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PEDIATRIC PULMONARY ARTERIAL HYPERTENSION: CHARACTERISTICS  
AND EFFICACY OF SPECIFIC THERAPY ON CLINICAL, ECHOCARDIOGRAPHIC  
AND HEMODYNAMIC PARAMETERS

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## ABBREVIATION LIST

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6MWT = six-minute walking test

BPD = bronchopulmonary dysplasia

CDH = congenital diaphragmatic hernia

CHD = congenital heart disease

CI = cardiac index

FC = functional class

I/HPAH = idiopathic/hereditary pulmonary arterial hypertension

mPAP = mean pulmonary arterial pressure

NYHA = New York Heart Association

PAH = pulmonary arterial hypertension

PAH-CHD = pulmonary arterial hypertension associated with congenital heartdisease

PAP = pulmonary arterial pressure

PAWP = pulmonary artery wedge pressure

PH = pulmonary hypertension

PPHN = persistent pulmonary hypertension of the newborn

Po-PAH = porto-pulmonary PAH

PVOD = pulmonary veno-occlusive disease

PVR = pulmonary vascular resistance

PVRI = pulmonary vascular resistance index

RAP = right atrial pressure

RHC = right heart catheterization

RV = right ventricle

sO<sub>2</sub> = oxygen saturation

# **Pediatric Pulmonary Arterial Hypertension: Characteristics and Efficacy of Specific Therapy on Clinical, Echocardiographic and Hemodynamic Parameters**

## **Abstract**

**Background and aim.** Pulmonary arterial hypertension (PAH) in children has peculiar features and require a unique approach. In pediatric PAH the role of right heart catheterization for risk assessment is hindered by a not negligible rate of complications, but the prognostic capabilities of non-invasive tools are still under investigation. For what concern treatment approach, data are limited because of the lack of robust scientific evidence on efficacy and safety of PAH-targeted drugs in children, so the current pharmacological approach of pediatric PAH is based mainly on real-world data and expert consensus statements.

This study describes the epidemiological features of pediatric PAH patients followed in a referral center during a > 40-year period and investigates the effects of PAH-targeted drugs on several clinical, functional, echocardiographic and hemodynamic parameters.

**Methods and Results.** Data from consecutive pediatric PAH patients referred to our center from September 1980 to October 2024 were collected. Treatment was per PAH updated guidelines at the time of evaluation. Of 137 patients, 60 (44%) had idiopathic/hereditary PAH (I/HPAH) and 60 (44%) had PAH associated with congenital heart disease (PAH-CHD). Less common causes of pediatric PAH were PAH with respiratory comorbidities, porto-pulmonary PAH, pulmonary veno-occlusive disease and persistent pulmonary hypertension of the newborn. PAH-CHD patients were slightly younger than I/HPAH at diagnosis and there was not a female predominance. When considering treatment strategy, among IPAH, 14 (23%) patients showed a positive response to acute vasoreactivity test at diagnosis and were treated with calcium-channel blocker, but only 3 (5%) were long-term responders. Excluding acute responders, compared to PAH-CHD, I/H PAH patients were usually treated with a more aggressive strategy, especially first-line. This is particularly true when considering the subgroup of patients (55) followed in our Center since 2014, in fact in these last 10 years, regulatory authorities have formally approved for use several oral PAH targeted drugs in pediatric population leading to a more standardized treatment approach. In this subgroup of patients, 60% of I/HPAH patients were treated with upfront combination therapy vs only 15% of PAH-CHD, but at the end of observational period, even in PAH-CHD population, only a minority of patients was treated with monotherapy (15%). Efficacy of first-line treatment strategy was confirmed by improvement in NYHA functional class ( $p < 0.001$ ), in 6-minute walking distance from 455.5 meters to 494 meters ( $p < 0.001$ ), in all the main echocardiographic parameters evaluating right ventricle (TAPSE, right atrial/ventricular area, tricuspid regurgitation velocity, S and E wave at tissue doppler, acceleration time in right ventricle outflow tract, eccentricity index) and in hemodynamics with a significant increase in cardiac index ( $2.7 \text{ L/min/m}^2$  vs  $3.1 \text{ L/min/m}^2$ ,  $p = 0.007$ ), in values of pulmonary artery oxygen saturation ( $68.5\%$  vs

71.7%,  $p = 0.03$ ) and reduction in pulmonary vascular resistance index (10.8 vs 8.3  $\text{WU}\cdot\text{m}^2$ ,  $p = 0.007$ ).

**Conclusions.** This series confirms a different distribution of pediatric PAH etiologies compared to adults, with children having a greater predominance of I/HPAH and PAH-CHD. In children with I/HPAH, especially in the last decade, treatment strategy is similar to adults with rapid sequential or upfront oral combination therapy if lower risk and initial parenteral combination therapy if high risk. In PAH-CHD, treatment strategy is characterized by a more prudential approach with first-line monotherapy and combination therapy (oral or parenteral) in case of inadequate response. Beyond hemodynamics, in this study PAH-targeted drugs' effects are demonstrated by a significant improvement in symptoms, exercise capacity and right ventricle echocardiographic parameters suggesting a role of this non-invasive and easily available tools in monitoring disease progression and treatment response.

# CLINICAL STUDY

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## Introduction

Pulmonary hypertension (PH) may present at all stages of life, ranging from newborns to children, adolescents and adults. PH in childhood shows similarities but also specific features as compared to adult disease. In fact, the prevalent etiologies of PH are different in children with developmental lung disorders as the major cause of pediatric PH; in addition, the clinical picture of pediatric patients is often characterized by severe comorbidities, including prematurity-related conditions, congenital malformations, and syndromic features: usually, the younger is the age of the patient the more complex is the underlying clinical setting. Accordingly, pediatric PH requires a specific approach for both diagnosis and treatment which may vary according to the age of the child.

### *Pediatric Pulmonary Hypertension: hemodynamic and clinical classification*

The hemodynamic definition of PH applied in children and infants beyond the first 3 months of life continues to be the same as in adults and is defined as mean pulmonary arterial pressure (mPAP)  $\geq 20$  mmHg at rest determined by right heart catheterization (RHC)<sup>1</sup>. As in adults, the definition of pre-capillary PH includes 2 additional parameters: pulmonary artery wedge pressure (PAWP) and pulmonary vascular resistance (PVR): the cut-off value of PAWP is the same as in the adult (PAWP  $< 15$  mmHg), while a different cut-off is recommended for PVR since the use of indexed PVR (PVRI) is required in children. Therefore, a specific definition of pre-capillary PH is adopted for children including a cut-off value of PVRI  $\geq 3$  Wood Units·m<sup>2</sup> (WU·m<sup>2</sup>)<sup>2</sup> (Figure 1). RHC remains the gold standard for diagnosis PH in neonates, infants and children. However, complication rates of cardiac catheterization are higher than in adults<sup>3,4</sup> and the balance between risks and benefits must always be carefully considered, especially in neonates and in patients with severe form of PH.

Current epidemiological data on pediatric PH are mainly derived from registry cohorts: the estimated incidence of PH is reported at 4–10 cases per million children per year with a prevalence of 20–40 cases per million in Europe and 5–8 cases per million children per year with a prevalence of 26–33 per million children in the USA<sup>5,6,7</sup>. Excluding patients with “transient” forms (e.g. persistent PH of the newborn - PPHN or repairable cardiac shunt defects), the most frequent form of PH in children is PH associated with developmental lung disease (Group 3) representing the 34% of the entire PH population and including bronchopulmonary dysplasia (BPD), congenital diaphragmatic hernia (CDH) and congenital pulmonary vascular abnormalities; 27% of patients have Group 1 Pulmonary Arterial Hypertension (PAH) with idiopathic/hereditary PAH (I/HPAH) and PAH associated with congenital heart disease (PAH-CHD) being the most frequent forms of PAH in children<sup>8</sup> (Figure 2). The prevalence of PAH-CHD is higher in children as compared with adults counting about 30-50% of patients with group 1 PAH. PAH-CHD includes a heterogeneous patient population<sup>2,9</sup> as showed in Figure 3. Group 2, 4 and 5 are extremely rare in pediatric population.

### *Risk stratification and treatment strategy*

Risk assessment plays a crucial role in the management of children with PAH. Risk assessment is used to determine the patient's risk for adverse outcome, to define the most appropriate treatment approach, and to monitor disease progression and child's response to treatment.

In pediatric PAH population, risk assessment is more complex than in adults: symptoms are blurred and more difficult to interpret, evaluation of exercise capacity with 6-minute-walk test (6MWT) is not reliable in younger children and RHC is performed in a minority of patients because of not negligible risks of procedural and anesthesiologic complications.

During last World Symposium in June 2024, a new risk stratification tool has been proposed. This includes, in addition to clinical, functional and hemodynamic parameters, newer non-invasive variables derived from cardiovascular imaging and natriuretic peptides<sup>2</sup>. Currently, echocardiography is the most used tool for longitudinal follow-up and treatment effect assessment.

As in adults, maintaining or reaching a low-risk profile during follow-up is associated with improved survival thus justifying its clinical use as a treatment goal<sup>10,11,12,13</sup>.

The use of specific drugs improved prognosis in pediatric PAH patients. However, treatment of pediatric PH continues to be hindered by the lack of randomized controlled clinical trials and only a few drugs are approved for use in children by regulatory authorities. Nevertheless, all PAH drugs approved for use in adults are commonly used in children and have been included in the treatment algorithm for pediatric PAH proposed in the guidelines (Figure 4).

### **Aim of the study**

The aim of the study was to evaluate the baseline clinical, functional, echocardiographic and hemodynamic characteristics of patients with pediatric PAH and to assess the effects of PAH targeted drugs on different clinical, functional, exercise, echocardiographic and hemodynamic parameters.

### **Methods**

This retrospective study was conducted in compliance with The Declaration of Helsinki.

Data from consecutive pediatric patients (< 18 years old) with PH assessed and followed at the Pulmonary Vascular Disease Centre of the Bologna University were collected. The observation period was from September 1980 to October 2024.

#### *Patients*

Consecutive pediatric patients with a diagnosis of Group 1 PAH referred to Bologna Pulmonary Vascular Disease Centre were included in the final analysis. Patients with other forms of PH (Group 2, 3, 4 and 5) were excluded.

#### *Treatment regimen*

During the long time frame of our study (> 40 years), different treatment approaches have been adopted according to the concomitant treatment guidelines recommendations which were updated over time based on the progressive

availability of scientific evidence of efficacy and safety of new PAH targeted drugs and of different treatment strategies.

Pediatric PAH patients (including patients with CHD and mild respiratory impairment with severe precapillary PH) were treated with PAH targeted therapy according to their risk profile. Risk assessment was performed in line with the updated guidelines at the time of evaluation.

Specific PAH drugs were prescribed at weight's adjusted dose. High-risk patients were mainly treated with combination therapy including a parenteral prostacyclin (intravenous epoprostenol or subcutaneous treprostinil) and considered for more invasive option such as lung transplantation or Potts procedure.

A subgroup analysis of patients included in our database in the last 10 years (January 2014 - October 2024) has been performed.

In this last decade, several oral PAH targeted drugs have been formally approved for use in pediatric population leading to a more standardized treatment approach. Accordingly, patients with I/HPAH were mainly treated with rapid sequential or upfront combination therapy if at lower risk, or with triple combination therapy including parenteral prostacyclin, when at high risk. A small group of patients included in the study was treated with triple oral combination therapy with Selexipag as they have been included in the SALTO trial (an ongoing randomized, multicenter, double-blind, placebo-controlled, parallel-group, event-driven, group-sequential study with open-label extension period to assess the efficacy and safety of selexipag as add-on treatment to standard of care in children aged 2 to 18 years with Pulmonary Arterial Hypertension).

Patients with PAH-CHD or with PAH and mild respiratory comorbidities have been treated with initial monotherapy and have been regularly reassessed and considered for sequential combination therapy.

### *Assessments*

Patients were systematically evaluated at Bologna pediatric outpatients' clinic. Standard assessment included the evaluation of NYHA Functional Class - FC, exercise capacity by 6MWT and echocardiography. In selected patients, in case of clinical deterioration, RHC was performed before treatment escalation.

### *Statistical analysis*

Baseline variables are presented as n (%) for categorical data and medians (interquartile range) for the continuous data. Categorical variables were compared using McNemar test, while continuous variables were analyzed using Student's t-test. We considered p-values < 0.05 to be statistically significant.

For the survival analysis, all causes of mortality were included in the Kaplan–Meier analysis. Patients who underwent heart–lung or lung transplantation or were lost to follow-up were censored at the time of the operation or at the time of the last personal contact with our Centre.

## **Results**

### *Patients*

A total of 163 PH pediatric patients were referred to Bologna Pulmonary Vascular Disease Centre from September 1980 to October 2024. Among these only 137 were

eligible for inclusion (Group 1 PAH): 60 (44%) had I/HPAH, 60 (44%) had PAH-CHD, 3 (2%) had PAH with respiratory comorbidities, 7 (5%) had porto-pulmonary PAH (po-PAH), 5 (4%) had pulmonary veno-occlusive disease (PVOD), 2 (1%) had PPHN. Baseline patients' characteristics of the main subgroups are shown in Table 1. When comparing demographic characteristics, PAH-CHD patients were slightly younger at diagnosis although age at referral did not differ significantly. When considering exercise capacity and principal echocardiographic parameters, the two groups were similar, while at RHC, PAH-CHD patients had a lower systemic cardiac index - CI (I/HPAH CI 3.1 (2.3 – 3.8) L/min/m<sup>2</sup> vs PAH-CHD CI 2.6 (2.1 – 3.3) L/min/m<sup>2</sup>,  $p = 0,027$ ) and lower values of systemic oxygen saturation - Syst SatO<sub>2</sub> (I/HPAH Syst SatO<sub>2</sub> 96 (94-98)% vs PAH-CHD Syst SatO<sub>2</sub> 93.2 (86.0-96.0)%,  $p = 0,001$ ) – Table 2.

#### *Idiopathic/Hereditary Pulmonary Arterial Hypertension*

The etiology of PAH was idiopathic in 45 (75%) and hereditary in 15 (25%) patients. Median age at diagnosis was 9.5 (5.1 – 13) years and age at referral was 11.3 (6.3 – 14.7) years. No female predominance was observed. At referral 53% of patients were naïve from PAH specific therapy, while 47% were already treated, mainly with monotherapy.

Fourteen (23%) patients showed a positive response to acute vasoreactivity test at diagnosis and were treated with calcium-channel blocker but only 3 (5%) were long-term responders during the follow-up. Three patients were characterized by very severe PAH and, despite the Sitbon's criteria were not completely fulfilled, they showed clear hemodynamic signs of pulmonary vasoreactivity. Accordingly, they were prudentially treated with a combined treatment strategy including PAH targeted drugs and calcium-channel blocker therapy.

Excluding vasoreactive patients, in 6 (13%) patients the first line treatment strategy was monotherapy with intravenous epoprostenol because of high-risk criteria or for the lack of available oral drugs at the time of diagnosis, 28 (61%) patients were treated with oral monotherapy (mainly bosentan – 46%) and 12 (26%) with upfront combination therapy (bosentan + sildenafil). Overall, at the end of the observation period, 3 (5%) patients were treated with calcium-channel blocker alone, 9 (15%) patients were treated with oral monotherapy, 7 (12%) patients were treated with calcium-channel blocker and oral monotherapy, 12 (20%) patients with double oral combination therapy, 6 (10%) patients with double parenteral combination therapy, 1 (1.5%) patient with calcium-channel blocker and double oral combination therapy, 4 (6.5%) patients with triple oral combination therapy, 15 (25%) patients with triple parenteral combination therapy and 3 (5%) patients with calcium-channel blocker and triple parenteral combination therapy – Table 1.

#### *PAH associated with Congenital Heart Disease*

Among patients with PAH-CHD, 25 (42%) had Eisenmenger Syndrome, 8 (13%) had PAH associated with prevalent left-to-right shunt, 11 (18%) had coincidental defects and 16 (27%) had a repaired defect. Median age at diagnosis was 5.4 (3.3-12.2) years and age at referral was 9.3 (5.2 – 17.2) years. No female predominance was observed. At referral 59% of patients were naïve from PAH specific therapy,

while 41% has already been treated, mainly with monotherapy. Baseline PAH-CHD patients' characteristics have been analyzed by clinical CHD subgroups and are reported in Supplementary Table 1 and 2.

In 3 (5%) patients, the first line treatment strategy was monotherapy with intravenous epoprostenol because of high-risk criteria or for the lack of available oral drugs at the time of diagnosis; 48 (80%) patients were treated with oral monotherapy (mainly bosentan – 50%) and 8 (13%) with upfront combination therapy (bosentan + sildenafil). One (2%) patient of the historical cohort was only treated with digoxin and oral anticoagulation for the absence of oral PAH specific drug at the time of diagnosis and because of safety concerns regarding the use of a central venous catheter for intravenous prostacyclin infusion in presence of an open intracardiac shunt. At the end of the observation period, 3 (5%) patients were treated with parenteral monotherapy, 12 (20%) with oral monotherapy, 30 (50%) with double oral combination therapy, 5 (8%) with triple oral combination therapy and 9 (15%) with triple parenteral combination therapy – Table 1.

### *Survival Analysis*

In the overall observation period, considering the two main subgroups (I/HPAH and PAH – CHD), 39 patients died (25 in I/H-PAH group and 14 in CHD-PAH): 21 were due to heart failure, 15 were sudden cardiac death, 2 were due to haemoptysis and 1 due to pneumonia. Four patients (3.3%) underwent double lung or heart – lung transplantation. Seven patients (5.8%) were lost to follow-up.

In patients with I/HPAH, 1-, 5-, 10-, and 15-year survival rates were 94% [95% confidence interval (CI), 87-100%], 69% (95% CI, 56-84%), 54% (95% CI, 40-72%), and 39% (95% CI, 26-60%), respectively).

In patients with PAH-CHD, 1-, 5-, 10-, and 15-year survival rates were 96% [95% confidence interval (CI), 90-100%], 84% (95% CI, 73-96%), 72% (95% CI, 59-88%), and 62% (95% CI, 47-83%), respectively. Cox survival analyses showed a better survival in PAH-CHD when compared to I/HPAH ( $p = 0.015$  – Figure 5).

### *First-line Pulmonary Arterial Hypertension targeted-drugs' effects*

In treatment naïve patients, we evaluated the effects of first-line PAH specific treatment on several clinical, functional, exercise, echocardiographic and hemodynamic parameters (Tables 4 and 5).

We observed a significant improvement in symptoms assessed by NYHA-FC ( $p < 0.001$ ), in exercise capacity with an increase in 6MWT test from 455.5 (366-522.7) meters to 494 (422 – 557) meters ( $p < 0.001$ ) with a median follow-up of 4.1 (3.2 – 5.2) months after initial therapy and in all the main echocardiographic parameters describing right ventricular dimension and function at a median follow-up of 4.7 (3.9 – 7.7) months. In 64 (46.7%) patients we also had a hemodynamic re-evaluation after initial therapy (median follow-up 5.3 (4 – 11.1) months) and we observed a significant increase of CI (2.7 (2.3 – 3.2) L/min/m<sup>2</sup> vs 3.1. (2.6 – 3.9) L/min/m<sup>2</sup>,  $p = 0.007$ ) and of pulmonary artery oxygen saturation - Pulm SatO<sub>2</sub> (68.5 (61 - 74) % vs 71.7 (64.7 – 77.2) %,  $p = 0.03$ ) and a significant reduction in PVRI (10.8 (8.4 – 20.2) WU·m<sup>2</sup> vs 8.3 (4.8 – 15.3) WU·m<sup>2</sup>,  $p = 0.007$ ).

## Subgroup Analysis: Pediatric Pulmonary Arterial Hypertension Patients followed in Bologna Pulmonary Vascular Disease Center from January 2014 to October 2024

### *Patients*

A total of 65 PH pediatric patients were followed at Bologna Pulmonary Vascular Disease Centre from January 2014 to October 2024. Among these, 10 patients were excluded from the analysis (4 had Group 3 PH and 6 had PH associated with pulmonary arteries stenosis – Group 4 PH).

Among the 55 Group 1 PAH pediatric patients included in the study, 20 (36%) had I/HPAH, 26 (47%) had PAH-CHD, 3 (5%) had PAH with mild respiratory comorbidities, 4 (7%) had po-PAH, 1 (2%) had PVOD and 1 (2%) had PPHN. Baseline patients' characteristics of the main subgroups are shown in Table 6.

### *Idiopathic/Hereditary Pulmonary Arterial Hypertension*

When considering the I/HPAH subgroup, the etiology of PAH was idiopathic in 13 (65%) and hereditary in 7 (35%) patients. Median age at diagnosis was 7.4 (5 – 11.1) years and age at referral was 8.1 (5.6 – 12.3) years. No female predominance was observed. At referral, 70% of patients were naïve from PAH specific therapy, while 30% were already treated, mainly with monotherapy.

At diagnosis, 5 (25%) patients showed a positive response to acute vasoreactivity test and were treated with calcium-channel blocker; 2 acute responders (10%) required a combined treatment strategy (PAH targeted drugs and calcium-channel blocker therapy) because of the severity of the disease at diagnostic RHC and only 1 patient (5%) could be considered a real long-term responder.

When considering non-vasoreactive patients, 9 (60%) were treated with upfront combination therapy (bosentan + sildenafil) and 6 (40%) with initial monotherapy. Overall, at the end of the observation period, 1 (5%) patient was treated with calcium-channel blocker alone, 2 (10%) patients were treated with oral monotherapy, 3 (15%) were treated with calcium-channel blocker and oral monotherapy, 6 (30%) were treated with double oral combination therapy, 3 (15%) were treated with triple oral combination therapy, 4 (20%) were treated with triple parenteral combination therapy and 1 (5%) patients was treated with calcium-channel blocker and triple parenteral combination therapy – Table 6.

### *PAH associated with Congenital Heart Disease*

Among the 26 PAH-CHD patients, 10 (38%) had Eisenmenger Syndrome, 3 (12%) had PAH associated with prevalent left-to-right shunt, 8 (31%) had coincidental defects and 5 (19 %) had a repaired defect. Median age at diagnosis was 5.4 (3.5-9.1) years and age at referral was 6.4 (5 – 12.7) years. At referral, 38% of patients were naïve from PAH specific therapy, while 62% were already treated, mainly with monotherapy.

At diagnosis, 22 (85%) patients were treated with initial monotherapy and only 4 (15%) were treated with upfront combination therapy (3 patients had repaired defect and 1 had a coincidental shunt). At the end of the observation period, 4 (15%) patients were treated with oral monotherapy, 15 (58%) with double oral combination therapy, 3 (12%) with triple oral combination therapy and 4 (15%) with triple parenteral combination therapy – Table 6.

### *First-line PAH specific treatment efficacy*

The effects of first-line treatment strategy in this subgroup of patients is consistent with the effects observed in the overall population: we observed a significant improvement of functional class assessed by NYHA – FC scale ( $p = 0.0026$ ), of exercise capacity assessed by 6MWT with an increase of distance walked from 477 (400.5 – 465.2) meters to 506 (462.5 – 553) meters ( $p = 0.005$ ) with a median follow-up of 4.6 (3.1 – 5.4) months after initial therapy and of the main echocardiographic parameters evaluating the right ventricle (see Table 7 and 8) at a median follow-up of 5 (3.9 – 9.4) months.

Regarding hemodynamics, only 18 patients repeated RHC after initial therapy and in this small cohort of patients no statistically significant differences were observed.

## **Discussion**

Pediatric PAH is a rare condition associated with significant morbidity and mortality.

This study describes the epidemiological, clinical, functional, echocardiographic and hemodynamic features of pediatric PAH patients referred to our Centre.

From an epidemiological stand point, I/HPAH and PAH-CHD are the most frequent PAH etiologies in our population; this is consistent with the main data available in the Literature on PAH etiology in pediatric age<sup>5,6,7</sup>. As expected, PAH-CHD patients are younger at diagnosis as compared with I/HPAH; in fact, the diagnostic delay due to the lack of specific symptoms is more relevant in those patients who are not receiving medical attention because of associated clinical conditions as usually occurs in patients with systemic-to-pulmonary shunts.

When selecting patient followed in the last 10 years, our study showed a lower median age and lower NYHA-FC at diagnosis both in CHD-PAH and in I/HPAH reflecting an improvement in the diagnostic work-up (especially for CHD that are early detected during prenatal care or at birth) and an increased knowledge and awareness of this condition. Interestingly, whereas 70–80% of adult patients with PAH are female, in pediatric PAH there are no clear gender differences<sup>6,14</sup> and our series confirms the absence of female predominance in all subgroups.

In the majority of our cohort, symptoms were not severe at diagnosis as more than half of patients presented with NYHA - FC I or II and with an acceptable exercise capacity (> 350 meters – cut off for lower risk criteria as reported by Ivy et al<sup>2</sup>). This is in line with echocardiographic parameters and the hemodynamic profile of our cohort. In fact, echocardiography only showed initial dilation of right atrium and mild tricuspid regurgitation grade (findings that suggest normal filling pressures) in absence of severe right ventricular (RV) systolic dysfunction despite direct and indirect signs of a significant elevation of pulmonary pressures.

Symptoms, exercise capacity and echocardiographic data are consistent with hemodynamics which documented a severe increase of pulmonary pressures and PVR with preserved RV function as defined by normal RV filling pressures and CI. In our series, baseline hemodynamic characteristics are similar to those reported in Netherland's pediatric PAH registry by van Loon et al<sup>6</sup>: normal right atrial pressure, isosystemic mPAP, severely elevated PVR, normal CI and lower Syst SatO<sub>2</sub> in PAH-

CHD than in I/HPAH. When focusing of hemodynamics in PAH-CHD subgroups, Eisenmenger patients had the worst hemodynamic profile with the highest values of mPAP and PVRI and cyanosis at rest (shunt-reversal), while in patients with small coincidental shunts the hemodynamic profile is very alike I/HPAH. As previously reported in other pediatric and adults PAH-CHD cohorts<sup>15,16</sup>, patients with repaired defects had higher value of right atrial pressure despite lower PVR probably because the lack of the shunt that allows right ventricle decompression.

Therefore, in pediatric PAH patients, a rather favorable clinical presentation in the presence of severe pulmonary vascular disease may be misleading and should not justify delay of medical treatment considering the significant morbidity and mortality of the disease<sup>17</sup>. The increased awareness of the progressive nature of PAH and of its potential life-threatening complications had led to the use of a more aggressive treatment approach. In our study, treatment strategy reflects the progressive availability of PAH-targeted drugs during the long observation period (epoprostenol - first drug approved for PAH in the 90's, bosentan and sildenafil approved for adult PAH in 2001 and 2005, respectively) and this justifies the relatively high percentage of patients treated with monotherapy when considering the entire cohort. When focusing on the last 10 years, according to guidelines' proposed treatment algorithms over time, most of PAH patients were treated with a rapid sequential/upfront double oral combination therapy if lower risk and triple combination including parenteral prostanoids (especially in I/HPAH) if high risk. Only 2 (10%) I/HPAH patients with mild pulmonary vascular disease and favorable clinical characteristics were treated with monotherapy in the last decade. Concerning PAH-CHD, our study shows that while historically this population was treated in a more prudential manner (safety concerns about intravenous prostanoids in patients with intracardiac shunts), more recently, treatment approach is similar to those used in I/HPAH, with a more extensive use of combination therapy, including oral and parenteral prostanoids.

As discussed above, an aggressive treatment strategy to maintain or reach a lower risk profile is associated with a better survival in pediatric PAH<sup>10,11,12,13</sup>. While in adults hemodynamic evaluation is extensively used for risk assessment providing useful prognostic data, in children the benefit to perform RHC should be balanced with the potential risks of the procedure (not negligible procedural and anesthesiologic morbi-mortality)<sup>3,4</sup>; so there is a strong need for other non-invasive risk assessment tools. This study investigated the effects of first-line PAH-targeted therapy on several parameters showing that NYHA-FC, 6MWT and many RV echocardiographic parameters, other than hemodynamics, may be helpful for monitoring treatment effects in children with PAH. These data were also confirmed in the subgroup analysis of patients referred to our Center since 2014.

In conclusion, this study provides a general picture of PAH pediatric population followed in a national referral center and support the relevance of a multiparametric approach for monitoring disease progression and treatment response.

## TABLES AND FIGURES

Haemodynamic characterisation of paediatric pulmonary hypertension (PH)	
	Haemodynamic characteristics
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg PAWP ≤15 mmHg PVRI >3 WU·m <sup>2</sup> (mmHg·L <sup>-1</sup> ·min·m <sup>2</sup> )
Isolated post-capillary PH	mPAP >20 mmHg PAWP >15 mmHg PVRI ≤3 WU·m <sup>2</sup> (mmHg·L <sup>-1</sup> ·min·m <sup>2</sup> )
Combined pre- and post-capillary PH	mPAP >20 mmHg PAWP >15 mmHg PVRI >3 WU·m <sup>2</sup> (mmHg·L <sup>-1</sup> ·min·m <sup>2</sup> )

mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVRI: indexed pulmonary vascular resistance; WU: Wood Units.

**Figure 1.** Hemodynamic definition of Pediatric Pulmonary Hypertension.

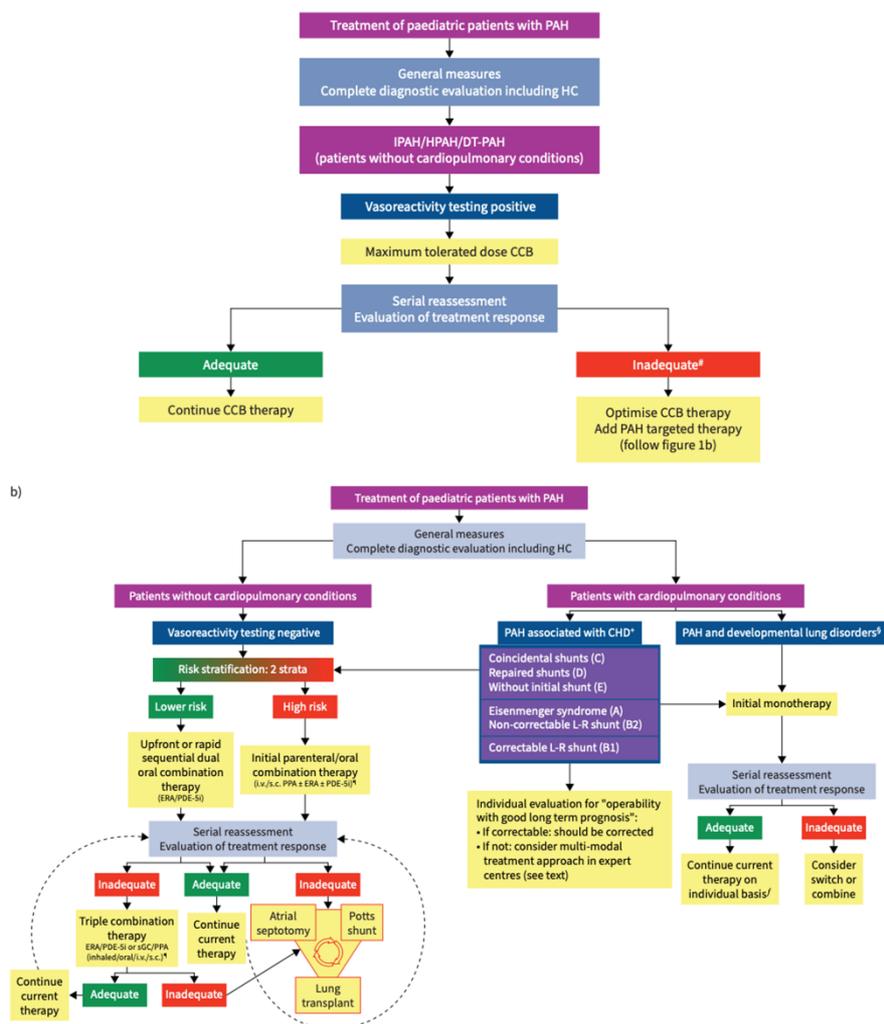
Updated clinical classification of pulmonary hypertension (PH)
<b>Group 1: PAH</b>
1.1 Idiopathic
1.1.1 Long-term responders to calcium channel blockers
1.2 Heritable <sup>#</sup>
1.3 Associated with drugs and toxins <sup>#</sup>
1.4 Associated with:
1.4.1 connective tissue disease
1.4.2 HIV infection
1.4.3 portal hypertension
1.4.4 congenital heart disease
1.4.5 schistosomiasis
1.5 PAH with features of venous/capillary (PVOD/PCH) involvement
1.6 Persistent PH of the newborn
<b>Group 2: PH associated with left heart disease</b>
2.1 Heart failure:
2.1.1 with preserved ejection fraction
2.1.2 with reduced or mildly reduced ejection fraction
2.1.3 cardiomyopathies with specific aetiologies <sup>†</sup>
2.2 Valvular heart disease:
2.2.1 aortic valve disease
2.2.2 mitral valve disease
2.2.3 mixed valvular disease
2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH
<b>Group 3: PH associated with lung diseases and/or hypoxia</b>
3.1 COPD and/or emphysema
3.2 Interstitial lung disease
3.3 Combined pulmonary fibrosis and emphysema
3.4 Other parenchymal lung diseases <sup>†</sup>
3.5 Nonparenchymal restrictive diseases:
3.5.1 hypoventilation syndromes
3.5.2 pneumonectomy
3.6 Hypoxia without lung disease (e.g. high altitude)
3.7 Developmental lung diseases
<b>Group 4: PH associated with pulmonary artery obstructions</b>
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions <sup>‡</sup>
<b>Group 5: PH with unclear and/or multifactorial mechanisms</b>
5.1 Haematological disorders <sup>†</sup>
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis and neurofibromatosis type 1
5.3 Metabolic disorders <sup>##</sup>
5.4 Chronic renal failure with or without haemodialysis
5.5 Pulmonary tumour thrombotic microangiopathy
5.6 Fibrosing mediastinitis
5.7 Complex congenital heart disease

**Figure 2.** Updated clinical classification of Pulmonary Hypertension.

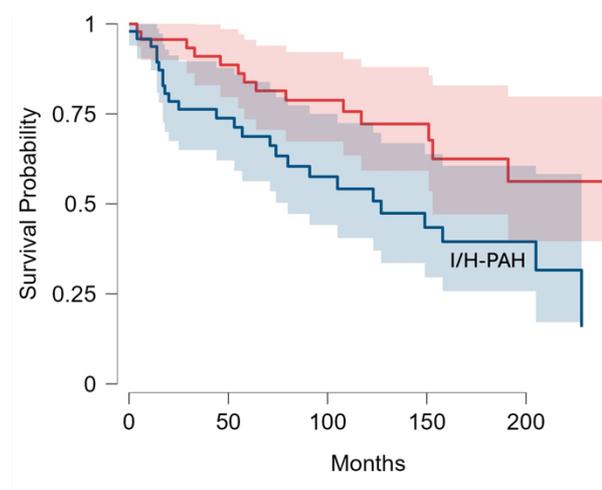
Classification of congenital heart disease (CHD)-associated pulmonary arterial hypertension	
Group	Condition
A	Eisenmenger syndrome
B	Left-to-right shunt: 1) correctable 2) not correctable
C	Coincidental defects, including all (isolated) ASDs in childhood
D	Corrected CHD
E	Without (prolonged) initial shunt, e.g. neonatal arterial switch operation for TGA

ASD: atrial septal defects; TGA: transposition of the great arteries.

**Figure 3.** Updated classification of Congenital Heart Disease-associated Pulmonary Arterial Hypertension.



**Figure 4.** Treatment algorithm for Pediatric Pulmonary Arterial Hypertension.



**Figure 5.** Kaplan–Meier survival curve of 120 Group 1 – PAH patients according to subgroups (I/H-PAH vs PAH-CHD)

Baseline characteristics	I/H-PAH (n= 60)	CHD-PAH (n=60)	<i>p</i>
Female gender (%)	55	51	<i>n.s.</i>
NYHA FC III-IV (%)	49	47	<i>n.s.</i>
Age at diagnosis (y)	9.4 (5.1 -13)	5.4 (3.3 - 12.2)	<i>n.s.</i>
Age at referral (y)	11.3 (6.3 -14.7)	9.3 (5.2 -17.2)	<i>n.s.</i>
Treatment naive (%)	53	59	<i>n.s.</i>
<b>Targeted therapy</b>			
Responder to AVT, n (%)	14 (23)	/	/
Long term CCB responder, n (%)	3 (5)	/	/
ERA, n (%)	44 (73)	51 (85)	/
PDE-5i, n (%)	41 (68)	47 (78)	/
Selexipag, n (%)	8 (13)	7 (12)	/
Prostanoids, n (%)	25 (42)	13 (22)	/
<b>Treatment profile at the end of observation period</b>			
CCB, n (%)	3 (5)	/	/
CCB + targeted PAH therapy, n (%)	11 (18)	/	/
No targeted PAH therapy, n (%)	/	1 (2)	/
Oral monotherapy, n (%)	9 (15)	12 (20)	/
Parenteral monotherapy, n (%)	/	3 (5)	/
Double CT (parenteral prostanoid), n (%)	6 (10)	/	/
Double oral CT, n (%)	12 (20)	30 (50)	/
Triple CT (selexipag), n (%)	4 (7)	5 (8)	/
Triple CT (parenteral prostanoid), n (%)	15 (25)	9 (15)	/

AVT: acute vasoreactivity test; CCB: calcium-channel blocker; ERA: endothelin receptor antagonist; PDE5-i: phosphodiesterase 5 (PDE5) inhibitors; PAH: Pulmonary Arterial Hypertension; CT: combined therapy

**Table 1.** Comparative baseline characteristics and treatment strategy in idiopathic/hereditary PAH and congenital heart disease-associated PAH

Exercise capacity	I/H-PAH	CHD-PAH	<i>p</i>
6MWT (m)	447.5 (357-513.5)	412 (328.5-483.5)	0.23
<b>Hemodynamics</b>			
RAP (mmHg)	6 (4 - 9)	7 (5 - 9)	0.47
mPAP (mmHg)	59.5 (45 - 83)	61 (48 - 78)	0.48
PAWP (mmHg)	8 (6 - 10)	10 (6 - 12)	0.09
mSAP (mmHg)	70 (63 - 85)	65.5 (59.5 - 74)	0.17
Syst CI (l/min/m <sup>2</sup> )	3.1 (2.3 - 3.8)	2.6 (2.1 - 3.3)	0.027
Pulm CI (l/min/m <sup>2</sup> )	3.1 (2.3 - 3.8)	2.6 (1.7 - 4.3)	0.8
PVRI (WU*m <sup>2</sup> )	15.4 (8.3 - 22.7)	15.5 (8.3 - 33.5)	0.49
SVRI (WU*m <sup>2</sup> )	15.5 (13.3-23.3)	19.2 (11.5 - 42.1)	0.27
Art O <sub>2</sub> Sat (%)	96 (94 - 98)	93.2 (86 - 96)	0.001
PA O <sub>2</sub> Sat (%)	68.4 (58.4 - 74.1)	72 (66.9 - 78.8)	0.07

6MWT: six-minute-walking test; RAP: right atrial pressure; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; mSAP: mean systemic arterial pressure; CI: cardiac index; PVRI: pulmonary vascular resistance index; SVRI: systemic vascular resistance index; ArtO<sub>2</sub> Sat: systemic oxygen saturation; PA O<sub>2</sub> Sat: pulmonary artery oxygen saturation

**Table 2.** Comparative baseline exercise capacity and hemodynamics in idiopathic/hereditary PAH and congenital heart disease-associated PAH

Ecocardiography	I/H-PAH	CHD-PAH	<i>p</i>
TAPSE (cm)	1.5 (1.3 - 1.7)	1.6 (1.4 - 1.9)	0.68
TR Area/RA Area (%)	0.2 (0.1 - 0.3)	0.2 (0.1 - 0.3)	0.48
RA Area Ind (cm <sup>2</sup> /m <sup>2</sup> )	11.8 (9.6 - 14.9)	11.7 (10.2 - 15.7)	0.33
TR jet velocity (cm/s)	436 (380 - 512)	460 (425 - 500)	0.55
RVOT Acc Time (ms)	78 (65.7 - 86.7)	80 (70 - 85)	0.98
TDI S wave (cm/s)	10 (8.6 - 11)	10.3 (8.9 - 11.2)	0.86
TDI E wave (cm/s)	11 (5.6 - 14)	9 (8.4 - 12.5)	0.92
RVED Area (cm <sup>2</sup> /m <sup>2</sup> )	18.3 (15.6 - 24.5)	20.2 (16.2 - 24.6)	0.72
LV Vol (ml/m <sup>2</sup> )	29.6 (23.4 - 36.1)	37 (23.3 - 46.3)	0.06
RV FAC (%)	24.5 (19.8 - 33.7)	30.5 (24.7 - 37.1)	0.11
LV EF (%)	70.7 (64.3 - 76.7)	63.3 (55.6 - 70.8)	< 0.001
Eccentricity Index	1.6 (1.4-2.2)	1.5 (1.3 -1.9)	0.03

TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation; RA: right atrial; RVOT: right ventricular outflow tract; TDI: tissue doppler imaging; RVED: right ventricle end-diastolic; LV: left ventricle; RV: right ventricle.

**Table 3.** Comparative echocardiographic parameters in idiopathic/hereditary PAH and congenital heart disease-associated PAH

Symptoms (99)	pre	post	<i>p</i>
NYHA III/IV (%)	32	12	< 0.001
Exercise capacity (74)	pre	post	<i>p</i>
6MWT (m)	455.50 (366 - 522.7)	494 (422 - 557)	< 0.001
Hemodynamics (64)	pre	post	<i>p</i>
RAP (mmHg)	7 (5 - 8)	7 (5 - 8)	0.54
mPAP (mmHg)	68 (53.7 - 81)	67 (51.7 - 78.5)	0.20
PAWP (mmHg)	9 (6 - 10)	10 (8.0 - 11)	0.08
mSAP (mmHg)	79 (68 - 86)	77 (69 - 86.2)	0.82
Syst CI (l/min/m <sup>2</sup> )	2.7 (2.3 - 3.2)	3.1 (2.6 - 3.9)	0.007
Pulm CI (l/min/m <sup>2</sup> )	2.1 (1.7 - 3.1)	2.5 (2.3 - 3.3)	0.97
PVRI (WU*m <sup>2</sup> )	10.7 (8.4 - 20.2)	8.3 (4.8 - 15.3)	0.006
SVRI (WU*m <sup>2</sup> )	14.5 (10.4 - 18.1)	10.5 (7.5 - 14.6)	0.007
Art O <sub>2</sub> Sat (%)	96 (94 - 98)	96 (94 - 98)	0.55
PA O <sub>2</sub> Sat (%)	68.5 (61 - 74)	71.7 (64.7 - 77.2)	0.03

\*Median follow-up for 6MWT 4.1 (3.2 - 5.2) months, for hemodynamics 5.3 (3.9 - 11.2) months

6MWT: six-minute-walking test; RAP: right atrial pressure; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; mSAP: mean systemic arterial pressure; CI: cardiac index; PVRI: pulmonary vascular resistance index; SVRI: systemic vascular resistance index; ArtO<sub>2</sub> Sat: systemic oxygen saturation; PA O<sub>2</sub> Sat: pulmonary artery oxygen saturation

**Table 4.** Treatment effects of first-line treatment strategy on symptoms, exercise capacity and hemodynamics.

Ecocardiography (83)	pre	post	<i>p</i>
TAPSE (cm)	1.5 (1.3 - 1.9)	1.7 (1.4 - 2.0)	< 0.001
TR Area/RA Area (%)	0.12 (0.1 - 0.35)	0.2 (0.1 - 0.3)	0.09
RA Area Ind (cm <sup>2</sup> /m <sup>2</sup> )	12.3 (7.2 - 18.0)	10.9 (9.2 - 13.9)	0.04
TR jet velocity (cm/s)	460 (391 - 530)	430 (371 - 500)	0.003
RVOT Acc Time (ms)	80 (70 - 90)	90 (80 - 102)	< 0.001
TDI S wave (cm/s)	10 (8.7 - 11.3)	11.7 (10.25 - 12.5)	< 0.001
TDI E wave (cm/s)	12 (8.3 - 14.6)	14.9 (9.2 - 17.1)	0.004
RVED Area (cm <sup>2</sup> /m <sup>2</sup> )	19.2 (11.6 - 31.9)	17.3 (14.4 - 22.3)	0.019
LV Vol (ml/m <sup>2</sup> )	32.3 (19.5 - 57)	34.7 (25.2 - 41.1)	0.03
RV FAC (%)	33.1 (23.8 - 37.8)	31.6 (24.6 - 41.4)	0.08
LV EF (%)	63.5 (57.3 - 70.1)	63.3 (55.6 - 70.2)	0.97
Eccentricity Index	1.6 (1.3 - 1.8)	1.5 (1.3 - 1.7)	0.004

\*Median follow-up 4.7 (3.9 - 7.8) months

TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation; RA: right atrial; RVOT: right ventricular outflow tract; TDI: tissue doppler imaging; RVED: right ventricle end-diastolic; LV: left ventricle; RV: right ventricle.

**Table 5.** Treatment effects of first-line treatment strategy on echocardiographic parameters.

Baseline characteristics	I/H-PAH (n= 20)	CHD-PAH (n= 26)
Female gender (%)	45	58
NYHA FC III-IV (%)	22	33
Age at diagnosis (y)	7.4 (5 – 11.1)	5.4 (3.5 - 9)
Age at referral (y)	8.1 (5.6 – 12.3)	6.4 (5 – 12.7)
Treatment naïve (%)	70	38
<b>Targeted therapy</b>		
Responder to AVT, n (%)	5 (25)	/
Long term CCB responder, n (%)	1 (5)	/
ERA, n (%)	16 (80)	26 (100)
PDE-5i, n (%)	17 (85)	24 (92)
Selexipag, n (%)	5 (25)	4 (15)
Prostanoids, n (%)	5 (25)	4 (15)
<b>Treatment profile at the end of observation period</b>		
CCB, n (%)	1 (5)	/
CCB + targeted PAH therapy, n (%)	4 (20)	/
Oral monotherapy, n (%)	2 (10)	4 (15)
Double oral CT, n (%)	6 (30)	15 (58)
Triple CT (selexipag), n (%)	3 (15)	3 (12)
Triple CT (parenteral prostanoid), n (%)	4 (20)	4 (15)

AVT: acute vasoreactivity test; CCB: calcium-channel blocker; ERA: endothelin receptor antagonist; PDE5-i: phosphodiesterase 5 (PDE5) inhibitors; PAH: Pulmonary Arterial Hypertension; CT: combined therapy

**Table 6.** Comparative baseline characteristics and treatment strategy in the subgroup of idiopathic/hereditary PAH and congenital heart disease-associated PAH patients followed in Bologna Pulmonary Vascular Disease Center from 2014 to 2024

Symptoms (47)	pre	post	p
NYHA III/IV (%)	31	3	0.0026
<b>Exercise capacity (23)</b>			
6MWT (m)	477 (400.5 – 538.5)	506 (462.5 - 553)	< 0.005
<b>Hemodynamics (18)</b>			
RAP (mmHg)	6 (5 - 7)	6 (5 – 8.5)	0.42
mPAP (mmHg)	54 (46 – 68.5)	57 (48.2 – 74.2)	0.53
PAWP (mmHg)	9 (6.2 - 10)	9.5 (7.2 – 12.7)	0.11
mSAP (mmHg)	63 (61 - 79)	73.5 (66 – 79.7)	0.43
Syst CO (l/min)	4.2 (2.2 – 4.9)	5.4 (4.4 – 7.0)	0.06
Syst CI (l/min/m <sup>2</sup> )	3 (2.8 - 3.6)	3.3 (2.5 - 3.9)	0.42
PVRI (WU*m <sup>2</sup> )	9.6 (5.5 – 13.1)	6.9 (3.6 – 13.9)	0.65
SVRI (WU*m <sup>2</sup> )	11.5 (8.5 – 15.1)	9.4 (6.3 – 15.2)	0.99
Art O <sub>2</sub> Sat (%)	97 (93.5 - 98)	98 (95 - 99)	0.58
PA O <sub>2</sub> Sat (%)	75 (70 - 79)	76 (67.3 – 80.5)	0.68

\*Median follow-up for 6MWT 4.6 (3.1 – 5.4) months, for hemodynamics 8.6 (4.6 – 20) months

6MWT: six-minute-walking test; RAP: right atrial pressure; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; mSAP: mean systemic arterial pressure; CO: cardiac output; CI: cardiac index; PVRI: pulmonary vascular resistance index; SVRI: systemic vascular resistance index; ArtO<sub>2</sub> Sat: systemic oxygen saturation; PA O<sub>2</sub> Sat: pulmonary artery oxygen saturation

**Table 7.** Treatment effects of first-line treatment strategy on symptoms, exercise capacity and hemodynamics in the subgroup of patients followed in Bologna Pulmonary Vascular Disease Center from 2014 to 2024

Echocardiography (47)	pre	post	p
TAPSE (cm)	1.6 (1.5 - 1.9)	1.9 (1.6 - 2.0)	< 0.001
TR Area/RA Area (%)	0.2 (0.1 - 0.3)	0.1 (0.1 - 0.3)	0.09
RA Area Ind (cm <sup>2</sup> /m <sup>2</sup> )	12.5 (10.5 - 15.5)	12.1 (10 - 14.3)	0.31
TR jet velocity (cm/s)	415 (378 - 494)	400 (352 - 438)	0.02
RVOT Acc Time (ms)	80.5 (73 - 90)	90 (81 - 100)	0.18
TDI S wave (cm/s)	10 (9 - 11)	11.4 (10.3 - 12.5)	0.004
TDI E wave (cm/s)	11.9 (9 - 13.8)	15 (10 - 18)	0.02
RVED Area (cm <sup>2</sup> /m <sup>2</sup> )	20.3 (16.7 - 23.5)	18 (14.9 - 21.5)	0.003
LV Vol (ml/m <sup>2</sup> )	35.2 (27.1 - 41.3)	38.7 (29.6 - 43.8)	0.11
RV FAC (%)	33.3 (26.2 - 38.8)	33.6 (27 - 41.9)	0.14
LV EF (%)	62.5 (55 - 66)	63.1 (57.1 - 70.4)	0.72
Eccentricity Index	1.5 (1.3 - 1.7)	1.4 (1.2 - 1.6)	0.03

\*Median follow-up 5 (3.9 - 9.4) months

TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation; RA: right atrial; RVOT: right ventricular outflow tract; TDI: tissue doppler imaging; RVED: right ventricle end-diastolic; LV: left ventricle; RV: right ventricle.

**Table 8.** Treatment effects of first-line treatment strategy on echocardiographic parameters in the subgroup of patients followed in Bologna Pulmonary Vascular Disease Center from 2014 to 2024.

Symptoms and Exercise capacity	Eisenmenger (n= 25)	L-R Shunt (n= 8)	Small Defects (n= 11)	Corrected (n= 16)
NYHA III/IV (%)	52	29	50	46
6MWT (m)	400 (293.5 - 463)	361 (335 - 420)	465 (365 - 477)	436 (373.5 - 500.5)
<b>Hemodynamics</b>				
RAP (mmHg)	6.5 (5 - 9)	7 (5.5 - 7-75)	6 (4 - 7)	7 (6 - 10)
mPAP (mmHg)	64.5 (54 - 79.7)	60 (55 - 63.5)	54 (48 - 75)	60 (36.5 - 76)
PAWP (mmHg)	10 (6 - 13)	11 (9.5 - 12.5)	7 (5.5 - 8.5)	9 (7 - 10)
mSAP (mmHg)	68 (60.5 - 77)	61 (58 - 68)	61 (52.5 - 67.5)	71 (60 - 79)
Syst CI (l/min/m <sup>2</sup> )	2.8 (2 - 3.3)	2.9 (2.6 - 3.1)	3.1 (2.4 - 3.8)	2.5 (1.9 - 2.7)
Pulm CI (l/min/m <sup>2</sup> )	2.4 (1.6 - 3.1)	4.5 (3.9 - 5.0)	3.3 (2.6 - 4.4)	2.5 (1.9 - 2.7)
PVRI (WU*m <sup>2</sup> )	21.2 (9.6 - 40.0)	7.1 (5.8 - 10.5)	17.2 (9.4 - 34.3)	12.2 (8.7 - 34.3)
SVRI (WU*m <sup>2</sup> )	19.2 (11 - 35.8)	12.7 (9.4 - 20.7)	18.9 (12.5 - 37.6)	31.7 (11.2 - 61.3)
Art O <sub>2</sub> Sat (%)	86 (83 - 93.4)	96 (95.5 - 96.4)	95 (91 - 97)	94.2 (92.5 - 95.5)
PA O <sub>2</sub> Sat (%)	72.1 (69.7 - 75.8)	82.5 (81.4 - 83.3)	70 (69.5 - 76.5)	65.6 (53.4 - 73.2)

6MWT: six-minute-walking test; RAP: right atrial pressure; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; mSAP: mean systemic arterial pressure; CO: cardiac output; CI: cardiac index; PVRI: pulmonary vascular resistance index; SVRI: systemic vascular resistance index; ArtO<sub>2</sub> Sat: systemic oxygen saturation; PA O<sub>2</sub> Sat: pulmonary artery oxygen saturation

**Supplementary Table 1.** Baseline symptoms, exercise capacity and hemodynamics in congenital heart disease-associated PAH divided by subgroups

Echocardiography	Eisenmenger (n= 25)	L-R Shunt (n= 8)	Small Defects (n= 11)	Corrected (n= 16)
TAPSE (cm)	1.7 (1.5 - 1.9)	1.7 (1.5 - 1.8)	1.9 (1.8 - 2.0)	1.4 (1.3 - 1.5)
TR Area/RA Area (%)	0.1 (0.1 - 0.25)	0.15 (0.1 - 0.3)	0.2 (0.2 - 0.4)	0.3 (0.1 - 0.35)
RA Area Ind (cm <sup>2</sup> /m <sup>2</sup> )	10.4 (8.4 - 16.4)	13.8 (11.4 - 22.3)	12.4 (11.6 - 13.8)	11.8 (10.1 - 14.1)
TR jet velocity (cm/s)	474 (450 - 500)	438.5 (397.5 - 464)	500 (421 - 535.5)	450 (431.5 - 487.5)
RVOT Acc Time (ms)	70 (65 - 85)	81 (75 - 85)	75.5 (70 - 85.7)	80 (75 - 80)
TDI S wave (cm/s)	9.3 (8.8 - 12.1)	10 (10 - 12)	10.8 (10.6 - 10.9)	7 (6.5 - 8.8)
TDI E wave (cm/s)	8.3 (6.1 - 9.1)	11.3 (9.9 - 12.6)	12.5 (10.5 - 14.2)	8.4 (8.2 - 8.6)
RVED Area (cm <sup>2</sup> /m <sup>2</sup> )	16 (11.8 - 23.6)	20.2 (16.7 - 24.5)	22.9 (20.3 - 26.1)	20 (17.6 - 22.9)
LV Vol (ml/m <sup>2</sup> )	34.7 (24.4 - 41.9)	33.6 (18.9 - 42.9)	41.4 (23.1 - 47.4)	38.1 (24.9 - 47.9)
RV FAC (%)	33.3 (26.9 - 38.1)	34.4 (21.4 - 44.2)	27.6 (14 - 30.5)	30 (24 - 35.5)
LV EF (%)	63.3 (52.7 - 71.6)	63.7 (55.4 - 70.1)	64.7 (58.3 - 70)	63 (58.1 - 70.1)
Eccentricity Index	1.4 (1.4 - 1.9)	1.4 (1.3 - 1.7)	1.5 (1.2 - 1.6)	1.5 (1.3 - 1.9)

TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation; RA: right atrial; RVOT: right ventricular outflow tract; TDI: tissue doppler imaging; RVED: right ventricle end-diastolic; LV: left ventricle; RV: right ventricle.

**Supplementary Table 2.** Baseline echocardiographic parameters in congenital heart disease-associated PAH divided by subgroups

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