Original Article

Prognostic Value of An Echocardiographic Index Reflecting Right Ventricular Operating Stiffness in Patients With Heart Failure

Ryosuke Fujisawa, MS[1], Kazunori Okada, PhD[2], Sanae Kaga, PhD[2], Michito Murayama, MS[1,3], Masahiro Nakabachi, MS[3], Shinobu Yokoyama[3], Hisao Nishino[3], Asuka Tanemura, BS[3], Nobuo Masauzi, MD, PhD[2], Ko Motoi, MD[4], Suguru Ishizaka, MD[4], Yasuyuki Chiba, MD[4], Shingo Tsujinaga, MD, PhD[4], Hiroyuki Iwano, MD, PhD[4] and Toshihisa Anzai, MD, PhD[4]

[1]Graduate School of Health Sciences, Hokkaido University

[2]Faculty of Health Sciences, Hokkaido University

[3]Diagnostic Center for Sonography, Hokkaido University Hospital

[4]Department of Cardiovascular Medicine, Faculty of Medicine and Graduate School of Medicine, Hokkaido University

***Corresponding author:** Kazunori Okada, Faculty of Health Sciences, Hokkaido University, N12-W5, Kita-Ku, Sapporo 060-0812, Japan.

Tel./Fax: +81-11-706-3730. Email: ichinori@hs.hokudai.ac.jp

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ABSTRACT

Purpose: We recently reported a noninvasive method for the assessment of right ventricular (RV) operating stiffness that is obtained by dividing the atrial-systolic descent of the pulmonary artery-RV pressure gradient ($PRPGD_{AC}$) derived from the pulmonary regurgitant velocity by the tricuspid annular plane movement during atrial contraction ($TAPM_{AC}$). Here, we investigated whether this parameter of RV operating stiffness, $PRPGD_{AC}/TAPM_{AC}$, is useful for predicting the prognosis of patients with heart failure (HF).

Methods: We retrospectively included 127 hospitalized patients with HF who underwent an echocardiographic examination immediately pre-discharge. The $PRPGD_{AC}/TAPM_{AC}$ was measured in addition to standard echocardiographic parameters. Patients were followed until 2 years post-discharge. The endpoint was the composite of cardiac death, readmission for acute decompensation, and increased diuretic dose due to worsening HF.

Results: 58 patients (46%) experienced the endpoint during follow-up. Univariable and multivariable Cox regression analyses demonstrated that the $PRPGD_{AC}/TAPM_{AC}$ was associated with the endpoint. In a Kaplan-Meier analysis, the event rate of the greater $PRPGD_{AC}/TAPM_{AC}$ group was significantly higher than that of the lesser $PRPGD_{AC}/TAPM_{AC}$ group. In a sequential Cox analysis for predicting the endpoint's occurrence, the addition of $PRPGD_{AC}/TAPM_{AC}$ to the model including age, sex, NYHA functional classification, brain natriuretic peptide level, and several echocardiographic parameters including tricuspid annular plane systolic excursion significantly improved the predictive power for prognosis.

Conclusion: A completely noninvasive index of RV operating stiffness, $PRPGD_{AC}/TAPM_{AC}$, was useful for predicting prognoses in patients with HF, and it showed an incremental prognostic value over RV systolic function.

Keywords: echocardiography, right ventricular stiffness, heart failure, prognosis

INTRODUCTION

Ventricular diastolic dysfunction is generally considered to precede systolic dysfunction **[1]**, and one of the pathophysiological mechanisms of diastolic dysfunction is ventricular operating stiffness **[1]**. An increase in the ventricular operating stiffness, which is usually associated with elevated end-diastolic pressure, may lead to a secondary increase of atrial pressure and subsequent congestion **[1,2]**. The detection of increased ventricular operating stiffness may thus contribute to the management of patients with early-stage heart failure (HF) by helping prevent acute decompensation **[1–7]**.

In the last decade, the prognostic significance of right ventricular (RV) systolic dysfunction in patients with left-sided HF has been reported **[8–10]**, and the importance of evaluating RV function has been attracting attention. The evaluation of RV stiffness rather than RV systolic function was reported to be more useful for predicting a poor prognosis in patients with pulmonary arterial hypertension **[11]**. Right ventricular operating stiffness may also be more useful for predicting the prognoses of patients with left-sided HF, but this has not been established. The standard measurement of ventricular operating stiffness requires invasive pressure recording, which cannot be performed in outpatients **[4,5]**. We recently reported a noninvasive method for the assessment of RV operating stiffness which is obtained by dividing the descent of the pulmonary artery (PA)-RV pressure gradient during atrial contraction derived from the pulmonary regurgitant (PR) velocity ($PRPGD_{AC}$) by the tricuspid annular plane movement during atrial contraction ($TAPM_{AC}$) **[12]**. We conducted the present study to determine whether the $PRPGD_{AC}/TAPM_{AC}$ method is useful for predicting the prognoses of patients with HF.

METHODS

Subjects and Protocol

We retrospectively included 404 consecutive chronic HF patients who were admitted to Hokkaido University Hospital from January 2014 to December 2017 for any reason and underwent an echocardiographic examination immediately before discharge. We excluded patients with an implanted left ventricular (LV) assist device (n=8) and those under hemodialysis (n=6), valvular heart disease with surgical indication (n=27), congenital heart disease (n=6), or chronic thromboembolic pulmonary hypertension (n=1). Patients with arrhythmias such as atrial fibrillation, atrial flutter, and advanced atrioventricular block (n=110), post-tricuspid annuloplasty (n=2), and those who were followed-up by other hospitals (n=77) were also excluded. Among the remaining 167 patients, an adequate Doppler flow velocity waveform of PR was not available in 40 patients; 127 patients were finally included in this study (**Fig. 1**).

We retrospectively investigated each patient's clinical demographics at the time of discharge by reviewing the patient's electronic medical records. The underlying diseases of these 127 patients were cardiomyopathy in 61 patients (48%), ischemic heart disease in 36 (29%), valvular heart disease in 19 (15%), hypertensive heart disease in nine (7%), and pericardial heart disease in one (1%).

Echocardiographic Measurements

A comprehensive echocardiographic examination was performed for each patient with a Vivid E9 ultrasound system equipped with an M5S probe (GE Healthcare, Little Chalfont, UK), an iE33 ultrasound system with an S5 probe (Philips Medical Systems, Eindhoven, The Netherlands), a prosound F75 ultrasound system with a UST-52127 probe (Hitachi Healthcare Systems, Shinagawa, Japan), or an Artida ultrasound system with a PST-30BT probe (Canon Medical Systems, Otawara, Japan) in accord with the guidelines of the American Society of Echocardiography (ASE) **[1,13]**.

The RV end-diastolic basal dimension, RV end-diastolic area, and RV end-systolic area were measured from the apical four-chamber image, and the RV fractional area change was calculated. The right atrial (RA) area was also measured and indexed for each patient's body surface area (BSA). The tricuspid annular plane systolic excursion (TAPSE) was measured in the apical four-chamber image **[14]**.

With standard Doppler echocardiography using the apical approach, the peak early-diastolic and atrial systolic transmitral flow velocities (E and A, respectively) were measured, and E/A was calculated. The peak early-diastolic mitral annular velocity (e′) was measured at the septal and lateral sides of the annulus and averaged, and E/e′ was calculated. The peak tricuspid regurgitant (TR) velocity was measured by continuous-wave Doppler echocardiography, and the peak systolic RV-RA pressure gradient (TRPG) was calculated using the simplified Bernoulli equation [**15**]. The LV diastolic function grade was assessed according to the ASE/EACVI (European Association of Cardiovascular Imaging) guidelines **[1]**. The pulmonary artery systolic pressure (PASP) was estimated as the sum of the TRPG and the estimated right atrial pressure, and the TAPSE/PASP was calculated as a surrogate for RV-PA coupling [**16**].

Estimation of RV Operating Stiffness

As we reported **[12]**, we measured the continuous-Doppler PR velocities just before RA contraction and at bottom of the dip during RA contraction to calculate the PA-RV pressure gradients at both time points by using a simplified Bernoulli equation. We then calculated the $PRPGD_{AC}$ by subtracting the latter time point's value from the former. We also measured the $TAPM_{AC}$, which reflects the RV volume change of the same time phase as the $PRPGD_{AC}$. We then calculated $PRPGD_{AC}/TAPM_{AC}$ as an index of RV operating stiffness (**Fig. 2**).

Follow-Up and Primary Endpoint

We retrospectively reviewed each patient's electronic medical records until 2 years after discharge, and we carefully investigated the occurrence of cardiac death, readmission due to acute decompensation of HF, and increased diuretic dose due to worsening HF. We defined the occurrence of these as a composite event as the primary endpoint.

Statistical Analyses

All statistical analyses were performed with standard statistical software (IBM SPSS ver. 25 for Windows, IBM, Armonk, NY). All continuous data are expressed as the mean ± SD or median (interquartile range) as appropriate, and all categorical data are expressed as counts and percentages. Normality for continuous data was checked using histograms and the Shapiro-Wilk test. The differences between two groups divided by the presence of composite endpoint occurrences were compared using the unpaired t-test or Mann-Whitney U-test, and the proportions between the two groups were compared using Fisher's exact test. The association between parameters and occurrences of the composite endpoint was assessed by univariate and multivariate Cox regression analyses. The cumulative event rate for the primary endpoint according to the $PRPGD_{AC}/TAPM_{AC}$ of >0.6, which is the optimal cut-off value predicting RV end-diastolic pressure >12 mmHg **[12]**, was compared by a Kaplan-Meier analysis with log-rank test. For identifying incremental values of $PRPGD_{AC}/TAPM_{AC}$, we performed a sequential Cox analysis and compared the change of global χ^2 with the previously mentioned clinical variables. For all statistical tests, a p-value <0.05 was deemed significant.

RESULTS

Patient Characteristics

The clinical, laboratory, and echocardiographic parameters of the patients are summarized in **Table 1**. Among the 127 patients, LV dilation (LV end-diastolic volume index >74 mL/m^2 for males, >61 mL/m^2 for females) was present in 67 (53%) patients; LV hypertrophy (LV mass index >115 g/m^2 for males, >95 g/m^2 for females) was present in 99 patients (78%), reduced LV systolic function (LV ejection fraction <40%) was present in 65 patients (51%), elevated estimated pulmonary artery pressure (TRPG >31 mmHg) was present in 32 patients (25%), and decreased RV systolic function (TAPSE <16 mm) was present in 36 patients (28%).

During a follow-up of 2 years, the primary endpoint occurred in 58 of the 127 patients (46%), which included cardiac death (n=1), readmissions for acute decompensation (n=24), and increased diuretics due to worsening HF (n=33). In the group of 58 patients with the primary endpoint, the values of systolic blood pressure (SBP), cholinesterase level, TAPSE, and $TAPM_{AC}$ were significantly smaller, and the proportions of NYHA functional classification ≥III, natural log-transformed plasma brain natriuretic peptide (BNP) level (Log-BNP), LA volume index, E/A, E/e′, the proportion of ASE diastolic function grade >II, TRPG, TAPSE/PASP, $PRPGD_{AC}$, and $PRPGD_{AC}/TAPM_{AC}$ were significantly greater than those of the patients without the primary endpoint.

The Prognostic Value of Non-invasive RV Operating Stiffness

The results of the univariable and multivariable Cox regression analyses are summarized in **Table 2** and **Table 3**. In the univariable analysis, the SBP, proportion of NYHA functional classification >III, cholinesterase level, Log-BNP, LA volume index, proportion of ASE diastolic function grade >II, TRPG, TAPSE, TAPSE/PASP, and $PRPGD_{AC}/TAPM_{AC}$ were significantly associated with the primary endpoint. In the multivariable analyses, in which the parameters showing p-values <0.05

in the univariable Cox regression analysis were incorporated as explanatory variables, $PRPGD_{AC}/TAPM_{AC}$ remained as a significant independent predictor of the primary endpoint in all models. The Kaplan-Meier analysis showed that the >0.6 $PRPGD_{AC}/TAPM_{AC}$ group (n=21) was at significantly higher risk of the composite events compared to the ≤0.6 $PRPGD_{AC}/TAPM_{AC}$ group (n=106), $p<0.001$ (**Fig. 3**).

In the sequential Cox analysis for predicting the occurrence of the primary endpoint, the addition of $PRPGD_{AC}/TAPM_{AC}$ to the model including age, sex, NYHA functional classification, Log-BNP, LV mass index, LV ejection fraction (LVEF), ASE diastolic function grade, and TAPSE significantly improved the predictive power for prognosis (**Fig. 4**).

DISCUSSION

The results of our present analyses demonstrated that the $PRPGD_{AC}/TAPM_{AC}$, an echocardiographic index reflecting RV stiffness, could independently predict the prognosis of patients with chronic HF, and we observed that the patients with a $PRPGD_{AC}/TAPM_{AC}$ value >0.6 experienced poor prognoses compared to those with a value ≤0.6. In addition, $PRPGD_{AC}/TAPM_{AC}$ showed an incremental prognostic value over RV systolic function assessed by TAPSE. To our knowledge, this is the first study to demonstrate that augmented RV stiffness was associated with poor prognosis in patients with chronic HF.

Importance of Assessing RV Stiffness

Several investigators reported that the HF patients with RV systolic dysfunction have a worse prognosis compared to those without it **[8–10]**. The chronic increase in the RV afterload due to an increase in the pulmonary artery pressure caused by chronically elevated LA pressure was thought

to lead to RV systolic dysfunction **[15–17]**. Trip et al. reported that in patients with pulmonary arterial hypertension, the RV diastolic stiffness index (calculated from an RV pressure-volume loop analysis using cardiac catheterization and cardiac magnetic resonance imaging [CMR]) had more predictive value than the CMR-derived RV ejection fraction **[11]**. In the present study, TAPSE, one of the indices of RV systolic function, and TAPSE/PASP, an index of RV-PA coupling, were significant predictors of patient prognosis in the univariable analysis but were not selected as an independent predictor in the multivariate analysis. In contrast, $PRPGD_{AC}/TAPM_{AC}$ remained as an independent predictor in the multivariable Cox regression analysis. These results suggest that, consistent with the aforementioned study, RV stiffness may be a better predictor of prognosis for patients with HF than the patients' RV systolic function.

Because increased RV stiffness is considered to be strongly related to increased right atrial pressure, an increase in right ventricular stiffness would be useful for detecting patients at high risk of venous congestion, regardless of whether the patient's TAPSE is reduced or not. For example, in patients without obvious HF symptoms but with abnormally increased RV stiffness, greater venous return to the heart caused by exercise or an excessive circulatory volume overload may cause increased RV end-diastolic pressure and RA pressure, resulting in systemic congestion and organ dysfunction **[18–20]**. We thus speculate that these factors may be the reasons why the prognostic value of increased right ventricular stiffness in the present study was superior to that of TAPSE.

Importance of non-invasive assessment of RV stiffness

The most established method to assess RV stiffness is the determination of the RV end-diastolic pressure-volume relationship **[11,21–23]**; however, this method requires an invasive pressure measurement and has a limitation of repeatability **[24]**. The ratio of the late-diastolic RV pressure

increase to the volume increase is considered to be a measure of RV operating stiffness, but this method still requires pressure measurement by cardiac catheterization **[25]**. Especially for patients with HF, an easily obtained and repeatable method is desirable because the hemodynamic parameters are variable depending on the patient's condition. We recently proposed a completely noninvasive index of RV operating stiffness, i.e., $PRPGD_{AC}/TAPM_{AC}$, which is derived by using the echocardiographic PR velocity waveform and the tricuspid annular movement during atrial contraction. The PR waveform reflects the diastolic pressure difference between PA and RV, thus, $PRPGD_{AC}$ would have reflected the RV pressure increase during the atrial contraction [**26**]. The tricuspid annular movement reflects RV volume change because RV longitudinal shortening has been recognized as an important factor determining RV contraction [**27**]. Actually, in an earlier investigation of 81 patients with varying cardiovascular diseases, the $PRPGD_{AC}$ was well correlated with invasively measured RV pressure increase (ΔP_{AC}) ($r=0.84$, $p<0.001$), $TAPM_{AC}$ was with atrial systolic RV volume increase (ΔV_{AC}) ($r=0.69$, $p<0.001$). Finally, the $PRPGD_{AC}/TAPM_{AC}$ was well correlated with the index of RV operating stiffness ($\Delta P_{AC}/\Delta V_{AC}$) and RV end-diastolic pressure ($r=0.84$, $p<0.001$ and $r<0.80$, $p<0.001$, respectively), and it showed excellent diagnostic performance for distinguishing patients with increased RV end-diastolic pressure **[12]**. Using the $PRPGD_{AC}/TAPM_{AC}$ allows the repeated assessment of RV operating stiffness and has a high cost-effectiveness ratio. We thus propose that this index will be useful for the assessment of RV stiffness in patients with HF.

Recently, Tello et al. performed a precise study that revealed the relationship between cardiac CMR-derived RV strain parameter (ratio of RV global longitudinal strain to RV end-diastolic volume index) and the invasive pressure-volume loop-derived RV diastolic stiffness parameter in patients with pre-capillary pulmonary hypertension [**28**]. This parameter may also be useful in HF patients. However, because several patients with cardiomyopathy or inferior myocardial infarction

have RV systolic dysfunction despite the absence of pulmonary hypertension, and this might affect the relationships between the RV strain parameter and RV stiffness. Further studies are required to determine whether CMR-derived RV strain parameters are also useful in assessing RV stiffness in patients with HF.

The Incremental Value of Assessing RV stiffness

The plasma BNP level and ASE diastolic function grade have been reported to be useful for evaluating hemodynamics and predicting the prognosis in patients with HF **[1,29–34]**. The BNP level reflects the magnitude of the hemodynamic ventricular load **[35–39]**, and the current ASE diastolic function grade focuses mainly on detecting elevated LV filling pressure **[1]**. Although these indices are useful for assessing worsening left HF, they are not suitable for detecting RV dysfunction. Our present findings demonstrate that in addition to detecting left-sided cardiac dysfunction with conventional echocardiographic indices and the BNP level, the detection of increased RV stiffness using $PRPGD_{AC}/TAPM_{AC}$ significantly improves the predictive power for the risk of the development of worsening HF (**Fig. 4**).

The evaluation of $PRPGD_{AC}/TAPM_{AC}$ in addition to conventional indices during echocardiography at HF patients' time of discharge or outpatient follow-up may provide more accurate discrimination of patients at a high risk of worsening HF who have increased RV stiffness but no RV systolic dysfunction. Intensified treatment and careful monitoring of such patients may help avoid the occurrence of cardiac events.

Limitations

There were several limitations to the present study. Firstly, the $PRPGD_{AC}/TAPM_{AC}$ cannot be measured when the PR waveform cannot be obtained. In this retrospective study, the rate of PR

waveform acquisition was 127 of 167 patients (76%). This rate might be improved if we had conducted a prospective study, but the existence of some unmeasurable patients is still a limitation of the new $PRPGD_{AC}/TAPM_{AC}$ method. In addition, this method cannot be applied to patients without effective atrial contraction or synchronized atrial activity due to arrhythmias such as atrial fibrillation, atrial flutter, and complete atrioventricular block. Secondly, we confirmed the relationship of the $PRPGD_{AC}/TAPM_{AC}$ to late-diastolic RV pressure increase per volume increase and RVEDP in the previous study. However, these are load-dependent indices and do not represent the gold standard RV stiff index, EDPVR, assessed from the invasive pressure-volume loop. A further study assessing the relationship between the $PRPGD_{AC}/TAPM_{AC}$ and EDPVR is desirable. Thirdly, the number of subjects was small, and the results were from a single institution. Finally, in this retrospective analysis, 58 patients experienced the primary endpoint, and more than half of the events were a soft endpoint (increased diuretics due to worsening HF). We confirmed that in all of the patients who experienced this event, it was driven by weight gain or increased shortness of breath during regular visits. However, it should be noted that the decision to increase the diuretic dose was left up to the attending physicians and may not be a uniform criterion.

CONCLUSION

The $PRPGD_{AC}/TAPM_{AC}$, a completely noninvasive index of RV operating stiffness, was more useful in predicting the prognosis in patients with chronic HF than the RV systolic function.

Compliance with Ethical Standards

Conflicts of Interest: Nothing to disclose.

Ethics approval: This study was carried out according to the principles of the Declaration of Helsinki and was approved as a retrospective observational study by both the Research Ethics Committee of Hokkaido University Hospital and the Ethics Committee of the Faculty of Health Sciences at Hokkaido University. Instead of obtaining informed consent, the program of the present study had been open to the public both through the Internet home page and on the bulletin board of Hokkaido University Hospital; patients who did not wish to participate could request that their data be deleted from the study at any time.

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Table 1. Patient characteristics

Variables	All patients (n=127)	Without endpoint (n=69)	With endpoint (n=58)	p-value
Baseline characteristics:				
Age, yrs	64±15	64±16	64±15	0.92
Male/female	83/44	47/22	36/22	0.48
BSA, m^2	1.60±0.20	1.63±0.22	1.57±0.18	0.10
BMI, kg/m^2	22.0±3.7	22.6±3.7	21.4±3.5	0.054
SBP, mmHg	108±18	112±18	103±16	0.004
Heart rate, bpm	64±12	65±12	62±11	0.15
NYHA functional classification ≥III, n, %	7 (6)	1 (1)	6 (10)	0.04
Ischemic heart disease, n, %	36 (28)	19 (28)	17 (29)	0.83
Laboratory findings:				
Hemoglobin, g/dL	12.3±1.8	12.4±1.9	12.2±1.8	0.46
Albumin, g/dL	3.9 (3.5–4.2)	3.9 (3.6–4.2)	3.8 (3.5–3.8)	0.41
Cholinesterase, U/L	261±78	276±80	243±72	0.02
Creatinine, mg/dL	0.86 (0.71–1.20)	0.86 (0.72–1.17)	0.90 (0.71–1.23)	0.82
Sodium, mEq/L	138±4	139±3	138±4	0.09
HbA1c, %	6.0±0.8	6.1±0.7	6.0±0.8	0.47
BNP, pg/mL	193 (83–444)	107 (57–232)	347 (158–531)	<0.001
Echocardiography:				
LV end-diastolic volume index, mL/m^2	89±48	84±43	94±53	0.25
LV mass index, g/m^2	129 (112–159)	131 (110–154)	127 (113–174)	0.64
LVEF, %	41±17	41±17	40±17	0.91

Left atrial volume index, mL/m^2	48 (37–60)	44 (36–55)	55 (42–74)	0.007
E/A	1.0 (0.7–1.8)	0.8 (0.6–1.2)	1.6 (0.9–2.6)	<0.001
E/e′	13.6±6.6	12.5±6.1	15.0±7.0	0.046
ASE diastolic function grade ≥II, n, %	58 (46)	21 (30)	37 (64)	<0.001
Mitral regurgitation ≥moderate, n, %	29 (23)	16 (23)	13 (22)	0.99
Tricuspid regurgitation ≥moderate, n, %	11 (9)	3 (4)	8 (14)	0.07
RV end-diastolic basal dimension, mm	38±7	39±7	38±8	0.51
TAPSE, mm	20±6	21±6	18±5	0.02
RV fractional area change, %	38±11	38±11	37±10	0.62
Right atrial area index, cm^2/m^2	10.2±2.6	9.9±2.6	10.6±2.6	0.15
Inferior vena cava dimension, mm	13±4	13±3	13±4	0.35
Estimated right atrial pressure ≥8 mmHg, n, %	15 (12)	5 (7)	10 (17)	0.08
TRPG, mmHg	28±12	24±9	31±13	0.005
TAPSE/PASP, mm/mmHg	0.65±0.27	0.57±0.26	0.73±0.26	0.001
$PRPG_{preA}$, mmHg	7±4	7±4	8±4	0.16
$PRPGD_{AC}$, mmHg	2.9±1.6	2.6±1.7	3.2±1.5	0.03
$TAPM_{AC}$, mm	9.0±3.3	10.1±3.4	7.7±2.8	<0.001
$PRPGD_{AC}/TAPM_{AC}$, mmHg/mm	0.36±0.27	0.27±0.19	0.48±0.30	<0.001

The primary endpoint was defined as the composite of cardiac death, readmission for acute decompensation of heart failure, and increased diuretics dose due to worsening heart failure. ASE: American Society of Echocardiography, BMI: body mass index, BSA: body surface area, E/A: ratio of the peak early-diastolic and peak atrial systolic transmitral flow velocities, E/e′: ratio of the peak early-diastolic transmitral flow velocity and the peak early-diastolic mitral annular velocity, HbA1c: hemoglobin A1c, Log-BNP: common log-transformed plasma brain natriuretic peptide, LV: left ventricular, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association, $PRPGD_{AC}$: pulmonary regurgitation pressure gradient difference during atrial contraction, $PRPG_{preA}$: end-diastolic pulmonary artery-right ventricular pressure

gradient, RV: right ventricular, SBP: systolic blood pressure, $TAPM_{AC}$: tricuspid annular plane movement during atrial contraction, TAPSE: tricuspid annular plane systolic excursion, TAPSE/PASP: ratio of the TAPSE to pulmonary artery systolic pressure, TRPG: systolic right ventricular-right atrial pressure gradient.

Table 2. Univariate Cox regression analysis results

Variables	χ^2	HR (95%CI)	p-value
Age	0.002	1.00 (0.98–1.02)	0.97
Sex	0.74	0.79 (0.47–1.35)	0.39
BSA	2.76	0.35 (0.10–1.21)	0.10
BMI	3.28	0.93 (0.86–1.01)	0.07
SBP	6.76	0.98 (0.96–0.99)	0.009
Heart rate	1.76	0.98 (0.96–1.01)	0.19
NYHA functional classification ≥III	11.5	4.50 (1.89–10.8)	0.001
Ischemic heart disease	0.02	0.96 (0.54–1.69)	0.88
Hemoglobin	1.63	0.91 (0.79–1.05)	0.20
Albumin	0.56	0.84 (0.53–1.33)	0.46
Cholinesterase	5.13	0.996 (0.992–0.999)	0.024
Creatinine	0.26	1.10 (0.77–1.55)	0.61
Sodium	2.22	0.95 (0.89–1.02)	0.14
HbA1c	0.77	0.85 (0.59–1.23)	0.85
Log-BNP	16.3	1.73 (1.33–2.25)	<0.001
LV end-diastolic volume index	1.22	1.00 (0.99–1.01)	0.27
LV mass index	1.83	1.01 (0.998–1.01)	0.18
LVEF	0.22	1.00 (0.99–1.02)	0.64
Mitral regurgitation ≥moderate	0.02	1.05 (0.57–1.95)	0.88
Tricuspid regurgitation ≥moderate	3.56	2.06 (0.97–4.34)	0.059
ASE diastolic function grade ≥II	16.0	3.06 (1.77–5.28)	<0.001
RV end-diastolic basal dimension	0.43	0.99 (0.95–1.03)	0.51
TAPSE	4.56	0.95 (0.90–0.996)	0.03
RV fractional area change	0.20	1.00 (0.97–1.02)	0.66
Right atrial area index	2.84	1.08 (0.98–1.19)	0.09
Estimated right atrial pressure	2.71	1.12 (0.98–1.29)	0.10
TAPSE/PASP	10.1	0.15 (0.05–0.49)	0.002
$PRPGD_{AC}/TAPM_{AC}$	18.5	4.25 (2.20–8.21)	<0.001

Abbreviations are the same as in Table 1.

Table 3. Multivariate Cox regression analysis results

Variables	Model 1			Model 2			Model 3			Model 4			Model 5		
	χ^2	HR (95%CI)	p	χ^2	HR (95%CI)	p	χ^2	HR (95%CI)	p	χ^2	HR (95%CI)	p	χ^2	HR (95%CI)	p
Age, per 5 yrs	1.60	1.06 (0.97–1.17)	0.21	0.71	1.04 (0.95–1.14)	0.40	0.99	1.05 (0.96–1.15)	0.32	0.46	1.03 (0.94–1.13)	0.50	1.37	1.05 (0.97–1.15)	0.24
SBP, per 10 mmHg	4.95	0.80 (0.66–0.97)	0.03	6.75	0.79 (0.66–0.94)	0.009	4.01	0.83 (0.70–0.99)	0.045	3.23	0.84 (0.70–1.02)	0.07	3.11	0.85 (0.71–1.02)	0.08
NYHA functional classification ≥III	4.99	3.27 (1.16–9.25)	0.03												
Cholinesterase, per 10 U/L				2.10	0.97 (0.94–1.01)	0.15									
Log-BNP, per 1 pg/mL							7.12	1.49 (1.11–2.01)	0.008						
ASE diastolic function grade ≥II										5.79	2.13 (1.15–3.94)	0.02			
TAPSE/PASP, per 0.1 mm/mmHg													2.55	0.87 (0.74–1.03)	0.11
TAPSE, per 1 mm	1.01	0.97 (0.92–1.03)	0.32	0.74	0.98 (0.92–1.03)	0.39	0.76	0.98 (0.92–1.03)	0.38	0.35	0.98 (0.93–1.04)	0.56	0.35	1.02 (0.95–1.10)	0.55
$PRPGD_{AC}/TAPM_{AC}$, per 0.1 mmHg/mm	18.8	1.17 (1.09–1.26)	<0.001	8.83	1.12 (1.04–1.21)	0.003	6.19	1.10 (1.02–1.19)	0.01	7.97	1.11 (1.03–1.20)	0.005	7.88	1.12 (1.03–1.21)	0.005

Abbreviations are the same as in Table 1.

Figure Legends

Fig. 1. Inclusion and exclusion criteria for the study subjects.

Fig. 2. Measurement of right ventricular operating stiffness index by echocardiography. A: Atrial systolic dip in the pulmonary regurgitation velocity waveform obtained by continuous-wave Doppler echocardiography ($PRPGD_{AC}$). **B:** Tricuspid annular plane movement during atrial contraction obtained by M mode echocardiography ($TAPM_{AC}$). The index of right ventricular operating stiffness was calculated by dividing A by B ($PRPGD_{AC}/TAPM_{AC}$).

Fig. 3. Kaplan-Meier analysis for the composite outcome of cardiac death, readmission for acute decompensation of heart failure, and increased diuretic dose due to worsening heart failure.

Fig. 4. Sequential Cox analysis of right ventricular stiffness index in predicting cardiac events. Model 1: age, sex, NYHA functional classification, Log-BNP. Model 2: Model 1+LVMI, LVEF. Model 3: Model 2+ASE diastolic function grade. Model 4: Model 3+TAPSE. Model 5: Model 4+$PRPGD_{AC}/TAPM_{AC}$.

Figure 1

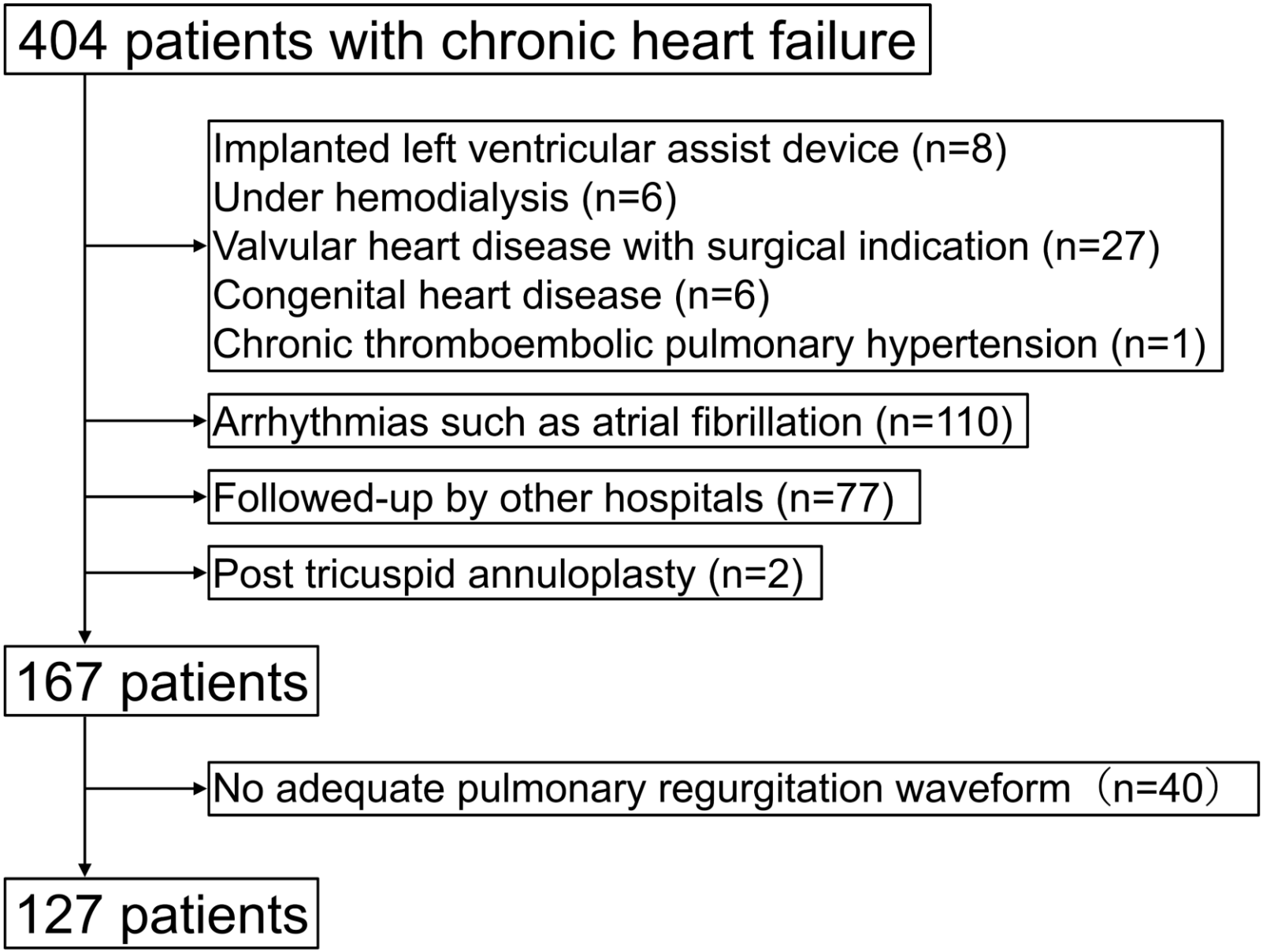
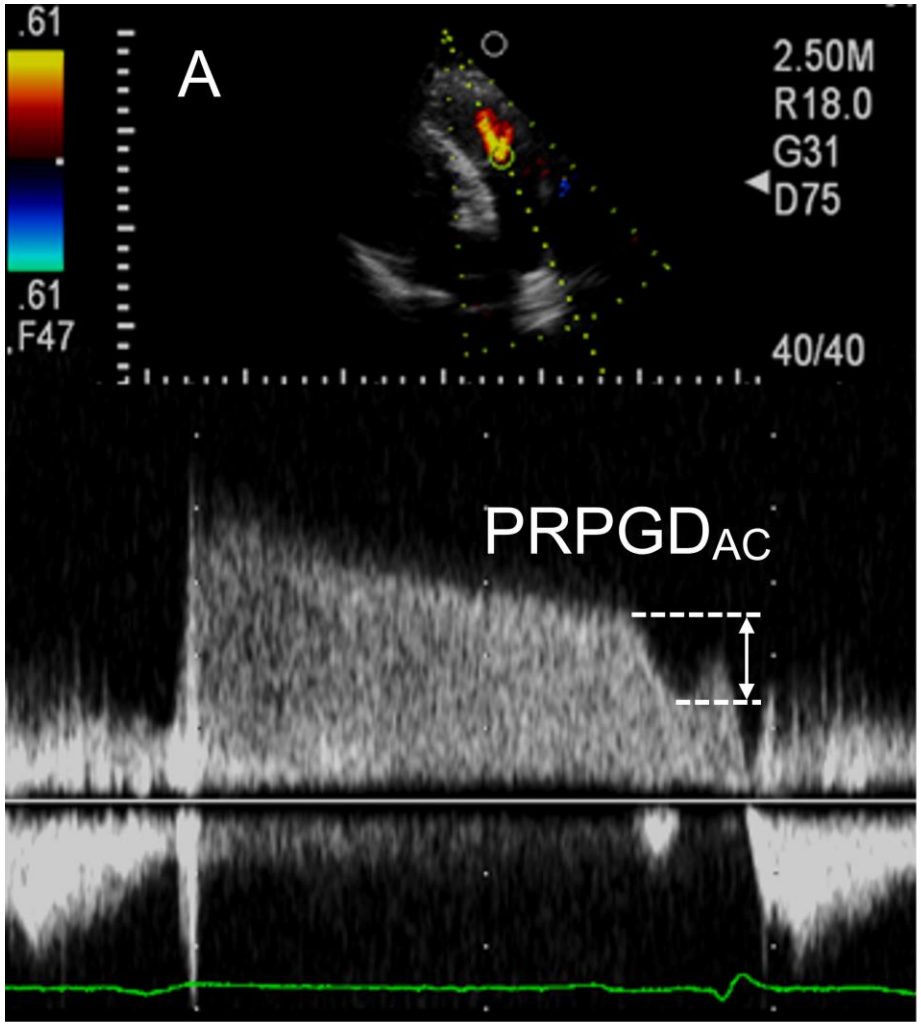

404 patients with chronic heart failure
Implanted left ventricular assist device (n=8)
Under hemodialysis (n=6)
Valvular heart disease with surgical indication (n=27)
Congenital heart disease (n=6)
Chronic thromboembolic pulmonary hypertension (n=1)
Arrhythmias such as atrial fibrillation (n=110)
Followed-up by other hospitals (n=77)
Post tricuspid annuloplasty (n=2)
167 patients
No adequate pulmonary regurgitation waveform（n=40）
127 patients

Figure 2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A
2.50M
R18.0
G31
D75
.61
F47
40/40
PRPGDAC

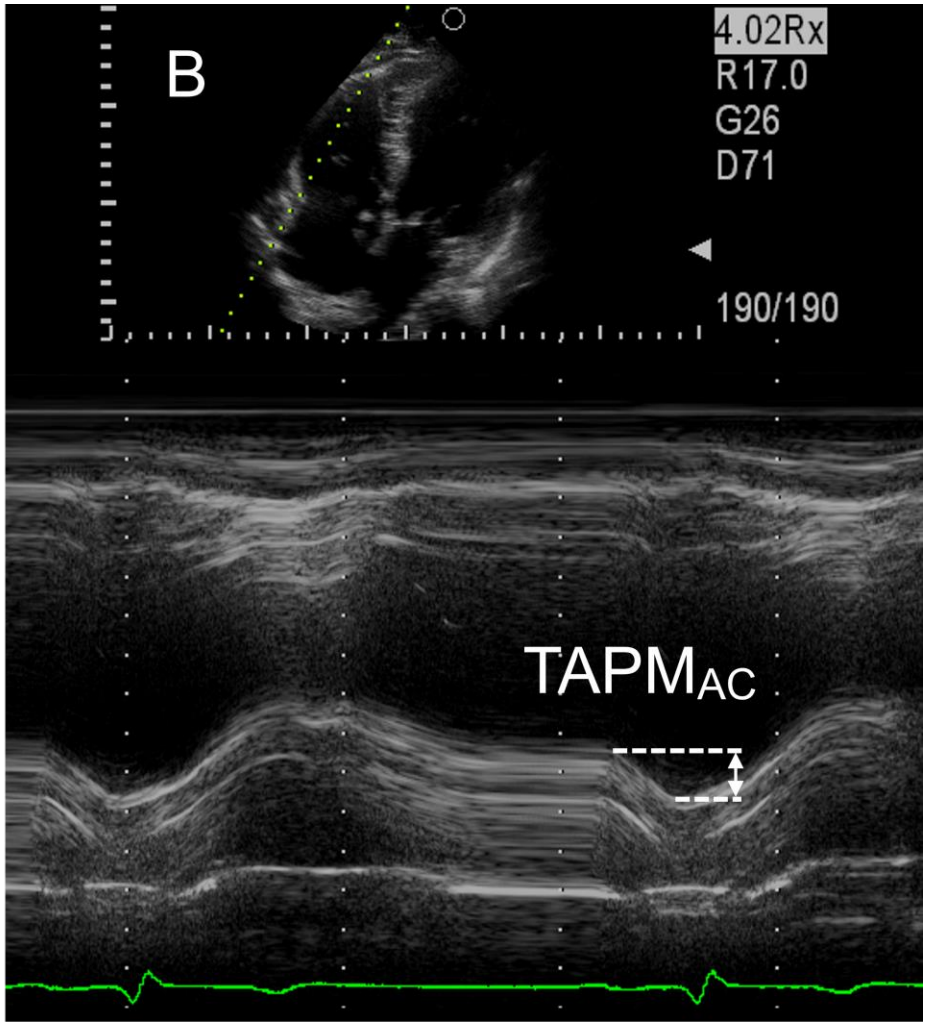
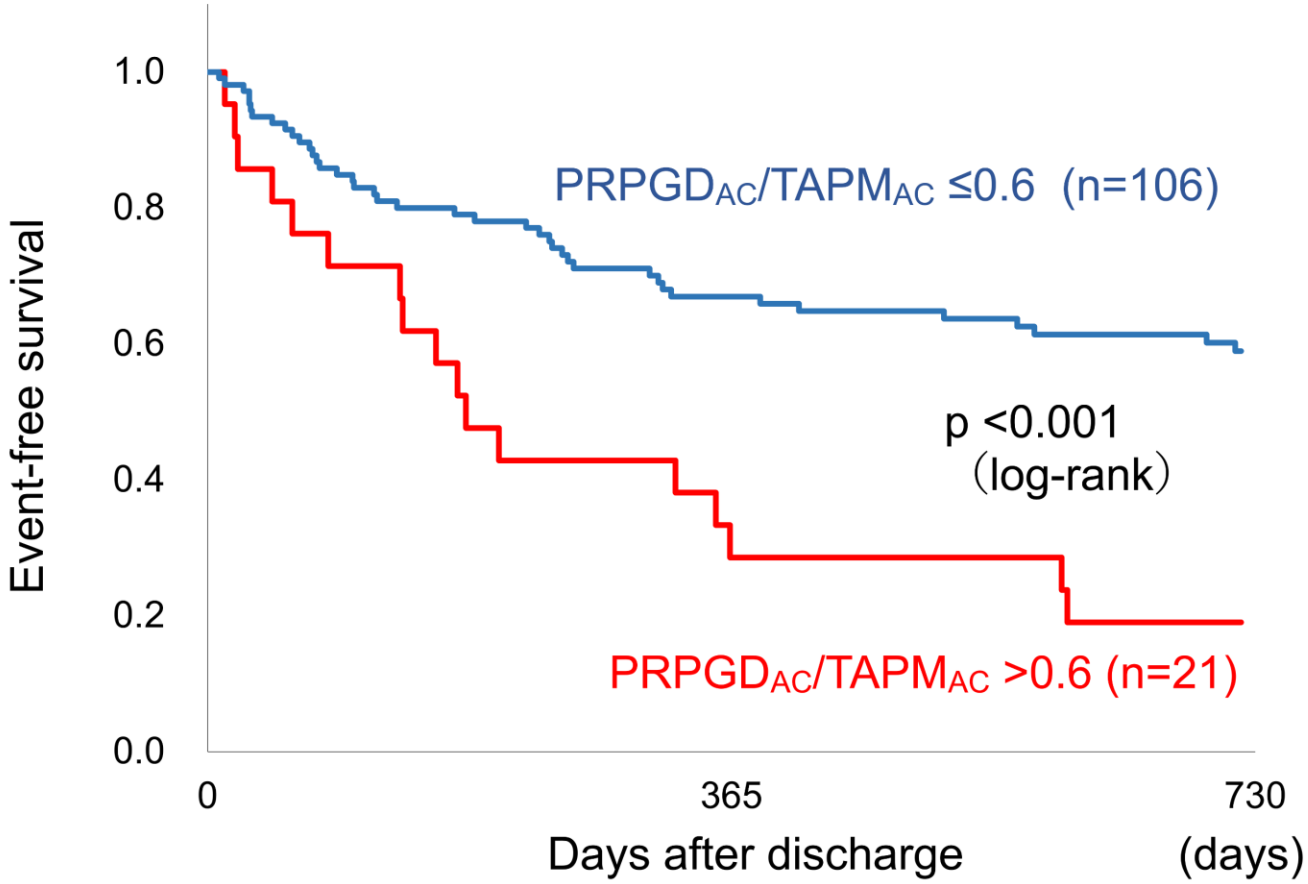

B
4.02Rx
R17.0
G26
D71
190/190
TAPMAC

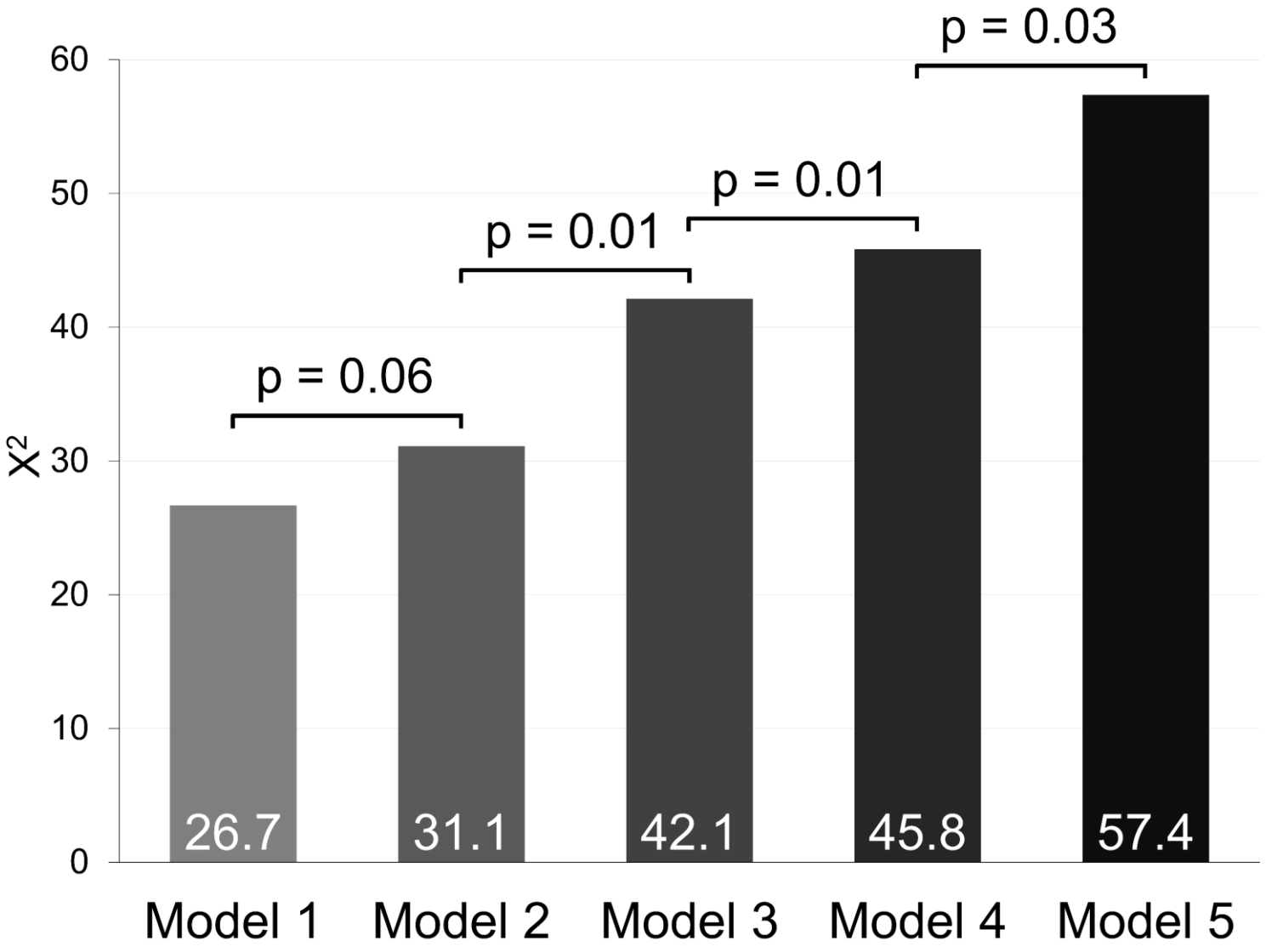
Figure 3



Number at risk

Days	0	180	365	545	730
PRPGD$_{AC}$/TAPM$_{AC}$ ≤0.6	106	80	63	55	46
PRPGD$_{AC}$/TAPM$_{AC}$ >0.6	21	10	6	6	4
Events	0	33	49	52	58

Figure 4


p = 0.03
p = 0.01
p = 0.01
p = 0.06
60
50
40
30
20
10
0
X2
26.7
31.1
42.1
45.8
57.4
Model 1
Model 2
Model 3
Model 4
Model 5