc is an important indicator of disease progression.
   (2) Six-minute walk distance: This refers to the longest distance that a patient can walk in 6 minutes. It is an important objective indicator for exercise capacity and therapeutic efficacy in PAH patients and is closely related to prognosis. The result of this test is influenced by many factors, including sex, age, height, weight, comorbidities, oxygen demend, learning curve, and motivation. It is used in combination with the BORG dyspnea index to assess cardiopulmonary function and the level of effort.
   (3) The cardiopulmonary exercise test: This is an important objective test that quantitatively evaluates the cardiopulmonary functional reserve and exercise capacity. It can be used to assess the therapeutic efficacy and predict the prognosis of PAH patients. PAH patients with significantly impaired exercise capacity, gas exchange, and ventilator efficacy, may present as low end-tidal partial pressure of carbon dioxide (pCO_2), high ventilator equivalents for carbon dioxide (VE/VCO_2), low oxygen pulse (VO_2/HR), and low peak oxygen uptake (peak VO_2). The maximum oxygen uptake <10.4 mL/min/kg is significantly associated with high mortality rate.
2. Imaging assessment is an important and noninvasive method in clinical practice to assess right ventricular function. It includes TTE and cardiac magnetic resonance. The signs of severe PAH that predict poor prognosis revealed by TTE include right ventricular or right atrial enlargement, decreased right ventricle fractional area change, increased Tei index, pericardial effusion, and tricuspid annular plane systolic excursion (TAPSE) <15 mm. Two-dimensional speckle tracking echocardiography can effectively evaluate right ventricular function in PAH patients. Some studies reported that right ventricular longitudinal strain was closely related to right heart failure and clinical deterioration in CTD-associated PAH and right ventricular longitudinal strain <22.9% was an independent risk factor for clinical deterioration. However, it should be emphasized that there is no definite correlation between pulmonary arterial pressure estimated from tricuspid regurgitation velocity alone and the severity of PAH.

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Cardiac magnetic resonance is currently regarded as the "gold standard" for evaluating the size, shape, and function of the right heart, with high reproducibility. Cardiac magnetic resonance can be used to assess the hemodynamic status and estimate stroke volume, CO, pulmonary artery elasticity, and right ventricular mass index. The parameters indicating the severity and prognosis of PAH include right ventricular ejection fraction, right ventricular stroke volume, right ventricular end-diastolic volume, left ventricular end-diastolic volume, ventricular mass index, change in main pulmonary artery area, degree of ventricular septal deviation, average blood flow velocity of pulmonary artery, and delayed enhancement. Cardiac magnetic resonance assessment is conditionally recommended for patients with CTD-associated PAH.

3. Serological markers, including brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP), are most commonly used in evaluating right heart function, PAH risk assessment, and prognosis assessment.[36] Elevated BNP and/or NT-proBNP levels indicate poor prognosis of PAH. Studies have shown that BNP is more closely related to PAH hemodynamic parameters, while NT-proBNP is better used for the prognostic assessment of PAH patients. Compared with BNP, NT-proBNP levels are greatly affected by age and renal function. In recent years, it has been found that red cell distribution width is related to poor prognosis of CTD-associated PAH.
4. Hemodynamic assessment is the most reliable method to assess the severity of PAH. Increase of RAP, decrease of CO, increased PVR, and decreased SvO_2 measured by RHC indicate the progression of PAH and poor prognosis. It is recommended that patients with CTD-associated PAH should receive RHC examination before treatment to evaluate the severity of PAH. During follow-up, RHC can be repeated to effectively evaluate the change of PAH status and help to determine whether treatment goal has been achieved or whether intensive treatment is needed.

In recent years, the concept of PAH risk assessment has been widely accepted. Prospective multicenter cohort studies in France,[37] Sweden,[38] and Germany[39] verified that the risk assessment in 2015 ESC/ERS PH guidelines could be applied to predict the outcome of PAH. The risk assessment formula of the U.S. REVEAL study cohort also has a similar predictive value.[40] In addition, several studies have shown that the risk assessment is also applicable to patients with SSc-associated PAH,[41] SLE-associated PAH, and SS-associated PAH.[42] However, the risk assessment in the 2015 ESC/ERS PH guidelines has several limitations. Some PAH patients may be classified into different risk groups based on various parameters. In addition, it is difficult to implement the risk assessment in real clinical practice due to numerous parameters included. It was proposed at the 2018 WSPH that a simplified PAH risk assessment scale might be applicable to clinical practice (see Table 2).[43] It should be noted that continuous monitoring of risk stratification and adjustment of treatment regimen accordingly during regular follow-up of patients with CTD-associated PAH could prompt better prognosis.[44]

Clinical Scenario 5: What are the Principles and Objectives of Treatment for CTD-associated PAH?

Recommendation 5: The treatment of CTD-associated PAH should follow the principle of early individualized treatment, which can delay disease progression, reduce organ damage, prolong survival, and improve the quality of life and prognosis to the maximum extent. The treatment goals for both CTD and PAH should be achieved.

The treatment goal of CTD-associated PAH is to improve the patient's symptoms in a timely manner, promote quality of life, and enhance prognosis to the maximum degree. Achieving treatment goals of both CTD and PAH is the basis (Figure 2).

(1) Clinical remission of CTD. In general, PGA < 1 indicates clinical goal achievement of CTD. Three common CTDs can be used as examples: low disease activity of SLE, defined as SLE activity score (SLEDAI-2K) of ≤4,

Table 2: Simplified risk assessment of PAH

Prognostic determinants		Low risk	Medium risk	High risk
A	WHO Fc	I, II	III	IV
B	6-minute walk distance	>440 m	165–440 m	<165 m
C	Plasma BNP/NT-proBNP level or RAP	BNP < 50 ng/L, NT-proB-NP < 300 ng/L or RAP < 8 mmHg	BNP 50–300 ng/L, NT-proB-NP300–1400 ng/L or RAP 8–14 mmHg	BNP > 300 ng/L, NT-proBNP > 1400 ng/L or RAP > 14 mmHg
D	Hemodynamic parameters	CI ≥ 2.5 L/min/m² SvO_2 > 65%	CI 2.0–2.4 L/min/m² SvO_2 60–65%	CI < 2.0 L/min/m² SvO_2 < 60%

BNP, brain natriuretic peptide; Fc, functional class; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; SvO_2, mixed venous oxygen saturation; RAP, right atrial pressure; WHO, World Health Organization. Judgment criteria: low risk: meets at least three low-risk criteria and none of the high-risk criteria; high risk: meets two high-risk criteria, including the cardiac index or SvO2; medium risk: with neither a low risk nor a high-risk criterion. The expected 1-year mortality rates of low-, medium- and high-risk patients are <5%, 5–10%, and >10%, respectively.

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classification of C/D/E in each category of the BILAG system, PGA of <1, prednisone dose of ≤7.5 mg per day, and no immunosuppressants used; remission of SLE is defined as SLEDAI scores of 0, PGA of <0.5, and use of only antimalarial drugs. Low disease activity of SS is defined as ESSDAI < 4; the treatment goal of SS is defined as reduction in ESSDAI ≥ 3. For SSc, even though there is no clearly defined disease activity assessment system, no progression in skin, lung interstitial fibrosis, or vascular lesions (fingertip ulcers, PAH) in a short term can be taken as the treatment goal. In the meantime, studies have shown that SLE-associated PAH may also have different clinical subtypes, including "vasculopathy" and "vasculitis" according to clinical features and disease activity. There are differences in the prognosis of the two types and the treatment strategies may also be different.[45]

(2) Treat the PAH to target. PAH should be treated to reach the goal, that is, to achieve a low-risk state according to the simplified PAH risk assessment.

Although PAH is not included in the assessment of disease activity of SLE, SS, or SSc, it should be taken as a part of the organ involvement for comprehensive assessment and individualized treatment in clinical practice.

Clinical Scenario 6: What is the Immunosuppressive Therapy Strategy for CTD-associated PAH?

Recommendation 6: Intensive immunosuppressive therapy contributes to the improvement of CTD-associated PAH. An individualized immunosuppressive regimen should be prescribed based on the types of CTD, disease activity, disease duration, organs involved, and disease severity.

Compared to idiopathic PAH (IPAH), the treatment of CTD-associated PAH is more complicated. Both PAH and the primary CTDs should also be well controlled to improve the long-term prognosis and quality of life of patients.

Pulmonary vascular injury due to inflammation plays an important role in the pathogenesis of PAH.[46] In patients with early onset and active disease, especially in patients with SLE or MCTD-associated PAH, high-dose glucocorticoids combined with immunosuppressants can effectively control or even "cure" PAH.[47, 48] Intensive immunosuppressants include cyclophosphamide, mycophenolate mofetil,[49] and calcineurin inhibitors, of which cyclophosphamide is the most well studied. It is recommended to choose immunosuppressants based on the organ involved and the severity of the CTD. For patients with a long disease course and stable CTD, it is suggested to continue immunosuppressive therapy with low-dose glucocorticoids and immunosuppressants, such as mycophenolate mofetil, azathioprine, methotrexate, or hydroxychloroquine, for remission maintenance. For patients with SSc-associated PAH, studies have shown that glucocorticoids and immunosuppressants may not improve symptoms, hemodynamics, or prognosis.[50] Therefore, the issue of whether glucocorticoids and immunosuppressants are used in SSc-associated PAH needs to be determined according to the stage of SSc and organ involvement.

A single-center prospective clinical cohort study from PUMCH indicated that in patients with SLE-associated PAH, intensive immunosuppressive therapy may achieve the treatment goal earlier and improve long-term prognosis compared with those without intensive immunosuppressive therapy. Patients with SS-associated PAH may also benefit from intensive immunosuppressive therapy. For a small proportion of patients with CTD-associated PAH, especially those with SLE-associated PAH, case reports showed that remission of SLE after adequate and intensive immunosuppressive therapy could reverse PAH.[51]

Clinical Scenario 7: What is the Supportive Treatment for CTD-associated PAH?

Recommendation 7: Special attention should be paid to the general and basic treatment for PAH in the management of CTD-associated PAH, including strict contraception measures, rehabilitation exercise, infection prevention, psychological support, diuresis, oxygen inhalation, cardiotonic and anticoagulant therapy, etc.

General measures

(1) Contraception: The mortality of PAH patients is significantly increased during pregnancy. Most patients with CTD are females of childbearing age. Patients should be instructed to follow contraceptive measures. As oral contraceptive agents may increase the risk of thrombosis, barrier contraceptive methods are generally recommended. If CTD-associated PAH is diagnosed during pregnancy, the termination of pregnancy should be considered. For those with continued pregnancy, the patients must be transferred to CTD-associated PAH referral centers for comprehensive assessment and treatment as soon as possible.

(2) Exercise rehabilitation: CTD-associated PAH patients who are relatively stabilized are recommended to undergo moderate level exercise and rehabilitation, which is helpful for improving exercise capacity, cardiopulmonary function, and quality of life.[52] It is recommended to implement rehabilitation programs in centers experienced with PAH patient rehabilitation and to avoid significant shortness of breath, vertigo, and chest pain.

(3) Infection prevention: For immunodeficiency and long-term use of immunosuppressive medications in CTD patients, it is necessary to pay attention to infection, which may lead to disease. Adjustment of the intensity

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of immunosuppressive therapy and regular immunization against influenza and pneumococcal pneumonia and other inactivated vaccine immunizations are recommended.

(4) Psychological support: As patients with CTD-associated PAH are prone to anxiety and depression,[53] their psychological status should be fully considered and assessed. Family members are encouraged to give psychological support. Patients and their families should be inspired to maintain confidence in treatment, avoid pessimism and abandonment of treatment, and actively cooperate with the diagnosis and treatment. If necessary, psychologists should be involved in intervention and counseling.

(5) Travel: Patients with WHO Fc III–IV or arterial blood gas [Partial pressure of oxygen (PaO_2)] < 60 mmHg should avoid travel under hypoxic conditions (such as travel to regions with an altitude > 1500–2000 m, air travel without O_2 supplementation, or diving).

Supportive treatment

(6) Diuretics: The CTD-associated PAH patients with decompensated right heart failure is often complicated by sodium and fluid retention, manifested as increased central venous pressure (CVP), liver congestion, ascites, and peripheral edema. Diuretics can effectively improve these symptoms. Commonly used diuretics include loop diuretics and aldosterone receptor antagonists.[54] During the application of diuretics, renal function and blood biochemistry should be monitored to avoid prerenal failure caused by decreased intravascular volume, as well as electrolyte imbalance. Clinically, diuretics should be used with caution in patients with volume depletion, especially low RAP measured by RHC, severe left ventricular compression on TTE, and low blood pressure.

(7) Oxygen: Studies have confirmed that for PAH patients, long-term oxygen therapy helps to reduce mPAP and PVR. When peripheral oxygen saturation is < 91% or arterial oxygen pressure is < 60 mmHg, oxygen therapy is recommended to maintain arterial blood gas [arterial oxygen pressure (PaO_2)] >60 mmHg. For patients with CTD and ILD, long-term oxygen therapy is beneficial.

(8) Digoxin: Digoxin can enhance cardiac contractility, improve CO, and control the ventricular rate in patients with PAH, but the long-term efficacy is still unknown.

(9) Iron supplements: Iron deficiency is common in PAH patients, especially those with CTD-associated PAH,[55] which may result in decreased exercise capacity and increased mortality. The etiology of iron deficiency in patients with PAH is iron metabolism disorder and long-term chronic inflammation. Patients with severe diseases may develop iron deficiency anemia.[56–58] Routine monitoring of iron status during follow-up is recommended, and iron substitution should be considered if necessary.

(10) Anticoagulation: The risk-benefit ratio of oral anticoagulant therapy in CTD-associated PAH is not clear, and anticoagulant strategies should be considered based on the thrombophilic predisposition of the patients.[59–61] For CTD patients with a moderate-to-high probability of pulmonary embolism indicated by radionuclide pulmonary ventilation/perfusion imaging, especially in those with positive antiphospholipid antibodies, oral vitamin K antagonists are recommended for long-term anticoagulation, with a targeted international normalized ratio (INR) of 2.0–3.0. The role of new oral anticoagulants in CTD-associated PAH is not clear.

(11) Calcium channel blockers (CCBs): Only AVC-positive IPAH patients may benefit from CCBs, while it remains unclear whether AVC-positive CTD-associated PAH patients could benefit from CCBs. For patients using CCBs, therapeutic response assessment should be performed every 3 months, and if the response is inadequate, the dose should be gradually reduced until discontinuation.

Clinical Scenario 8: How to Select Targeted Drug Therapy for CTD-associated PAH?

Recommendation 8: It is recommended to initiate PAH-targeted therapy or combination therapy based on risk assessment, and the regimen should be adjusted based on risk assessment during regular follow-up, and finally reach a "low-risk state."

With the advancement in the treatment of PAH, targeted medications have greatly improved the prognosis. The targeted medications currently available include endothelin receptor antagonists (ERAs), prostacyclin analogs (PGs),[62, 63] prostacyclin IP receptor agonists, phosphodiesterase type-5 inhibitors (PDE-5i),[64] and guanylate cyclase agonists (Table 3). All targeted medications can be used alone or combined in the treatment of CTD-associated PAH. Currently, there are 7 targeted medications with indications for PAH in China, including bosentan,[65] ambrisentan,[66] macitentan,[67] iloprost,[62] treprostinil,[63] selexipag,[68] and riociguat.[69] In most phase II/III clinical studies of targeted medications, including the SERIPHIN,[70] GRIPHON,[71] and AMBITION[70] studies, a significant proportion of patients with CTD-associated PAH were included, and in the subgroup analysis of CTD-associated PAH, patients with CTDs, especially those with SSc, had a significant benefit.[72, 73] Additionally, sildenafil,[71] tadalafil,[74] vardenafil, and other PDE-5i have been approved internationally for the treatment of PAH. Although currently there is no indication for PAH in China, these inhibitors have been widely used due to their reliable efficacy and relatively low price.

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Table 3: Types, recommended dosage, and adverse reactions of PAH-targeted drugs

Generic name	Indications	Recommended dosage (adults)	Adverse reactions
Endothelin receptor antagonist			
Bosentan	PAH	oral; 62.5–125 mg, twice daily	Blood transaminase elevation, peripheral edema, anemia
Ambrisentan	PAH	oral; 5–10 mg, once daily	Headache, peripheral edema, anemia
Macitentan	PAH	oral; 10 mg, once daily	Anemia
PGs			
Iloprost	PAH	Aerosol inhalation; 10–20 μg each time, 6–9 times a day, special atomization device is required	Flushing, hypotension, cough, headache
Treprostinil	PAH	Titration is required, continuous subcutaneous and intravenous pumping; starting at 1.25 ng/kg/min, gradually increasing to 20–40 ng/kg/min is allowed	Injection site pain, headache, gastrointestinal discomfort
Beraprost	None	oral; 40–120 μg, four times daily	Headache, flushed face
Prostacyclin IP receptor agonist			
Selexipag	PAH	Titration is required, oral; 200 μg, twice daily, dose titrated up every week by 200 μg increments to the maximum tolerated dose of 1600 μg, twice daily	Headache, gastrointestinal symptoms, jaw pain
Phosphodiesterase type-5 inhibitor(s)			
Sildenafil	None	oral; 20–80 mg, thrice daily	Flushing, visual disturbance
Tadalafil	None	oral; 10–40 mg, once daily	Flushing, myalgia
Vardenafil	None	oral; 5–10 mg, twice daily	Flushing, myalgia
Guanylate cyclase agonist			
Riociguat	PAH and CTEPH	Titration is required, oral; 1 mg, initially thrice daily, titrated up every 2 weeks by 0.5 mg increments and gradually increase to the maximum tolerated dose of 2.5 mg, thrice daily	Hypotension, gastrointestinal symptoms, headache

CTEPH, chronic thromboembolic pulmonary hypertension; PGs, prostacyclin analogs; PAH, pulmonary arterial hypertension.

Although great progress has been made in PAH drug therapy in recent years, the long-term prognosis of patients is still unsatisfactory. For PAH, a disease with multiple pathogenic pathways, combined therapy is theoretically more effective than monotherapy.[75] Combined therapy with PAH-targeted drugs can be carried out with two strategies: sequential combination therapy and initial combination therapy. The results of multiple randomized controlled trials published in recent years have shown that both sequential combination therapy and initial combination therapy can significantly reduce the occurrence of clinical exacerbation. Therefore, PAH patients with a medium- or high-risk state, except those who are older, or who are suspected to have PVOD/PCH, are recommended to receive initial combination therapy. With the increased number of PAH-targeted medications, reduction in drug price, and increasing support of the national health insurance policy, the proportion of patients with CTD-associated PAH receiving combination therapy in China has been significantly increased; yet, the proportion of patients receiving initial combination therapy or intensive combination therapy is still very low.

Lung transplantation or combined heart-lung transplantation should be considered in patients with a poor response after adequate medical treatment combined with PAH-targeted therapy (intravenous or subcutaneous prostacyclin has been used as part of the combination therapy).[76] CTD-associated PAH is not a contraindication for organ transplantation, and it has been shown that patients with SSc-associated PAH and IPAH have a comparable prognosis from organ transplantation.[77] However, as most patients with CTD-associated PAH are in a state of immunodeficiency due to the long-term use of glucocorticoids and immunosuppressants, the risk of opportunistic infection during perioperative periods of organ transplantation is significantly increased. Therefore, it is necessary to strengthen monitoring.

Clinical Scenario 9: What is the Standardized Management of Patients with CTD-associated PAH?

Recommendation 9: Regular follow-up is helpful for disease control and prognosis improvement of CTD-associated PAH. It is recommended that patients with CTD-associated PAH should be transferred to the CTD-associated PAH diagnosis and treatment center for management and follow-up.

CTD-associated PAH is a high-risk state. Regular follow-up, adherence to doctor's advice for medications, and enhancement

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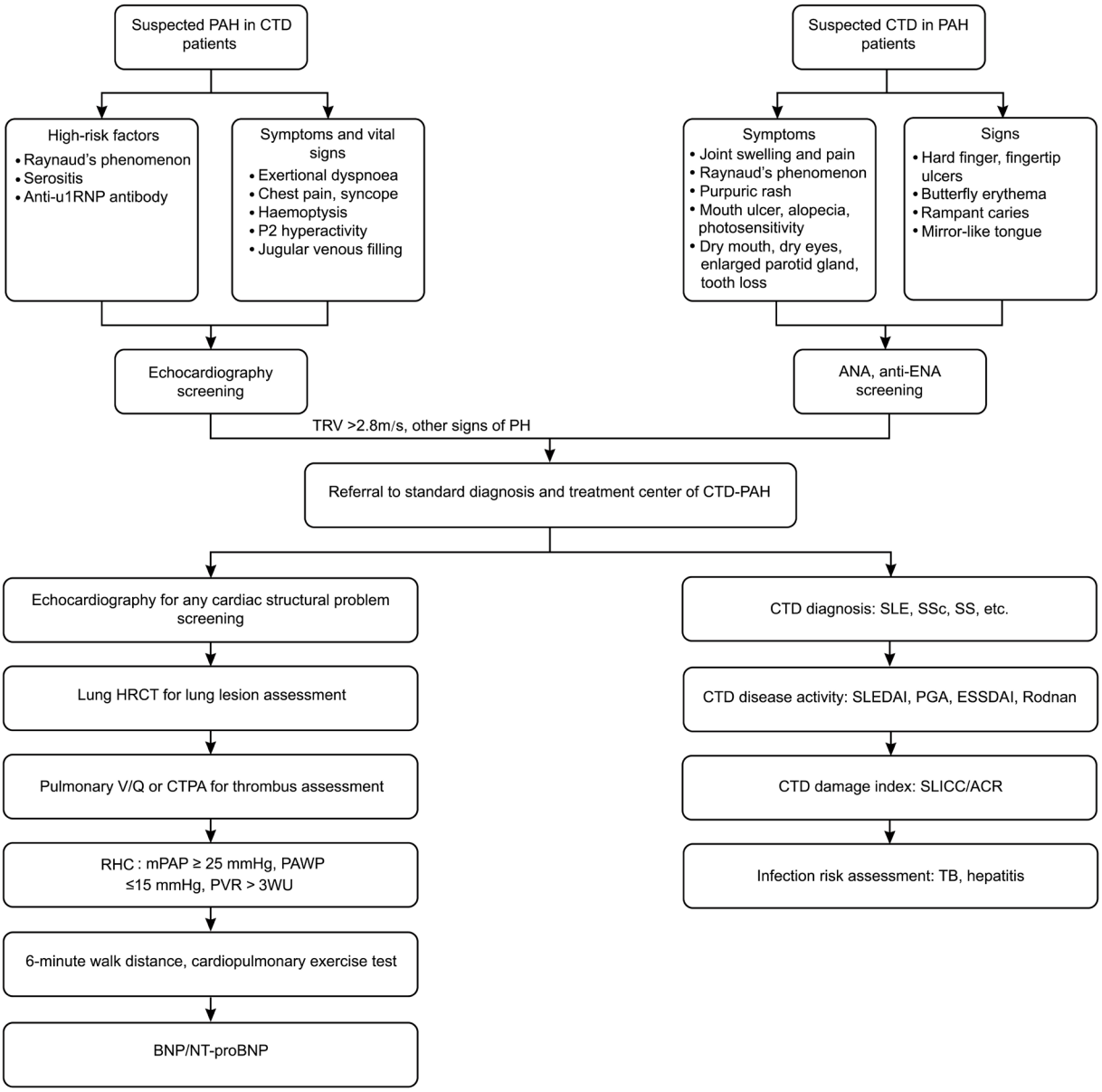

Figure 1: Screening and assessment flow-chart of CTD-associated PAH. BNP, brain natriuretic peptide; CTD, connective tissue disease; CTPA, CT pulmonary angiogram; ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; PAWP, pulmonary artery wedge pressure; PGA, physician's global assessment; RHC, right heart catheterization; SS, Sjögren's syndrome; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SSc, systemic sclerosis. RNP, ribonucleoprotein; ANA, antinuclear antibody; ENA, extractable nuclear antigen; TRV, tricuspid regurgitated velocity; HRCT, high-resolution computed tomography; SLICC, Systemic Lupus Erythematosus International Collaborating Clinics; ACR, American College of Rheumatology; TB, tuberculosis

of disease-related education should be emphasized in the management. The follow-up team should be composed of rheumatologists, cardiologists, and respiratory specialists.

1. Purpose of follow-up: The follow-up of patients with CTD-associated PAH is aimed to evaluate and monitor treatment efficacy to achieve the "double targets" in the shortest time possible.
2. Frequency of follow-up: The follow-up frequency should be adjusted according to each patient's characteristics (sex, age), underling CTDs, PAH risk stratification, and complications (pulmonary infection,

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ILD, or heart failure). In general, the follow-up interval should be every 1–3 months when CTD or PAH is not stable. The follow-up interval should be adjusted according to the treatment response. The follow-up interval can be adjusted to once every 3–6 months when the CTD is in remission and the target of PAH has been reached, i.e., when the "double target" has been achieved. Patients should be advised to make visits at any time when their clinical condition deteriorated, or complications occur.

3. Assessment during follow-up: Noninvasive methods are preferred to CTD and PAH assessment. For CTD, disease activity of the primary diseases, organ damages, and complications should be assessed during each visit. In terms of PAH, WHO Fc, 6-minute walk distance, cardiopulmonary exercise test (conditional), BNP/NT-proBNP, echocardiography, or cardiac magnetic resonance imaging should be included. When the cause of disease aggravation is unknown or an accurate assessment of risk is needed, a repeated RHC may be considered. Rheumatologists should not rely on the pulmonary arterial pressure estimated by TTE. The importance of comprehensive assessment of PAH should be emphasized.
4. Most patients with CTD-associated PAH require multiple concomitant medications. Special attention should also be paid to drug interactions and drug-related adverse reactions during follow-up. For example, CYP3A family isoenzyme 4 (CYP3A4) inhibitors (with a typical representative of triazole antifungal drugs) and CYP2C9 inhibitors may lead to a significant increase in plasma concentration of bosentan, and thus the combination of these drugs is contraindicated. CYP3A4 inducers such as carbamazepine, phenytoin, phenobarbital, and rifampicin may significantly reduce the plasma concentrations of PDE-5i.

Members of the consensus expert group

Wang Qian (Department of Rheumatology, Peking Union Medical College Hospital (PUMCH), Chinese Academy of Medical Sciences, National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID), Key Laboratory of Rheumatology and Clinical Immunology, Ministry of Education, Chinese Rheumatism Data Center (CRDC), Chinese SLE Treatment and Research Group (CSTAR)); Wang Yan (Department of Rheumatology, First Affiliated Hospital Affiliated to Harbin Medical University); Wang Yining (Department of Radiology, Peking Union Medical College Hospital (PUMCH), Chinese Academy of Medical Sciences); Wang Qiang (Department of Rheumatology, The First Affiliated Hospital of Nanjing Medical University); Lu Xin (Department of Rheumatology, China–Japan Friendship Hospital); Ye Shuang (Department of Rheumatology, Ren Ji Hospital South Campus, School of Medicine, Shanghai Jiao Tong University); Tian Zhuang (Department of Cardiology, Peking Union Medical College Hospital (PUMCH), Chinese Academy of Medical Sciences); Tian Jing (Department of Rheumatology, Xiangya Second Hospital, Central South University); Shi Xiaofei (Department of Rheumatology, The First Affiliated Hospital of Henan University of Science and Technology); Zhu Ping (Department of Clinical Immunology, PLA Specialised Research Institute of Rheumatology and Immunology, Xijing Hospital, Fourth Military Medical University); Liu Shengyun (Department of Rheumatology, the First Hospital affiliated of Zhengzhou University); Liu Yongtai (Department of Cardiology, Peking Union Medical College Hospital (PUMCH), Chinese Academy of Medical Sciences); Li Mengtao (Department of Rheumatology, Peking Union Medical College Hospital (PUMCH), Chinese Academy of Medical Sciences, National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID), Key Laboratory of Rheumatology and Clinical Immunology, Ministry of Education, Chinese Rheumatism Data Center (CRDC), Chinese SLE Treatment and Research Group (CSTAR)); Li Hongbin (Department of Rheumatology, The Affiliated Hospital of Inner Mongolia Medical University); Li Yisha (Department of Rheumatology, Xiangya Hospital, Central South University); Yang Yuanhua (Department of Pulmonary and Critical Care Medicine, Beijing Chaoyang Hospital, Capital Medical University); Wu Chanyuan (Department of Rheumatology, Peking Union Medical College Hospital (PUMCH), Chinese Academy of Medical Sciences, National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID), Key Laboratory of Rheumatology and Clinical Immunology, Ministry of Education, Chinese Rheumatism Data Center (CRDC), Chinese SLE Treatment and Research Group (CSTAR)); Karamet · Yimaiti (Department of Rheumatology, Xinjiang Uygur Autonomous Region People's Hospital); Zhang Yongfeng (Department of Rheumatology, Beijing Chaoyang Hospital, Capital Medical University); Zhang Hongfeng (Department of Rheumatology, the First Affiliated Hospital of Dalian Medical University); Zhang Na (Department of Rheumatology, Tianjin Medical University General Hospital); Zhang Xiao (Department of Rheumatology, Guangdong Provincial General Hospital); Zhang Rong (Department of Rheumatology, The First Affiliated Hospital of China Medical University); Zheng Yi (Department of Rheumatology, Beijing Chaoyang Hospital, Capital Medical University); Zhao Jiuliang (Department of Rheumatology, Peking Union Medical College Hospital (PUMCH), Chinese Academy of Medical Sciences, National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID), Key Laboratory of Rheumatology and Clinical Immunology, Ministry of Education, Chinese Rheumatism Data Center (CRDC), Chinese SLE Treatment and Research Group (CSTAR)); Liu Zhihong (Department of Cardiology, Fuwai Hospital, Chinese Academy of Medical Sciences); Duan

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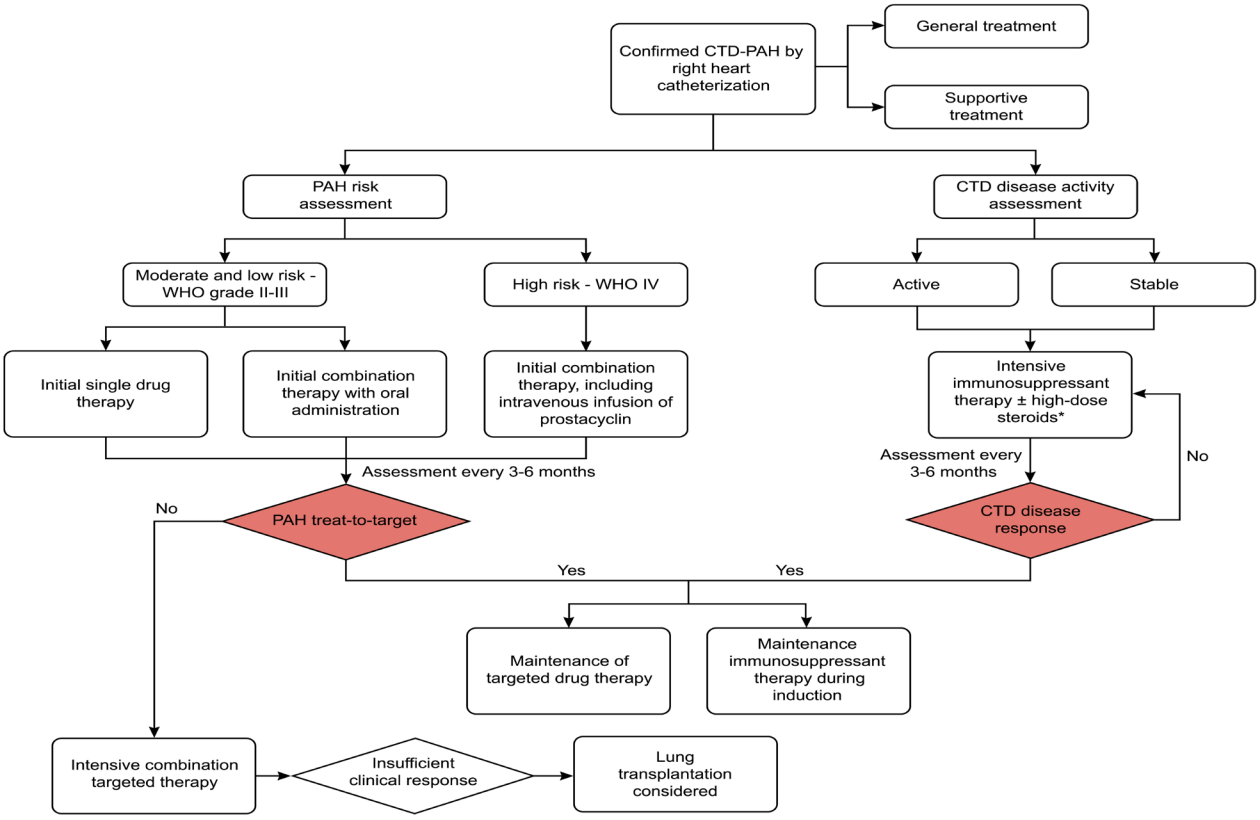

Figure 2: Diagnosis and treatment strategy of CTD-associated PAH in China. CTD, connective tissue disease; PAH, pulmonary arterial hypertension; WHO, World Health Organization.

Xinwang (Department of Rheumatology and Immunology, Second Affiliated Hospital of Nanchang University); Shi Chunhua (Department of Rheumatology, Jiangxi Provincial People's Hospital); Jiang Zhenyu (Department of Rheumatology, the First Bethune Hospital of Jilin University); Hong Xiaoping (Department of Rheumatology, Shenzhen People's Hospital); Jia Junfeng (Department of Clinical Immunology, PLA Specialised Research Institute of Rheumatology and Immunology, Xijing Hospital, Fourth Military Medical University); Cui Yang (Department of Rheumatology, Guangdong Provincial General Hospital); Cui Ruomei (Department of Rheumatic Immunology, First Affiliated Hospital of Kunming Medical University); Dong Xin (Department of Rheumatology, Beijing Chaoyang Hospital, Capital Medical University); Cheng Yongjing (Department of Rheumatology, Beijing Hospital); Lu Fu'ai (Department of Rheumatology, the First Affiliated Hospital of Baotou Medical College); Zeng Xiaofeng (Department of Rheumatology, Peking Union Medical College Hospital (PUMCH), Chinese Academy of Medical Sciences, National Clinical Research Center for Dermatologic and Immunologic Diseases (NCRC-DID), Key Laboratory of Rheumatology and Clinical Immunology, Ministry of Education, Chinese Rheumatism Data Center (CRDC), Chinese SLE Treatment and Research Group (CSTAR)); Lei Yunxia (Department of Rheumatology, Guangdong Provincial General Hospital); Tan Chunyu (Department of Rheumatology, Huaxi Hospital, Sichuan University); Zhai Zhenguo (Department of Pulmonary and Critical Care Medicine, China–Japan Friendship Hospital); Xiong Changming (Department of Cardiology, Fuwai Hospital, Chinese Academy of Medical Sciences); Xue Jing (Department of Rheumatology, The Second Affiliated Hospital of Zhejiang University, School of Medicine); Wei Wei (Department of Rheumatology, Tianjin Medical University General Hospital).

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Conflict of Interest

Xiaofeng Zeng is the Editor-in-Chief of the journal, Xinping Tian is the executive Editor-in-Chief, Mengtao Li is an Associate Editor-in- Chief, and Qian Wang is an Editorial Board Member. The article was subject to the journal's standard procedures, with peer review handled independently of these members and their research groups.

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