Association between Right Ventricular Contractile Function and Cardiac Events in Isolated Post-capillary and Combined Pre- and Post-capillary Pulmonary Hypertension

Brief title: RV Strain in PH due to Left Heart Disease

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ABSTRACT

Background: Recent studies showed that the combined pre- and post-capillary pulmonary hypertension (CpcPH) had worse outcomes compared with isolated post-capillary (Ipc) PH. However, the prognostic factors including right ventricular (RV) function have not been well documented. The aim of this study was to assess the differentiation of PH phenotypes using echocardiography, and the association between RV longitudinal strain and cardiac events.

Methods and Results: We prospectively recruited consecutive patients who had undergone right heart catheterization. The primary endpoint was cardiovascular death or readmission due to heart failure. One hundred thirty-seven patients with Group 2 PH were included. A RV longitudinal strain of 17% was sensitive (85%) and specific (70%) to determine the CpcPH. During a median period of 31 months, 43 patients had the primary endpoint during follow-up. In a multivariate analysis, RV longitudinal strain was associated with the primary endpoint in both CpcPH and IpcPH (hazard ratio: HR: 0.84, p =0.003 and HR: 0.86, p =0.001).

***Conclusions*:** Lower RV longitudinal strain was independently associated with worse outcomes in CpcPH and IpcPH. RV longitudinal strain may play a prognostic role among PH phenotypes.

Key Words: pulmonary hypertension; combined pre- and post-capillary; isolated post-capillary; pulmonary arterial hypertension; right ventricular function.

Although pulmonary hypertension (PH) due to left heart disease (LHD) accounts for the largest proportion of PH, there were few reports on the prognosis.[1] Recent epidemiological studies in group 2 PH focused on markers of pulmonary vascular remodeling, such as pulmonary vascular resistance (PVR) and diastolic pulmonary gradient (DPG).[2] PH with LHD is initiated by backward conduction of elevated left atrial (LA) pressure. An elevation of LA pressure results in a passive increase in pulmonary venous pressure, so called isolated post-capillary (Ipc) PH. With longstanding severe heart failure (HF), some patients have development of pulmonary vascular remodeling, so called combined pre- and post-capillary (Cpc) PH. Several reports showed that CpcPH had worse outcomes compared with IpcPH.[3, 4] However, development of PH in HF is highly variable, and prognostic factors including cardiac function have not been well documented.[5]

Right ventricular (RV) function has been well established by functional and prognostic parameters in several cardiac diseases.[6-11] Several investigator showed that patients with suspected PH who had lower RV function showed significantly worse outcomes.[12, 13] This result suggested that RV function may contribute to important prognostic factors in PH. However, few data are available on the prognostic implications of RV function in the setting of group 2 PH, especially in the CpcPH phenotype. We hypothesized that RV function measured by 2-D speckle tracking could be used to better predict heart failure events in PH, especially with the CpcPH phenotype. The aim of this study was to assess the differentiation of PH phenotypes using echocardiography, and the association between RV longitudinal strain and cardiac events.

Methods

Study population. We prospectively recruited 391 consecutive patients who had undergone right heart catheterization (RHC) for evaluation of pulmonary hemodynamics in patients with heart failure symptom including exertional dyspnea (n=156), or PH sign by imaging modalities including echocardiography or/and computed tomography (n=235) from January 2012 to July 2018. From this potential group, we excluded patients with normal pulmonary artery pressure (PAP) (mean PAP ≤20 mmHg in RHC, n=116), unstable clinical condition with New York Heart Association (NYHA) functional class (FC) IV (n=18), history of cardiac surgery for complex congenital heart disease (n=10), acute/chronic pulmonary embolism (Group 4 PH: n=18), advanced lung disease (Group 3 PH: n=17), and poor echocardiographic images (n=14). To diagnose PH, mean PAP, pulmonary artery wedge pressure (PAWP), and PVR at rest were used according to the most recent World Symposium.[14] To focus on Group 2 PH, we have excluded Group1 PH (mean PAWP ≤15 mmHg in RHC, n=61). We performed echocardiographic studies including strain imaging within two days prior to RHC. The Institutional Review Board of the Tokushima University Hospital approved the study protocol, and written informed consent was obtained from all subjects.

Echocardiography. Echocardiography was performed using a commercially available ultrasound machine (iE33/EPIC; Philips Healthcare, Amsterdam, The Netherlands; Vivid E9/E95; and GE Healthcare, Waukesha, WI). All echocardiographic measurements were obtained according to the recommendations.[15] HF with reduced ejection fraction (HFrEF) patients were defined as having a left ventricular ejection fraction (LVEF) <50 % and HF with preserved EF (HFpEF) patients were defined as LVEF ≥50 %. Peak systolic longitudinal strain measurements were obtained from gray-scale images recorded in the apical 4-chamber, 2-chamber, and long-axis views. The frame rate was maintained at a level >40 frame/s. All strains were analyzed offline

using speckle tracking vender-independent software (EchoInsight, Epsilon Imaging, Ann Arbor, MI). Global longitudinal strain (GLS) was obtained by averaging all segmental strain values from the apical 4-chamber, 2-chamber, and long-axis views. In RV longitudinal strain analysis from the RV focused apical 4-chamber view, the interventricular septum was included in the region-of-interest for speckle-tracking echocardiography, but that only the free wall strain values were included and the septal strain values were discarded in order to avoid LV interaction (**Figure 1**). These offline analyses were independently performed in a blinded manner by 2 observers who were not involved in the image acquisition and had no knowledge of examination dates and other echocardiographic or clinical data. The reproducibility of RV longitudinal strains, expressed as the coefficient of variation, has been well described by our group as 5% to 7% and 7% to 9%, respectively, for intra-observer and inter-observer variations.[16, 17] In patients with atrial fibrillation, an index beat, which was the beat after the nearly equal preceding and pre-preceding intervals, was used for strain measurement. Index-beat determination of ventricular systolic function was accurate in several studies (index-beat vs. multi-beats measurement, Pearson's correlation $r = 0.94\text{-}0.96$, $p<0.001$).[18, 19]

Cardiac Catheterization. RHC was performed using a Swan-Ganz catheter. Pressure measurements were obtained at end-expiration while the patient was supine. The following hemodynamic parameters were recorded: mean PAWP, mean PAP, mean right atrial pressure (RAP), and cardiac output (CO). CO was measured using the indirect Fick equation. The DPG was defined as the difference between diastolic pulmonary artery pressure and mean PAWP. Pulmonary vascular resistance (PVR) was defined as (mean PAP- mean PAWP)/CO. The PH classification of patients was performed using hemodynamic measurements according to the recent guidelines: PH due to left heart disease (mean PAP >20mmHg, PAWP >15mmHg).

Additionally, patients with PH due to left heart disease were divided into two groups: CpcPH (PVR ≥3 Wood Units) and IpcPH (PVR <3 Wood Units).

Clinical Outcomes. All patients were followed in our hospital according to the clinical protocol (follow-up visits at least every 3 months). Clinical follow-up and management were independent of assessment including strain imaging and finding on right heart catheterization. The duration of follow up was begun at the time of the initial tests and ended in November 2018. The end points in this study were cardiovascular death and admission due to HF with decompensated RV function. Decompensated RV function was defined by echocardiographic signs including assessment of dilatation of RV, inferior vena cava size (diameter >21 mm with decreased inspiratory collapse), elevated TR velocity (>2.8m/sec), or clinical findings including pretibial edema, abdominal fluid, and jugular vein distension. Either death or first admission due to HF after RHC was considered the event.

Statistical analysis. Data are presented as mean±SD if the Kolmogorov–Smirnov test showed a normal distribution. Otherwise, the median and interquartile ranges were used. One-way general linear model analysis of variance, followed by Dunnett T3 post hoc test analysis, was used to assess the difference between parameters among groups. Receiver-operating characteristic (ROC) curve analysis was used to identify parameters that were best to differentiate CpcPH and IpcPH. The best cutoff value was defined as the upper limit of the confidence interval (CI) of the Youden index. We conducted bootstrapping with 1000 resamples to assess the internal validation using a simple random sampling method.[20] The DeLong method was used to compare the C-statistic.[21] The association of several parameters with endpoints was identified by Cox proportional-hazards models in univariable and multivariable analyses. Identified variables ($p < 0.10$ in the univariate model) were considered to enter in a backwards stepwise manner into a

multivariate model. A hazard ratio (HR) with a 95% CI was calculated for each variable. To assess prognostic value, PH types and RV longitudinal strain values were used to divide patients into groups for Kaplan–Meier analysis, with event-free survival compared using a 2-sided log-rank test. Statistical analysis was performed using standard statistical software packages (SPSS software 21.0; SPSS Inc, Chicago, IL, USA, MedCalc Software 17; Mariakerke, Belgium). Statistical significance was defined by $p<0.05$.

Results

Patient characteristics. In this cohort, 47 patients were diagnosed with CpcPH and 90 patients were diagnosed with IpcPH (**Figure 2**). Baseline clinical characteristics of the study group were presented in **Table 1**. There were 66 patients with HFrEF and 71 patients with HFpEF. All patients with ischemic cardiomyopathy were completely revascularized in this cohort.

Hemodynamic parameters and Types of PH. Hemodynamic and echocardiographic data are presented in **Table 2**. In hemodynamic variables, mean PAP were significantly higher in the CpcPH group compared with the IpcPH groups in both HFrEF and HFpEF. RV longitudinal strain was significantly lower in the CpcPH group compared with the IpcPH group. Results of the receiver operating characteristic curve analysis used to identify the optimal cutoff point for differentiating the CpcPH and IpcPH groups are shown in **Figure 3**. A RV longitudinal strain of 17% was sensitive (85%) and specific (70%) to determine the CpcPH. We found that the cut-off value using 1000 bootstrap samples ~~is~~ was 17% (95% bootstrap CI: 15-18) for distinguishing CpcPH from IpcPH. This RV longitudinal strain had the highest area under the curve (0.79; 95% CI: 0.71 to 0.85; $p < 0.001$) among echocardiographic variables.

Event free survival among PH Types. The average follow-up period was 31 months (range, 4–99 months) and 43 patients (31%) experienced the primary endpoint. Primary endpoint causes included cardiovascular death (n=7) and admission due to HF (n=36). Twenty-five CpcPH patients (5 death and 20 HF) reached the primary endpoint and 18 IpcPH patients (2 death and 16 HF) reached the primary endpoint. **Figure 4 and Figure 5** illustrate the time to primary endpoints stratified according to the PH phenotypes and HF phenotypes. Kaplan-Meier survival estimates showed that the CpcPH had a significantly lower event-free rate compared to the IpcPH (p <0.001). Median survival time for CpcPH was 33 months (95% CI, 14 to 79). Moreover, CpcPH patients with both HFpEF and HFrEF had a significantly lower event-free rate compared to the IpcPH with both HFpEF and HFrEF (p =0.002). Median survival time for CpcPH patients with both HFpEF and HFrEF were 63 months (95% CI, 13 to 79) and 29 months (95% CI, 12 to 58). There were no association between ischemic cardiomyopathy/valvular dysfunction and the primary outcome.

Association between RV function and Event Free Survival. The hazard ratios obtained by univariate and multivariate Cox proportional-hazards regression are shown in **Table 3 and 4**. In the CpcPH group, RV longitudinal strain (HR: 0.84, 95% CI: 0.74-0.94, p =0.003) was associated with the primary endpoint in a multivariate analysis (**Table 3**). In the IpcPH group, RV longitudinal strain (HR: 0.86, 95% CI: 0.78-0.94, p =0.001) was also associated with the primary endpoint in a multivariate analysis (**Table 4**). Thus, preserved RV longitudinal strain had a protective effect on the primary outcome. **Figure 6** illustrates the time to cardiac event stratified according to the median value of RV longitudinal strain. Patients with lower RV longitudinal strain had significantly shorter event-free survival than those with higher RV longitudinal strain in both CpcPH (p <0.001) and IpcPH (p <0.001).

Discussion

Our study sought to assess the association between echocardiographic variables and cardiovascular events in patients with PH due to LHD. Our study brings several insights into the understanding of PH: 1) RV systolic function was significantly lower in the CpcPH compared with the IpcPH; 2) the CpcPH groups had a significantly lower event-free rate compared to the IpcPH; and 3) RV longitudinal strain was the most powerful independent predictor of cardiovascular events in the CpcPH and IpcPH. This information might provide insight into RV function in PH and be useful for clinical evaluation and follow-up during optimal medical therapy.

Event Free Survival among PH Phenotypes. Recent studies have demonstrated that hemodynamic parameters including the DPG and PVR are important prognostic factors in patients with PH.[2-4, 22] PH due to LHD is classified into Group 2 PH, with the prognostic import dependent on whether PVR or DPG is elevated. CpcPH is characterized by the presence of an elevated PVR, whereas IpcPH sustains a normal PVR. Several investigators reported that CpcPH was associated with all-cause death in PH due to LHD.[5] In our study, CpcPH groups had a significantly lower event-free rates compared to IpcPH. Our study results are consistent with previous work linking PH phenotypes with worse outcomes. Thus, PH phenotype should be considered an important prognostic factor in the clinical setting.

RV Function among PH phenotypes. The cause of RV dysfunction in PH patients is not fully explained given the complex interaction between left and right sides of the heart.[23] In PH with LHD, increased PA pressure leads to elevated RV afterload, which is the major source of RV dysfunction. RV systolic function was significantly lower in the CpcPH compared with the

IpcPH. This result suggested that that longstanding increased PA pressure may cause RV dysfunction in LHD. In patients with longstanding severe heart failure, the clinical condition reflected not only the development of pulmonary vascular remodeling, but also the occult RV dysfunction with ventricular interaction. RV longitudinal strain may be used for detailed RV analysis in patients with PH.

Predictors of Prognosis among PH phenotypes. The 2018 world symposium of pulmonary hypertension (European Paediatric Pulmonary Vascular Disease Network) discussed the importance of risk stratification in PH. All clinician should determine the risk in each patient to decide clinical management and treatment.[24, 25] Recently, there is increasing recognition of the prognostic information provided by RV function in cardiovascular disorders such as HF. However, there is little knowledge about RV function among PH phenotypes for prognostic information. In this study, RV longitudinal strain was a predictor of cardiovascular events in both CpcPH and IpcPH. In a preceding study, RV scar was associated with RV systolic function independent of pulmonary artery pressure in valvular disease.[8] This result suggested that RV scar as primary RV dysfunction may occur independent of PAP in LHD. In another report, the preserved RV response to pulmonary artery endarterectomy or lung transplantation provides evidence that the RV has the capacity to recover over short periods following afterload changes.[16, 26]

In PH with LHD, RV longitudinal strain may be influenced by not only RV afterload, but also LV-RV interaction. RV longitudinal strain was related to both mean PAP ($r = 0.20$, $p = 0.04$) and LV strain ($r = 0.37$, $p < 0.001$). The LV and RV are connected in series and may influence one another in parallel. Coupling of LV and RV function may reflect common cardiomyopathy (e.g., ischemia) or ventricular interdependence. This ventricular interaction explains the strong

association between RV function and cardiovascular events in PH with LHD. Another explanation for the predictive value of strain in LDH was that the intrinsic LV myocardial disease extending to the RV could occur depending on the underlying disease. In our cohort, the Group 2 PH consisted of 40% of patients with ischemic cardiomyopathy. These cardiomyopathies may influence RV function. Thus, our data suggest that RV longitudinal strain may play a different prognostic role among PH phenotypes.

Clinical Implications. The management of PH differs among individuals due to the severity of disease. Expert consensus for PH recommends careful risk evaluation of cardiovascular events to select treatment strategies. Thus, the predictors of events in the PH field are required. Our results suggested that in IpcPH or CpcPH, patients at higher risk, such as those with reduced RV longitudinal strain, have cardiovascular events.

Limitations. Despite starting out with a cohort of 391 patients enrolled in the study, the sample size of patients with Group 2 PH is indeed small: 90 with IpcPH and 47 with CpcPH. The sample size was relatively small. We believe that it can serve as an impetus for a properly designed large validation study. In our cohort, the estimated LV filling pressures by E/e' was not different among groups. A previous study suggested that lower right ventricular function was associated with incident heart failure or death independent of left ventricular ejection fraction or N-terminal pro b-type natriuretic peptide.[27] This report might be applicable in the current study.

Conclusions. RV longitudinal strain was a good predictor of cardiovascular events in both CpcPH and IpcPH. RV longitudinal strain may play a prognostic role among PH phenotypes.

Disclosures: None.

References:

[1] Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J. 2016;37:67-119.
[2] Gerges C, Gerges M, Lang MB, Zhang Y, Jakowitsch J, Probst P, et al. Diastolic pulmonary vascular pressure gradient: a predictor of prognosis in "out-of-proportion" pulmonary hypertension. Chest. 2013;143:758-66.
[3] Aronson D, Eitan A, Dragu R, Burger AJ. Relationship Between Reactive Pulmonary Hypertension and Mortality in Patients With Acute Decompensated Heart Failure. Circulation: Heart Failure. 2011;4:644-50.
[4] Tatebe S, Fukumoto Y, Sugimura K, Miyamichi-Yamamoto S, Aoki T, Miura Y, et al. Clinical significance of reactive post-capillary pulmonary hypertension in patients with left heart disease. Circ J. 2012;76:1235-44.
[5] Opitz CF, Hoeper MM, Gibbs JS, Kaemmerer H, Pepke-Zaba J, Coghlan JG, et al. Pre-Capillary, Combined, and Post-Capillary Pulmonary Hypertension: A Pathophysiological Continuum. J Am Coll Cardiol. 2016;68:368-78.
[6] Jellis CL, Yingchoncharoen T, Gai N, Kusunose K, Popovic ZB, Flamm S, et al. Correlation between right ventricular T1 mapping and right ventricular dysfunction in non-ischemic cardiomyopathy. Int J Cardiovasc Imaging. 2018;34:55-65.
[7] Kusunose K, Phelan D, Seicean S, Seicean A, Collier P, Boden KA, et al. Relation of Echocardiographic Characteristics of the Right-Sided Heart With Incident Heart Failure and Mortality in Patients With Sleep-Disordered Breathing and Preserved Left Ventricular Ejection Fraction. Am J Cardiol. 2016;118:1268-73.
[8] Sabe MA, Sabe SA, Kusunose K, Flamm SD, Griffin BP, Kwon DH. Predictors and Prognostic Significance of Right Ventricular Ejection Fraction in Patients With Ischemic Cardiomyopathy. Circulation. 2016;134:656-65.
[9] Motoki H, Borowski AG, Shrestha K, Hu B, Kusunose K, Troughton RW, et al. Right ventricular global longitudinal strain provides prognostic value incremental to left ventricular ejection fraction in patients with heart failure. J Am Soc Echocardiogr. 2014;27:726-32.
[10] Haeck ML, Scherptong RW, Marsan NA, Holman ER, Schalij MJ, Bax JJ, et al. Prognostic value of right ventricular longitudinal peak systolic strain in patients with pulmonary hypertension. Circ Cardiovasc Imaging. 2012;5:628-36.
[11] Park SJ, Park J-H, Lee HS, Kim MS, Park YK, Park Y, et al. Impaired RV global longitudinal strain is associated with poor long-term clinical outcomes in patients with acute inferior STEMI. JACC: Cardiovascular Imaging. 2015;8:161-9.
[12] Fine NM, Chen L, Bastiansen PM, Frantz RP, Pellikka PA, Oh JK, et al. Outcome prediction by quantitative right ventricular function assessment in 575 subjects evaluated for pulmonary hypertension. Circ Cardiovasc Imaging. 2013;6:711-21.
[13] Shukla M, Park J-H, Thomas JD, Delgado V, Bax JJ, Kane GC, et al. Prognostic value of right ventricular strain using speckle-tracking echocardiography in pulmonary hypertension: a systematic review and meta-analysis. Canadian Journal of Cardiology. 2018;34:1069-78.
[14] Vachiéry J-L, Tedford RJ, Rosenkranz S, Palazzini M, Lang I, Guazzi M, et al. Pulmonary hypertension due to left heart disease. European Respiratory Journal. 2019;53:1801897.

[15] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16:233-70.
[16] Kusunose K, Tsutsui RS, Bhatt K, Budev MM, Popovic ZB, Griffin BP, et al. Prognostic value of RV function before and after lung transplantation. JACC Cardiovasc Imaging. 2014;7:1084-94.
[17] Goodman A, Kusunose K, Popovic ZB, Parikh R, Barr T, Sabik JF, et al. Synergistic Utility of Brain Natriuretic Peptide and Left Ventricular Strain in Patients With Significant Aortic Stenosis. J Am Heart Assoc. 2016;5.
[18] Kusunose K, Yamada H, Nishio S, Tomita N, Hotchi J, Bando M, et al. Index-beat assessment of left ventricular systolic and diastolic function during atrial fibrillation using myocardial strain and strain rate. J Am Soc Echocardiogr. 2012;25:953-9.
[19] Chou S-H, Kuo C-T, Hsu L-A, Ho W-J, Wang C-L. Single-Beat Determination of Right Ventricular Function in Patients with Atrial Fibrillation. Echocardiography. 2010;27:1188-93.
[20] Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BMC medicine. 2015;13:1.
[21] DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44:837-45.
[22] Ibe T, Wada H, Sakakura K, Ikeda N, Yamada Y, Sugawara Y, et al. Pulmonary hypertension due to left heart disease: The prognostic implications of diastolic pulmonary vascular pressure gradient. Journal of Cardiology. 2016;67:555-9.
[23] Bogaard HJ, Natarajan R, Henderson SC, Long CS, Kraskauskas D, Smithson L, et al. Chronic pulmonary artery pressure elevation is insufficient to explain right heart failure. Circulation. 2009;120:1951-60.
[24] Hansmann G, Apitz C, Abdul-Khaliq H, Alastalo T-P, Beerbaum P, Bonnet D, et al. Executive summary. Expert consensus statement on the diagnosis and treatment of paediatric pulmonary hypertension. The European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK. Heart. 2016;102:ii86-ii100.
[25] Kusunose K, Yamada H, Hotchi J, Bando M, Nishio S, Hirata Y, et al. Prediction of Future Overt Pulmonary Hypertension by 6-Min Walk Stress Echocardiography in Patients With Connective Tissue Disease. J Am Coll Cardiol. 2015;66:376-84.
[26] Berman M, Gopalan D, Sharples L, Screaton N, Maccan C, Sheares K, et al. Right ventricular reverse remodeling after pulmonary endarterectomy: magnetic resonance imaging and clinical and right heart catheterization assessment. Pulm Circ. 2014;4:36-44.
[27] Nochioka K, Querejeta Roca G, Claggett B, Biering-Sorensen T, Matsushita K, Hung CL, et al. Right Ventricular Function, Right Ventricular-Pulmonary Artery Coupling, and Heart Failure Risk in 4 US Communities: The Atherosclerosis Risk in Communities (ARIC) Study. JAMA Cardiol. 2018.

Figure legends:

Figure 1: Measurement of Right Ventricular Strain

Figure 2: Patient Selection. mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance.

Figure 3: ROC Curve Analysis of Echocardiographic Variables for Differentiating PH Phenotypes. The RV longitudinal strain had the highest AUC (AUC: 0.79) among echocardiographic variables. AUC = area under the curve; ROC = receiver-operating characteristic.

Figure 4: Kaplan-Meier analysis of event-free survival. Patients were stratified according to PH phenotypes. IpcPH, isolated post-capillary pulmonary hypertension; CpcPH, combined pre- and post-capillary pulmonary hypertension.

Figure 5: Kaplan-Meier analysis of event-free survival. Patients were stratified according to PH phenotypes and ejection fraction. HFpEF, heart failure preserved ejection fraction; HFrEF, heart failure reduced ejection fraction. Abbreviations: See Figure 4.

Figure 6: Kaplan-Meier analysis of event-free survival. Patients with CpcPH and Ipc PH were stratified according to median values of RV longitudinal strain. Abbreviations: See Figure 4.

Table 1: Clinical characteristics

	HFrEF (n=66)			HFpEF (n=71)		
	Cpc PH	Ipc PH	p value	Cpc PH	Ipc PH	p value
Number	26	40		21	50	
Age, y.o.	70±12	57±13	<0.001	73±11	61±15	0.001
Male, %	81	95	0.07	62	68	0.63
Body surface area, m^2	1.6±0.2	1.7±0.2	0.04	1.6±0.2	1.7±0.2	0.02
NYHA Class I/II/III/IV	9/12/5/0	20/19/1/0		12/7/2/0	24/23/3/0	
History						
Diabetes mellitus, %	27	43	0.20	24	32	0.49
Atrial fibrillation, %	19	23	0.76	24	14	0.32
Ischemic cardiomyopathy, %	54	36	0.16	38	37	0.92
Medication						
ACEi or ARB, %	77	63	0.23	67	60	0.61
Beta blocker, %	81	93	0.16	43	46	0.81
Diuretic, %	76	53	0.07	67	75	0.48
Heart Rate, beat/min	81±14	76±13	0.32	82±19	75±16	0.32
Systolic BP, mmHg	108±19	116±17	0.06	128±24	130±18	0.72
Diastolic BP, mmHg	65±12	70±14	0.19	66±16	69±14	0.54
GFR, mL/min/1.73m^2	47±11	60±14	0.22	55±16	58±12	0.66
BNP, pg/ml	458 (402-545)	377 (199-553)	0.89	338 (176-685)	169 (82-260)	<0.001

Data are presented as number of patients (percentage), mean ± SD or median (interquartile range).

Abbreviations: Cpc PH, combined pre- and post- capillary pulmonary hypertension; Ipc PH, isolated post-capillary PH; NYHA, New York Heart Association; ACEi, angiotensin converting enzyme inhibitor; ARB, Angiotensin II Receptor Blocker; BP, blood pressure; GFR, glomerular filtration rate; BNP, brain natriuretic peptide.

Table 2: Hemodynamic and Echocardiographic Data

	HFrEF (n=66)			HFpEF (n=71)		
	Cpc PH	Ipc PH	p value	Cpc PH	Ipc PH	p value
Hemodynamic variables						
Mean RAP, mmHg	9±3	8±5	0.72	10±5	11±5	0.67
Mean PAP, mmHg	34±11	28±6	0.003	35±8	28±4	<0.001
PAWP, mmHg	21±5	21±5	0.48	21±5	22±4	0.30
Cardiac output, L/min	3.6±1.3	4.7±1.2	<0.001	4.1±1.2	4.7±1.3	0.09
PVR, wood unit	4.9±1.7	1.8±0.6	<0.001	4.5±1.8	1.8±0.6	<0.001
DPG, mmHg	8±7	1±1	<0.001	7±3	2±2	<0.001
Echocardiographic variables						
LVEDVi, ml/m^2	78±22	88±22	0.06	60±22	60±20	0.98
LVESVi, ml/m^2	53±18	57±18	0.37	25±11	22±9	0.32
LVEF, %	32±7	36±7	0.07	58±6	63±5	<0.001
GLS, %	11±2	11±3	0.92	14±3	15±2	0.23
LAVi, ml/m^2	56±21	63±27	0.32	54±16	51±25	0.66
E/e'	14±5	14±7	0.98	18±10	15±8	0.16
>= moderate mitral regurgitation, %	12	5	0.33	10	22	0.22
>= moderate aortic regurgitation, %	0	5	0.25	19	6	0.10
>= moderate aortic stenosis, %	0	5	0.25	10	6	0.58
>= moderate tricuspid regurgigation, %	12	0	0.03	11	2	0.13
TR-velocity, m	3.1±0.4	3.0±0.5	0.37	3.4±0.6	2.9±0.5	0.04
RVFAC, %	28±6	29±7	0.38	30±7	34±10	0.12
TAPSE, mm	11±5	14±5	0.02	12±3	14±4	0.04
RV longitudinal strain, %	13±4	18±6	0.001	15±4	20±5	0.002

Data are presented as number of patients (percentage), mean ± SD or median (interquartile range).

Abbreviations: RAP, right atrial pressure; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; DPG, diastolic pulmonary gradient; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LVESVi; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; LVMi, left ventricular mass index; LAVi, left atrial volume index; E, early diastolic transmitral flow velocity; e', early diastolic mitral annular motion; TR, tricuspid regurgitation; RVFAC, right ventricular functional area change; TAPSE, tricuspid annular plane systolic excursion; RV, right ventricular.

Table 3: Univariable and Multivariable Association of Primary Outcomes in Combined pre- and post-capillary PH

	Cpc PH					
	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Age	1.01	0.97-1.04	0.78			
Male	6.90	1.62-29.4	0.009	5.67	1.33-24.2	0.02
Ischemic cardiomyopathy	0.41	0.17-1.01	0.05	†		
Medication						
ACEi or ARB	0.59	0.23-1.51	0.27			
Beta blocker	0.78	0.35-1.72	0.53			
Diuretic	1.69	0.62-4.58	0.30			
HR	1.03	0.98-1.08	0.29			
Systolic BP	1.01	0.99-1.02	0.67			
GFR	1.01	0.94-1.08	0.79			
Hemodynamic variables						
Mean RAP	0.97	0.88-1.07	0.54			
Mean PAP	1.00	0.96-1.04	0.99			
PAWP	0.94	0.85-1.04	0.22			
Cardiac output	1.24	0.93-1.66	0.15			
PVR	1.09	0.85-1.38	0.50			
DPG	1.02	0.94-1.10	0.68			
Echocardiographic variables						
LVEDVi	1.01	0.99-1.02	0.62			
LVESVi	1.01	0.99-1.02	0.68			
LVEF	0.99	0.97-1.02	0.66			
GLS	1.02	0.89-1.16	0.78			
LAVi	1.01	0.99-1.03	0.45			
E/e'	1.03	0.98-1.08	0.23			
RVFAC	0.95	0.88-1.02	0.12			
TAPSE	0.92	0.83-1.01	0.08	†		
RV longitudinal strain	0.82	0.73-0.92	0.001	0.84	0.74-0.94	0.003

† Eliminated through the stepwise method.

Abbreviations: See Tables 1 and 2.

Table 4: Univariable and Multivariable Association of Primary Outcomes in Isolated post-capillary PH

	Ipc PH					
	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Age	1.01	0.98-1.05	0.46			
Male	1.68	0.48-5.82	0.42			
Ischemic cardiomyopathy	0.62	0.22-1.73	0.36			
Medication						
ACEi or ARB	0.41	0.16-1.05	0.06	0.36	0.13-0.96	0.025
Beta blocker	2.91	0.84-10.1	0.09	†		
Diuretic	1.37	0.49-3.84	0.55			
HR	1.02	0.97-1.07	0.47			
Systolic BP	0.99	0.96-1.01	0.31			
GFR	0.97	0.90-1.04	0.35			
Hemodynamic variables						
Mean RAP	1.03	0.94-1.13	0.55			
Mean PAP	0.98	0.89-1.08	0.63			
PAWP	0.94	0.83-1.05	0.27			
Cardiac output	0.74	0.66-1.35	0.74			
PVR	1.37	0.58-3.23	0.48			
DPG	1.24	1.01-1.53	0.04			
Echocardiographic variables						
LVEDVi	1.01	1.00-1.02	0.05	†		
LVESVi	1.02	1.00-1.03	0.04	†		
LVEF	0.97	0.94-1.00	0.06	†		
GLS	0.92	0.79-1.05	0.19			
LAVi	1.00	0.98-1.02	0.69			
E/e'	0.92	0.85-1.00	0.06	†		
RVFAC	0.96	0.91-1.01	0.13			
TAPSE	0.91	0.82-1.01	0.09	†		
RV longitudinal strain	0.86	0.78-0.94	0.001	0.86	0.78-0.94	0.001

† Eliminated through the stepwise method.

Abbreviations: See Tables 1 and 2.

Figure 1

RV Longitudinal strain

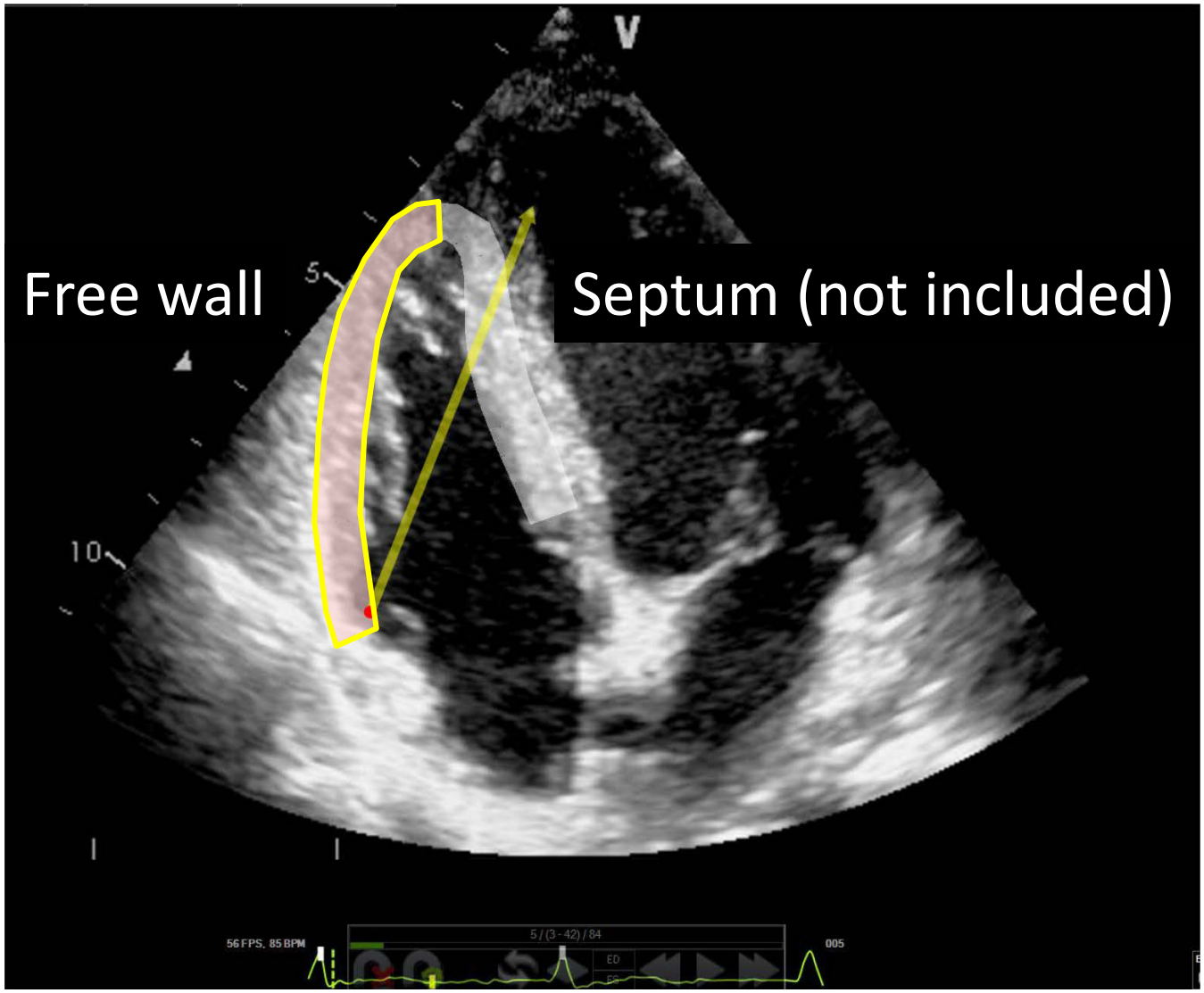


Figure 2

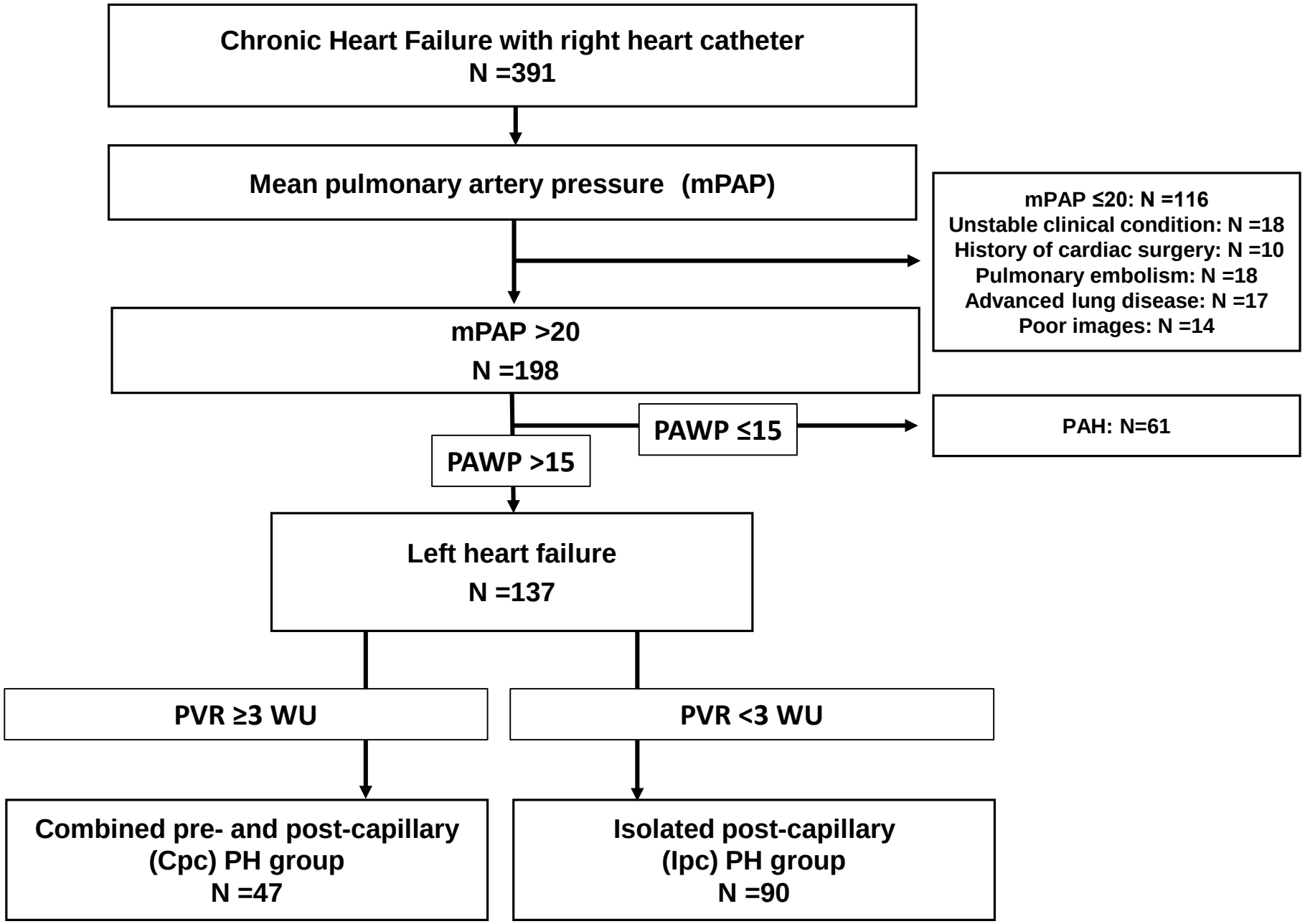

Chronic Heart Failure with right heart catheter
N =391
Mean pulmonary artery pressure (mPAP)
mPAP ≤20: N =116
Unstable clinical condition: N =18
History of cardiac surgery: N =10
Pulmonary embolism: N =18
Advanced lung disease: N =17
Poor images: N =14
mPAP >20
N =198
PAWP ≤15
PAH: N=61
PAWP >15
Left heart failure
N =137
PVR ≥3 WU
PVR <3 WU
Combined pre- and post-capillary (Cpc) PH group
N =47
Isolated post-capillary (Ipc) PH group
N =90

Figure 3

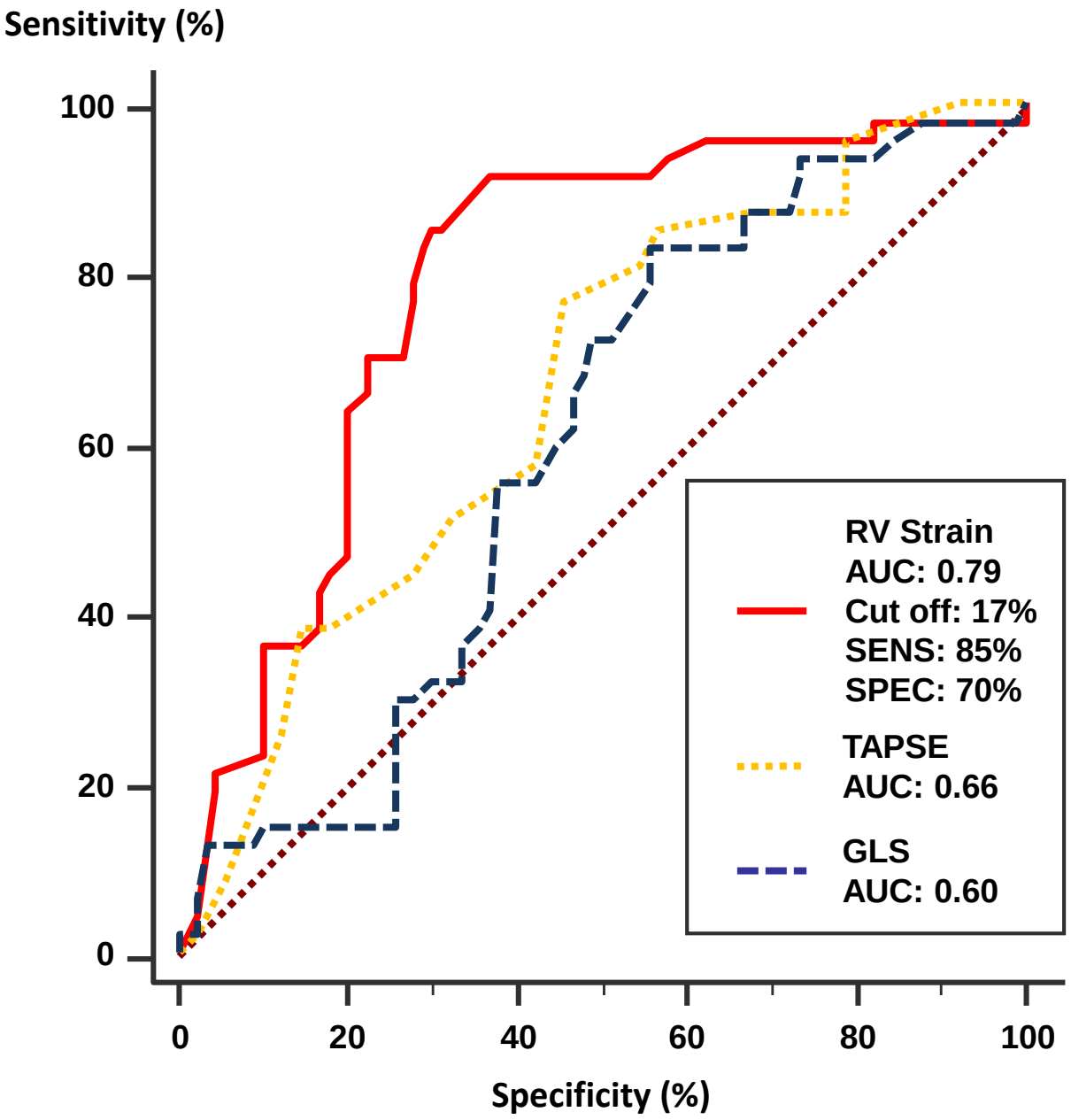

Sensitivity (%)
100
80
60
40
20
0
0
20
40
60
80
100
Specificity (%)
RV Strain
AUC: 0.79
Cut off: 17%
SENS: 85%
SPEC: 70%
TAPSE
AUC: 0.66
GLS
AUC: 0.60

Figure 4

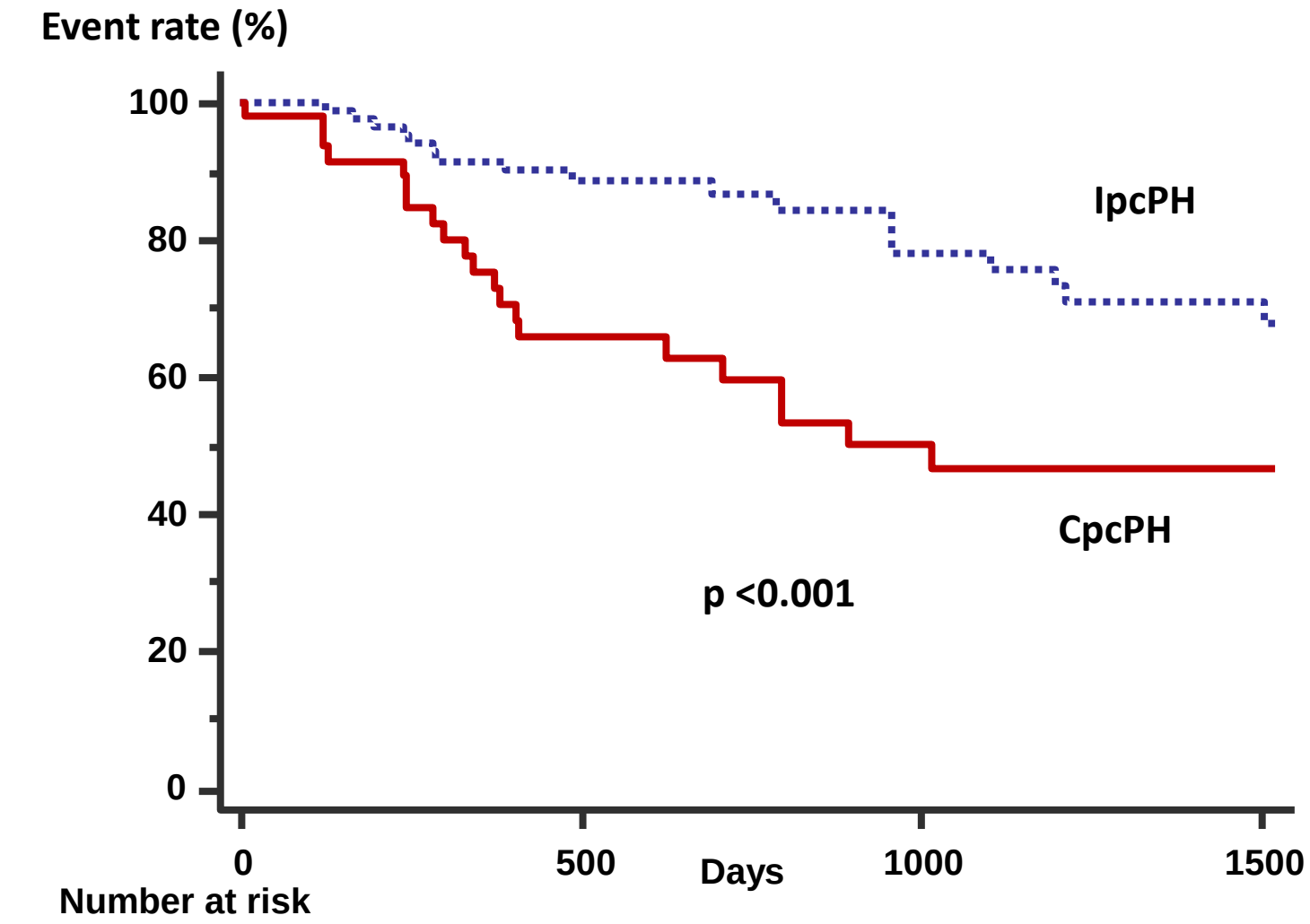
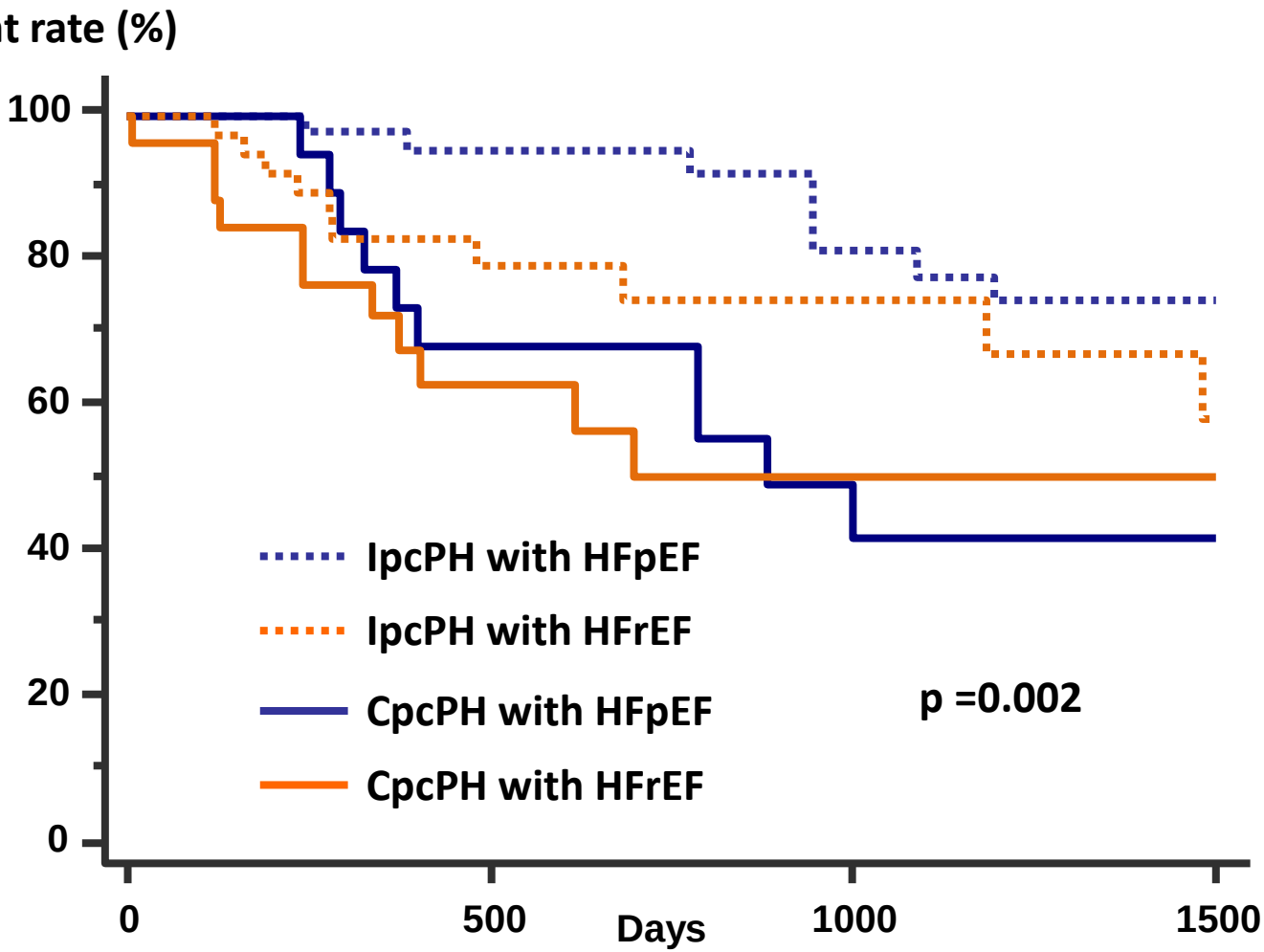
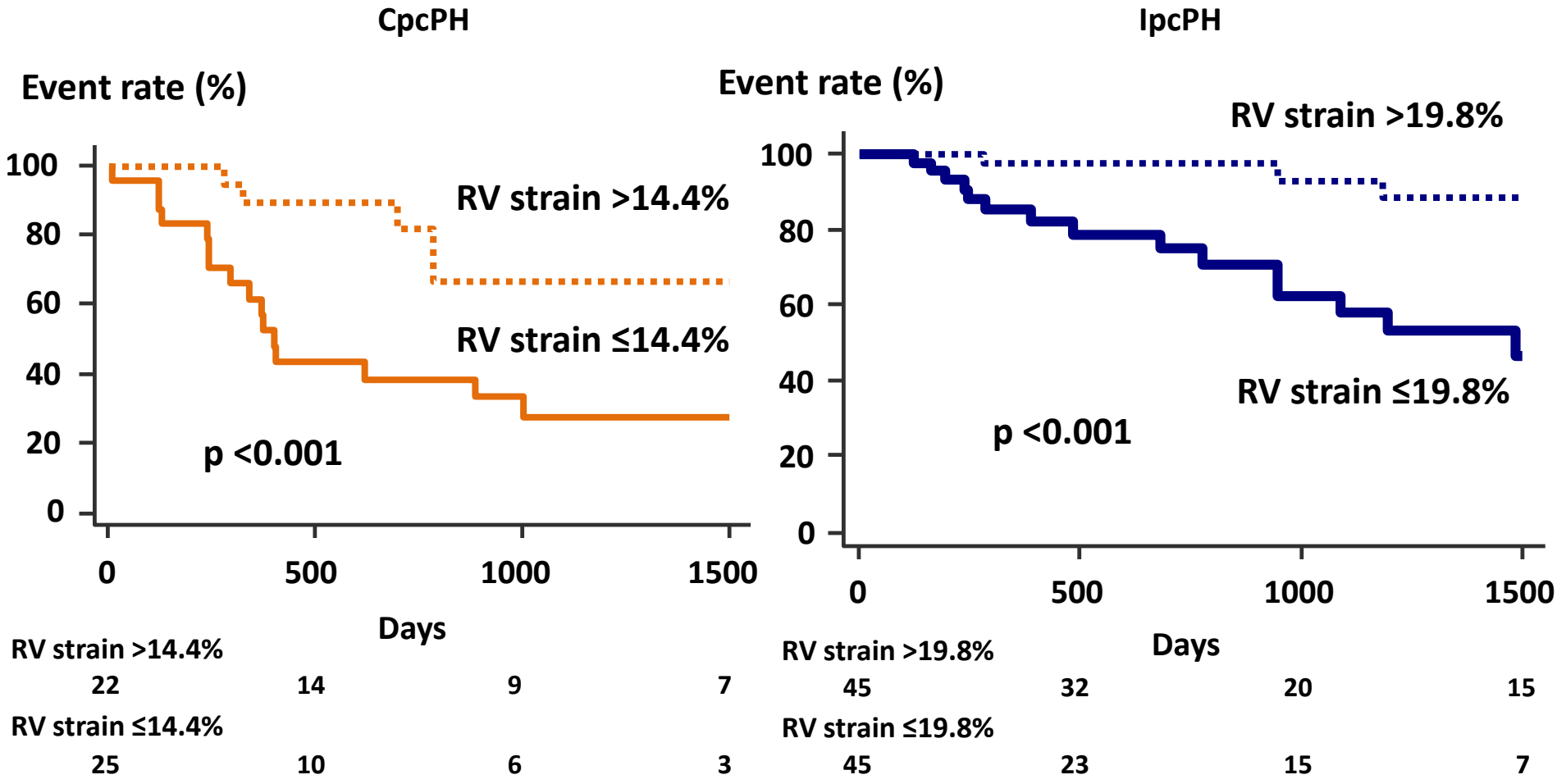

Event rate (%)
100
80
60
40
20
0
IpcPH
CpcPH
p <0.001
0
500
Days
1000
1500
Number at risk
Ipc PH 90 55 35 22
Cpc PH 47 24 15 10

Figure 5



Number at risk				
IpcPH with HFpEF	50	35	23	15
CpcPH with HFpEF	21	13	7	4
IpcPH with HFrEF	40	20	12	7
CpcPH with HFrEF	26	11	8	6

Figure 6


CpcPH
Event rate (%)
100
80
60
40
20
0
RV strain >14.4%
RV strain ≤14.4%
p <0.001
0
500
1000
1500
Days
RV strain >14.4%
22
14
9
7
RV strain ≤14.4%
25
10
6
3
IpcPH
Event rate (%)
RV strain >19.8%
RV strain ≤19.8%
p <0.001
RV strain >19.8%
45
32
20
15
RV strain ≤19.8%
45
23
15
7