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Current status of long-term prognosis among all subtypes of pulmonary hypertension in Japan

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ABSTRACT

Background: In the current era of treatment of pulmonary hypertension (PH) in Japan, combination therapy has been frequently used thanks to the medical insurance system. Additionally, pulmonary balloon angioplasty (BPA) is widely performed for chronic thromboembolic PH (CTEPH).
Methods: To elucidate the long-term prognosis and the prognostic factors among all five subtypes of PH in this new era, we examined the current status of management of PH from November 2012 to April 2016 in the multicenter registry by the Japanese Pulmonary Circulation Society.
Results: Among 1253 consecutive patients registered from 20 PH centers in Japan, we analyzed 997 patients with mean pulmonary arterial pressure ≥ 25 mmHg by right heart catheterization. Transplant-free survival at 5 years in pulmonary arterial hypertension (PAH), PH due to left-heart disease, PH due to lung diseases, CTEPH, and miscellaneous PH were 74.0, 69.3, 63.7, 92.0, and 55.3%, respectively. Of note, 32% of PAH patients were treated with double combination therapy and 42% of those with triple combination therapy, and 66% of CTEPH patients with BPA. Although PAH patients with triple combination therapy had worse hemodynamic parameters than those with other medications, triple combination therapy showed the best prognosis. BPA in CTEPH improved survival even when adjusted for the key background factors.
Conclusions: In the current era of PH treatment in Japan, the five-year transplant-free survival rate in this study was 74% for PAH and 92% for CTEPH, in which active combination medical therapy for PAH and higher performance rate of BPA for CTEPH may be involved.

1. Introduction

Pulmonary hypertension (PH) is a disease characterized by elevated pulmonary arterial pressure and finally leads to right heart failure and premature death [1]. PH is classified into five subgroups, including group 1, pulmonary arterial hypertension (PAH), group 2, PH associated with left-heart disease (PH-LHD), group 3, PH associated with lung disease (PH-lung), group 4, chronic thromboembolic pulmonary hypertension (CTEPH), and group 5, miscellaneous PH (PH-misc) [2].

In the past two decades, the disease-targeted medical therapy, originally for PAH, for major three pathways have been developed, including prostacyclin, endothelin-1, and nitric oxide [3]. Despite the progress in the treatment, the prognostic information on all the five subgroups of PH in the same population still lacks due to the rarity of the disease [4–6]. Furthermore, the details of patients' characteristics and status of PAH-targeted drugs in all five groups remain to be examined in the modern era. In Japan, the triple combination therapy has been frequently used for PAH thanks to the national medical insurance system that allows the insured to secure medical expenses that are too expensive to prepare on their own. Additionally, pulmonary balloon angioplasty (BPA) is nation-widely performed for CTEPH.

In the present study, we thus conducted a multicenter, observational registry study by the Japanese Pulmonary Circulation Society to

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elucidate the long-term prognosis and prognostic factors among all five subtypes of PH in the current era in Japan.

2. Methods

2.1. Study population

The present study is a multicenter, observational registry by the Japanese Pulmonary Circulation Society (UMIN000022449) to establish the optimal therapy for PH by investigating the current situation of treatment and prognosis for PH prospectively in Japan. From November 2012 to April 2016, we enrolled a total of 1253 consecutive patients with PH from 20 of the 61 institutions that had the board members and/or councilors of the Society.

PH was defined as mean pulmonary arterial pressure (mPAP) ≥25 mm Hg at rest by right heart catheterization (RHC) [7]. The Nice clinical classification of PH [7] was used based on the established approaches, including physical examination, blood tests, echocardiography, pulmonary function test, chest X-ray, computed tomography, ventilation-perfusion scanning, and RHC [8], and was assigned by the physician specializing in PH at each hospital. Prevalent cases were patients diagnosed as PH before registration, and incident cases were those diagnosed initially at registration. PH-specific drugs available during the study period in Japan included oral and intravenous prostacyclin analogues since 1999, endothelin receptor antagonists (ERA) since 2005, phosphodiesterase type-5 (PDE-5) inhibitors since 2008, and a soluble guanylate cyclase (sGC) stimulator since 2014. These drugs were chosen by a physician in charge as a monotherapy or combination therapy and listed for the present analysis when the maximum number of drugs was used during the follow-up. Therapeutic other medicines were also entered into the database at a maximum dose used. Baseline demographic data were collected from the medical records of each patient. Follow-up was completed in November 2016. The primary outcome was the composite end-point of all-cause death and heart or lung transplantation [9].

The study protocol conforms to the ethical guidelines of the Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. The study was conducted under the Ethical Guidelines for Clinical Studies from the Japanese Ministry of Health, Labour and Welfare, and all applicable laws and regulations in Japan. The protocol was reviewed and approved by the Institutional Review Boards or Ethics Committees at all participating sites. All patients provided a written informed consent.

2.2. Statistical analysis

Continuous variables are expressed as the mean ± SD or median (interquartile range), and categorical variables as the number (%). Means, medians, and percentages were compared using a paired *t*-test, Wilcoxon signed-rank test, and $\chi 2$ or Fisher exact test, as appropriate. Event-free survival time was calculated from the date of diagnostic catheterization to the date of any cause of death, heart or lung transplantation, or last follow-up. A Kaplan-Meier curve was used to estimate the overall event-free survival, and differences between survival curves were assessed using the log-rank test and Cox proportional hazard models. Univariable and multivariable Cox proportional hazard models were used to estimate the hazard ratios (HR) and 95% confidence intervals (CI). *P* values of <0.05 were regarded to be statistically significant for all analyses. All analyses were performed with JMP Pro 12.2.0 (Japanese version, SAS Institute Inc., Tokyo, Japan). The Japanese Pulmonary Circulation Study Group Investigators (supplementary material) designed the trial. All authors agreed to submit the manuscript for publication and vouch for adherence to the study protocol and the accuracy and completeness of the data. Missing values were not imputed in the analyses.

3. Results

Among 1253 consecutive patients with PH, we analyzed 997 patients with mean mPAP ≥25 mmHg at rest by RHC, where 436 incident cases were included (Supplementary Fig. 1). Two hundred and fifty-six patients were excluded, including 37 with mPAP<25 mmHg diagnosed as PH by other diagnostic methods, 19 whose mPAP were not obtained by RHC, and 200 without treatment information.

3.1. Clinical characteristics of PH patients

The number of patients with the clinical classification of PH was as follows; PAH and pulmonary veno-occlusive disease (PVOD) in 316, PH-LHD in 425, PH-lung in 37, CTEPH in 183, and PH-misc in 36 (Supplementary Fig. 1). Clinical characteristics, the hemodynamic profile, and the maximal therapy during the follow-up of the 997 patients are shown in Table 1. The parenteral prostanoids used during the registry period were as follows; intravenous epoprostenol for 89 PH patients including PAH, PH-lung, CTEPH, and PH-misc, inhaled iloprost for one idiopathic PAH (IPAH), and subcutaneous treprostinil for 1 IPAH.

3.2. Long-term prognosis of PH patients

The event-free survival at 1, 3, 5, and 10 years in all PH patients was 91.9%, 82.2%, 74.0%, and 58.7%, respectively. Survival in Groups 3 and 5 were inferior to Group 1 (Group 1 vs. 3, $P = .04$; and Group 1 vs. 5, $P = .02$) and that in Group 4 was superior to all other subgroups ($P < .0001$, respectively) (Fig. 1A). In the main 3 groups of PAH, PH-LHD, and CTEPH with many patients in this registry, the prognosis for the prevalent cases and the incident cases was comparable (Supplementary Fig. S2A, B, and C).

3.3. Analysis by clinical classification

3.3.1. Group 1: PAH

Baseline characteristics of patients with PAH and PVOD are shown in Supplementary Table S1. Event-free survival at 1, 3, 5, and 10 years in PAH patients was 92.9%, 82.9%, 74.0%, and 59.5%, respectively (Fig. 1A). Patients with systemic sclerosis (SSc) had poorer survival than those with non-SSc connective tissue disease (CTD) ($P = .02$), and those with PVOD had the worst prognosis compared with those with other subtypes (Fig. 1B). CTD accounted for the largest proportion among PAH, and the survival of PAH patients with CTD was comparable with those of IPAH patients ($P = .54$) (Supplementary Fig. S3A). In PAH patients with CTD, systemic lupus erythematosus (SLE) had better survival than SSc ($P = .001$) (Supplementary Fig. S3B).

Importantly, among 311 patients with PAH, most of them ($N = 287$, 92%) received PH-specific medications, including double combination therapy in 101 (32%), and triple combination therapy in 131 (42%) (Table 1). The most common double combination therapy was that of ERA and PDE-5 inhibitor or sGC stimulator (16%), followed by ERA and oral prostacyclin analogue (6%) (Fig. 2A). The most frequent triple combination therapy was that of ERA, PDE-5 inhibitor or sGC stimulator, and beraprost (28%) (Fig. 2A). Although patients with monotherapy and double combination therapy showed a similar prognosis ($P = .83$), those with triple combination therapy showed significantly better prognosis than those with other treatments (vs. monotherapy, $P = .049$; vs. double combination therapy, $P = .042$) (Fig. 2B). Notably, patients with triple combination therapy had higher baseline mPAP and pulmonary vascular resistance (PVR) than those with other treatments (Supplementary Table S2).

Multivariable analysis showed that significant prognostic factors at baseline were male sex, age ≥ 75, BMI < 18.5, WHO FC III/IV, and lower mixed venous oxygen saturation (SvO_2) (Supplementary Table S3). Although eGFR was also a significant prognostic factor in unadjusted analysis, the significance disappeared when SvO_2 was incorporated as a

Table 1
Patient characteristics at baseline and maximal therapy during the follow-up in the five subgroups of PH.

	Overall	Group 1 (PAH)	Group 2 (PH-LHD)	Group 3 (PH-lung)	Group 4 (CTEPH)	Group 5 (PH-misc)
N	997	311 (31)	425 (43)	37 (4)	183 (18)	36 (4)
Follow-up duration, years	3.8 (2.3–6.4)	4.2 (2.5–7.1)	3.7 (2.2–5.5)	2.7 (0.9–4.5)	4.3 (2.7–6.9)	2.8 (0.9–5.6)
Event	278 (28)	91 (29)	139 (33)	13 (35)	16 (9)	15 (42)
Male	424 (43)	73 (23)	269 (63)	22 (59)	42 (23)	16 (44)
Age, years	58 ± 17	49 ± 18	63 ± 14	62 ± 11	62 ± 14	55 ± 15
BMI, kg/m^2	22.6 ± 4.6	21.0 ± 3.9	23.6 ± 4.9	22.6 ± 5.3	23.3 ± 4.3	21.8 ± 4.1
WHO FC I[a]	78 (9)	27 (9)	45 (12)	1 (4)	4 (2)	1 (3)
II	365 (41)	117 (39)	162 (45)	6 (23)	71 (40)	8 (26)
III	361 (40)	131 (44)	114 (32)	17 (65)	81 (46)	17 (55)
IV	96 (11)	26 (9)	40 (11)	2 (8)	20 (11)	5 (16)
6MWD, m	344 ± 123	347 ± 132	340 ± 114	339 ± 97	345 ± 114	291 ± 114
BNP, pg/ml	224 (71–604)	105 (36–310)	444 (195–954)	146 (16–466)	123 (32–304)	478 (129–656)
eGFR, ml/min/1.73 m^2	58 ± 29	76 ± 31	45 ± 22	70 ± 30	60 ± 17	63 ± 53
LVEF, %	61 ± 18	69 ± 11	51 ± 20	65 ± 10	69 ± 9	63 ± 19
FVC, % predicted	85 ± 21	83 ± 21	83 ± 19	65 ± 28	96 ± 18	71 ± 23
FEV1, % predicted	91 ± 22	85 ± 21	101 ± 18	83 ± 33	88 ± 18	86 ± 30
DLCO, % predicted	71 ± 33	58 ± 24	82 ± 27	33 ± 10	87 ± 34	78 ± 58
mPAP, mm Hg	39 ± 13	45 ± 17	33 ± 7	37 ± 13	43 ± 11	40 ± 12
PAWP, mm Hg	15 ± 8	9 ± 5	22 ± 6	12 ± 6	9 ± 4	16 ± 8
RAP, mm Hg	8 ± 5	6 ± 4	10 ± 5	7 ± 7	6 ± 5	10 ± 5
CI, L/min/m^2	2.8 ± 0.9	3.0 ± 1.1	2.6 ± 0.8	3.1 ± 0.9	2.6 ± 0.7	3.0 ± 1.1
PVR, wood units	4.6 (2.4–8.7)	7.9 (4.8–12.6)	2.3 (1.6–3.4)	5.3 (3.7–6.8)	8.3 (5.8–11.1)	5.1 (2.1–7.5)
SvO_2,%	66 ± 9	68 ± 9	65 ± 9	70 ± 8	64 ± 9	65 ± 11
PAC, mL/mm Hg	2.0 ± 1.2	1.7 ± 1.0	2.5 ± 1.3	2.0 ± 0.8	1.3 ± 0.6	1.9 ± 1.1
PH-specific medication	524 (53)	287 (92)	23 (5)	27 (73)	164 (90)	18 (50)
Prostacyclin analogue						
Parenteral prostacyclin analogue	91 (9)	65 (21)	0 (0)	1 (3)	18 (10)	3 (8)
Beraprost	255 (26)	138 (44)	13 (3)	13 (35)	86 (47)	6 (17)
Endothelin receptor antagonist	337 (34)	227 (73)	4 (1)	15 (41)	77 (42)	10 (28)
PDE-5 inhibitor	345 (35)	214 (69)	9 (2)	23 (62)	84 (46)	12 (33)
sGC stimulator	57 (6)	6 (2)	0 (0)	2 (5)	49 (27)	0 (0)
Monotherapy	151 (15)	55 (18)	20 (5)	7 (19)	59 (32)	9 (25)
Double combination therapy	185 (19)	101 (32)	3 (1)	13 (35)	60 (33)	7 (20)
Triple combination therapy	188 (19)	131 (42)	0 (0)	7 (19)	45 (25)	2 (6)
Calcium channel blocker	265 (27)	63 (20)	139 (33)	8 (22)	51 (28)	3 (8)
Loop diuretics	599 (60)	142 (46)	328 (77)	18 (49)	89 (49)	18 (50)
Mineralocorticoid receptor antagonist	414 (42)	97 (31)	237 (56)	10 (27)	54 (30)	12 (33)
Tolvaptan	63 (6)	14 (5)	43 (10)	0 (0)	4 (2)	1 (3)
Anticoagulants	548 (55)	116 (37)	241 (57)	8 (22)	167 (91)	13 (36)

Data are presented as n (%), mean ± SD or median (interquartile range), unless otherwise stated. Percentages in this column may not add up exactly 100% because of rounding. BMI, body-mass index; BNP, brain natriuretic peptide; CI, cardiac index; CTEPH, chronic thromboembolic pulmonary hypertension; DLCO, diffusing capacity of the lung for carbon monoxide; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; PAC, pulmonary arterial capacitance; PAH, pulmonary arterial hypertension; PAWP, pulmonary artery wedge pressure; PDE-5, phosphodiesterase type-5; PH, pulmonary hypertension; PH-LHD, pulmonary hypertension associated with left-heart disease; PH-lung, pulmonary hypertension associated with lung disease; PH-misc, miscellaneous pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; sGC, soluble guanylate cyclase; SvO_2, mixed venous oxygen saturation; WHO FC, World Health Organization functional class; 6MWD, 6-minute walk distance.
[a] Percentage of the cases in which the data were obtained.

variable (Supplementary Table S4). Brain-type natriuretic peptide (BNP) was not an independent prognostic factor, however, when adding the administration of parental prostacyclin analogue as a variable, significant interaction for the administration of parental prostacyclin analogue was noted in terms of the BNP as a prognostic factor ($P = .05$) (Supplementary Table S5).

In patients with parental prostacyclin analogues, those with double combination therapy and those with triple combination therapy similarly showed a tendency to improve survival compared with those with monotherapy when adjusted for the independent prognostic factors listed above ($P = .09$ and $P = .06$, respectively) (Supplementary Table S6). On the other hand, in patients without parental prostacyclin analogues, only those with triple combination therapy showed significantly better prognosis compared with those with 0 or 1 PH-specific drug ($P = .03$).

3.3.2. Group 2: PH-LHD

Twenty-three (5%) patients with PH-LHD were treated with PH-specific medications (Table 1). According to the etiology of PH-LHD, patients with left ventricular (LV) systolic dysfunction (LHD-systolic) had a lower cardiac index, and a higher BNP compared with those with LV diastolic dysfunction (LHD-diastolic) and valvular heart disease (LHD-valvular) (Supplementary Table S7). However, the survival of those with LHD-systolic was comparable with that of those with the other two etiologies (vs. LHD-diastolic, $P = .63$; and vs. LHD-valvular, $P = .09$) (Fig. 1C). Multivariable analysis showed that significant prognostic factors at baseline were age ≥ 75, WHO FC III/IV, and lower eGFR (Supplementary Table S8).

3.3.3. Group 3: PH-lung disease

Among the 37 patients with PH-lung, the most frequent cause was interstitial lung disease (41%), followed by chronic obstructive lung disease (22%), other lung diseases with mixed restrictive and obstructive patterns (16%), alveolar hypoventilation (16%), and sleep-disordered breathing (5%) (Supplementary Fig. 1). Among them, 27 (73%) were treated with PH-specific medications and 23 (62%) with PDE-5 inhibitors (Table 1). Although a detailed analysis of survival for patients with PH-lung was not performed due to the limited number of patients, the long-term survival of Group 3 was as poor as Group 5 among all PH subgroups.

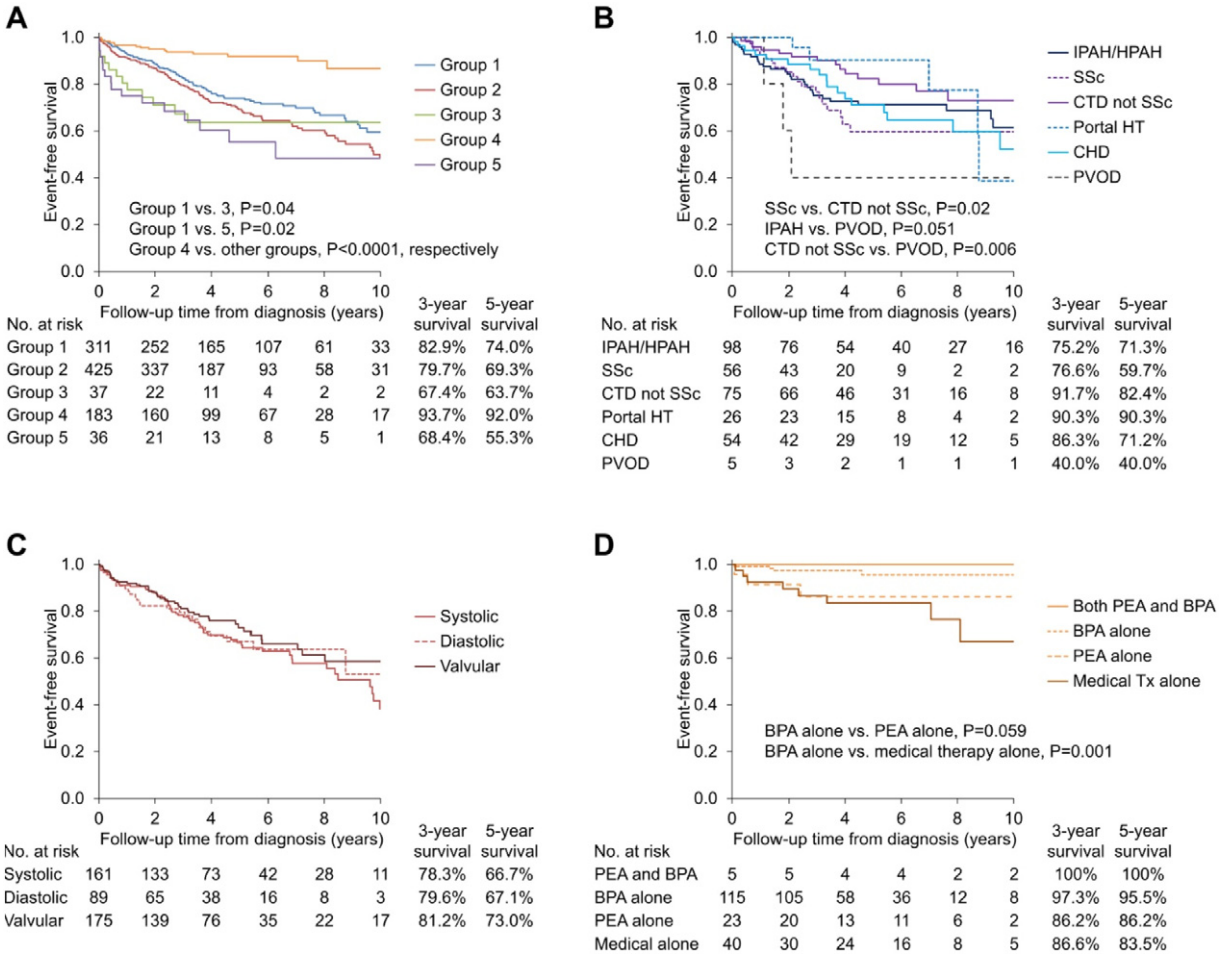

Fig. 1. Long-term prognosis of patients in terms of (A) pulmonary hypertension by diagnostic groups, (B) pulmonary arterial hypertension by clinical subtypes, (C) pulmonary hypertension associated with left-heart disease by clinical subtypes, and (D) chronic thromboembolic pulmonary hypertension by treatment during the follow-up. BPA, balloon pulmonary angioplasty; CHD, congenital heart disease; CTD, connective tissue disease; HPAH, heritable pulmonary arterial hypertension; HT, hypertension; IPAH, idiopathic pulmonary arterial hypertension; PEA, pulmonary endarterectomy; PVOD, pulmonary veno-occlusive disease; SSc, systemic sclerosis; Tx, therapy.

3.3.4. Group 4: CTEPH

Among 183 patients with CTEPH, 143 (78%) received invasive treatments, including pulmonary endarterectomy (PEA) (15%) and BPA (66%) (Supplementary Fig. 1). The event-free survival at 1, 3, and 5 years in CTEPH patients was 96.7%, 93.7%, and 92.0%, respectively. BMI ≥ 25 at baseline was a poor prognostic factor in CTEPH patients (Supplementary Table S9 and Fig. S3C). The patients with PEA alone had poorer hemodynamics than those with medical therapy alone (Table 2). The prognosis of patients with both PEA and BPA and those with BPA alone was better than that of those with PEA alone or those with medical therapy alone (both PEA and BPA vs. medical therapy alone, $P = .10$; BPA alone vs. PEA alone, $P = .059$; and BPA alone vs. medical therapy alone, $P = .001$) (Fig. 1D). BPA significantly improved survival when adjusted for each variable one by one, including age, BMI group, PVR, and PEA (Supplementary Table S10).

3.3.5. Group 5: PH-misc

The highest prevalence of composite end-point was noted in PH-misc among all PH subgroups (42%) (Table 1). PH due to systemic disorders was most common in PH-misc (50%) (Supplementary Fig. 1).

4. Discussion

The novel findings of this study are as follows; (1) transplant-free survival at 5 years in PAH, PH-LHD, PH due to lung diseases, CTEPH, and miscellaneous PH were 74.0, 69.3, 63.7, 92.0, and 55.3%, respectively, (2) in PAH patients, male sex, age ≥ 75, WHO FC III/IV, lower SvO_2, and BMI < 18.5 were independent predictors for mortality, (3) triple combination therapy showed better survival compared with other treatments, especially in patients without administration of parental prostacyclin analogues, (4) in patients with PH-LHD, lower eGFR was independently associated with an increased mortality, and (5) in CTEPH patients, multivariable analysis demonstrated that BPA was an effective procedure to improve prognosis, and BMI ≥ 25 was a poor prognostic factor. This study is the first to show detailed information on long-term prognosis and prognostic factors in a large cohort of Japanese PH patients, especially the subgroups of PH with many patients such as PAH, PH-LHD, and CTEPH. Comparisons of PAH and CTEPH in this study with those in recent Western registries are shown in Supplementary Table S11 and S12 [4,10–15].

4.1. Beneficial prognostic effects of combination therapy for PAH patients

Currently, upfront combination therapies for severe PAH have attracted much attention [16,17]. Sitbon et al. reported significant improvement in hemodynamics and 6-minute walk distance with upfront triple combination therapy for 19 patients with severe PAH using bosentan, sildenafil, and intravenous epoprostenol as initial treatment [16]. These beneficial effects were continued to the final follow-up evaluation at 32 ± 10 months [16]. Additionally, the AMBITION study was the first randomized control study with a large number of patients

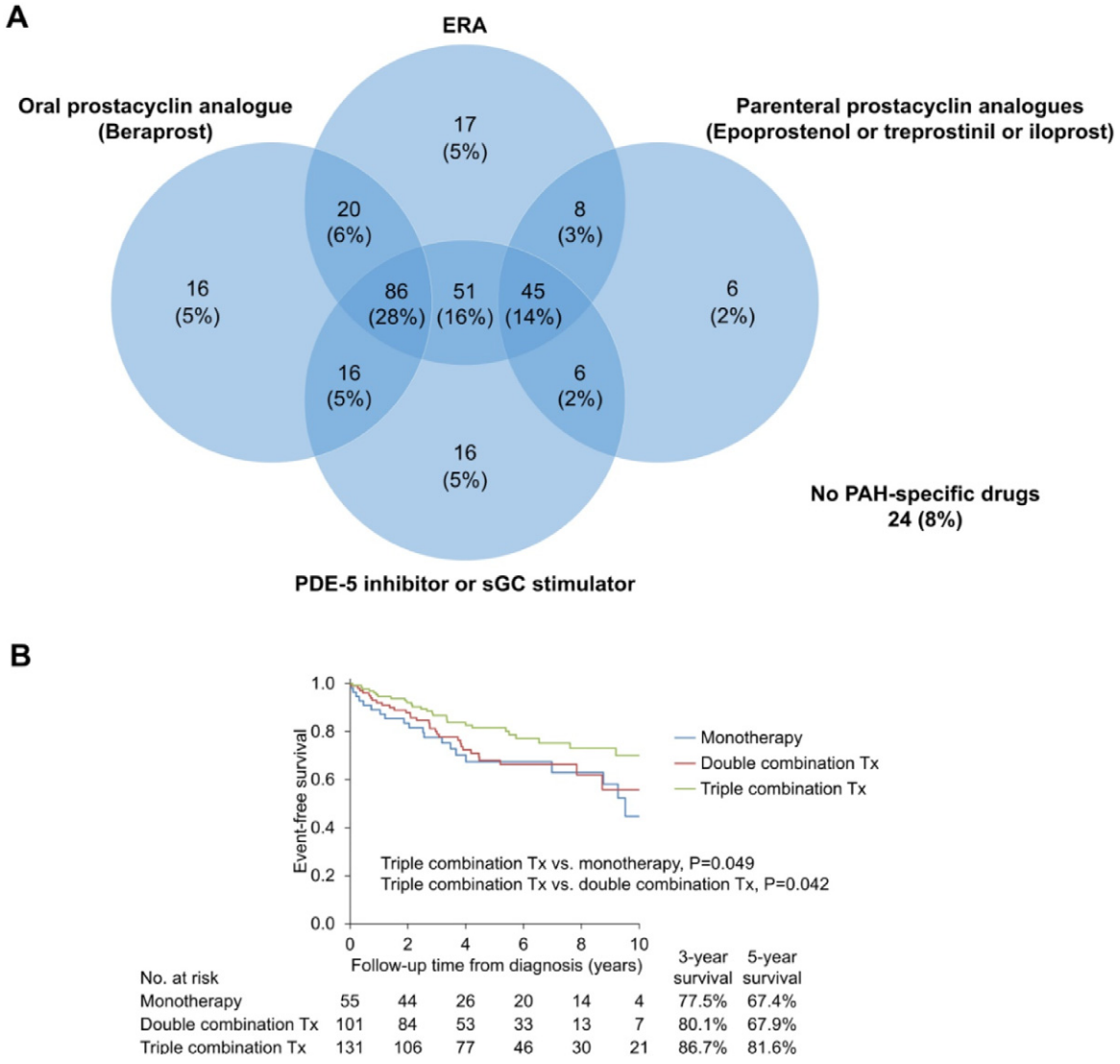

Fig. 2. (A) Pulmonary arterial hypertension (PAH) specific medication use when the largest number of drugs was used during the follow-up. (B) Long-term prognosis of PAH patients by the number of PAH-targeted drugs. CI, confidence interval; HR, hazard ratio; Tx, therapy.

with PAH, to compare dual upfront combination therapy with monotherapy, using ambrisentan and tadalafil [17]. This previous study showed that upfront combination therapy was superior to monotherapy with better prognostic effects. In Japan, the triple combination therapy has been frequently used for PAH thanks to the medical insurance system that allows the insured to secure medical expenses which are too expensive to prepare on their own. Recently, another Japanese PAH cohort, in which one-third of treatment-naïve patients received upfront combination therapy, showed a remarkable 3-year survival rate of 95.7%, and patients with upfront combination therapy were 5-fold more likely to show hemodynamic improvement compared with monotherapy [18]. In the present registry, the rate of combination therapy was as much as 32% in double and 42% in triple, which was higher than that of other recent registries, such as ASPIRE (combination therapy 28%) [4], Swiss registry (double 29% and triple 14%) [5], and prevalent cases in REVEAL (combination therapy 46%) [19]. Besides, patients treated with parenteral prostacyclin analogue plus one or more PH-specific drugs tended to have a better prognosis than those with monotherapy with a parenteral prostacyclin analogue. Additionally, in patients without parenteral prostacyclin analogue, only those with triple combination therapy were significantly associated with a better prognosis than those with 0 or 1 PH-specific drug. Thus, the higher rate of the combination therapies could explain, at least in part, the better prognosis of PAH patients in Japan.

The type and dose of calcium channel blockers (CCBs) were confirmed in 56 out of 63 PAH patients; amlodipine in 27, nifedipine in 13, diltiazem in 9, and other CCBs in 7. The average daily dose was 4.4 mg for amlodipine, 34 mg for nifedipine, and 157 mg for diltiazem, which were not high doses as recommended for IPAH [20,21]. Furthermore, since 31 cases (49%) received combination with CCB and renin-angiotensin system inhibitor, more than half of patients received CCB presumably for systemic hypertension.

4.2. Prognostic factors in PAH

It is the same as previous reports that male sex, older age, higher WHO FC, lower SvO_2 at baseline are strong predictors for worse survival [22,23]. Since patients aged >60 years with PAH and a certain number of children with IPAH have been reported to have a poor prognosis [19,24], we classified the patients into 5 groups every 15 years of age in this study to examine the outcome in more detail. The sharp deterioration in the prognosis was observed at 75 years of age or older, suggesting that the average life span of PAH patients is extended. In the Japanese cohort, the risk of all-cause mortality for BMI is known to draw a U-

Table 2
Baseline patient characteristics of CTEPH by treatment.

	PEA alone	BPA alone	Both PEA and BPA	Medical Tx alone
N	23 (13)	115 (63)	5 (3)	40 (22)
Male	6 (26)	25 (22)	1 (20)	10 (25)
Age, years	55 ± 11[†,‡]	63 ± 14	52 ± 16	67 ± 15
BMI, kg/m^2	24.0 ± 7.1	23.3 ± 3.8	20.7 ± 1.8	23.2 ± 4.0
WHO FC I[*]	1 (4)	2 (2)	0 (0)	1 (3)
II	4 (17)	48 (42)	2 (40)	17 (50)
III	11 (48)	52 (46)	3 (60)	15 (44)
IV	7 (30)	12 (11)	0 (0)	1 (3)
6MWD, m	347 ± 121	346 ± 120	343 ± 21	339 ± 98
BNP, pg/ml	221 (142–596)[§]	92 (27–245)	143 (55–202)	115 (38–403)
eGFR, ml/min/1.73 m^2	59 ± 21	61 ± 16	69 ± 1	58 ± 19
LVEF, %	65 ± 11	70 ± 9	67 ± 15	71 ± 8
FVC, % predicted	92 ± 13	99 ± 18	88 ± 18	90 ± 19
FEV1, % predicted	86 ± 17	90 ± 18	93 ± 10	81 ± 20
DLCO, % predicted	60 ± 11[§]	93 ± 35	74	69 ± 16
mPAP, mm Hg	49 ± 9[†,‡]	42 ± 11	41 ± 11	41 ± 11
PAWP, mm Hg	10 ± 6	9 ± 4	8 ± 3	9 ± 5
RAP, mm Hg	9 ± 7	6 ± 4	5 ± 4	6 ± 4
CI, L/min/m^2	2.3 ± 0.6[‡,§]	2.6 ± 0.7	2.8 ± 0.5	2.8 ± 0.7
PVR, wood units	10.8 (6.9–13.0)[§]	8.1 (5.8–10.2)	8.2 (4.9–11.1)	7.7 (5.1–12.0)
SvO_2, %	60 ± 7[‡,§]	64 ± 9[‖]	67 ± 3	67 ± 9
PAC, mL/mm Hg	1.0 ± 0.4[†,‖]	1.3 ± 0.6	1.4 ± 0.8	1.4 ± 0.7

Data are presented as n (%), mean ± SD or median (interquartile range), unless otherwise stated. Percentages in this column may not add up exactly 100% because of rounding. BMI, body-mass index; BNP, brain natriuretic peptide; BPA, balloon pulmonary angioplasty; CI, cardiac index; CTEPH, chronic thromboembolic pulmonary hypertension; DLCO, diffusing capacity of the lung for carbon monoxide; eGFR, estimated glomerular filtration rate; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; PAC, pulmonary arterial capacitance; PAWP, pulmonary artery wedge pressure; PEA, pulmonary endarterectomy; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SvO_2, mixed venous oxygen saturation; Tx, therapy; WHO FC, World Health Organization functional class; 6MWD, 6-minute walk distance.

[*] Percentage of the cases in which the data were obtained.
[†] $P < .01$ in comparison to BPA alone.
[‡] $P < .01$ in comparison to Medical Tx alone
[§] $P < .05$ in comparison to BPA alone.
[‖] $P < .05$ in comparison to Medical Tx alone.

curve [25]; thus, patients were classified into 3 groups according to their BMI, resulting in an increased risk for those with BMI below 18.5. It has been shown that right ventricular dysfunction in advanced heart failure frequently presented cachexia, and decreased BMI was associated with a higher adverse event rate [26]. Lower BMI has also been reported to correlate with higher PAP, and inferior vena cava dilation in PAH patients [27]. Further studies including follow-up data may clarify whether lower BMI is the result of right heart failure or exacerbation factor for PH.

The REVEAL registry showed that eGFR was an independent predictor of survival in PAH patients [28]. However, in the present study, there was no significant correlation between eGFR and mortality when adjusted for essential variables including SvO_2, which was not included in the REVEAL registry [28]. Since SvO_2 is also a well-known crucial predictor of PAH [23], renal dysfunction in PAH may be a result of circulatory failure and SvO_2 may be a more robust marker than eGFR.

Unlike the previous reports, BNP was not an independent prognostic factor in this study [19,23]. However, significant interaction for the use of parental prostacyclin analogue was noted in terms of the prognostic significance of BNP, suggesting that BNP may be a useful predictor particularly in patients without parenteral prostacyclin analogue. The aggressive treatment for lowering mPAP, which resulted in a sufficient decrease in BNP, may explain why baseline BNP did not correlate with the long-term prognosis especially in patients treated with parental prostacyclin analogue.

4.3. Therapeutic background and prognostic factors in PH-LHD

Patients with PH-LHD in the present study had better survival than those in other registries for all subgroups of PH [4,6]. However, this registry showed lower proportion of WHO FC III/IV, younger age than the UK [4] or Germany registry [6], and that the percentage of combined post- and pre-capillary PH based on PVR was smaller than that of the Germany registry, which may result in the better prognosis in our survey.

Few reports are available on the surrogate biomarker for long-term prognosis in PH-LHD. Renal function as a strong predictor of survival in patients with LHD is well established [29]. The present study demonstrates that lower eGFR is independently associated with increased mortality in patients with PH-LHD, providing evidence that renal function could be a useful marker for the disorder. However, the cause of PH-LHD is heterogeneous, and the previous study had a limited number of patients (<1000 patients) [30]. Thus, further large-scale prospective registries including all causes of left-sided heart failure are needed.

4.4. Beneficial prognostic effects of BPA for CTEPH patients

A recent study reported that non-operated CTEPH patients had a poorer prognosis compared with operated CTEPH patients [6,14,15]. On top of that, medical therapy improved hemodynamics but not prognosis in CTEPH patients [15]. In the present study, CTEPH patients treated with BPA alone had a better prognosis than those with medical therapy alone despite the comparable clinical characteristics. Additionally, the long-term prognosis of CTEPH patients treated with BPA tended to be better compared with those treated with PEA. Recently, we and others demonstrated the beneficial effects of BPA for CTEPH patients [31–35], including the beneficial prognostic effects [36]. Moreover, BPA is an effective treatment for inoperable CTEPH cases with several comorbidities [37] and is also useful for the hybrid strategy with PEA [38]. Indeed, in the present registry, CTEPH patients with both PEA and BPA had the best long-term prognosis, where multivariable analysis showed that BPA was therapy with significant prognostic effects. Notably, BPA was performed in 66% of CTEPH patients, one of the most characteristics of this registry in Japan. These findings, including the result that baseline WHO FC and hemodynamics were not prognostic predictors, suggest that inoperable CTEPH would be a more treatable disease than previously known.

4.5. Study limitations

Several limitations should be mentioned in the present study. First, this registry included beraprost, which has been approved for the treatment of PAH only in Japan and South Korea [39]. However, excluding beraprost, the proportion of combination therapy was higher than other registries (double combination therapy 49%, triple combination therapy 14%). Second, compared with Western registries, the proportion of SSc-associated PAH in CTD-PAH was smaller (Japanese, 43%; ASPIRE, 83%) [4]. Furthermore, SLE-associated PAH, which is known to have a better prognosis than SSc-associated PAH [40], was relatively frequent although not so much as China (Japanese, 21%; Chinese 58%) [41]. The distribution of CTD-PAH may have affected the difference in outcomes between the Japanese and Western registries. Third, the performance rate of PEA for CTEPH in the present registry (15%) was low than in other registries, such as ASPIRE (45%) [4] and the international registry (60%) [15]. Although details of lesion type in CTEPH were not available in the present study, the incidence of distal type disease has been reported to be higher in Japanese than in the San Diego group [42,43]. Furthermore, in Japan, BPA-enabled referral centers are available throughout the country. Additionally, CTEPH patients who did not undergo PEA in the present registry had relatively less severe symptoms and hemodynamic parameters compared with recent studies [4,15], which might have been associated with a better prognosis.

Fourth, the inclusion of prevalent cases might have led to an overestimate of long-term survivors due to possible selection bias, and there might be immortal time bias because triple combination therapy was introduced in clinical practice since 2008. Indeed, recent studies suggested that the better outcome of prevalent cases may be associated with the stability of disease as compared with incident cases [4,10,12]. However, in the present study, there was no difference in event-free survival between the prevalent and incident cases, which was confirmed in the recent randomized survey that addressed the prognostic effects of macitentan in PAH patients [44]. Fifth, no detailed data were available on whether combination therapy was performed as an initial combination or as a sequential combination. This point may be a confounding factor when comparing the prognosis from the baseline by the number of therapeutic drugs. Nevertheless, we would like to underline the finding that patients who received triple therapy in this study had more severe hemodynamics at baseline. This comparison would be more validated by examining the add-on manner of drugs and improvement in hemodynamic status in future randomized trials. Sixth, the number of patients with PH-lung and PH-misc were small in the present registry. In Japan, PH-lung is mainly examined by respirologists, while patients in this study were registered from cardiologists in Japan. However, the small number of PH-misc patients was similar to that of the Western registries [4,5]. Finally, a small portion of PH-LHD and PH-misc, and a substantial proportion of PH-lung patients were treated with off-label PH-specific medications [2], which was similar to ASPIRE and the German registry [4,6]. Although there is no substantial evidence validated by randomized controlled trials to support the use of PH-specific drugs in PH-LHD, patients with severe RV dysfunction have been reported to benefit from pulmonary vasodilation [45,46]. For this reason, PH-specific medications have probably been administered as a last option for severe right heart failure. In PH-lung, the use of pulmonary vasodilators should be considered only for patients with mild lung parenchymal abnormalities and hemodynamics showing PAH phenotype [2]. The usefulness of PH-targeted medications for severe PH-lung patients has recently been reported in Japan, presumably resulting from the high usage rate of the medications, especially PDE-5 inhibitor [47,48]. However, the effectiveness of PH-targeted drugs remained unsolved in this study because the number of patients with both PH-LHD and PH-lung was too small to analyze prognosis.

5. Conclusions

In the present multicenter registry study in Japan, we were able to provide the latest information on the long-term prognosis and the prognostic factors in PH patients among all classes in the same cohort. Transplant-free survival at 5 years in this study was 74% for PAH and 92% for CTEPH, in which active combination medical therapy for PAH and higher performance rate of BPA for CTEPH may be involved.

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Declaration of competing interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.11.139.

References

[1] N.F. Voelkel, J. Gomez-Arroyo, A. Abbate, H.J. Bogaard, M.R. Nicolls, Pathobiology of pulmonary arterial hypertension and right ventricular failure, Eur. Respir. J. 40 (2012) 1555–1565.
[2] N. Galie, M. Humbert, J.L. Vachiery, S. Gibbs, I. Lang, A. Torbicki, 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. 37 (2016) 67–119.
[3] M. Humbert, O. Sitbon, G. Simonneau, Treatment of pulmonary arterial hypertension, N. Engl. J. Med. 351 (2004) 1425–1436.
[4] J. Hurdman, R. Condliffe, C.A. Elliot, C. Davies, C. Hill, J.M. Wild, et al., ASPIRE registry: assessing the spectrum of pulmonary hypertension identified at a REferral centre, Eur. Respir. J. 39 (2012) 945–955.
[5] S. Mueller-Mottet, H. Stricker, G. Domenighetti, A. Azzola, T. Geiser, M. Schwerzmann, et al., Long-term data from the Swiss pulmonary hypertension registry, Respiration. 89 (2015) 127–140.
[6] H. Gall, J.F. Felix, F.K. Schneck, K. Milger, N. Sommer, R. Voswinckel, et al., The Giessen Pulmonary Hypertension Registry: survival in pulmonary hypertension subgroups, J. Heart Lung Transplant. 36 (2017) 957–967.
[7] G. Simonneau, M.A. Gatzoulis, I. Adatia, D. Celermajer, C. Denton, A. Ghofrani, et al., Updated clinical classification of pulmonary hypertension, J. Am. Coll. Cardiol. 62 (2013) D34–D41.
[8] M.M. Hoeper, H.J. Bogaard, R. Condliffe, R. Frantz, D. Khanna, M. Kurzyna, et al., Definitions and diagnosis of pulmonary hypertension, J. Am. Coll. Cardiol. 62 (2013) D42–D50.
[9] T. Pulido, I. Adzerikho, R.N. Channick, M. Delcroix, N. Galie, H.A. Ghofrani, et al., Macitentan and morbidity and mortality in pulmonary arterial hypertension, N. Engl. J. Med. 369 (2013) 809–818.
[10] H.W. Farber, D.P. Miller, A.D. Poms, D.B. Badesch, A.E. Frost, E. Muros-Le Rouzic, et al., Five-year outcomes of patients enrolled in the REVEAL Registry, Chest. 148 (2015) 1043–1054.
[11] M. Humbert, O. Sitbon, A. Chaouat, M. Bertocchi, G. Habib, V. Gressin, et al., Pulmonary arterial hypertension in France: results from a national registry, Am. J. Respir. Crit. Care Med. 173 (2006) 1023–1030.
[12] M. Humbert, O. Sitbon, A. Yaici, D. Montani, D.S. O'Callaghan, X. Jais, et al., Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension, Eur. Respir. J. 36 (2010) 549–555.
[13] P. Escribano-Subias, I. Blanco, M. Lopez-Meseguer, C.J. Lopez-Guarch, A. Roman, P. Morales, et al., Survival in pulmonary hypertension in Spain: insights from the Spanish registry, Eur. Respir. J. 40 (2012) 596–603.
[14] P. Escribano-Subias, R. Del Pozo, A. Roman-Broto, J.A. Domingo Morera, A. Lara-Padron, T. Elias Hernandez, et al., Management and outcomes in chronic thromboembolic pulmonary hypertension: from expert centers to a nationwide perspective, Int. J. Cardiol. 203 (2016) 938–944.
[15] M. Delcroix, I. Lang, J. Pepke-Zaba, P. Jansa, A.M. D'Armini, R. Snijder, et al., Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: results from an international prospective registry, Circulation. 133 (2016) 859–871.
[16] O. Sitbon, X. Jais, L. Savale, V. Cottin, E. Bergot, E.A. Macari, et al., Upfront triple combination therapy in pulmonary arterial hypertension: a pilot study, Eur. Respir. J. 43 (2014) 1691–1697.
[17] N. Galie, J.A. Barbera, A.E. Frost, H.A. Ghofrani, M.M. Hoeper, V.V. McLaughlin, et al., Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension, N. Engl. J. Med. 373 (2015) 834–844.
[18] Y. Tamura, H. Kumamaru, T. Satoh, H. Miyata, A. Ogawa, N. Tanabe, et al., Effectiveness and outcome of pulmonary arterial hypertension-specific therapy in Japanese patients with pulmonary arterial hypertension, Circ. J. 82 (2017) 275–282.
[19] R.L. Benza, D.P. Miller, M. Gomberg-Maitland, R.P. Frantz, A.J. Foreman, C.S. Coffey, et al., Predicting survival in pulmonary arterial hypertension insights from the registry to evaluate early and long-term pulmonary arterial hypertension disease management (REVEAL), Circulation. 122 (2010) 164–172.
[20] S. Rich, E. Kaufmann, P.S. Levy, The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension, N. Engl. J. Med. 327 (1992) 76–81.
[21] O. Sitbon, M. Humbert, X. Jais, V. Ioos, A.M. Hamid, S. Provencher, et al., Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension, Circulation. 111 (2005) 3105–3111.
[22] M.D. McGoon, R.L. Benza, P. Escribano-Subias, X. Jiang, D.P. Miller, A.J. Peacock, et al., Pulmonary arterial hypertension: epidemiology and registries, J. Am. Coll. Cardiol. 62 (2013) D51–D59.
[23] N. Nickel, H. Golpon, M. Greer, L. Knudsen, K. Olsson, V. Westerkamp, et al., The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension, Eur. Respir. J. 39 (2012) 589–596.
[24] G.E. D'Alonzo, R.J. Barst, S.M. Ayres, E.H. Bergofsky, B.H. Brundage, K.M. Detre, et al., Survival in patients with primary pulmonary hypertension. Results from a national prospective registry, Ann. Intern. Med. 115 (1991) 343–349.

[25] S. Sasazuki, M. Inoue, I. Tsuji, Y. Sugawara, A. Tamakoshi, K. Matsuo, et al., Body mass index and mortality from all causes and major causes in Japanese: results of a pooled analysis of 7 large-scale cohort studies, J Epidemiol. 21 (2011) 417–430.
[26] V. Melenovsky, M. Kotrc, B.A. Borlaug, T. Marek, J. Kovar, I. Malek, et al., Relationships between right ventricular function, body composition, and prognosis in advanced heart failure, J. Am. Coll. Cardiol. 62 (2013) 1660–1670.
[27] A. Kawamoto, T. Kato, E. Minamino-Muta, Y. Okano, T. Shioi, T. Kimura, Relationships between nutritional status and markers of congestion in patients with pulmonary arterial hypertension, Int. J. Cardiol. 187 (2015) 27–28.
[28] M.M. Chakinala, D.W. Coyne, R.L. Benza, A.E. Frost, M.D. McGoon, B.K. Hartline, et al., Impact of declining renal function on outcomes in pulmonary arterial hypertension: a REVEAL registry analysis, J. Heart Lung Transplant. 37 (2018) 696–705.
[29] Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur. Heart J. 2014;35:455–69.
[30] A. Guha, J. Amione-Guerra, M.H. Park, Epidemiology of pulmonary hypertension in left heart disease, Prog. Cardiovasc. Dis. 59 (2016) 3–10.
[31] H. Mizoguchi, A. Ogawa, M. Munemasa, H. Mikouchi, H. Ito, H. Matsubara, Refined balloon pulmonary angioplasty for inoperable patients with chronic thromboembolic pulmonary hypertension, Circ Cardiovasc Interv. 5 (2012) 748–755.
[32] K. Sugimura, Y. Fukumoto, K. Satoh, K. Nochioka, Y. Miura, T. Aoki, et al., Percutaneous transluminal pulmonary angioplasty markedly improves pulmonary hemodynamics and long-term prognosis in patients with chronic thromboembolic pulmonary hypertension, Circ. J. 76 (2012) 485–488.
[33] T. Inami, M. Kataoka, N. Shimura, H. Ishiguro, R. Yanagisawa, H. Taguchi, et al., Pulmonary edema predictive scoring index (PEPSI), a new index to predict risk of reperfusion pulmonary edema and improvement of hemodynamics in percutaneous transluminal pulmonary angioplasty, JACC Cardiovasc Interv. 6 (2013) 725–736.
[34] S. Fukui, T. Ogo, Y. Morita, A. Tsuji, E. Tateishi, K. Ozaki, et al., Right ventricular reverse remodelling after balloon pulmonary angioplasty, Eur. Respir. J. 43 (2014) 1394–1402.
[35] Y. Taniguchi, K. Miyagawa, K. Nakayama, H. Kinutani, T. Shinke, K. Okada, et al., Balloon pulmonary angioplasty: an additional treatment option to improve the prognosis of patients with chronic thromboembolic pulmonary hypertension, EuroIntervention. 10 (2014) 518–525.
[36] T. Aoki, K. Sugimura, S. Tatebe, M. Miura, S. Yamamoto, N. Yaoita, et al., Comprehensive evaluation of the effectiveness and safety of balloon pulmonary angioplasty for inoperable chronic thrombo-embolic pulmonary hypertension: long-term effects and procedure-related complications, Eur. Heart J. 38 (2017) 3152–3159.
[37] R. Yanagisawa, M. Kataoka, T. Inami, N. Shimura, H. Ishiguro, K. Fukuda, et al., Safety and efficacy of percutaneous transluminal pulmonary angioplasty in elderly patients, Int. J. Cardiol. 175 (2014) 285–289.
[38] C.B. Wiedenroth, C. Liebetrau, A. Breithecker, S. Guth, H.J. Lautze, E. Ortmann, et al., Combined pulmonary endarterectomy and balloon pulmonary angioplasty in patients with chronic thromboembolic pulmonary hypertension, J. Heart Lung Transplant. 35 (2016) 591–596.
[39] K.K. Mubarak, A review of prostaglandin analogs in the management of patients with pulmonary arterial hypertension, Respir. Med. 104 (2010) 9–21.
[40] R. Condliffe, D.G. Kiely, A.J. Peacock, P.A. Corris, J.S. Gibbs, F. Vrapi, et al., Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era, Am. J. Respir. Crit. Care Med. 179 (2009) 151–157.
[41] J. Zhao, Q. Wang, Y. Liu, Z. Tian, X. Guo, H. Wang, et al., Clinical characteristics and survival of pulmonary arterial hypertension associated with three major connective tissue diseases: a cohort study in China, Int. J. Cardiol. 236 (2017) 432–437.
[42] Jamieson SW, Kapelanski DP, Sakakibara N, Manecke GR, Thistlethwaite PA, Kerr KM, et al. Pulmonary endarterectomy: experience and lessons learned in 1,500 cases. Ann Thorac Surg. 2003;76:1457–62; discussion 62–4.
[43] H. Ogino, M. Ando, H. Matsuda, K. Minatoya, H. Sasaki, N. Nakanishi, et al., Japanese single-center experience of surgery for chronic thromboembolic pulmonary hypertension, Ann. Thorac. Surg. 82 (2006) 630–636.
[44] G. Simonneau, R.N. Channick, M. Delcroix, N. Galie, H.A. Ghofrani, P. Jansa, et al., Incident and prevalent cohorts with pulmonary arterial hypertension: insight from SERAPHIN, Eur. Respir. J. 46 (2015) 1711–1720.
[45] M. Guazzi, M. Vicenzi, R. Arena, M.D. Guazzi, Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study, Circulation. 124 (2011) 164–174.
[46] Forfia PR, Borlaug BA. Letter by Forfia and Borlaug regarding article, "Pulmonary hypertension in heart failure with preserved ejection fraction: a target of phosphodiesterase-5 inhibition in a 1-year study". Circulation. 2012;125:e408; author reply e9–10.
[47] N. Tanabe, H. Taniguchi, I. Tsujino, F. Sakamaki, N. Emoto, H. Kimura, et al., Multiinstitutional retrospective cohort study of patients with severe pulmonary hypertension associated with respiratory diseases, Respirology. 20 (2015) 805–812.
[48] T. Sato, I. Tsujino, A. Sugimoto, T. Nakaya, T. Watanabe, H. Ohira, et al., The effects of pulmonary vasodilating agents on right ventricular parameters in severe group 3 pulmonary hypertension: a pilot study, Pulm Circ. 6 (2016) 524–531.