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Right ventricular relative wall thickness as a predictor of outcomes and of right ventricular reverse remodeling for patients with pulmonary hypertension

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Abstract

Mid-term right ventricular (RV) reverse remodeling after treatment in patients with pulmonary hypertension (PH) is associated with long-term outcome as well as baseline RV remodeling. However, baseline factors influencing mid-term RV reverse remodeling after treatment and its prognostic capability remain unclear. We studied 54 PH patients. Mid-term RV remodeling was assessed in terms of the RV area, which was traced planimetrically at the end-systole (RVESA). RV reverse remodeling was defined as a relative decrease in the RVESA of at least 15% at 10.2 ± 9.4 months after treatment. Long-term follow-up was 5 years. Adverse events occurred in 10 patients (19%) and mid-term RV reverse remodeling after treatment was observed in 37 (69%). Patients with mid-term RV reverse remodeling had more favorable long-term outcomes than those without (log-rank: p=0.01). Multivariate logistic regression analysis showed that RV relative wall thickness (RV-RWT), as calculated as RV free-wall thickness/RV basal linear dimension at end-diastole, was an independent predictor of mid-term RV reverse remodeling (OR 1.334; 95% CI, 1.039-1.713; p=0.03). Moreover, patients with RV-RWT≥0.21 showed better long-term outcomes than did those without (log-rank p=0.03), while those with RV-RWT≥0.21 and mid-term RV reverse remodeling had the best long-term outcomes. Patients with RV-RWT<0.21 and without mid-term RV reverse remodeling, on the other hand, had worse long-term outcomes than other sub-groups. In conclusions, RV-RWT could predict mid-term RV reverse remodeling after treatment in PH patients, and was associated with long-term outcomes. Our finding may have clinical implications for better management of PH patients.

Key words; pulmonary hypertension; right ventricular function; right ventricular reverse remodeling; echocardiography

Introduction

Survival of patients with pulmonary hypertension (PH) is closely related to right ventricular (RV) remodeling including that of RV systolic function, while the right ventricle adapts to the increased afterload by increasing its wall thickness and contractility[1-7]. Thus, assessment of RV systolic function is one of the most important determinants of outcomes for patients with PH, but factors associated with prognosis for such patients are heterogeneous. A chronic increase in pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) leads to RV remodeling in PH patients, and the RV compensates for the increased afterload by means of RV hypertrophy. When the right ventricle is continually exposed to increased afterload, it can respond with myocardial hypertrophy as an adaptive response tempered by an increase in wall thickness in accordance with LaPlace's law[8]. However, if the right ventricle cannot manage the pressure overload, it eventually initiates a transition to dilation. The resultant morphological changes including progressive RV remodeling lead to RV dysfunction and subsequent right-sided heart failure and death[9]. In addition, our group previously reported that mid-term RV reverse remodeling at 5.7 ± 4.0 months after treatment was associated with long-term survival of PH patients[10]. Furthermore, preserved baseline RV systolic function and significant mid-term RV reverse remodeling were associated with more favorable long-term outcomes. Although mid-term RV reverse remodeling after treatment was associated with long-term outcomes for PH patients, it remains unclear which baseline factors influence mid-term RV reverse remodeling after treatment. The present study thus aimed to investigate which and what kind of baseline RV morphologic features are associated with post-treatment mid-term RV reverse remodeling in PH patients. We also investigated

whether such associated baseline RV morphologic features can be useful for predicting long-term prognosis.

Methods

Study population

This study was a retrospective analysis of 80 consecutive PH inpatients diagnosed with pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH) who visited PH Clinic in Kobe University Hospital between April 2008 and May 2015. PH was defined as resting mean pulmonary artery pressure (mPAP) >25mmHg measured by means of right-heart catheterization (RHC). Patients with pulmonary capillary wedge pressure≥15mmHg as measured with RHC, atrial fibrillation, coronary artery disease, defined as a single coronary artery stenosis of >50% of the diameter of a major epicardial vessel or a previous history of myocardial infarction, and more than mild aortic and/or mitral valvular heart disease were excluded from this study. Of the 80 PH patients, 13 (14%) did not undergo follow-up RHC, 8 (9%) did not undergo follow-up echocardiography and RHC simultaneously, and 5 (6%) had suboptimal images due to poor echocardiographic windows. Eventually, 54 PH patients were included in this study. Patients with CTEPH had been treated with either pulmonary endarterectomy (PEA) or balloon pulmonary angioplasty (BPA), and patients with PAH had been treated with PH-specific drugs including prostacyclines, endothelin receptor antagonists, and phosphodiesterase 5 inhibitors, either as a single drug or combined in concordance with current guideline recommendations[11]. At the time of enrollment, 17 patients (31%) took PH-specific drugs at baseline, and remaining 37 patients (69%) were new patients. This study was approved by the local ethics

committee, and written informed consent was obtained from all patients at date of admission.

Echocardiographic examination

All echocardiographic studies were performed with commercially available echocardiography systems equipped with a 3.5-MHz transducer (Vivid 7 or E9; GE Vingmed Ultrasound AS, Horten, Norway). Digital routine grayscale 2-D cine loops and tissue Doppler cine loops were obtained from 3 consecutive beats with end-expiratory apnea from standard apical and parasternal views. Mean frame rates were 62±11 Hz for grayscale imaging in the RV-focused apical 4-chamber view used for speckle-tracking analysis. Sector width was optimized to allow for complete myocardial visualization while frame rate was maximized regardless of heart rate. Standard echocardiographic measurements were obtained according to the current guidelines of the American Society of Echocardiography/European Association of Cardiovascular Imaging[6]. Digital data were transferred to dedicated offline software (EchoPAC version BTO8; GE Vingmed Ultrasound AS) for subsequent offline speckle-tracking analysis. All echocardiographic data were analyzed in random order by one observer who was blinded to the clinical characteristics of patients with level III of training in echocardiography[12]. Follow-up echocardiography was performed 10.2±9.6 months after the treatment.

Assessment of RV function

We used two-dimensional longitudinal speckle-tracking strain from RV free-wall for the assessment of RV function because this parameter was proved to be a robust predictor of long-term outcome for pH patients compared to conventional parameters such as tricuspid annular plane systolic excursion, RV fractional area change,

RV index of myocardial performance, and tissue Doppler-derived tricuspid lateral annular systolic velocity[4, 5, 7, 13, 14]. The assessment of RV function by means of two-dimensional longitudinal speckle-tracking strain from RV free-wall was previously described in detail[4-7, 10, 13-17]. Briefly, a region of interest was traced on the RV endocardium at end-diastole from the RV-focused apical 4-chamber view and a larger region of interest was generated and manually adjusted near the epicardium. The RV was then divided into 6 standard segments, followed by the generation of 6 corresponding time-strain curves. RV free-wall longitudinal strain was calculated by averaging each of the 3 regional peak systolic strains along the entire RV free-wall, and was expressed as an absolute value. On the basis of previous findings, the predefined cutoff for RV systolic dysfunction was set at an RV free-wall strain of ≤20 %[6].

Definition of mid-term RV reverse remodeling

RV remodeling was assessed in terms of the RV area, which was measured by means of planimetric tracing both at the end-diastole and end-systole (RVESA) from the annulus, along the free-wall to the apex, and then back to the annulus, the interventricular septum from RV-focused apical 4-chamber views[6]. Mid-term RV reverse remodeling was defined as a relative decrease in post-treatment RVESA (ΔRVESA) of at least 15% observed during echocardiographic follow-up[10].

Evaluation of RV relative wall thickness

RV relative wall thickness (RV-RWT) was calculated from RV free-wall thickness/basal RV linear dimensions at end-diastole according to the current guidelines of the American Society of Echocardiography/European Association of Cardiovascular Imaging[6].

Hemodynamic measurements

All patients underwent right-heart cardiac catheterization (RHC) for hemodynamic measurements. Mean PAP (mPAP), PVR, right atrial (RA) pressure and stroke volume were calculated by using the Fick principle for estimations. Pressure was measured by an investigator who was blinded to the echocardiographic data.

Definitions of long-term outcome

Long-term unfavorable outcome events were pre-specified as primary end points of death or hospitalization for deteriorating right-sided heart failure, which was defined as dyspnea with an appearance of pitting peripheral edema and/or ascites, and/or hepatomegaly. Mean long-term follow-up after treatment was 3.1±1.9 years.

Statistical analysis

All group data were compared by using the 2-tailed Student's t test for paired and unpaired data and are presented as mean ± SD. Proportional differences were assessed by means of Fisher's exact test or the χ^2 test as appropriate. The initial univariate logistic regression analysis to identify univariate predictors of mid-term RV reverse remodeling was followed by a multivariate logistic regression model using stepwise selection, with the p levels for entry from the model set at <0.10. Optimal cutoff values for association of baseline parameters with mid-term RV reverse remodeling were determined on the basis of receiver-operator characteristics (ROC) curve analysis findings. Event-free survival curves were determined with the Kaplan-Meier method and comparisons of cumulative event rates with the log-rank test. The initial univariate Cox proportional-hazards analysis to identify univariate predictors of long-term events was followed by a multivariate Cox proportional hazards model using stepwise selection, with the p levels for entry from the model set at <0.10. Sequential Cox models were performed to determine incremental benefits in terms of

increases in clinical, hemodynamic parameters of RV performance and RV function. A statistically significant increase in the global log-likelihood χ^2 of the model was defined as an improvement in prognostic value. The inter- and intra-observer variability of RV-RWT was assessed using Bland-Altman analysis from 10 randomly selected patients. For assessment of intra-observer reproducibility, measurements of these patients were analyzed on two consecutive days, by an observer blinded to the results of the previous measurements. For assessment of inter-observer reproducibility, measurements for selected patients were analyzed by the second observer, blinded to the values obtained by the first observer. For all tests, p value <0.05 was considered statistically significant. All the analyses were performed with commercially available software (MedCalc software version 10.4.0.0; MedCalc Software, Mariakerke, Belgium).

Results

Patient characteristics

The baseline characteristics of the 54 PH patients are summarized in Table 1. Their mean age was 61±15 years old and 38 (70%) were female. mPAP and PVR were 38±10 mmHg and 657±333 dyne*sec*cm^{-5}, respectively. Twenty-three patients (43%) had CTEPH, and 31 (57%) had associated PAH such as idiopathic pulmonary arterial hypertension, connective tissue disease, portopulmonary hypertension, and congenital heart disease. One patient (2%) was classified as World Health Organization functional class I, 18 (33%) as class II, 28 (52%) as class III, and 7 (13%) as class IV. Reproducibility of RV-RWT was excellent, showing that the bias and limit of agreement for inter-observer reproducibility were 0.00 and -0.06 to 0.05, whereas the

corresponding the bias and limit of agreement for intra-observer reproducibility were 0.00 and -0.04 to 0.04.

Predictors of mid-term RV reverse remodeling after treatment

Mid-term RV reverse remodeling after treatment was observed in 37 patients (69%), and the remaining 17 (31%) were classified as without mid-term RV reverse remodeling (Table 1). The two groups had similar baseline clinical and hemodynamic and echocardiographic parameters, except for RV-RWT of patients with mid-term RV reverse remodeling was significantly higher than that of patients without mid-term RV reverse remodeling (0.21 ± 0.02 vs. 0.18 ± 0.04, $p=0.007$).

An important finding of multivariate logistic regression analysis was that RV-RWT (odds ratio, 1.334; 95% confidential interval, 1.039-1.713; $p=0.03$) and etiology of CTEPH (odds ratio, 6.794; 95% confidential interval, 1.016-45.41; $p=0.048$) proved to be an independent predictor of mid-term RV reverse remodeling (Table 2). In addition, ROC curve analysis identified the optimal cutoff of RV-RWT for predicting mid-term RV reverse remodeling as ≥ 0.21, with sensitivity of 49%, specificity of 88%, and area under the curve of 0.715 ($p<0.01$, Figure 1) .

Predictors of long-term outcomes

Univariate Cox proportional hazards analysis showed that WHO functional class III-IV, RV free-wall strain and RV-RWT were associated with long-term outcome. The hazard ratio and 95% confidence interval for each of these variables are given in Table 3. An important finding of the multivariate Cox proportional hazards analysis was that RV free-wall strain and RV-RWT were independent predictors of long-term outcomes.

Associations with long-term outcomes

Adverse events occurred in 10 patients (19%) with 5 deaths and 5 hospitalizations for deteriorating right-sided heart failure during long-term follow-up. Patients with mid-term RV reverse remodeling showed more favorable long-term outcomes than those without (log-rank p=0.01). The Kaplan-Meier curve indicated that patients with RV-RWT≥0.21 attained more favorable long-term outcomes than those with RV-RWT < 0.21 (log-rank p=0.03, Figure 2).

There were 18 patients with higher RV-RWT and mid-term RV reverse remodeling (RV-RWT≥0.21 and ΔRVESA≥15%). This pattern was associated with better long-term outcome in comparison with other sub-groups (Figure 3). In addition, there were 14 patients with lower RV-RWT and without mid-term RV reverse remodeling (RV-RWT<0.21 and ΔRVESA<15%). This pattern was associated with worse long-term outcome than for other sub-groups (Figure 3).

The incremental benefit of using sequential Cox models for prediction of long-term outcomes is shown in Figure 4. One of the sequential Cox models, which was based on WHO functional class III-IV of clinical variables (χ^2=4.8) was improved by addition of hemodynamic parameters of RV performance including mPAP and PVR, and RV free-wall strain (χ^2=13.3; p=0.04), and further improved by addition of RV-RWT (χ^2=26.9; p<0.001).

Discussion

The findings of the present study indicate that RV-RWT is an independent parameter for predicting mid-term RV reverse remodeling, and is associated with long-term post-treatment survival of PH patients. RV-RWT also proved its significant incremental value for prediction of survival, and the combined assessment of RV-RWT

and mid-term RV reverse remodeling resulted in more accurate prediction of outcome for such patients.

RV remodeling and hypertrophy in PH patients

Chronic increases in PAP and PVR lead to RV remodeling, and the RV of PH patients develops hypertrophy to compensates for the increase in afterload by RV hypertrophy in PH patients. The resultant morphological changes including progressive RV remodeling results in RV dysfunction and subsequent right-sided heart failure and death[9]. RV remodeling in PH patients is heterogeneous, and the characteristic forms consists of two patterns: adaptive remodeling and maladaptive remodeling[18-20]. Adaptive remodeling is generally characterized by concentric hypertrophy with minimal RV dilatation, and maladaptive remodeling by eccentric hypertrophy with RV dilation. RV remodeling is induced by severe pulmonary vascular disease as well as neurohormonal activation, myocardial metabolism, coronary perfusion, oxidative stress and inflammation[21-24].

Molecular features of heterogeneous RV hypertrophy with adaptive and maladaptive have recently been described[25]. In addition, Badagliacca et al used cardiac magnetic resonance imaging to determine that RV mass/volume ratio, representing RV adaptive remodeling, was an independent predictor of prognosis for 74 patients with idiopathic pulmonary arterial hypertension[26]. Steiner et al recently reported that RV hypertrophy was independently associated with mortality in 152 PH patients in 5 years[27]. However, these studies made little mention of the association of RV hypertrophy with RV remodeling in PH patients. In our study, RV-RWT detected by means of echocardiography was used to classify adaptive or maladaptive remodeling, and it was found that an increase in RV-RWT denoted RV adaptive remodeling. We also

showed demonstrated that higher an increase in RV-RWT was an independent predictor of mid-term RV reverse remodeling, and was strongly associated with prognosis. Therefore, evaluation of RV-RWT, and not only of RV function at baseline, plays an important role in disease progression and prognosis of PH patients and thus may have implications for better management in clinical practice.

Clinical Implications

Response to PH-specific therapy by PH patients cannot be expected to be homogeneous, since there are many prognostic predictors for PH patients, not all of which can be used for individual patients. The development of one of these predictors, RV remodeling such as RV systolic dysfunction in PH patients, has been associated with adverse outcomes regardless of the underlying clinical entity, so that assessment of RV remodeling has become increasingly important in the management of PH patients[28-30]. We previously demonstrated that mid-term RV reverse remodeling and preserved baseline RV systolic function were associated with long-term post-treatment survival of PH patients[10]. The predictive capability of mid-term RV reverse remodeling was also significantly enhanced compares with that of hemodynamic parameters and RV systolic function. Furthermore, combined preserved baseline RV function and significant mid-term RV reverse remodeling were associated with more favorable long-term outcomes, and, according to the results of our study, may be a valuable additional factor for predicting long-term outcomes for PH patients. Thus, combining assessment of post-treatment baseline RV-RWT and mid-term RV reverse remodeling may well lead to better clinical management of PH patients compared to individual assessment of either of these predictors alone.

Study limitations

This study covered a small number of patients in a single-center retrospective study, so that future studies involving larger numbers of patient are required to verify our findings. Since RV performance is actually a three-dimensional phenomenon, three-dimensional speckle tracking strain imaging may be a better modality for assessment of RV performance[31, 32].

Conclusions

RV-RWT was found to be associated with RV reverse remodeling, and may be a valuable additional factor for predicting long-term outcomes for PH patients. Thus, the combined assessment of RV-RWT and mid-term RV reverse remodeling may well result in better clinical management of PH patients.

Compliance with Ethical Standards

Conflict of interest: Hiroyuki Sano declares that he has no conflict of interest. Hidekazu Tanaka declares that he has no conflict of interest. Yoshiki Motoji declares that he has no conflict of interest. Yuko Fukuda declares that he has no conflict of interest. Yasuhide Mochizuki declares that he has no conflict of interest. Yutaka Hatani declares that he has no conflict of interest. Hiroki Matsuzoe declares that she has no conflict of interest. Keiko Hatazawa declares that he has no conflict of interest. Hiroyuki Shimoura declares that he has no conflict of interest. Junichi Ooka declares that he has no conflict of interest. Keiko Ryo-Koriyama declares that he has no conflict of interest. Kazuhiro Nakayama declares that he has no conflict of interest. Kensuke Matsumoto declares that he has no conflict of interest. Noriaki Emoto declares that he has no conflict of interest. Ken-ichi Hirata declares that he has no conflict of interest.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent: Informed consent was obtained from the patient.

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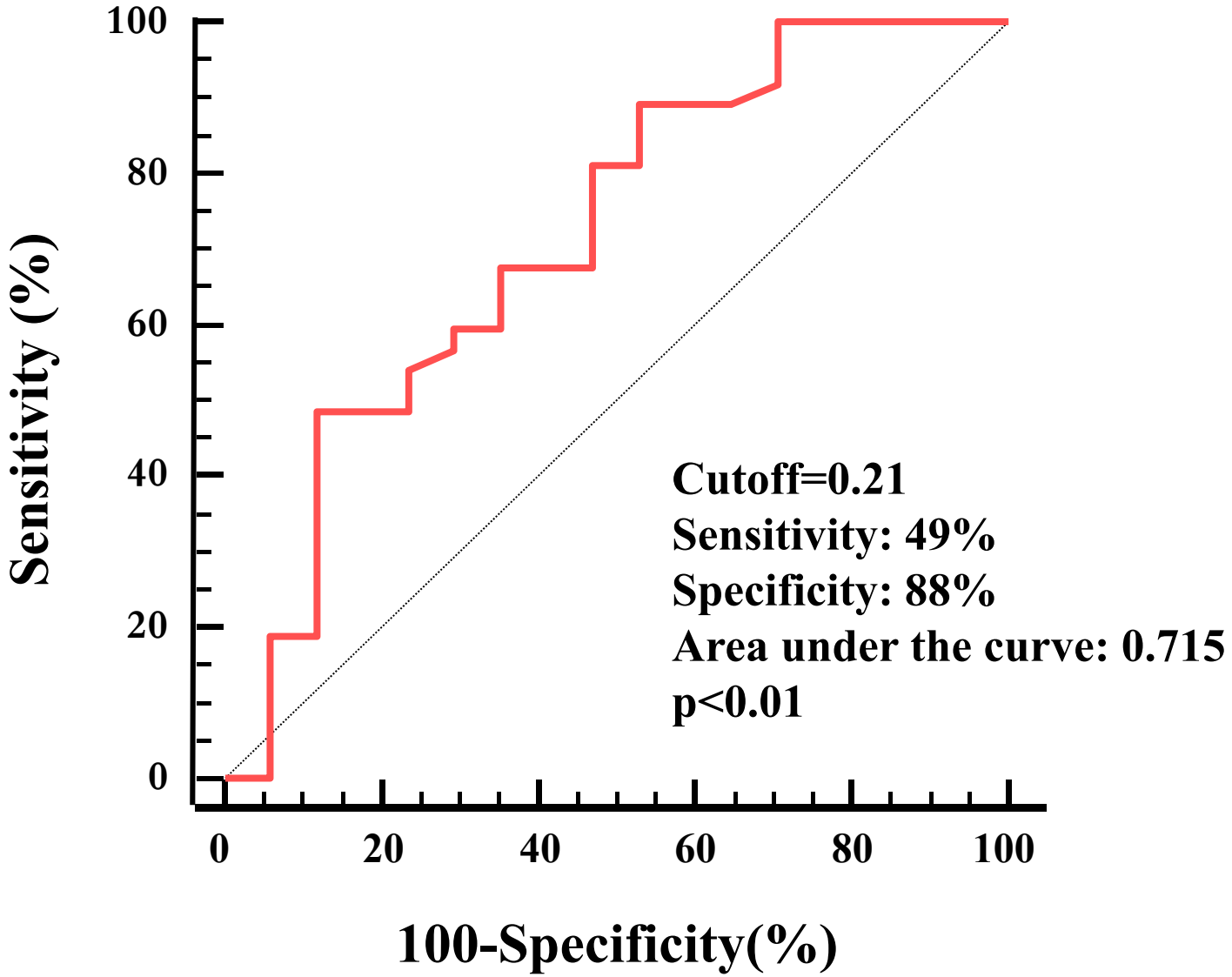
Figure Legends

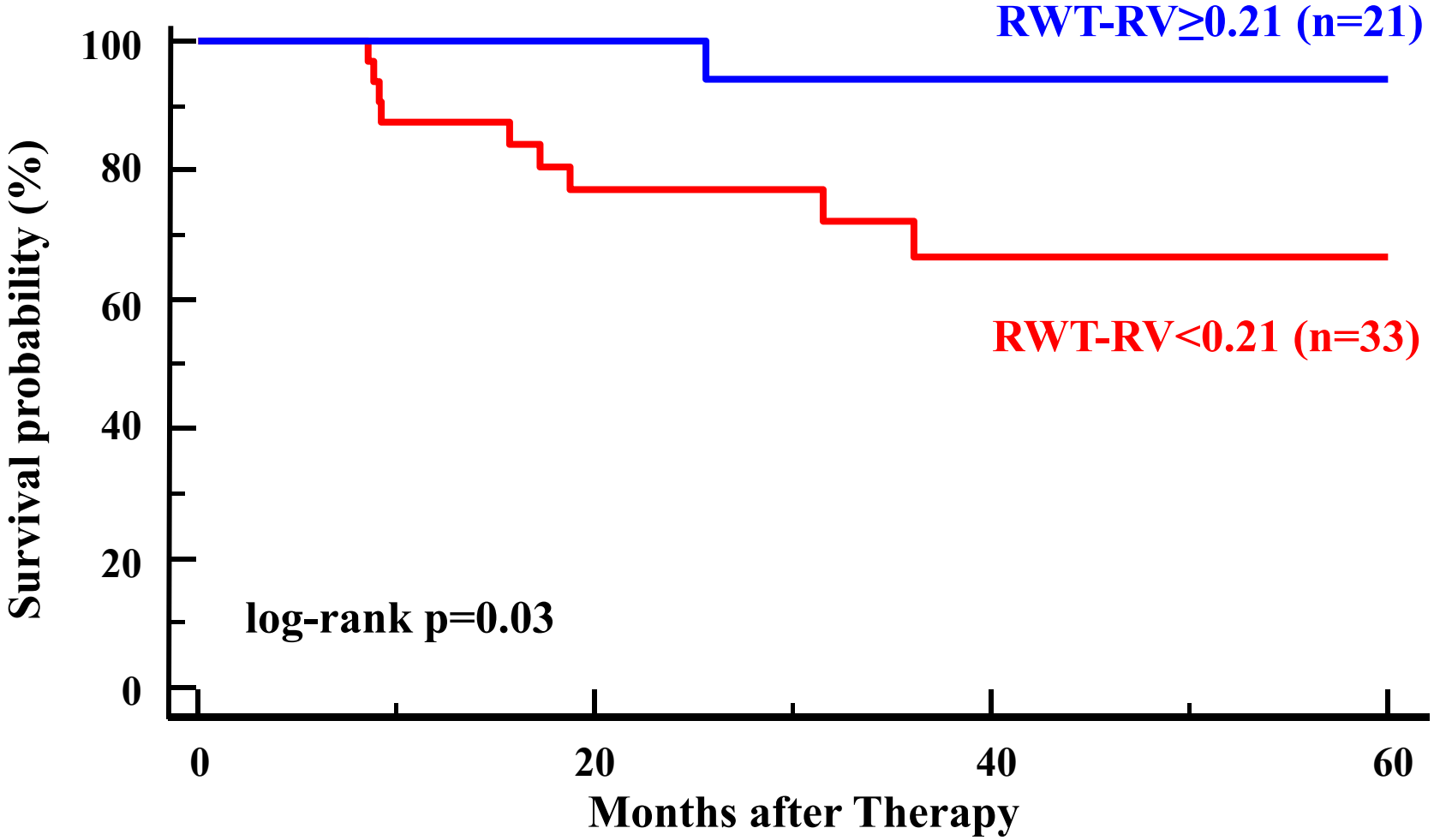
Figure 1: The receiver-operator characteristics curve analysis identified the optimal cutoff value for right ventricular (RV) relative wall thickness for the prediction of mid-term RV reverse remodeling as ≥0.21, with sensitivity of 49%, specificity of 88%, and area under the curve of 0.715.

Figure 2: The Kaplan-Meier curve indicates that patients with right ventricular relative wall thickness (RV-RWT) ≥0.21 showed more favorable long-term outcomes than did those with RV-RWT < 0.21.

Figure 3: There were 18 patients with higher right ventricular relative wall thickness (RV-RWT) and mid-term RV reverse remodeling. This pattern was associated with better long-term survival than for the other sub-groups. In addition, there were 14 patients with reduced RV-RWT and without mid-term RV reverse remodeling. This pattern was associated with worse long-term survival compared to that of the other sub-groups.

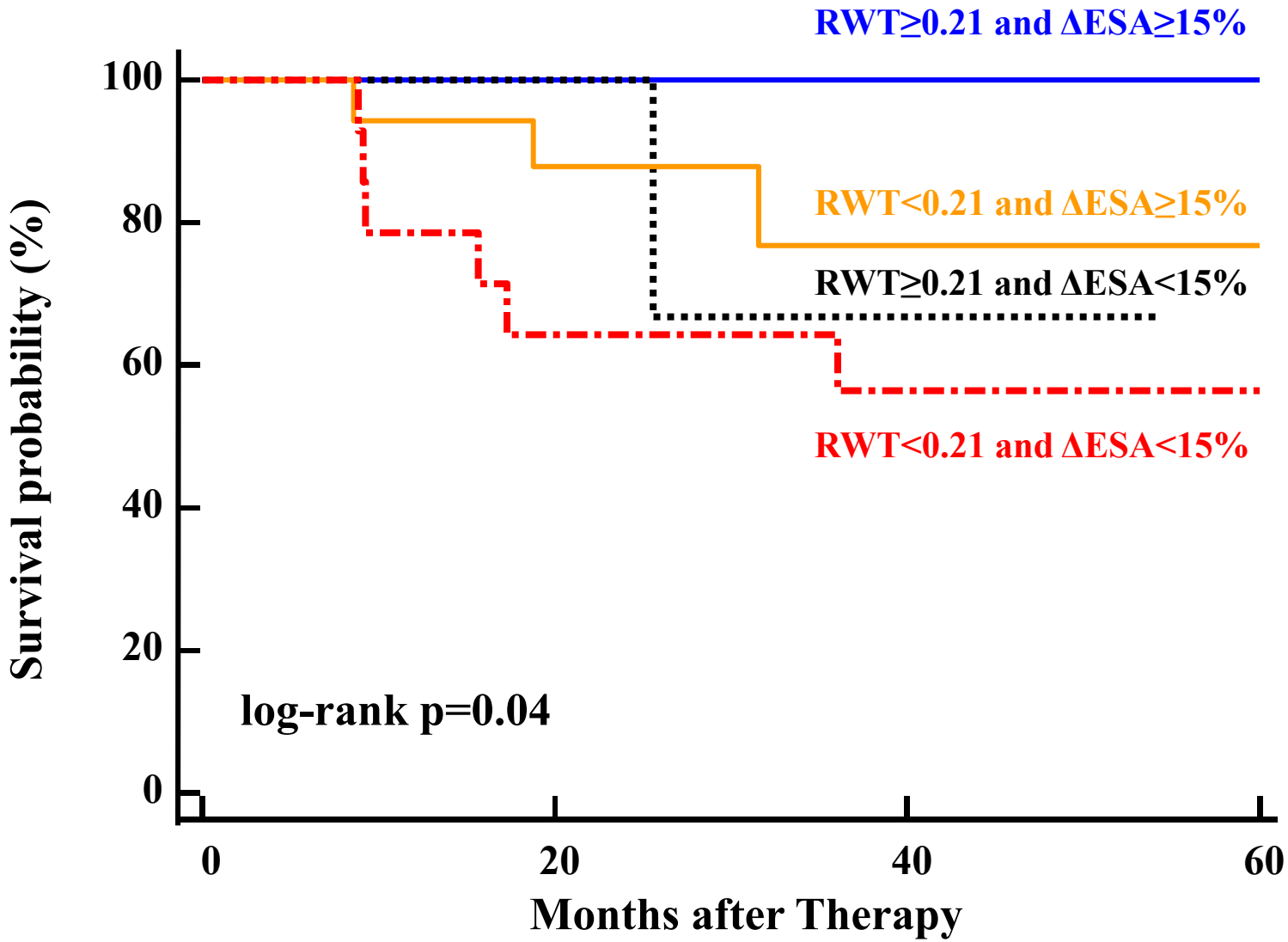
Figure 4: The incremental benefit of using sequential Cox models for the prediction of long-term outcomes. One of the sequential Cox models, which was based on World Health Organization (WHO) functional class III-IV of clinical variables, was improved by addition of hemodynamic parameters of RV performance, including mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR), and of right ventricular (RV) free-wall strain, and was further improved by addition of RV relative wall thickness (RV-RWT).


100
80
60
40
20
0
Sensitivity (%)
0
20
40
60
80
100
100-Specificity(%)
Cutoff=0.21
Sensitivity: 49%
Specificity: 88%
Area under the curve: 0.715
p<0.01



Number at risk

RWT-RV≥0.21	33	22	11	5
RWT-RV<0.21	21	19	9	3



Number at risk

RV-RWT≥0.21 and ΔRVESA≥15%	18	16	8	3
RV-RWT≥0.21 and ΔRVESA<15%	3	3	1	0
RV-RWT<0.21 and ΔRVESA≥15%	19	13	4	2
RV-RWT<0.21 and ΔRVESA<15%	14	9	7	3

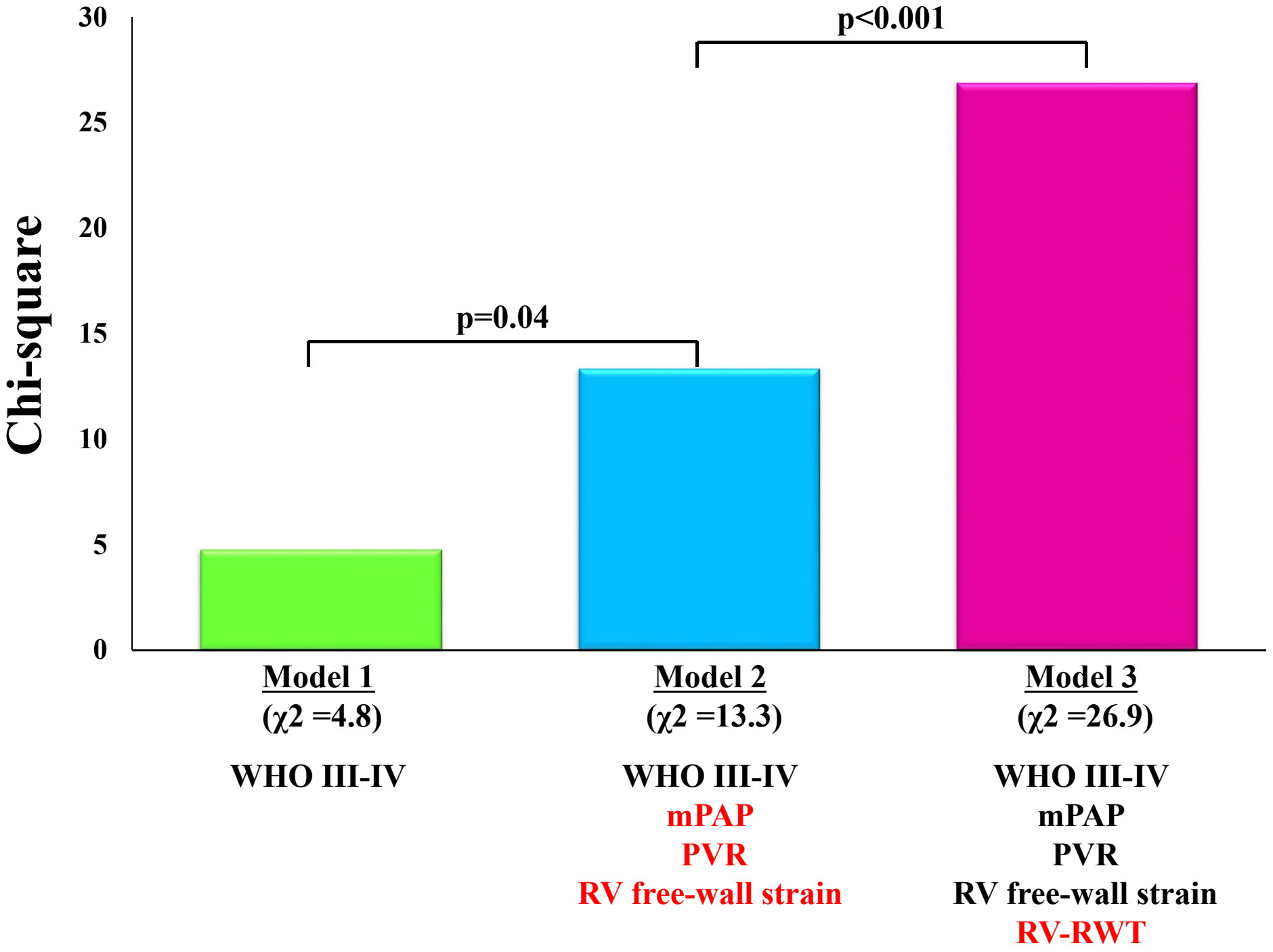

Chi-square
30
25
20
15
10
5
0
p<0.001
p=0.04
Model 1
(χ2 =4.8)
WHO III-IV
Model 2
(χ2 =13.3)
WHO III-IV
mPAP
PVR
RV free-wall strain
Model 3
(χ2 =26.9)
WHO III-IV
mPAP
PVR
RV free-wall strain
RV-RWT

Table 1
Baseline characteristics of patients

Variables	All patients (n=54)	Patients with RV reverse remodeling (n=37)	Patients without RV reverse remodeling (n=17)	p value
Age (years)	61 ± 15	61 ± 15	61 ± 15	0.97
Gender (M/F)	16/38	9/28	7/10	0.21
Systolic BP (mmHg)	118 ± 17	120 ± 19	113 ± 11	0.22
Diastolic BP(mmHg)	69 ± 11	71 ± 13	66 ± 6	0.11
Heart rate (bpm)	72 ± 13	72 ± 12	73 ± 15	0.73
BNP (pg/ml)	85 [36-289]	86 [41-226]	66 [28-300]	0.42
6MWD (m)	311±97	320 ± 85	290 ± 120	0.35
WHO Functional Class, n (%)				
I	1 (2)	0 (0)	1 (6)	0.14
II	18 (33)	14 (38)	4 (24)	0.31
III	28 (52)	19 (51)	9 (53)	0.92
IV	7 (13)	4 (11)	3 (18)	0.50
Etiology of PH, n (%)				

PAH	23 (43)	11 (30)	12 (71)	<0.01
Idiopathic PH	9 (17)	4 (11)	5 (29)	0.09
Connective tissue disease	10 (19)	5 (14)	5 (29)	0.17
Portopulmonary hypertension	3 (6)	2 (5)	1 (6)	0.94
Congenital heart disease	1 (2)	0 (0)	1 (6)	0.13
CTEPH	31(57)	26 (70)	5 (29)	<0.01
Hemodynamic parameters				
mPAP (mmHg)	38 ± 10	38 ± 11	37 ± 9	0.80
PVR (dyne· s^{-1}· cm^{-5})	657 ± 333	660 ± 327	648 ± 357	0.90
Stroke volume (ml)	59 ± 21	58 ± 19	59 ± 25	0.91
Mean RA pressure (mmHg)	4.7 ± 4.7	4.2 ± 4.6	5.6 ± 5.0	0.31
Echocardiographic parameters				
LVEF (%)	67 ± 7	69 ± 6	66 ± 7	0.21
RV wall thickness (mm)	7.2 ± 1.5	7.4 ± 1.6	6.8 ± 1.2	0.17
Pericardial effusion (%)	18 (33)	11 (30)	7 (41)	0.42
RV free-wall strain (%)	18 ± 6	18 ± 6	17 ± 6	0.74
RVEDA (cm^2)	24 ± 7	24 ± 7	24 ± 7	0.87
RVESA (cm^2)	18 ± 7	18 ± 7	18 ± 6	0.99
RV relative wall thickness	0.21 ± 0.04	0.21 ± 0.02	0.18 ± 0.04	<0.01
RA area (cm^2)	18 ± 7	18 ± 7	19 ± 6	0.52
Tricuspid Regurgitation, n (%)				
Mild	28 (52)	21 (57)	7 (41)	0.30

Moderate	16 (30)	11 (30)	5 (29)	0.98
Severe	10 (19)	5 (13)	5 (29)	0.17

BNP= plasma brain natriuretic peptide; 6MWD= 6-min walk test distance; WHO=World Health Organization; PAH= Pulmonary arterial hypertension; CTEPH= Chronic thromboembolic pulmonary hypertension; PH= pulmonary hypertension; mPAP= mean Pulmonary artery pressure; PVR= pulmonary vascular resistance; RA= right atrial; LVEF= left ventricular ejection fraction; RV= right ventricular; RVEDA= right ventricular end-diastolic area; RVESA= right ventricular end-systolic area; RWT=relative wall thickness

Table 2
Univariate and multivariate logistic regression analysis for predicting RV reverse remodeling

Covariate	Univariate analysis			Multivariate analysis		
	OR	95% CI	p value	OR	95% CI	p value
Clinical Characteristics						
Age	1.008	0.962-1.041	0.97			
Gender (female)	2.178	0.641-7.403	0.21			
Systolic blood pressure	1.024	0.987-1.062	0.22			
Diastolic blood pressure	1.051	0.988-1.118	0.12			
Heart rate	0.719	0.951-1.035	0.72			
WHO (III-IV)	0.737	0.212-2.561	0.63			
Log-transformed BNP	1.420	0.534-3.775	0.48			
6MWD	1.004	0.996-1.011	0.35			
Etiology of PH (CTEPH)	5.673	1.611-19.98	0.007	6.794	1.016-45.41	0.048
Conventional Echocardiographic Parameters						
LVEF	1.055	0.972-1.158	0.26			
RV free-wall strain	1.018	0.921-1.125	0.73			
RA area	0.973	0.896-1.056	0.51			
Pericardial effusion	0.604	0.183-1.998	0.41			
RV-RWT (per increase 0.01)	1.313	1.056-1.633	0.01	1.334	1.039-1.713	0.03
Hemodynamics						
mPAP	1.008	0.951-1.067	0.80			
PVR	1.000	0.998-1.002	0.90			
Stroke volume	0.998	0.971-1.027	0.91			

CI=confidence interval; HR=hazard ratio

Other abbreviations as in Table 1

Table 3

Univariate and Multivariate Cox Proportional-Hazards Analysis

Covariate	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Age	1.005	0.964-1.049	0.81			
Gender (female)	1.058	0.275-4.067	0.94			
mPAP	1.048	0.998-1.101	0.06			
PVR	1.000	0.999-1.002	0.67			
Mean RA pressure	1.046	0.951-1.151	0.39			
Log-transformed BNP	0.994	0.792-1.248	0.96			
WHO (III-IV)	5.630	0.716-44.60	0.03			
Pericardial effusion	2.760	0.783-9.733	0.11			
RV free-wall strain	0.828	0.728-0.947	0.006	0.795	0.686-0.921	0.002
RV-RWT (per 0.01 increase)	0.776	0.665-0.905	0.001	0.739	0.617-0.884	0.001

Abbreviations as in Table 1 and 2 s