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RESEARCH ARTICLE

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Incorporation of noninvasive assessments in risk prediction for pulmonary arterial hypertension

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Abstract

Risk assessment for pulmonary arterial hypertension (PAH) utilizing noninvasive prognostic variables could be more practical in real-world scenarios, especially at follow-up reevaluations. Patients who underwent comprehensive evaluations both at baseline and at follow-up visits were enrolled. The primary endpoint was all-cause mortality. Predictive variables identified by Cox analyses were further incorporated with the French noninvasive risk prediction approach. A total of 580 PAH patients were enrolled. During a median follow-up time of 47.0 months, 112 patients (19.3%) died. By multivariate Cox analyses, tricuspid annular plane systolic excursion (TAPSE), TAPSE/pulmonary arterial systolic pressure (PASP), and cardiopulmonary exercise testing-derived peak oxygen consumption (VO_2) remained independent predictors for survival. Regarding the French noninvasive risk prediction method, substituting N-terminal pro-b-type natriuretic peptide (NT-proBNP) with the newly derived low-risk criteria of a TAPSE ≥ 17 mm or a TAPSE/PASP > 0.17 mm/mmHg, or alternating 6-min walking distance with a peak VO_2 ≥ 44 %predicted retained the discrimination power. When recombining the low-risk criteria, the combination of World Health Organization functional class (WHO FC), TAPSE and peak VO_2 at baseline, and the combination of WHO FC, NT-proBNP, and peak VO_2 at follow-up showed better discriminative ability than the other combinations. In

Abbreviations: 6MWD, 6-min walking distance; CI, confidence interval; CPET, cardiopulmonary exercise testing; ERS, European Respiratory Society; ESC, European Society of Cardiology; HR, hazard ratio; IQR, interquartile range; IRB, Institutional Review Board; LAAPD, left atrial anteroposterior diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-b-type natriuretic peptide; PAH, pulmonary arterial hypertension; PASP, pulmonary arterial systolic pressure; REVEAL, the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management; RHC, right heart catheterization; RV, right ventricular/ventricle; RVAPD, right ventricular anteroposterior diameter; TAPSE, tricuspid annular plane systolic excursion; VO_2, oxygen consumption; WHO FC, World Health Organization functional class.

Ruilin Quan and Xiaoxi Chen contributed equally to this study.

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conclusion, Peak VO_2, TAPSE, and TAPSE/PASP are significant prognostic predictors for survival in PAH, with incremental prognostic value when incorporated with the French noninvasive risk prediction approach, especially at reevaluations. For better risk prediction, WHO FC, at least one measurement of exercise capacity and one measurement of right ventricular function should be considered.

KEYWORDS
cardiopulmonary exercise testing, echocardiography, pulmonary arterial hypertension, risk prediction, survival

INTRODUCTION

Pulmonary arterial hypertension (PAH), characterized by progressive remodeling of the small pulmonary arteries, could lead to exercise intolerance, right heart failure, and ultimately, death.[1] Recent advances in PAH-targeted treatments contribute to an improvement in survival and emphasize the importance of the rationale for regular comprehensive assessments of disease severity.[2–4] Several risk stratification strategies have been proposed as useful tools for periodic comprehensive evaluations, which can guide treatment decisions, improve clinical management, and help clinicians identify patients with potentially worse prognosis.[2–11] Various variables were included in these risk stratifications, including demographics, clinical assessments, comorbid conditions, biomarkers, hemodynamics, and other functional tests.[2–11] However, in daily clinical practice, insufficient data on the required measurements could impede the application of these risk assessment tools.[5] Particularly, it could be much more difficult to conduct invasive procedures at follow-ups, which leads to the suboptimal status of follow-up reevaluations in real-world settings. Under such circumstances, risk assessment using noninvasive variables could be more practical.

As underlined by the European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines for pulmonary hypertension, the assessments of World Health Organization functional class (WHO FC), exercise capacity, and right ventricular (RV) function are especially important among the multidimensional approaches for risk prediction, and accordingly, WHO FC, 6-min walking distance (6MWD) and brain natriuretic peptide (BNP)/N-terminal pro-brain natriuretic peptide (NT-proBNP) are regarded as the key variables with the highest predictive value.[2,3] Nevertheless, although the guidelines have emphasized the utility of the above three noninvasive variables, the application of other noninvasive parameters included in the risk assessment table, such as peak oxygen consumption (VO_2) derived by cardiopulmonary exercise testing (CPET) or tricuspid annular plane systolic excursion (TAPSE)/pulmonary arterial systolic pressure (PASP) obtained by echocardiography, still remains to be explored.[2,3] The prognostic value of those variables has been acknowledged in PAH patients, but there still lack studies investigating the optimal cutoff values of those variables or exploring their corporation with the established prediction strategies.[12–21]

Accordingly, the objectives of our study were to explore the prognostic value of noninvasive variables derived by CPET or echocardiography on the basis of WHO FC, 6MWD and NT-proBNP, and to incorporate those predictive variables in the established risk assessment tool to investigate their incremental prognostic value in patients with PAH.

METHODS

Study design and participants

From a national prospective multicenter observational registry study in China, patients who first underwent right heart catheterization (RHC) and were diagnosed with PAH between August 2009 and December 2019 were recruited. The diagnosis of PAH was based on 2009 (before January 2016) or the 2015 ESC/ERS guidelines.[2,22] Other causes of PH were judged and excluded carefully by multidisciplinary teams according to guidelines-recommended algorithms to ensure the accurate diagnosis of PAH. Details for the inclusion and exclusion criteria are illustrated in our previous report.[23] The study protocol, which was approved by the Institutional Review Board (IRB) of Fuwai Hospital (Approval No. 2009-208), complies with the Declaration of Helsinki and is registered on ClinicalTrials.gov (Identifier: NCT01417338). All authors had full access

to all the data in the study and vouch for the integrity of the data and the manuscript.

In the current study, patients who were enrolled at Fuwai Hospital ($n = 750$) were reviewed for further analyses. Patients were included in the present study if they had at least three kinds of the following noninvasive evaluations (including at least one out of the latter two), both at baseline and at the first follow-up visit: (1) WHO FC; (2) NT-proBNP measurement; (3) 6MWD; (4) transthoracic echocardiography including the measurement of TAPSE; and (5) CPET. Patients without follow-up information on vital status were excluded. Written informed consent was obtained from all enrolled patients.

Measurements and data collection

RHC (necessary for diagnosis), electrocardiogram, chest X-ray, transthoracic echocardiography, pulmonary function test, high-resolution computed tomography of the chest, ventilation/perfusion scintigraphy lung scan (if necessary), pulmonary angiography (if necessary), and laboratory tests were performed to assist in the diagnosis and guide the management of PAH. For enrolled patients, the following data were collected at baseline: (1) demographics, medical history, clinical symptoms, and vital signs; (2) examination results; and (3) treatments. At follow-up, the reevaluated examination results and changes in treatments were recorded.

Transthoracic echocardiography was performed by experienced ultrasonologists on an ultrasound system (Vivid 7 or E9, GE Healthcare) according to the recommendations of the American Society of Echocardiography.[24,25] TAPSE was measured with M-mode at the four-chamber apical view. PASP was calculated based on peak tricuspid regurgitant velocity and estimated right atrial pressure (RAP) using the simplified Bernoulli equation. In the current study, echocardiography-derived left ventricular end-diastolic diameter (LVEDD), left atrial anteroposterior diameter (LAAPD), right ventricular anteroposterior diameter (RVAPD), left ventricular ejection fraction (LVEF), PASP, and TAPSE were collected for further analysis.

CPET was performed on a bicycle ergometer using the COSMED Quark CPET system. The detailed protocol for CPET has been described previously.[26] Briefly, oxygen uptake (VO_2), carbon dioxide output (VCO_2), expiratory gas concentrations, and minute ventilation (VE) were measured breath-by-breath and were averaged every 10 s during the entire process. Peak VO_2 was defined as the highest 30-s average of VO_2 in the last minute of exercise, and the percentages of peak predicted values were calculated using the Wasserman formula.[27] Based on previous reports on the prognostic value of CPET-derived parameters in patients with cardiopulmonary diseases, the current study only collected peak VO_2 (absolute and percentage of peak predicted) for relevant analyses.[2,3,12,13,28,29]

The French Registry noninvasive risk stratification method was employed as previously described.[9] Briefly, it classifies patients according to the presence of the following three ESC/ERS low-risk criteria: WHO FC of I/II, 6MWD > 440 m, and NT-proBNP < 300 ng/L.

Endpoint and follow-up

The primary endpoint of this study was all-cause mortality. Overall survival was measured from the date of RHC (or the date the reevaluation was completed) to the date of death from any cause. Follow-up was performed by telephone calls, outpatient visits, or inpatient admissions every 6 months ± 2 weeks. Regarding the patients who could not be contacted through the above three methods, vital status was further confirmed via the country's health care insurance system. Patients were followed until death or until the cutoff date of the current study (February 28, 2021).

Statistical analysis

Analyses were performed with SPSS Statistics (version 22.0, SPSS Inc.) and the R statistical package (version 4.0.0, R Foundation for Statistical Computing). Differences were considered statistically significant when the two-sided p value was <0.05.

Continuous variables are presented as the mean ± standard deviation or median (interquartile range [IQR]). For difference comparisons of the independent subgroups, the unpaired t-test or the Mann–Whitney U test were utilized for two groups, and one-way analysis of variance or the Kruskal–Wallis test was performed for multiple groups, as appropriate. Categorical variables are shown as frequencies and percentages and were compared with the χ^2 or Fisher's exact tests. For the comparison between baseline and follow-up data, paired two-tailed t-tests or Wilcoxon's rank-sum tests were utilized for normally distributed and nonnormally distributed continuous variables, respectively. McNemar's test, the κ test, and Cochran's Q test were used for categorical variables, as appropriate. Multiple imputations was used to replace missing values for the following variables: WHO FC (percentage of missing data: 0 at baseline; 1.0% at follow-up), 6MWD (4.5% at

baseline; 9.8% at follow-up), NT-proBNP (1.9% at baseline; 3.2% at follow-up), peak VO_2 (8.6% at baseline; 5.2% at follow-up), and TAPSE (16.9% at baseline; 11.0% at follow-up). Survival analysis, truncated at 5 years, was carried out by means of Kaplan–Meier analysis and the differences were compared by the log-rank test. Cox proportional hazards analyses were performed to compute hazard ratios (HRs) with 95% confidence intervals (CIs). The proportional hazards assumption was examined by the Schoenfeld residuals method. We first conducted univariable Cox analyses to screen the candidate variables and then based on the univariate results, together with the literature and clinical expertise, multivariate Cox analyses were performed to obtain adjusted HRs and CIs. The cutoff values for continuous variables were determined by X-tile 3.6.1 software (Yale University). Relevant variables were categorized by the derived cutoffs, and new low-risk criteria were generated accordingly. For example, cutoff values of 12 and 17 mm were determined for TAPSE, and accordingly, a TAPSE ≥ 17 mm satisfied a low-risk criterion. Similarly, a TAPSE/PASP > 0.17 mm/mmHg and a peak VO_2 ≥ 44 %predicted were employed as low-risk criteria. New prediction models were established in terms of the French Registry approach, where the number of low-risk criteria was counted. Harrell's C-index was used to assess the discriminatory power of the risk stratification models.

Sample size calculation was based on the principles reported by Riley et al.[30] The difference between apparent and adjusted R^2 was assumed to be 0.05, with a shrinkage factor of 0.9 and a margin of error in the estimation of the overall risk of 0.05. Event rate and adjusted Cox-Snell R^2 statistic was calculated based on the previous external validation of the French non-invasive risk prediction method, in terms of the equations reported by Riley et al.[31] Accordingly, regarding new model development, the present study with 6 candidate parameters (WHO FC, 6MWD, NT-proBNP, peak VO_2 %predicted, TAPSE, and TAPSE/PASP) required minimum sample size of 570 PAH patients.

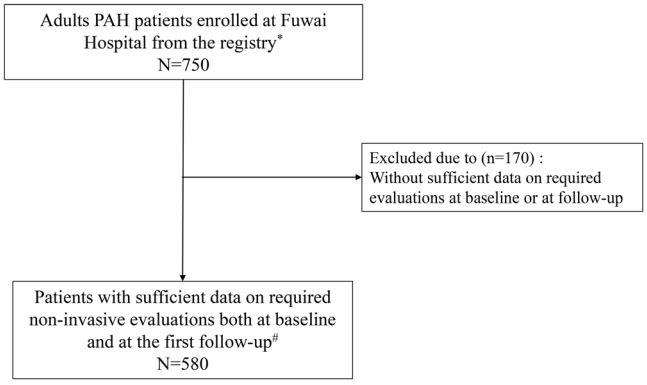

FIGURE 1 Flowchart of the study population. Among all PAH patients enrolled at Fuwai Hospital in the registry, a total of 580 patients with PAH who had sufficient data on the required evaluations were enrolled in the current study. *Referred to the national prospective multicenter observational registry study in China (Identifier: NCT01417338). #Patients should have data on at least three kinds of the following noninvasive evaluations (including at least one out of the latter two) both at baseline and at the first follow-up visit: (1) WHO FC; (2) NT-proBNP measurement; (3) 6MWD; (4) transthoracic echocardiography including the measurement of TAPSE; and (5) cardiopulmonary exercise test. 6MWD, 6-min walking distance; NT-proBNP, N-terminal pro-b-type natriuretic peptide; PAH, pulmonary arterial hypertension; WHO FC, World Health Organization functional class.

RESULTS

Baseline characteristics

A total of 580 patients with PAH were enrolled in the current study (Figure 1). The mean age of the cohort was 34 ± 10 years, and 76.6% of the patients were females. The most common etiology was idiopathic pulmonary arterial, accounting for 57.9% of the participants. At the time of enrollment, 50.9% of the patients were in WHO FC III or IV, with a mean 6MWD of 419 ± 98 m. Regarding hemodynamics, the mean value of mPAP was 58.46 ± 17.09 mmHg, with 5.57 ± 4.55 mmHg for RAP, 3.00 ± 1.03 L/min/m^2 for CI, and 974.91 ± 455.2 dyn s cm^{-5} for PVR. A mean value of 32.72 ± 7.11 mm for RVAPD, 15.44 ± 3.34 mm for TAPSE, and 0.18 ± 0.07 mm/Hg for TAPSE/PASP were determined by echocardiography. By CPET, the mean peak VO_2 of the cohort was 13.46 ± 3.65 ml/min/kg (40.17 ± 11.61 %predicted). At baseline, 90.7% of the patients received at least one PAH-targeted drug, and 29.8% received combination-targeted therapy (Table 1).

Longitudinal changes from baseline to the first follow-up reevaluation

The enrolled patients received their first reevaluations at a median follow-up time of 4 (3, 8) months. At reevaluation, there tended to be an improvement in exercise capacity, indicated by a higher percentage of patients in WHO FC I/II (69.3% at follow-up vs. 49.1% at baseline, $p < 0.001$), an increased 6MWD (446.13 ± 95.46 vs. 419.11 ± 98.00 m, $p < 0.001$), and peak VO_2 (absolute

TABLE 1 Baseline and follow-up characteristics of the overall analyzed cohort

	Baseline	Follow-up	*p* Value[a]
Age (years)	34 ± 10	–	–
Females, *n* (%)	444 (76.6)	–	–
PAH etiology, *n* (%)			
IPAH	336 (57.9)	–	–
CHD-PAH	173 (29.8)	–	–
CTD-PAH	42 (7.2)	–	–
Others[b]	29 (5.0)	–	–
WHO FC, *n* (%)			**<0.001**
I/II	285 (49.1)	402 (69.3)	
III	268 (46.2)	158 (27.2)	
IV	27 (4.7)	20 (3.4)	
6MWD (m)	419.11 ± 98.00	446.13 ± 95.46	**<0.001**
Hemodynamics (available in 81 patients at follow-up)			
HR (beats)	81.45 ± 13.73	82.70 ± 14.70	0.268
SBP (mmHg)	111.00 ± 15.10	113.08 ± 16.91	0.883
DBP (mmHg)	74.55 ± 12.08	67.70 ± 6.91	**<0.001**
SvO_2 (%)	70.32 ± 7.51	68.20 ± 9.97	0.333
RAP (mmHg)	5.57 ± 4.55	6.94 ± 4.61	**0.042**
mPAP (mmHg)	58.46 ± 17.09	56.73 ± 16.79	**0.046**
CI ($L/min/m^2$)	3.00 ± 1.03	2.98 ± 1.13	0.113
PAWP (mmHg)	7.10 ± 3.20	8.72 ± 3.26	0.669
PVR ($dyn\ s\ cm^{-5}$)	974.91 ± 455.2	1007.03 ± 538.39	0.972
Laboratory test			
NT-proBNP (pg/ml)[c]	1406.00 [443.30, 5442.98]	496.75 [155.90, 1365.98]	**<0.001**
Echocardiography			
LVEF (%)	64.18 ± 6.46	65.55 ± 6.76	**<0.001**
LAAPD (mm)	30.1 ± 5.19	31.06 ± 5.23	**<0.001**
LVEDD (mm)	36.99 ± 6.59	38.47 ± 7.05	**<0.001**
RVAPD (mm)	32.72 ± 7.11	32.54 ± 8.32	0.586
TAPSE (mm)	15.44 ± 3.34	16.74 ± 4.02	**<0.001**
PASP (mmHg)	92.8 ± 22.36	89.03 ± 24.16	**<0.001**
TAPSE/PASP (mm/mmHg)	0.18 ± 0.07	0.21 ± 0.09	**<0.001**
Pericardial effusion, *n* (%)	78 (13.4)	70 (12.1)	0.484
Cardiopulmonary exercise testing			
Peak VO_2 (ml/min/kg)	13.46 ± 3.65	14.95 ± 3.7	**<0.001**
Peak VO_2 (%predicted)	40.17 ± 11.61	45.24 ± 12.21	**<0.001**
Targeted drugs, *n* (%)	526 (90.7)	532 (91.7)	0.361
Phosphodiesterase type 5 inhibitors	396 (68.3)	455 (78.4)	**<0.001**
Endothelin receptor antagonists	233 (40.2)	289 (49.8)	**<0.001**

(Continues)

TABLE 1 (Continued)

	Baseline	Follow-up	*p* Value[a]
Prostacyclin analogues	74 (12.8)	84 (14.5)	0.268
IP receptor agonists	0	1 (0.2)	–
Guanylate cyclase stimulators	2 (0.3)	4 (0.7)	0.500
Combination therapy	173 (29.8)	281 (48.4)	**<0.001**

Note: Bold values are statistically significant at $P < 0.05$.

Abbreviations: 6MWD, 6-min walking distance; CHD, congenital heart disease; CI, cardiac index; CTD, connective tissue disease; DBP, diastolic blood pressure; HR, heart rate; IPAH, idiopathic pulmonary arterial; LAAPD, left atrial anteroposterior diameter; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary artery pressure; NT-proBNP, N-terminal pro-b-type natriuretic peptide; PASP, pulmonary arterial systolic pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVAPD, right ventricular anteroposterior diameter; SBP, systolic blood pressure; SvO_2, mixed venous oxygen saturation; TAPSE, tricuspid annular plane systolic excursion; VO2, oxygen consumption; WHO FC, World Health Organization functional class

[a]Comparison between baseline and follow-up.

[b]Others subtypes of PAH were combined because of the small sample sizes, including heritable PAH, drugs and toxins induced PAH, HIV-related PAH, and PVOD/PCH.

[c]Median (interquartile range).

value: 14.95 ± 3.7 vs. 13.46 ± 3.65 ml/min/kg, $p < 0.001$; percentage of predicted: 45.24 ± 12.21 vs. $40.17 \pm 11.61\%$, $p < 0.001$). Additionally, better indices of RV function were observed, including lower NT-proBNP levels (median: 496.75 vs. 1406.00 pg/ml, $p < 0.001$) and higher TAPSE (16.74 ± 4.02 vs. 15.44 ± 3.34 mm, $p < 0.001$) and TAPSE/PASP (0.21 ± 0.09 vs. 0.18 ± 0.07, $p < 0.001$). Although hemodynamics was only available for 81 patients at the follow-up reevaluation, better hemodynamics was demonstrated (Table 1).

Survival

During a median follow-up time of 47.0 months (IQR: 29.5, 72.8), 112 patients (19.3%) died. The survival estimates at 1, 3, and 5 years were 98.3% (95% CI: 97.2%–99.3%), 90.9% (88.4%–93.4%), and 79.8% (75.9%–83.9%), respectively.

At baseline, compared to survivors, deceased patients tended to have worse exercise capacity, with lower peak VO_2 (absolute value: 12.23 ± 3.48 vs. 13.76 ± 3.64 ml/min/kg, $p < 0.001$; percentage of predicted: 36.43 ± 11.55 vs. 41.07 ± 11.45, $p < 0.001$), and higher percentages of patients in WHO III/IV (64.3% vs. 47.7%, $p = 0.013$). Nonsurvivors also demonstrated lower TAPSE (14.35 ± 3.01 vs. 15.71 ± 3.37 mm, $p < 0.001$), higher NT-proBNP levels (median: 7019.73 vs. 1049.5 pg/ml, $p < 0.001$), and worse hemodynamics, indicating more severely compromised RV function (Supporting Information: Table S1).

When comparing survivors and non-survivors using follow-up information, in addition to the abovementioned parameters, differences were also observed in the values of 6MWD (410.49 ± 103.45 vs. 454.65 ± 91.53 m, $p < 0.001$), TAPSE/PASP (0.16 ± 0.06 vs. 0.22 ± 0.09 mm/mmHg, $p < 0.001$), and RVAPD (36.84 ± 8.65 vs. 31.52 ± 7.91 mm, $p < 0.001$) (Table 2).

Outcome correlates

Utilizing baseline data, the variables of PAH etiology, 6MWD, RAP, cardiac index, mixed venous oxygen saturation (SvO_2), peak VO_2, and TAPSE were significant prognostic predictors for survival (Supporting Information: Table S2). When analyzed using follow-up data, the significance of the above variables was maintained, and RVAPD and TAPSE/PASP also showed significant prognostic value. The changes of the above parameters except 6MWD were also significant predictors for survival (Supporting Information: Table S3).

By multivariate Cox analyses, after adjusting for age, sex, PAH etiology, and DLCO, RVAPD [HR (95% CI) for per 1 mm increase: 1.032 (1.002–1.062) and 1.072 (1.051–1.094) for baseline and follow-up data, respectively], TAPSE [per 1 mm increase: 0.885 (0.821–0.954); 0.847 (0.800–0.898)], TAPSE/PASP [per 0.01 mm/mmHg increase: 0.945 (0.906–0.985); 0.899 (0.869–0.931)], and peak VO_2 [absolute value per 1 ml/min/kg increase: 0.873 (0.818–0.931); 0.835 (0.783–0.890); percentage of predicted per 5% increase: 0.823 (0.739–0.917); 0.679 (0.610–0.755)] remained independent predictors for survival at both baseline and follow-up visits (Table 3).

TABLE 2 Follow-up characteristics of survivors and nonsurvivors

	Survivors	Nonsurvivors	*p* Value[a]
Subjects, *n* (%)	468 (80.7)	112 (19.3)	–
WHO FC, *n* (%)			**<0.001**
I/II	361 (77.1)	41 (36.6)	
III	101 (21.6)	57 (50.9)	
IV	6 (1.3)	14 (12.5)	
6MWD (m)	454.65 ± 91.53	410.49 ± 103.45	**<0.001**
Hemodynamics			
HR (beats)	83.25 ± 14.24	79.92 ± 17.25	0.477
SBP (mmHg)	111.56 ± 17.52	120.92 ± 11.94	0.081
DBP (mmHg)	66.86 ± 11.08	72.08 ± 9.81	0.132
SvO_2 (%)	70.38 ± 8.26	59.14 ± 11.59	**<0.001**
RAP (mmHg)	6.45 ± 3.89	9.21 ± 6.82	**0.041**
mPAP (mmHg)	57.64 ± 17.33	52.36 ± 13.64	0.287
CI ($L/min/m^2$)	3.17 ± 1.11	2.21 ± 0.85	**0.005**
PAWP (mm Hg)	8.46 ± 3.22	10.25 ± 3.24	0.153
PVR ($dyn\ s\ cm^{-5}$)	942.26 ± 505.95	1719.47 ± 382.5	**0.014**
Laboratory test			
NT-proBNP (pg/ml)[b]	361.75 [118.25, 913.65]	1591.35 [765.93, 2850.70]	**<0.001**
Echocardiography			
LVEF (%)	65.7 ± 6.55	64.96 ± 7.58	0.343
LAAPD (mm)	31.3 ± 5.23	30.07 ± 5.14	**0.026**
LVEDD (mm)	39.54 ± 6.49	33.99 ± 7.54	**<0.001**
RVAPD (mm)	31.52 ± 7.91	36.84 ± 8.65	**<0.001**
TAPSE (mm)	17.24 ± 3.95	14.66 ± 3.67	**<0.001**
PASP (mmHg)	87.33 ± 24.25	96.15 ± 22.53	**<0.001**
TAPSE/PASP (mm/mmHg)	0.22 ± 0.09	0.16 ± 0.06	**<0.001**
Pericardial effusion, *n* (%)	41 (8.8)	29 (25.9)	**<0.001**
Cardiopulmonary exercise testing			
Peak VO_2 (ml/min/kg)	15.41 ± 3.63	13.04 ± 3.42	**<0.001**
Peak VO_2 (%predicted)	46.71 ± 12.13	39.09 ± 10.5	**<0.001**
Targeted drugs, *n* (%)	432 (92.3)	100 (89.3)	0.297
Phosphodiesterase type 5 inhibitors	379 (81.0)	76 (67.9)	**0.002**
Endothelin receptor antagonists	244 (52.1)	45 (40.2)	**0.023**
Prostacyclin analogues	58 (12.4)	26 (23.2)	**0.003**
IP receptor agonists	1 (0.2)	0	0.624

(Continues)

TABLE 2 (Continued)

	Survivors	Nonsurvivors	*p* Value[a]
Guanylate cyclase stimulators	4 (0.9)	0	0.326
Combination therapy	239 (51.1)	42 (37.5)	**0.010**

Note: Abbreviations are the same as Table 1. Bold values are statistically significant at $P < 0.05$.

[a]Comparison between survivors and nonsurvivors.

[b]Median (interquartile range).

TABLE 3 Adjusted Cox analyses for variables measured at baseline and at follow-up

	Baseline		Follow-up	
Variables	Adjusted HR (95% CI)[a]	*p* Value	Adjusted HR (95% CI)[a]	*p* Value
RVAPD (per 1 mm increase)	1.032 (1.002–1.062)	0.035	1.072 (1.051–1.094)	<0.001
TAPSE (per 1 mm increase)	0.885 (0.821–0.954)	0.001	0.847 (0.800–0.898)	<0.001
TAPSE/PASP (per 0.01 mm/mmHg increase)	0.945 (0.906–0.985)	0.007	0.899 (0.869–0.931)	<0.001
Peak VO2 (per 1 ml/min/kg increase)	0.873 (0.818–0.931)	<0.001	0.835 (0.783–0.890)	<0.001
Peak VO2 %predicted (per 5% increase)	0.823 (0.739–0.917)	<0.001	0.679 (0.610–0.755)	<0.001

Abbreviations: CI, confidence interval; DLCO, diffusing capacity of the lung for carbon monoxide; PASP, pulmonary arterial systolic pressure; RVAPD, right ventricular anteroposterior diameter; TAPSE, tricuspid annular plane systolic excursion; VO2, oxygen consumption.

[a]Adjusted for age, sex, PAH etiology, and DLCO.

Incorporation of noninvasive variables in risk prediction

Applied in the current cohort, the French Registry noninvasive risk stratification approach showed significant discrimination power for predicting survival [C-index (95% CI): 0.634 (0.581–0.687) for baseline data and 0.743 (0.702–0.784) for follow-up data]. Regarding the noninvasive independent variables explored above, patients with fewer low-risk criteria showed lower values of peak VO_2 %predicted, TAPSE, and TAPSE/PASP at both visits (Figure 2).

We thereafter incorporated peak VO_2 %predicted, TAPSE, and TAPSE/PASP with the French noninvasive approach to explore their relationships. For better clinical utility, the three variables were all classified into three categories: ≥44, 34–43, and ≤33 %predicted for peak VO_2; ≥17, 12–16, and <12 mm for TAPSE; >0.17, 0.12–0.17, and ≤0.12 mm/mmHg for TAPSE/PASP.

When categorizing the analyzed cohort in terms of the cutoff values of 6MWD according to the guidelines,[2] 54.5% of the patients were in intermediate risk, while only seven patients (1.2%) were in a high-risk stratum. In patients with an intermediate risk of 6MWD, 15.6% were reclassified as high-risk according to the categories of peak VO_2. Regarding NT-proBNP, 50.2% of the patients were in the high-risk stratum, while lower percentages were observed in the high-risk category of TAPSE (10.5%) or TAPSE/PASP (15.9%) (Table 4).

Incremental prognostic value of noninvasive variables

We further explored the incremental prognostic value of peak VO_2 %predicted, TAPSE, and TAPSE/PASP on the basis of the French Registry noninvasive risk prediction method.

As individual categorical variables, the survival of patients with different strata of peak VO_2, TAPSE, or TAPSE/PASP varied significantly, with patients who met low-risk strata showing better survival than the other patients (p value for the three subgroup comparisons: $p < 0.0001$ for the peak VO_2 subgroups, $p < 0.0001$ for the TAPSE subgroups, and $p = 0.009$ for the TAPSE/PASP subgroups, Supporting Information: Figure S1). When applied at follow-up, patients with different strata of the three noninvasive variables showed consistent differences in survival (all $p < 0.001$, Supporting Information: Figure S1).

When adding the three newly derived low-risk criteria of a peak $VO_2 \geq 44$ %predicted, a TAPSE ≥ 17 mm, and a TAPSE/PASP > 0.17 mm/mmHg to the original French noninvasive risk prediction method,

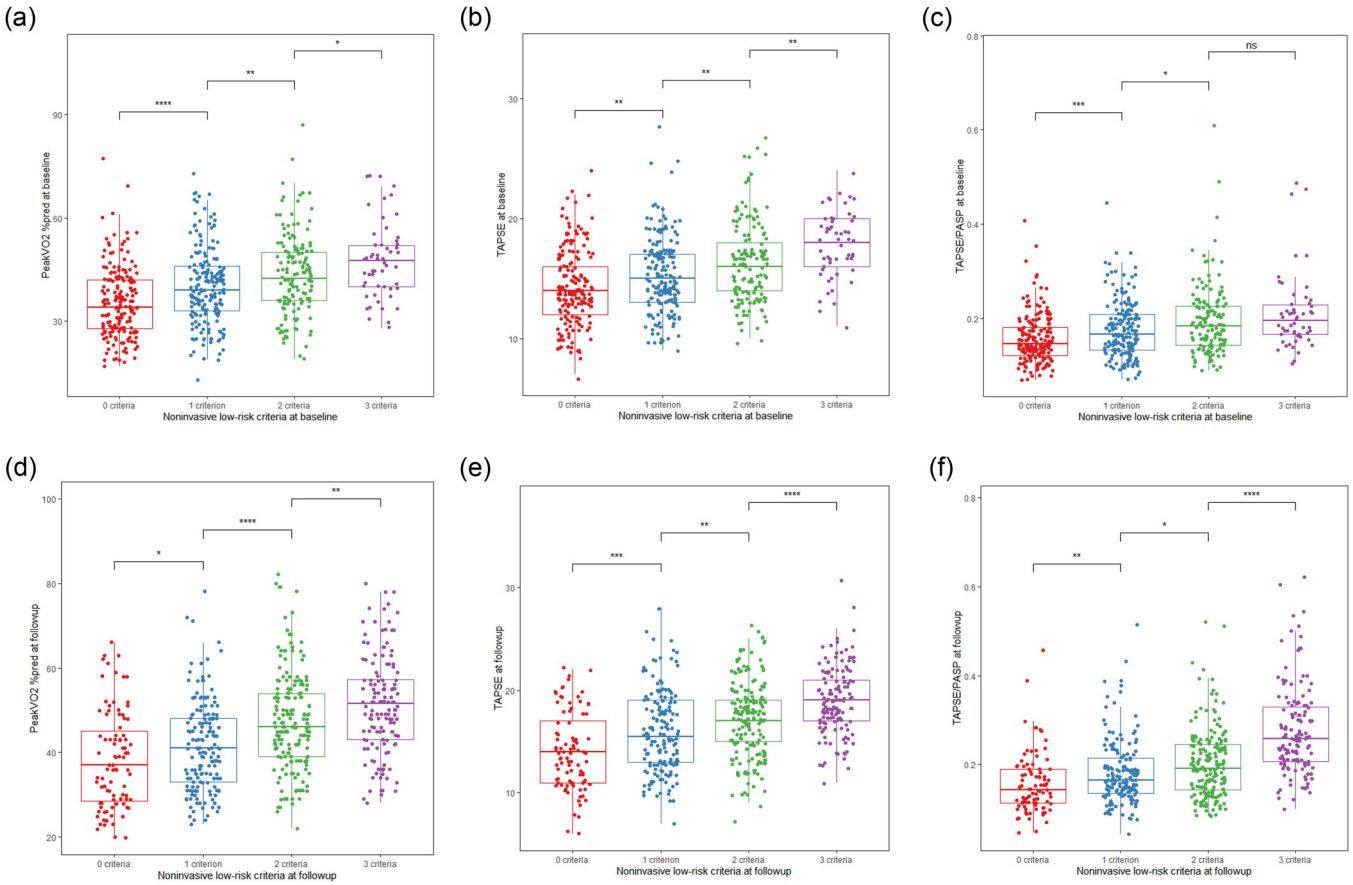

FIGURE 2 Values of peak %predicted VO_2 (a, d), TAPSE (b, e), and TAPSE/PASP (c, f) in patients meeting different numbers of the French noninvasive low-risk criteria at baseline (a–c) or at follow-up (d–f). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$. ns, nonsignificant; PASP, pulmonary arterial systolic pressure; TAPSE, tricuspid annular plane systolic excursion; VO_2, oxygen consumption.

better discrimination power was demonstrated. When utilized at follow-up, the C-index further improved [C-index (95% CI) for the original method plus TAPSE at follow-up: 0.750 (0.707–0.793); for the original method plus TAPSE/PASP at follow-up: 0.760 (0.719–0.801); and for the original method plus peak VO_2 at follow-up: 0.773 (0.732–0.814)] (Table 5).

When substituting the criteria of 6MWD > 440 m with peak $VO_2 \geq 44$ %predicted, the discrimination power was maintained at both visits [baseline: 0.646 (0.597–0.695); follow-up: 0.778 (0.739–0.817)]. We further substituted NT-proBNP <300 ng/L with TAPSE ≥ 17 mm or TAPSE/PASP > 0.17 mm/mmHg, and the risk prediction models also maintained their significance. When recombining the abovementioned low-risk criteria, we found that the combination of WHO FC, TAPSE, and peak VO_2 at baseline, and the combination of WHO FC, NT-proBNP, and peak VO_2 at follow-up, showed better discriminative ability than the other combination groups [0.660 (0.613–0.707) and 0.778 (0.739–0.817), respectively] (Table 5). The survival was significantly different between patients with different numbers of low-risk criteria defined by the new combinations mentioned above (Figure 3).

DISCUSSION

The present study not only sufficiently confirmed the prognostic value of TAPSE, TAPSE/PASP and PeakVO_2 in PAH with the largest sample size including CPET and echocardiography data to date, but also illustrated the utility of flexible combinations of different non-invasive variables for more accessible and applicable clinical usage.

The ESC/ERS guidelines for pulmonary hypertension recommend a goal-oriented treatment strategy for PAH management, where therapeutic decisions depend on the severity assessed by risk stratification strategies.[2–4] As a single variable could unlikely be sufficient for accurate prognosis prediction, a multidimensional approach is recommended by the guidelines.[2–4] However, in real-world clinical practice, not all patients could undergo tests for all the measurements required in the established

TABLE 4 Agreement between noninvasive variables, *n* (%)

Category	Peak VO_2		
	Low	**Intermediate**	**High**
6MWD			
Low	125 (48.6)	88 (34.2)	44 (17.1)
Intermediate	81 (25.6)	120 (38.0)	115 (36.4)
High	1 (14.3)	2 (28.6)	4 (57.1)
	TAPSE/PASP		
	Low	**Intermediate**	**High**
NT-proBNP			
Low	77 (70.6)	27 (24.8)	5 (4.6)
Intermediate	84 (46.7)	68 (37.8)	28 (15.6)
High	117 (40.2)	115 (39.5)	59 (20.3)
	TAPSE		
	Low	**Intermediate**	**High**
NT-proBNP			
Low	81 (74.3)	24 (22.0)	4 (3.7)
Intermediate	65 (36.1)	95 (52.8)	20 (11.1)
High	78 (26.8)	176 (60.5)	37 (12.7)

Abbreviations: 6MWD, 6-min walking distance; NT-proBNP, N-terminal pro-b-type natriuretic peptide; PASP, pulmonary arterial systolic pressure; TAPSE, tricuspid annular plane systolic excursion; VO_2, oxygen consumption.

risk stratifications. Therefore, the lack of data could be one of the barriers to the clinical implementation of comprehensive risk assessments. Notably, although RHC is critical for risk assessment, it could be extremely hard to repeat at follow-up visits due to patients' unwillingness or other socioeconomic reasons, especially in developing countries.[5,32] In our cohort, among the patients who had comprehensive baseline and follow-up evaluations, only 81 patients (14.0% of the study cohort) underwent RHC at follow-up. Therefore, taking full advantage of available prognostic variables, especially noninvasive variables, is essential for expediting the application of comprehensive evaluations in daily practice. In addition, it could also be beneficial if we can take advantage of different combinations of various accessible parameters and confirm their predictive power.

To this end, we focused our study on noninvasive evaluations and found that several noninvasive variables, including peak VO_2 derived by CPET, RVAPD, TAPSE, and TAPSE/PASP obtained by echocardiography, were significant predictors for the survival of patients with PAH. Furthermore, we thereafter confirmed that low-risk criteria defined as a peak $VO_2 \geq 44$ %predicted, a TAPSE ≥ 17 mm and a TAPSE/PASP > 0.17 mm/mmHg could serve as significant components to incorporate with the French noninvasive approach for risk prediction. In other words, the discriminative power of the models was maintained or even improved when adding the three newly derived low-risk criteria to the original French model, or substituting the NT-proBNP level, which is regarded as an index of RV function, with TAPSE or TAPSE/PASP, or alternating 6MWD, the measurement for exercise capacity, with peak VO_2. Additionally, we found that although the different combinations all illustrated tolerable discriminative power, the combination of WHO FC, TAPSE, and peak VO_2 at baseline, and the combination of WHO FC, NT-proBNP, and peak VO_2 at follow-up showed better discriminative ability than the other combination groups. These findings support that WHO FC should be included as a basic variable, and at least one measurement of exercise capacity and some information on RV function should be considered.[2] The results also indicate a better prognostic value of peak VO_2 than 6MWD, which was consistent with the previous report.[12]

Peak VO_2, as a measure of functional capacity, integrates the cardiovascular, pulmonary, and skeletal muscle systems.[9] Its prognostic relevance has been reported in patients with PAH and other cardiovascular diseases, and the guidelines have recommended it as one of the predictive variables for risk assessment.[2–4,12–16] Nevertheless, regarding assessment for exercise capacity, 6MWD is utilized more widely because of its convenience. However, as shown in the present study, only a few patients could be categorized into a high-risk stratum of 6MWD, leaving most patients in an intermediate risk. Similarly, the newly derived four-strata method still retains the high cutoff value of 165 m for 6MWD. As the results of 6MWD are shown in absolute values and can be influenced by common clinical characteristics such as age, sex, and comorbidities, in a cohort consisting of young and stable patients, CPET can be more sensitive and accurate to reflect the functional state. Furthermore, at follow-up evaluations, we found that the increase of peak VO_2, instead of the changes of 6MWD, was significantly associated with survival, also indicating peak VO_2 is a more sensitive predictor of survival. Although its experience is still limited in some medical centers, we believe it would be helpful if we could recognize its prognostic value and interpret it appropriately. To utilize it easily, the optimal cutoff value is another remaining question. The thresholds for low- and high-risk groups used in the guidelines are >65% and <35%predicted, respectively. Nevertheless, Wensel et al.[12] reported that the prognosis of PAH patients was still acceptable if the peak $VO_2 > 46$ %predicted. Similar

TABLE 5 C-index (95% CI) of different risk models[a]

Model description	Baseline	Follow-up
Based on the original three variables in the French noninvasive risk prediction method		
WHO FC + NT-proBNP + 6MWD	0.634 (0.581–0.687)	0.743 (0.702–0.784)
WHO FC + NT-proBNP + 6MWD + TAPSE	0.651 (0.600–0.702)	0.750 (0.707–0.793)
WHO FC + NT-proBNP + 6MWD + TAPSE/PASP	0.651 (0.596–0.706)	0.760 (0.719–0.801)
WHO FC + NT-proBNP + 6MWD + peak VO_2 %predicted	0.658 (0.605–0.711)	0.773 (0.732–0.814)
Based on at least two variables in the French noninvasive risk prediction method		
WHO FC + NT-proBNP	0.610 (0.559–0.661)	0.739 (0.698–0.780)
WHO FC + NT-proBNP + peak VO_2 % predicted	0.646 (0.597–0.695)	**0.778 (0.739–0.817)**
WHO FC + 6MWD	0.620 (0.565–0.675)	0.703 (0.658–0.748)
WHO FC + 6MWD + TAPSE	0.647 (0.596–0.698)	0.724 (0.679–0.769)
WHO FC + 6MWD + TAPSE/PASP	0.643 (0.586–0.700)	0.737 (0.694–0.780)
New combinations of the variables		
TAPSE + peak VO_2 %predicted		
WHO FC + TAPSE + peak VO_2 % predicted	**0.660 (0.613–0.707)**	0.762 (0.719–0.805)
TAPSE/PASP + peak VO_2 %predicted	0.629 (0.580–0.678)	0.716 (0.673–0.759)
WHO FC + TAPSE/PASP + peak VO_2 % predicted	0.658 (0.609–0.707)	0.770 (0.731–0.809)

Note: Bold values indicate the highest C-index at baseline or at follow-up.

Abbreviations: 6MWD, 6-min walking distance; CI, confidence interval; NT-proBNP, N-terminal pro-b-type natriuretic peptide; PASP, pulmonary arterial systolic pressure; TAPSE, tricuspid annular plane systolic excursion; VO2, oxygen consumption; WHO FC, World Health Organization functional class.

[a]Models counted the number of low-risk criteria as follows: WHO FC I/II, 6MWD > 440 m, NT-proBNP <300 ng L^{-1}, peak $VO_2 \geq 44$ %predicted, TAPSE ≥ 17 mm, or TAPSE/PASP > 0.17 mm/mmHg.

to the cutoffs reported by Wensel et al.[12] (i.e., 65, 46, and 34 %predicted), we defined the best discriminative cutoffs of peak VO_2 at 33 and 44 %predicted. Notably, we found that only a few patients met the criteria of a peak $VO_2 > 65$ %predicted, accounting for only 3.4% of the cohort at baseline and 6.0% of the cohort at follow-up, leading to the insignificant prognostic value of these thresholds. Therefore, it may indicate that lower cutoff values should be utilized for peak VO_2 assessment.

RV function is the main determinant of the outcomes in PAH patients.[33] Echocardiography, as an important noninvasive modality for assessing RV function, tends to be more involved in risk assessment.[2–4] TAPSE, an easily obtainable measure of RV longitudinal function, shows good correlations with parameters estimating RV global systolic function.[25] Furthermore, the prognostic value of TAPSE has been confirmed in PAH patients, and it has also been used as a marker to document therapeutic efficacy.[17,20] TAPSE/PASP has been introduced as a noninvasive, easy-to-use surrogate of RV-pulmonary arterial (PA) coupling, which reflects the progressive course of RV dysfunction from adaption to RV-PA uncoupling and right heart failure.[18,19,21] TAPSE/PASP has been validated as a marker of disease severity and a predictor of outcomes in heart failure and PAH patients.[18,19,21,34] In the present study, TAPSE and TAPSE/PASP show comparable predictive power to NT-proBNP. Because of the great variability of NT-proBNP among different patient groups, TAPSE and TAPSE/PASP could serve as great surrogates for risk prediction in some scenarios. The cutoffs of the two variables varied in different studies, with a range of 15–17 mm for TAPSE and 0.184–0.32 mm/mmHg for TAPSE/PASP.[18,19,21,34,35] The upper threshold derived in our study (17 mm for TAPSE and 0.17 mm/mmHg for TAPSE/PASP) resembles previous reports, but we also

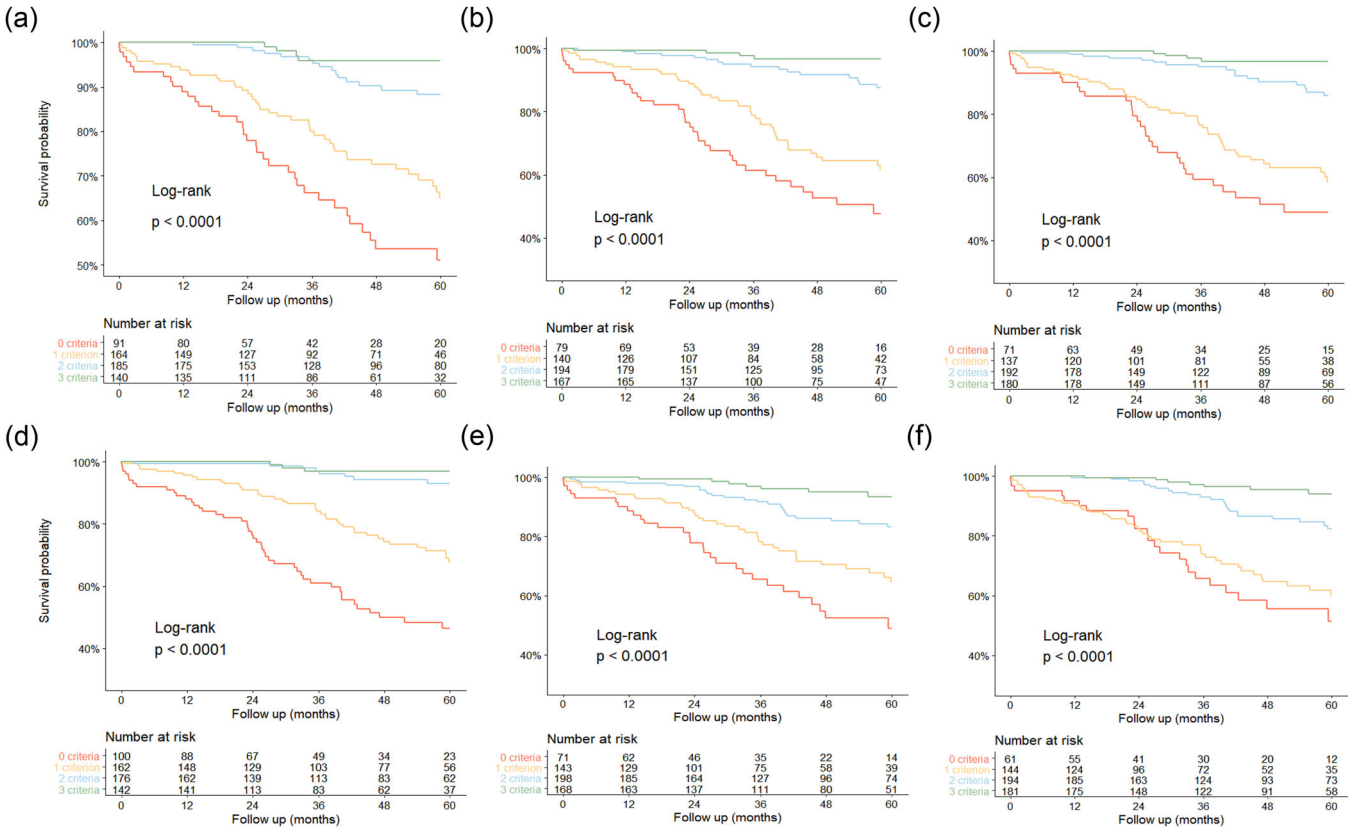

FIGURE 3 Comparison of Kaplan–Meier survival curves according to the number of noninvasive low-risk criteria met at follow-up. (a) Defined by the original three noninvasive low-risk criteria in the French Registry approach (i.e., WHO FC I/II, 6MWD > 440 m, and NT-proBNP <300 ng/L). (b) Defined by the presence of the following low-risk criteria: (1) WHO FC I/II; (2) peak $VO_2 \geq 44$ %predicted; and (3) TAPSE ≥ 17 mm. (c) Defined by the presence of the following low-risk criteria: (1) WHO FC I/II; (2) peak $VO_2 \geq 44$ %predicted; and (3) TAPSE/PASP > 0.17 mm/mmHg. (d) Defined by the presence of the following low-risk criteria: 1) WHO FC I/II; 2) NT-proBNP <300 ng/L; and (3) peak $VO_2 \geq 44$ %predicted; (e) defined by the presence of the following low-risk criteria: 1) WHO FC I/II; (2) 6MWD > 440 m; and (3) TAPSE ≥ 17 mm; (f) defined by the presence of the following low-risk criteria: (1) WHO FC I/II; (2) 6MWD > 440 m; and (3) TAPSE/PASP > 0.17 mm/mmHg. 6MWD, 6-min walking distance; NT-proBNP, N-terminal pro-b-type natriuretic peptide; PASP, pulmonary arterial systolic pressure; TAPSE, tricuspid annular plane systolic excursion; VO_2, oxygen consumption; WHO FC, World Health Organization functional class.

defined a lower cutoff value (12 mm for TAPSE and 0.12 mm/mmHg for TAPSE/PASP) to identify patients with worse survival, which requires further validation for its applicability in another independent cohort.

There are several limitations to be acknowledged. First, the main limitation is associated with the registry-based observational study design, with common missing data. As the current study focused on exploring the prognostic value of noninvasive measurements, only patients who underwent comprehensive evaluations both at baseline and at follow-up were enrolled. Nevertheless, when comparing included ($n = 580$) and excluded ($n = 170$) patients, their characteristics were comparable, indicating unlikely selection bias (Supporting Information: Table S4). Also, the reason why the current study tried several combinations of noninvasive variables was to help the utilization of risk assessment in more clinical scenarios, with better-investigated cutoff values and more circumstances of missing data, which could be more practical in real-world settings. Second, the present study only explored the incremental value in addition to the French noninvasive risk prediction strategy, how those variables could be better corporated with other risk assessment methods with optimally weighted scores needs to be further explored. Third, during the relatively long enrollment period, progress in the diagnosis and treatment of PAH, to some extent, could influence the interpretation of our data. PAH treatment strategies have been more aggressive since the 2015 ESC/ERS guidelines for pulmonary hypertension were released, where the importance of initial combination therapy was addressed.[2] Thus, although the patients enrolled in the registry were treated in accordance with contemporaneous guidelines, the combination rate, especially the

initial combination rate (29.8%), was relatively low in the current cohort, with more patients tending to receive sequential treatments.[2,22] In addition, the lack of accessibility to some PAH-targeted drugs, high costs, poor economic status, and inadequate coverage by the medical insurance system could also be alternative reasons for the low combination rate, which could be common clinical scenarios in developing countries.

CONCLUSIONS

Peak VO_2, TAPSE, and TAPSE/PASP are significant prognostic predictors for survival in PAH. Incorporating the newly derived noninvasive low-risk criteria of a peak $VO_2 \geq 44$ %predicted, a TAPSE ≥ 17 mm, or a TAPSE/PASP > 0.17 mm/mmHg with the French noninvasive risk prediction approach can provide incremental prognostic value for predicting survival, especially when utilized at follow-up reevaluations. For better risk prediction, WHO FC, at least one measurement of exercise capacity and one measurement of RV function should be considered.

AUTHOR CONTRIBUTIONS

Contributing to the conception and design: Ruilin Quan, Qing Gu, and Jianguo He. *Patient enrollment and data collection*: Ruilin Quan, Xiaoxi Chen, Tao Yang, Wen Li, Yuling Qian, and Yangyi Lin. *Data analysis and interpretation*: Ruilin Quan, Xiaoxi Chen, and Guangliang Shan. *Drafting the article*: Ruilin Quan. *Revising the article*: Ruilin Quan, Xiaoxi Chen, Qing Gu, and Jianguo He. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

The study protocol, which was approved by the Institutional Review Board (IRB) of Fuwai Hospital (Approval No. 2009-208). Written informed consent was obtained from all enrolled patients.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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