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Differential effects of combination therapy on the components of the risk stratification table in patients with idiopathic or heritable pulmonary arterial hypertension in a Japanese population

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ABSTRACT

Risk stratification by ESC/ERS guideline is recommended to estimate the vital prognosis and select the treatment strategy in patients with idiopathic or heritable pulmonary arterial hypertension (IPAH/HPAH). However, we are not confident whether we can achieve low-risk status in the risk table at the follow-up shortly after combination therapy. Therefore, we aimed to verify the effects of combination therapy in IPAH/HPAH on each category of the risk table at diagnosis and at the first follow-up. We retrospectively analyzed 10 consecutive patients with IPAH/HPAH with no previous treatment history diagnosed at Nagoya University Hospital between October 2014 and January 2019. Four categories including symptoms, exercise tolerance, BNP levels and hemodynamics were validated both at baseline and at the first follow-up of right heart catheterization. Score of 1, 2 and 3 were assigned to the low risk, intermediate risk and high risk, respectively. In each category the highest score was adopted. The scores at diagnosis were compared with those at the first follow-up. The result shows that all patients were female, median age was 32 years old, and were treated with initial combination therapy. The median total risk score also was improved from 2.6 to 1.4 ($p<0.01$). However, the score in exercise tolerance was not improved (3 to 2.5 $p=0.16$). In conclusion, at the first follow up shortly after the initial combination therapy of IPAH/HPAH, the mean total risk score was significantly improved, however, even patients in the low-risk status may not achieve improvement in exercise tolerance.

Keywords: pulmonary arterial hypertension, risk score, exercise tolerance

Abbreviations:
IPAH: idiopathic pulmonary hypertension
HPAH: hereditary pulmonary hypertension
WHO: World Health Organization
VO_2: oxygen uptake
VE/VCO_2: ventilation/carbon dioxide output
PAP: pulmonary arterial pressure
6MWD: 6-min walk distance

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INTRODUCTION

There has been dramatic progress in the treatment of pulmonary arterial hypertension (PAH) in recent years, and the usefulness of treatment that combines multiple drugs with three different mechanisms of action from the early stage has been demonstrated.[1-4] The guidelines for the diagnosis and treatment of pulmonary hypertension by the European Society of Cardiology (ESC)/ European Respiratory Society (ERS) revised in 2015 (2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension) recommends multidrug therapy from the early stage of PAH. In addition, the guidelines recommend comprehensive evaluation of prognostic factors, such as subjective symptoms, biomarker results, exercise tolerance, and measures of hemodynamics, to classify the risk of patient during treatment.[5] The prognostic factors are classified as indicators of low, moderate, or high risk on the basis of the estimated mortality after 1 year, and the treatment goal of PAH is to achieve and maintain the low risk.[6] Furthermore, at the 6th World Symposium on Pulmonary Hypertension held in Nice, France in 2018, it was recommended that risk assessment be repeated at 3–6 months after the start of treatment to determine if the risk has reduced. Multiple subsequent validation data indicated that the result of a reassessment of the risk at 3–6 months from the start of treatment is an excellent prognostic/predictive factor.[7-9]

However, the detailed assessments of how risk classification of each prognostic factor changes by treatment in patients with PAH have been rarely performed. Herein, based on the 2015 ESC/ ERS guidelines, we evaluated how the abridged version of the risk score changed before and after treatment in Japanese treatment-naïve patients with PAH and if there was any difference in the degree of improvement in each factor.

METHODS

We retrospectively analyzed 10 consecutive patients with idiopathic and hereditable PAH (IPAH/HPAH) with no previous treatment history who were diagnosed at Nagoya University Hospital between October 2014 and January 2019. On contrast-enhanced computed tomography (CT) and lung ventilation/perfusion scintigraphy, no thrombus was found in the pulmonary arteries of these patients, and no signs of connective tissue disease, liver cirrhosis, lung disease, or left heart disease were observed. Of these, six patients were treated with upfront combination therapy, and four patients were treated with sequential combination therapy. The prognostic/ predictive factors were classified into the following four categories: (i) subjective symptoms such as signs of right heart failure, progression of symptoms, and functional classification by World Health Organization (WHO); later referred to as symptoms; (ii) exercise capacity indicated by either six-min walk distance (6MWD) and/or cardiopulmonary exercise (CPX); later referred to as exercise tolerance; (iii) B-type natriuretic peptide (BNP); later referred to as a biomarker; and (iv) echocardiography and right heart catheterization ;later referred to as hemodynamics. In addition, low, moderate, and high risk of prognostic/predictive factors were scored as 1, 2, and 3, respectively, and the score of the most severe prognostic/predictive factor within each item was used as the score of the item (Figure 1). Data are collected at the time of diagnosis (baseline; i.e., the time of the first right heart catheterization) and at the time of first follow-up (first follow-up; the time of the second right heart catheterization) at least in 6-month intervals. The average score of each item was rounded off and used as the abridged version risk score

	Risk score	1	2	3
	Determinants of prognosis (estimated 1-year mortality)	Low risk <5%	Intermediate risk 5-10%	High risk >10%
(i)	Clinical signs of right heart failure	Absent	Absent	Present
	Progression of symptoms	No	Slow	Rapid
	Syncope	No	Occasional Syncope	Repeated Syncope
	WHO functional class	Ⅰ, Ⅱ	Ⅲ	Ⅳ
(ii)	6MWD	>440 m	165-440 m	<165 m
	Cardiopulmonary exercise testing	PeakVO2 >15ml/min/Kg (>65% pred.)] VE/VCO2 slope < 36	PeakVO2 11-15ml/min/Kg (35-65% pred.)] VE/VCO2 slope 36-44.9	PeakVO2 <11ml/min/Kg (<35% pred.)] VE/VCO2 slope >45
(iii)	BNP/NT-proBNP plasma levels	BNP <50 ng/l NT-proBNP <300 ng/l	BNP 50-300 ng/l NT-proBNP 300-1400 ng/l	BNP >300 ng/l NT-proBNP >1400 ng/l
(iv)	Imaging (echocardiography, CMR imaging)	RA area <18 cm^2 No pericardial effusion	RA area 18-26 cm^2 No or minimal, pericardial effusion	RA area >26 cm^2 Pericardial effusion
	Hemodynamics	RAP <8 mmHg CI >2.5 l/min/m^2 SvO_2 >65 %	RAP 8-14 mmHg CI 2.0-2.4 l/min/m^2 SvO_2 60-65 %	RAP >14mmHg CI <2.0 l/min/m^2 SvO_2 <60%

Fig. 1 Abridged risk assessment in pulmonary arterial hypertension
The prognostic/predictive factors were classified into the following four categories based on the risk assessment table for pulmonary arterial hypertension (PAH) patients proposed in the 2015 European Society of Cardiology/ Society European Respiratory (6,7). The prognostic/predictive factors were classified into the following four categories: (i) subjective symptoms such as signs of right heart failure, progression of symptoms, and functional classification by WHO; referred to as symptoms; (ii) exercise capacity indicated by either 6-min walk distance (6MWD) and/or cardiopulmonary exercise (CPX); referred to as exercise tolerance; (iii) B-type natriuretic peptide (BNP); referred to as a biomarker; and (iv) echocardiography and right heart catheterization referred to as hemodynamics. Low, moderate, and high risk of prognostic factors were scored as 1, 2, and 3, respectively.
WHO: World Health Organization
6WMD: six-minute walk distance
VO_2: oxygen uptake
VE/VCO_2: ventilation/carbon dioxide output
BNP: brain natriuretic peptide
NT-proBNP: N-terminal pro-brain natriuretic peptide
CMR: cardiovascular magnetic resonance
RAP: right atrial pressure
CI: cardiac index

at each time point. The changes in risk scores between the initial visit and first follow-up were compared for each patient. Furthermore, for exercise tolerance, changes in each parameter of 6MWD and CPX were comparatively analyzed. The median time until the first follow-up was 161 days. Values exhibiting normal and non-normal distributions are shown as mean (± standard deviation: SD) and median (25th–75th percentile), respectively. Wilcoxon signed rank test was used for the analysis. p value of <0.05 was considered to be statistically significant. Statistical analyses were performed using SPSS software version 26 (Armonk, NY, USA).

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 of this study.

RESULTS

The subjects were all female patients with a median age of 32 years. IPAH was diagnosed in nine patients and HPAH in one. Nine patients had right heart failure and three had a previous history of syncope at diagnosis. Seven patients were WHO Functional Classification Class III and three were Class IV. Median 6MWD was 351 m, median peak VO_2 and VE/VCO_2 slope by CPX were 12.6 ml/min/kg and 43.9, respectively, and median BNP was 303 ng/L. The median right atrial pressure, median cardiac index, and median SvO_2 were 5.0 mmHg, 1.86 L/min/m^2, and 61.7%, respectively, and pericardial effusion was reported in six patients. The median abridged version risk score at the initial visit was 2.6. The median values of the mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance (PVR) were 53.5 mmHg and 16.6 Wood units, respectively (Table 1).

Table 1 Baseline characteristics

	n = 10
Age (year)	32 (27–43)
Female (%)	10 (100)
IPAH : HPAH	9:1
Medication: n (%)	
double oral therapy	4 (40)
triple oral therapy	3 (30)
double oral therapy + i.v. epoprostenol	3 (30)
Time to first follow up (days)	161 (40–178)
Symptom n (%)	
clinical sign of right heart failure	9 (90)
progression of symptom	9 (90)
syncope	3 (30)
WHO functional class III n (%)	7 (70)
IV	3 (30)
Exercise tolerance	
six-minute walk distance (m)	359 (306–404)
Peak VO_2 (mL/min/kg)	12.6 (11.1–13.3)
Peak VO_2 Predict (%)	45 (42–51)
VE/VCO_2 slope	43.9 (34.7–44.6)
BNP (ng/L)	303 (59.2–660)
Hemodynamics	
Mean PAP (mmHg)	53.5 (46.5–64.5)
PVR (wood)	16.5 (12.0–23.1)
RAP (mmHg)	5 (3.25–9.75)
CI (L/min/m^2)	1.86 (1.54–2.15)

SVO_2 (%)	61.7 (56.6–67)
Pericardial effusion n (%)	6 (60)
Total risk score average	2.6 (2.1–2.8)

Values are average ± SD, Median (25^{th} percentile–75^{th} percentile) or n (%)
IPAH: idiopathic pulmonary hypertension
HPAH: hereditary pulmonary hypertension
WHO: World Health Organization
VO_2: oxygen uptake
VE/VCO_2: ventilation/carbon dioxide output
BNP: brain natriuretic peptide
PAP: pulmonary arterial pressure
PVR: pulmonary vascular resistance,
RAP: right atrial pressure
CI: cardiac Index
i.v.: intravenous

At the first follow-up, the following drugs were used for treatment: two oral pulmonary hypertension drugs in four, and two oral drugs plus epoprostenol by continuous intravenous infusion in three patients. The mPAP and PVR at the first follow-up were 41.0 mmHg and 7.3 Wood units, respectively, both of which showed significant improvement ($p < 0.01$) (Figure 2). The risk score significantly reduced from 2.6 to 1.4 ($p < 0.01$) (Figure 3).

Thereafter, changes in the risk score of each item over time were compared. The risk scores of symptoms (i), biomarker (ii), and hemodynamics (iv) significantly decreased from 3 to 2 ($p = 0.015$), 2.5 to 1.5 ($p = 0.03$), and 3 to 1 ($p = 0.02$), respectively, whereas the score of exercise tolerance (iii) changed from 3 to 2.5 (P=0.16), which was not significant (Figure 4).

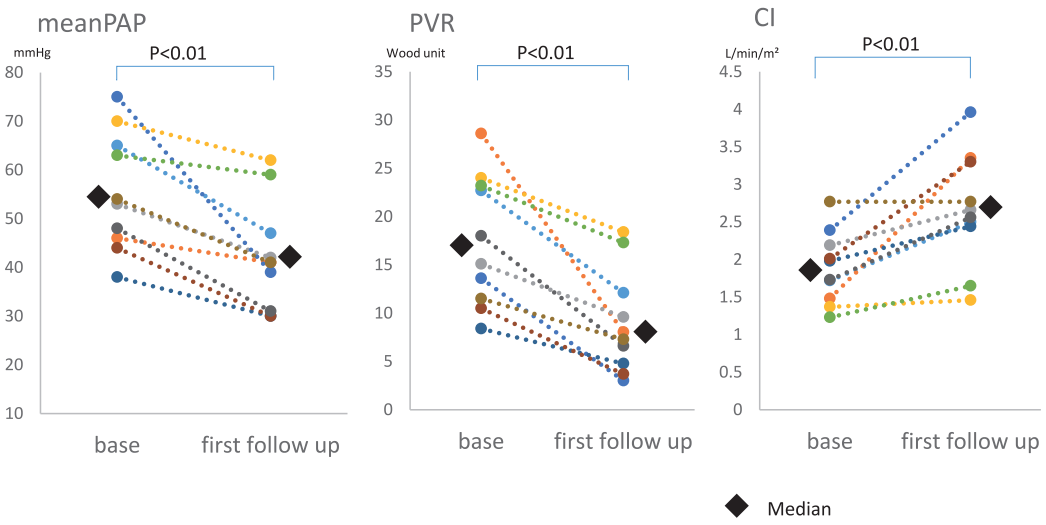

Fig. 2 Changes in mean PAP, PVR and CI, between baseline and first follow-up
PAP: pulmonary arterial pressure
PVR: pulmonary vascular resistance
CI: cardiac index

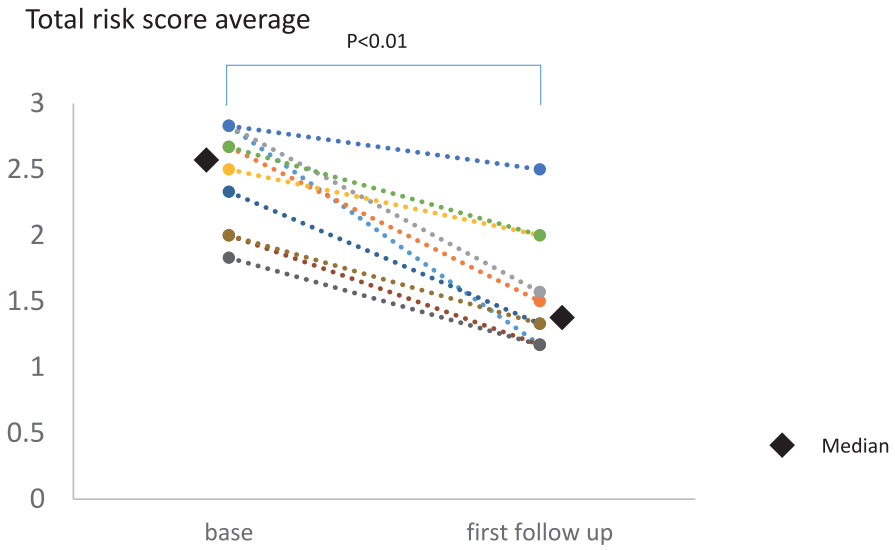

Fig. 3 Changes in total risk score average, between baseline and first follow-up

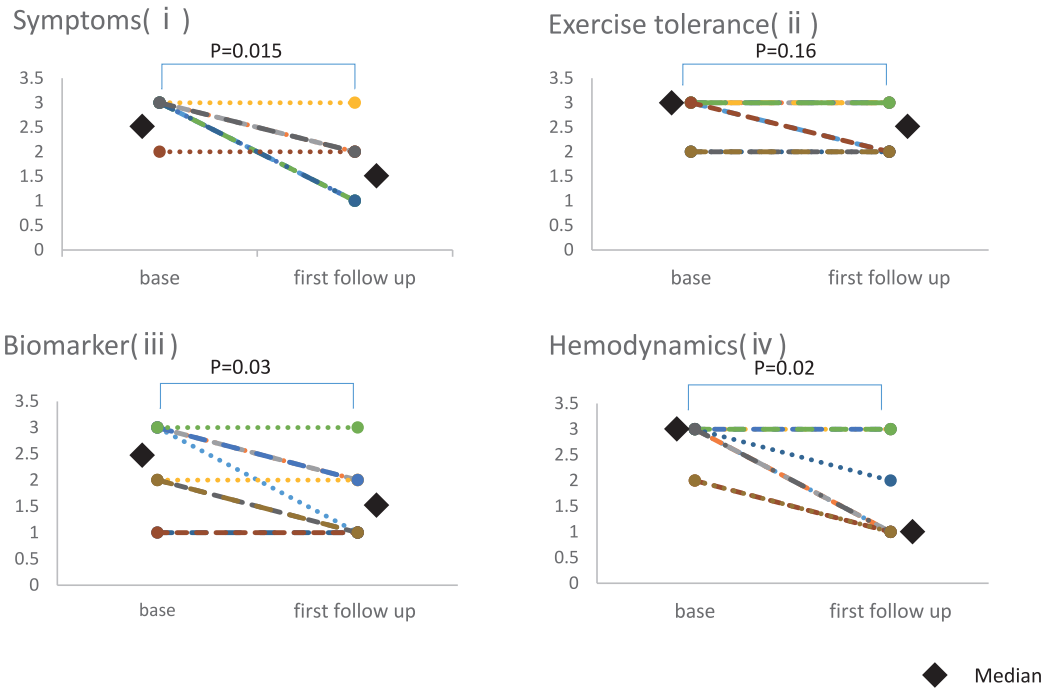

Fig. 4 Changes in risk score average of Symptoms (i), Exercise tolerance (ii), Biomarker (iii) and Hemodynamics (iv), between baseline and first follow-up

After the treatment, mPAP decreased, hemodynamics improved, and right heart failure symptoms and the biomarker significantly improved. However, of the four items used for the risk score evaluation, only the improvement in exercise tolerance was poor; therefore, for each of the small items used for exercise tolerance evaluation (6MWD, peak VO_2, predict, and VE/VCO_2 slope), risk scores were calculated respectively to determine the reason for the poor improvement in exercise tolerance. The risk score of peak VO_2 significantly improved from 3 to 2 (p = 0.014). The risk scores of the predicted VE/VCO_2 slope and predicted peak VO_2 showed an improvement from 3 to 2 (p = 0.08) and from 3 to 2 (p = 0.16), respectively, although the changes were not statistically significant. However, the risk score for 6MWD remained at 2 with no improvement (Figure 5). The risk scores of 6MWD at baseline were relatively lower than those of the other items, and the improvement of the risk scores at the follow-up was not observed. However the median value of the actual measurement of 6MWD increased from 359 m to 415 m (p = 0.09), which was not significant.

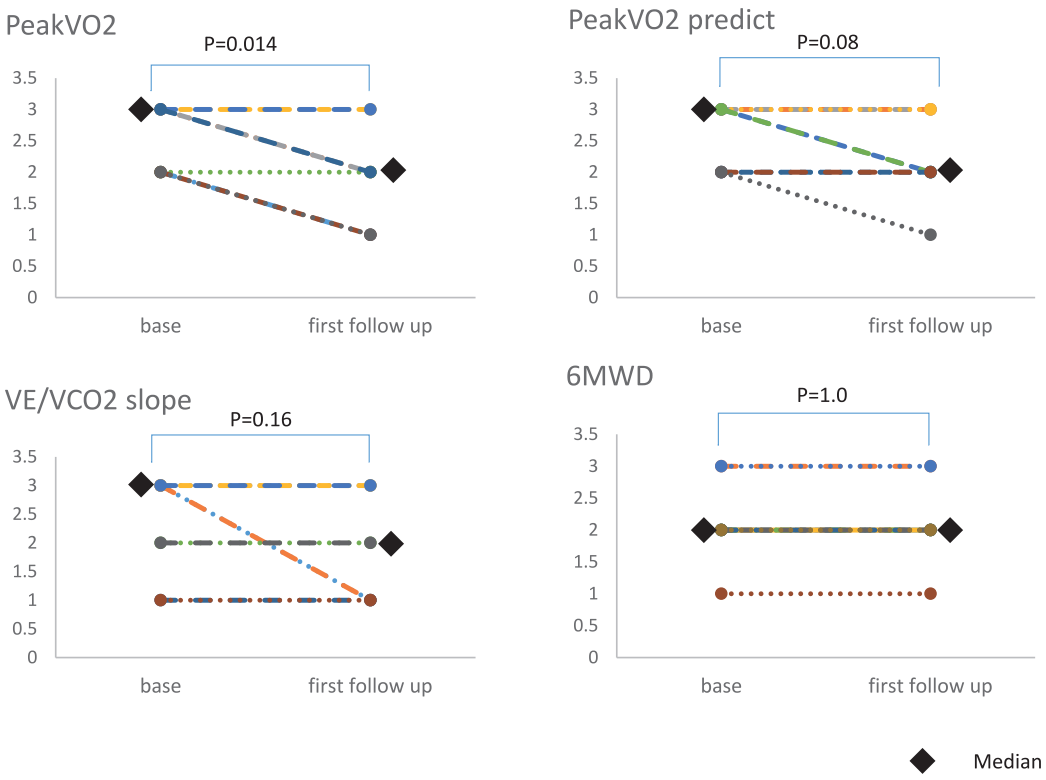

Fig. 5 Changes in risk score average of $PeakVO_2$, $PeakVO_2$ predict, VE/VCO_2 slope and 6WMD, between baseline and first follow-up

VO_2: oxygen uptake
VE/VCO_2: ventilation/carbon dioxide output
6WMD: six-minute walk distance

DISCUSSION

In this study, combination therapy for treatment-naïve patients with PAH significantly reduced the abridged version of ESC risk score that was evaluated using the following four indicators: symptoms (i), exercise tolerance (ii), biomarkers (iii), and hemodynamics (iv). These results clearly indicated the usefulness of the abridged version of the ESC risk score in a certain Japanese population. Moreover, the study revealed that, of the four indicators, exercise tolerance did not improve during the short-term follow-up period.

Pulmonary hypertension drugs improved hemodynamics of the patients during the early stage of treatment: symptoms (i), biomarkers (ii) and hemodynamics (iii) were ameliorated along with the change. But, the effect of improving exercise tolerance was poor or delated: exercise tolerance (iv) is determined by a comprehensive evaluation of hemodynamics, pulmonary function, and skeletal muscle function, as shown by the three factors of Wasserman.[10] Therefore, even if hemodynamics are improved by pulmonary hypertension drugs, exercise tolerance remains low unless pulmonary and skeletal functions are improved.

Physiological mechanisms that reduce exercise tolerance in patients with pulmonary hypertension include decreased gas exchange efficiency in the lungs due to ventilation-perfusion mismatch, increased minute ventilation, decreased carbon monoxide-diffusing capacity, hypoxia, and decreased oxygen transport to the tissue. Particularly, patients with pulmonary hypertension have decreased blood flow to the skeletal muscles and a decline in oxygen supply.[11] Consequently, chronic hypoxia in the skeletal muscles results in muscle atrophy. Therefore, in patients with severe pulmonary hypertension, it may take time to improve atrophied muscle even after PAP and PVR are improved in a short period of time due to the treatment.[12] In the treatment of pulmonary hypertension, the evaluation of exercise tolerance is an essential item for measuring treatment effects; however, early in the treatment, it may be incorrect to conclude that the treatment effect is insufficient on the basis of poor improvement in exercise tolerance.

In this study, because the improvement in the exercise tolerance risk score was poor, we compared each result of CPX and 6MWD to examine the causes. Regarding CPX, peak VO_2 showed significant improvement, whereas the VE/VCO_2 slope, which indicates the degree of ventilation-perfusion mismatch, showed an improving trend that was not significant and did not contribute to the risk score improvement. Peak VO_2 is regulated by not only cardiac output, but also vascular endothelial function. PAH drugs are reported to improve peripheral endothelial function.[13,14] Therefore, in a relatively short follow-up period of this population, an improvement in peak VO_2 may be better than that in VE/VCO_2 slope by amelioration of peripheral endothelial function.

Moreover, 6MWD did not contribute to the improvement in the risk score, but the walking distance showed an improvement. These results reaffirmed that various factors need to be considered when assessing the effects of PAH-treatment drugs on the basis of 6MWD. For example, when assessing 6MWD, the influence of a difference in the stride length caused by a difference in physiques should not be ignored.[15] Walking with the same number of steps can result in greatly different 6MWD values. IPAH/HPAH is more common in females than in males. In particular, because of the relatively smaller body size of Japanese females relative to the body size of Western Europeans and Americans, uniform evaluations without an adjustment for sex and race may result in incorrect assessments. According to a previous report on Japanese data,[16] 6MWD that indicates a severe disease state is <332 m, suggesting that the value of 440 m for the low-risk cutoff stated in the ESC guidelines may not be suitable for the small body sizes of Japanese individuals. Another possibility is that because of the large range of moderate risk (165–440 m), it may have been difficult to extend the distance to ≥440 m during the early

stage of treatment.

Exercise tolerance is a combination of various predisposing factors. Therefore, it is considered insufficient to simply classify exercise tolerance as low, moderate, and high risk. Improvement to low risk is the first step of goal in PAH treatment; however, it is necessary to adjust 6MWD by considering the patient's characteristics such as sex and body type. In addition, the effectiveness of the 6MWD test may be limited to assess exercise tolerance in a short period of time after the start of treatment when skeletal muscle level has still not recovered. In addition to PAH drug treatment, appropriate rehabilitation with an approach to skeletal muscle could lead to improvement in long-term exercise tolerance.[17-19]

LIMITATION

The study has some limitations. The study was conducted at a single facility and the number of cases was limited. Additionally, this was a retrospective study, and some patients could not be evaluated on the basis of all evaluation items. Therefore, the evaluation items were classified into four groups for examination.

CONCLUSION

The abridged version of the ESC risk score was a good indicator of improvement risk in short-term evaluations of patients with new-onset PAH who underwent combination therapy in a Japanese population. In contrast, exercise tolerance showed poor improvement among the items included in the abridged version risk score, so interpretation of the risk score in short-term evaluations of the effect of PAH treatment requires careful attention. Presently, the physique and race are not considered for exercise tolerance evaluation based on 6MWD. Future reconsideration of the low-risk group is necessary.

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RESEARCH ETHICS AND PATIENT CONSENT

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.

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CONFLICT OF INTEREST

Both Takahisa Kondo and Yoshihisa Nakano belong to an endowed department of Actelion Pharmaceuticals Japan Ltd (now Jansen Pharmaceutical K.K.).

REFERENCES

1 Galiè N, Barbera JA, Frost AE, et al. Initial Use of Ambrisentan plus Tadalafil in Pulmonary Arterial Hypertension. *N Engl J Med*. 2015;373(9):834–844. doi:10.1056/NEJMoa1413687.
2 Sitbon O, Jaïs X, Savale L, et al. Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study. *Eur Respir J*. 2014;43(6):1691–1697. doi:10.1183/09031936.00116313.
3 Ogawa A, Satoh T, Tamura Y, Fukuda K, Matsubara H. Survival of Japanese Patients With Idiopathic/Heritable Pulmonary Arterial Hypertension. *Am J Cardiol*. 2017;119(9):1479–1484. doi:10.1016/j.amjcard.2017.01.015.
4 Kondo T, Okumura M, Adachi S, Murohara T. Pulmonary Hypertension: Diagnosis, Management, and Treatment. *Nagoya J Med Sci*. 2019;81(1):19–30. doi:10.18999/nagjms.81.1.19.
5 Galiè N, Humbert M, Vachiery JL, 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(1):67–119. doi:10.1093/eurheartj/ehv317.
6 Galiè N, Humbert M, Vachiery JL, 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 Respir J*. 2015;46(4):903–975. doi:10.1183/13993003.01032-2015.
7 Hoeper MM, Kramer T, Pan Z, et al. Mortality in pulmonary arterial hypertension: prediction by the 2015 European pulmonary hypertension guidelines risk stratification model. *Eur Respir J*. 2017;50(2): 1700740. doi:10.1183/13993003.00740-2017.
8 Boucly A, Weatherald J, Savale L, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. *Eur Respir J*. 2017;50(2): 1700889. doi:10.1183/13993003.00889-2017.
9 Weatherald J, Sitbon O, Humbert M. Validation of a risk assessment instrument for pulmonary arterial hypertension. *Eur Heart J*. 2018;39(47):4182–4185. doi:10.1093/eurheartj/ehx301.
10 Wasserman K, Van Kessel AL, Burton GG. Interaction of physiological mechanisms during exercise. *J Appl Physiol*. 1967;22(1):71–85. doi:10.1152/jappl.1967.22.1.71.
11 Zafrir B. Exercise training and rehabilitation in pulmonary arterial hypertension: rationale and current data evaluation. *J Cardiopulm Rehabil Prev*. 2013;33(5):263–273. doi:10.1097/HCR.0b013e3182a0299a.
12 Breda AP, Pereira de Albuquerque AL, Jardim C, et al. Skeletal muscle abnormalities in pulmonary arterial hypertension. *PLoS One*. 2014;9(12):e114101. doi:10.1371/journal.pone.0114101.
13 Liang F, Yang S, Yao L, Belardinelli L, Shryock J. Ambrisentan and tadalafil synergistically relax endothelin-induced contraction of rat pulmonary arteries. *Hypertension*. 2012;59(3):705–711. doi:10.1161/HYPERTENSIONAHA.111.182261.
14 Hirashiki A, Adachi S, Nakano Y, et al. Effects of bosentan on peripheral endothelial function in patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension. *Pulm Circ*. 2016;6(2):168–173. doi:10.1086/685715.
15 Yamazaki M, Sato H. Human Walking With Reference to Step Length, Cadence, Speed and Energy Expenditure[in Japanese]. *J Anthrop Soc. Nippon*. 1990;98(4):385–401.doi:10.1537/ase1911.98.385.
16 Miyamoto S, Nagaya N, Satoh T, et al. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. *Am J Respir Crit Care Med*. 2000;161(2 Pt 1):487–492. doi:10.1164/ajrccm.161.2.9906015.
17 de Man FS, Handoko ML, Groepenhoff H, et al. Effects of exercise training in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J*. 2009;34(3):669–675. doi:10.1183/09031936.00027909.
18 Mereles D, Ehlken N, Kreuscher S, et al. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. *Circulation*. 2006;114(14):1482–1489. doi:10.1161/CIRCULATIONAHA.106.618397.
19 Fox BD, Kassirer M, Weiss I, et al. Ambulatory rehabilitation improves exercise capacity in patients with pulmonary hypertension. *J Card Fail*. 2011;17(3):196–200. doi:10.1016/j.cardfail.2010.10.004.