NRC Research Press

ARTICLE

Single-center prognostic validation of the risk assessment of the 2015 ESC/ERS guidelines in patients with pulmonary arterial hypertension in Japan[1]

Ryo Imai, Shiro Adachi, Masahiro Yoshida, Shigetake Shimokata, Yoshihisa Nakano, Naoki Okumura, Toyoaki Murohara, and Takahisa Kondo

Abstract: The 2015 European Society of Cardiology/European Respiratory Society guidelines for the diagnosis and treatment of pulmonary hypertension include a multidimensional risk assessment for patients with pulmonary arterial hypertension (PAH). However, prognostic validations of this risk assessment are limited, especially outside Europe. Here, we validated the risk assessment strategy in PAH patients in our institution in Japan. Eighty consecutive PAH patients who underwent right heart catheterization between November 2006 and December 2018 were analyzed. Patients were classified as low, intermediate, or high risk by using a simplified version of the risk assessment that included seven variables: World Health Organization functional class, 6-min walking distance, peak oxygen consumption, brain natriuretic peptide, right atrial pressure, mixed venous oxygen saturation, and cardiac index. The high-risk group showed significantly higher mortality than the low- or intermediate-risk group at baseline ($P < 0.001$ for both comparisons), and the mortalities in the intermediate- and low-risk groups were both low ($P = 0.989$). At follow-up, patients who improved to or maintained a low-risk status showed better survival than those who did not ($P = 0.041$). Our data suggest that this risk assessment can predict higher mortality risk and long-term survival in PAH patients in Japan.

Key words: pulmonary arterial hypertension, ESC/ERS guidelines, risk assessment, mortality, Japan.

Résumé : Les lignes directrices des Société européenne de cardiologie/European Respiratory Society quant au diagnostic et au traitement de l'hypertension pulmonaire comprennent une évaluation multidimensionnelle du risque pour les patients atteints d'hypertension artérielle pulmonaire (HAP). Cependant les validations du pronostic pour cette évaluation du risque présentent des limites, en particulier en dehors de l'Europe. Nous avons ici validé la stratégie d'évaluation du risque chez des patients atteints d'HAP dans notre établissement au Japon. Nous avons étudié 80 patients atteints d'HAP consécutifs sur lesquels a été réalisé un cathétérisme du cœur droit entre novembre 2006 et décembre 2018. Nous avons classé les patients selon des risques faible, intermédiaire ou élevé à l'aide d'une version simplifiée de l'évaluation du risque comprenant sept variables : classe fonctionnelle de l'Organisation mondiale de la santé, distance de marche pendant 6 min, consommation d'oxygène de pointe, peptide natriurétique cérébral, pression dans l'atrium droit, saturation veineuse mixte en oxygène et indice cardiaque. Le groupe exposé à un risque élevé a présenté un taux de mortalité nettement plus élevé que les groupes exposés à un risque faible ou intermédiaire ($P < 0{,}001$ pour les deux comparaisons), et les taux de mortalité dans les groupes exposés à des risques intermédiaire et faible étaient tous deux peu élevés ($P = 0{,}989$). Au suivi, les patients dont le risque auquel ils étaient exposés devenait faible ou demeurait à ce stade présentaient un meilleur taux de survie que les autres ($P = 0{,}041$). Nos données laissent entendre que cette évaluation du risque pourrait prédire un risque de mortalité plus élevé, ainsi que le taux de survie à long terme chez des patients atteint d'HAP au Japon. [Traduit par la Rédaction]

Mots-clés : hypertension artérielle pulmonaire, lignes directrices des SEC/ERS, évaluation du risque, taux de mortalité, Japon.

Introduction

Although pulmonary arterial hypertension (PAH) is a progressive life-threatening disease, prognosis has improved with the development of PAH-specific therapy targeting the endothelin, nitric oxide, and prostacyclin pathways (Kondo et al. 2019). Today, there are many treatment choices available and physicians must select the most appropriate strategy for a patient, with choices including whether to use mono- or combination therapy and whether to use oral and (or) intravenous drugs. To help in the decision-making process, a multidimensional risk assessment for PAH was proposed in the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines for the diagnosis and treatment of pulmonary hypertension, in which reaching a low-risk status is a recommended treatment goal (Galie et al. 2016). The variables in the risk assessment include clinical symptoms, exercise tolerance status, right ventricular function, and hemodynamic parameters. Recently, the risk assessment strategy was retrospectively validated using European registries and was

Received 25 November 2019. Accepted 26 March 2020.

R. Imai, S. Shimokata, N. Okumura, and T. Murohara. Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan.
S. Adachi and M. Yoshida. Department of Cardiology, Nagoya University Hospital, Nagoya, Japan.
Y. Nakano and T. Kondo. Department of Advanced Medicine in Cardiopulmonary Disease, Nagoya University Graduate School of Medicine, Nagoya, Japan.
Corresponding author: Takahisa Kondo (email: takahisa@med.nagoya-u.ac.jp).

[1]This paper is part of a Special Issue of selected papers from the Sixteenth International Conference on Endothelin, held in Kobe, Japan, in September 2019.

Published at www.nrcresearchpress.com/cjpp on 13 September 2020.

Table 1. Variables evaluated in the risk assessment and their cut-off values.

	Low risk	Intermediate risk	High risk
1. WHO FC	I/II	III	IV
2. Exercise tolerance			
6MWD (m)	>440	165–440	<165
Peak VO2 (mL·min^{-1}·kg^{-1})	>15	11–15	<11
3. BNP (ng/L)	<50	50–300	>300
4. RAP (mm Hg)	<8	8–14	>14
5. Circulatory dynamics			
SvO2 (%)	>65	60–65	<60
CI (L·min^{-1}·m^{-2})	≥2.5	2.0–2.4	<2.0

Note: For exercise tolerance and circulatory dynamics, the worst score of the two indicated variables was used. WHO FC, World Health Organization functional class; 6MWD, 6 min walking distance; peak VO2, peak oxygen consumption; BNP, brain natriuretic peptide; RAP, right atrial pressure; SvO2, mixed venous oxygen saturation; CI, cardiac index.

reported to provide an accurate prediction of mortality and the clinical advantage of reaching low-risk status (Boucly et al. 2017; Hoeper et al. 2017; Kylhammar et al. 2018). However, the risk assessment strategy has not yet been fully validated in Japanese PAH patients. Here, we retrospectively validated the risk assessment and explored the prognostic impact of achieving low-risk status in PAH patients in our institution.

Methods

We undertook a retrospective review of PAH patients who underwent right heart catheterization (RHC) at Nagoya University Hospital (Nagoya, Japan) between November 2006 and December 2018. We enrolled all PAH patients including treatment-naïve cases. Patients were classified as idiopathic/heritable PAH (I/HPAH), connective tissue disease-associated PAH (CTD-PAH), congenital heart disease-associated PAH (CHD-PAH), portopulmonary hypertension (PoPH), or drug-associated PAH (DPAH). PAH and the associated etiology were diagnosed according to the 2017 Japanese Guidelines for the treatment of pulmonary hypertension (Fukuda et al. 2019).

Of the variables used in the 2015 ESC/ERS risk stratification, we used only the following seven: World Health Organization functional class (WHO FC), 6 min walking distance (6MWD), peak oxygen consumption (peak VO2), brain natriuretic peptide (BNP), right atrial pressure (RAP), mixed venous oxygen saturation (SvO2), and cardiac index (CI). To simplify the evaluation, clinical signs of right heart failure, progression of symptoms, syncope, and imaging data were not assessed. CI was measured by the thermodilution technique.

For each patient, each variable was assigned a score of 1 (low risk), 2 (intermediate risk), or 3 (high risk) based on predefined cut-off values (Table 1). To assess "exercise tolerance", we used the worst score of 6MWD and peak VO2 when data for both tests were available. When neither the 6 min walk test nor the cardiopulmonary exercise test could be performed due to exercise intolerance, a score of 3 was assigned. Similarly, to assess "circulatory dynamics", we used the worst score of SvO2 and CI. Thus, each patient was assigned scores for a maximum of five variables (Table 1). Then, the sum of the scores was divided by the number of available variables and rounded to the nearest integer and patients were classified as low, intermediate, or high risk according to the mean score (1, low risk; 2, intermediate risk; 3, high risk).

The risk assessment was performed a maximum of two times for each patient: first at baseline when the first RHC was performed at our institution and again at follow-up at between 3 months and 2 years after the baseline assessment when the patient was reevaluated and a second RHC was performed.

Table 2. Characteristics of the overall population and treatment-naïve subpopulation at baseline.

	Overall population (n = 80)	Treatment-naïve subpopulation (n = 55)
Age (years)	48±18	51±17
Female	63 (79%)	44 (80%)
Etiology of PAH		
I/HPAH	29 (36%)	15 (27%)
CTD-PAH	29 (36%)	23 (42%)
CHD-PAH	10 (13%)	8 (15%)
PoPH	9 (11%)	6 (11%)
Drug-induced PAH	3 (4%)	3 (5%)
WHO FC		
I/II	31 (39%)	20 (36%)
III	41 (51%)	33 (60%)
IV	8 (10%)	2 (4%)
6MWD (m)	370±128 (n = 53)	363±129 (n = 38)
Peak VO2 (mL·min^{-1}·kg^{-1})	14.0±4.7 (n = 57)	13.0±4.5 (n = 40)
BNP (ng/L)	75 (23–215) (n = 78)	76 (34–215) (n = 54)
Hemodynamics		
RAP (mm Hg)	5.9±4.1	4.8±3.2
mPAP (mm Hg)	45±15	43±13
SvO2 (%)	64±9	65±8
CI (L·min^{-1}·m^{-2})	2.9±0.9	2.7±0.8
PVR (WU)	8.9±5.3	9.2±5.3
Risk assessment		
Low	30 (38%)	18 (33%)
Intermediate	44 (55%)	36 (65%)
High	6 (8%)	1 (2%)

Note: Data are presented as n (%), mean ± standard deviation, or median (interquartile range). PAH, pulmonary arterial hypertension; I/H, idiopathic or heritable; CTD, connective tissue disease; CHD, congenital heart disease; PoPH, portopulmonary hypertension; WHO FC, World Health Organization functional class; 6MWD, 6 min walking distance; peak VO2, peak oxygen consumption; BNP, brain natriuretic peptide; RAP, right atrial pressure; mPAP, mean pulmonary arterial pressure; SvO2, mixed venous oxygen saturation; CI, cardiac index; PVR, pulmonary vascular resistance.

All statistical analyses were performed by using IBM SPSS Statistics 26 (IBM Corporation, Armonk, New York, USA). Continuous variables are presented as mean ± standard deviation or median with the interquartile range (IQR), as appropriate. Categorical variables are presented as a count and (or) as a percentage. Survival analysis was assessed by Kaplan–Meier analysis with the log-rank test, truncated at 5 years. Survival was compared between the low-, intermediate-, and high-risk groups at baseline and between the low-risk group and a composite group comprising the intermediate- and high-risk groups at follow-up. To evaluate the differences between the patients that had improved to low-risk status at follow-up and those that had not, the paired t test, Mann–Whitney U test, χ^2 test, and Fisher's exact test were used. Hazard ratios with 95% confidence intervals were determined. In all analyses, $P < 0.05$ was considered statistically significant.

This study was approved by the ethics committee of Nagoya University Hospital (No. 2016-0372). Informed consent was obtained by allowing subjects to opt out of the study; no patient opted out in this study.

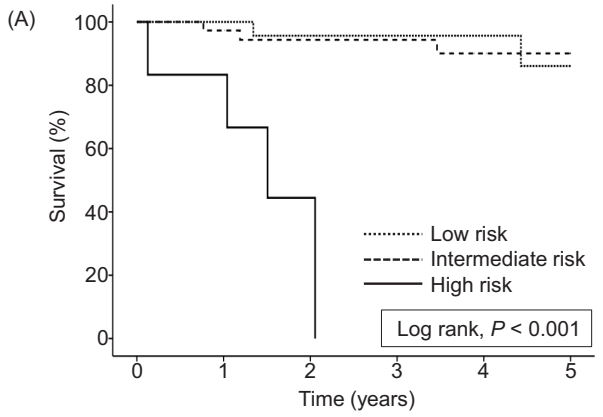
Results

Patients and risk assessment at baseline

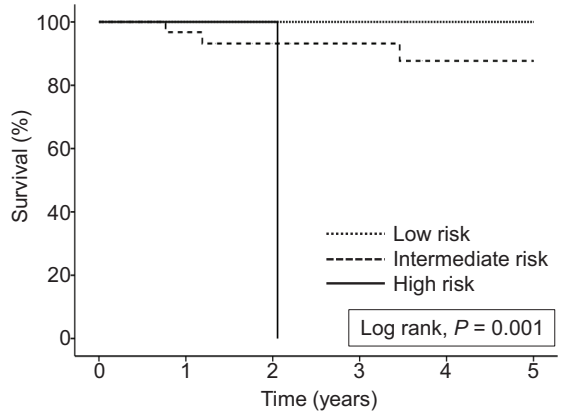
Eighty patients with PAH (I/HPAH = 29, CTD-PAH = 29, CHD-PAH = 10, PoPH = 9, DPAH = 3) were enrolled, which included 55 treatment-naïve patients. The median (IQR) observation period was 29 (14–61) months in the overall population and 35 (14–60) months in the treatment-naïve subpopulation.

Table 2 shows the characteristics of the overall population and the treatment-naïve subpopulation at baseline. All patients under-

Fig. 1. Kaplan–Meier survival analysis based on risk status at baseline for the (A) overall population and (B) treatment-naïve subpopulation.



Number at risk						
Low	30	25	18	14	10	8
Intermediate	44	35	27	22	18	13
High	6	5	1	0	0	0
Survival (%)						
Low	100	100	95.7	95.7	95.7	86.1
Intermediate	100	97.3	94.3	94.3	90.1	90.1
High	100	83.3	44.4	0	0	0
Overall	100	97.3	90.9	88.9	86.3	83.0



Number at risk						
Low	18	15	12	10	7	6
Intermediate	36	29	22	17	13	11
High	1	1	1	0	0	0
Survival (%)						
Low	100	100	100	100	100	100
Intermediate	100	96.8	93.2	93.2	87.7	87.7
High	100	100	100	0	0	0
Overall	100	97.9	95.6	92.8	89.2	89.2

went RHC, and we evaluated RAP, SvO2, and CI. BNP was measured in 78 (98%) patients. The 6 min walk test was performed in 53 (66%) patients in the overall population and 38 (69%) patients in the treatment-naïve subpopulation and cardiopulmonary exercise testing was performed in 57 (71%) and 40 (73%) patients, respectively, and both tests were performed in 47 (59%) and 34 (62%) patients, respectively. Ten and four patients, respectively, were not able to undergo either test due to exercise intolerance at baseline. Of the risk assessment variables examined, all five were available in 73 (91%) patients, four were available in 6 (8%) patients, and three were available in 1 (1%) patient. Medication profiles at baseline are shown in Table S1.[2] Seven patients in the overall population and two patients in the treatment-naïve subpopulation were not treated with a PAH-specific medicine during the whole observation period.

Figure 1 shows overall survival according to risk status at baseline. During the observation period, nine patients died in the overall population (Fig. 1A), four of whom were treatment-naïve (Fig. 1B): two and zero in the low-risk group, three and three in the intermediate-risk group, and four and one in the high-risk group, respectively. Of the nine deaths, the most common cause was right heart failure (six cases). No patient underwent lung transplantation.

Kaplan–Meier analysis revealed significant differences in survival between the three risk groups. In the overall population, there were significant differences between the low-risk group and the high-risk group ($P < 0.001$) and between the intermediate-risk group and the high-risk group ($P < 0.001$) but not between the low-risk group and the intermediate-risk group ($P = 0.989$). The same trend was observed for the treatment-naïve subpopulation ($P = 0.001$, $P = 0.006$, and $P = 0.211$, respectively).

Patients and risk assessment at follow-up

Reevaluation and RHC at between 3 months and 2 years after baseline was performed in 61 patients, which included 44 treatment-naïve patients. The median (IQR) interval from baseline to reevaluation was 8 (5–12) months.

Patient characteristics at follow-up are shown in Table 3. All patients underwent RHC, and BNP was measured in 59 (97%) patients. The 6 min walk test was performed in 43 (70%) patients in the overall population and 33 (75%) patients in the treatment-naïve subpopulation; cardiopulmonary exercise testing was performed in 40 (66%) and 31 (70%) patients, respectively, and both tests were performed in 34 (56%) and 27 (61%) patients, respectively. Of the risk assessment variables examined, all five variables were available in 48 (79%) patients and four were available in 13 (21%) patients. Medication profiles at follow-up are shown in Table S2.[2] Five patients received epoprostenol, an intravenous prostacyclin analogue, at follow-up and the mean (± standard deviation) dosage was 31.4 ± 17.9 ng·kg^{-1}·min^{-1}.

Figure 2 shows overall survival according to risk status at follow-up. The high-risk group included only two patients, one of which was treatment naïve. In the follow-up subjects, five patients in the overall population had died (Fig. 2A) and three in the treatment-naïve subpopulation had died (Fig. 2B) during the observation period: one and zero in the low-risk group and four and three in the intermediate-risk group, respectively. Kaplan–Meier analysis revealed that survival significantly differed between the low-risk group and a composite of the intermediate- and high-risk groups in the overall population ($P = 0.041$). A significant difference was also observed in the treatment-naïve subpopulation ($P = 0.030$).

Finally, the treatment-naïve patients who had improved from intermediate- or high-risk status to low-risk status ($n = 13$) or who remained as intermediate- or high-risk status ($n = 17$) at follow-up were compared (Table 4). At baseline, the clinical characteristics between the two groups did not differ significantly. At follow-up, 12 (92%) patients in the improved group and 16 (94%) patients in the unimproved group were being treated with PAH-specific medicines, with 10 (77%) and 10 (59%) patients, respectively, receiving combination medical therapy. There was no significant difference in the time from diagnosis to initiation of PAH-specific therapy between the two groups (1 (0.5–1) versus 1 (1–60) days, $P = 0.085$).

[2]Supplementary data are available with the article through the journal Web site at http://nrcresearchpress.com/doi/suppl/10.1139/cjpp-2019-0640.

Table 3. Characteristics of the overall population and treatment-naïve subpopulation at follow-up.

	Overall population (n = 61)	Treatment-naïve subpopulation (n = 44)
Age (years)	47±17	49±16
Female	47 (77%)	35 (80%)
Etiology of PAH		
I/HPAH	22 (36%)	13 (30%)
CTD-PAH	22 (36%)	17 (39%)
CHD-PAH	7 (11%)	6 (14%)
PoPH	7 (11%)	5 (11%)
Drug-induced PAH	3 (5%)	3 (7%)
WHO FC		
I/II	39 (64%)	30 (68%)
III	21 (34%)	13 (30%)
IV	1 (2%)	1 (2%)
6MWD (m)	410±129 (n = 43)	408±133 (n = 33)
Peak VO2 (mL·min^{-1}·kg^{-1})	15.2±4.6 (n = 40)	14.8±4.1 (n = 31)
BNP (ng/L)	27 (10–68) (n = 59)	29 (10–75) (n = 43)
Hemodynamics		
RAP (mm Hg)	5.9±3.4	5.6±3.5
mPAP (mm Hg)	38±12	35±13
SvO2 (%)	68±8	68±9
CI (L·min^{-1}·m^{-2})	3.4±0.9	3.4±0.7
PVR (WU)	5.8±3.7	5.3±3.5
Risk assessment		
Low	36 (59%)	26 (59%)
Intermediate	23 (38%)	17 (39%)
High	2 (3%)	1 (2%)

Note: Data are presented as n (%), mean ± standard deviation, or median (interquartile range). PAH, pulmonary arterial hypertension; I/H, idiopathic or heritable; CTD, connective tissue disease; CHD, congenital heart disease; PoPH, portopulmonary hypertension; WHO FC, World Health Organization functional class; 6MWD, 6 min walking distance; peak VO2, peak oxygen consumption; BNP, brain natriuretic peptide; RAP, right atrial pressure; mPAP, mean pulmonary arterial pressure; SvO2, mixed venous oxygen saturation; CI, cardiac index; PVR, pulmonary vascular resistance.

On the other hand, combination medical therapy was initiated significantly earlier in the improved group than in the unimproved group (59 ± 64 versus 121 ± 54 days, P = 0.028).

Discussion

Here, we retrospectively validated the risk stratification strategy proposed in the 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension in a cohort of PAH patients from an institution in Japan. Using a simplified version of the risk assessment, we demonstrated that patients in the high-risk group at baseline had significantly higher mortality than those in the intermediate- and low-risk groups. It is notable that prognosis in the intermediate-risk group at baseline was relatively good compared with European reports and was comparable with that in the low-risk group (Hoeper et al. 2017; Kylhammar et al. 2018). Follow-up analysis revealed that patients who had achieved low-risk status showed a better outcome. In addition, early initiation of combination therapy was significantly associated with improvement to low-risk status in the intermediate- or high-risk group.

The 2015 ESC/ERS risk assessment strategy has also been validated using European registries: Swedish PAH Registry (SPAHR), Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA), and French Pulmonary Hypertension Network (FPHN) (Boucly et al. 2017; Hoeper et al. 2017; Kylhammar et al. 2018). Those studies used two types of simplified risk assessment: a score-and-average method or a low-risk–focused method (Galie et al. 2019). It was reported that the low-risk–focused method of the study using FPHN provided a more accurate prediction of long-term survival than the score-and-average method of the study using COMPERA (Hoeper et al. 2018). However, in this report, 23% of the patients in the original study population were excluded with the low-risk-focused method due to incomplete data sets. In contrast, score-and-average methods are able to assess almost all patients, even when not all of the risk variables are available. Certainly, fewer variables makes for a less accurate assessment, but the ability to assess almost all patients is a major advantage of that approach. In the present study, we referred to the score-and-average method of the study using COMPERA and partially modified that method to increase the accuracy of prognostic prediction. With our method, we found that the high-risk group showed the highest mortality. Furthermore, 5 year survival rates were 100% in the treatment-naïve patients in both the low-risk group at baseline and the group achieving low-risk status at follow-up. Although the present study included a relatively small number of patients, our results suggest that our modified score-and-average method can predict those patients who stand to achieve long-term survival with an accuracy similar to that of low-risk-focused methods.

In the intermediate-risk group of the treatment-naïve subpopulation, the 5 year mortality rate in our study was 12.3%, which is much lower than that reported from studies using COMPERA (48.1%) and SPAHR (48%) (Hoeper et al. 2017; Kylhammar et al. 2018). Even when we used the risk assessment method that was used to validate COMPERA, we still obtained a low mortality rate (12.5%). These differences in mortality rate may be a result of racial or national differences between the populations in Japan and Europe, such as the characteristics of CTD-PAH (Condliffe et al. 2009; Shirai et al. 2012). Or, they could be a result of differences in the medical treatment strategies used. That is, in the intermediate-risk patients of the treatment-naïve subpopulation, combination medical therapy was initiated in 69% of patients at follow-up and in 31% of patients within 3 months from diagnosis in our cohort, whereas it was initiated in 40% and 14% of patients, respectively, in a study using COMPERA (Hoeper et al. 2017). In addition, we found that early initiation of combination therapy was associated with achieving low-risk status at follow-up, which could also be an underlying cause of the observed differences in mortality.

The early initiation of combination therapy at our institution is likely a result of the characteristics of the Japanese healthcare system; that is, all people in Japan are required to have health insurance coverage, and personal payment for medical services is covered by a universal health insurance system (Ikegami et al. 2011). Furthermore, some diseases including PAH are classified as “intractable diseases”, and the associated medical services are provided at almost no cost to the patient (Kanatani et al. 2017). Therefore, almost all patients with PAH in Japan are able to receive the necessary medical therapy without excessive economic burden, even when multiple PAH-specific drugs are indicated. Indeed, a recent report of a multicenter registry for PAH from Japan showed that combination therapy was initiated in 28.3% of treatment-naïve PAH patients within 90 days after diagnosis (Tamura et al. 2017); this finding is comparable with our present finding.

Our study has some limitations. First, it was a retrospective observational study; therefore, the interval between baseline and reevaluation was not standardized. Also, because in some cases, RHC was not reperformed between 3 months and 2 years after baseline, our follow-up data were incomplete. Second, this was a single-center study and the sample size was small. In particular, there were few patients in the high-risk group, so we were unable to fully investigate that group of patients. In addition, our study showed that the prognosis in the intermediate-risk group at baseline was comparable with that in the low-risk group, which may suggest that modification of the ESC/ERS risk assessment is needed for Japanese PAH patients to discriminate between the two groups. Additional Japanese multicenter studies with larger

Fig. 2. Kaplan–Meier survival analysis based on risk status at follow-up for the (A) overall population and (B) treatment-naïve subpopulation.

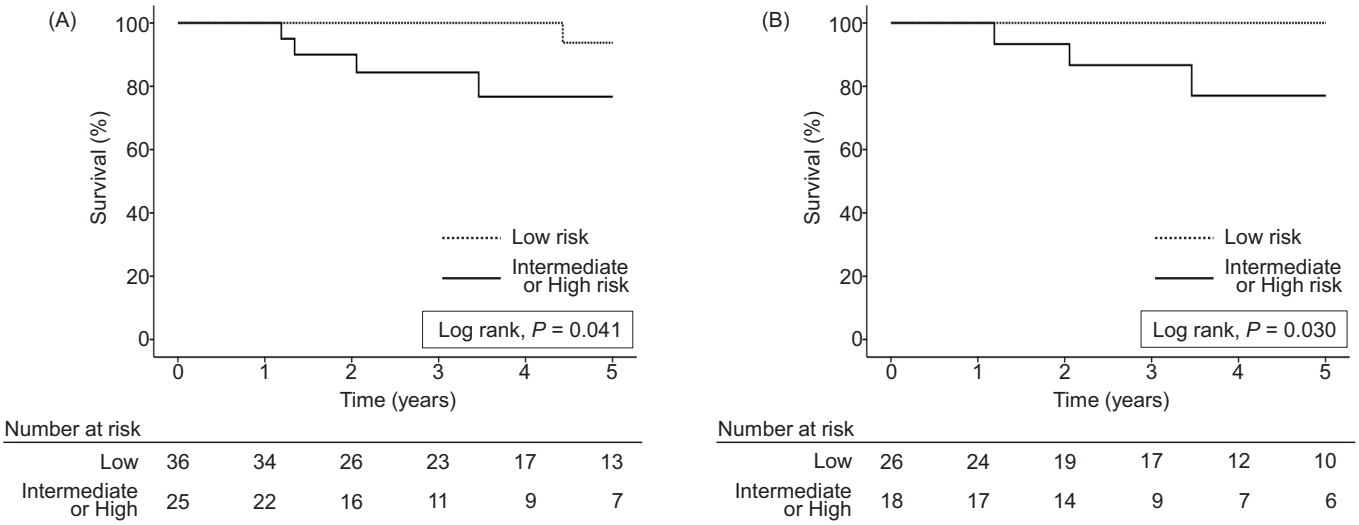


Table 4. Comparison between treatment-naïve patients who improved from intermediate- or high-risk to low-risk status or who remained as intermediate- or high-risk status.

	Improved to low risk (n = 13)	Remained as intermediate or high risk (n = 17)	P
Etiology of PAH			0.403
I/HPAH	6 (46%)	4 (24%)	
CTD-PAH	4 (31%)	10 (59%)	
CHD-PAH	1 (8%)	2 (12%)	
PoPH	2 (15%)	1 (6%)	
WHO FC[a]			1.000
I/II	2 (15%)	3 (18%)	
III	11 (85%)	13 (76%)	
IV	0 (0%)	1 (6%)	
6MWD (m)[a]	341±72	318±127	0.636
Peak VO2 (mL·min^{-1}·kg^{-1})[a]	12.4±3.8	11.0±3.5	0.373
BNP (ng/L)[a]	131 (60–343)	130 (72–241)	0.592
Hemodynamics[a]			
RAP (mm Hg)	5.2±3.4	5.9±3.5	0.540
mPAP (mm Hg)	50±12	44±12	0.238
SvO2 (%)	63±6	62±6	0.458
CI (L·min^{-1}·m^{-2})	2.3±0.7	2.5±0.7	0.444
PVR (WU)	12.8±6.2	9.0±5.1	0.078
Time from diagnosis to initiation of PAH-specific therapy (days)	1 (0.5–1)	1 (1–60)	0.085
Combination therapy at follow-up	10 (77%)	10 (59%)	0.259
Time from diagnosis to initiation of combination therapy (days)[b]	59±64	122±54	0.028

Note: Data are presented as n (%), mean ± standard deviation, or median (interquartile range). PAH, pulmonary arterial hypertension; I/H, idiopathic or heritable; CTD, connective tissue disease; CHD, congenital heart disease; PoPH, portopulmonary hypertension; WHO FC, World Health Organization functional class; 6MWD, 6 min walking distance; peak VO2, peak oxygen consumption; BNP, brain natriuretic peptide; RAP, right atrial pressure; mPAP, mean pulmonary arterial pressure; SvO2, mixed venous oxygen saturation; CI, cardiac index; PVR, pulmonary vascular resistance; f/u, follow-up.

[a]Characteristics at baseline.

[b]Analysis in patients who received combination therapy at follow-up.

study populations are needed to examine these issues further. Finally, values for all of the risk variables were not available for all patients. For example, only 59% of the overall population underwent both the 6 min walk test and the cardiopulmonary exercise test. However, the five variables, including the two composite variables that we defined as exercise tolerance and circulatory dynamics, were assessed in over 90% of patients at baseline and 79% of patients at follow-up, which are higher proportions compared with previous studies using score-and-average methods.

In conclusion, we found that the risk assessment strategy proposed in the 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension is valid for the prediction of long-term prognosis in PAH patients undergoing treatment at our institution in Japan. Achieving low-risk status appears to be an

appropriate treatment goal for our patients; however, treatment strategies such as early initiation of combination therapy remain to be validated with respect to achieving this goal.

Conflict of interest statement

Both Takahisa Kondo and Yoshihisa Nakano belong to an endowed department of Actelion Pharmaceuticals Japan Ltd.

Acknowledgements

The authors thank Emiko Watanabe for assisting our research. We also express our gratitude to all of the medical staff who are involved in the treatment of pulmonary arterial hypertension at our hospital. This work was supported in part by a Grant-in-Aid for Scientific Research (C) (17K09551) from the Japan Society for the Promotion of Science.

References

Boucly, A., Weatherald, J., Savale, L., Jais, X., Cottin, V., Prevot, G., et al. 2017. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. Eur. Respir. J. **50**(2). doi:10.1183/13993003.00889-2017. PMID: 28775050.

Condliffe, R., Kiely, D.G., Peacock, A.J., Corris, P.A., Gibbs, J.S., Vrapi, F., et al. 2009. Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. Am. J. Respir. Crit. Care Med. **179**(2): 151–157. doi:10.1164/rccm.200806-953OC. PMID:18931333.

Fukuda, K., Date, H., Doi, S., Fukumoto, Y., Fukushima, N., Hatano, M., et al. 2019. Guidelines for the Treatment of Pulmonary Hypertension (JCS 2017/JPCPHS 2017). Circ. J. **83**(4): 842–945. doi:10.1253/circj.CJ-66-0158. PMID: 30853682.

Galie, N., Humbert, M., Vachiery, J.L., Gibbs, S., Lang, I., Torbicki, A., et al. 2016. 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. **37**(1): 67–119. doi:10.1093/eurheartj/ehv317. PMID:26320113.

Galie, N., Channick, R.N., Frantz, R.P., Grunig, E., Jing, Z.C., Moiseeva, O., et al. 2019. Risk stratification and medical therapy of pulmonary arterial hypertension. Eur. Respir. J. **53**(1): 1801889. doi:10.1183/13993003.01889-2018.

Hoeper, M.M., Kramer, T., Pan, Z., Eichstaedt, C.A., Spiesshoefer, J., Benjamin, N., et al. 2017. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. Eur. Respir. J. **50**(2): 1700740. doi:10.1183/13993003.00740-2017. PMID: 28775047.

Hoeper, M.M., Pittrow, D., Opitz, C., Gibbs, J.S.R., Rosenkranz, S., Grunig, E., et al. 2018. Risk assessment in pulmonary arterial hypertension. Eur. Respir. J. **51**(3): 1702606. doi:10.1183/13993003.02606-2017. PMID:29599117.

Ikegami, N., Yoo, B.-K., Hashimoto, H., Matsumoto, M., Ogata, H., et al. 2011. Japanese universal health coverage: evolution, achievements, and challenges. Lancet, **378**(9796): 1106–1115. doi:10.1016/S0140-6736(11)60828-3. PMID: 21885107.

Kanatani, Y., Tomita, N., Sato, Y., Eto, A., Omoe, H., and Mizushima, H. 2017. National Registry of Designated Intractable Diseases in Japan: Present Status and Future Prospects. Neurol. Med. Chir (Tokyo). **57**(1): 1–7. doi:10.2176/nmc.st.2016-0135. PMID:27666154.

Kondo, T., Okumura, N., Adachi, S., and Murohara, T. 2019. Editors' Choice Pulmonary Hypertension: Diagnosis, Management, and Treatment. Nagoya J. Med. Sci. **81**(1): 19–30. doi:10.18999/nagjms.81.1.19. PMID:30962652.

Kylhammar, D., Kjellstrom, B., Hjalmarsson, C., Jansson, K., Nisell, M., Soderberg, S., et al. 2018. A comprehensive risk stratification at early follow-up determines prognosis in pulmonary arterial hypertension. Eur. Heart J. **39**(47): 4175–4181. doi:10.1093/eurheartj/ehx257. PMID:28575277.

Shirai, Y., Yasuoka, H., Okano, Y., Takeuchi, T., Satoh, T., and Kuwana, M. 2012. Clinical characteristics and survival of Japanese patients with connective tissue disease and pulmonary arterial hypertension: a single-centre cohort. Rheumatology (Oxford), **51**(10): 1846–1854. doi:10.1093/rheumatology/kes140. PMID:22740623.

Tamura, Y., Kumamaru, H., Satoh, T., Miyata, H., Ogawa, A., Tanabe, N., et al. 2017. Effectiveness and Outcome of Pulmonary Arterial Hypertension-Specific Therapy in Japanese Patients with Pulmonary Arterial Hypertension. Circ. J. **82**(1): 275–282. doi:10.1253/circj.CJ-17-0139. PMID:28747612.