Clinical Rheumatology (2019) 38:3619–3626
https://doi.org/10.1007/s10067-019-04690-3

ORIGINAL ARTICLE

Simplified risk stratification for pulmonary arterial hypertension associated with connective tissue disease

Xiaodi Li[1] · Xiaoxuan Sun[1] · Yingheng Huang[1] · Yuanyuan Wang[1] · Xiaoman Yang[1] · Jingya Wang[1] · Ning Zhang[1] · Lei Gu[1] · Miaojia Zhang[1] · Qiang Wang[1]

Received: 4 March 2019 / Revised: 4 July 2019 / Accepted: 10 July 2019 / Published online: 5 August 2019

Abstract

Objective To explore the long-term prognostic value of a simplified risk assessment strategy based on the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) pulmonary hypertension (PH) guidelines in Chinese patients with connective tissue disease (CTD) associated with pulmonary arterial hypertension (PAH).

Methods We identified 50 CTD-PAH patients diagnosed by right heart catheterization. A retrospective chart review was completed to assess their clinical presentation and laboratory test results. A simplified version of the risk stratification model proposed by the 2015 ESC/ERS PH guidelines was applied, which included the WHO functional class, the 6-minute walking distance test, N-terminal pro-B-type natriuretic peptide plasma levels, pericardial effusion, right atrial pressure (RAP), cardiac index (CI), and mixed venous oxygen saturation (SvO_2). The risk grades were defined as follows: low risk = at least 3 low-risk variables and no high-risk variables; high risk = at least 2 high-risk variables, including SvO_2 or CI; and intermediate risk = when the above definitions of low or high risk were not fulfilled. The study endpoint was 3-year all-cause mortality.

Results Twenty patients were defined as a low-risk group, while 30 were classified into a combined intermediate-high-risk group at the baseline assessment. All 20 patients in the low-risk group remained in the low-risk group at follow-up, 20 patients in the intermediate-high-risk group were downgraded to the low-risk group, and eight patients remained in the intermediate-high-risk group at the follow-up assessment. Patients in the intermediate-high-risk group exhibited higher 3-year mortality than the low-risk group at baseline (26% vs 14%, $P = 0.0384$). Compared with patients who remained in the intermediate-high-risk group, patients who were downgraded to the low-risk group showed lower 3-year mortality ($P = 0.0281$).

Conclusion A simplified risk stratification model based on the 2015 ESC/ERS PH guidelines helped to identify CTD-PAH patients with poor long-term prognosis , which was useful in evaluating the severity and treatment response of patients with CTD-PAH.

Key Point

•*This study showed that the simplified version of the 2015 ESC/ERS risk stratification model could help identify Chinese CTD-PAH patients with poor prognosis at diagnosis and after treatment initiation.*

Keywords Connective tissue disease · Prognosis · Pulmonary arterial hypertension · Risk stratification

Abbreviations

PAH	Pulmonary arterial hypertension
CTD	Connective tissue disease
IPAH	Idiopathic pulmonary arterial hypertension
ESC	European Society of Cardiology
ERS	European Respiratory Society
PH	Pulmonary hypertension
FC	Functional class
6MWD	6-minute walking distance
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PVR	Pulmonary vascular resistance
RHC	Right heart catheterization
mPAP	Mean pulmonary arterial pressure
PAWP	Pulmonary arterial wedge pressure
ILD	Interstitial lung disease
HRCT	High-resolution computer tomography

✉ Miaojia Zhang
miaojia_zhang@163.com

✉ Qiang Wang
jerrytortoise@163.com

[1] Department of Rheumatology, The first affiliated hospital of Nanjing Medical University, Nanjing, China

SLE	Systematic lupus erythematosus
ACR	American Rheumatism Association
pSS	Primary Sjogren's syndrome
SSc	Systemic sclerosis
MCTD	Mixed connective tissue disease
UCTD	Undifferentiated connective tissue disease
SvO_2	Mixed venous oxygen saturation
CI	Cardiac index
RAP	Right atrial pressure

Introduction

Pulmonary arterial hypertension (PAH) is a destructive complication of connective tissue disease (CTD). Lack of effective treatment was the primary cause of poor outcomes in CTD-PAH patients before the availability of PAH-specific drugs [1]. Although the overall survival rate of group I PAH patients has improved with the development of PAH-targeted drugs over the past decades, patients with CTD-PAH have worse long-term outcomes than patients with idiopathic pulmonary arterial hypertension (IPAH) [2–4]. This suggests that a more effective strategy for management of CTD-PAH patients is needed. The 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines for the diagnosis and treatment of pulmonary hypertension (PH) recommended a risk stratification assessment instrument to evaluate the clinical severity and response to treatment in group I PAH patients. The guidelines divide patients into three grades: low, intermediate, and high risk [5]. The estimated 1-year mortality rate has been reported to be less than 5% in low-risk patients who were stable after reaching PAH-specific treatment goals [5]. Therefore, risk class assignments may be helpful in determining post-treatment prognoses in these patients.

Many variables are included in the risk stratification instrument, including clinical signs of right heart failure, the progression of symptoms, syncope, the WHO functional class (FC), the 6-minute walking distance (6MWD), cardiopulmonary exercise examination, N-terminal pro-B-type natriuretic peptide (NT-proBNP) plasma levels, imaging, and hemodynamics, which are inconvenient for practical application. Importantly, cardiopulmonary exercise testing is not available in some PH centers, especially in less-developed areas. A relatively simplified risk stratification instrument may be more conducive to the management of PAH patients. Kylhammar et al. and Hoeper et al. validated the effectiveness of the 2015 ESC/ERS risk stratification instrument for discriminating the outcomes of group I Caucasian PAH patients [6, 7]. Unfortunately, most studies conducted in China have only focused on individual variables, such as the 6MWD and pulmonary vascular resistance (PVR), which could not sufficiently predict the prognosis of Chinese CTD-PAH patients [8, 9].

In order to evaluate the prognostic value of the simplified risk stratification instrument based on the 2015 ESC/ERS PH guidelines in Chinese CTD-PAH patients at baseline and long-term follow-up, we analyzed all consecutive right heart catheterization (RHC)-diagnosed CTD-PAH patients in the First Affiliated Hospital of Nanjing Medical University.

Methods

Design

This was a retrospective study of patients with RHC-diagnosed CTD-PAH who were evaluated and treated at the Department of Rheumatology in the First Affiliated Hospital of Nanjing Medical University from 2009 to 2018. This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (number 2018-SR-333).

Patients

We identified and reviewed the medical records of hospitalized patients with CTD and RHC-confirmed PAH. All patients were evaluated as part of routine clinical care at the outpatient clinic at the Department of Rheumatology in the First Affiliated Hospital of Nanjing Medical University. PAH was defined as follows: mean pulmonary arterial pressure (mPAP) $\geq$ 25 mmHg at rest, pulmonary arterial wedge pressure (PAWP) $\leq$ 15 mmHg, and PVR $\geq$ 3 Wood units [5]. Patients with significant interstitial lung disease (ILD) or chronic obstructive pulmonary disease detected by chest high-resolution computed tomography (HRCT) and evidence of pulmonary venous hypertension (PAWP > 15 mmHg) were excluded. Patients with a history of IPAH, chronic thromboembolic pulmonary disease, drug or toxin exposure, HIV infection, portal hypertension, or any other diseases known to be associated with PH were also excluded.

The CTDs included systemic lupus erythematosus (SLE) diagnosed according to the 1997 American College of Rheumatology (ACR) criteria [10], primary Sjogren's syndrome (pSS) defined according to the 2002 international classification criteria [11], systematic sclerosis (SSc) defined according to the 1980 ACR criteria [12], and mixed CTD (MCTD) defined by the Sharp criteria [13]. Patients who had clinical and serological manifestations suggestive of systemic autoimmune diseases but did not fulfill the classification criteria for CTD were defined as having undifferentiated CTD (UCTD). Patients with systemic vasculitis were excluded from the study.

Data collection and outcome assessment

A standard case report form was established to retrospectively collect demographic data, the onset of symptoms, the WHO FC, the 6MWD test results, blood biochemistry results, echocardiography parameters, RHC parameters, and HRCT parameters. The initial modalities used to treat the patients, such as glucocorticoids, immunosuppressants, supportive therapy, and PAH-targeted drugs, were also recorded.

The main endpoint was 3-year all-cause mortality. The survival period was calculated either as the number of months from the initial diagnosis to May 2018, which was the end of the follow-up period in this study, or the time of the patient's death.

Simplified risk stratification assessment

A simplified risk assessment instrument was derived from the 2015 ESC/ERS PH guidelines risk assessment model, which included the WHO FC, the 6MWD, NT-proBNP plasma levels, pericardial effusion, right atrial pressure (RAP), cardiac index (CI), and mixed venous oxygen saturation (SvO_2) (Table 1). The risk grades were defined as low risk = at least 3 low-risk variables and no high-risk variables; high-risk = at least 2 high-risk variables, including SvO_2 or CI and; intermediate risk = when the above definitions of low or high risk were not fulfilled. The cut-off value of each variable is shown in Table 1.

Statistical analyses

Continuous variables are presented as means ± standard errors and the categorical variables are presented as numbers and percentages. The baseline characteristics were compared between the different groups. The Student *t* test or Wilcoxon rank-sum tests were used to compare continuous variables, while chi-squared tests or Fisher's exact test was used to compare categorical variables. Survival rates were evaluated using Kaplan-Meier analysis and two-group comparisons were performed by the log-rank test. Patients who had at least one additional visit after diagnosis were included in the statistical analyses. A two-tailed *P* value less than 0.05 was considered statistically significant. All data were analyzed by GraphPad Prism 5 Statistics software.

Results

Study population and baseline characteristics

Fifty-six patients underwent RHC assessment between April 2009 and May 2018. Six patients were excluded. Four patients had mPAP ≤ 25 mmHg, one patient had severe ILD, one patient had chronic thromboembolic pulmonary disease, and one patient had amyloidosis. Finally, 50 CTD-PAH patients were included in the study.

The mean age was 39.12 ± 1.90 years and 47 (94%) were female (Table 2). Twelve (24%) of the 50 patients had PAH-related symptoms and nine (18%) patients had CTD and PAH simultaneously. The most common CTD-PAH subtype was SLE-PAH, which accounted for 44% of the CTD-PAH patients, followed by pSS-PAH (28%). At baseline, the mean 6MWD was 368.8 ± 31.91 m, and 32 (64%) patients were WHO functional class III–IV. Forty-six (92%) patients were treated with PAH-targeted drugs for a mean treatment duration of 17.57 ± 2.98 months. Forty-six (92%) patients were treated with glucocorticoids and 38 (76%) patients received immunosuppressants. Cyclophosphamide (74%) was the most commonly used immunosuppressant.

Risk stratification at baseline

According to the simplified risk stratification model, 30 patients were in the intermediate-high-risk group (21 in the intermediate-risk group and nine in the high-risk group), while 20 patients were in the low-risk group.

Patients in the low-risk group had lower mPAP (P = 0.0022) and higher PVR (P = 0.0013). The other parameters, such as sex ratio, CTD type, and disease duration and treatment, were similar in the two groups at baseline. The detailed information is shown in Table 2.

Table 1 Included variables and cut-off values used for simplified risk assessment model

Variables	Low risk	Intermediate risk	High risk
WHO FC	I-II	III	IV
6MWD	> 440 m	165–440 m	< 165 m
NT-proBNP plasma levels	< 300 ng/L	300–1400 ng/L	> 1400 ng/L
Imaging (echocardiography)	No pericardial effusion	Minimal pericardial effusion	Moderate-severe pericardial effusion
Hemodynamics	RAP < 8 mmHg CI ≥ 2.5 L/min/m^2 SvO_2 > 65%	RAP 8–14 mmHg CI 2.0–2.4 L/min/m^2 SvO_2 60–65%	RAP > 14 mmHg CI < 2.0 L/min/m^2 SvO_2 < 60%

Table 2 Characteristics of patients included in different risk group at baseline assessment.

Characteristic	All patients	Low risk	Intermediate-high risk	*P* value
Patients, *n*	50	20	30	–
Female, *n* (%)	47 (94%)	19 (95%)	28 (93%)	1.0000
Age (years)	39.12 ± 1.90	38.30 ± 2.88	39.67 ± 2.56	0.7289
Duration from diagnosis of CTD to diagnosis of PAH (months)	54.78 ± 10.50	74.25 ± 23.02	42.17 ± 8.12	0.6405
Duration from symptom onset to diagnosis of PAH (months)	16.22 ± 3.82	18.91 ± 8.03	14.43 ± 3.55	0.4539
Onset with PAH, *n* (%)	12 (24%)	4 (20%)	8 (27%)	0.7400
Underlying CTD				
SLE, *n* (%)	22 (44%)	7 (35%)	15 (50%)	0.3869
Non-SLE, *n* (%)	28 (56%)	13 (65%)	15 (50%)	0.3869
Echocardiography				
Pericardial effusion, *n* (%)	15 (30%)	2 (10%)	14 (47%)	0.0119
RHC parameters				
RAP (mmHg)	7.04 ± 0.77	4.56 ± 0.65	8.71 ± 1.12	0.0069
mPAP (mmHg)	45.60 ± 1.57	39.90 ± 1.13	49.37 ± 2.12	0.0022
PAWP (mmHg)	8.74 ± 0.54	9.26 ± 0.84	8.37 ± 0.70	0.4391
PVR (Wood units)	10.63 ± 1.37	5.68 ± 0.63	14.17 ± 1.98	0.0013
CI (L/min/m^2)	2.74 ± 0.19	3.60 ± 0.31	2.18 ± 0.16	< 0.0001
SvO_2 (%)	61.47 ± 1.70	68.85 ± 1.45	56.42 ± 1.98	0.0002
6MWD (m)	369.8 ± 31.91	441.00 ± 21.05	336.10 ± 24.44	0.0128
WHO functional class				
I–II, *n* (%)	18 (36%)	16 (80%)	2 (7%)	< 0.0001
III–IV, *n* (%)	32 (64%)	4 (20%)	28 (93%)	–
NT-proBNP (ng/L)	1790.00 ± 393.10	657.90 ± 236.00	2720.00 ± 848.50	0.0013
Uric acid (μmol/L)	364.8 ± 17.04	344.60 ± 26.00	378.60 ± 22.49	0.4000
HRCT				
Mild ILD, *n* (%)	25 (50%)	9 (45%)	18 (60%)	0.3883
CTD treatment				
Glucocorticoid, *n* (%)	46 (92%)	17 (85%)	29 (97%)	0.2885
Immunosuppressant, *n* (%)	38 (76%)	15 (75%)	23 (77%)	1.000
PAH-targeted therapy				
None, *n* (%)	4 (8%)	1 (5%)	3 (10%)	0.6411
PDE5I, *n* (%)	17 (34%)	10 (50%)	7 (23%)	–
ERA, *n* (%)	13 (26%)	5 (25%)	8 (27%)	–
ERA + PDE5I, *n* (%)	16 (32%)	5 (25%)	11 (37%)	–
Treatment duration (months)	17.57 ± 2.98	15.79 ± 5.17	18.41 ± 3.60	0.4376

Risk stratification at follow-up visit

Forty-eight patients had at least one additional assessment after diagnosis, at an average of 18.06 ± 2.96 months later. All 20 patients in the low-risk group were stable at follow-up, while 20 patients in the intermediate-high-risk group were downgraded to the low-risk group, and eight patients remained in the intermediate-high-risk group. More female patients were downgraded to the low-risk group than males ($P = 0.0741$). The CTD subtypes, disease duration, and treatments were similar between the two groups (Table 3).

Survival analysis

After a mean of 2.9 ± 0.3-year follow-up, a total of 10 patients died. Seven patients died of right heart failure, one patient died of gastrointestinal bleeding, and two patients died of serious infections. The overall survival rates at 1, 3 and 5 years were 98%, 78%, and 59%, respectively.

The survival rates were different between the low-risk group and the intermediate-high-risk groups at baseline assessment ($P = 0.0384$). The 1-, 3-, and 5-year survival rates were 96%, 74%, and 41% for the intermediate-high-risk group and 100%, 86%, and 86% for the low-risk

Table 3 Baseline characteristics of the patients with risk grade changes during follow-up

Characteristic	Downgraded into low risk	Remained in the intermediate-high risk	*P* value
Patients, *n*	20	8	–
Female, *n* (%)	20 (100%)	6 (75%)	0.0741
Age (years)	38.60 ± 2.93	42.25 ± 6.48	0.5579
Duration from diagnosis of CTD to diagnosis of PAH (months)	36.15 ± 9.58	60.25 ± 18.06	0.3448
Duration from symptom onset to diagnosis of PAH (months)	9.70 ± 2.54	23.88 ± 11.06	0.3549
Underlying CTD			
SLE, *n* (%)	11 (55%)	3 (38%)	0.6776
Non-SLE, *n* (%)	9 (45%)	5 (62%)	–
WHO functional class			
I–II, *n* (%)	0	1 (12%)	0.6776
III–IV, *n* (%)	20 (100%)	7 (88%)	–
NT-proBNP (ng/L)	2648.00 ± 12.40	3177.00 ± 1311.00	0.3917
Echocardiography			
Pericardial effusion, *n* (%)	9 (45%)	4 (50%)	1.0000
RHC parameters			
RAP (mmHg)	7.56 ± 1.50	9.75 ± 1.57	0.2306
mPAP (mmHg)	48.40 ± 2.72	49.88 ± 4.03	0.9190
PAWP (mmHg)	8.65 ± 0.84	6.88 ± 1.26	0.2412
PVR (Wood units)	12.67 ± 2.51	12.84 ± 1.77	0.2412
CI (L/min/m^2)	2.27 ± 0.22	1.87 ± 0.14	0.5986
SvO_2 (%)	59.00 ± 2.33	52.20 ± 2.87	0.1384
PAH-targeted therapy, *n* (%)	18 (90%)	7 (88%)	1.0000
Treatment duration (months)	18.78 ± 4.76	22.50 ± 7.57	0.4871

group, respectively (Fig. 1a). The estimated 1-, 3-, and 5-year survival rates for patients downgraded to the low-risk group were 100%, 87%, and 65%, while they were 86%, 26%, and 26%, respectively, for the patients who remained in the intermediate-high-risk group (Fig. 1b)

The predictive value of the variables included in the simplified risk stratification instrument at baseline is shown in Fig. 2. WHO FC III–IV and NT-proBNP > 300 ng/L at baseline may have contributed to the poorer prognoses in the intermediate-high-risk group.

Discussion

In this single-center retrospective study, we found that the simplified risk stratification model derived from the 2015 ESC/ERS PH guidelines could help predict the long-term outcomes of Chinese CTD-PAH patients. CTD-PAH patients in the low-risk group at the time of first diagnosis had lower 3-year mortality, while the all-cause mortality significantly declined in treated patients who were downgraded from the intermediate-high-risk to low-risk group at an average of 18 months of follow-up.

The risk stratification strategy recommended by the 2015 ESC/ERS PH guidelines included clinical status evaluation, exercise capacity, and right heart function evaluation [5]. Kylhammar et al. and Hoeper et al. used a simplified risk assessment model to validate the effectiveness of the 2015 ESC/ERS risk stratification strategy in group I PAH patients [6, 7]. The simplified risk assessment tool, which includes the WHO FC, the 6MWD, NT-proBNP, the CI, PAP, SvO_2, and/or pericardial effusion, has been proven to identify the group I PAH patients with poorer prognoses [6, 7]. In those studies, parameters such as the WHO FC, the 6MWD, NT-proBNP plasma levels, and pericardial effusion were the main parameters used in the follow-up assessments because they are non-invasive and practical, making them especially suitable for use in developing countries. We selected a few variables from the simplified version of risk assessment model, including the WHO FC, the 6MWD, NT-proBNP plasma levels, the CI, RAP, SvO_2, and pericardial effusion and used them to assess patients with CTD-PAH. The simplified risk assessment model mainly focuses on the evaluation of right heart function and exercise capacity in order to identify right heart dysfunction in a timely fashion. Apart from the hemodynamic parameters, the rest of the measurement methods were readily available,

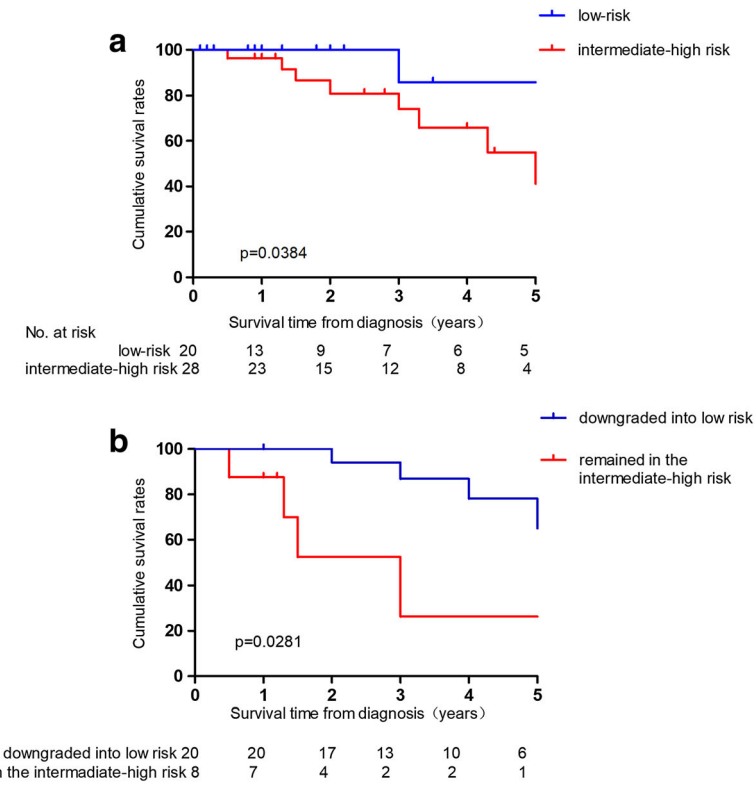

Fig. 1 Kaplan-Meier analysis of survival in different risk group patients at baseline and follow-up visit. **a** Three-year survival rate of CTD-PAH patients based on baseline risk stratification. The estimated survival was differed between low-risk group and intermediate-high-risk group ($P = 0.0384$). **b** Three-year survival rate of CTD-PAH patients based on follow-up risk assessment. Patients who remained in the intermediate-high-risk group after treatment initiation have a higher 3-year mortality ($P = 0.0281$)

making them relatively convenient to evaluate at each visit after treatment initiation.

In our study, the 3-year all-cause mortality was significantly higher in patients placed in the intermediate-high-risk group at baseline than those in the low-risk group, suggesting that when PAH is more severe, a stronger PAH-associated treatment might delay the progression of the disease. The CTD-PAH patients who were stable in the low-risk group or who were downgraded into the low-risk group after treatment were defined as having reached their PAH treatment goals. Forty (89%) patients reached the PAH treatment goal in our study. Compared with patients that remained in the intermediate-high-risk group, patients who were downgraded to the low-risk group after treatment showed a lower 3-year all-cause mortality. These results may indicate that the simplified risk stratification model was a useful tool to evaluate the severity and treatment response of Chinese CTD-PAH patients. However, there was just one follow-up visit after diagnosis with a mean follow-up time of 18 months. These parameters were insufficient (too few and too far apart) to validate the results as a useful measure of prognosis. A well-designed prospective study is needed in the future.

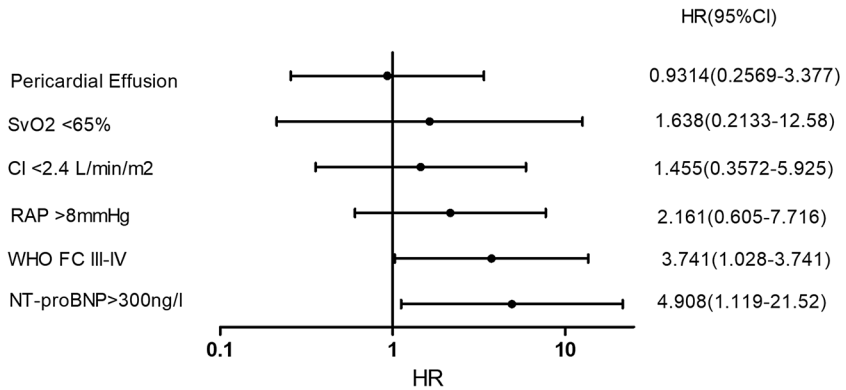

Fig. 2 Forest plot showing the prognostic values of variables included in simplified risk stratification model. Patients with WHO functional class III–IV and NT-proBNP ≥ 300 ng/L may contribute to the poorer prognosis in intermediate-high-risk group at baseline assessment. Values for the parameters were obtained at baseline. The reference value is from the respective low-risk group

For the simplified risk stratification model, the variables strongly associated with all-cause mortality were the WHO FC III–IV and the NT-proBNP ≥ 300 ng/L. These findings are not completely consistent with the study by Hoeper et al. (WHO FC III-IV, NT-proBNP ≥ 300 ng/L, 6MWD ≤ 440 m, $SvO_2 \leq 65\%$) [7]. The potential reasons for the differences may be that 64% of the patients were WHO FC III–IV at the time of diagnosis in our study, the 6MWD was not performed in all patients for safety reasons, our study was limited by its retrospective nature, and the SvO_2 levels were not available in some patients' medical records. In addition, the small sample size may also have imparted bias to the evaluation.

Nonetheless, several findings of this study are noteworthy. First, SLE-PAH accounted for the highest proportion (44%) of CTD-PAH patients, followed by pSS-PAH (28%). Second, the use of target drugs has demonstrated favorable clinical outcomes in patients with CTD-PAH, and the overall long-term survival rate was improved in Chinese CTD-PAH patients. However, a proportion of patients still failed to respond to the current target drugs. The initial treatment time and duration of target drug treatment are still critical challenges in developing countries.

Our study had some limitations. First, we divided all patients into low-risk and intermediate-high-risk groups because of the small sample size. We failed to evaluate the prognoses in the intermediate- and high-risk groups separately. Second, these data were based on a Chinese Han population, and there are 56 ethnic groups in China, so a nationwide multi-center prospective study is needed before the results of this study can be broadly applied. Third, the simplified risk assessment did not include all 13 variables recommended in the 2015 ESC/ERS risk assessment instrument but the remaining variables, like the cardiopulmonary examination test, may also provide important prognostic information [14]. Moreover, the 6MWD and SvO_2 were not evaluated in some patients at baseline, and the missing data may have affected the accuracy of the results. Last, hemodynamic evaluations were not conducted after treatment initiation due to the invasive nature of RHC and the expense involved, which may have affected the assessment of the therapeutic responses.

In conclusion, our results suggest that the simplified version of the 2015 ESC/ERS risk stratification model is a useful tool for evaluating the severity and treatment response of Chinese patients with CTD-PAH. The WHO FC, the 6MWD, NT-proBNP plasma level, RAP, the CI, and SvO_2 were the basic elements for the simplified risk stratification model used in this study. However, further research into the optimal variables for inclusion in a simplified risk stratification model is needed.

Acknowledgments Thanks to all patients involved in this retrospective study.

Funding This study was supported by the National Natural Science Foundation of China (NSFC) (81671615, 81701610, and 81302575), a project funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD), Young Medical People Project in Jiangsu Province, and Medical Talent of Empowering Medicine through Science and Education Program.

Compliance with ethical standards

This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Nanjing Medical University and it has been performed in accordance with the ethical standard laid down in the 1964 Declaration of Helsinki.

Disclosures None.

References

1. Koh ET, Lee P, Gladman DD et al (1996) Pulmonary hypertension in systemic sclerosis: an analysis of 17 patients. Br J Rheumatol 35(10):989–993
2. Condliffe R, Kiely DG, Peacock AJ, Corris PA, Gibbs JSR, Vrapi F, Das C, Elliot CA, Johnson M, DeSoyza J, Torpy C, Goldsmith K, Hodgkins D, Hughes RJ, Pepke-Zaba J, Coghlan JG (2009) Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. Am J Respir Crit Care Med 179(2):151–157
3. Zhang R, Dai LZ, Xie WP, Yu ZX, Wu BX, Pan L, Yuan P, Jiang X, He J, Humbert M, Jing ZC (2011) Survival of Chinese patients with pulmonary arterial hypertension in the modern treatment era. Chest. 140(2):301–309
4. Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD (2012) An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. Chest. 142(2):448–456
5. Galie N, Humbert M, Vachiery JL et al (2016) 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J 37:67–119
6. Kylhammar D, Kjellström B, Hjalmarsson C, Jansson K, Nisell M, Söderberg S, Wikström G, Rådegran G (2018) A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. Eur Heart J 39(47):4175–4181
7. Hoeper MM, Kramer T, Pan Z, Eichstaedt CA, Spiesshoefer J, Benjamin N, Olsson KM, Meyer K, Vizza CD, Vonk-Noordegraaf A, Distler O, Opitz C, Gibbs JSR, Delcroix M, Ghofrani HA, Huscher D, Pittrow D, Rosenkranz S, Grünig E (2017) Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. Eur Respir J 50:1700740
8. Zhao J, Wang Q, Liu Y, Tian Z, Guo X, Wang H, Lai J, Huang C, Yang X, Li M, Zeng X (2017) Clinical characteristics and survival of pulmonary arterial hypertension associated with three major

connective tissue diseases: a cohort study in China. Int J Cardiol 236:432–437
9. Hao YJ, Jiang X, Zhou W, Wang Y, Gao L, Wang Y, Li GT, Hong T, Huo Y, Jing ZC, Zhang ZL (2014) Connective tissue disease-associated pulmonary arterial hypertension in Chinese patients. Eur Respir J 44(4):963–972
10. Hochberg MC (2014) Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 40(9):1725–1725
11. Vitali C, Bombardieri S, Jonsson R et al (2002) Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 61(6):554–558
12. Hoogen FVD, Khanna D, Fransen J et al (2013) Classification criteria for systemic sclerosis: an ACR-EULAR collaborative initiative. Arthritis Rheum 65(11):2737–2747
13. Sharp GC, Irvin WS, Tan EM, Gould RG, Holman HR (1972) Mixed connective tissue disease-an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). Am J Med 52(2):148–159
14. Wensel R, Francis DP, Meyer FJ, Opitz CF, Bruch L, Halank M, Winkler J, Seyfarth HJ, Gläser S, Blumberg F, Obst A, Dandel M, Hetzer R, Ewert R (2013) Incremental prognostic value of cardiopulmonary exercise testing and resting haemodynamics in pulmonary arterial hypertension. Int J Cardiol 167(4):1193–1119