



# Red blood cell distribution width as a potential predictor of survival of pulmonary arterial hypertension associated with primary Sjogren's syndrome: a retrospective cohort study

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## Abstract

Pulmonary arterial hypertension (PAH) is a severe complication and leading cause of mortality in patients with primary Sjogren's syndrome (pSS). This study was to investigate the overall survival rates and the utility of red blood cell distribution width (RDW) as a potential prognostic factor of pSS-PAH. This cohort study retrospectively enrolled 55 patients with pSS-PAH who were followed up at the Department of Rheumatology of Peking Union Medical College Hospital (PUMCH) between August 2007 and May 2017. The patients were stratified according to the level of RDW ( $\leq 15.0$  and  $> 15.0\%$ ). Baseline demographics, laboratory results, pulmonary function conditions, hemodynamic assessments, and treatment regimens were analyzed. Cox proportional hazards regression analysis was used to identify whether RDW level is a factor related to adverse outcome. A total of 55 patients were recruited, with an average age of  $38.9 \pm 9.3$  years. Fifty-four were female (98.2%), and the average duration at the time of PAH diagnosis was  $25.5 \pm 33.2$  months. Higher RDW levels were found in patients who deceased in follow-up ( $13.8 \pm 2.6$  vs  $16.5 \pm 1.6\%$ ,  $p = 0.003$ ) and with higher NYHA classes ( $13.8 \pm 1.8$  vs  $16.5 \pm 2.9\%$ ,  $p < 0.001$ ). Patients with RDW  $> 15\%$  had a significantly worse overall survival than patients with RDW  $\leq 15\%$  (3-year survival rate 59.5 vs. 88.7% log-rank  $p = 0.015$ ). Cox regression analysis identified RDW  $> 15\%$  as a prognostic factor for adverse outcome (HR 1.786, 95% CI 1.137–2.803,  $p = 0.012$ ). RDW can serve as a potential negative prognostic factor of pSS-PAH.

**Keywords** Primary Sjogren's syndrome · Prognosis · Pulmonary arterial hypertension · Red blood cell distribution width

## Introduction

Pulmonary artery hypertension (PAH) is a severe complication of primary Sjogren's syndrome (pSS) and one of the

leading causes of morbidity and mortality for these patients. Although pSS (15.3%) is less likely to be the underlying connective tissue disease of the PAH patients than systemic lupus erythematosus (SLE) (58.4%) and systemic sclerosis (SSc) (26.3%) [1], outcomes are generally poor for patients with pSS-PAH and are even worse than patients with idiopathic PAH (iPAH) [2]. Treatment of PAH associated with pSS (pSS-PAH) is still challenging, though several PAH-specific therapies have been implemented since the last decades. Accurate risk stratification of patients with pSS-PAH is critically important to efficiently target the use of evidence-based therapies and identify high-risk patients who may benefit from advanced treatments. Thus, new prognostic markers may aid to identify at-risk patients early and may provide insight into therapeutic avenues for patients with pSS-PAH. A variety of such markers have been used to create predictive models for survival in patients with chronic heart failure, as well as idiopathic pulmonary arterial hypertension (IPAH), the experience of which could be gained to enlighten prognosis prediction in patients with pSS-PAH [3, 4].

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Red blood cell distribution width (RDW) is one of the parameters routinely reported in the complete blood cell count test, pointing to the degree of an isocytosis in the complete blood count. It has been used in routine practice for several decades to make a differential diagnosis for various cases of anemia, such as an iron deficiency anemia [5, 6]. RDW level is elevated in several aberrations (e.g., iron deficiency, inflammation, and uremia), as both destruction and decreased production of red blood cells can increase its value. An independent association between increased RDW and the risk for adverse outcomes has been revealed in patients with acute and chronic heart failure, as well as iPAH, where it outperformed plenty of widely used markers, including NT-proBNP and 6-min walking distance (6MWD) [4, 7–9]. Furthermore, a lot more recent studies demonstrated that higher RDW levels may also correlate with long-term survival of other cardiopulmonary diseases, such as chronic obstructive pulmonary disease (COPD), pulmonary embolism (PE), and acute coronary syndrome (ACS) [10–12]. RDW has been identified as a simple and readily available marker of the development of PAH in patients with SSc [13]. However, no study till now has examined the association of RDW with the overall survival of PAH in pSS patients. Since identification of more readily prognostic markers may improve clinical decision making, provide insights into the pathophysiology of disease, and also help improve patient management, confirming the validity of RDW level as a prognostic predictor seems to be necessary.

We hypothesized that elevated RDW levels may be associated with the outcome of pSS-PAH patients and may serve as a potential prognostic predictor. The aim of this single-center, retrospective cohort study was to investigate the overall survival and utility of RDW as a simple and readily available prognostic factor of pSS-PAH patients, and its potential function in clinical practice.

## Materials and methods

### Study population

Fifty-five patients with pSS-PAH who were followed up at the Rheumatology Department of Peking Union Medical College Hospital (PUMCH) from August 2007 to May 2017 were enrolled in this study. Written informed consent was obtained from each patient before enrollment. pSS was diagnosed according to the revised criteria proposed by the American-European Consensus Group in 2002 [14]. Identification of PAH was based on the 2015 European Society of Cardiology/European Respiratory Society guidelines as mean pulmonary arterial pressure (mPAP)  $\geq 25$  mmHg at rest, pulmonary artery wedge pressure (PAWP)  $\leq 15$  mmHg, and pulmonary vascular resistance (PVR)  $> 3$  Wood units in right heart catheterization (RHC) assessment [15]. The exclusion

criteria were: (1) patients with pulmonary venous hypertension, chronic thromboembolic disease, or significant interstitial lung disease (ILD); (2) patients with comorbidities that may influence RDW levels, such as renal insufficiency, severe anemia, existing left heart diseases, cerebrovascular diseases, malnutrition, or blood transfusion. Renal insufficiency is defined as serum creatinine greater than 1.5 mg/dL (132.6  $\mu\text{mol/L}$ ) in men and greater than 1.2 mg/dL (106.1  $\mu\text{mol/L}$ ) in women. Anemia is defined as hemoglobin lower than 120 g/L. This study was approved by the medical ethics committee of PUMCH and was conducted in compliance with the ethics committee requirements. The ethical approval number is S-191.

### Data collection

Demographic characteristics and clinical features, such as age, gender, disease duration, as well as the comorbidities which could affect prognosis (such as COPD, diabetes melitus, obesity, malignancy, and so on), were recorded at baseline from electronic medical record system. Results of laboratory tests, including complete blood count (covering RDW, mean cell volume, and hematocrit), inflammatory markers (including erythrocyte sedimentation rate (ESR) and high sensitivity C reactive protein (hsCRP)), creatinine (Cr), blood urea nitrogen (BUN), and N-terminal pro-brain natriuretic peptide (NT-pro BNP), were measured using an automatic hematology system on the day when the patient was diagnosed with PAH. RDW lower than 15% in our laboratory is defined as normal. The 6MWD and New York Heart Association (NYHA) functional classification was determined on the same day with blood sample collection by a team of experienced physicians. All the patients underwent RHC at baseline to firmly diagnose PAH, and various hemodynamic parameters, including mPAP, PAWP, cardiac indexes (CI), and PVR, were measured during assessment. Pulmonary function tests, including forced vital capacity (FVC), total lung capacity (TLC), and diffusing capacity for carbon monoxide (DLCO), were performed using standard methods. Conditions of treatments were also gathered on enrollment. Glucocorticoids and immune suppressants were routinely administered. Basic treatments for PAH (e.g., diuretics, digoxin, antiplatelet, and anticoagulant therapy) were given when it is necessary. PAH-targeted therapies, including endothelial blockers, phosphodiesterase inhibitors, and prostacyclin derivatives, were used in compliance with current guidelines and depending on their availability in China.

### Statistical analysis

All the patients were stratified according to the level of RDW ( $< 15.0\%$ , and  $> 15.0\%$ ). Continuous variables were expressed as mean  $\pm$  SD and compared using Student's *t* test

between groups. Categorical variables were presented as numbers and percentages (%), the clinically relevant differences of which were evaluated by Chi-square test or Fischer's exact test, as appropriate. Because of the ambiguously ascribed causes of death, the primary end-point of this study was all-cause death. Survival analysis was performed using Kaplan-Meier analysis, while comparison between groups using the log-rank test. Besides the analysis of all-cause mortality, 1-, 3-, and 5-year survival rates were also assessed. Correlations between RDW and some relevant variables in clinical practice were determined using Spearman's correlation coefficient. Univariate Cox proportional regression analyses were performed to identify whether the RDW level is a potential predictor of mortality. Statistical analyses were performed using SPSS statistics version 24.0 (IBM, Armonk, NY, USA). A  $p$  value  $< 0.05$  was considered statistically significant.

## Results

### Demographics and clinical characteristics

The baseline characteristics of 55 patients divided according to levels of RDW are presented in Table 1. For the overall study population, the mean age was  $38.9 \pm 9.3$  (24–62) years old with 98.2% female subjects. There were no significant differences in gender, age, disease duration, or comorbidities between the group with normal RDW levels and the other group with elevated RDW levels. RDW ranged from 12.3 to 23.9% (mean  $14.9 \pm 2.5\%$ SD), and 22 patients (40.0%) had an RDW above the upper limit of normal (15%). Patients with higher RDW did not differ significantly from other subjects in most red blood cell variables, including the frequency of anemia, levels of hemoglobin and hematocrit. Although it is not statistically significant ( $p = 0.053$ ), elevated RDW was associated with lower mean corpuscular volume (MCV). Neither impaired renal function parameters, including creatinine levels and blood urea nitrogen, nor NT-proBNP levels which usually increase in heart failure showed significant difference between groups with normal and elevated RDW levels. Meanwhile, no strong increases in ESR and hsCRP as RDW levels elevated were found as expected. RHC was undertaken in all the subjects. Overall, all the patients in this study cohort had hemodynamic changes (right atrial pressure  $6.81 \pm 5.02$  mmHg, mPAP  $49.9 \pm 9.5$  mmHg, cardiac index  $2.5 \pm 0.75$  L/min/  $m^2$ , and PVR  $8.2 \pm 3.0$  Wood units) and poor cardiac function status (52.7% in WHO class II and 47.3% in class III). However, no significant differences are found between the two groups. As for the respiratory markers, TLC was significantly lower in patients with elevated RDW ( $p = 0.017$ ). The patients in the elevated RDW levels had markedly lower DLCO% compared to patients in the normal range ( $p = 0.034$ ). The 6MWD showed no significant

difference. At the therapeutic level, although the patients had received different therapies at baseline, there was no significant difference in the medication usage between the group with normal RDW level and the one with elevated RDW level. Patients who deceased in the follow-up tended to have higher baseline RDW values ( $13.8 \pm 2.6$  vs  $16.5 \pm 1.6\%$ ,  $p = 0.003$ ; shown in Fig. 1a). Mean RDW levels were significantly higher among patients in WHO class III than those in class II ( $13.8 \pm 1.8$  vs  $16.5 \pm 2.9\%$ ,  $p < 0.001$ , shown in Fig. 1b).

### Red blood cell distribution width and survival

During a mean follow-up period of  $40.2 \pm 31.5$  (2.8–146) months, 7 (12.7%) patients died. Four patients were lost to follow-up. For the entire study population, overall 1-, 3-, and 5-year survival rates from the time of diagnosis were 98.1, 82.2, and 75.3%, respectively. Patients with RDW  $> 15\%$  had a significantly worse 3-year overall survival than patients with RDW  $\leq 15\%$  ( $59.5$  vs.  $88.7\%$ , log rank test,  $p = 0.015$ ). Patients with elevated RDW had shorter expected overall survival than patients with normal RDW ( $132.7$  vs  $52.7$  months, log-rank test,  $p = 0.015$ ). The Kaplan-Meier overall survival curves showed a significant separation in the two subgroups (Fig. 2).

### Identification of RDW as a prognostic factor

The results of univariate Cox proportional regression analysis verified that elevated baseline RDW level (HR 1.79, 95% CI 1.14–2.80,  $p = 0.012$ ) was a potential risk factor for poor overall survival and clinical outcomes (Table 2). A graphic representation of the Spearman's correlation coefficient between RDW and NT-proBNP, as well as that between RDW and 6MWD is presented in Fig. 3. Spearman's correlation coefficient for the suspected correlations was 0.271 ( $p = 0.087$ ) for the correlation between RDW and NT-proBNP (Fig. 3a) and 0.107 ( $p = 0.560$ ) for the correlation between RDW and 6-min walking distance (Fig. 3b). NT-proBNP, which has been established as reliable diagnostic and prognostic markers in heart failure and a serum indicator for the degree of ventricular dysfunction, tended to have no statistically significant correlation with RDW. In addition, the irregular distribution of 6MWD across RDW levels could also exclude the impact of impaired exercise capacity on RDW. We also calculated Spearman correlation coefficients between RDW and other potential related variables, including hemoglobin (0.118,  $p = 0.400$ ), mean corpuscular volume ( $-0.395$ ,  $p = 0.056$ ), mean pulmonary artery pressure (0.024,  $p = 0.864$ ), cardiac index ( $-0.141$ ,  $p = 0.320$ ), and pulmonary vascular resistance (0.139,  $p = 0.317$ ), which collectively exhibit no significant correlations. According to previous analysis, RDW at diagnosis in patients with pSS-PAH was concluded to be a potential predictor for overall survival and clinical outcomes.

**Table 1** Baseline clinical characteristics of 55 patients with pSS-PAH

	All (n = 55)	RDW ≤ 15% (n = 33)	RDW > 15% (n = 22)	p value
RDW, %	14.85(2.46)	13.52(0.87)	16.85(2.73)	0.000
Age, years	38.87(9.32)	37.58(9.96)	40.82(8.09)	0.209
Female, %	54 (98.2%)	32 (97%)	22 (100%)	0.419
Disease duration, m	25.51(33.15)	27.55(37.05)	22.45(26.80)	0.582
Comorbidities	14 (25.5%)	8 (24.2%)	6 (27.3%)	0.800
Laboratory tests				
Hemoglobin, g/L	133.49(18.91)	134.84(19.02)	131.43(19.02)	0.525
MCV, fL	92.50(6.63)	95.08(4.39)	89.91(7.61)	0.053
Hematocrit, %	40.40(5.65)	40.51(5.70)	40.24(5.69)	0.864
NT-pro BNP, pg/mL	1394.57(1248.40)	1276.61(1209.78)	1531.15(1311.17)	0.522
hsCRP, mg/L	4.62(6.10)	4.17(6.60)	5.18(5.54)	0.588
ESR, mm/h	24.51(21.25)	26.33(20.38)	21.78(22.80)	0.487
Creatinine, μmol/L	70.45(21.62)	70.33(13.98)	70.63(30.06)	0.960
BUN, mmol/L	5.19(1.97)	5.05(1.34)	5.40(2.68)	0.521
6MWD, m	417.41(108.96)	424.56(87.78)	408.21(134.44)	0.681
WHO classification				
II	29 (52.7%)	20 (60.6%)	9 (40.9%)	0.157
III	26 (47.3%)	13 (39.4%)	13 (59.1%)	
Hemodynamics				
mPAP, mmHg	49.85(9.48)	50.50(9.25)	48.91(9.94)	0.549
PCWP, mmHg	8.19(2.97)	8.42(3.2)	7.86(2.61)	0.508
mRAP, mmHg	6.81(5.02)	6.77(4.39)	6.88(6.07)	0.948
CI, L/min/m <sup>2</sup>	2.52(0.75)	2.52(0.67)	2.52(0.87)	0.995
PVR, Woods unit	11.52(5.10)	10.99(3.27)	12.29(6.98)	0.363
Pulmonary function				
FVC, %Pred	85.80(9.67)	88.07(9.65)	83.81(9.52)	0.219
DLCO, %Pred	60.04(12.69)	65.56(14.53)	55.81(9.47)	0.034
TLC, %Pred	90.75(8.69)	94.74(7.35)	87.45(8.49)	0.017
FVC%/DLCO %	1.48(0.27)	1.41(0.29)	1.53(0.25)	0.252
Medications				
Glucocorticoid	50 (90.9%)	31 (93.9%)	19 (86.4%)	0.338
Immunosuppressive agents	48 (87.3%)	29 (87.9%)	19 (86.4%)	0.869
Diuretics	43 (78.2%)	24 (72.7%)	19 (86.4%)	0.238
Digoxin	29 (52.7%)	18 (54.5%)	11 (50.0%)	0.746
Endothelin blockers	18 (36.7%)	8 (27.6%)	10 (50.0%)	0.114
Phosphodiesterase inhibitors	36 (73.5%)	20 (69.0%)	16 (80.0%)	0.400
Prostacyclin	0	0	0	–

Data are expressed as mean (SD) or as number (percentage)

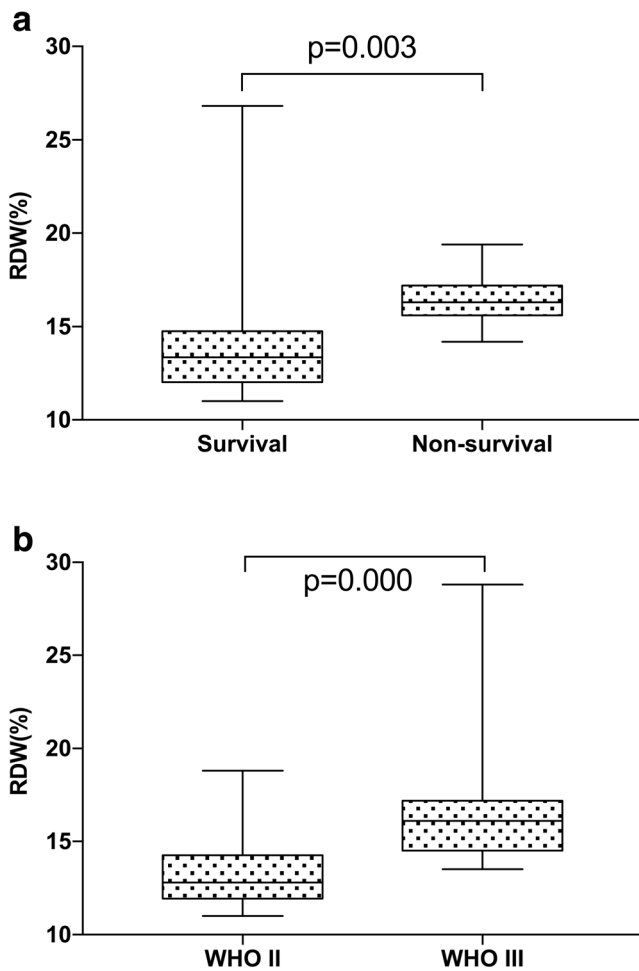
RDW red blood cell distribution width, MCV erythrocyte mean corpuscular volume, NT-pro BNP N-terminal pro-brain natriuretic peptide, hsCRP hypersensitive C-reactive protein, ESR erythrocyte sedimentation rate, BUN blood urea nitrogen, 6MWD 6-min walk distance, WHO classification World Health Organization heart function classification, mPAP mean pulmonary arterial pressure, PCWP pulmonary capillary wedge pressure, mRAP mean right atrial pressure, CI cardiac index, PVR pulmonary vascular resistance, FVC forced vital capacity, DLCO carbon monoxide diffusing capacity, TLC total lung capacity

Disease duration, the time interval between onset of pSS and confirmation of PAH by right heart catheterization (RHC)

## Discussion

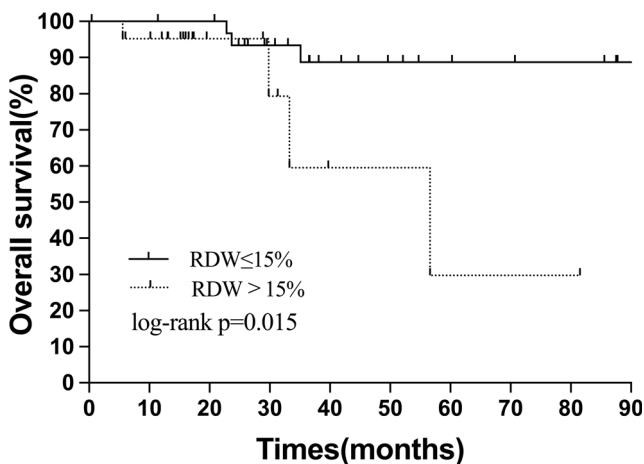
In this retrospective cohort study of 55 patients, we investigated the clinical outcomes and overall survival rates in a

cohort of Chinese patients with pSS-PAH. Moreover, we confirmed, for the first time, that RDW can serve as a negative prognostic factor of pSS-PAH, in addition to some established predictors such as NT-pro BNP, 6MWD, cardiac function



**Fig. 1** **a** Comparison of baseline RDW values: survival versus non-survival. **b** Comparison of baseline RDW values: WHO II versus WHO III

class, etc. In light of the capability to provide robust mortality prediction, the simple and readily available marker could be widely applied in clinical practice and inspire progression on patient management.



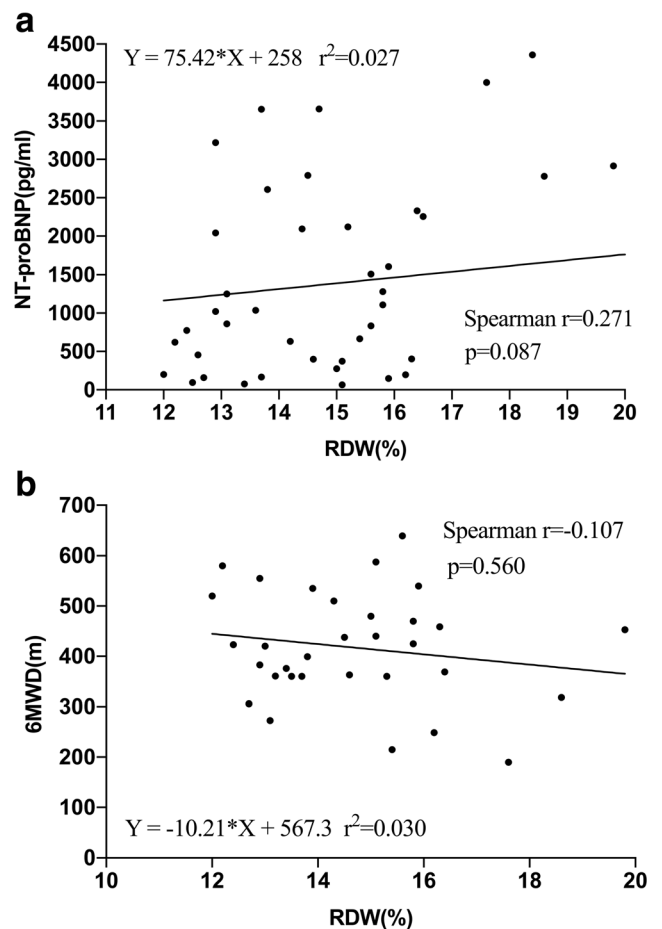
**Fig. 2** Kaplan-Meier survival curves by RDW levels

**Table 2** Univariate proportional hazard analysis

Variable	Univariate analysis	
	HR (95% CI)	<i>p</i> value
Age, years	1.034(0.960–1.113)	0.382
Gender	0.046(0.000–1,079,879.60)	0.722
RDW, %	1.786(1.137–2.803)	0.012
NT-pro BNP, pg/mL	1.000(0.999–1.001)	0.486
6MWD, m	0.994(0.985–1.004)	0.243
mPAP, mmHg	1.033(0.956–1.116)	0.413
PCWP, mmHg	0.979(0.779–1.229)	0.853
mRAP, mmHg	1.049(0.888–1.238)	0.576
CI, L/min/m <sup>2</sup>	0.148(0.032–0.685)	0.014
PVR, Woods unit	1.121(1.039–1.210)	0.003

HR hazard ratio, CI confidence interval, RDW red blood cell distribution width, NT-pro BNP N-terminal pro-brain natriuretic peptide, 6MWD 6-min walk distance, mPAP mean pulmonary arterial pressure, PCWP pulmonary capillary pressure, mRAP mean right atrial pressure, CI cardiac index, PVR pulmonary vascular resistance

$p < 0.05$  = statistically significant



**Fig. 3** **a** Plot showing correlation between NT-proBNP and RDW. **b** Plot showing correlation between 6MWD and RDW



pSS is a chronic autoimmune disease, possibly involving different organs and systems along with exocrine glands. Lung involvement is one of the important extra-glandular presentations, in which pulmonary artery involvement is among the most prominent findings [16]. PAH associated with pSS may progress into a fatal outcome by resulting in congestive heart failure, pulmonary edema, arrhythmia, and/or even sudden death. The overall 1-, 3-, and 5-year survival rates calculated in this literature were 98.1, 82.2, and 75.3%, respectively. Several other prior studies have examined survival rates in patients with iPAH. One multicenter research conducted by National Institutes of Health (NIH) Registry from 1981 through 1985 show that the median survival was 2.8 years with 1-, 3-, and 5-year survival rates of 68, 48, and 34%, respectively [17]. More recently, French Registry has shed light on the prognosis of patients with iPAH, demonstrating that the survival of patients with PAH has improved compared with the predicted survival based on the NIH Registry, although it still remains suboptimal with 1-, 2-, and 3-year survival of 85.7, 69.5, and 54.9% for incident cases [18]. Despite the great enhancement of survival rates after decades of endeavor, the overall outcome of iPAH patients seems to be still worse than that of pSS-PAH patients, according to findings of this study. One possible explanation for this result is that patients with pSS-PAH tend to screen on cardiopulmonary function through pulmonary function test, ultrasonic cardiography, or RHC and confirm PAH diagnosis at an earlier stage, attributed to onset of symptoms from existing pSS. Besides, these differences in survival may also be due to the standard patient managements in PUMCH, as well as the application of some newly developed targeted medications.

Increased RDW is usually an indicator of ineffective red cell production or hemolysis but has recently been reported to be related to adverse outcomes in cardiovascular and non-cardiovascular disease states [19]. In a prospective cohort without specific classification of pulmonary hypertension, RDW was found to be independently correlated to death and superior to NT-proBNP as a prognostic indicator [20]. Several prior literatures have proved the prognostic significance of NT-proBNP and 6MWD in iPAH [21, 22]. Almost at the same time, Christopher J Rhodes et al. [4] reported that circulating RDW is related to disease severity and may be used to predict survival in patients with iPAH. Moreover, RDW was identified to add significant prognostic value to measurements of NT-proBNP and exercise capacity and may prove value in a multiple biomarker approach to disease stratification in patients with iPAH in the same study. In an ambulatory cohort of patients with chronic heart failure, baseline and serial increase in RDW was associated with poor long-term outcomes independent of standard cardiac, hematologic, and renal indices [23], although RDW are used to be regarded as a combined presentation of chronic inflammation, dysfunctional erythropoiesis, kidney dysfunction, oxidative stress, and nutritional state [24]. In survival analysis of this study, elevated RDW levels showed a significantly negative relation with clinical outcomes and

long-term survival rates. The survival curves intersect twice within approximately 2 years and then diverge, the cause of which is unknown. This phenomenon may reflect the ability of RDW to provide insight into risk for more chronic causes of death that are the culmination of multiple pathophysiologic processes. Besides, those patients who deceased during follow-up have an obviously higher average level of RDW than those who stayed alive, which is conformed to the survival analysis. A hazard rate more than 1.0 shed lights on a negative predictive value of pSS-PAH prognosis. The prognostic value of RDW was independent of 6MWD or NT-pro BNP, based on the insignificant Spearman's correlation analysis results. Even so, general correlative trends between the 6MWD or NT-pro BNP and RDW levels in pSS-PAH were still shown in this analysis, but without significance. The possible causes of the insignificance could be as follows: (1) the sample size is not large enough; (2) plenty of interfering factors for RDW leads to its variability; (3) continuous elevation in repetitive measurements may be more indicative than single elevation. Although anemia is also a strong prognostic marker in heart failure syndromes, the association between RDW and adverse outcomes of pSS-PAH in our study was independent of baseline hemoglobin and mean corpuscular volume, according to the insignificant difference between the two groups as well as the insignificant Spearman's correlation analysis results. These findings lead to the identification of RDW as a potential negative predictor of survival in patients with PAH associated with pSS. As part of the complete blood count, RDW is widely available to clinicians and brought no additional costs, thus may be widely applied in clinical practice to provide guidance for patient management.

The mechanisms underlying the association between RDW and adverse outcomes in pSS-PAH patients are not fully understood. However, we still identified some interesting clues which could possibly bring them to light. TLC (total lung capacity) and DLCO (carbon monoxide diffusing capacity), as meaningful parameters reflecting pulmonary function, differed significantly between the two groups with normal and elevated RDW, marking a possible pathologic process of fibrosis in pulmonary interstitial which are usually irreversible and predicts adverse outcome. Besides, in accordance with previous article [25], we observed higher RDW levels in patients with higher NYHA class, showing that decrease in cardiac function may be an underlying contributor to mortality as well. It could be confirmed by a previous Chinese cohort study, revealing that worse cardiac function is a predictor of mortality in patients with pSS-PAH [26]. Impaired exercise capacity or exercise tolerance, a reflection of decrease in cardiac function, was reported to be linked with elevated RDW levels in chronic heart failure patients [27], based on which a speculation that exercise inactivity may have joined the mechanisms causing mortality could be made, even if 6MWD was not significantly different between groups in this study. 6MWD used to be regarded as a simple,

safe, noninvasive, reproducible parameter of exercise capacity, but a recent editorial challenged its validity in management of SSc-PAH. Although 6MWD is clearly sensitive to the presence of cardiovascular and pulmonary complications of SSc, such as PAH, SSc patients are also limited by musculoskeletal dysfunction and pain, conclusion of which may improve the status of RDW as a stable index in pSS-PAH management [28]. Meanwhile, an EPIC—Norfolk study claimed that RDW levels were associated with physical inactivity, but this did not influence the RDW-associated risk of heart failure [29]. In addition, elevation of RDW levels was also found to be related with a chronic inflammatory state in patients with heart failure, or even in an unselected patient population, with increased circulating pro-inflammatory cytokines, such as tumor necrosis factor  $\alpha$ , interleukin (IL)-1, and IL-6 [30, 31], which may also be a potential factor affecting survival rates in pSS-PAH patients. Qunying Xi et al. [32] pointed out that RDW independently predicts responsiveness of acute pulmonary vasodilator testing in patients with iPAH. Patients with lower RDW levels are prone to have a positive response in acute pulmonary vasodilator testing indicating a greater possibility to benefit from long-term use of calcium channel blocker. Based on these facts, RDW level works to predict a better survival in iPAH patients by aiding selection of more appropriate medical therapy and more delightful responsiveness to medications, and similar principles may also exist in PAH caused by pSS. Furthermore, they also concluded that RDW is associated with disease severity of both iPAH, which may mediate the correlation between RDW levels and the all-cause mortality in patients with iPAH, while another research confirmed the same principle in chronic heart failure [33]. Therefore, it could be reasonably inferred that the reason why RDW levels can be a potential predictor of survival in pSS-PAH patients may be due to the role as a marker of disease severity, waiting for verification in larger populations. As is shown in results, there was no significant association between RDW levels and hemodynamic variables, suggesting that the relation between RDW and death is not simply due to hemodynamic abnormalities in patients with elevated RDW.

As far as we know, this is the first study reporting the correlation between the RDW levels and survival rates for pSS-PAH in a large cohort of patients confirmed by RHC. Primary SS is a common systemic autoimmune disease and pulmonary involvement in pSS consists mainly of small airway disease and ILD. PAH is a rare complication, with few case reports and case series describing the clinical characteristics and survival of patients with pSS-PAH. Since delayed diagnosis and non-standard treatment may account for the comparatively poor outcomes in pSS-PAH, our results highlight a simple and rapid way to assess pSS-PAH patients on their prognosis so they can benefit from advanced treatments. Thus, future studies are needed to predict the prognosis more accurately in patients with pSS-PAH.

There are several limitations of this study. Since PUMCH is a referral center which concentrate on difficult and complicated diseases, a probability of selection bias can hardly be avoided. A considerable number of patients in this study had never been screened for PAH before admission in PUMCH due to non-specific and insidious presentations, resulting in longer disease durations, increased severity of PAH, as well as more adverse outcomes. Moreover, the single-center study in which the cohort was recruited from only PUMCH led to the limited sample size. As a consequence, multi-variable Cox analysis cannot be made, since the number of death cases is no more than seven. It is obvious that large-scale, multi-center studies are still required. In conclusion, in this study, we investigate the role RDW plays in the prognosis of pSS-PAH. Our study is the first to describe the correlation between RDW levels and outcomes of patients with pSS-PAH and to identify RDW as a potential negative prognostic factor for pSS-PAH. Further studies are needed to confirm its validity in larger population and develop its function in patient management.

**Authors' contributions** Min Hui, Juliang Zhao, and Zhuang Tian were the authors who contributed to interpretation of data, completed drafting of the article, and revised it critically.

Jieying Wang was in charge of original data collection for forming the entire cohort.

Junyan Qian and Xiaoxi Yang contributed to the basic conception and the design of the retrospective cohort study.

Qian Wang, Mengtao Li, Yan Zhao, and Xiaofeng Zeng did a lot for reading and the approval of final version. Xiaofeng Zeng and Yan Zhao were both the correspondence authors of this manuscript.

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## Compliance with ethical standards

**This study was approved by the medical ethics committee of PUMCH and was conducted in compliance with the ethics committee requirements. The ethical approval number is S-191.**

**Disclosures** None.

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