Clinical Rheumatology (2023) 42:3131–3142
https://doi.org/10.1007/s10067-023-06667-9

ORIGINAL ARTICLE

Retrospective cohort study of pulmonary arterial hypertension associated with connective tissue disease effect on patients' prognosis

Jing Huang[1] · Qi An[1] · Hongyang Shi[2] · Cong Li[2] · Wei Zhang[3] · Lei Wang[2]

Received: 21 February 2023 / Revised: 5 June 2023 / Accepted: 7 June 2023 / Published online: 29 June 2023

Abstract

Objective The objectives of this study are to clarify clinical characteristics and recognize prognostic factors of CTD-PAH patients.

Methods A retrospective cohort study of consecutive patients with documented CTD-PAH diagnosis from Jan 2014 to Dec 2019 was conducted, the ones who have other comorbid conditions that cause PH were excluded. Survival functions were plotted using the Kaplan–Meier method. Univariable and multivariable Cox regression analysis was applied to determine the survival-related factors.

Results In 144 patients with CTD-PAH analyzed, the median sPAP value was 52.5 (44.0, 71.0) mmHg, the overall targeted drug usage rate was 55.6%, and only 27.5% patients were given combination. Twenty-four non-PAH-CTD patients with sPAP value were included as the control group. Compared with non-PAH-CTD groups, CTD-PAH patients had worse cardiac function, higher NT-pro BNP and γ-globulin level, and lower $PaCO_2$ level. Compared with the mild PAH group, the moderate-severe PAH group had worse cardiac function; increased Hb, HCT, and NP-pro BNP level; and decreased PaO_2. Kaplan–Meier analysis showed significant difference for survival among non-PAH-CTD, mild CTD-PAH, and moderate-severe CTD-PAH groups. The univariate analyses showed that Hb, pH, and Ln (NT-pro BNP) were identified as factors significantly associated with survival, and Hb and pH showed significant association with risk of death in the multivariate model. Kaplan–Meier analysis also showed that Hb > 109.0 g/L and pH > 7.457 affected CTD-PAH patients' survival significantly.

Conclusions PAH is not rare in CTDs patients; PAH affects CTD patients' prognosis significantly. Higher Hb and pH were associated with an increased risk of death.

Key Points
- *Pulmonary arterial hypertension affects connective tissue disease patients' prognosis significantly.*
- *The significantly factors associated with survival is hemoglobin, pH, and Ln (NT-pro BNP).*

Keywords CTD-PAH · Prognosis · Survival

Introduction

Pulmonary hypertension (PH) is currently defined by a mean pulmonary arterial pressure (mPAP) > 20 mmHg at rest. Pulmonary arterial hypertension (PAH) is a subtype of PH (WHO Group 1 PH) characterized by pulmonary arterial remodeling [1], which may present with underlying diseases [2]. PAH is not only a dreaded complication of connective tissue diseases (CTDs), but also a major cause of morbidity and mortality in CTDs [3]. It is reported that around 30% of scleroderma-related deaths are due to PAH [4]. In a France national multicenter PAH registry study, CTD-PAH counted for 15.3% in the PAH

Jing Huang and Qi An are co-first authors.

✉ Lei Wang
wl860806wb@163.com

[1] Department of Rheumatism and Immunology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China

[2] Department of Respiratory and Critical Care Medicine, The Second Affiliated Hospital of Xi'an Jiaotong University (Xibei Hospital), No.157, Xiwu Road, Xincheng District, Xi'an 710004, People's Republic of China

[3] Department of Emergency, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, China

cohort [5]. PAH-CTD is the second most prevalent type of PAH in Western countries, and systemic sclerosis (SSc) is the leading cause of CTD-PAH in Western countries [6], which accounting for almost 75% of CTD-PAH. Different from Western countries, CTD-PAH is the most prevalent type of PAH in China, and the most common cause of CTD-PAH in Chinese people is systemic lupus erythematosus (SLE) [7], while the epidemiological data of CTD-PAH in Chinese people is still limited up to now.

Since the mid-1990s, medications have become available to target three key pathophysiologic derangements in PAH-the prostacyclin, endothelin, and nitric oxide pathways [8], which improved quality of life, exercise capacity, and survival of these PAH patients [9]. CTD-PAH patients constitute at least 20% of patients included in all major trials of PH-specific targeted therapy [3]. However, despite the growing numbers of available PAH-targeted medications, many patients with PAH continue to deteriorate and the disease ultimately remains fatal; the outcome of patients with CTD-PAH remains poor [10]. Furthermore, the unadjusted risk of death for SSc-associated PAH compared with Idiopathic pulmonary arterial hypertension (IPAH) is 2.9, and the predictors of outcome are broadly similar to those for IPAH [10, 11]. For SSc-associated PAH, overall survival was 90%, 78%, and 56% at 1, 2, and 3 years from PAH diagnosis, respectively [11]. Therefore, it is important to recognize prognostic predictors for CTD-PAH patients, which means a lot to improve patients' prognosis and long-term survival.

The objectives of this retrospective study are to analyze clinical characteristics and recognize survival and prognostic factors of CTD-PAH patients in a tertiary teaching hospital of Northwest of China.

Materials and methods

Study design

This is a retrospective cohort study of consecutive patients with documented CTD-PAH diagnosed at Department of Rheumatology at a tertiary teaching hospital in Xi'an, center of Northwest of China, from Jan 2014 to Dec 2019. All patient's demographic, clinical characteristics, and clinical measures were retrieved from the hospital electronic medical records (EMR).

The study received favorable opinion from the Ethics Committee of First affiliated hospital of Xi'an Jiaotong University. The study protocol and data collection instruments were submitted and approved by the Data Protection Commission of Xi'an Jiaotong University. All patients provided their written informed consent prior to inclusion in the study.

Patient population

Patients of CTD were eligible to include in the study if they were ≥ 18 years old and discharge diagnosis including pulmonary hypertension. Patients were excluded as follows: (1) systolic pulmonary artery pressure (sPAP) estimated by first documented echocardiography when PAH diagnosis was absent; (2) HIV infection, congenital heart disease, acute heart failure and portal hypertension associated pulmonary arterial hypertension, pulmonary veno-occlusive disease, and drugs and toxins induced pulmonary arterial hypertension; (3) left heart disease; (4) chronic obstructive pulmonary disease, interstitial lung disease and sleep apnea; (5) when there is a high clinical suspicion for chronic pulmonary embolism, computed tomography pulmonary angiography (CTPA) or ventilation/perfusion (V/Q) imaging has been undertaken, and chronic pulmonary embolism patients in this study was excluded.

Data collection and instruments

Clinical and laboratory data during hospitalization at first-time PAH diagnosis were retrieved from the database of the dedicated EMR software of the hospital. The primary outcome of interest was all-cause mortality, which was ascertained from our electronic medical record and telephone follow-up calls to patients or bereaved family members.

sPAP estimation by echocardiography

Pulmonary artery systolic pressure (sPAP) was estimated using a modified Bernoulli equation: sPAP = 4 × (tricuspid systolic jet)^2 + estimated right atrial pressure (RAP) [12]. Pulmonary hypertension was defined as a systolic pulmonary artery pressure (sPAP) > 35 mmHg estimated using echocardiograms [13]. Various sPAP cutoffs have been applied in previous studies, but a Doppler-derived sPAP of 35 mmHg is the most widely accepted threshold [14, 15]. PH severity was categorized according to the sPAP as follows: mild (35–50 mmHg), moderate (50–70 mmHg), and severe (> 70 mmHg) [16].

Statistical analysis

Normally distributed continuous variables were presented as mean (SD) and compared using *t*-tests. Nonnormally distributed continuous variables were presented as median (IQR) and compared using rank-sum tests. Categorical variables were presented as number (percentage) and were compared using the chi-square test. Survival functions were plotted using the Kaplan–Meier method and comparison of survival

functions was performed by the log-rank test. The predictive values of biomarkers were assessed through time-dependent receiver operating characteristic analyses (ROC). Univariable Cox regression analysis and multivariable Cox analysis were applied to determine the survival-related factors. The univariable Cox regression models included Hb, HCT, pH, PaCO2, PaO2, Ln (NT-pro BNP), IgG, Fib, and sPAP. Factors with statistical significance in univariate analysis were included in a multivariate analysis. For data with skewed distribution (i.e., NT-pro BNP), logarithmic transformation with natural constant as the base was done in the Cox regression analysis and ROC analysis. A 2-tailed $P < 0.05$ was considered statistically significant in all analyses. R software, version 4.2.2 (http://www.R-project.org/), was used for all statistical analyses. Univariate log-rank test and cox regression analysis were performed in R using the survival package and the survminer package.

Results

1. Prevalence of PAH in CTD patients

From Jan 2014 to Dec 2019, there were 144 patients (2.80%) diagnosed as PAH among a total of 5142 CTD patients; we also collected 24 non-PAH-CTD patients with sPAP value estimated by echocardiography as control. The average follow-up period of all patients was 3.33 years. Of the 144 CTD-PAH patients (Table 1), there were 89 SLE patients (60.0%), 19 SSc patients (14.7%), 11 mixed connective tissue disease (MCTD) patients (7.6%), 7 rheumatoid arthritis (RA) patients (4.1%), 6 Sjögren's syndrome (SS) patients (3.5%), 5 dermatomyositis (DM) patients (3.5%), 4 vasculitis patients (4.7%, 3 cases of microscopic polyangiitis and one case of Takayasu arteritis), and 3 primary biliary cholangitis (PBC) patients (1.8%). In this study, the prevalence of PAH was 7.97% in SLE, 15.32% in SSc, 14.10% in MCTD, 0.55% in RA, 2.74% in SS, 2.56% in DM, 2.63% in vasculitis, and 11.54% in PBC.

The duration from CTD onset to PAH diagnosis was 75.4 ± 81.4 months (Table 1). The duration for SLE, SSc, MCTD, DM, SS, RA, vasculitis, and PBC was 39.0 (10.0, 101.0) months, 92.0 (6.5, 153.5) months, 27.0 (13.5, 98.0) months, 6.0 (0, 12.0) months, 127.0 (78.3, 139.0) months, 126.7 ± 100.5 months, 60.8 ± 88.5 months, and 65.0 ± 59.2 months respectively.

2. Clinical characteristics of CTD-PAH patients

Baseline clinical characteristics for these patients divided into CTD-PAH and non-PAH-CTD groups are summarized in Table 2. Demographic analysis showed that the median age of CTD-PAH patients was 46.0 years old and had high female predominance (94.4%); the median sPAP value of CTD-PAH patients was 52.5 (44.0,71.0) mmHg. Compared with non-PAH-CTD groups, CTD-PAH patients had worse cardiac function ($P = 0.019$), higher NT-pro BNP ($P = 0.022$), and γ-globulin ($P = 0.023$) level and lower $PaCO_2$ level ($P = 0.045$). Although without statistically significant difference, the CTD-PAH group had higher D-dimer and IgG, lower serum vitamin D levels.

The disease severity was classified as "mild" in 61 (42.36%) patients and "moderate-severe" in 83 (57.64%) patients using sPAP cutoff of 50 mmHg (Table 3). The average follow-up period of CTD-PAH patients was 3.19 years. Both groups had similarly high female predominance (96.7% vs 92.8%). Compared with mild group, moderate-severe group had worse cardiac function ($P < 0.001$), increased Hb ($P = 0.014$), HCT ($P = 0.005$), and NP-pro BNP ($P = 0.011$) level, decreased PaO_2 ($P = 0.023$). Although without statistically significant difference, the moderate-severe group had decreased $PaCO_2$ and dsDNA level. The most common cause of CTD-PAH in both groups is SLE (55.7% vs 66.3%).

Table 1 Prevalence of PAH among CTDs

Protopathy diseases	Number (%)	Prevalence of PAH	Duration from CTD onset to PAH diagnosis (months)
SLE	89 (60.0)	7.97% (89/1117)	39.0 (10.0, 101.0)
SSc	19 (14.7)	15.32% (19/124)	92.0 (6.5, 153.5)
MCTD	11 (7.6)	14.10% (11/78)	27.0 (13.5, 98.0)
RA	7 (4.1)	0.55% (7/1274)	126.7 ± 100.5
SS	6 (3.5)	2.74% (6/219)	127.0 (78.3, 139.0)
DM	5 (3.5)	2.56% (5/195)	6.0 (0, 12.0)
Vasculitis	4 (4.7)	2.63% (4/152)	60.8 ± 88.5
PBC	3 (1.8)	11.54% (3/26)	65.0 ± 59.2
Total	144	2.80% (144/5,142)	75.4 (81.4)

SLE systemic lupus erythematosus, *SSc* systemic sclerosis, *MCTD* mixed connective tissue disease, *RA* rheumatoid arthritis, *SS* Sjögren's syndrome, *DM* dermatomyositis, *PBC* primary biliary cholangitis

Table 2 Comparison of baseline clinical characteristics between non CTD-PAH and CTD-PAH patients

	Total	Baseline sPAP (mmHg)		*P*-value
		≤ 35	> 35	
n	168	24	144	
Age	46.0 (30.8, 57.2)	45.5 (35.2, 60.8)	46.0 (30.8, 56.0)	0.552
Gender				0.126
Male	12 (7.1)	4 (16.7)	8 (5.6)	
Female	156 (92.9)	20 (83.3)	136 (94.4)	
Protopathy diseases				0.385
Non-SLE	67 (39.9)	12 (50.0)	55 (38.2)	
SLE	101 (60.1)	12 (50.0)	89 (61.8)	
WHO-FC				0.019
I–II	100 (59.5)	20 (83.3)	80 (55.6)	
III–IV	68 (40.5)	4 (16.7)	64 (44.4)	
Hb	106.5 ± 22.7	113.7 ± 19.0	105.3 ± 23.1	0.093
HCT	33.3 ± 6.6	35.0 ± 5.3	33.0 ± 6.8	0.183
PLT	144.0 (102.0, 205.5)	160.5 (118.2, 207.0)	142.0 (91.0, 204.5)	0.151
Arterial blood gas				
pH	7.434 (7.419, 7.466)	7.420 (7.400, 7.470)	7.436 (7.420, 7.462)	0.397
$PaCO_2$	34.5 (30.9, 38.4)	38.0 (34.9, 39.0)	34.0 (30.2, 38.0)	0.045
PaO_2	80.1 (70.0, 91.6)	79.9 (71.0, 90.0)	80.2 (70.0, 91.9)	0.797
NT-pro BNP	755.9(218.8, 3362.5)	316.0 (108.2, 771.6)	900.9(269.6, 3802.0)	0.022
CRP	10.0 (3.4, 18.8)	8.9 (3.3, 14.1)	10.0 (3.6, 18.9)	0.372
ESR	44.0 (17.0, 72.0)	43.0 (17.0, 62.8)	44.0 (17.0, 75.0)	0.69
D-dimer	1.2 (0.6, 2.9)	0.7 (0.6, 1.3)	1.4 (0.6, 2.9)	0.054
Fib	3.4 (2.5, 4.1)	3.6 (2.8, 4.5)	3.4 (2.5, 4.0)	0.286
C3	0.8 ± 0.3	0.8 ± 0.3	0.8 ± 0.3	0.171
C4	0.1 (0.1, 0.2)	0.2 (0.1, 0.3)	0.1 (0.1, 0.2)	0.16
IgG	16.2 (12.5, 21.8)	15.6 (11.9, 16.5)	16.8 (12.6, 24.1)	0.077
dsDNA	6.3 (1.7, 33.9)	7.4 (3.3, 77.2)	6.3 (1.6, 33.7)	0.692
γ-globulin	24.2 (19.0, 31.2)	22.2 (18.6, 24.0)	25.3 (19.1, 32.6)	0.023
Baseline sPAP	49.0 (41.0, 68.2)	30.0 (26.8, 33.0)	52.5 (44.0, 71.0)	< 0.001
Serum vitamin D3 levels	11.1 (7.5, 16.3)	15.8 (8.1, 26.1)	10.4 (7.4, 15.9)	0.064

SLE systemic lupus erythematosus, *WHO-FC* World Health Organization functional class, *Hb* hemoglobin, *HCT* hematocrit, *PLT* platelet, *pH* pondus hydrogenii, $PaCO_2$ partial pressure of carbon dioxide, PaO_2 partial pressure of oxygen, *NT-pro BNP* N-terminal-pro B-type natriuretic peptide, *CRP* c-reactive protein, *ESR* erythrocyte sedimentation rate, *Fib* fibrinogen, *C3* complement component 3, *C4* complement component 4, *IgG* immunoglobulin G, *dsDNA* double-stranded DNA, *sPAP* systolic pulmonary artery pressure

The targeted drugs used in this study were PDE-5Is (Sildenafil), ERAs (Ambrisentan, Bosentan), and PGI_2 analogues (Beraprost, Treprostinil), the overall targeted drug usage rate was 55.6% (80/144), and the most used drug was Sildenafil. Only 27.5% patients were given combination, compared with mild patients; moderate-severe patients tended to use combination. In addition, only one patient used oral triple combination therapy.

3. Evaluation of outcomes

Kaplan–Meier curves were generated for analysis of final follow-up sPAP > 35 mmHg and death for the non-PAH-CTD, mild CTD-PAH, and moderate-severe CTD-PAH groups; patients lost to follow up were excluded from analysis. As showed in Fig. 1A, in terms of final follow-up sPAP > 35 mmHg, no significant difference was found among the 3 groups. While significant difference for survival was found among the 3 groups (Fig. 1B), it indicates that baseline sPAP value affects patients' survival.

4. Determination of prognostic factors

The results of the univariate and multivariate analyses using Cox regression model of the data for the CTD-PAH group are summarized in Table 4. Patients lost to follow up were excluded from Cox regression analysis. The variables with *P* value < 0.1 between groups in Table 1 were

Table 3 Comparison of baseline clinical characteristics between mild and moderate-severe CTD-PAH patients

	Total	Baseline sPAP (mmHg)		*P*-value
		< 50	≥ 50	
n	144	61	83	
Age	46.0 (30.8, 56.0)	46.0 (31.0, 53.0)	46.0 (31.0, 56.5)	0.687
Gender				0.513
Male	8 (5.6)	2 (3.3)	6 (7.2)	
Female	136 (94.4)	59 (96.7)	77 (92.8)	
Protopathy diseases				0.266
Non-SLE	55 (38.2)	27 (44.3)	28 (33.7)	
SLE	89 (61.8)	34 (55.7)	55 (66.3)	
WHO-FC				< 0.001
I–II	80 (55.6)	53 (86.9)	27 (32.5)	
III–IV	64 (44.4)	8 (13.1)	56 (67.5)	
Hb	105.3 ± 23.1	99.8 ± 22.6	109.3 ± 22.8	0.014
HCT	33.0 ± 6.8	31.2 ± 6.7	34.4 ± 6.6	0.005
PLT	142.0 (91.0, 204.5)	124.5 (75.8, 178.2)	156.0 (103.5, 221.5)	0.052
Arterial blood gas				
pH	7.436 (7.420, 7.462)	7.428 (7.410, 7.450)	7.440 (7.421, 7.470)	0.032
$PaCO_2$	34.0 (30.2, 38.0)	36.0 (32.0, 38.2)	32.9 (29.7, 37.8)	0.079
PaO_2	80.2 (70.0, 91.9)	85.0 (76.1, 92.9)	75.3 (65.6, 90.8)	0.023
NT-pro BNP	900.9 (269.6, 3802.0)	432.2 (147.7, 1643.5)	1613.5 (352.8, 4954.2)	0.011
CRP	10.0 (3.6, 18.9)	10.0 (3.3, 18.9)	10.0 (3.9, 18.8)	0.697
ESR	44.0 (17.0, 75.0)	44.0 (21.5, 76.0)	43.0 (15.5, 72.5)	0.48
D-dimer	1.4 (0.6, 2.9)	1.5 (0.7, 3.2)	1.4 (0.6, 2.8)	0.435
Fib	3.4 (2.5, 4.0)	3.6 (2.4, 4.3)	3.3 (2.6, 3.9)	0.314
C3	0.8 (0.5, 1.0)	0.7 (0.4, 1.0)	0.8 (0.5, 1.0)	0.471
C4	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	0.958
IgG	16.8 (12.6, 24.1)	16.2 (11.9, 20.0)	17.7 (13.0, 27.9)	0.053
dsDNA	6.3 (1.6, 33.7)	6.8 (1.7, 100.0)	4.6 (1.4, 31.9)	0.201
γ-Globulin	25.3 (19.1, 32.6)	24.6 (18.7, 29.7)	26.0 (19.4, 36.8)	0.160
Baseline sPAP	52.5 (44.0, 71.0)	43.0 (41.0, 46.0)	69.0 (56.0, 80.5)	< 0.001
Serum vitamin D3 levels	10.4 (7.4, 15.9)	10.0 (7.8, 15.7)	11.1 (7.1, 16.2)	0.977
Target drugs				
Beraprost				0.919
No	133 (92.4)	57 (93.4)	76 (91.6)	
Yes	11 (7.6)	4 (6.6)	7 (8.4)	
Treprostinil				1.00
No	143 (99.3)	61 (100.0)	82 (98.8)	
Yes	1 (0.7)	0 (0.0)	1 (1.2)	
Ambrisentan				< 0.001
No	127 (88.2)	61 (100.0)	66 (79.5)	
Yes	17 (11.8)	0 (0.0)	17 (20.5)	
Bosentan				0.021
No	135 (93.8)	61 (100.0)	74 (89.2)	
Yes	9 (6.2)	0 (0.0)	9 (10.8)	
Sildenafil				0.015
No	81 (56.2)	42 (68.9)	39 (47.0)	
Yes	63 (43.8)	19 (31.1)	44 (53.0)	
Drug free				< 0.001
No	80 (55.6)	22 (36.1)	58 (69.9)	
Yes	64 (44.4)	39 (63.9)	25 (30.1)	

Table 3 (continued)

	Total	Baseline sPAP (mmHg)		*P*-value
		< 50	≥ 50	
Treatment regimen				0.221
Monotherapy	58 (72.5)	19 (86.4)	39 (67.2)	
Dual combination	21 (26.2)	3 (13.6)	18 (31.0)	
Triple combination	1 (1.2)	0 (0.0)	1 (1.7)	

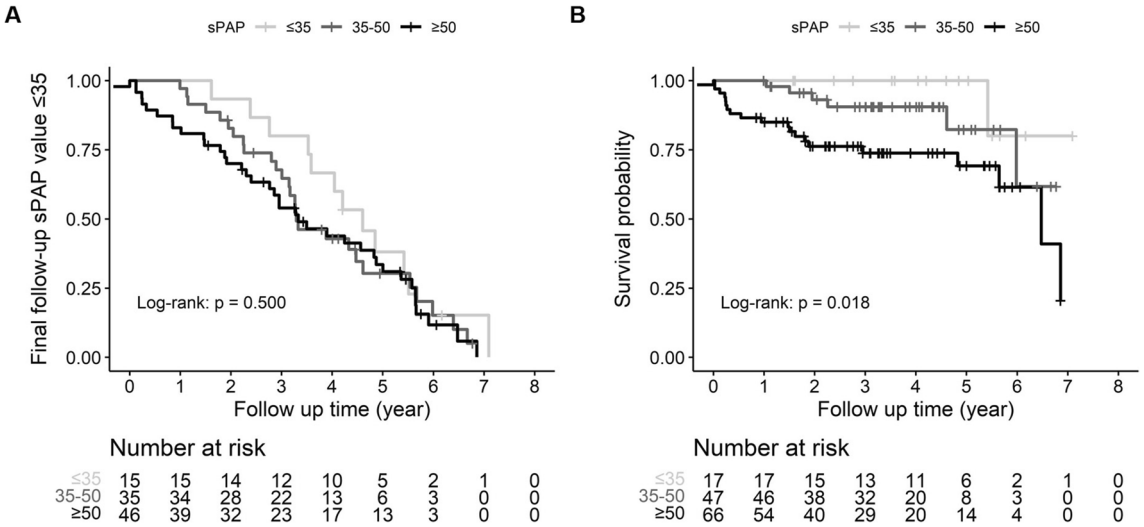

Fig. 1 Kaplan–Meier curves in subgroups. **A** Final follow-up sPAP value ≤ 35 mmHg, **B** survival. Log-rank test was conducted for comparison among the 3 groups (sPAP ≤ 35 mmHg, sPAP 35–50 mmHg, sPAP ≥ 50 mmHg)

Table 4 Prognostic factors for survival in PAH-CTD patients

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Hb	1.02 (1, 1.04))	0.041	1.02 (0.99, 1.04)	0.124
HCT	1.08 (1.01, 1.15)	0.026		
pH	2,849,708.43 (16.84, inf)	0.016	12,293,025.36 (14.16, inf)	0.019
$PaCO_2$	0.99 (0.95, 1.03)	0.690		
PaO_2	0.99 (0.97, 1.01)	0.451		
Ln (NT-pro BNP)	1.31 (1.04, 1.66)	0.023	1.3 (0.97, 1.75)	0.082
IgG	1.02 (0.98, 1.06)	0.301		
Fib	1.06 (0.81, 1.39)	0.668		
sPAP	1.02 (1.01, 1.04)	0.004	1.01 (0.99, 1.04)	0.261

selected to be included in the Cox regression model. When as continuous variables, Hb, HCT, pH, Ln (NT-pro BNP), and sPAP were identified as factors significantly associated with survival. Factors with statistical significance in univariate analysis were included in a multivariate analysis. Due to the strong correlation between Hb and HCT, in order to prevent collinearity, only Hb, pH, Ln (NT-pro BNP), and sPAP were selected to be included in the multivariate model. Results showed significant association between pH and risk of death.

For the 4 prognostic factors identified as impacting patients' survival by univariate analysis as continuous variables (i.e., Hb, pH, Ln (NT-pro BNP) and sPAP), the areas under the ROC curves (AUCs) were calculated to be 0.655, 0.667, 0.678, and 0.669, respectively (Fig. 2A–D). Based on the ROC curves, the cutoff values were determined to be 109.0 g/L, 7.457, 7.267, and 62.5 mmHg, respectively. When using cutoff values of Hb, pH, Ln (NT-pro BNP) and sPAP, Hb, pH, and Ln (NT-pro BNP) were identified as factors significantly associated with survival

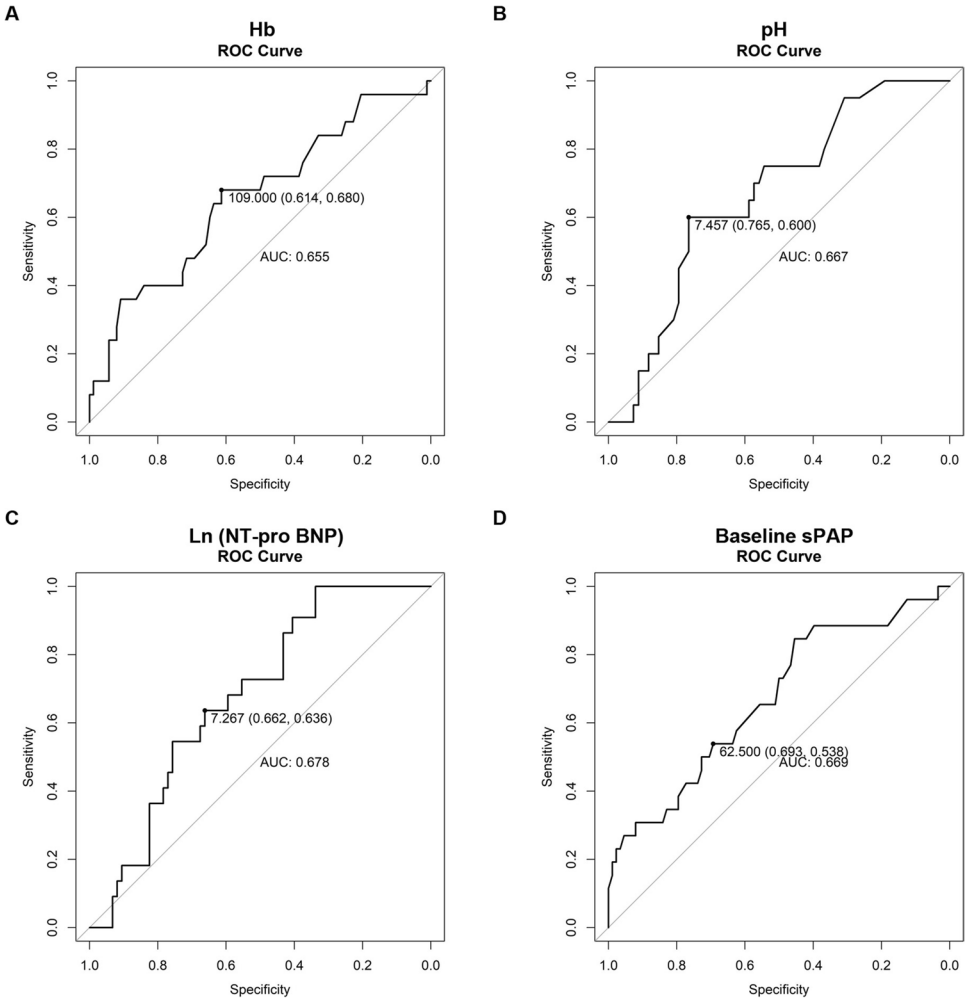

Fig. 2 ROC curves based on survival. **A** Hemoglobin, **B** pH, **C** Ln (NT-pro BNP), **D** baseline pulmonary artery systolic pressure

by univariate analysis (Table 5). In the multivariate model, Hb and pH showed significant association with risk of death. Kaplan–Meier curves according to the cutoff values of Hb and pH were shown in Fig. 3, which proved further that Hb > 109.0 g/L (Fig. 3A) and pH > 7.457 (Fig. 3B) were independent unfavorable predictors of survival.

Table 5 Prognostic factors for survival in PAH-CTD patients (based on cutoff values)

	N	Event (%)	Univariate analysis		Multivariate analysis	
			HR (95%CI)	*P*	HR (95%CI)	*P*
Hb						
< 109.0	62	8 (12.9)	Reference		Reference	
≥ 109.0	51	17 (33.3)	2.48 (1.07, 5.77)	0.035	2.98 (1.08, 8.18)	0.035
pH						
< 7.457	59	8 (13.6)	Reference		Reference	
≥ 7.457	29	12 (41.4)	4.55 (1.78, 11.62)	0.002	4.75 (1.74, 12.99)	0.002
Ln (NT-pro BNP)						
< 7.267	57	8 (14.0)	Reference		Reference	
≥ 7.267	39	14 (35.9)	2.91 (1.2, 7.05)	0.018	2.70 (0.93, 7.84)	0.068
sPAP						
< 62.5	73	12 (16.4)	Reference		Reference	
≥ 62.5	41	14 (34.1)	2.1 (0.96, 4.63)	0.065	1.16 (0.43, 3.14)	0.776

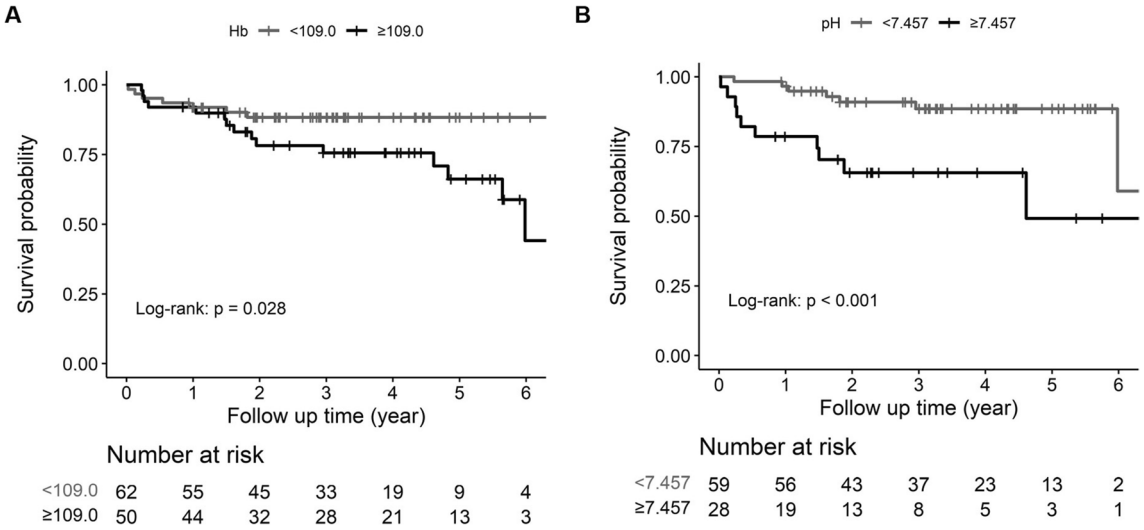

Fig. 3 Kaplan–Meier curves divided by cutoff values of Hb and pH in CTD-PAH. A log-rank test was conducted in CTD-PAH for comparisons among the groups divided by each cutoff value. **A** Hemoglobin, **B** pH

Discussion

This study describes the characteristics of CTD-PAH patients and provides insight into their PAH-targeted treatment status and survival. Our data reveal the protopathy distribution of CTDs, PAH prevalence in CTDs, PAH-target drugs usage, survival, and prognostic factors for death of CTD-PAH. Knowing these features may prove helpful for clinicians evaluating CTD patients who present with PAH timely, risk assessment, and predicting prognosis in patients with CTD-PAH.

We showed that SLE is the leading cause of CTD-PAH, which is consist with previous data. The second cause of CTD-PAH is SSc. Previous cohort studies in Asia reported that PAH is most commonly associated SLE, followed by SS and MCTD [17–19]. In Europe, a study showed that of CTD-PAH patients, 75% had SSc, 7% had SLE, 9% had MCTD, and 12% had another CTD [20]. In the USA, study showed that of patients with CTD-PAH, 67.7% had SSc, 18.7% had SLE, and 8.8% had MCTD [21]. The relationship between RA and PAH is not established [22], this study showed that 7 RA patients (7/144, 4.1%) were presented with PAH, and the prevalence of PAH in RA was only 0.55%. Few data describe when PAH occurs in CTDs, our results showed that PAH can occur early after DM onset. In addition, our study also showed that PAH could occur in ANCA-associated vasculitis and Takayasu's arteritis. PAH is a rare occurrence in vasculitis, previous studies also showed that PAH could occur in vasculitis [23–25], and CTDs-PAH studies also included vasculitis patients [19, 26]. The exact pathophysiology of how PAH develops in vasculitis is yet unknown which needs to be investigated further, as has been hypothesized with other CTDs, endothelial dysfunction and remodeling of pulmonary arteries, and immune dysregulation can all play a role [27]. And researcher also showed that pulmonary artery vasculitis, pulmonary artery sclerosis/stenoses and elevated left ventricular filling pressure during Takayasu's arteritis may contribute to PAH development [28]. Clinicians should be aware that PAH can occur at early stage of CTDs, and patients with RA and vasculitis should also be alert to the occurrence of PAH. Regular echocardiography monitor is recommended strongly in the CTD patients management to identify CTD-PAH as early as possible.

PAH has generally been thought to affect predominantly younger individuals, mostly females [29], female sex is a risk factor for PAH, yet females have better survival than males [30]. In industrialized countries, PAH affects mainly elderly people, whereas mostly young people are diagnosed in the developing world including China. In our study, the median age of CTD-PAH was 46 years old with high female predominance, but older age and female was not found to be an independent risk factor for disease severity of PAH in our study.

Worse World Health Organization functional class (WHO-FC) and NT-pro BNP were found in this study in CTD-PH patients, especially for the moderate-severe CTD-PH patients. The WHO-FC is one of the strongest predictors of survival both at diagnosis and follow-up of PH patients; worsening WHO-FC is one of the most alarming indicators of disease progression. In addition, although BNP and NT-proBNP are not specific for PH, they remain the only biomarkers routinely and frequently used for PH patients, which is correlating with myocardial stress and providing prognostic information [1]. Both WHO-FC and NT-pro BNP are one of the three important indicators of the simplified non-invasive risk-assessment tool for prognostic evaluation,

risk assessment, and treatment evaluation of PH [31], which need to be assessed every 3–6 months.

Immunity/inflammation is an important mechanism in the pathogenesis of PAH [32]; anti-inflammatory therapy has been evaluated for years. The most significant γ-globulins are immunoglobulins (IgA, IgG, and IgM antibodies), although some immunoglobulins are not gamma globulins, and some gamma globulins are not immunoglobulins. Hypergammaglobulinemia is often found in patients with autoimmune diseases, and its level may correlate with disease activity, such as lymphoid cell infiltration, treatment responsiveness, and also PAH [33, 34]. It is known that SLE and MCTD often display hypergammaglobulinemia or a high IgG titer; auto-antibodies participate in the CTD-PAH development [35]. In this study, γ-globulin was significantly increased in CTD-PH patients, and serum IgG level was higher in the moderate-severe group than the mild group although without statistical difference. Nowadays, elucidating the process of immunoglobulin production is in great need to provide new treatment strategies for PH.

D-Dimer level was higher and Vitamin D3 (VitD3) was lower in CTD-PAH patients compared with CTD patients without PAH, although without statistical differences. We have found previously that SLE-PAH had high D-dimer and FDP levels, and D-dimer was an independent predictor for SLE-PAH, which mediated effect of low low-density lipoprotein on SLE-PAH [36]. While the latest guideline of the long-term risk/benefit ratio of oral anticoagulation is unfavorable because of an increased risk of bleeding, vitamin K antagonists are recommended in PAH-CTD with a thrombophilic predisposition [37]. For VitD3, studies have proved that VitD3 deficiency is frequently seen and indicates worse prognosis in PH patient. VitD3 supplementation could improve PH survival in rat and endothelial function, while there is still controversy about that whether VitD3 could ameliorate pulmonary vascular remodeling and right ventricle hypertrophy [38–40]. The effect of VitD3 on pulmonary hemodynamics, pulmonary vascular remodeling, and right ventricle hypertrophy in PH and its potential mechanisms need to be clarified further.

Except WHO-FC and NT-pro BNP, increased Hb and decreased PaO_2 were identified to be associated with PAH severity in CTD patients in the present study; $PaCO_2$ was decreased significantly in CTD-PAH patients without association with PAH severity. In addition, we found that the factors associated with a higher risk for death in CTD-PAH patients (in the multivariate model) were Hb and pH. Our results indicated that hemoglobin in blood and arterial blood gas analysis was important for risk and prognosis assessment of CTD-PAH patients. Both iron deficiency and anemia have been linked to the clinical course of PH [41], we also found that Hb level was decreased in CTD-PAH patients compared CTD patients without PAH, and current treatment guidelines suggest regular iron status assessment and the implementation of iron supplementation strategies in these patients [1]. While it is reported that as the Hb level decreases, blood viscosity decreases, cardiac output increases, filling pressures tend to decrease, and systemic and pulmonary vascular resistances decrease substantially [42, 43]. Previous study proved that PH patients who died had significantly lower hemoglobin levels than those survived, and anemic PH patients were 3.3 times more likely to die than non-anemic PH patients [44]; it is also reported that higher Hb levels associated with higher risk for cardiovascular disease-related mortality [45]. While the optimal hemoglobin level for prognosis of PH patients is still unknown, in this study, we showed that Hb > 109.0 g/L was an independent unfavorable predictors of survival. Hypoxia induces erythropoietin and secondary increase in Hb [46]; it is reported that erythropoietin attenuates pulmonary vascular remodeling and induces a reduction in pulmonary arterial pressure [47, 48], while higher level of Hb may inhibit the increase of erythropoietin level. In the meanwhile, chronic hypoxia is a well-known cause of PH; anemia can lead to a hypoxic state which leading to development of PH. Therefore, the complex interaction of hemoglobin level and PH need to be investigated further, aiming to give guidance on how to select PH patients who might benefit from iron supplementation, and help to set treatment goal.

Hypoxic stress is a key driving force in the vascular remodeling observed in PH, which could induce hyperventilation/alkalosis compensatorily; respiratory alkalosis is observed commonly in PH. In this study, abnormal arterial blood gas analysis was found in CTD-PAH patients, PaO_2 was negatively associated with PAH severity as expected, and interestingly, pH > 7.457 was an independent unfavorable predictor of survival. It has been proved that acute hypoxic pulmonary vasoconstriction is attenuated by respiratory alkalosis, but respiratory alkalosis failed to attenuate vascular reactivity to subsequent pressor stimuli [49]. Although hypoxia-induced vasoconstriction leads to compensatory respiratory alkalosis that has vasodilating effect, it also can worsen intrapulmonary shunt and systemic oxygenation [50]. Therefore, it is important to correct hypoxemia for PH patients to reverse alkalosis.

Since 2007, PAH-targeted medications have been available in China, but because of low disease awareness, difficult access to experienced diagnostic facilities, and financial constraints, quite a few PAH patients have not received sufficient targeted drug use, which affects patients' prognosis further and needs to be improved. In this study, PAH-targeted treatment rate was 55.6%, which needs to be improved. One study based on Chinese population had showed that over 50% of 174 participants did not use any kind of PAH-specific therapies because of the financial burden [51]. Most patients of this study chose

monotherapy, PDE5I was used most often in both monotherapy and combination therapy because of its relatively low price, and only one patient with combination therapy did not use PDE5I. Combining drugs with different mechanisms of action, in order to optimize clinical benefit while minimizing side effects, a study in the USA states that only 5% of patients began initial combination therapy for PAH [52]. Treatment strategy for PAH has thereby changed significantly over the past decade; clinicians should know that combination therapy is becoming progressively the gold standard of care in patients with PAH and is becoming widely used in clinical practice [53]. The benefit of combination over monotherapy was demonstrated in patients with CTD-PAH, particularly in those with typical PAH hemodynamics characteristics at baseline [54], while randomized controlled trials (RCTs) showed that the magnitude of the targeted drugs response in the PAH-CTD was lower than in the IPAH patients [55]. The limited data precludes consensus on which combined treatment or strategy should be preferred; drugs targeting the ET and NO pathways are most commonly used as first-line combination therapy, but the association of ERA and PDE5I, both available in oral form, offers an interesting option [56]. In our study, the majority of patients using combination treatment is treated with an ERA combined with a PDE-5I. Also, no long-term evaluation of combination therapy is available; it is reported that combination therapy had no proven effect on mortality and had a much higher incidence of withdrawal due to adverse effects than monotherapy [57]. With this in mind, treating patients with more than one of these drugs may result in additive side effects; it is reported that edema and headache occurred more frequently in patients taking a combination of ambrisentan and tadalafil compared with patients treated with either drug as monotherapy in the AMBITION study [58].

The results of the present study should be interpreted in the context of several limitations. First, due to the invasive nature and cost of RHC, echocardiography was used to diagnose PAH in patients in this study. Estimates of sPAP by echocardiography are based on the peak TRV. This technique can lead to under- or over-diagnosis of PAH rates as TR may not be present in mild PAH cases without signs of right heart failure and also could be found in elderly or obese patients without PAH. Second, the present study concerns the small sample size; the results would be not vigorous. Third, as a non-interventional trial, a cause-and-effect relationship between PAH and mortality cannot be established. Fourth, although multiple Cox regression analysis was done to control for the effect of potential confounders, there might be other potential confounding variables that were not considered in this study.

In conclusion, PAH is not rare in CTDs patients; PAH affects CTD patients' prognosis significantly. Higher Hb and pH were associated with an increased risk of death. Future studies are needed to explore the mechanisms underlying these associations to identify some potential therapeutic interventions for this high-risk population.

Author contribution Jing Huang, Hongyang Shi, and Lei Wang made substantial contributions to the design of the work; Jing Huang, Qi An, Cong Li, and Wei Zhang made substantial contributions to the acquisition, analysis, or interpretation of data; Lei Wang drafted the work and revised it; all authors approved the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding This paper was supported by National Natural Science Foundation of China (grant number 82270055), Chinese Postdoctoral Science Foundation (grant number 2021M702610), and Natural Science Foundation of Shaanxi Province (grant number 2022JQ-940).

Data availability The data used to support the findings of this study are available from the corresponding author upon request.

Compliance with ethical standards

Ethics approval This retrospective cohort study received favorable opinion from the Ethics Committee of First affiliated hospital of Xi'an Jiaotong University (approval NO. 2022-1026, approval date 2022.01). The study protocol and data collection instruments were submitted and approved by the Data Protection Commission of Xi'an Jiaotong University. All subjects gave written informed consents prior to inclusion in the study.

Disclosures None.

References

1. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M et al (2022) 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 43(38):3618–3731
2. Hassoun PM (2021) Pulmonary arterial hypertension. N Engl J Med 385(25):2361–2376
3. Aithala R, Alex AG, Danda D (2017) Pulmonary hypertension in connective tissue diseases: an update. Int J Rheum Dis 20(1):5–24
4. Athanasiou KA, Sahni S, Rana A, Talwar A (2017) Diagnosing and managing scleroderma-related pulmonary arterial hypertension. JAAPA. 30(9):11–18
5. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V et al (2006) Pulmonary arterial hypertension in France: results from a national registry. Am J Respir Crit Care Med 173(9):1023–1030
6. Thakkar V, Lau EM (2016) Connective tissue disease-related pulmonary arterial hypertension. Best Pract Res Clin Rheumatol 30(1):22–38
7. Li M, Wang Q, Zhao J, Li Z, Ye Z, Li C et al (2014) 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 23(10):1085–1091
8. Nakamura K, Akagi S, Ejiri K, Yoshida M, Miyoshi T, Toh N et al (2019) Current treatment strategies and nanoparticle-mediated

drug delivery systems for pulmonary arterial hypertension. Int J Mol Sci 20(23):5885
9. Humbert M, Sitbon O, Simonneau G (2004) Treatment of pulmonary arterial hypertension. N Engl J Med 351(14):1425–1436
10. Ramjug S, Hussain N, Hurdman J, Billings C, Charalampopoulos A, Elliot CA et al (2017) Idiopathic and systemic sclerosis-associated pulmonary arterial hypertension: a comparison of demographic, hemodynamic, and MRI characteristics and outcomes. Chest. 152(1):92–102
11. Launay D, Sitbon O, Hachulla E, Mouthon L, Gressin V, Rottat L et al (2013) Survival in systemic sclerosis-associated pulmonary arterial hypertension in the modern management era. Ann Rheum Dis 72(12):1940–1946
12. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K et al (2010) 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 23(7):685–713 quiz 86-8
13. Agarwal R (2012) Prevalence, determinants and prognosis of pulmonary hypertension among hemodialysis patients. Nephrol Dial Transplant 27(10):3908–3914
14. Bolignano D, Rastelli S, Agarwal R, Fliser D, Massy Z, Ortiz A et al (2013) Pulmonary hypertension in CKD. Am J Kidney Dis 61(4):612–622
15. McQuillan BM, Picard MH, Leavitt M, Weyman AE (2001) Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects. Circulation. 104(23):2797–2802
16. Faqih SA, Noto-Kadou-Kaza B, Abouamrane LM, Mtiou N, El Khayat S, Zamd M et al (2016) Pulmonary hypertension: prevalence and risk factors. Int J Cardiol Heart Vasc 11:87–89
17. Shirai Y, Yasuoka H, Okano Y, Takeuchi T, Satoh T, Kuwana M (2012) Clinical characteristics and survival of Japanese patients with connective tissue disease and pulmonary arterial hypertension: a single-centre cohort. Rheumatology (Oxford) 51(10):1846–1854
18. Kang KY, Jeon CH, Choi SJ, Yoon BY, Choi CB, Lee CH et al (2017) 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 20(9):1227–1236
19. Hao YJ, Jiang X, Zhou W, Wang Y, Gao L, Wang Y et al (2014) Connective tissue disease-associated pulmonary arterial hypertension in Chinese patients. Eur Respir J 44(4):963–972
20. Humbert M, Segal ES, Kiely DG, Carlsen J, Schwierin B, Hoeper MM (2007) Results of European post-marketing surveillance of bosentan in pulmonary hypertension. Eur Respir J 30(2):338–344
21. Chung L, Liu J, Parsons L, Hassoun PM, McGoon M, Badesch DB et al (2010) Characterization of connective tissue disease-associated pulmonary arterial hypertension from REVEAL: identifying systemic sclerosis as a unique phenotype. Chest. 138(6):1383–1394
22. Montani D, Henry J, O'Connell C, Jais X, Cottin V, Launay D et al (2018) Association between rheumatoid arthritis and pulmonary hypertension: data from the French Pulmonary Hypertension Registry. Respiration 95(4):244–250
23. Li Y, Yi Q (2015) Pulmonary arterial hypertension associated with rare cause of ANCA-associated vasculitis misdiagnosed as idiopathic one. Int J Clin Exp Med 8(9):16850–16853
24. Launay D, Souza R, Guillevin L, Hachulla E, Pouchot J, Simonneau G et al (2006) Pulmonary arterial hypertension in ANCA-associated vasculitis. Sarcoidosis Vasc Diffuse Lung Dis 23(3):223–228
25. Cabello-Ganem A, Serrano-Roman J, Espejel-Guzman A, Ramirez-Perea F, Aparicio-Ortiz AD, Martinez-Martinez LA et al (2023) Pulmonary hypertension secondary to Takayasu arteritis and atrial septal defect. Clin Rheumatol
26. Young A, Nagaraja V, Basilious M, Habib M, Townsend W, Gladue H et al (2019) Update of screening and diagnostic modalities for connective tissue disease-associated pulmonary arterial hypertension. Semin Arthritis Rheum 48(6):1059–1067
27. Johnson PA, Alexander HD, McMillan SA, Maxwell AP (1997) Up-regulation of the endothelial cell adhesion molecule intercellular adhesion molecule-1 (ICAM-1) by autoantibodies in autoimmune vasculitis. Clin Exp Immunol 108(2):234–242
28. Chung L, Kawut SM (2014) Connective tissue disease-associated pulmonary arterial hypertension: "Beijing style". Eur Respir J 44(4):839–841
29. Rich S, Dantzker DR, Ayres SM, Bergofsky EH, Brundage BH, Detre KM et al (1987) Primary pulmonary hypertension. A national prospective study. Ann Intern Med 107(2):216–223
30. Ventetuolo CE, Praestgaard A, Palevsky HI, Klinger JR, Halpern SD, Kawut SM (2014) Sex and haemodynamics in pulmonary arterial hypertension. Eur Respir J 43(2):523–530
31. Hoeper MM, Pittrow D, Opitz C, Gibbs JSR, Rosenkranz S, Grunig E et al (2018) Risk assessment in pulmonary arterial hypertension. Eur Respir J 51(3)
32. Rabinovitch M, Guignabert C, Humbert M, Nicolls MR (2014) Inflammation and immunity in the pathogenesis of pulmonary arterial hypertension. Circ Res 115(1):165–175
33. Saito T, Fukuda H, Arisue M, Matsuda A, Shindoh M, Amemiya A et al (1991) Periductal lymphocytic infiltration of salivary glands in Sjogren's syndrome with relation to clinical and immunologic findings. Oral Surg Oral Med Oral Pathol 71(2):179–183
34. Komai K, Shiozawa K, Tanaka Y, Yoshihara R, Tanaka C, Sakai H et al (2009) Sjogren's syndrome patients presenting with hypergammaglobulinemia are relatively unresponsive to cevimeline treatment. Mod Rheumatol 19(4):416–419
35. Shu T, Xing Y, Wang J (2021) Autoimmunity in pulmonary arterial hypertension: evidence for local immunoglobulin production. Front Cardiovasc Med 8:680109
36. Huang J, An Q, Zhang CL, He L, Wang L (2022) Decreased low-density lipoprotein and the presence of pulmonary arterial hypertension among newly diagnosed drug-naive patients with systemic lupus erythematosus: D-dimer as a mediator. Exp Ther Med 24(3):595
37. Olsson KM, Delcroix M, Ghofrani HA, Tiede H, Huscher D, Speich R et al (2014) Anticoagulation and survival in pulmonary arterial hypertension: results from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA). Circulation. 129(1):57–65
38. Tanaka H, Kataoka M, Isobe S, Yamamoto T, Shirakawa K, Endo J et al (2017) Therapeutic impact of dietary vitamin D supplementation for preventing right ventricular remodeling and improving survival in pulmonary hypertension. PloS One 12(7):e0180615
39. Callejo M, Morales-Cano D, Mondejar-Parreno G, Barreira B, Esquivel-Ruiz S, Olivencia MA et al (2021) Restoration of vitamin D levels improves endothelial function and increases TASK-Like K(+) currents in pulmonary arterial hypertension associated with vitamin D deficiency. Biomolecules. 11(6):795
40. Yu H, Xu M, Dong Y, Liu J, Li Y, Mao W et al (2018) 1,25(OH)2D3 attenuates pulmonary arterial hypertension via microRNA-204 mediated Tgfbr2/Smad signaling. Exp Cell Res 362(2):311–323
41. Sonnweber T, Pizzini A, Tancevski I, Loffler-Ragg J, Weiss G (2020) Anaemia, iron homeostasis and pulmonary hypertension: a review. Intern Emerg Med 15(4):573–585
42. Brannon ES, Merrill AJ, Warren JV, Stead EA (1945) The cardiac output in patients with chronic anemia as measured by the technique of right atrial catheterization. J Clin Invest 24(3):332–336
43. Roy SB, Bhatia ML, Mathur VS, Virmani S (1963) Hemodynamic effects of chronic severe anemia. Circulation. 28:346–356

44. Krasuski RA, Hart SA, Smith B, Wang A, Harrison JK, Bashore TM (2011) Association of anemia and long-term survival in patients with pulmonary hypertension. Int J Cardiol 150(3):291–295
45. Tapio J, Vahanikkila H, Kesaniemi YA, Ukkola O, Koivunen P (2021) Higher hemoglobin levels are an independent risk factor for adverse metabolism and higher mortality in a 20-year follow-up. Sci Rep 11(1):19936
46. Haase VH (2010) Hypoxic regulation of erythropoiesis and iron metabolism. Am J Physiol Renal Physiol 299(1):F1–F13
47. van Loon RL, Bartelds B, Wagener FA, Affara N, Mohaupt S, Wijnberg H et al (2015) Erythropoietin attenuates pulmonary vascular remodeling in experimental pulmonary arterial hypertension through interplay between endothelial progenitor cells and heme oxygenase. Front Pediatr 3:71
48. Buemi M, Senatore M, Gallo GC, Crasci E, Campo S, Sturiale A et al (2007) Pulmonary hypertension and erythropoietin. Kidney Blood Press Res 30(4):248–252
49. Moreira GA, O'Donnell DC, Tod ML, Madden JA, Gordon JB (1999) Discordant effects of alkalosis on elevated pulmonary vascular resistance and vascular reactivity in lamb lungs. Crit Care Med 27(9):1838–1842
50. Domino KB, Lu Y, Eisenstein BL, Hlastala MP (1993) Hypocapnia worsens arterial blood oxygenation and increases VA/Q heterogeneity in canine pulmonary edema. Anesthesiology. 78(1):91–99
51. Zhai Z, Zhou X, Zhang S, Xie W, Wan J, Kuang T et al (2017) The impact and financial burden of pulmonary arterial hypertension on patients and caregivers: results from a national survey. Medicine (Baltimore) 96(39):e6783
52. Burger CD, Ozbay AB, Lazarus HM, Riehle E, Montejano LB, Lenhart G et al (2018) Treatment patterns and associated health care costs before and after treatment initiation among pulmonary arterial hypertension patients in the United States. J Manag Care Spec Pharm 24(8):834–842
53. Burks M, Stickel S, Galie N (2018) Pulmonary arterial hypertension: combination therapy in practice. Am J Cardiovasc Drugs 18(4):249–257
54. Kuwana M, Blair C, Takahashi T, Langley J, Coghlan JG (2020) 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 79(5):626–634
55. Humbert M, Coghlan JG, Ghofrani HA, Grimminger F, He JG, Riemekasten G et al (2017) Riociguat for the treatment of pulmonary arterial hypertension associated with connective tissue disease: results from PATENT-1 and PATENT-2. Ann Rheum Dis 76(2):422–426
56. Mathai SC, Girgis RE, Fisher MR, Champion HC, Housten-Harris T, Zaiman A et al (2007) Addition of sildenafil to bosentan monotherapy in pulmonary arterial hypertension. Eur Respir J 29(3):469–475
57. Liu HL, Chen XY, Li JR, Su SW, Ding T, Shi CX et al (2016) Efficacy and safety of pulmonary arterial hypertension-specific therapy in pulmonary arterial hypertension: a meta-analysis of randomized controlled trials. Chest. 150(2):353–366
58. Galie N, Barbera JA, Frost AE, Ghofrani HA, Hoeper MM, McLaughlin VV et al (2015) Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med 373(9):834–844