



## Prognostic Factors for Survival in Pulmonary Hypertension Due to Left Heart Disease

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**Background:** The epidemiological data of pulmonary hypertension (PH) due to left heart disease (LHD) are limited. This study investigated hemodynamic and clinical factors associated with mortality in patients with PH due to LHD.

**Methods and Results:** We conducted a retrospective review in 243 patients with PH due to LHD, defined as mean pulmonary arterial pressure  $\geq 25$  mmHg and pulmonary wedge pressure  $> 15$  mmHg at rest in right heart catheterization. Kaplan-Meier and Cox proportional hazard regression analyses were performed. Seventy-five patients died during an average follow-up of 52 months (range, 20–73 months). On multivariate analysis, only diastolic pulmonary vascular pressure gradient (DPG)  $\geq 7$  mmHg among hemodynamic measurements was a predictor of mortality. Elevated N-terminal pro-brain natriuretic peptide (NT-pro BNP), more severe New York Heart Association (NYHA) class, anemia, and renal dysfunction were more strongly associated with mortality. Mean right atrial pressure (RAP) and currently available markers of pulmonary vascular remodeling including transpulmonary pressure gradient (TPG) and pulmonary vascular resistance (PVR) had no effect on survival.

**Conclusions:** DPG is weakly associated with mortality in PH due to LHD. Clinical factors such as NT-pro BNP, NYHA class, anemia and renal dysfunction are superior predictors. The prognostic ability of hemodynamic factors such as mean RAP, TPG, PVR and DPG is limited. (*Circ J* 2016; **80**: 243–249)

**Key Words:** Left heart disease; Prognosis; Pulmonary hypertension

**P**ulmonary hypertension (PH) due to left heart disease (LHD), classified as group 2 PH according to the latest classification (Nice 2013), has the largest population among 5 groups of PH. PH due to LHD is caused by passive downstream elevation in the left atrial pressure (LAP), or by a combination of pulmonary vasculopathy.<sup>1,2</sup> Recent epidemiological studies in group 2 PH focused on markers of pulmonary vascular remodeling, such as transpulmonary pressure gradient (TPG),<sup>3–6</sup> pulmonary vascular resistance (PVR),<sup>3,4,6</sup> and diastolic pulmonary vascular pressure gradient (DPG).<sup>5–8</sup> The results obtained so far, however, are controversial. Furthermore, sustained PH leads to right ventricular dysfunction, which is partly represented as elevated mean right atrial pressure (RAP). The prognostic ability of these hemodynamic parameters including mean RAP, TPG, PVR, and DPG in the setting of group 2 PH has not been established. In this retrospective study, we reviewed 243 patients to characterize mortality, and to clarify hemodynamic parameters and clinical characteristics for predicting mortality in patients with PH due to LHD.

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### Methods

The subjects consisted of 243 patients with PH due to LHD enrolled from 1,098 consecutive patients who underwent right heart catheterization (RHC) between February 2000 and May 2013 at Hiroshima University Hospital, Hiroshima, Japan. Volume overload was treated with conventional diuretics prior to the RHC. To diagnose PH due to LHD, mean pulmonary arterial pressure (PAP)  $\geq 25$  mmHg and pulmonary wedge pressure (PWP)  $> 15$  mmHg at rest were used according to the guideline of the European Society of Cardiology.<sup>3</sup> The algorithm for patient selection is shown in **Figure 1**. In this retrospective review, hemodynamic measurements as well as clinical, laboratory, and echocardiographic parameters at the time of RHC were collected from medical records. RHC was performed on the 2nd hospital day (range, 1st–8th hospital day), and echocardiography was performed at the time of

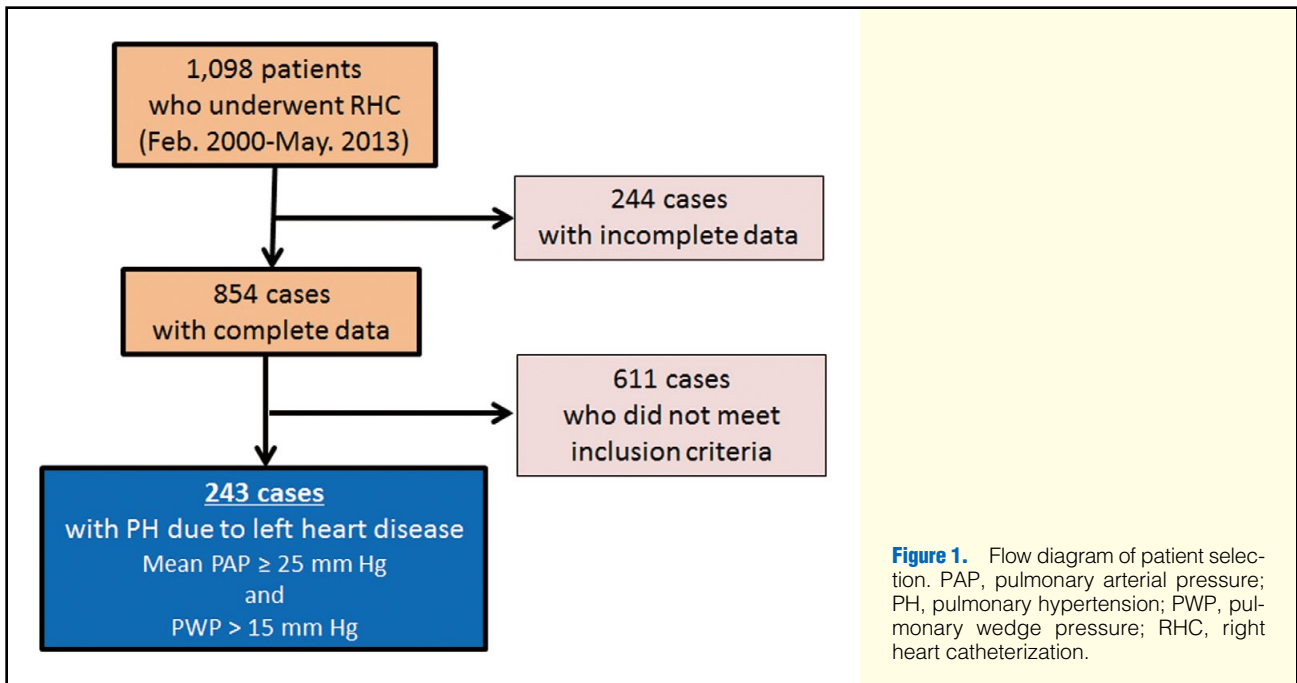
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admission (range, 0–6th hospital day). TPG (defined as mean PAP–mean PWP), PVR (defined as TPG/cardiac output [CO]), and DPG (defined as diastolic PAP–mean PWP) were obtained by calculation.<sup>3</sup> Moderate or severe valvular dysfunction were considered as potential etiologies. Left ventricular (LV) mass index was assessed using the M-mode method on echocardiography. Informed consent was obtained from each patient and this study was approved by the ethics committee at Hiroshima University.

### Statistical Analysis

Continuous variables are shown as mean±SD for normally distributed variables and as median (IQR) for non-normally distributed variables. To compare difference between survivors and non-survivors, unpaired t-test or Mann-Whitney test was used as appropriate. Categorical variables are shown as numbers (percentages) and were compared using the chi-squares test. The date of RHC was used as the enrolment date into the study. The endpoint was all-cause death. The data were censored in October 2014 or at the last time of visit for patients who were lost to follow-up (n=19, 7.8%). Survival was estimated using the Kaplan-Meier method and compared with the log-rank test. Cox proportional hazard regression analysis was performed to determine prognostic factors. Univariate analysis was performed with all baseline characteristic variables. Seven variables with P<0.05 and mean RAP (P=0.059) remained candidates for multivariate analysis. On multivariate analysis, 3 efficient models were considered after cross-validation to minimize interaction between candidates. The fact that the number of data on New York Heart Association (NYHA) class and N-terminal pro-brain natriuretic peptide (NT-pro BNP) was small was also taken into consideration when selecting covariates in a model. The cut-off points for age, systolic blood pressure, NT-pro BNP, estimated glomerular filtration rate (eGFR), hemoglobin, RAP, PAP, PWP, and LV mass index were obtained using receiver operating characteristic curves. Other cut-off points were determined if they were clinically important or easy to interpret. All statistical

analysis was performed using JMP10 (SAS Institute, Cary, NC, USA), and results were considered statistically significant at P<0.05.

### Results

Mean patient age was 66±13 years, and 87 (34%) of the patients were women. **Table 1** lists patient baseline characteristics. The average follow-up period was 52 months (range, 20–73 months) and 75 patients (31%) died during follow-up. The causes of deaths are as follows: cardiac death, n=31 (48.4%); cancer, n=6 (9.4%); intracranial hemorrhage, n=2 (3.1%); other causes, n=9 (14.1%); and unspecified, n=16 (25.0%). The 1-, 3- and 5-year survival rates for all patients were 89%, 80% and 70%, respectively. Admission for heart failure was higher in non-survivors. Kaplan-Meier survival estimates showed that only DPG among the hemodynamic measurements differentiated survivors from non-survivors, whereas other measurements including TPG and PVR did not (**Figure 2**). Elevated mean RAP showed a borderline significant association with mortality (P=0.058), although it significantly differentiated the survivors from non-survivors in the earlier phase (**Figure 2**). Elevated NT-pro BNP, decreased eGFR, anemia and the presence of coronary artery disease clearly differentiated survivors from non-survivors (**Figure 3**).

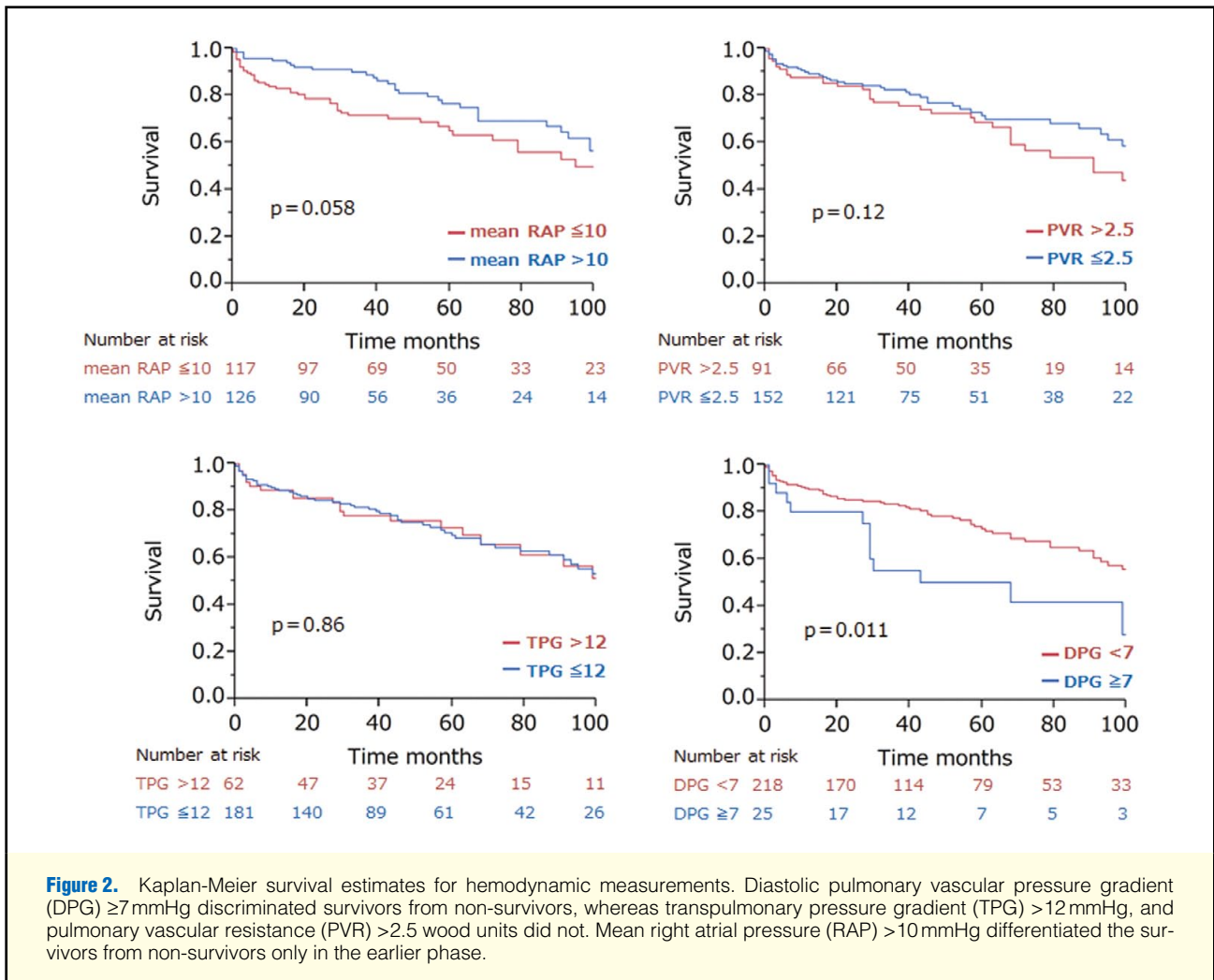
On univariate Cox proportional hazard regression analysis, 8 variables remained candidates for multivariate analysis (**Table 2**). On multivariate analysis, age, more severe NYHA class, elevated NT-pro BNP, decreased eGFR, and anemia were associated with mortality (**Table 3**). Among hemodynamic measurements, only DPG was associated with mortality, but it had lower prognostic ability.

### Discussion

In the present study, we reviewed 243 patients with PH due to LHD, defined as mPAP ≥25 mmHg and PWP >15 mmHg, to identify prognostic factors. On multivariate analysis only DPG

Table 1. Baseline Characteristics						
Variables	n†	All patients (n=243)	Non-survivors (n=75)	Survivors (n=168)	P-value	
Age (years)	243	66.1±13.2	69.5±1.5	64.6±1.0	0.0063*	
Female	243	87 (35.8)	23 (30.7)	64 (38.1)	0.26	
BMI (kg/m <sup>2</sup> )	242	23.2±3.8	22.3±0.4	23.6±0.3	0.020*	
NYHA III or IV	139	91 (65.5)	30 (83.3)	61 (59.2)	0.0063*	
Leg edema	164	63 (38.4)	22 (47.8)	41 (34.8)	0.12	
Etiology						
CAD	226	90 (39.8)	34 (51.5)	56 (35.0)	0.021*	
Aortic stenosis	200	25 (12.5)	7 (12.7)	18 (12.4)	0.95	
Aortic regurgitation	201	31 (15.4)	9 (16.4)	22 (15.1)	0.82	
Mitral stenosis	200	12 (6.0)	5 (8.9)	7 (4.9)	0.28	
Mitral regurgitation	207	105 (50.7)	28 (48.3)	77 (51.7)	0.66	
Tricuspid regurgitation	203	71 (35.0)	25 (43.1)	46 (31.7)	0.13	
I.v. medications prior to RHC						
Carperitide	204	18 (8.8)	7 (11.7)	11 (7.6)	0.36	
Catecholamines	204	24 (11.8)	8 (13.3)	16 (11.1)	0.65	
Medications						
Diuretics	241	174 (72.2)	51 (68.9)	123 (73.7)	0.45	
ACEI or ARB	241	125 (51.9)	41 (55.4)	84 (50.3)	0.46	
β-blocker	241	112 (46.5)	28 (37.8)	84 (50.3)	0.072	
Statin	241	68 (28.2)	16 (21.6)	52 (31.1)	0.12	
Amiodarone	241	25 (10.3)	6 (8.1)	19 (11.4)	0.43	
Spirolactone	241	110 (45.6)	33 (44.6)	77 (46.1)	0.83	
Inotropic agent	241	17 (7.1)	6 (8.1)	11 (6.6)	0.67	
Blood pressure (mmHg)						
Systolic	242	121.6±22.6	121.8±2.6	121.6±1.8	0.94	
Diastolic	242	67.9±16.0	70.1±1.8	66.9±1.2	0.16	
Laboratory findings						
NT-pro BNP (pg/ml)	129	2,251 (1,024–7,416)	5,526 (1,736–13,972)	1,784 (834–5,375)	0.0079*	
Creatinine (mg/dl)	242	0.95 (0.77–1.32)	1.18 (0.81–2.23)	0.91 (0.75–1.24)	0.0035*	
eGFR (ml/min/1.73 m <sup>2</sup> )	242	55.0 (38.4–71.2)	45.9 (25.2–68.0)	58.0 (43.0–74.8)	0.0039*	
Hb (g/dl)	241	12.1±2.4	11.1±0.3	12.6±0.2	<0.001*	
HbA1c (%)	220	6.0±1.0	6.2±0.1	6.0±0.1	0.14	
Hemodynamics						
Heart rate (beats/min)	242	77.2±18.2	80.9±2.1	75.5±1.4	0.031*	
Mean RAP (mmHg)	243	11.7±6.0	12.0±0.7	11.5±0.5	0.56	
Systolic PAP (mmHg)	243	46.8±12.9	49.3±1.5	45.7±1.0	0.046*	
Diastolic PAP (mmHg)	243	24.6±7.2	25.4±0.8	24.2±0.6	0.20	
Mean PAP (mmHg)	243	34.1±8.5	35.7±1.0	33.4±0.7	0.048*	
PWP (mmHg)	243	24.3±6.2	24.6±0.7	24.1±0.5	0.56	
CO (L/min)	243	4.4±1.5	4.4±0.2	4.3±0.1	0.77	
Cardiac index (L·min <sup>-1</sup> ·m <sup>-2</sup> )	243	2.7±0.9	2.7±0.1	2.7±0.1	0.55	
TPG (mmHg)	243	9 (6–13)	10 (7–13)	8.5 (5–12)	0.057	
PVR (Wood units)	243	2.0 (1.3–3.2)	2.3 (1.5–3.4)	1.9 (1.3–3.0)	0.063	
DPG (mmHg)	243	0 (–3 to 3)	1 (–4 to 4)	0 (–3 to 3)	0.37	
Echocardiography						
LVEF (%)	230	50.1±17.2	46.7±2.1	51.4±1.3	0.053	
LVDd (cm)	226	5.3±1.0	5.3±0.1	5.3±0.1	0.58	
LVDs (cm)	224	3.8 (3.1–4.6)	3.9 (3.2–4.6)	3.7 (3.0–4.5)	0.32	
LAD (cm)	225	4.5±0.9	4.6±0.1	4.5±0.1	0.25	
LV mass index (g/m <sup>2</sup> )	222	125.3±46.0	134.0±5.6	122.4±3.6	0.08	
E/A	135	1.2 (0.78–2.0)	1.0 (0.72–1.8)	1.3 (0.81–2.3)	0.16	
E/e'	132	18.0 (12.9–24.8)	19.3 (13.2–25.3)	17.4 (12.8–24.2)	0.79	
Admission for heart failure	243	67 (27.6)	27 (36.0)	40 (23.8)	0.049*	

Data given as mean ± SD, median (IQR) or n (%). \*P<0.05. †No. patients available for analysis. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; CAD, coronary artery disease; CO, cardiac output; DPG, diastolic pulmonary vascular pressure gradient; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; LAD, left atrial dimension; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; LVEF, left ventricular ejection fraction; NT-pro BNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; PWP, pulmonary wedge pressure; RAP, right atrial pressure; TPG, transpulmonary pressure gradient.



among the hemodynamic measurements had a weak prognostic ability. Mean RAP and current markers of pulmonary vascular remodeling such as TPG and PVR did not have a significant prognostic effect in this study. Clinical factors including NT-pro BNP, NYHA class, anemia, and renal dysfunction were superior in prognostication.

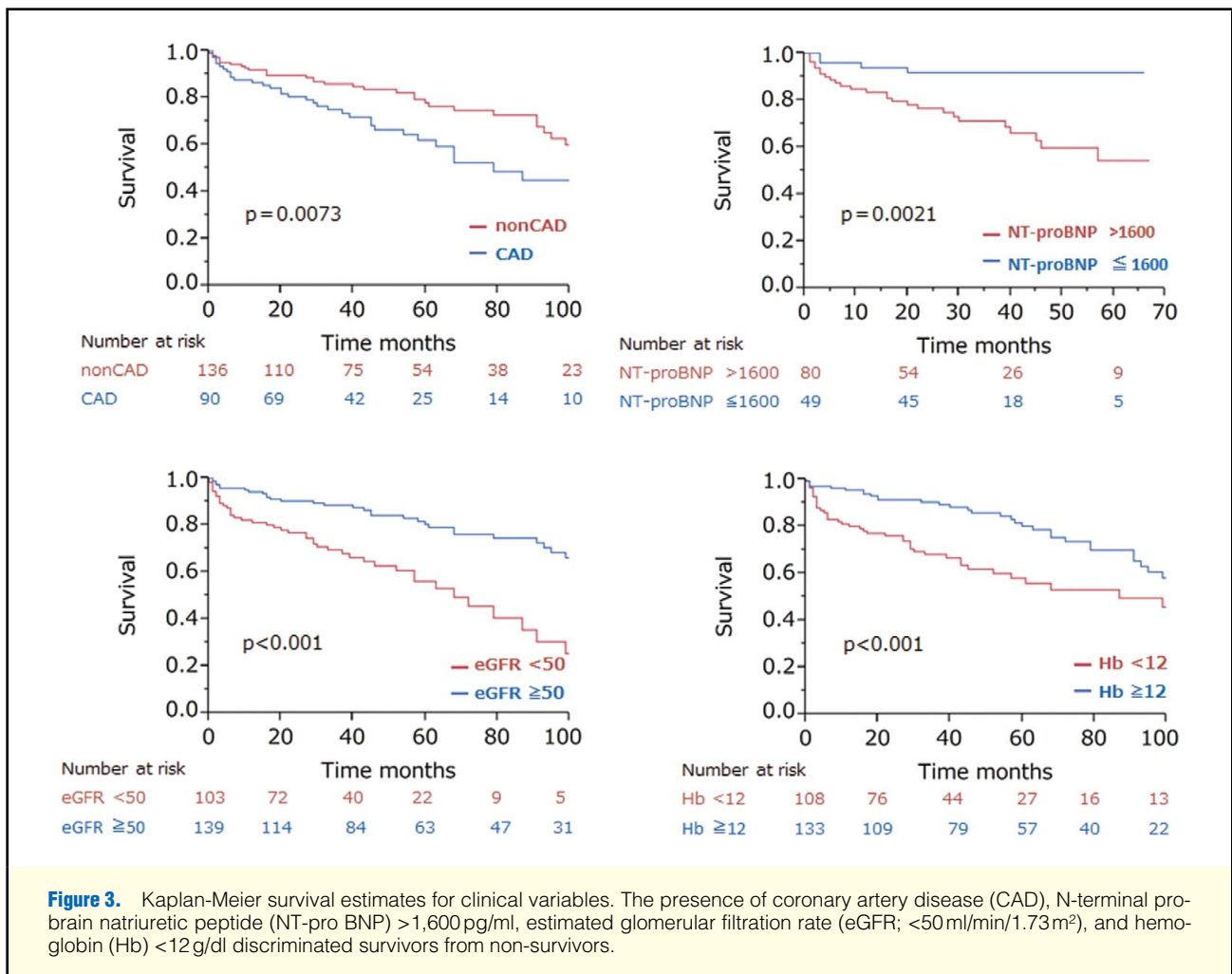
PH due to LHD is initiated by backward transmission of elevated LAP, and then followed by pulmonary vascular remodeling, so-called reactive PH.<sup>2</sup> Sustained PH causes right ventricular hypertrophy, which ultimately leads to irreversible right heart failure. The present study focused on the 2 conditions of right ventricular dysfunction and pulmonary vascular remodeling, and evaluated the prognostic abilities of the hemodynamic parameters that represent these conditions.

The RA appears to compensate for right ventricular dysfunction via distensibility, according to an experiment with dogs under treatment with chronic pulmonary artery banding.<sup>9</sup> The RA maintains CO with a minimal rise<sup>9</sup> or a decrease in RAP.<sup>10</sup> In other words, elevated mean RAP can reflect decompensated right ventricular dysfunction. Previous studies in patients with pulmonary arterial hypertension have reported that mean RAP was associated with survival.<sup>11-16</sup> Right ventricular function, mainly right ventricular ejection fraction (RVEF), evaluated on echocardiography and magnetic resonance imaging is closely related to survival in patients with

PAH,<sup>17-20</sup> and similar findings on echocardiography, thermolysis catheterization, and radionuclide ventriculography have been reported in the setting of LHD.<sup>21-24</sup> Using thermolysis-derived RVEF, Ghio et al clearly showed that the combination of PH and right ventricular dysfunction had a worse effect on survival in patients with chronic heart failure than in patients with either PH or right ventricular dysfunction.<sup>25</sup> Thus, elevated mean RAP, partly caused by right ventricular dysfunction was expected to have a prognostic impact on survival in patients with PH due to LHD. In the present study, Kaplan-Meier analysis for elevated mean RAP showed a borderline significant association with mortality, but the multivariate analysis failed to confirm an independent prognostic ability. The previous studies reported the prognostic effect of central venous pressure<sup>26</sup> and jugular venous pressure as ascertained on physical examination<sup>27</sup> in patients with heart failure. The present study however, showed that the prognostic ability of mean RAP is poor in the setting of group 2 PH. With regard to right ventricular function, RAP has 2 major problems. First, the elevation in mean RAP was caused by PH, volume overload, tricuspid valvular disease, left-right shunt, right ventricular infarction, and cardiac tamponade other than right ventricular dysfunction. Second, right ventricular filling indices including mean RAP was markedly load dependent.

Recent studies have investigated the relationships between





markers of pulmonary vascular remodeling and survival in patients with LHD,<sup>4-8</sup> but the usefulness of such markers in prognostication is still controversial. TPG, which has been found to be associated with mortality, is used for the definition of reactive PH in the relevant guideline.<sup>3</sup> Tatebe et al showed that PVR was associated with mortality, but their subjects included non-PH patients, and the presence of PH was not adjusted for in multivariate analysis.<sup>4</sup> Hirashiki et al showed that there were no differences between reactive and passive PH in the incidence of cardiac events, although the sample size was small.<sup>5</sup> The problem is that TPG and PVR are affected by cardiac output,<sup>28</sup> whereas DPG is less sensitive to this effect. Gerges et al showed that DPG ≥7 mmHg identified high-risk patients with reactive PH (PH due to LHD and TPG >12 mmHg) on Kaplan-Meier analysis and that DPG was associated with more severe pulmonary vascular remodeling on histological analysis.<sup>6</sup> In contrast, Tedford et al reported the poor prognostic ability of DPG in patients with PH due to LHD even though they used multiple cut-off points.<sup>7,8</sup> Their subjects included younger patients<sup>7,8</sup> and those with less coronary artery disease<sup>8</sup> compared with the Gerges et al study.<sup>6</sup> The problem is that DPG is sensitive to measurement error because the absolute value is small, and DPG is affected by many factors including lung disease, sepsis, hypoxia, acidosis, and coronary artery bypass surgery.<sup>7,8</sup> We conclude that DPG might have a weak prognostic ability, but the use of DPG in

prognostication is limited in the setting of group 2 PH.

In addition, PWP does not predict mortality because PWP can paradoxically decrease owing to impaired LV filling in patients with severe PH due to LHD.<sup>29</sup> In the present study the E/e' cut-off point of 13 mmHg did not have a prognostic ability, possibly because most of the present patients (75%) had E/e' ≥13. The paradoxical decrease in PWP can also influence E/e' because E/e' reflects LAP or PWP. A recent study showed that underweight patients had worse prognosis for advanced heart failure than overweight patients.<sup>30</sup> In the present study, there was a tendency for poor prognosis in patients with lower BMI, but BMI did not remain a candidate for multivariate analysis. Reduced eGFR and anemia are well-known to be associated with increased mortality in heart failure.<sup>31-33</sup> Similarly, we showed that renal dysfunction and anemia are potent prognostic factors in patients with PH due to LHD.

### Study Limitations

This was a retrospective, single-center study that targeted a heterogeneous population involving different etiologies of heart failure. Although physical findings including jugular vein distension and heart sounds can have prognostic impact in patients with PH due to LHD, sufficient data for analysis were not obtained. Data on right ventricular function were unavailable.

Variables	Univariate		
	HR	95% CI	P-value
Age ≥60 years	1.79	1.03–3.33	0.038*
Female	0.92	0.71–1.20	0.55
BMI <18.5 kg/m <sup>2</sup>	1.60	0.66–3.29	0.27
BMI 18.5–25 kg/m <sup>2</sup>	1.00		
BMI ≥25 kg/m <sup>2</sup>	0.68	0.38–1.17	0.17
NYHA III or IV	3.05	1.36–8.13	0.0054*
NYHA I or II	1.00		
Leg edema	1.64	0.91–2.93	0.098
CAD	1.92	1.18–3.12	0.0089*
Tricuspid regurgitation	1.66	0.98–2.79	0.060
β-blocker	0.72	0.44–1.14	0.16
Statin	0.73	0.40–1.24	0.25
SBP >140 mmHg	1.21	0.69–2.01	0.50
NT-pro BNP >1,600 pg/ml	4.51	1.75–15.3	<0.001*
eGFR <50 ml/min/1.73 m <sup>2</sup>	3.08	1.92–5.01	<0.001*
Hb <12 g/dl	2.34	1.48–3.76	<0.001*
HbA1c ≥7.0%	1.53	0.81–2.68	0.18
<b>Hemodynamics</b>			
Heart rate >100 beats/min	1.98	0.95–3.69	0.065
Mean RAP >10 mmHg	1.55	0.98–2.47	0.059
Systolic PAP >60 mmHg	1.51	0.84–2.56	0.16
Diastolic PAP >30 mmHg	1.69	0.95–2.84	0.071
Mean PAP >50 mmHg	1.41	0.59–2.85	0.41
PWP >30 mmHg	1.17	0.65–1.98	0.59
CO <4.0 L/min	1.21	0.77–1.92	0.41
Cardiac index <2.5 L·min <sup>-1</sup> ·m <sup>-2</sup>	1.26	0.80–1.98	0.32
TPG >12 mmHg	1.05	0.62–1.71	0.86
PVR >2.5 wood units	1.36	0.86–2.14	0.19
DPG ≥7 mmHg	2.12	1.11–3.74	0.024*
<b>Echocardiography</b>			
LVEF <50%	1.41	0.88–2.27	0.15
LVDd >5.5 cm	0.91	0.54–1.49	0.71
LVDs >4.0 cm	1.14	0.70–1.85	0.60
LAD >4.0 cm	1.29	0.76–2.30	0.36
LV mass index >130 g/m <sup>2</sup>	1.08	0.66–1.76	0.75
E/A >2.0	0.49	0.17–1.15	0.10
E/e' ≥13	1.12	0.51–2.80	0.80
Admission for heart failure	1.40	0.86–2.23	0.17

\*P<0.05. SBP, systolic blood pressure. Other abbreviations as in Table 1.

Variables	Regression 1			Regression 2			Regression 3		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Age >60 years	2.80	1.03–9.81	0.042*	1.98	1.03–9.81	0.029*	2.06	1.11–4.18	0.020*
NYHA III or IV	3.19	1.22–9.92	0.017*						
CAD	2.04	0.89–4.99	0.093	1.57	0.95–2.59	0.077	1.70	1.04–2.79	0.034*
NT-pro BNP >1,600 pg/ml	4.04	1.22–18.4	0.021*						
eGFR <50 ml/min/1.73 m <sup>2</sup>	0.98	0.40–2.44	0.96	1.78	1.03–3.12	0.040*			
Hb <12 g/dl	1.44	0.60–3.70	0.42	1.81	1.06–3.13	0.029*	2.23	1.36–3.72	0.034*
Mean RAP >10 mmHg	0.84	0.32–2.11	0.70	1.31	0.80–2.16	0.29	1.29	0.79–2.15	0.31
DPG ≥7 mmHg	1.33	0.40–3.89	0.62	1.81	0.93–3.29	0.079	2.07	1.07–3.72	0.031*

\*P<0.05. Abbreviations as in Table 1.

## Conclusions

This retrospective study of 243 patients with PH due to LHD evaluated the prognostic ability of mean RAP and markers of pulmonary vascular remodeling such as TPG, PVR, and DPG. Conclusively, the use of these hemodynamic parameters in prognostication is limited. Clinical factors including NT-pro BNP, NYHA class, renal dysfunction, and anemia are superior in prognostication in these patients.

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