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The prognostic value of HFA-PEFF score in connective tissue disease-associated PAH: evidence from a cohort study

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Abstract

Background Connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) patients with left heart dysfunction may have worse prognosis. This study was to investigate the prognostic value of HFA-PEFF score in connective tissue disease-associated PAH.

Methods This single-center retrospective cohort study enrolled 147 CTD-PAH patients diagnosed via right heart catheterization (RHC), divided into two groups based on their HFA-PEFF scores: < 5 ($n = 74$) and ≥ 5 ($n = 73$). The clinical characteristics were compared between the two groups. The primary end point was all-cause mortality, and the secondary end point was clinical worsening events. Survival was analyzed using Kaplan–Meier analysis and Cox proportional hazards models.

Results Compared to the HFA-PEFF score < 5 group, the ≥ 5 group exhibited significantly higher levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), a greater proportion of WHO functional class III–IV, shorter 6-min walk distance (6MWD), larger right ventricular (RV) volume, worse RV function, smaller left ventricular (LV) volume, and higher native T1 values. An HFA-PEFF score ≥ 5 was a predictor for all-cause mortality in CTD-PAH (HR 5.022, $P = 0.020$) and for clinical worsening events (HR 2.670, $P = 0.020$). At follow-up, 17.9% of CTD-PAH had an HFA-PEFF score ≥ 5 . Patients with follow-up HFA-PEFF scores ≥ 5 had a significantly lower event-free survival rate ($P < 0.001$).

Conclusion An HFA-PEFF score ≥ 5 was associated with all-cause mortality and clinical worsening events in CTD-PAH patients.

Trial registration NCT05980728. Connective Tissue Disease Patients With Pulmonary Hypertension. Oct 17, 2023.

Keywords Connective tissue disease (CTD), Pulmonary arterial hypertension (PAH), HFA-PEFF score, All-cause mortality, Clinical worsening events

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Introduction

Pulmonary arterial hypertension (PAH) is a severe complication of connective tissue disease (CTD) [1]. It is a progressive cardiopulmonary disease that leads to right ventricular (RV) failure and death, which is one of the main causes for death in CTD [2, 3]. Besides RV dysfunction, approximately 7.9%–33.0% PAH patients have complication of left heart diseases (LHD) risk factors [4–6]. The effect of LHD risk factors on prognosis of PAH remains unclear [7, 8]. Previous study showed that systemic sclerosis-related pulmonary hypertension with biventricular failure had worse prognosis than those with normal left heart function [9].

Heart failure with preserved ejection fraction (HFpEF) is characterized by diastolic dysfunction, accounting for over half of whole heart failure [10, 11]. CTD and PAH are both important causes for HFpEF because of the inflammation and myocardial fibrosis resulting from CTD and the compression from the right heart [12–14]. However, CTD-PAH was classified as pre-capillary pulmonary hypertension according to the guideline, which is in contradiction with the hemodynamics characteristics of HFpEF [15]. A recent study suggested that group 1 pulmonary hypertension patients with a high risk of HFpEF had poorer quality of life and survival [16]. To date, limited research has focused on the clinical implications of HFpEF in CTD-PAH patients.

The Heart Failure Association (HFA)-PEFF algorithm, recommended by the European Society of Cardiology (ESC), provides a structured approach for diagnosing HFpEF [17]. This algorithm comprises four steps: (1) pre-test assessment to screen for heart failure signs, (2) calculation of the HFA-PEFF score, (3) functional testing for intermediate scores, and (4) investigation of specific etiologies. Patients with an HFA-PEFF score ≥ 5 can be diagnosed with HFpEF, while those with a score ≤ 1 are unlikely to have HFpEF. Scores between 2 and 4 require further evaluation via functional testing, including exercise stress echocardiography and resting or exercise hemodynamic testing. The fourth step investigates the underlying causes of HFpEF. The HFA-PEFF score emphasizes structural cardiac changes and has been validated in various populations, including the general population, patients with cardiac amyloidosis, connective tissue diseases, the elderly with HFpEF, and those with subclinical HFpEF [18–21].

In this study, we applied the HFA-PEFF score to CTD-PAH patients to explore the characteristics of those with HFpEF and assess the clinical value of HFpEF as a complication in CTD-PAH.

Methods

Study design and population

This was a single-center retrospective study recruited CTD-PAH patients diagnosed by right heart catheterization (RHC) in the First Affiliated Hospital of Nanjing Medical University from June 2016 to January 2024. The inclusion criteria of our study are (1) over 18 years old, (2) having a diagnosis of PAH confirmed by RHC with the hemodynamic definition: mean pulmonary arterial pressure (mPAP) > 20 mmHg, pulmonary arterial wedge pressure (PAWP) ≤ 15 mmHg, pulmonary vascular resistance (PVR) > 2 WU, (3) undergoing ultrasound cardiogram (UCG) examination within 1 month of RHC, (4) being followed up at least 3 months. We excluded the cases (1) with left heart diseases or congenital heart diseases, (2) with portal hypertension, (3) with drug or toxin exposure associated with PAH, (4) with human immunodeficiency virus (HIV) infection, (5) with obstructive or restrictive lung diseases or hypoxia, (6) with a complication of chronic obstructive pulmonary disease, (7) with systemic vasculitis. The flow chart is shown in Fig. 1.

For all the patients enrolled, the following data were collected by case report forms: (1) demographic data, (2) subtype and duration of CTD, (3) assessment of PAH including WHO function class, 6-min walking distance (6MWD) and N-terminal pro-brain natriuretic peptide (NT-proBNP), (4) laboratory examination, (5) treatment including PAH-targeted drugs, glucocorticoid, immunosuppressant and diuretic, (6) hemodynamic, echocardiography and cardiac magnetic resonance (CMR) parameters.

Patients were followed up every 3 months to update their status. The primary endpoint was all-cause death and the secondary endpoint was clinical worsening events, including all-cause death and rehospitalization due to PAH. The time from baseline to the first adjudicated endpoint was recorded. Our study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (2018-SR-333) and all the patients signed the informed consent. The clinical trial ID of our study is NCT05980728.

UCG measurement and HFA-PEFF score

UCG measurements were performed with the patients at rest in the left lateral decubitus position using a Vivid E9 instrument (GE Medical Systems, Horten, Norway). Pulsed Doppler echocardiography was used to measure early (E) and late (A) diastolic velocities of the transmitral flow from the apical four-chamber view. Peak early diastolic myocardial velocity (E') was calculated on tissue Doppler echocardiography from the left ventricular (LV) apical four-chamber view, using a 2-mm sample volume

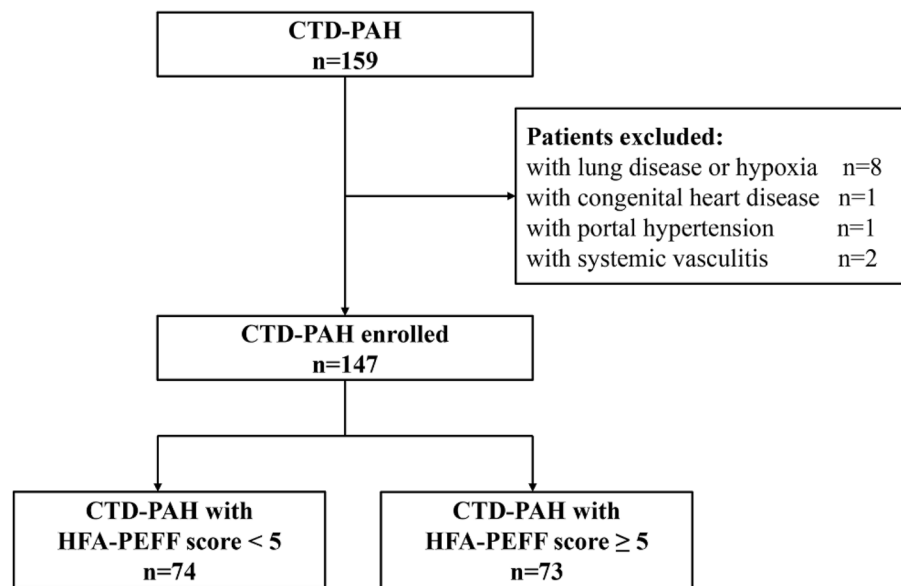


Fig. 1 Flow chart of the study participants

at the level of the basal portion of the septal (E'_{sep}) and lateral mitral valve annulus (E'_{lat}) [22]. LV Mass and relative wall thickness (RWT) were estimated through the following formulas: LV Mass = $1.4 \times 0.8 \times [(IVS + LVDd + LVPW)^3 - LVDd^3] + 0.6$ g; RWT = $(2 \times LVPW) / LVDd$. IVS is end-diastolic intraventricular septum thickness, LVDd is LV end-diastolic diameter, LVPW is LV end-diastolic posterior wall thickness. HFA-PEFF score was calculated as the sum of functional, morphological and biomarker scores. In each part, a major criterion scores 2 points and a minor criterion 1 point. Patients were divided into HFA-PEFF score ≥ 5 (high probability of HFpEF) and < 5 (low and intermediate probability of HFpEF) [17].

Statistical analysis

Normally distributed variables were described as mean $\pm$ S.D. and non-normally distributed variables were described as median and interquartile range (Q1–Q3). Categorical variables were described as numbers and percentages. The Student's *t*-test or Mann–Whitney U test was used to compare the difference between two groups for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. Univariable and multivariable cox proportional hazard regression were applied to identify associated factors between HFA-PEFF score and all-cause mortality or clinical worsening events. Kaplan–Meier curves were used to compare the prognosis between the two groups. A two-tailed *P*-value < 0.05 was considered significant. All the statistical analysis was performed by R 4.4.2.

Results

Clinical characteristics of CTD-PAH

A total of 147 CTD-PAH patients were enrolled according to the inclusion and exclusion criteria, with 73 (49.7%) patients having HFA-PEFF score ≥ 5 and 74 (50.3%) patients < 5 . The baseline characteristics between two groups are shown in Table 1. The patients with HFA-PEFF score ≥ 5 were characterized by shorter CTD duration [0.90 (0.00–92.40) vs. 31.50 (0.17–91.50) months, $P = 0.046$], higher serum NT-proBNP level [2094 (786–4360) vs. 202 (102–598) pg/ml, $P < 0.001$], shorter 6MWD [386 (291–460) vs. 465 (400–525) m, $P < 0.001$] and more WHO functional class III–IV (68.1% vs. 28.4%, $P < 0.001$). Baseline serum urea nitrogen (BUN), creatinine (Cr), uric acid (UA) and complement C4 were significantly higher in the HFA-PEFF score ≥ 5 group but both groups were within the normal range. There were no differences in gender, age, CTD subtype and medications.

Baseline RHC, UCG and CMR characteristics of CTD-PAH classified by HFA-PEFF score

Table 2 showed the hemodynamic, structural and functional comparison between the HFA-PEFF score ≥ 5 and < 5 groups. The CTD-PAH with HFA-PEFF score ≥ 5 had higher mPAP, PVR, mean right atrial pressure (mRAP), mean right ventricular pressure (mRVP) and lower cardiac index (CI). Among characteristics associated with right heart, patients with HFA-PEFF score ≥ 5 were characterized by larger RV end-diastolic volume index (RVEDVI), RV end-systolic volume index (RVESVI), RV mass index (RVMI)

Table 1 Baseline characteristics of CTD-PAH patients

	HFA-PEFF score < 5	HFA-PEFF score ≥ 5	P value
	<i>n</i> = 74	<i>n</i> = 73	
Gender,n(%)			0.275
Male	2 (2.7%)	5 (6.9%)	
Female	72 (97.3%)	68 (93.2%)	
Age,years	39.6 (33.7–50.5)	47.1 (32.1–57.0)	0.153
CTD,n(%)			0.402
SLE	26 (35.1%)	20 (27.4%)	
OS	19 (25.7%)	20 (27.4%)	
SS	12 (16.2%)	18 (24.7%)	
SSc	6 (8.1%)	8 (11.0%)	
UCTD	3 (4.1%)	5 (6.9%)	
MCTD	5 (6.8%)	1 (1.4%)	
RA	3 (4.1%)	1 (1.4%)	
CTD duration,months	31.50(0.17–91.50)	0.90(0.00–92.40)	0.046
NT-proBNP,pg/mL	202 (102–598)	2094 (786–4360)	< 0.001
6MWD,m	465 (400–525)	386 (291–460)	< 0.001
WHO class,n(%)			< 0.001
I-II	53 (71.6%)	23 (31.9%)	
III-IV	21 (28.4%)	49 (68.1%)	
PAH therapy,n(%)			0.420
None	2 (2.7%)	2 (2.7%)	
Monotherapy	23 (31.1%)	16 (21.9%)	
Combination therapy	49 (66.2%)	55 (75.3%)	
Glucocorticoid,n(%)	68 (91.9%)	63 (86.3%)	0.410
Immunosuppressant, n(%)	49 (66.2%)	54 (75.0%)	0.326
Diuretic,n(%)	13 (33.3%)	23 (54.8%)	0.086
Laboratory examination			
ALT,U/L	17.80 (12.90–29.40)	19.60 (13.40–35.40)	0.360
AST,U/L	25.40 (19.10–35.00)	31.70 (22.70–40.00)	0.067
BUN,mmol/L	5.30 (4.00–6.49)	6.11 (4.98–8.51)	0.004
Cr,μmol/L	52.20 (47.20–60.80)	66.60 (56.20–81.40)	< 0.001
UA,μmol/L	317.00 (244.00–386.00)	404.00 (329.00–508.00)	< 0.001
ESR,mm/h	22.00 (8.00–52.50)	21.00 (10.00–55.80)	0.994
RF,IU/mL,n(%)			0.302
< 20.0	37 (56.9%)	45 (67.2%)	
≥ 20.0	28 (43.1%)	22 (32.8%)	
CRP,mg/L	3.62 (2.13–8.93)	3.59 (2.97–10.7)	0.516
IgG,g/L	15.70 (11.40–22.70)	12.70 (10.10–19.00)	0.084
IgA,g/L	2.60 (1.97–3.38)	2.49 (1.86–3.38)	0.895
IgM,g/L	1.18 (0.70–1.70)	0.97 (0.60–1.52)	0.160
C3,g/L	0.74 ± 0.26	0.77 ± 0.24	0.508
C4,g/L	0.14 (0.10–0.18)	0.16 (0.12–0.20)	0.047
Tnl(+),n(%)	11 (26.2%)	4 (8.7%)	0.058

CTD-PAH: connective tissue disease-associated pulmonary arterial hypertension; SLE: systemic lupus erythematosus; OS: overlap syndrome; SS: Sjögren's syndrome; SSc: systemic sclerosis; UCTD: undifferentiated CTD; MCTD: mixed CTD; RA: rheumatoid arthritis; NT-proBNP: N-terminal pro-brain natriuretic peptide; 6MWD: 6 min walk distance; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen; Cr: creatinine; UA: uric acid; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; CRP: C-reaction protein; Tnl: troponin I

Bold text indicates $P < 0.05$

Table 2 Baseline RHC, UCG and CMR characteristics of CTD-PAH patients

	HFA-PEFF score < 5	HFA-PEFF score ≥ 5	P value
	n = 74	n = 73	
RHC			
mPAP,mmHg	37.0 (33.0–44.8)	48.0 (38.0–52.0)	< 0.001
PAWP,mmHg	7 (5–10)	8 (6–11)	0.098
PVR,WU	5.43 (3.94–8.79)	9.66 (6.67–14.20)	< 0.001
mRAP,mmHg	4.00 (3.00–7.00)	6.00 (3.75–8.25)	0.022
mRVP,mmHg	22.0 (17.2–27.0)	27.0 (23.5–34.0)	< 0.001
CI,L/min/m ²	3.10 (2.70–3.69)	2.54 (2.00–3.14)	< 0.001
UCG			
RAD,mm	39 (35–42)	43 (40–48)	< 0.001
RVDd,mm	40 (37–43)	45 (41–49)	< 0.001
LAD,mm	32 (29–35)	31 (28–35)	0.270
LVDd,mm	42.6 ± 4.5	38.8 ± 5.7	< 0.001
IVS,mm	9 (8–10)	10 (9–10)	0.001
LVPW,mm	8 (8–9)	9 (9–10)	< 0.001
EF,%	65.4 (63.6–66.9)	64.8 (62.7–66.7)	0.315
E' _{sep} ,cm/s	6.47 ± 1.61	5.67 ± 1.47	0.004
E' _{lat} ,cm/s	11.80 ± 3.19	9.14 ± 2.88	< 0.001
E/A	0.95 (0.80–1.20)	0.90 (0.70–1.00)	0.014
E/e'	7.00 (6.10–8.20)	7.90 (6.40–9.30)	0.119
Tapse,mm	17.30 ± 3.19	15.30 ± 3.30	0.001
Tapse/PASP	0.29 (0.21–0.36)	0.19 (0.16–0.23)	< 0.001
RV FAC,%	32.9 ± 7.3	28.2 ± 7.3	0.002
TVR,cm/s	374.0 ± 53.8	423.0 ± 55.4	< 0.001
Pericardial effusion,n(%)	25 (33.8%)	38 (52.8%)	0.032
CMR			
LVEF,%	56.2 (51.5–61.3)	57.3 (49.0–62.8)	0.742
LVEDVI,ml/m ²	68.9 ± 15.6	54.7 ± 21.1	0.001
LVESVI,ml/m ²	29.3 (23.8–38.4)	22.5 (17.6–27.5)	< 0.001
LVMI,g/m ²	43.4 (36.9–48.3)	38.2 (34.2–42.9)	0.014
RVEF,%	39.3 ± 11.6	27.0 ± 10.1	< 0.001
RVEDVI,ml/m ²	89.3 (80.5–115.0)	115.0 (87.1–140.0)	0.025
RVESVI,ml/m ²	54.3 (42.6–73.1)	75.1 (62.4–104.0)	< 0.001
RVMI,g/m ²	10.4 (8.0–13.0)	16.1 (11.1–20.1)	< 0.001
Native T1,ms	1258 (1225–1288)	1285 (1246–1341)	0.013
ECV,%	29.50 ± 7.15	31.10 ± 6.58	0.292

CTD-PAH: connective tissue disease-associated pulmonary arterial hypertension; RHC: right heart catheterization; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; mRAP: mean right atrial pressure; mRVP: mean right ventricular pressure; CI: cardiac index; UCG: ultrasound cardiogram; RV: right ventricular; LV: left ventricular; RAD: right atrial diameter; RVDd: RV end-diastolic diameter; LAD: left atrial diameter; LVDd: LV end-diastolic diameter; IVS: intraventricular septum thickness, LVPW: LV posterior wall thickness; EF: ejection fraction; FAC: fractional area change; CMR: cardiac magnetic resonance; EDVI: end-systolic volume index; ESVI: end-systolic volume index; MI: mass index; ECV: extra-cellular volume

Bold text indicates $P < 0.05$

and smaller tricuspid annular plane systolic excursion (TAPSE), TAPSE/pulmonary artery systolic pressure (PASP), RV fractional area change (FAC) and RV ejection fraction (RVEF). In regards to the structure of left heart, LV end-systolic volume index (LVEDVI), LV end-systolic volume index (LVESVI), LV mass

index (LVMI) in CMR were significantly smaller in the HFA-PEFF score ≥ 5 group. There were no differences in left ventricular systolic function between the two groups. Because of the definition of HFA-PEFF score, E'_{sep}, E'_{lat}, E/A were smaller in the HFA-PEFF score ≥ 5 group.

HFA-PEFF score was associated with poor prognosis in CTD-PAH

The univariable Cox regression showed HFA-PEFF score ≥ 5 was a prognostic factor of all-cause mortality in CTD-PAH (HR 5.865, 95%CI 1.678–20.500, $P=0.006$). After adjusting for age, gender, CTD duration and mPAP, HFA-PEFF score ≥ 5 was still an independent predictor for all-cause mortality in CTD-PAH (HR 5.022, 95%CI 1.294–19.492, $P=0.020$) (Table 3). Multivariable cox indicated HFA-PEFF score ≥ 5 was also an independent predictor for clinical worsening events (HR 2.670, 95%CI 1.166–6.117, $P=0.020$) (Table 4). Up to April 30 2024, primary endpoint occurred in 17 patients and secondary endpoint occurred in 33 patients after a mean follow up of 35.9 ± 27.3 months. All the readmission of PAH is due to worsening PAH. The estimate 1-, 3- and 5-year survival rate was 98.6%, 95.9%, 95.9% in HFA-PEFF score < 5 group and 91.1%, 75.8%, 75.8% in HFA-PEFF score ≥ 5 group, respectively. The estimate 1-, 3- and 5-year event-free survival rate was 97.3%, 90.2%, 87.2% in HFA-PEFF score < 5 group and 84.1%, 58.7%, 50.0% in HFA-PEFF score ≥ 5 group, respectively. Kaplan–Meier curves showed the accumulate survival rate ($P=0.002$) and event-free survival rate ($P<0.001$) were

significantly lower in the HFA-PEFF score ≥ 5 group (Fig. 2).

HFA-PEFF score at follow up

The follow-up HFA-PEFF score at least 1 year from baseline was recorded and 78 patients had the follow-up data. All of the 78 patients received PAH targeted therapy and none of them received heart failure therapy. Five patients had their therapy optimized because of clinical worsening events. Among the 46 patients with HFA-PEFF score < 5 at baseline, 40 (87.0%) patients had HFA-PEFF score < 5 and 6 (13.0%) ≥ 5 at follow up. And among 32 patients with HFA-PEFF score ≥ 5 at baseline, 24 (75.0%) patients had HFA-PEFF score < 5 at follow up and 8 (25.0%) patients remained ≥ 5 (Fig. 3).

Supplementary Table 1 showed the characteristics of CTD-PAH classified by follow-up HFA-PEFF score. Patients with HFA-PEFF score ≥ 5 at follow up were characterized by higher serum NT-proBNP level, shorter 6MWD and more WHO functional class III-IV. There was no significant difference in inflammatory and immune indexes between the two groups. For RV structural and functional parameters, RVEDVI, RVESVI, RVMI were larger and RVEF was smaller in the follow-up HFA-PEFF ≥ 5 group. Interestingly, LVEDVI, LVESVI and LVMI were larger in the follow-up HFA-PEFF ≥ 5 group

Table 3 Univariable and multivariable Cox proportional hazard regression analysis for all-cause mortality in CTD-PAH

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
HFA-PEFF score ≥ 5	5.865(1.678–20.500)	0.006	5.022(1.294–19.492)	0.020
Age	1.040(1.006–1.075)	0.021	1.034(0.995–1.074)	0.088
Male	6.730(1.896–23.890)	0.003	7.296(1.922–27.694)	0.004
CTD duration	1.000(0.994–1.006)	0.982	1.001(0.995–1.007)	0.763
mPAP	1.014(0.980–1.049)	0.435	1.008(0.968–1.051)	0.691

CTD-PAH: connective tissue disease-associated pulmonary arterial hypertension; HR: hazard ratio; mPAP: mean pulmonary arterial pressure

Bold text indicates $P<0.05$

Table 4 Univariable and multivariable Cox proportional hazard regression analysis for clinical worsening events in CTD-PAH

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
HFA-PEFF score ≥ 5	3.859(1.779–8.367)	<0.001	2.670(1.166–6.117)	0.020
Age	1.013(0.988–1.039)	0.314	1.021(0.994–1.050)	0.135
Male	2.791(0.842–9.252)	0.093	2.644(0.781–8.948)	0.118
CTD duration	0.999(0.994–1.004)	0.592	1.000(0.995–1.004)	0.916
mPAP	1.046(1.021–1.072)	<0.001	1.044(1.014–1.074)	0.004

CTD-PAH: connective tissue disease-associated pulmonary arterial hypertension; HR: hazard ratio; mPAP: mean pulmonary arterial pressure

Bold text indicates $P<0.05$

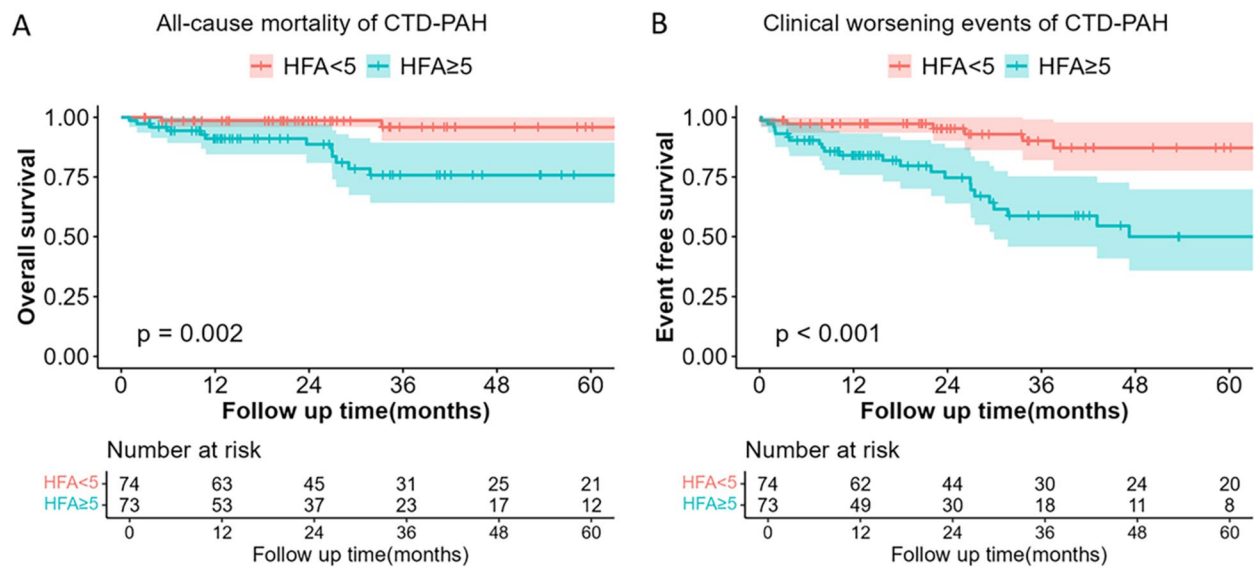


Fig. 2 Kaplan–Meier curve of CTD-PAH. **A** All-cause mortality was significantly higher in HFA-PEFF ≥ 5 group. **B** The probability of clinical worsening events was significantly higher in HFA-PEFF ≥ 5 group. CTD=connective tissue disease, PAH=pulmonary arterial hypertension

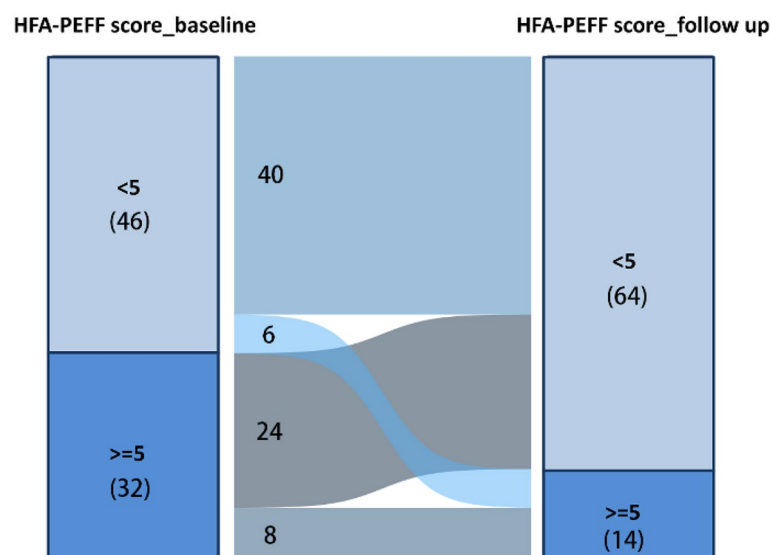


Fig. 3 Sankey diagram of changes in HFA-PEFF score from baseline to follow up. There were 73(49.7%) CTD-PAH having HFA-PEFF score ≥ 5 and 74(50.3%) patients < 5 at baseline. Among 78 patients who had the follow-up data, 64(82.1%) patients having HFA-PEFF score ≥ 5 and 14(17.9%) patients < 5 at follow up. CTD=connective tissue disease, PAH=pulmonary arterial hypertension

although the difference of LVEDVI and LVESVI was not significant, which was different from the characteristics of baseline HFA-PEFF score.

HFA-PEFF score ≥ 5 at follow up was associated with poor prognosis in CTD-PAH

Survival rates were compared between the follow-up HFA-PEFF score ≥ 5 group and < 5 group (survival time was estimated from the time of enrollment). The estimate

1-, 3- and 5-year survival rate was 100.0%, 90.1%, 90.1% in follow-up HFA-PEFF score < 5 group and 85.7%, 77.1%, 77.1% in ≥ 5 group, respectively. The estimate 1-, 3- and 5-year event-free survival rate was 92.2%, 80.0%, 77.1% in follow-up HFA-PEFF score < 5 group and 71.4%, 57.1%, 19.1% in ≥ 5 group, respectively. The event-free survival rate was lower in the patients with HFA-PEFF score ≥ 5 at follow up ($P < 0.001$) while there was no significant difference in all-cause mortality (Fig. 4).

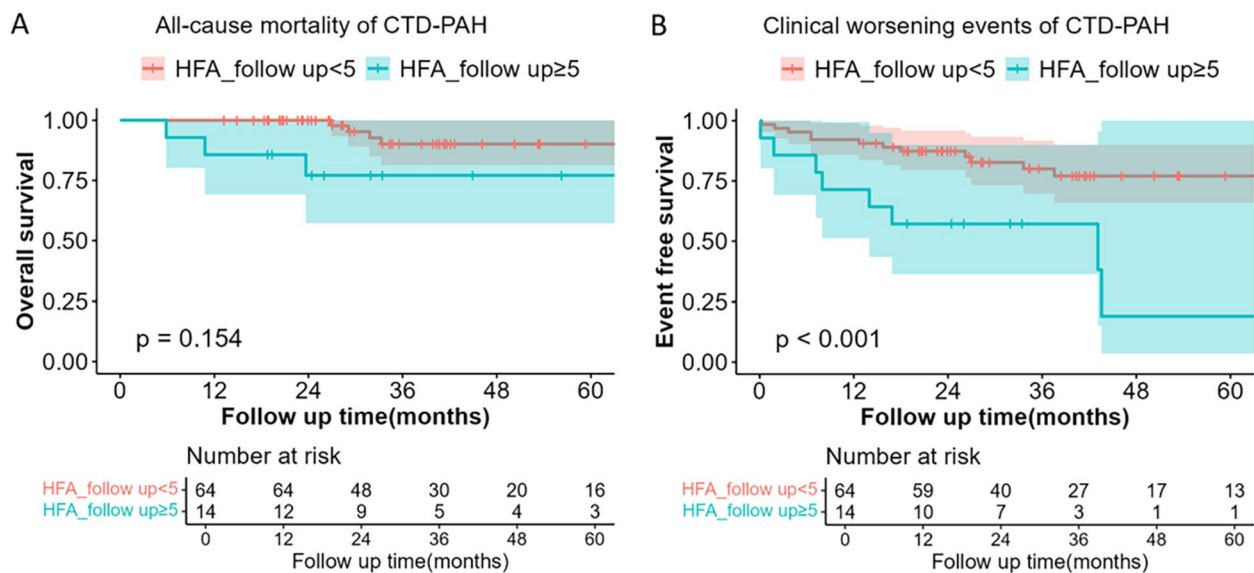


Fig. 4 Kaplan–Meier curve of CTD-PAH. **A** There was no difference in all-cause mortality between follow-up HFA-PEFF ≥ 5 and < 5 groups. **B** The probability of clinical worsening events was significantly higher in follow-up HFA-PEFF ≥ 5 group. CTD = connective tissue disease, PAH = pulmonary arterial hypertension

Discussion

Our study revealed that, when assessed by the HFA-PEFF score, nearly half of CTD-PAH patients had HFpEF as a complication. We demonstrated that PAH severity was greater in CTD-PAH patients with HFpEF, evidenced by significant right ventricular (RV) dilation and poorer RV function. Moreover, an HFA-PEFF score ≥ 5 at baseline was independently associated with both all-cause mortality and clinical worsening events. Additionally, an HFA-PEFF score ≥ 5 , whether at baseline or follow-up, was associated with a worse prognosis.

The coexistence of PAH and LHD has garnered increasing attention in recent years [5]. Liu et al. found that PAH patients with LV dysfunction, as defined by global longitudinal strain (GLS), had worse outcomes than those with normal LV function [9]. In the AMBITION study, the definition of PAH with LHD risk factors included clinical criteria (three or more of the following: systemic hypertension, significant coronary artery disease, diabetes mellitus, or BMI $> 30 \text{ kg/m}^2$) and hemodynamic criteria (PVR 3–3.75 WU or PVR 3.75–6.25 WU with PAWP 13–15 mmHg) [23]. However, most of CTD-PAH population are young or middle-aged female with a lower risk of traditional cardiovascular diseases [24, 25]. In our cohort, there were only 8 patients with hypertension, 5 patients with BMI $> 28 \text{ kg/m}^2$ and 2 patients with diabetes. The hemodynamic criteria tend to exclude patients with lower PVR, and the presence of LHD risk factors does not necessarily indicate LV dysfunction. Therefore, this definition may not effectively capture HFpEF

in CTD-PAH. Diagnosing HFpEF remains challenging, with two widely used models: the H₂FPEF and HFA-PEFF scores [17, 26]. The H₂FPEF score is more effective in identifying patients with obesity, atrial fibrillation, or systemic hypertension, highlighting a male-dominated, comorbidity-driven phenotype of HFpEF. However, it may underestimate the incidence of HFpEF in CTD-PAH [18]. The HFA-PEFF score, which assesses cardiac structure, function, and serum biomarkers, proved effective in our study, where nearly half of the CTD-PAH patients had a high score, confirming HFpEF. Furthermore, an HFA-PEFF score ≥ 5 was strongly predictive of prognosis in this population.

Our findings indicated that CTD-PAH patients with high HFA-PEFF scores exhibited higher RV and RA pressures, larger RV volumes, and worse RV systolic function. The right and left ventricles are interdependent, sharing a common superficial myocardial layer, with myocytes arranged circumferentially around the atrioventricular groove [27, 28]. The LV has diastolic interdependence with the RV and RV dilatation shifts diastolic pressure–volume curve of LV toward higher. Animal studies have demonstrated that RV distension can directly mechanically impact the muscle bundles encircling both ventricles, ultimately leading to LV dysfunction [29]. This diastolic ventricular interdependence is particularly pronounced when the pericardium is intact [30, 31]. Kasner et al. reported that IPAH patients maintained preserved LV ejection fraction but exhibited increased diastolic stiffness, as shown by invasive pressure–volume loop

analysis [32]. Thus, RV enlargement and constriction appear to be the primary drivers of HFpEF in PAH.

There is complex relationship between LV diastolic dysfunction and pulmonary hypertension. The previous view was that LV diastolic dysfunction is one of the causes of pulmonary hypertension. However, recent studies suggested that increased PVR in primary pulmonary hypertension could activate sympathetic system and lead to right ventricular fibrosis, then results in left heart diseases [33]. HFA-PEFF score was associated with mean left atrial pressure, which reflects LV diastolic dysfunction [34]. In addition, recent study found HFA-PEFF score was associated with pulmonary arterial stiffness [35]. A higher HFA-PEFF score could reflect dysfunction in left heart and pulmonary circulation.

Unlike HFpEF caused by traditional cardiovascular diseases, CTD-PAH-associated HFpEF is characterized by smaller LV diameters and decreased LV mass, as observed in our cohort. In severe PAH, LV atrophy often occurs [28, 36]. Hardziyenka et al. found that PAH rats exhibited smaller LV free wall myocytes and reduced LV mass [37]. Interestingly, LV mass increased when RV function was restored after pulmonary endarterectomy. Mechanistically, reduced LV preload due to RV failure leads to LV unloading, down-regulating genes involved in myocardial metabolism and function (e.g., α -MHC and SERCA-2) [37]. This LV atrophy, coupled with thickening of the interventricular septum and posterior wall observed in our study, suggests that autoimmune-driven inflammation and myocardial edema or fibrosis may contribute to HFpEF [38–40]. In line with these findings, Shi et al. reported that the HFA-PEFF score correlated positively with disease activity in idiopathic inflammatory myopathy [20]. In our cohort, patients with an HFA-PEFF score ≥ 5 exhibited higher native T1 values, indicating myocardial edema or increased interstitial and extracellular space [41]. The median CTD duration was 0.9 months in HFA-PEFF score ≥ 5 group and 31.5 months in the other group, suggesting that long-term glucocorticoid and immunosuppressant use may mitigate diastolic dysfunction caused by immunity and inflammation. Notably, 17.9% of CTD-PAH patients exhibited a high risk of HFpEF at follow-up, and these patients had larger LV and RV volumes, possibly reflecting irreversible myocardial fibrosis or potential subclinical LV disease, despite targeted therapy for PAH and CTD. The mechanism remains to be studied further.

We also found that an HFA-PEFF score ≥ 5 at baseline could predict all-cause mortality and clinical worsening events in CTD-PAH, and HFA-PEFF scores ≥ 5 at follow up could predict clinical worsening events. The lack of difference in all-cause mortality between the follow-up HFA-PEFF score ≥ 5 and < 5 groups may be due to early

death before follow-up assessments. Furthermore, based on the recognized risk stratification of PAH, risk stratification combined with HFA-PEFF score could enhance the ability of prediction for all-cause death and clinical worsening events (Supplementary Figure S1, Supplementary Figure S2). Current risk assessment strategies for PAH, such as the 2022 ESC/ERS guidelines, the 2018 World Symposium on Pulmonary Hypertension (WSPH) framework and Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) 2.0, emphasize hemodynamic parameters to estimate prognosis [15, 42, 43]. However, these methods are not suitable for long-term follow-up. While non-invasive assessments like REVEAL Lite 2.0 and COMPARE 2.0 focus on RV structure and function, they neglect the prognostic role of the LV [44, 45]. Our study is the first to highlight the prognostic significance of HFpEF in CTD-PAH based on the HFA-PEFF score, suggesting its utility for both follow-up assessments and therapeutic guidance.

Study limitations

Our study had several limitations. First, it was a retrospective single-center study with a small sample size, introducing potential selection bias. Future research with larger, multi-center cohorts is needed to confirm our findings. Second, only a small proportion of patients underwent CMR or RHC during follow-up. Third, because of the limited condition, none of the patient accepted the step 3 of HFA-PEFF algorithm: exercise stress echocardiography, which could underestimate the proportion of HFpEF. Exercise echocardiography is needed in the future study to investigate the prognosis of different HFpEF phenotypes [46]. Finally, none of the patients received sodium-dependent glucose transporters 2 (SGLT2) inhibitors (such as dapagliflozin or empagliflozin) for HFpEF treatment. Further studies are needed to evaluate the impact of SGLT2 inhibitors on CTD-PAH with HFpEF.

Conclusions

An HFA-PEFF score ≥ 5 was significantly correlated to all-cause mortality and clinical worsening events in patients with CTD-PAH. The primary contributors to HFpEF in this population appear to be RV enlargement and myocardial edema or fibrosis. These findings highlight the importance of using the HFA-PEFF score for risk stratification and prognosis in CTD-PAH patients, allowing for more targeted management and improved outcomes.

Abbreviations

HFpEF	Heart failure with preserved ejection fraction
CTD	Connective tissue disease
PAH	Pulmonary arterial hypertension
LDH	Left heart diseases
CMR	Cardiac magnetic resonance
RV	Right ventricle/ventricular

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Authors' contributions

LZ and QW provided the idea of this study and supervised our study. JD, LM and YZ collected the data, analyzed the data and wrote the manuscript. LS, DL, LL, QH and ZZ did the work of follow-up of the patients. XS was responsible for enrollment and treatment. All authors reviewed the manuscript.

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Data availability

To protect participant privacy, data is not available. Data will be shared upon reasonable requests to the corresponding author.

Declarations

Ethics approval and consent to participate

Our study complies with the Declaration of Helsinki. Our study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (2018-SR-333). All the participants have signed informed consent.

Competing interests

The authors declare no competing interests.

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