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ORIGINAL RESEARCH

Prognostic Role of Pulmonary Function in Patients With Heart Failure With Reduced Ejection Fraction

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BACKGROUND: Both ventilatory abnormalities and pulmonary hypertension (PH) are frequently observed in patients with heart failure with reduced ejection fraction. We aim to investigate the association between ventilatory abnormalities and PH in heart failure with reduced ejection fraction, as well as their prognostic impacts.

METHODS AND RESULTS: A total of 440 ambulatory patients (age, 66.2±15.8 years; 77% men) with left ventricular ejection fraction ≤40% who underwent comprehensive echocardiography and spirometry were enrolled. Total lung capacity, forced vital capacity, and forced expiratory volume in the first second were obtained. Pulmonary arterial systolic pressure was estimated. PH was defined as a pulmonary arterial systolic pressure of >50 mm Hg. The primary end point was all-cause mortality at 5 years. Patients with PH had significantly reduced total lung capacity, forced vital capacity, and forced expiratory volume in the first second. During a median follow-up of 25.9 months, there were 111 deaths. After accounting for age, sex, body mass index, renal function, smoking, left ventricular ejection fraction, and functional capacity, total lung capacity (hazard ratio [HR] per 1 SD, 0.66; 95% CI per 1 SD, 0.46–0.96), forced vital capacity (HR per 1 SD, 0.64; 95% CI per 1 SD, 0.48–0.84), and forced expiratory volume in the first second (HR per 1 SD, 0.72; 95% CI per 1 SD, 0.53–0.98) were all significantly correlated with mortality in patients without PH. Kaplan-Meier curve demonstrated impaired pulmonary function, defined as forced expiratory volume in the first second ≤58% of predicted or forced vital capacity ≤65% of predicted, was associated with higher mortality in patients without PH (HR, 2.85; 95% CI, 1.66–4.89), but not in patients with PH (HR, 1.05; 95% CI, 0.61–1.82).

CONCLUSIONS: Ventilatory abnormality was more prevalent in patients with heart failure with reduced ejection fraction with PH than those without. However, such ventilatory defects were related to long-term survival only in patients without PH, regardless of their functional status.

Key Words: heart failure with reduced ejection fraction ■ pulmonary function test ■ pulmonary hypertension ■ risk stratification

Heart failure with reduced ejection fraction (HFrEF) is a disabling syndrome that causes functional decline and impaired quality of life.[1] It is believed that dilated left ventricle and elevated left ventricular (LV) end-diastolic pressure in heart failure (HF) may further jeopardize the normal ventilation,[2] and the cardiopulmonary interaction has been widely reported.[3] Even in healthy subjects, the rapid infusion of saline is associated with the reductions in total lung capacity (TLC) and forced vital capacity (FVC), and diuresis may reverse the changes.[4,5] Although the ventilatory capacity is reduced as a function of disease severity in HFrEF, the impaired pulmonary function has been independently related to mortality among patients with HF.[6–10]

The elevated LV filling pressure not only leads to ventilatory abnormalities, the backward pressure transmission also causes pulmonary hypertension (PH). In HFrEF, the prevalence of PH is about 40% to 75%, and the associated mortality is twice that of isolated LV

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CLINICAL PERSPECTIVE

What Is New?

- Ventilatory abnormalities are more prevalent in patients with heart failure with reduced ejection fraction and pulmonary hypertension (PH) than those without PH.
- Pulmonary function has a prognostic value for long-term outcomes in patients without PH, but not in patients with PH, regardless of the functional status.

What Are the Clinical Implications?

- The presence of PH interacts with pulmonary function results and renders spirometric indexes ineffective to provide prognostic information for long-term outcomes in patients with heart failure with reduced ejection fraction.
- Despite the fact that static spirometric measurement fails to be associated with long-term outcomes in the presence of PH, whether exercise capacity is a more reliable prognostic factor requires more investigation.

Nonstandard Abbreviations and Acronyms

HFrEF	heart failure with reduced ejection fraction
NYHA	New York Heart Association
PASP	pulmonary arterial systolic pressure
PH	pulmonary hypertension

dysfunction.[11–13] Although it has been reported that the presence of PH may also affect the pulmonary function,[14,15] the correlation between ventilatory abnormalities and the presence of PH attributable to left heart disease has yet been well studied. Therefore, we aim to investigate whether the ventilatory abnormalities in patients with HFrEF are affected by the presence of PH, and whether the prognostic significance of pulmonary function indexes differs in patients with HFrEF with or without PH.

METHODS

Study Population

The study population was drawn from an administrative registry to INvestigate HeArt and Lung intERaction (INHALER registry) at a tertiary medical center in Taiwan.[16] Ambulatory outpatients with exertional dyspnea were prospectively recruited from August 2005 to December 2012. All the participants are required to complete both echocardiography and pulmonary function test within a month. Subjects with stable HF symptoms and an LV ejection fraction of ≤40% were eligible for the study. Patients with severe hepatic disease, hematopoietic diseases, active malignancy, or asthma were excluded. Data of demographic characteristics, body mass index, smoking status, functional capacity, assessed by New York Heart Association (NYHA) functional classification, comorbidities, hemogram, and biochemistry were prospectively input to a web-based medical recording system. Estimated glomerular filtration rate was calculated using the Chinese Modification of Diet in Renal Disease equation.[17] Medications, including renin-angiotensin system inhibitors, β-blockers, mineralocorticoid receptor antagonists, bronchodilators, such as inhaled long-acting β agonists, long-acting muscarinic antagonists, steroids, and theophylline, were recorded. The investigation conformed to the principles outlined in the Declaration of Helsinki. The institutional review committee of Taipei Veterans General Hospital approved the use of the registry data for research purposes and waived the requirement for informed consent. Data supporting the findings of this study are available from the corresponding author on reasonable request.

Study Protocol

Echocardiography

The transthoracic echocardiographic study was conducted according to the recommendations from the American Society of Echocardiography.[18] Left atrial dimension was measured by M-mode. LV ejection fraction was calculated from the LV end-diastolic volume and end-systolic volume estimates by biplane Simpson method. *E/A* ratio represented the ratio of LV early (*E*) to late (*A*) filling flow velocity at diastole. *E/e'* was the ratio of early ventricular filling flow velocity (*E*) to septal mitral annulus tissue velocity (*e'*) at early diastole. Pulmonary artery systolic pressure (PASP) was estimated using Doppler echocardiography by calculating transtricuspid pressure gradient during systole and right atrial pressure by the dimension and collapsibility of inferior vena cava. To specify the patients with high echocardiographic probability of PH, we used the criteria of peak tricuspid regurgitation velocity of 3.4 m/s as the cutoff value, according to the published guideline.[19] PASP of 50 mm Hg (=46.2 mm Hg, approximated by the modified Bernoulli equation, plus the least estimated right atrial pressure of 3 mm Hg) was therefore used to dichotomize the study population into with PH or not.

Pulmonary Function Tests

Pulmonary function test was performed using spirometry (CPFS/D USB; Medical Graphics, St Paul,

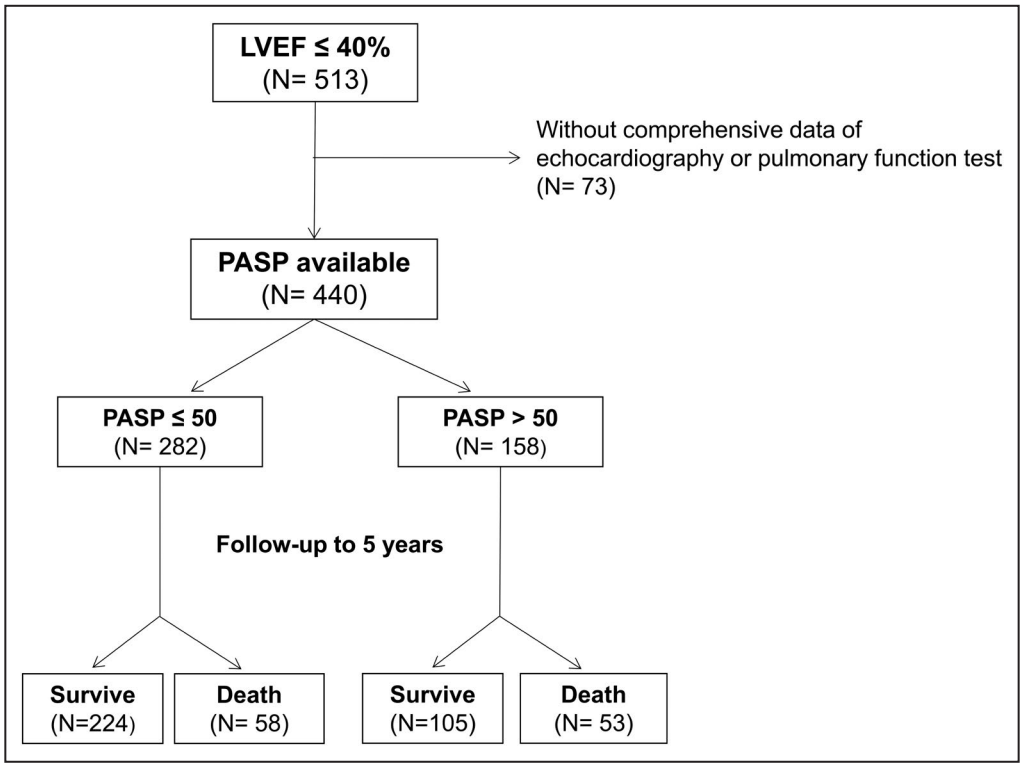

Figure 1. Flowchart of the study population and analysis.
LVEF indicates left ventricular ejection fraction; and PASP, pulmonary arterial systolic pressure.

MN) and body plethysmograph (MasterScreen Body Plethysmograph; Erich Jaeger GmbH, Würzburg, Germany), according to the American Thoracic Society standards.[20] After a 5-minute rest in a seated position, spirometric parameters were measured in all ambulatory subjects without any respiratory distress. The predicted values were calculated using validated spirometric prediction equations,[21,22] and TLC, FVC, and forced expiratory volume in the first second (FEV1) were presented as the percentage of their relevant predicted values. The ventilatory abnormalities were further categorized into 4 types: obstructive type was defined as FEV1/FVC <70% and FVC ≥80% of the predicted value; restrictive type was defined as FEV1/FVC ≥70% and FVC <80% of the predicted value; mixed type was defined as FEV1/FVC <70% and FVC <80% of the predicted value; and normal.[20]

Outcome Measures

All study participants were followed up for up to 5 years. Clinical outcomes and mortality were acquired by linking the database to the National Death Registry. The National Death Registry database registers valid information according to the *International Classification of Diseases, Ninth Revision* (*ICD-9*). The *ICD-9* codes for cardiovascular deaths ranged from 390 to 459.

Statistical Analysis

Baseline characteristics were described as mean±SD for continuous variables and percentages for categorical variables. The Student *t* test was used to compare continuous variables, whereas the χ^2 test was used to compare categorical variables. Linear regression analysis was used to evaluate the determinants of the pulmonary function indexes. Cox proportional hazards models were used to evaluate the independence of spirometric variables in the association with long-term mortality, with further adjustment for the putative confounders by backwards selection in the multivariable analyses. For the optimal cutoff value for increased risk of all-cause mortality, we performed receiver-operating characteristic curve analysis and determined the cutoff value with a maximal Youden index. Kaplan-Meier survival curve was used to assess the prognostic significance of the independent pulmonary function indexes. The median time to event was estimated in the subpopulations, who had a mortality rate of ≥0.5 during the follow-up period. All statistical analyses were performed using SPSS version 24.0 (SPSS Incorporation, Chicago, IL) and MedCalc Version 19.0.4 (MedCalc Software, Ostend, Belgium). All tests were 2-sided, and $P<0.05$ was considered statistically significant.

Table 1. Baseline Characteristics of the Study Population

Variables	PASP ≤50 mm Hg (N=282)	PASP >50 mm Hg (N=158)	*P* value
Age, y	66.1±16.2	66.5±15.0	0.770
Men, n (%)	219 (78.2)	120 (76.9)	0.756
BMI, kg/m^2	24.3±5.0	23.9±4.1	0.372
Ever smoker, n (%)	113 (40.1)	51 (32.3)	0.105
Pack years*	38.6±29.1	38.3±36.9	0.957
NYHA class III/IV, n (%)	133 (47.2)	96 (60.8)	0.006
Comorbidities, n (%)			
Hypertension	124 (44)	73 (46.2)	0.652
Diabetes	82 (29.1)	51 (32.3)	0.483
Coronary artery disease	149 (52.8)	89 (56.3)	0.481
Atrial fibrillation	21 (7.4)	16 (10.1)	0.331
Stroke	18 (5.7)	10 (6.3)	0.780
COPD	77 (27.3)	44 (27.8)	0.903
Prescribed medications, n (%)			
RAS inhibitors	189 (67.0)	103 (65.2)	0.696
β-Blockers	132 (46.8)	66 (41.8)	0.308
MRAs	124 (44.0)	65 (41.1)	0.565
Inhaled bronchodilators	21 (7.4)	6 (3.8)	0.126
Inhaled or systemic steroids	10 (3.5)	6 (3.8)	0.893
Theophylline	29 (10.3)	16 (10.1)	0.958
Laboratory data			
Hemoglobin, g/dL	12.9±2.2	12.4±2.3	0.015
eGFR, mL/min per 1.73 m^2	67.8±30.6	61.1±31.7	0.034
Cholesterol, mg/dL	161.1±36.6	152.1±37.9	0.024
Uric acid, mg/dL	7.6±2.7	8.3±2.7	0.020
Echocardiography			
LA diameter, mm	43.2±9.1	48.4±9.5	<0.001
LVEDV, mL	120.3±62.8	133.8±61.2	0.153
LVEF, %	30.4±7.4	29.0±8.1	0.073
E/A	1.2±0.9	1.9±0.8	<0.001
E/e′	17.0±7.5	24.3±10.8	<0.001
Pulmonary function test			
TLC, % predicted	83.8±18.7	78.3±17.5	0.007
FVC, % predicted	70.5±21.8	62.6±18.5	<0.001
FEV1, % predicted	72.4±23.2	63.9±19.9	<0.001
FEV1/FVC, %	75.3±4.7	75.5±4.3	0.621
Types of ventilatory abnormalities, n (%)			0.004
Obstructive type	29 (10.3)	15 (9.5)	
Restrictive type	142 (50.4)	96 (60.8)	
Mixed type	37 (13.1)	28 (17.7)	
Normal type	74 (26.2)	19 (12.0)	

Data are given as mean±SD, unless otherwise indicated. The Student *t* test was used to compare continuous variables, whereas the χ^2 test was used to compare categorical variables. A indicates late diastolic transmitral inflow velocity; BMI, body mass index; COPD, chronic obstructive pulmonary disease; E, early diastolic transmitral inflow velocity; e', early diastolic mitral annular velocity; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; LA, left atrial; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PASP, pulmonary arterial systolic pressure; RAS, renin-angiotensin system; and TLC, total lung capacity.

*Among ever smokers.

Table 2. Linear Regression Analysis on the Determinants of Pulmonary Function Indexes

Variables	TLC				FVC				FEV1			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	β*	*P* value†	β*	*P* value†	β*	*P* value†	β*	*P* value†	β*	*P* value†	β*	*P* value†
Age	−0.062	0.242	−0.106	0.140	−0.131	0.006	−0.205	0.001	−0.004	0.927	−0.014	0.823
Sex	−0.041	0.447	−0.156	0.032	0.134	0.005	0.118	0.060	0.177	<0.001	0.165	0.009
Smoking	0.028	0.599	0.103	0.181	0.036	0.446	0.064	0.343	0.016	0.732	0.021	0.761
BMI	−0.017	0.766	−0.135	0.063	0.003	0.958	−0.107	0.091	−0.032	0.530	−0.105	0.097
NYHA III/IV	−0.175	0.001	−0.168	0.021	−0.141	0.003	−0.131	0.04	−0.159	0.001	−0.143	0.026
LVEF	0.057	0.457	−0.055	0.466	0.089	0.196	−0.051	0.433	0.123	0.074	−0.023	0.730
E/e'	−0.112	0.035	−0.063	0.388	−0.299	<0.001	−0.146	0.02	−0.265	<0.001	−0.119	0.061
PASP	−0.160	0.003	−0.115	0.111	−0.203	<0.001	−0.184	0.004	−0.225	<0.001	−0.194	0.003

BMI indicates body mass index; E, early diastolic transmitral inflow velocity; e', early diastolic mitral annular velocity; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PASP, pulmonary arterial systolic pressure; and TLC, total lung capacity.

*Standardized β coefficient.

†Univariate and multivariate linear regression analyses were conducted.

RESULTS

Baseline Characteristics

A total of 440 patients (age, 66.2±15.8 years; 77% men) were included in the analysis. Among them, 282 (64.1%) patients had PASP ≤50 mm Hg, whereas 158 (35.9%) patients had PH (Figure 1).

The baseline characteristics of the study population are shown in Table 1. Patients with PH had more NYHA class III/IV, lower levels of hemoglobin, estimated glomerular filtration rate, and cholesterol, and higher level of uric acid than those without PH. The body mass index, smoking status, and the presence of comorbidities were similar between both groups, as were the prescribed medications. Comparing with those without PH, patients with PH had significantly enlarged left atrium, increased mitral inflow E/A ratio, and increased E/e' ratio. For the pulmonary function indexes, TLC (PH versus non-PH: 78.3%±17.5% of the predicted versus 83.8%±18.7% of the predicted; *P*=0.007), FVC (62.6%±18.5% versus 70.5%±21.8%; *P*<0.001), and FEV1 (63.9%±19.9% versus 72.4±23.2%; *P*<0.001) were all significantly lower in patients with PH than those without PH. On the contrary, FEV1/FVC were about the same between the 2 groups (PH versus non-PH: 75.5%±4.3% versus 75.3%±4.7%; *P*=0.621). Although normal ventilatory function was found more in patients without PH (26.2% versus 12% in PH), the restrictive ventilatory abnormality was more prevalent in patients with PH (60.8% versus 50.4% in non-PH).

In univariate linear regression analyses, PASP was significantly associated with FEV1 (standardized β=−0.160; *P*=0.003), FVC (standardized β=−0.203; *P*<0.001), and TLC (standardized β=−0.225; *P*<0.001) (Table 2). After adjusting for age, sex, smoking status,

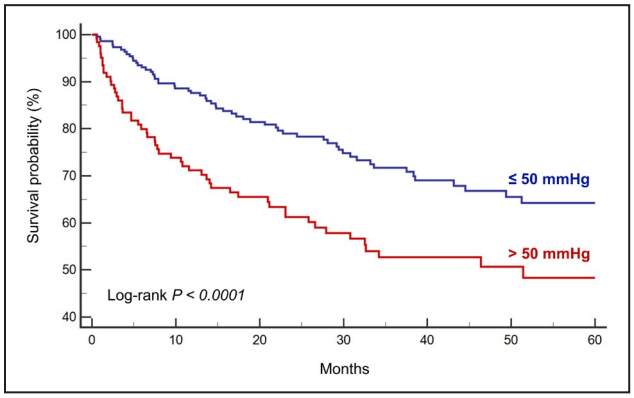

Figure 2. Kaplan-Meier survival curves for the 5-year all-cause mortality in patients with heart failure with reduced ejection fraction, stratified by the presence of pulmonary hypertension.

The red line indicates patients with PASP > 50 mmHg, whereas the blue line indicates patients with PASP ≤ 50 mmHg. PASP indicates pulmonary arterial systolic pressure.

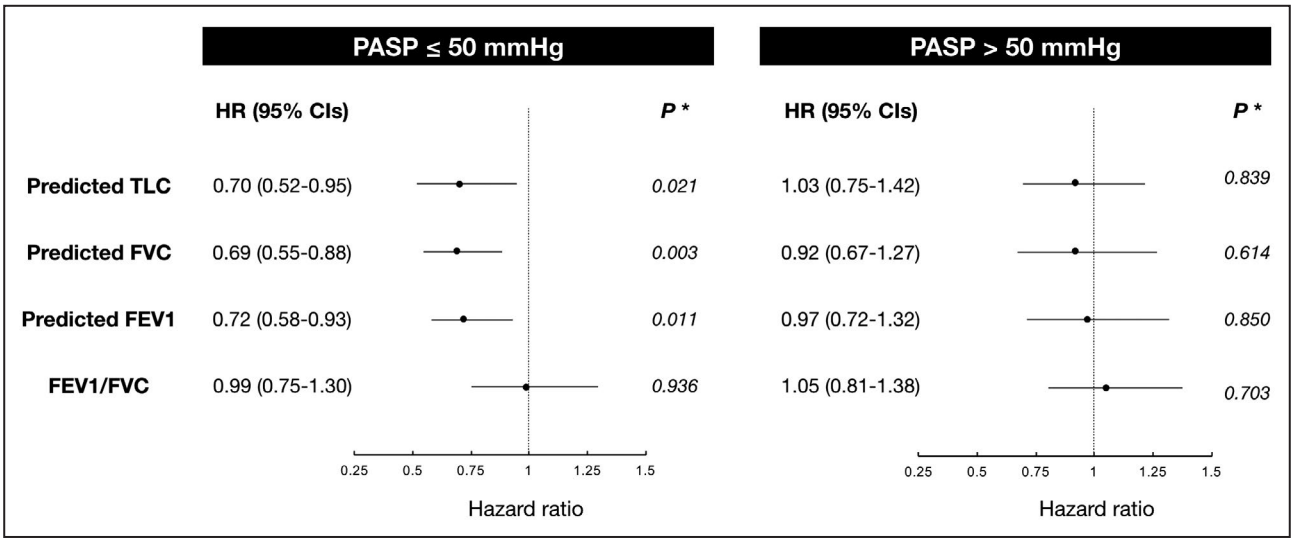

Figure 3. Hazard ratios (HRs) and 95% CIs per 1-SD change of the pulmonary function indexes for the 5-year all-cause mortality.
FEV1 indicates forced expiratory volume in the first second; FVC, forced vital capacity; PASP, pulmonary arterial systolic pressure; and TLC, total lung capacity. **P* value derived from Cox regression analysis.

body mass index, NYHA class, LV ejection fraction, and E/e' ratio, PASP remained significantly associated with FVC (standardized β=−0.184; *P*=0.004) and FEV1 (standardized β=−0.194; *P*=0.003).

Survival Analysis

During a median follow-up duration of 25.9 months, there were a total of 111 (25.2%) deaths. The Kaplan-Meier survival curve analysis clearly demonstrated patients with PH (53 deaths [33.5%]) were associated with higher risks of mortality than those without (58 deaths [20.6%]) (Figure 2). Among them, 34 deaths (64.2%) in patients with PH and 32 deaths (55.2%) in patients without PH could be attributed to cardiovascular causes. In the subjects with PASP ≤50 mm Hg, TLC (hazard ratio [HR] per 1 SD, 0.70; 95% CI per 1 SD, 0.52–0.95), FVC (HR per 1 SD, 0.69; 95% CI per 1 SD, 0.55–0.88), and FEV1 (HR per 1 SD, 0.72; 95% CI per 1 SD, 0.58–0.93) were all significantly correlated with long-term survival in the univariate analysis (Figure 3 and Table S1). However, none of the above spirometric variables was associated with the outcomes in patients with PH (Figure 3). After accounting for age, sex, body mass index, estimated glomerular filtration rate, smoking status, LV ejection fraction, and NYHA class, TLC (HR per 1 SD, 0.66; 95% CI, per 1 SD, 0.46–0.96), FVC (HR per 1 SD, 0.64; 95% CI per 1 SD, 0.48–0.84), and FEV1 (HR per 1 SD, 0.72; 95% CI per 1 SD, 0.53–0.98) remained independently correlated with the long-term mortality in patients without PH (Table 3).

The optimal cutoff values derived from the receiver-operating characteristic curve analysis for the prediction of mortality among subjects without PH were 70% for predicted TLC, 65% for predicted FVC, and 58% for predicted FEV1. The Kaplan-Meier survival curves clearly demonstrated patients with low TLC (HR per 1 SD, 3.54; 95% CI per 1 SD, 1.60–7.81; log-rank *P*=0.002), low FVC (HR per 1 SD, 2.47; 95% CI per 1 SD, 1.42–4.29; log-rank *P*=0.001), or low FEV1 (HR per 1 SD, 2.77; 95% CI per 1 SD, 1.50–5.09; log-rank *P*=0.001) would have higher long-term mortality than their counterparts (Figure 4 and Table 4). When we further stratified the patients by the presence of impaired pulmonary function, defined as either FVC ≤65% or FEV1 ≤58%, the presence of impaired pulmonary function was associated with

Table 3. Multivariable Cox Regression Analysis for the Prognostic Association of the Pulmonary Function Indexes with 5-Year All-Cause Mortality in Patients With HFrEF and PASP ≤50 mm Hg

Variables	HR (95% CI)	*P* value*
TLC, % predicted (1 SD=18.5%)	0.66 (0.46–0.96)	0.027
FVC, % predicted (1 SD=21%)	0.64 (0.48–0.84)	0.001
FEV1, % predicted (1 SD=22.4%)	0.72 (0.53–0.98)	0.039
FEV1/FVC, % (1 SD=12.1%)	1.018 (0.991–1.044)	0.189

FEV1 indicates forced expiratory volume in the first second; FVC, forced vital capacity; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; PASP, pulmonary arterial systolic pressure; and TLC, total lung capacity.
*Multivariable Cox regression analysis with backwards selection, adjusting for age, sex, body mass index, estimated glomerular filtration rate, smoking status, left ventricular ejection fraction, and New York Heart Association class.

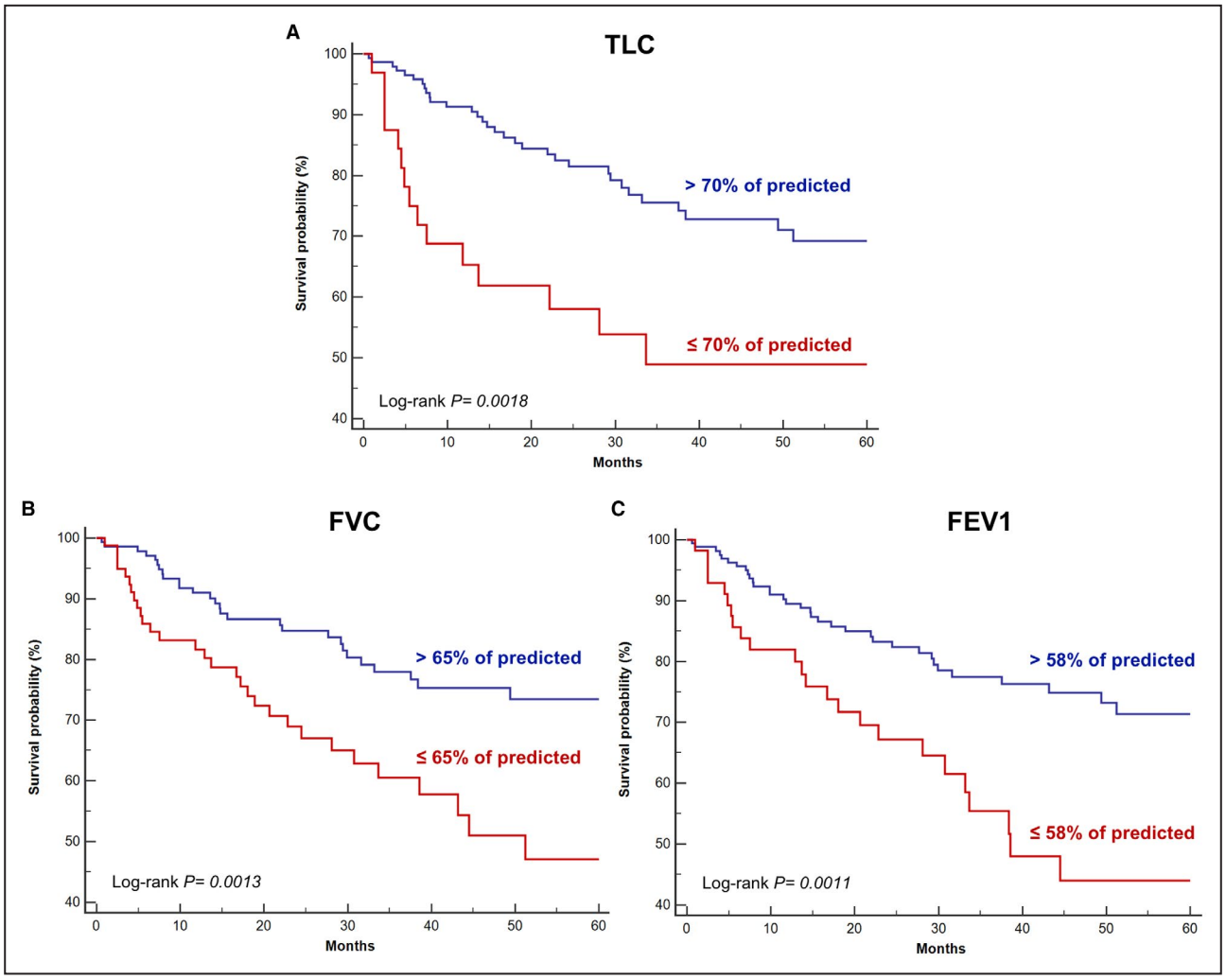

Figure 4. Kaplan-Meier survival curves for 5-year all-cause mortality in patients with heart failure with reduced ejection fraction without pulmonary hypertension (pulmonary arterial systolic pressure [PASP] ≤50 mm Hg), stratified by total lung capacity (TLC) (A), forced vital capacity (FVC) (B), and forced expiratory volume in the first second (FEV1) (C).
(**A**) The red line indicates patients with TLC ≤ 70% of predicted, and the blue line indicates patients with TLC > 70% of predicted; (**B**) red line indicates patients with FVC ≤ 65% of predicted, and the blue line indicates patients with FVC > 65% of predicted; (**C**) red line indicates patients with FEV1 ≤ 58% of predicted, and the blue line indicates patients with FEV1 > 58% of predicted.

the worse long-term survival in patients without PH (HR, 2.85; 95% CI, 1.66–4.89; log-rank *P*<0.001), but not in patients with PH (HR, 1.05; 95% CI, 0.61–1.82; log-rank *P*=0.859) (Figure 5 and Table 4). Impaired pulmonary function was significantly associated with long-term mortality among patients without PH, regardless of their functional status (NYHA class I/II: HR, 3.75; 95% CI, 1.46–9.65; log-rank *P*=0.006; NYHA class III/IV: HR, 2.11; 95% CI, 1.10–4.06; log-rank *P*=0.026) (Figure 6A and Table 5). However, if PH presented, pulmonary function indexes were not related to the survival in patients with preserved functional capacity (NYHA class I/II) or in patients with limited functional capacity (NYHA class III/IV) (Figure 6B and Table 5).

DISCUSSION

The present study has demonstrated that PH and impaired ventilation prevailed in patients with HFrEF, whereas 35.9% of the study population had a PASP of >50 mm Hg, and 88% of them had restrictive, obstructive, or mixed ventilatory defects. Subjects with PH had further deteriorated pulmonary functions, indexed by TLC, FVC, and FEV1, as well as higher long-term mortality compared with those without PH. Pulmonary function provided prognostic information for long-term survival in patients without PH, but not in patients with PH, regardless of their functional capacity. The study suggested that spirometric variables could be sensitive markers to reflect the

Table 4. Survival Analyses in Patients With HFrEF, Stratified by the Presence of Pulmonary Function and Pulmonary Function Indexes

Variables	Categories	Mortality, %	Median time to event (95% CI), mo	Log-rank test *P* value	Hazard ratio (95% CI)
All patients					
PASP	≤50 mm Hg	20.6	…	<0.001	Reference
	>50 mm Hg	33.5	51.5 (26.6–51.5)		2.04 (1.36–3.04)
PASP ≤50 mm Hg					
TLC	>70%	17.4	…	0.002	Reference
	≤70%	35.7	33.6 (11.8–33.6)		3.54 (1.60–7.81)
FVC	>65%	15.6	…	0.001	Reference
	≤65%	29.1	51.2 (33.6–51.2)		2.47 (1.42–4.29)
FEV1	>58%	16.7	…	0.001	Reference
	≤58%	30.8	38.6 (30.8–44.5)		2.77 (1.50–5.09)
Pulmonary function*	Preserved	14.3	…	<0.001	Reference
	Impaired	29.8	44.5 (33.2–51.2)		2.85 (1.66–4.89)
PASP >50 mm Hg					
TLC	>70%	31.2	…	0.253	Reference
	≤70%	38.2	13.1 (5.5–27.9)		1.53 (0.74–3.15)
FVC	>65%	32.9	51.5 (25.9–51.5)	0.826	Reference
	≤65%	34.2	34.2 (23.1–34.2)		1.07 (0.62–1.84)
FEV1	>58%	30.9	51.5 (25.9–51.5)	0.627	Reference
	≤58%	35.0	46.4 (23.1–46.4)		1.15 (0.65–2.03)
Pulmonary function*	Preserved	32.2	34.2 (16.5–34.2)	0.859	Reference
	Impaired	35.2	51.5 (26.6–51.5)		1.05 (0.61–1.82)

FEV1 indicates forced expiratory volume in the first second; FVC, forced vital capacity; HFrEF, heart failure with reduced ejection fraction; PASP, pulmonary arterial systolic pressure; and TLC, total lung capacity.

*Impaired pulmonary function was defined as either FVC ≤65% of predicted or FEV1 ≤58% of predicted.

cardiopulmonary interaction in HF; however, the significant prognostic information could only be limited to patients without PH.

Ventilatory Abnormalities in HF

Because heart and lungs are contained within a closed thoracic cavity, they are inevitably interacted.

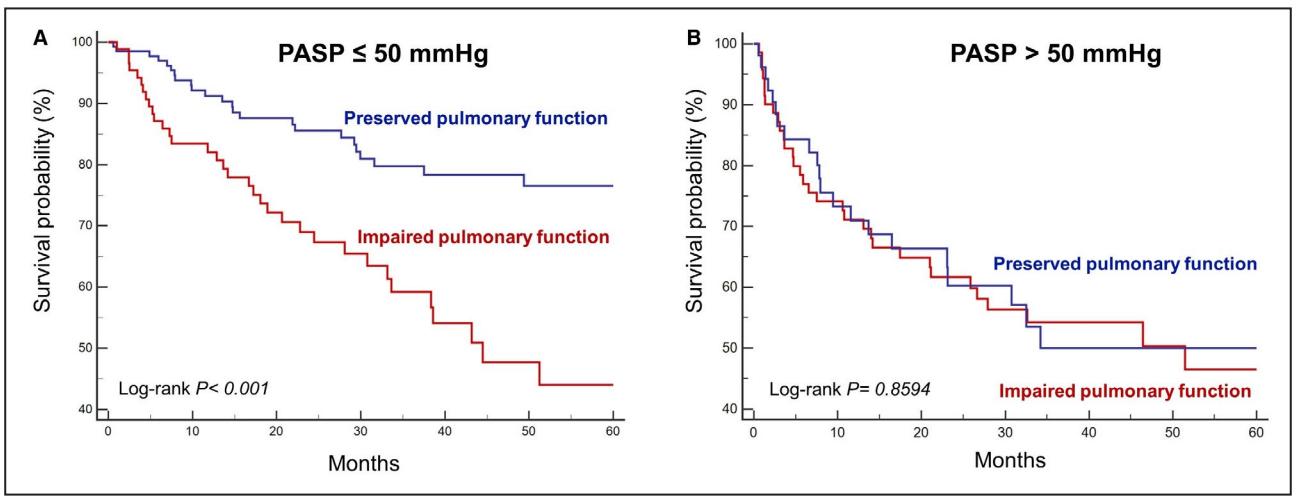

Figure 5. Kaplan-Meier survival curves for 5-year all-cause mortality in patients with heart failure with reduced ejection fraction without pulmonary hypertension (pulmonary arterial systolic pressure [PASP] ≤50 mm Hg) (A) and with pulmonary hypertension (PASP >50 mm Hg) (B), stratified by pulmonary function.

For both **A** and **B**, the red line indicates patients with impaired pulmonary function, while the blue line indicates patients with preserved pulmonary function.

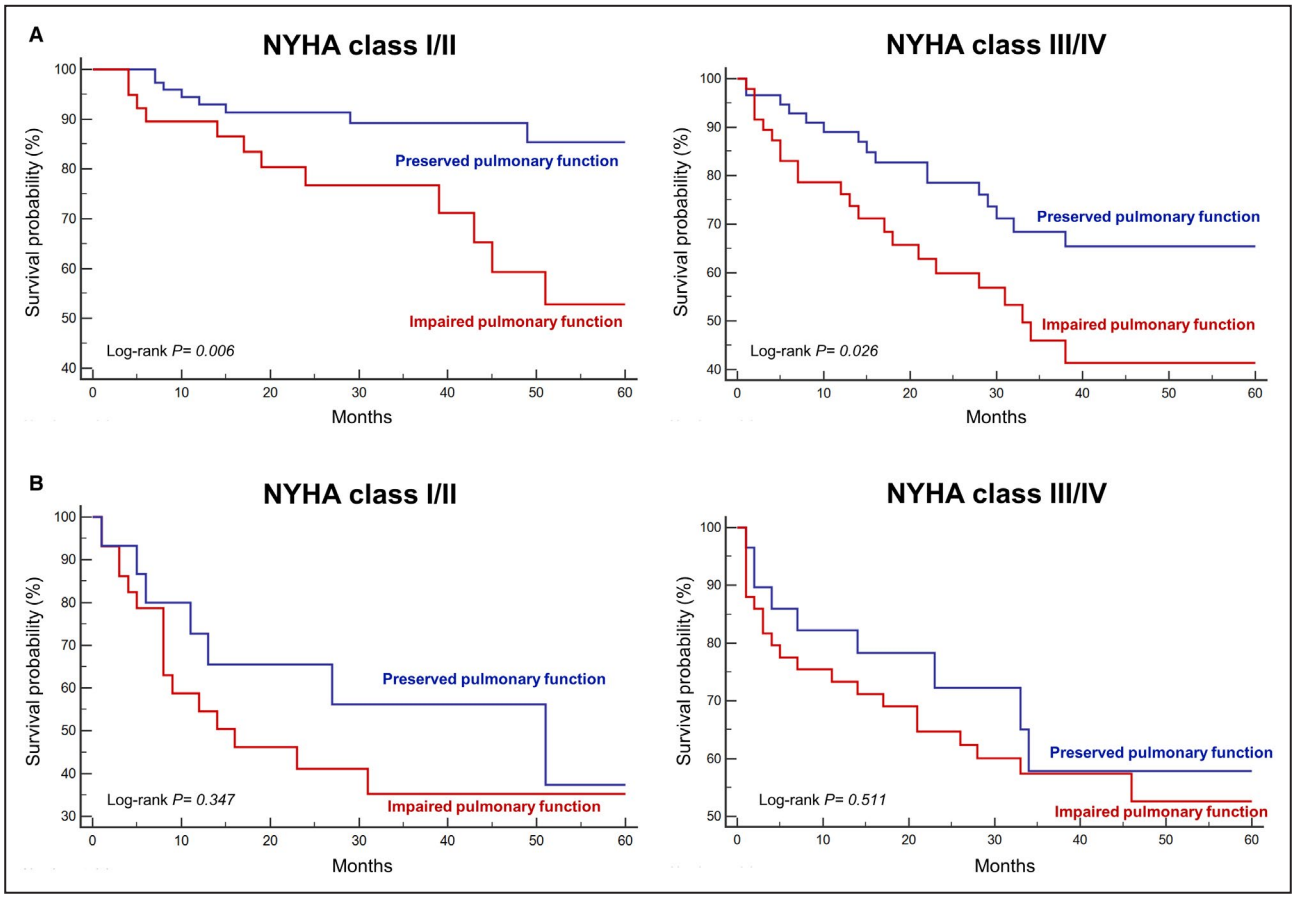

Figure 6. Kaplan-Meier survival curves for 5-year all-cause mortality in patients with heart failure with reduced ejection fraction without (A) and with (B) pulmonary hypertension, stratified by functional status and pulmonary function.
For both **A** and **B**, red lines indicate patients with impaired pulmonary function, while the blue lines indicate patients with preserved pulmonary function. NYHA indicates New York Heart Association.

Ventilatory abnormalities have been previously described in patients with both acute and chronic HF, ranging from mild restrictive to mixed restrictive and obstructive patterns.[14] In a cohort of 132 patients with HFrEF evaluated for potential cardiac transplantation, Wright et al reported that ventilatory abnormalities

Table 5. Survival Analyses in Patients With HFrEF, Stratified by the Presence of Pulmonary Hypertension and Functional Status

Variables	Categories	Mortality, %	Median time to event (95% CI), mo	Log-rank test *P* value	Hazard ratio (95% CI)
PASP ≤50 mm Hg, NYHA class I/II					
Pulmonary function*	Preserved	8.1	…	0.006	Reference
	Impaired	24	…		3.75 (1.46–9.65)
PASP ≤50 mm Hg, NYHA class III/IV					
Pulmonary function*	Preserved	23.2	…	0.026	Reference
	Impaired	34.4	33.2 (22.6–43.7)		2.11 (1.10–4.06)
PASP >50 mm Hg, NYHA class I/II					
Pulmonary function*	Preserved	26.9	51.5 (5.0–97.9)	0.347	Reference
	Impaired	44.4	16.5 (1.4–31.6)		1.49 (0.64–3.49)
PASP >50 mm Hg, NYHA class III/IV					
Pulmonary function*	Preserved	25.7	…	0.511	Reference
	Impaired	34.4	…		1.30 (0.61–2.77)

HFrEF indicates heart failure with reduced ejection fraction; NYHA, New York Heart Association; and PASP, pulmonary arterial systolic pressure.
*Impaired pulmonary function was defined as either forced vital capacity ≤65% of predicted or forced expiratory volume in the first second ≤58% of predicted.

occurred in up to around 80% of the patients, with majority of restrictive pattern.[23] The extent of restrictive defect was prominently associated with the severity of pulmonary congestion as assessed by either radiographs or cardiopulmonary exercise test, which could be reversed by either fluid reduction therapies or heart transplantation.[7,24–27] Melenovsky et al compared wet lung with dry lung mechanics in patients with chronic HF, showing that wet lung was associated with 25% lower lung compliance, 23% to 35% higher pulmonary vascular resistance, and higher PSAP.[28] Even in euvolemic conditions, patients with HFrEF may present a 20% reduction in both FVC and FEV1, compared with the matched controls.[29] The present study has shown similar prevalence as previous findings that 88% of the study population had abnormal pulmonary functions, with majority of restrictive impairment in patients with HFrEF.

Association Between PH and Ventilatory Defects

In addition to ventilatory defects, PH is also frequently observed among patients with HFrEF, and it is closely related to limited exercise capacity and worse prognosis.[30] Butler et al reported that the reduced peak exercise oxygen consumption and cardiac output response to exercise were paralleling to the severity of PH in 320 patients with HFrEF.[31] However, the interaction between PH and ventilatory impairment has not been explored. To the best of our knowledge, our study is the first to show that patients with PH have further reduced FVC and FEV1, coupled with more restrictive defects but similar FEV1/FVC compared with those without PH. Despite the fact that patients with pulmonary function defects were more functionally limited (NYHA class III/IV; pulmonary function impaired versus preserved, 62.2% versus 43.5%; $P<0.001$), the presence of PH could further impair pulmonary function independent of their functional status (Table S2). As the extent of ventilatory defects is proportionate to the levels of E/e' and PASP, our data suggest that the levels of PASP may reflect the scale of the transmitted left-sided pressure on pulmonary vasculature that may also affect the airway physiology in the meanwhile. The cardiopulmonary interaction underlying HFrEF thus can be manifested as a continuum of elevated pulmonary venous pressure, ventilatory impairment, and the development of PH.[15]

Prognostic Impacts of Pulmonary Functions on HFrEF

The prognostic value of ventilatory abnormalities has been proposed to add incremental prognostic information beyond the known risk factors in patients with HF, irrespective of acute or chronic presentations. Iversen et al reported that every 10% decline of FEV1 added 16% higher risk of mortality in 532 patients admitted for decompensated HF.[9] Olson et al also observed that the lower resting FVC, FEV1, and diffusion capacity of the lung for carbon monoxide were all associated with less event-free survival in 134 patients with stable HFrEF.[10] Previous cohort studies have reported restrictive spirometric pattern, or preserved ratio impaired spirometry, a significant risk of mortality among general populations.[32–34] The present study may have further extended the prognostic significance of impaired spirometry in subjects with less advanced stage of HFrEF.

Our study has shown that ventilatory indexes were associated with mortality in early but not in late stage of HFrEF.[35] PH was found to interact with the prognostic role of pulmonary function in long-term outcomes in patients with HFrEF, regardless of the functional status. For patients with severe HF and concomitant PH, Ingle et al have reported the lower contribution of spirometric variables to the exercise capacity,[36] as well as insufficient power to predict long-term outcomes. Exercise capacity perhaps would be a more reliable prognostic factor than static spirometric measurement, especially in patients with advanced HF or PH, and this might explain why pulmonary function by spirometry in our study failed to be associated with outcomes in patients with concomitant PH.

Study Limitations

There were several study limitations. First, the study was limited by its single-center setting and the retrospective analysis. Although we had adjusted for all the available confounders, other unobserved variables influencing pulmonary function results can still be present. Second, the presence of PH was estimated from echocardiography, but rather catheter-based measurements. Although we used the cutoff value of 50 mm Hg to avoid misclassification of the borderline cases into the group of PH, right heart catheterization remains the gold standard for the diagnosis of PH. Considering right heart catheterization may not make differences on the pharmacological therapy of HFrEF, only limited patients with clinical indications of surgery or transplantation have received such invasive hemodynamic study.[37] Third, given that chronic obstructive pulmonary disease frequently coexists in patients with HF, the presence of chronic obstructive pulmonary disease may complicate the pulmonary function results and lead to poor prognosis. The prevalence of chronic obstructive pulmonary disease was 27.5% in our study, which was similar to the previous reports.[38] Although a comprehensive survey for all kinds of pulmonary diseases was not routinely

applied to every study participant, some types of lung diseases could be underdiagnosed. Although the present study showed that chronic obstructive pulmonary disease was not related to long-term survival in HFrEF, the results clearly demonstrated that the presence of PH, by either advanced heart disease or pulmonary diseases, has rendered spirometric indexes ineffective to provide significant prognostic information in patients with HFrEF. Fourth, the spirometries were conducted without prior bronchodilators. Although the measures of spirometries could be confounded by the presence of bronchospasm, all patients underwent spirometry in stable condition without any respiratory distress. In addition, diffusion capacity of the lung for carbon monoxide and alveolar volume have been proposed as independent predictors of mortality in patients with HFrEF.[39,40] However, those parameters were not routinely checked in our registry. Fifth, our study showed that cardiovascular death accounted for around 60% of mortality, which was compatible with previous reports.[41,42] Considering the poor agreement of cause-of-death coding as previously validated,[43] only all-cause mortality was used for analysis as the primary outcome in the present study. Furthermore, whether the association between the spirometric abnormalities and the presence of PH could be extrapolated to patients with HF with preserved ejection fraction warrants further investigation.

CONCLUSIONS

Patients with HFrEF and PH exhibit more deteriorated pulmonary functions, and the extent of ventilatory abnormalities is significantly correlated with the levels of pulmonary arterial pressure. Pulmonary function obtained by a simple spirometry can be regarded as a window to assess the underlying cardiopulmonary interaction and is also a sensitive prognostic indicator in patients with stable and compensated HFrEF. However, the clinical impacts of the ventilatory abnormalities on long-term survival can be only limited to patients without PH.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Univariate Cox regression analysis of the clinical and spirometric variables for five-year all-cause mortality in patients with HFrEF and PASP ≤ 50mmHg.

Variables	HR (95% CI)	*P*
Age, years	1.021 (1.004-1.039)	*0.017*
Male	3.152 (1.259-7.889)	*0.014*
BMI	0.923 (0.877-0.991)	*0.024*
Smoking	1.131 (0.668-1.916)	*0.647*
NYHA class III/IV	2.393 (1.392-4.114)	*0.002*
Hypertension	0.918 (0.545-1.549)	*0.750*
Diabetes mellitus	1.049 (0.582-1.891)	*0.873*
Coronary artery disease	0.638 (0.380-1.072)	*0.089*
Atrial fibrillation	1.170 (0.423-3.234)	*0.763*
Stroke	1.243 (0.450-3.433)	*0.675*
COPD	1.127 (0.630-1.984)	*0.680*
Hemoglobin, g/dL	0.874 (0.762-1.003)	*0.055*
eGFR, ml/min/1.73m^2	0.985 (0.975-0.994)	*0.002*

Cholesterol, mg/dL	0.996 (0.987-1.004)	*0.281*
Uric acid, mg/dL	1.085 (0.991-1.188)	*0.076*
LA diameter, mm	1.013 (0.984-1.042)	*0.380*
LVEDV, ml	1.000 (0.997-1.004)	*0.834*
LVEF, %	0.990 (0.952-1.029)	*0.598*
E/A	1.023 (0.643-1.629)	*0.923*
E/e’	0.973 (0.825-1.146)	*0.741*
TLC, % predicted	0.981 (0.965-0.997)	*0.021*
FVC, % predicted	0.983 (0.972-0.994)	*0.003*
FEV1, % predicted	0.986 (0.975-0.997)	*0.011*
FEV1/FVC, %	0.999 (0.977-1.022)	*0.936*

Abbreviations: BMI= body mass index; CI= confidence interval; COPD= chronic obstructive pulmonary disease; eGFR= estimated glomerular filtration rate; FEV1= forced expiratory volume in the first second; FVC= forced vital capacity; HR= hazard ratio; LA= left atrium; LVEDV= left ventricular end-diastolic volume; LVEF= left ventricular ejection fraction; NYHA= New York heart Association; PASP= pulmonary arterial systolic pressure; TLC= total lung capacity.

Table S2. Comparison of pulmonary function indices between patients without and with PH among different functional status.

Variables	NYHA class I/II			NYHA class III/IV		
	Without PH	**With PH**	***P***	**Without PH**	**With PH**	***P***
TLC, % predicted	86.3±16.2	83.6±15.5	*0.340*	81.6±20.6	75.1±18.0	*0.025*
FVC, % predicted	72.5±21.2	66.4±18.6	*0.005*	68.6±22.4	62.2±20.8	*0.03*
FEV1, % predicted	75.9±23.4	66.4±18.4	*0.039*	68.2±22.4	60.1±18.0	*0.004*
FEV1/FVC, %	102.8±17.1	100.7±17.5	*0.520*	103.1±17.5	101.8±16.6	*0.630*

Abbreviations: FEV1= forced expiratory volume in the first second; FVC= forced vital capacity; NYHA= New York heart Association; PH= pulmonary hypertension; TLC= total lung capacity.